Janssen Research & Development

Summary of Biopharmaceutic Studies and Associated Analytical Methods

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults and Adolescents

D/C/F/TAF (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide)

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ABBREVIATIONS

ART	antiretroviral therapy
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{24h}	area under the plasma concentration-time curve over 24 hours
AUC_{∞}	area under the plasma concentration-time curve measured from time zero to the last quantifiable concentration and extrapolated to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
AUC_{tau} [a]	area under the plasma concentration-time curve over the dosing interval (tau, from time zero to the time of next dosing)
C_{0h}	predose (trough) plasma concentration
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COBI	cobicistat
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DRV	darunavir
DRV/COBI	darunavir/cobicistat
eq.	equivalent
EVG	elvitegravir
FDC	fixed-dose combination
F/TAF	emtricitabine/tenofovir alafenamide
FTC	emtricitabine
F/TDF	emtricitabine/tenofovir disoproxil fumarate
HIV-1	human immunodeficiency virus type 1
HPC	hydroxypropyl cellulose
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
LS	least square
MCC	microcrystalline cellulose
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PK	pharmacokinetic
RPV	rilpivirine
rtv	low-dose ritonavir
SD	standard deviation
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum plasma concentration

[a.] Unless specified in the text, $AUC_{tau}=AUC_{24h}$

SUMMARY OF BIOPHARMACEUTIC FINDINGS

The darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF, hereafter referred to as D/C/F/TAF) fixed-dose combination (FDC) tablet is a combination of 4 single agents, darunavir (DRV), cobicistat (COBI), emtricitabine (FTC) and tenofovir alafenamide (TAF). Darunavir is an approved human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI) with a high genetic barrier to resistance.[10] It is also a cytochrome P450 (CYP) 3A substrate. Cobicistat is a potent mechanism-based inhibitor of CYP3A, and is an approved pharmacokinetic (PK) enhancer that boosts systemic exposures of the HIV-1 PIs atazanavir (ATV) and DRV. Cobicistat has no antiviral activity. Emtricitabine is an approved nucleoside reverse transcriptase inhibitor (NRTI) that is generally well tolerated. Tenofovir alafenamide is an oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir alafenamide is more stable in plasma than tenofovir disoproxil fumarate (TDF; another widely used oral prodrug of TFV) and is predominantly hydrolyzed to TFV intracellularly by cathepsin A, resulting in higher intracellular levels of the active phosphorylated metabolite TFV-diphosphate (TFV-DP) and lower circulating plasma levels of TFV, relative to TDF.[1,11] The distinct metabolism of TAF is intended to both maximize antiviral potency and improve clinical safety compared with TDF.

The D/C/F/TAF 800/150/200/10 mg FDC tablet development program is based on two pivotal Phase 3 studies, TMC114FD2HTX3001 and TMC114IFD3013 (discussed in more detail in Module 2.7.2, 2.7.3 and 2.7.4 Summary of Clinical Pharmacology Studies, Efficacy and Safety, respectively). The current document summarizes bioequivalence and bioavailability data in healthy subjects for the D/C/F/TAF FDC tablet combining the 4 components in 1 tablet. Where applicable, this is complemented with data from the clinical development programs with the DRV, COBI, FTC and TAF single agents, and FDCs thereof (DRV/COBI and emtricitabine/tenofovir alafenamide [F/TAF]).

This Summary of Biopharmaceutic Studies and Associated Analytical Methods presents data from 3 relative bioavailability studies and 1 bioequivalence study with the D/C/F/TAF FDC. Additionally, the food effect for DRV, COBI, FTC, and TAF following single-dose administration of the D/C/F/TAF FDC is discussed, as well as relevant data from historical studies with the separate agents. Pharmacokinetic data for the components of the D/C/F/TAF FDC in the Phase 2 and 3 studies are described in the Summary of Clinical Pharmacology Studies (Module 2.7.2). The bioanalytical methods used, an overview of the formulation development and in vitro dissolution profiles supporting the D/C/F/TAF FDC are also summarized.

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

- The D/C/F/TAF monolayer tablet containing 10 mg TAF (GS-US-299-0101) resulted in TAF and intracellular TFV-DP exposures associated with potent antiviral activity (similar to those observed with TAF 25 mg administered as a single agent proof-of-concept study GS-US-120-0104) and markedly lower systemic TFV plasma concentrations, as compared with administration of TDF as a single agent or as part of FDCs containing TDF, or

compared with TDF coadministered with boosted PIs (see also Mod2.7.2/Sec3.5). Therefore, this formulation was selected for further development.

- The D/C/F/TAF FDC tablet is bioequivalent to combined administration as separate formulations of DRV, F/TAF FDC, and COBI. The 90% confidence intervals (CIs) of the least square (LS) means ratios of all main PK parameters for all 4 components (DRV, COBI, FTC, and TAF) were within the 80.00% to 125.00% bioequivalence limits.
- Intake of the D/C/F/TAF FDC as a split tablet compared to swallowed whole did not impact the relative bioavailability (C_{max}, AUC_{last}, and AUC_{∞}) of the different components (DRV, COBI, FTC, and TAF), except for an 11% decrease in the TAF C_{max}, which is not considered clinically relevant. Therefore, for patients who are unable to swallow, the D/C/F/TAF FDC may be split.
- 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 is administered with food. This is based on the results from the food effect panel in study TMC114FD2HTX1002 which were in line with earlier observations for other formulations with the components of D/C/F/TAF.
    - The maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), and area under the plasma concentration-time curve measured from time zero and extrapolated to infinity (AUC_{∞}) were lower after administration of the D/C/F/TAF FDC under fasted compared to fed conditions (high-fat high-calorie breakfast) for both DRV (30% to 45% lower) and COBI (16% to 29% lower); the C_{max} of FTC and TAF were 1.26- and 1.82-fold higher, respectively, under fasted compared to fed conditions, while the AUC_{last} for both FTC and TAF was comparable for both conditions.
    - The impact of food on the PK of COBI, FTC and TAF is not considered to be clinically relevant.
    - The type of food does not affect the exposure to DRV.

1. BACKGROUND AND OVERVIEW

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 analog of rtv and is a potent mechanism-based CYP3A inhibitor. Cobicistat has no anti-HIV-1 activity but is licensed as a PK enhancer of either atazanavir (ATV) 300 mg once daily or DRV 800 mg once daily. Cobicistat increases the systemic exposure of other coadministered drugs metabolized by CYP3A, including the HIV-1 integrase strand transfer inhibitor elvitegravir (EVG) as well as the HIV-1 PIs ATV and DRV. Darunavir and COBI (DRV/COBI; REZOLSTA®/PREZCOBIX®) 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 analog 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 analog 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.[2,5,11]

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.[1,11] 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.

Once daily combined ART regimens are aimed at reducing the pill burden for patients with HIV-1. Currently, there are only 6 effective, once-daily FDC tablets approved as a complete regimen for the treatment of HIV-1 infection: Atripla® (efavirenz/FTC/TDF), Complera®/Eviplera® (FTC/rilpivirine [RPV]/TDF), Stribild (EVG/COBI/FTC/TDF, hereafter referred to as E/C/F/TDF), Genvoya® (EVG/COBI/FTC/TAF, hereafter referred to as

E/C/F/TAF), Triumeq® (dolutegravir/abacavir/lamivudine) and Odefsey® (FTC/RPV/TAF). There remains a need for simplified PI-based ART that combines potent and sustained efficacy, favorable 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, Inc. have coformulated TAF with DRV, COBI, and FTC to form the first PI-based FDC single-tablet option darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) FDC. Gilead Sciences, Inc. has transferred further development of the regimen to the Applicant and, subject to regulatory approval, the manufacturing, registration, distribution and commercialization of the product worldwide. 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 registered, extended to adolescents.

This Summary of Biopharmaceutic Studies and Associated Analytical Methods summarizes information from the 4 biopharmaceutic studies that have been conducted in healthy subjects to support the development of the D/C/F/TAF FDC tablet formulation intended for marketing. Study GS-US-299-0101 compared 3 formulations of the D/C/F/TAF FDC. The proposed formulation for further development was subsequently compared to administration of the individual components: DRV/COBI or FTC + TAF. A bioequivalence study (TMC114FD2HTX1001) was conducted to establish bioequivalence of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet compared with a single oral dose of DRV as 1 x 800 mg tablet, F/TAF as 1 x 200/10 mg FDC tablet, and COBI as 1 x 150 mg tablet. Study TMC114FD2HTX1002 compared D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet with a single oral dose of DRV as 1 x 800 mg tablet, F/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet (Panel 2) and with E/C/F/TAF 150/150/200/10 mg as 1 x FDC tablet (Panel 1).

In study TMC114FD2HTX1002, the effect of concomitant food intake (standardized high-fat breakfast versus fasted) 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 also investigated. In study TMC114FD2HTX1004, different administration modes (whole tablet, split tablet, crushed tablet) for the D/C/F/TAF FDC tablet were compared, to accommodate recommendations for those subjects unable to swallow the D/C/F/TAF FDC as a whole.

Additionally, relevant supportive information from historical biopharmaceutic studies included in the DRV/COBI and F/TAF marketing authorizations is referenced in this Summary of Biopharmaceutic Studies and Associated Analytical Methods for the D/C/F/TAF FDC.

1.1. Formulation Development

1.1.1. Overview and Rationale

A comprehensive overview of the formulation development process is provided in [redacted]. An overview of the formulations used across clinical studies with D/C/F/TAF is shown in Appendix 2, the composition and characteristics of the formulations are provided in [redacted].

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. [redacted]

Both monolayer and bilayer tablet formulation concepts were evaluated. [redacted] For all formulations, DRV, COBI, and FTC were used at 800, 150, and 200 mg eq, respectively. [redacted] D/C/F/TAF concept formulations containing TAF 25 mg or TAF 10 mg were evaluated clinically. [redacted]

Monolayer: [redacted] monolayer tablet formulations (A and B) [redacted] as shown in Table 1.

Bilayer Formulation: [redacted] the bilayer formulation (Table 2) [redacted]

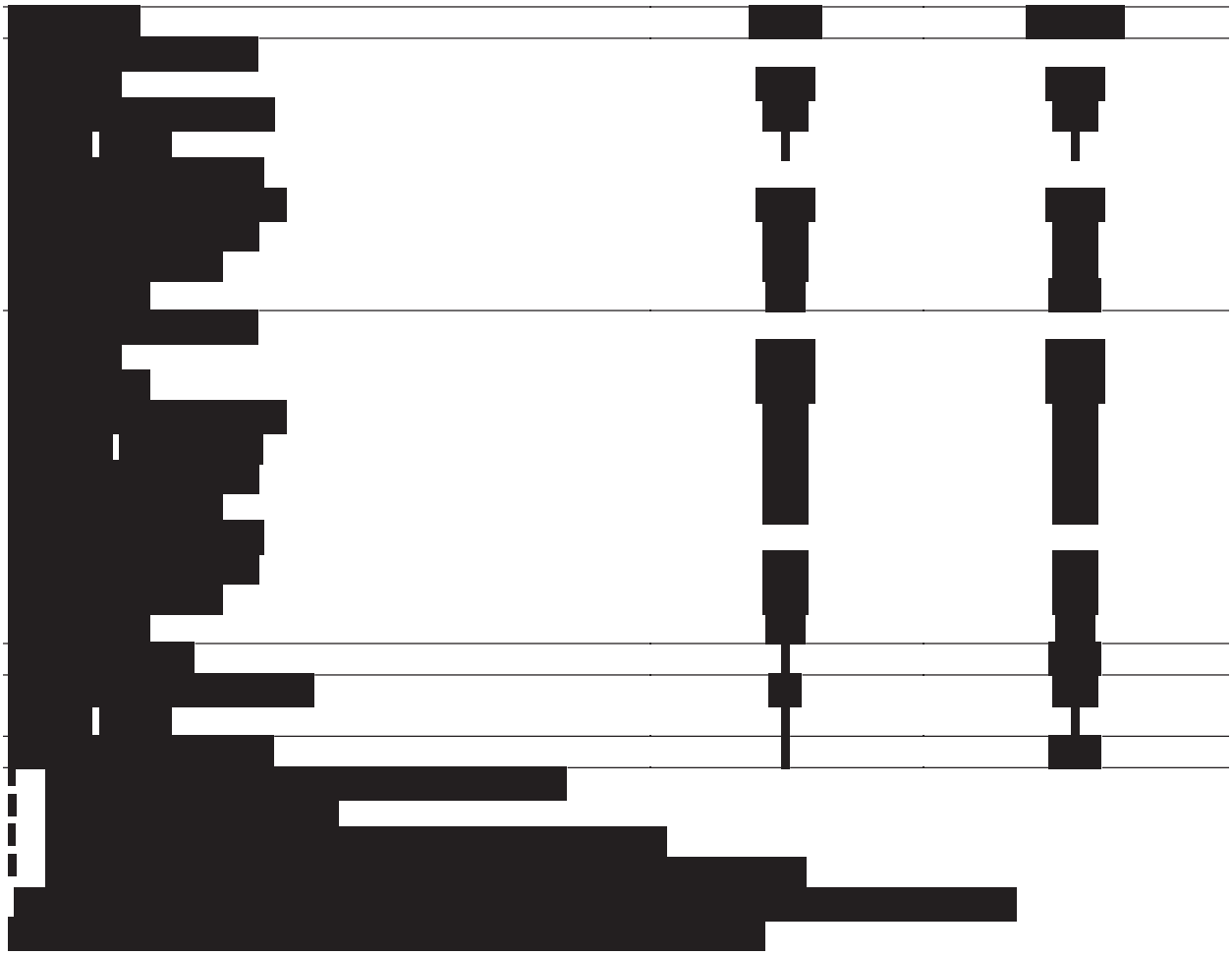
The monolayer and bilayer tablet formulations described above were evaluated in a relative bioavailability study GS-US-299-0101 (refer to Section 2.1.1.2). The monolayer formulation containing 10 mg TAF (monolayer A [denoted as Formulation 3 in the GS-US-299-0101 study]) was selected as the Phase 2 formulation.

The Phase 2 formulation was used in study GS-US-299-0102 in HIV-1 infected subjects (Mod2.7.2/Sec2.2.1.3.1).

This G001 formulation ( ) was used in the D/C/F/TAF pivotal Phase 3 studies TMC114IFD3013 and TMC114FD2HTX3001, and in a bioequivalence study (TMC114FD2HTX1001) that compared the intended commercial D/C/F/TAF FDC G001 formulation to the combination of the separate agents (DRV + COBI + F/TAF).

Table 1: Quantitative Composition of Monolayer Tablet Formulations A and B

Table 2: Quantitative Composition of Bilayer Tablet



1.1.2. In Vitro Release

1.1.2.1. Dissolution Evaluation Methods and Specifications

[redacted]

[redacted]

[redacted] the proposed dissolution methods [redacted] D/C/F/TAF FDC [redacted] in Table 3 and Table 4 [redacted] DRV/COBI FDC [redacted] in Table 5 and Table 6.

1.1.2.2. Dissolution Profiles of DRV, COBI, FTC and TAF in D/C/F/TAF FDC Tablet

A summary of the results of in vitro dissolution studies for the D/C/F/TAF FDC tablet is presented in Appendix 1.

Table 3: Parameters of the Proposed Dissolution Method for DRV in the D/C/F/TAF FDC



Table 4: Parameters of the Proposed Dissolution Method for Cobicistat, Emtricitabine, and Tenofovir Alafenamide in the D/C/F/TAF FDC



Table 5: Approved Product Dissolution Method and Specifications for DRV/COBI FDC Tablet - DRV



Table 6: Approved Product Dissolution Method and Specifications for DRV/COBI FDC Tablet – COBI



1.2. Biopharmaceutic Studies

1.2.1. Overview and Rationale

An overview of clinical studies with D/C/F/TAF is presented in Appendix 2. More details per study are given in Section 2, in the tabular listing of all clinical studies (Mod5.2) and in the individual study reports (Mod5.3).

There were 4 clinical biopharmaceutic studies evaluating the bioavailability of DRV, COBI, FTC and TAF when administered as the D/C/F/TAF FDC tablet formulation. Bioequivalence of the D/C/F/TAF FDC tablet was established in TMC114FD2HTX1001. The effect of concomitant food intake on the oral bioavailability of DRV, COBI, FTC and TAF when administered as the D/C/F/TAF FDC tablet was investigated in TMC114FD2HTX1002. The effect of splitting or crushing the D/C/F/TAF FDC tablet on the oral bioavailability of DRV, COBI, FTC and TAF was investigated in TMC114FD2HTX1004. An overview of these studies, including the formulations used is provided in Table 7. More details are described in Section 2.

Table 7: Clinical Biopharmaceutic Studies With D/C/F/TAF, Including Information on Dosage Form, Formulation Number, and Dose

Study Type Clinical Study Number	**Dosage Form**	**Formulation Number**	**Dose**
Relative Oral Bioavailability:			
TMC114FD2HTX1002 (Panel 1 and Panel 2) (Section 2.1.1.1)	1 x D/C/F/TAF FDC tablet	G001	800/150/200/10 mg
	1 x DRV, 1 x COBI and 1 x F/TAF tablet	Commercial formulations	800 mg, 150 mg and 200/10 mg
	1 x E/C/F/TAF FDC tablet	Commercial formulation	150/150/200/10 mg
GS-US-299-0101 (Section 2.1.1.2)	1 x D/C/F/TAF FDC tablet	Formulation 1 (monolayer)	800/150/200/25 mg
	1 x D/C/F/TAF FDC tablet	Formulation 2 (bilayer)	800/150/200/25 mg
	1 x D/C/F/TAF FDC tablet	Formulation 3[a] (monolayer)	800/150/200/10 mg
	1 x DRV and 1 x COBI	Commercial formulations	800 mg and 150 mg
	1 x FTC and 1 x TAF	Commercial formulation (FTC) TAF tablet formulation	200 mg and 25 mg
TMC114FD2HTX1004 (Section 2.1.1.3)	1 x D/C/F/TAF FDC tablet (swallowed whole, split, or crushed)	G001	800/150/200/10 mg
Bioequivalence:			
TMC114FD2HTX1001 (Section 2.2.1.1)	1 x D/C/F/TAF FDC tablet	G001	800/150/200/10 mg
	1 x DRV, 1 x COBI and 1 x F/TAF tablet	Commercial formulations (EU for F/TAF)	800 mg, 150 mg and 200/10 mg
Food Effect:			
TMC114FD2HTX1002 (Panel 3) (Section 2.1.1.1)	1 x D/C/F/TAF FDC tablet	G001	800/150/200/10 mg

[a] Formulation 3 was subsequently denoted as G001; FDC=fixed-dose combination

Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR; Mod5.3.1.1/GS-US-299-0101-CSR; Mod5.3.1.2/TMC114FD2HTX1001-CSR; Mod5.3.1.1/TMC114FD2HTX1004_CSR

A total of 300 healthy subjects were included in the 4 completed biopharmaceutic studies summarized in this document (Table 8).

Table 8: Numbers of Subjects Included in Completed D/C/F/TAF FDC Biopharmaceutic Studies

Type of Study (Study Number)	Number of Studies	Population	Number of Subjects
Relative oral bioavailability and food effect (TMC114FD2HTX1002, GS-US-299-0101, TMC114FD2HTX1004)	3	Healthy subjects	204 (72 + 102 + 30)
Bioequivalence (TMC114FD2HTX1001)	1	Healthy subjects	96
Total	3	Healthy subjects	300

Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR; Mod5.3.1.1/GS-US-299-0101_CSR; Mod5.3.1.1/TMC114FD2HTX1004_CSR; Mod5.3.1.2/TMC114FD2HTX1001_CSR

Historical studies from the previous applications for DRV/COBI and F/TAF that are considered to be supportive for this application are also referenced where applicable within this Summary of Biopharmaceutic Studies and Associated Analytical Methods.

1.2.2. Critical Aspects of Methods Used

Critical aspects of methods used for all biopharmaceutic and clinical pharmacology studies are further described in Mod2.7.2/Sec1.

In all 4 studies with the D/C/F/TAF FDC summarized in this Summary of Biopharmaceutic Studies and Associated Analytical Methods, randomization was used to minimize bias in the assignment of subjects to treatment groups, thereby enhancing the validity of statistical comparisons across treatment groups. All studies had an open-label, randomized design, which is a widely accepted means of comparing the PK of different formulations administered in different conditions. Crossover design allowed for intrasubject comparison.

Pairwise comparisons between 2 treatments for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values in the biopharmaceutic studies were based on least square (LS) means ratios and their 90.00% confidence intervals (CIs) except for study TMC114FD2HTX1001 where 90.14% CIs were derived because of the intermediate sample size reestimation (see Section 2.2.1.1). Equivalence between treatments or absence of food effect were concluded if these CIs were within 80.00% to 125.00%.[3]

1.3. Bioanalytical Methods

1.3.1. Introduction

The bioanalytical results for each study are presented in the respective bioanalytical study summaries or sample analysis reports, associated with the clinical study reports (CSRs).

All assays for unchanged drug in plasma were validated according to the applicable guidelines and all acceptance criteria as specified in the guidelines were met.[7] An overview of the validation parameters for each method is provided in Appendix 3. An overview of the analytical methods for the components of the D/C/F/TAF FDC that were used for each clinical study is provided in

Appendix 4, including information on whether this method was previously used in studies included in an approved marketing indication. The in-study method validation parameters are described in the individual clinical study reports.

1.3.1.1. Darunavir and Cobicistat

In the pivotal Phase 3 studies TMC114IFD3013 and TMC114FD2HTX3001, the bioequivalence study TMC114FD2HTX1001 and the relative bioavailability/food effect studies TMC114FD2HTX1002 and TMC114FD2HTX1004, DRV and COBI were analyzed together using analytical method BA10833, validated at [redacted] ([redacted], The Netherlands). Briefly, 50 µL of plasma was precipitated with acetonitrile, and analyzed on a Waters XBridge C18 column, 30 x 4.6 mm, 3.5 µm. Detection was performed on an API-5000 mass spectrometer. Further details are available in the method validation report in Mod5.3.1.4/BA10833.

In previous studies (eg DRV/COBI Phase 3 study GS-US-216-0130), DRV was analyzed using analytical method BA10243, which is a partial validation based on analytical method BA1389, both methods validated at [redacted]. Like BA10833, analytical method BA10243 also uses precipitation with acetonitrile, analytical column is also a Waters XBridge C18 column, 30 x 4.6 mm, 3.5 µm, detection is done on an API-5000 mass spectrometer. In D/C/F/TAF Phase 2 study GS-US-299-0102 and relative bioavailability study GS-US-299-0101, DRV was analyzed using analytical method [redacted] 42-0902, validated at [redacted] ([redacted], United States) under the responsibility of Gilead Sciences Inc. The calibrated range for DRV is 20 to 10,000 ng/mL; the lower limit of quantification is 20 ng/mL; the interassay precision range is 2.8% to 10.6%; the interassay accuracy range is -3.9% to -1.0%.

In Phase 2 study GS-US-299-0102 and Phase 1 study GS-US-299-0101, as well as in previous studies (eg DRV/COBI Phase 3 study GS-US-216-0130), COBI was measured using analytical method [redacted] 60-0949, validated at [redacted] ([redacted], United States) under the responsibility of Gilead Sciences Inc. Briefly, 50 µL of plasma was extracted using solid-phase extraction on an Oasis HLB (30 µm, 10 mg) column. Elution was done with acetonitrile:water:formic acid (90:10:0.1/v:v:v). Samples were analyzed on a Waters XBridge 50 mm x 2.1 mm, 3.5 µm C18 column. Detection was performed on an API 4000 mass spectrometer. The calibrated range for COBI is 5 to 2,500 ng/mL; the lower limit of quantification is 5 ng/mL; the interassay precision range is 3.9% to 8.3%; the interassay accuracy range is -0.3% to 9.7%.

1.3.1.2. Emtricitabine

In studies TMC114FD2HTX1001, TMC114FD2HTX1002 and TMC114FD2HTX1004, FTC was analyzed using analytical method BA10878, validated at [redacted] ([redacted], The Netherlands). Briefly, 50 µL of plasma was precipitated with acetonitrile, and analyzed on a Waters Acquity HSS T3 column, 50 x 2.1 mm, 1.8 µm. Detection was performed on an API-5000 mass spectrometer. Further details are available in the method validation report Mod5.3.1.4/BA10878.

In studies GS-US-299-0101 and GS-US-299-0102, as well as in previous studies (eg DRV/COBI Phase 3 study GS-US-216-0130), FTC was analyzed using analytical method [redacted] 42-0831,

validated at [redacted] ([redacted], United States) under the responsibility of Gilead Sciences Inc. The calibrated range for FTC is 5 to 3,000 ng/mL; the lower limit of quantification is 5 ng/mL; the interassay precision range is 1.4% to 5.7%; the interassay accuracy range is -7.8% to 2.4%.

1.3.1.3. Tenofovir Alafenamide

In studies TMC114FD2HTX1002, GS-US-299-0101 and GS-US-299-0102, TAF was analyzed using analytical method [redacted] 60-1115, validated at [redacted] ([redacted], United States) under the responsibility of Gilead Sciences Inc. In studies TMC114FD2HTX1001 and TMC114FD2HTX1004, TAF was analyzed using analytical method [redacted] 60-1578, validated at [redacted] under the responsibility of Gilead Sciences Inc. The TAF method was revalidated in between the two Phase 1 studies TMC114FD2HTX1002 and TMC114FD2HTX1001 to increase the throughput. The main difference between [redacted] 60 1115 and [redacted] 60-1578 is a change in mobile phase and LC parameters (run time brought down from ~6.5 min to 3.5 min). There is no difference in the sample extraction process: in both methods, 50 µL of plasma was precipitated and analyzed through LC-MS/MS. Cross validation between the two TAF methods (60-1115 and 60-1578) was done by using Gilead study samples and the results were found to be well within the limits.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

The clinical biopharmaceutic studies that support the development program of the D/C/F/TAF FDC are summarized in this section and listed in Appendix 2. Supplementary information about these studies is provided in the tabular listing of all clinical studies (Mod5.2) and in the individual study reports (Mod5.3).

2.1. Relative Bioavailability and Food Effect Studies

2.1.1. D/C/F/TAF FDC

2.1.1.1. Study TMC114FD2HTX1002: Relative Bioavailability of Different Formulations/Combinations and Impact of Food on Pharmacokinetics of Darunavir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide Administered as a Fixed-dose Combination Tablet

Mod5.3.1.1/TMC114FD2HTX1002_CSR

2.1.1.1.1. Objective

To evaluate:

- The relative oral bioavailability of TAF and FTC after single-dose administration of a FDC with DRV, COBI, and F/TAF (D/C/F/TAF) compared to an FDC with EVG, COBI, and F/TAF (E/C/F/TAF); Panel 1.
- The relative oral bioavailability of DRV, COBI, FTC, and TAF after single-dose administration as an FDC (D/C/F/TAF) compared to the separate agents (DRV plus COBI plus F/TAF); Panel 2.
- The effect of food on the bioavailability of DRV, COBI, FTC, and TAF following single dose administration of the D/C/F/TAF FDC; Panel 3.

2.1.1.1.2. Subjects and Methods

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 (Treatments A and B in Panel 1, Treatments C and D in Panel 2, and Treatments E and F in Panel 3), 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 treatments were as follows:

Panel 1:

- Treatment A: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet under fed (regular-fat standard breakfast) conditions (test).
- Treatment B: single oral dose of E/C/F/TAF 150/150/200/10 mg as 1 x FDC tablet under fed (regular-fat standard breakfast) conditions (reference).

Panel 2:

- Treatment C: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet under fed (regular-fat standard breakfast) conditions (test).
- Treatment D: single oral dose of 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) conditions (reference).

Panel 3:

- Treatment E: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet under fasted conditions (test).
- Treatment F: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet under fed (high-calorie/high-fat breakfast) conditions (reference).

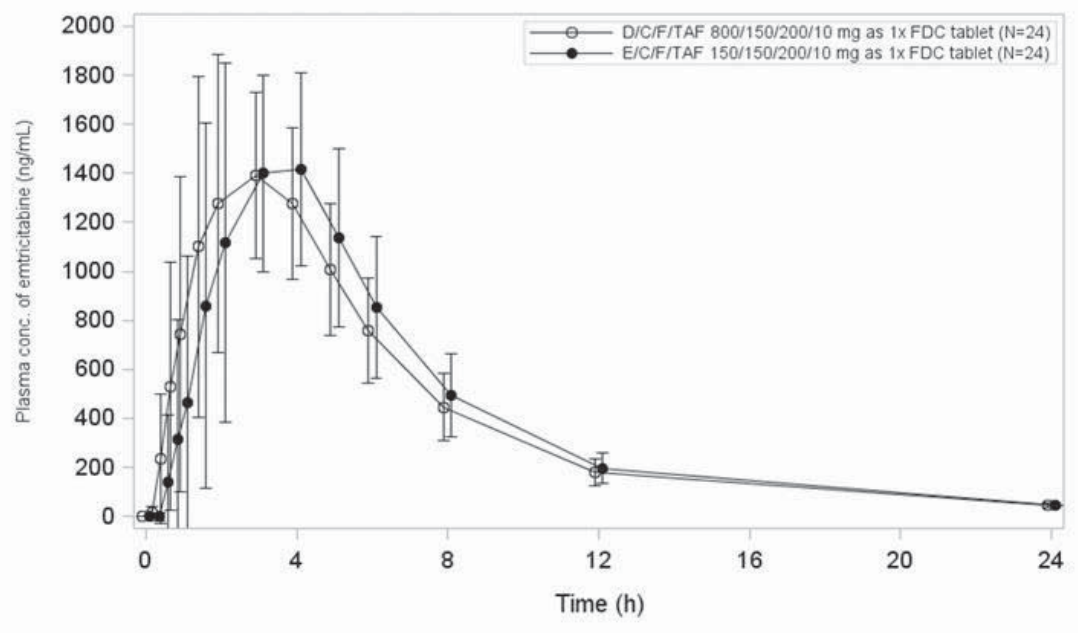
2.1.1.1.3. Results

2.1.1.1.3.1. Results - Panel 1 of Study TMC114FD2HTX1002

All data presented in this section is under fed conditions (standardized regular-fat breakfast) and compares D/C/F/TAF 800/150/200/10 mg taken as 1 x FDC tablet (Treatment A; test) with E/C/F/TAF 150/150/200/10 mg as 1 x FDC tablet (Treatment B; reference).

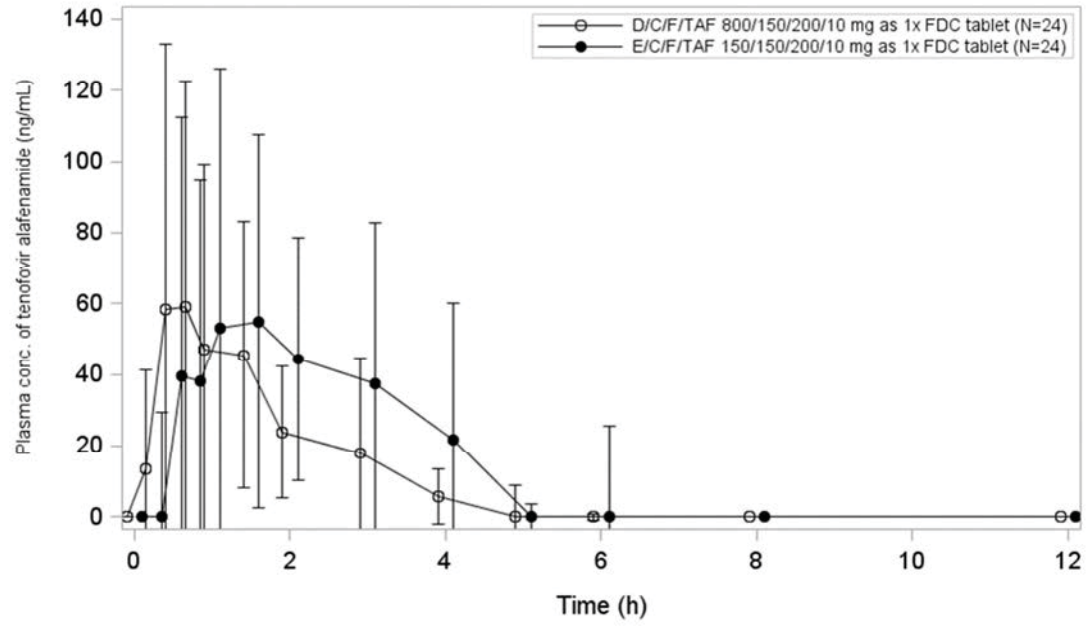
No major differences were observed regarding the shape of the FTC mean PK profile for both FDC tablets (Figure 1); the C_{max} and area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}) of FTC were comparable for both treatments (Table 9). An apparent difference in absorption of TAF between both treatments resulted in the mean time to reach maximum plasma concentration (t_{max}) occurring faster for D/C/F/TAF compared to E/C/F/TAF; a very large intersubject variability in TAF plasma concentrations was however observed for both treatments, especially during the absorption phase (Figure 2). The C_{max} and AUC_{last} of TAF were 20% and 30% lower, respectively, for D/C/F/TAF versus E/C/F/TAF (Table 9).

Figure 1: Mean Plasma Concentration-time Profiles of FTC (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (Treatment A) and a Single Oral Dose of E/C/F/TAF 150/150/200/10 mg as 1 x FDC Tablet (Treatment B), Under Fed Conditions (Study TMC114FD2HTX1002, Panel 1)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig3

Figure 2: Mean Plasma Concentration-time Profiles of TAF (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (Treatment A) and a Single Oral Dose of E/C/F/TAF 150/150/200/10 mg as 1 x FDC Tablet (Treatment B), Under Fed Conditions (Study TMC114FD2HTX1002, Panel 1)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig6

Table 9: Single-dose Pharmacokinetic Parameters of FTC and TAF, Panel 1 (D/C/F/TAF versus E/C/F/TAF) (Study TMC114FD2HTX1002)

Parameter	Mean (SD); t_{max}: Median (Range) D/C/F/TAF (Test) N=24[a]	E/C/F/TAF (Reference) N=24[a]	Test versus Reference LS Mean Ratio (90% CI)
FTC			
C_{max}, ng/mL	1691 (414)	1789 (353)	94.05 (87.78; 100.77)
t_{max}, h	2.50 (1.00; 5.00)	3.00 (1.00; 4.00)	-
AUC_{last}, ng.h/mL	10595 (1777)	10851 (1964)	97.86 (95.82; 99.94)
AUC_{∞}, ng.h/mL	10223[b] (1693)	10455[b] (1174)	-
TAF			
C_{max}, ng/mL	102 (62.0)	124 (67.3)	79.92 (64.30; 99.34)
t_{max}, h	1.50 (0.50; 5.00)	1.75 (0.50; 4.00)	-
AUC_{last}, ng.h/mL	114 (55.8)	165 (85.1)	69.87 (62.82; 77.72)
AUC_{∞}, ng.h/mL	138[b](72.2)	174 (57.6)	-

[a] N=maximum number of subjects with data
[b] Accurate determination not possible for more than 50% of subjects; interpret with caution and rejected as main pharmacokinetic parameter for statistical analysis

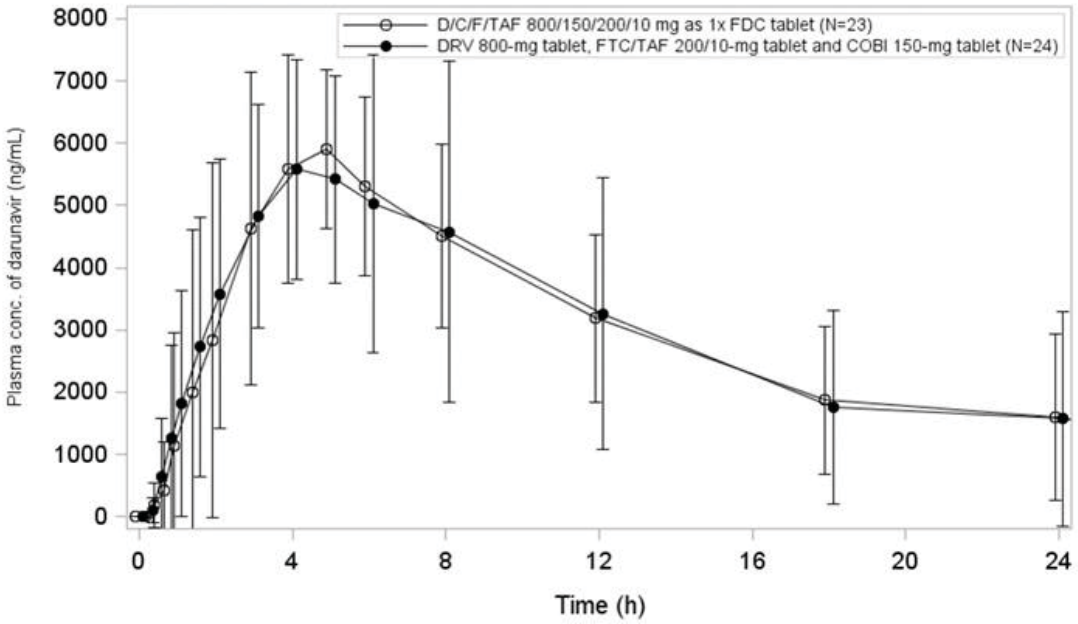
AUC_{∞}=area under the plasma concentration-time curve measured from time zero and extrapolated to infinity; AUC_{last}=area under the plasma concentration-time curve from time zero to the last quantifiable concentration after dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; t_{max}=actual sampling time to reach the maximum plasma concentration
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Tab7, Tab8, Tab13, and Tab14

2.1.1.1.3.2. Results - Panel 2 of Study TMC114FD2HTX1002

This section presents data under fed conditions (standardized regular-fat breakfast) and compares D/C/F/TAF 800/150/200/10 mg taken as 1 x FDC tablet (Treatment C; hereafter D/C/F/TAF FDC) with a single oral dose of DRV as 1 x 800 mg tablet, F/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet (Treatment D; hereafter single component intake).

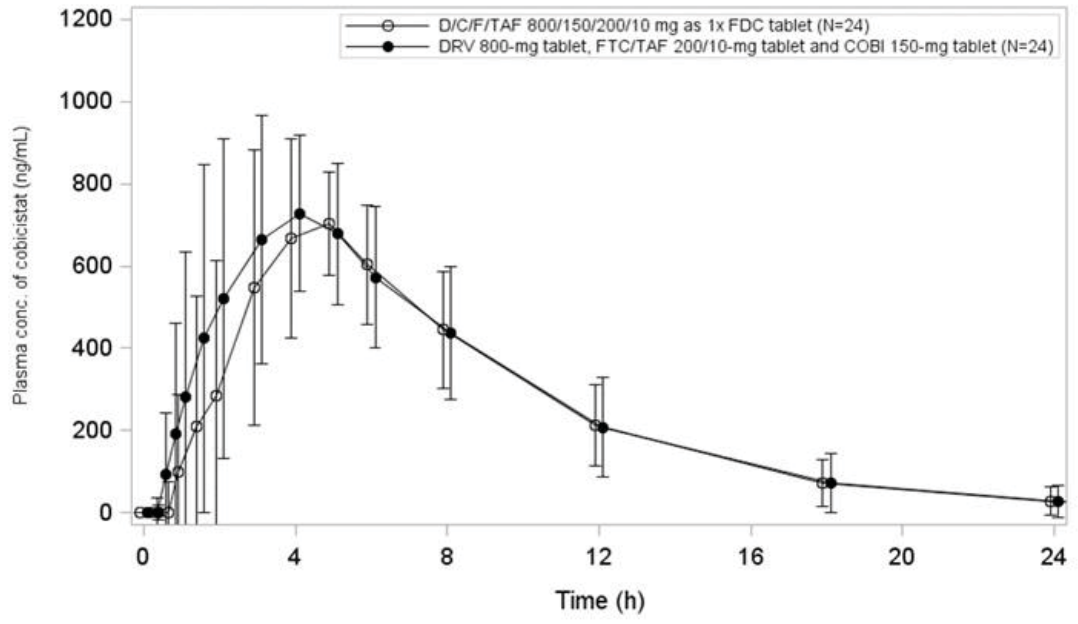
Darunavir, COBI, FTC and TAF mean plasma concentrations over time were comparable after intake as the D/C/F/TAF FDC tablet and after the single component intake (Figure 3, Figure 4, Figure 5, and Figure 6). A very large variability in TAF plasma concentrations was observed for both treatments, especially during the absorption phase (Figure 6) and to a lesser extent also for COBI (Figure 4).

Figure 3: Mean Plasma Concentration-time Profiles of DRV (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (Treatment C) and a Single Oral Dose of DRV as 1 x 800 mg Tablet, F/TAF as 1 x 200/10 mg Tablet and COBI as 1 x 150 mg Tablet (Treatment D), Under Fed Conditions (Study TMC114FD2HTX1002, Panel 2)



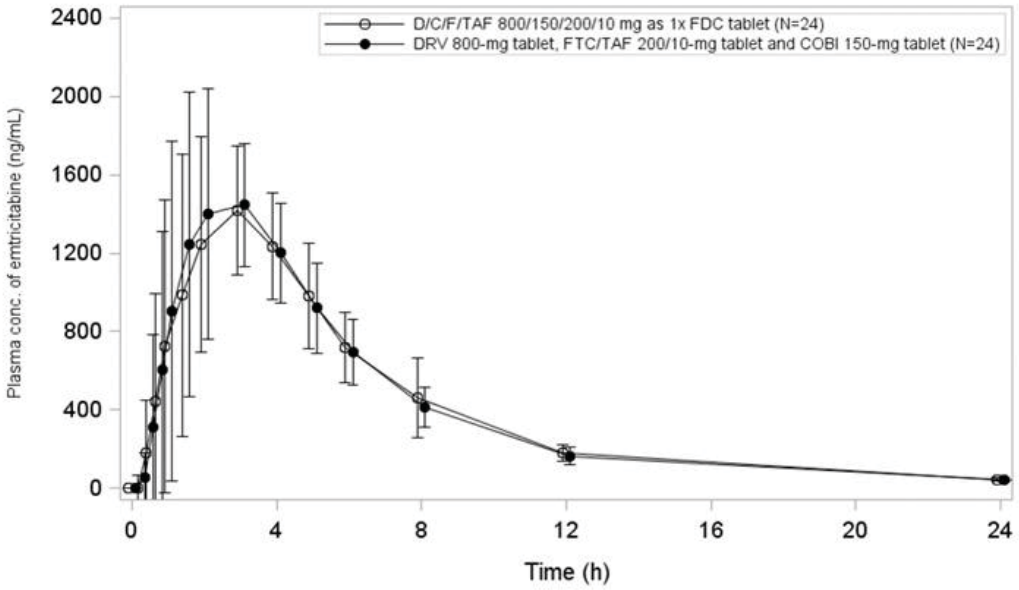
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig9

Figure 4: Mean Plasma Concentration-time Profiles of COBI (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (Treatment C) and a Single Oral Dose of DRV as 1 x 800 mg Tablet, F/TAF as 1 x 200/10 mg Tablet and COBI as 1 x 150 mg Tablet (Treatment D), Under Fed Conditions (Study TMC114FD2HTX1002, Panel 2)



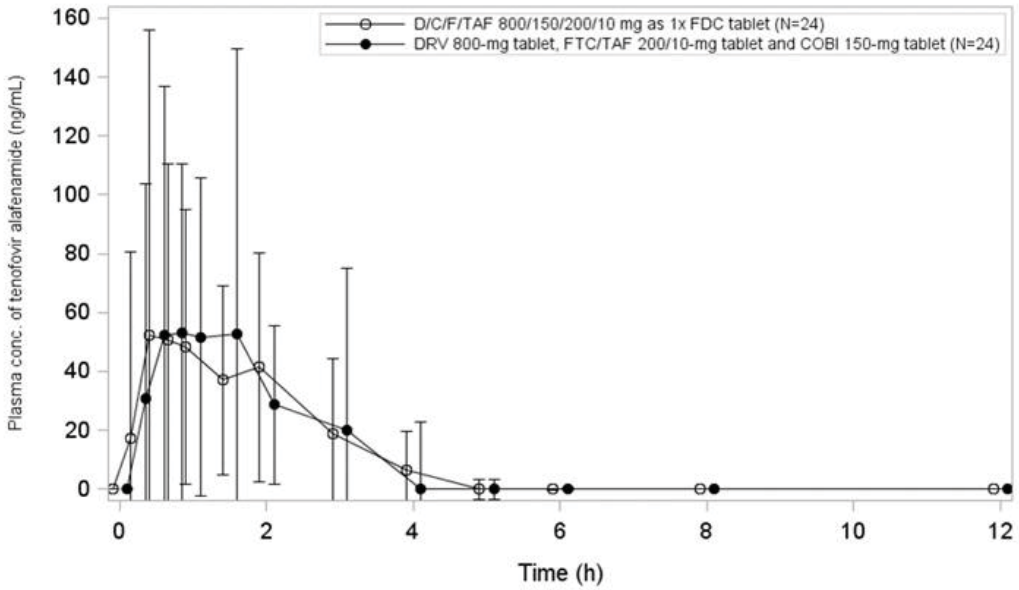
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig11

Figure 5: Mean Plasma Concentration-time Profiles of FTC (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (Treatment C) and a Single Oral Dose of DRV as 1 x 800 mg Tablet, F/TAF as 1 x 200/10 mg Tablet and COBI as 1 x 150 mg Tablet (Treatment D), Under Fed Conditions (Study TMC114FD2HTX1002, Panel 2)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig4

Figure 6: Mean Plasma Concentration-time Profiles of TAF (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (Treatment C) and a Single Oral Dose of DRV as 1 x 800 mg Tablet, F/TAF as 1 x 200/10 mg Tablet and COBI as 1 x 150 mg Tablet (Treatment D), Under Fed Conditions (Study TMC114FD2HTX1002, Panel 2)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig7

The exposures of DRV, COBI and FTC were comparable following intake of the D/C/F/TAF FDC tablet and intake of the combined single components. The ranges of individual values of C_{max}, AUC_{last} and area under the plasma concentration-time curve measured from time zero and extrapolated to infinity (AUC_{∞}) of DRV, COBI and FTC largely overlapped between both treatments and the 90% CIs of the LS mean ratios were all within the 80.00% to 125.00% interval.

Based on the LS mean ratios, TAF C_{max} was 9% lower after intake of the D/C/F/TAF FDC tablet under fed conditions compared to the combined single component intake. AUC_{last} of TAF was comparable for test and reference, with the 90% CI of the LS mean ratio within the 80.00% to 125.00% interval. The median t_{max} and terminal half-life ($t_{1/2}$) were comparable between treatments for all components (Table 10).

Table 10: Pharmacokinetic Parameters of DRV, COBI, FTC and TAF, Panel 2 (D/C/F/TAF versus DRV+COBI+F/TAF) (Study TMC114FD2HTX1002)

Parameter	Mean (SD); t_{max}: Median (Q1; Q3)		Test versus Reference LS Mean Ratio, % (90% CI)
	Test D/C/F/TAF FDC; N=24[a]	Reference DRV + COBI + F/TAF; N=24[a]	
DRV			
C_{max}, ng/mL	6670 (1521)	6554 (2568)	104.32 (96.95; 112.26)
t_{max}, h	5.00 (2.00; 8.00)	4.00 (1.50; 8.00)	-
AUC_{last}, ng.h/mL	90809 (44208)	90414 (57071)	102.99 (97.46; 108.83)
AUC_{∞}, ng.h/mL	93308 (44140)	90792 (57221)	102.61 (96.93; 108.62)
$t_{1/2}$, h	6.8 (1.9)	6.8 (1.9)	-
COBI			
C_{max}, ng/mL	801 (159)	874 (197)	92.12 (87.72; 96.74)
t_{max}, h	4.00 (1.50; 6.00)	3.00 (1.50; 5.02)	-
AUC_{last}, ng.h/mL	6224 (1886)	6668 (2349)	93.96 (89.62; 98.50)
AUC_{∞}, ng.h/mL	6301 (1903)	6757 (2387)	93.93 (89.62; 98.45)
$t_{1/2}$, h	3.6 (0.7)	3.6 (0.7)	-
FTC			
C_{max}, ng/mL	1677 (411)	1828 (478)	92.16 (84.40; 100.63)
t_{max}, h	3.00 (1.00; 4.98)	2.00 (1.00; 5.00)	-
AUC_{last}, ng.h/mL	10365 (1753)	10341 (1455)	99.91 (97.36; 102.52)
AUC_{∞}, ng.h/mL	10135 (1650)[b]	11279 (1692)[b]	-
$t_{1/2}$, h	10.0 (0.6)[b]	10.1 (0.8)[b]	-
TAF			
C_{max}, ng/mL	105 (94.9)	120 (113)	91.44 (71.57; 116.84)
t_{max}, h	1.28 (0.50; 3.00)	1.25 (0.25; 3.00)	-
AUC_{last}, ng.h/mL	123 (67.8)	128 (109)	106.81 (93.04; 122.61)
AUC_{∞}, ng.h/mL	119 (42.0)[b]	156 (129)[b]	-
$t_{1/2}$, h	0.4 (0.1)[b]	0.4 (0.2)[b]	-

[a] N=maximum number of subjects with data

[b] For FTC and TAF more than 50% of the individual values of AUC_{∞} and $t_{1/2}$ term could not be determined accurately and AUC_{∞} was rejected as primary pharmacokinetic parameter for the statistical analysis; values to be interpreted with caution.

AUC_{∞}= area under the plasma concentration-time curve measured from time zero and extrapolated to infinity; AUC_{last}= area under the plasma concentration-time curve from time zero to the last quantifiable (non-below quantification limit) concentration after dosing; CI=confidence interval; C_{max}=maximum plasma concentration; FDC=fixed-dose combination; LS=least square; t_{max}=actual sampling time to reach the maximum plasma concentration; $t_{1/2}$=terminal half-life

Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Tab9, Tab10, Tab15, Tab16, Tab19, Tab20, Tab23, and Tab24

2.1.1.1.3.3. Results - Panel 3 of Study TMC114FD2HTX1002; Food Effect

Mean maximum DRV, COBI, FTC and TAF concentrations following intake of the D/C/F/TAF FDC were reached earlier under fasted compared to fed conditions. Under fasted conditions slightly higher mean DRV plasma concentrations occurred during the absorption phase until 2 hours after intake, while from 3 hours after intake onwards the mean DRV plasma concentrations were lower under fasted compared with fed conditions (Figure 7). Higher mean COBI, FTC and TAF plasma concentrations were observed early on during the absorption phase under fasted conditions. During the distribution/elimination phase, mean COBI, FTC and TAF plasma concentrations were lower under fasted compared with fed conditions. A very large variability for TAF was observed for both treatments, especially during the absorption phase.

The C_{max}, AUC_{last}, and AUC_{∞} were lower under fasted compared to fed condition for both DRV (30% to 45% lower) and COBI (16% to 29% lower, Table 11). The 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 condition, and the AUC_{last} for both FTC and TAF were comparable for test and reference.

2.1.1.1.4. Conclusion

Panel 1 (D/C/F/TAF versus E/C/F/TAF)

The primary PK parameters of TAF were 20% to 30% lower, and the primary PK parameters of FTC were comparable (limits of 90% CI within 80% to 125%) between intake of the D/C/F/TAF FDC and the E/C/F/TAF FDC.

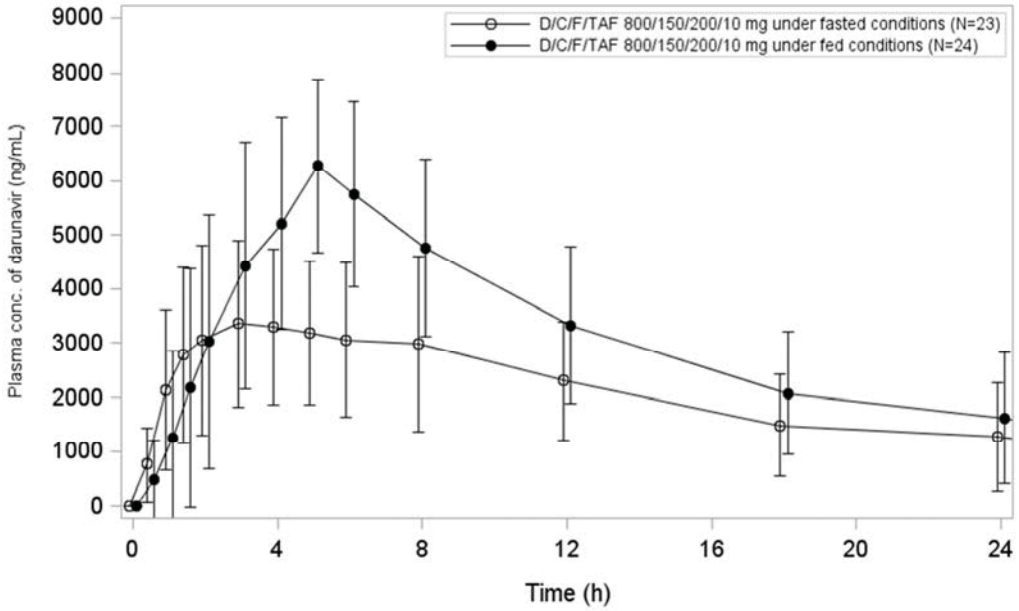
Panel 2 (D/C/F/TAF versus DRV+COBI+F/TAF)

The primary PK parameters of FTC, DRV and COBI were comparable between intake of the D/C/F/TAF FDC and combined intake of the separate agents DRV, COBI and F/TAF. For TAF, the AUC_{last} was also comparable between intake of the D/C/F/TAF FDC and combined intake of the separate agents, while the C_{max} was 9% lower after intake of the FDC (LS mean ratio 91.44%; lower limit 90%CI 71.57% <80.00%).

Panel 3 (Food Effect for D/C/F/TAF)

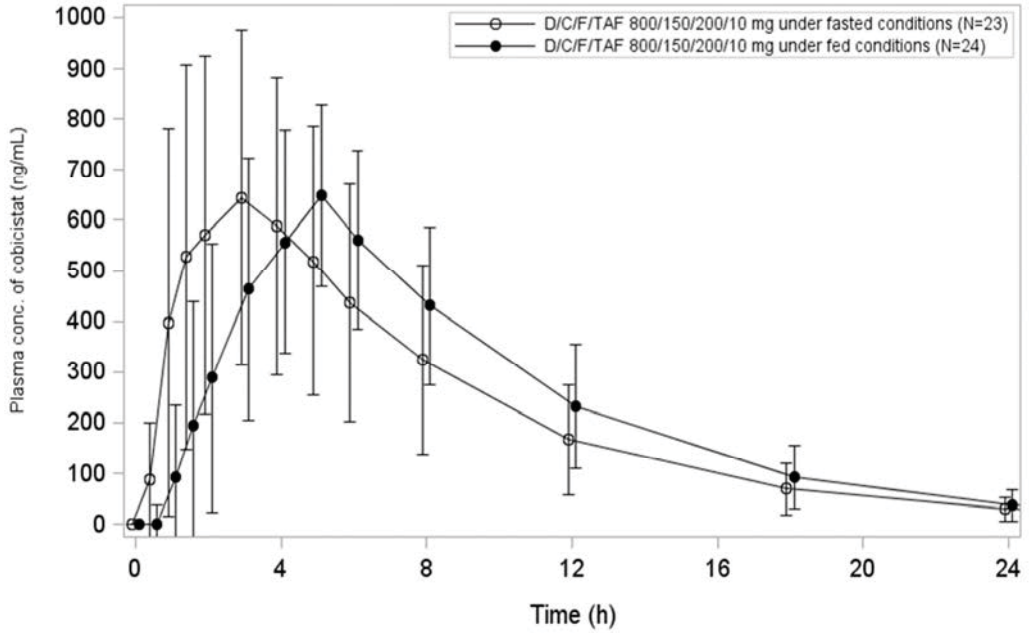
The exposure to DRV and COBI administered as the D/C/F/TAF FDC was 30% to 45% lower and 16% to 29% lower, respectively, in fasted conditions compared with fed conditions. For FTC, the C_{max} was 1.26-fold higher in fasted conditions, while the AUC was comparable in fed and fasted conditions. For TAF, the C_{max} was 1.82-fold higher in fasted conditions, while the AUC was 20% lower (AUC_{∞}) to comparable (AUC_{last}) in fasted compared to fed conditions.

Figure 7: Mean Plasma Concentration-time Profiles of DRV (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet Under Fasted Conditions (Treatment E) and Fed Conditions (Standardized High-fat Breakfast, Treatment F) (Study TMC114FD2HTX1002, Panel 3)



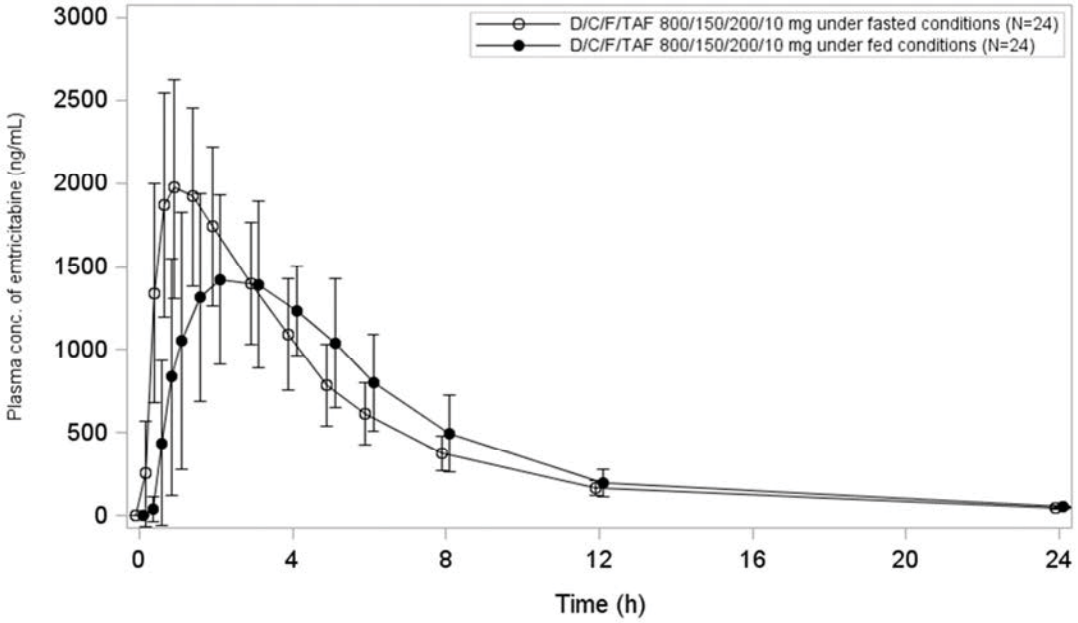
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig10

Figure 8: Mean Plasma Concentration-time Profiles of COBI (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet Under Fasted Conditions (Treatment E) and Fed Conditions (Standardized High-fat Breakfast, Treatment F) (Study TMC114FD2HTX1002, Panel 3)



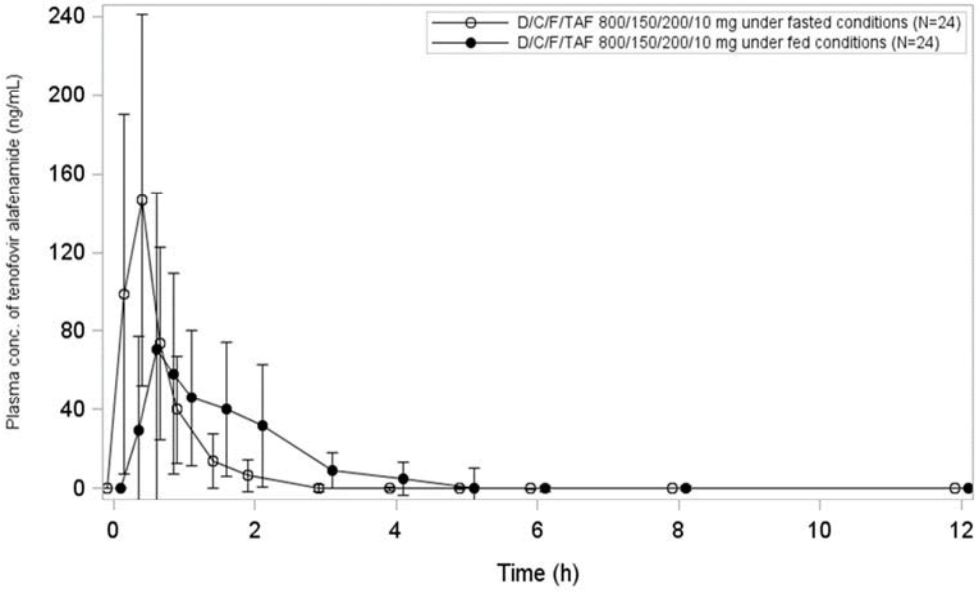
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig12

Figure 9: Mean Plasma Concentration-time Profiles of FTC (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet Under Fasted Conditions (Treatment E) and Fed Conditions (Standardized High-fat Breakfast, Treatment F) (Study TMC114FD2HTX1002, Panel 3)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig5

Figure 10: Mean Plasma Concentration-time Profiles of TAF (Including SD Bars) After Administration of a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet Under Fasted Conditions (Treatment E) and Fed Conditions (Standardized High-fat Breakfast, Treatment F) (Study TMC114FD2HTX1002, Panel 3)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Fig8

Table 11: Pharmacokinetic Parameters of DRV, COBI, FTC and TAF, Panel 3 (Food Effect D/C/F/TAF) (Study TMC114FD2HTX1002)

Parameter	Mean (SD); t_{max}: Median (Range)		Test versus Reference LS Mean Ratio (90% CI)
	D/C/F/TAF fasted (Test) N=24[a]	D/C/F/TAF fed (Reference) N=24[a]	
DRV			
C_{max}, ng/mL	4089 (1846)	6629 (1543)	54.99 (46.73; 64.71)
t_{max}, h	3.00 (1.00; 8.02)	5.00 (1.50; 8.00)	
AUC_{last}, ng.h/mL	67504 (35642)	93541 (39730)	65.65 (56.76; 75.92)
AUC_{∞}, ng.h/mL	72147 (36009)	94686 (40882)	70.25 (59.49; 82.95)
COBI			
C_{max}, ng/mL	704 (368)	711 (164)	76.96 (55.70; 106.33)
t_{max}, h	3.00 (1.00; 6.00)	5.00 (2.00; 6.10)	
AUC_{last}, ng.h/mL	5771 (3206)	6168 (2260)	70.90 (51.13; 98.30)
AUC_{∞}, ng.h/mL	6136 (3064)	6258 (2268)	84.39 (68.52; 103.95)
FTC			
C_{max}, ng/mL	2247 (573)	1785 (486)	125.99 (112.85; 140.65)
t_{max}, h	1.00 (0.50; 2.00)	2.00 (0.75; 5.00)	
AUC_{last}, ng.h/mL	11593 (2573)	11499 (2055)	100.12 (96.29; 104.10)
AUC_{∞}, ng.h/mL	12286 (2729)	10029[b] (1079)	
TAF			
C_{max}, ng/mL	180 (90.6)	107 (65.2)	182.29 (140.50; 236.50)
t_{max}, h	0.50 (0.25; 0.75)	0.88 (0.25; 5.00)	
AUC_{last}, ng.h/mL	106 (44.7)	117 (51.5)	89.54 (81.20; 98.72)
AUC_{∞}, ng.h/mL	109 (47.7)	125 (57.3)	80.38 (73.04; 88.45)

[a] N=maximum number of subjects with data

[b] Accurate determination not possible for more than 50% of subjects; interpret with caution and rejected as main pharmacokinetic parameter for statistical analysis

AUC_{∞}=area under the plasma concentration-time curve measured from time zero and extrapolated to infinity; AUC_{last}=area under the plasma concentration-time curve from time zero to the last quantifiable concentration (non- below quantification limit) after dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; t_{max}=actual sampling time to reach the maximum plasma concentration

Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Tab11, Tab17, Tab21, and Tab25

2.1.1.2. Study GS-US-299-0101: Bioavailability of 3 Different Formulations of Darunavir, Cobicistat, Emtricitabine and Tenofovir Alafenamide Administered as a Fixed-dose Combination Tablet Relative to the Administration of the Individual Components

Mod5.3.1.1/GS-US-299-0101_CSR

2.1.1.2.1. Objective

The primary objectives of this study were as follows:

Part 1:
To evaluate 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.

Part 2:
To evaluate the PK and bioavailability of DRV, COBI, FTC, and TFV when administered as COBI-boosted DRV (DRV + COBI) plus F/TDF FDC relative to the administration of DRV/COBI or F/TDF FDC alone.

Part 3:
To evaluate 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/COBI or FTC + TAF (25 mg) alone.

2.1.1.2.2. Subjects and Methods

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).

The treatments were:

Part 1: Comparison of 3 FDC D/C/F/TAF Formulations

- Treatment A: D/C/F/TAF FDC Formulation 1 monolayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 25 mg)
- Treatment B: D/C/F/TAF FDC Formulation 2 bilayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 25 mg)
- Treatment C: D/C/F/TAF FDC Formulation 3 monolayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg)

Part 2: Assessment of DRV/COBI and F/TDF Drug-Drug Interaction

Subjects in Part 2 were assigned to either Cohort 1 or Cohort 2:

Cohort 1:

- Treatment D: DRV 800 mg + COBI 150 mg + F/TDF (FTC 200 mg/TDF 300 mg)

- Treatment E: DRV 800 mg + COBI 150 mg

Cohort 2:

- Treatment D: DRV 800 mg + COBI 150 mg + F/TDF (FTC 200 mg/TDF 300 mg)
- Treatment F: F/TDF (FTC 200 mg/TDF 300 mg)

Part 3: PK and Bioavailability of Selected D/C/F/TAF FDC Formulation

Upon review of PK and safety data from Part 1, Treatment C (Formulation 3; monolayer) was selected for evaluation in Part 3. Subjects in Part 3 were assigned to either Cohort 1 or Cohort 2.

Cohort 1:

- Treatment C: D/C/F/TAF FDC Formulation 3 monolayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg)
- Treatment E: DRV 800 mg + COBI 150 mg

Cohort 2:

- Treatment C: D/C/F/TAF FDC Formulation 3 monolayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg)
- Treatment G: FTC 200 mg + TAF 25 mg

2.1.1.2.3. Results

2.1.1.2.3.1. Results - Part 1 of Study GS-US-299-0101

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 (Table 12, Table 13, Table 14, Table 15, Figure 14 and Figure 15).

Tenofovir exposures from each formulation were consistent across Day 12 (Table 14) and Day 21 (Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-2), 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 (also see Table 12).

The LS mean ratio for TAF C_{max} for Formulation 3 tablet relative to both Formulation 1 and 2 was 37% and for AUC was 35% (Formulation 3 versus 1) and 39% (Formulation 3 versus 2). The LS mean ratio for TFV C_{max} for Formulation 3 tablet relative to both Formulation 1 and 2 were 41% and 38%, respectively. The LS mean ratio AUC was 40% and 36%, respectively.

Darunavir, COBI and FTC exposures were comparable across treatments; the LS mean ratio 90% CIs for C_{max} and AUC were generally within the 80.00% to 125.00% bounds (Table 14 and Table 15).

Table 12: Single-dose Pharmacokinetic Parameters of TAF and TFV, Part 1, Day 1 (Study GS-US-299-0101)

Parameter	Mean (SD); t_{max}: Median (Range)		
	Formulation 1 (N=10)[a]	Formulation 2 (N=10)[a]	Formulation 3 (N=10)[a]
TAF			
C_{max}, ng/mL	470.3 (35.6)	474.3 (47.2)	171.7 (37.0)
t_{max}, h	0.75 (0.50; 1.00)	1.00 (1.00; 1.00)	0.75 (0.50; 1.00)
AUC_{last}, ng.h/mL	449.7 (20.0)	503.9 (19.0)	165.6 (25.0)
$t_{1/2,}$ h	0.38 (0.38; 0.45)	0.40 (0.37; 0.46)	0.42 (0.36; 0.58)
TFV			
C_{max}, ng/mL	23.2 (20.4)	26.4 (27.9)	10.1 (32.6)
t_{max}, h	1.50 (1.00; 1.50)	1.50 (1.00; 2.00)	1.50 (1.00; 2.00)
AUC_{last}, ng.h/mL	275.6 (10.0)	283.9 (14.2)	110.5 (20.1)
$t_{1/2,}$ h	35.44 (28.60; 48.32)	37.39 (30.78; 48.36)	32.39 (26.23; 42.27)

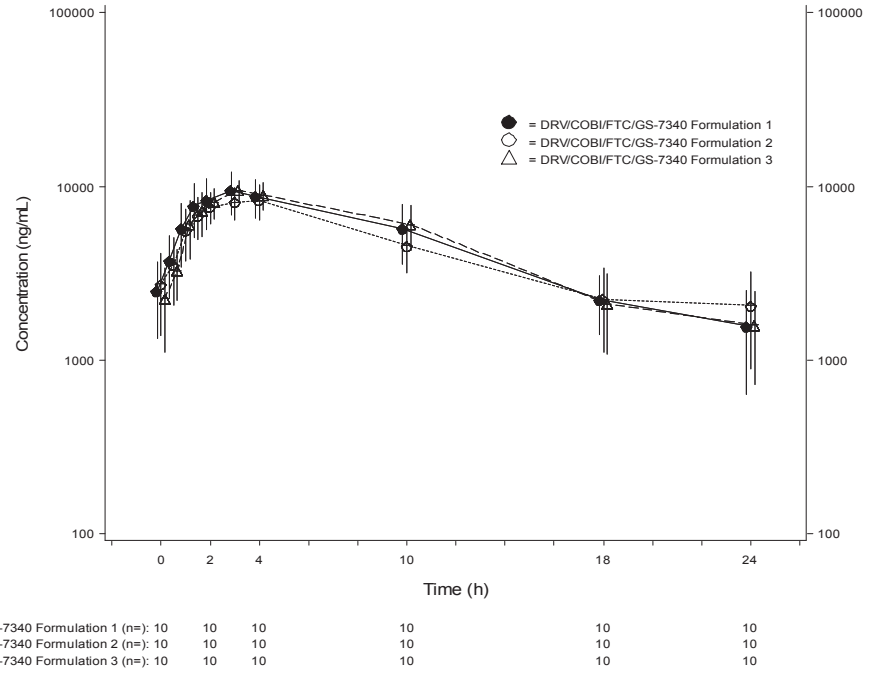
[a] N=maximum number of subjects with data
AUC_{last}= area under the plasma concentration-time curve from time zero to the last quantifiable (non- below quantification limit) concentration after dosing; AUC_{tau}= area under the plasma concentration-time curve from 0h to the time of next dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; t_{max}=actual sampling time to reach the maximum plasma concentration; $t_{1/2}$=terminal half-life
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-1

Table 13: Statistical Comparisons of Single-dose Pharmacokinetic Parameters of FTC and GS-7340 (TAF) and TFV, Between 3 Formulations, Part 1, Day 1 (Study GS-US-299-0101)

Parameter	Test versus Reference LS Mean Ratio (90% CI)		
	Formulation 2 versus Formulation 1 (N=10)[a]	Formulation 3 versus Formulation 1 (N=10)[a]	Formulation 3 versus Formulation 2 (N=10)[a]
TAF			
C_{max}, ng/mL	100.33 (75.93; 132.57)	36.78 (27.83; 48.60)	36.66 (27.74; 48.44)
AUC_{last}, ng.h/mL	111.83 (94.63, 132.17)	36.42 (30.82; 43.05)	32.57 (27.56; 38.49)
TFV			
C_{max}, ng/mL	112.46 (91.93; 137.57)	42.25 (34.54; 51.69)	37.57 (30.71; 45.96)
AUC_{last}, ng.h/mL	102.60 (90.69; 116.07)	39.47 (34.89; 44.65)	38.46 (34.00; 43.51)

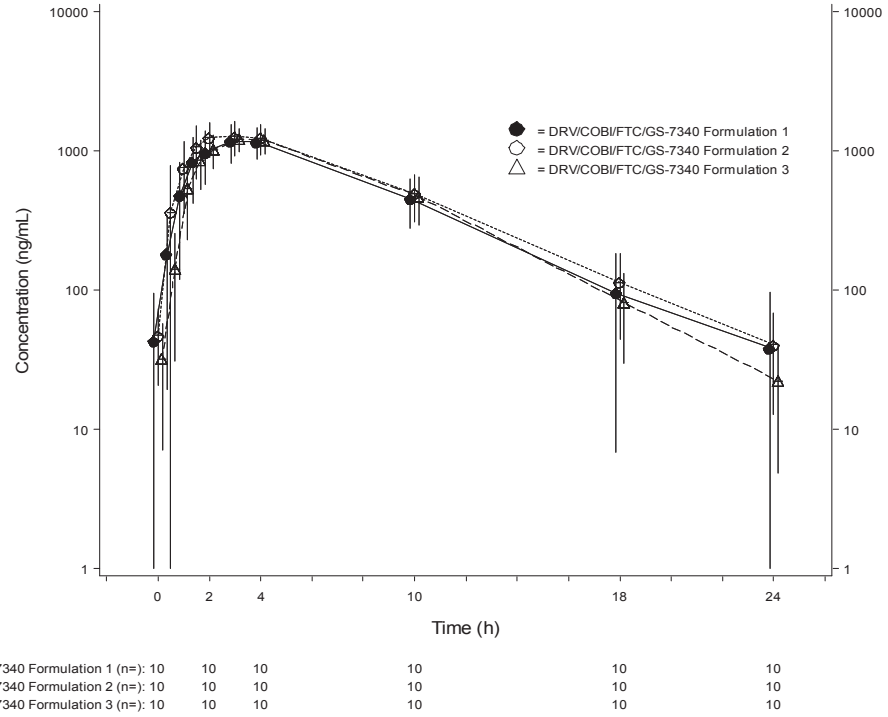
[a] N=maximum number of subjects with data
AUC_{last}= area under the plasma concentration-time curve from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square
Source: Mod5.3.1.1/GS-US-299-0101_CSR/SupplTab5.1

Figure 11: Mean Plasma Concentration-time Profile of DRV (Including SD Bars) After Administration of Multiple-doses of D/C/F/TAF Formulation 1, 2 and 3; Part 1, Day 12 (Study GS-US-299-0101)



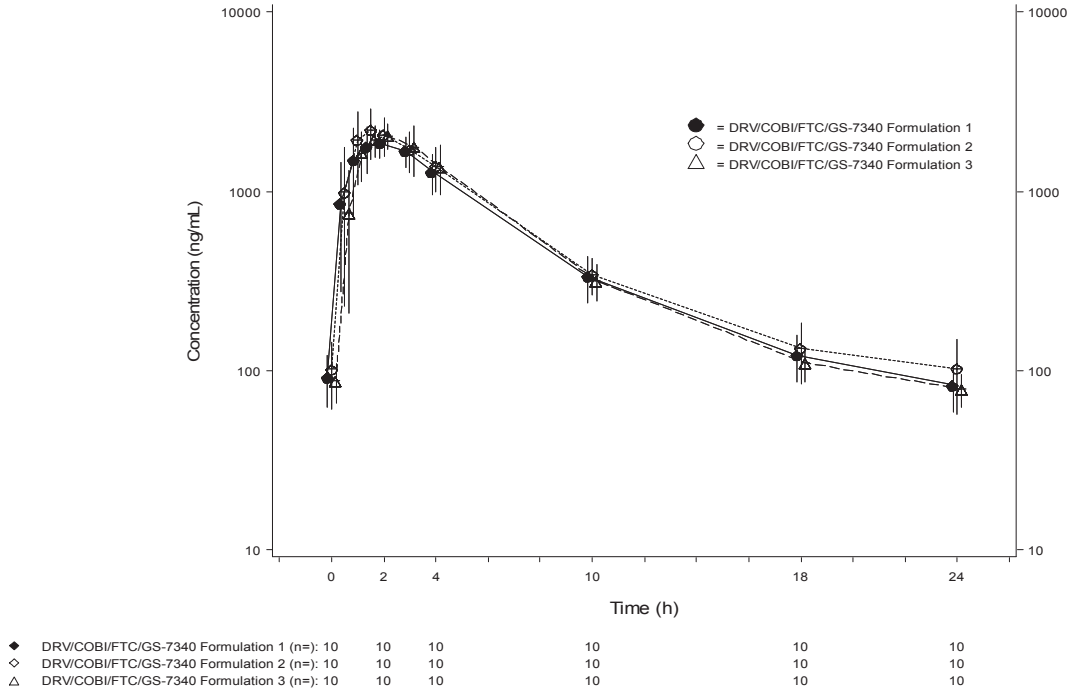
SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-3

Figure 12: Mean Plasma Concentration-time Profile of COBI (Including SD Bars) After Administration of Multiple-doses of D/C/F/TAF Formulation 1, 2 and 3; Part 1, Day 12 (Study GS-US-299-0101)



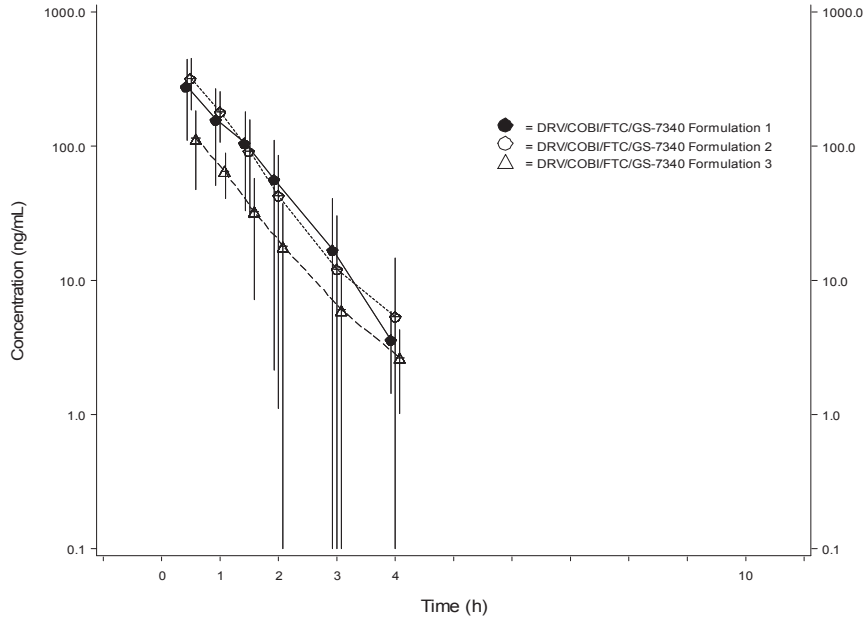
SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-4

Figure 13: Mean Plasma Concentration-time Profile of FTC (Including SD Bars) After Administration of Multiple-doses of D/C/F/TAF Formulation 1, 2 and 3; Part 1, Day 12 (Study GS-US-299-0101)



SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-5

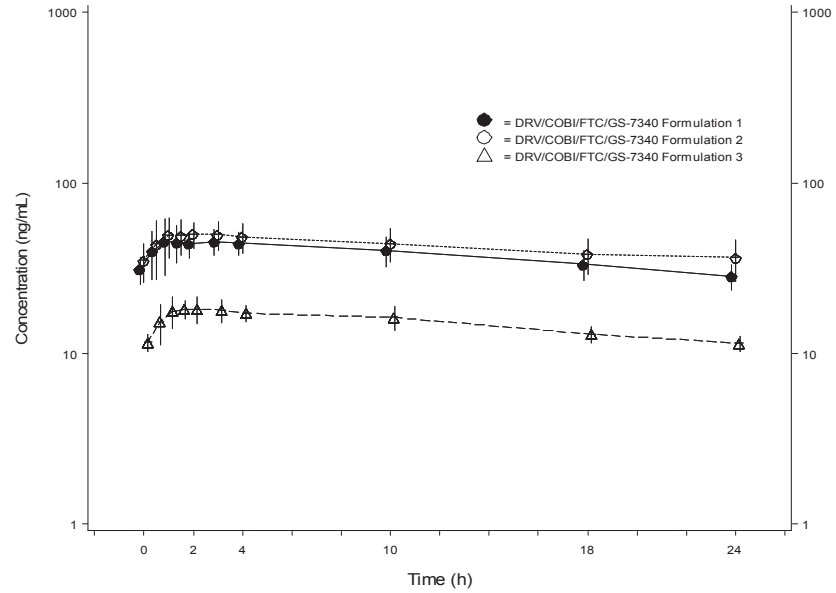
Figure 14: Mean Plasma Concentration-time Profile of TAF (Including SD Bars) After Administration of Multiple-doses of D/C/F/TAF Formulation 1, 2 and 3; Part 1, Day 12 (Study GS-US-299-0101)



◆ DRV/COBI/FTC/GS-7340 Formulation 1 (n=):	10	10	10	5
◇ DRV/COBI/FTC/GS-7340 Formulation 2 (n=):	10	10	10	6
△ DRV/COBI/FTC/GS-7340 Formulation 3 (n=):	10	10	8	2

SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-1

Figure 15: Mean Plasma Concentration-time Profile of TFV (Including SD Bars) After Administration of Multiple-doses of D/C/F/TAF Formulation 1, 2 and 3; Part 1, Day 12 (Study GS-US-299-0101)



◆ DRV/COBI/FTC/GS-7340 Formulation 1 (n=):	10	10	10	10	10	10
◇ DRV/COBI/FTC/GS-7340 Formulation 2 (n=):	10	10	10	10	10	10
△ DRV/COBI/FTC/GS-7340 Formulation 3 (n=):	10	10	10	10	10	10

SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-2

Table 14: Multiple-dose Pharmacokinetic Parameters of DRV, COBI, FTC and TAF and TFV, Part 1, Day 12 (Study GS-US-299-0101)

Parameter	Mean (SD); t_{max}: Median (Range)		
	Formulation 1 (N=10)[a]	Formulation 2 (N=10)[a]	Formulation 3 (N=10)[a]
DRV			
C_{max}, ng/mL	9698 (25.3)	9122 (14.5)	9743 (14.3)
t_{max}, h	3.00 (3.00; 3.00)	3.49 (2.00; 4.00)	3.00 (3.00; 4.00)
AUC_{tau}, ng.h/mL	112,572 (28.6)	102,986 (27.1)	113,655 (23.8)
$t_{1/2,}$ h	8.85 (4.34; 10.67)	9.10 (7.76; 15.02)	7.13 (6.53; 9.01)
COBI			
C_{max}, ng/mL	1227 (24.0)	1366 (23.9)	1305 (13.8)
t_{max}, h	3.00 (3.00; 4.00)	3.00 (2.00; 3.00)	3.00 (2.00; 4.00)
AUC_{tau}, ng.h/mL	10,002(36.9)	11,316 (31.5)	10,097 (23.7)
$t_{1/2,}$ h	3.40 (2.84; 3.72)	3.81 (3.47; 4.16)	2.90 (2.81; 3.42)
FTC			
C_{max}, ng/mL	2067 (12.0)	2363 (25.3)	2199 (20.7)
t_{max}, h	1.50 (1.00; 2,00)	1.75 (1.50; 2.00)	1.75 (1.50; 2.00)
AUC_{tau}, ng.h/mL	12, 327.0 (14.5)	13, 460.3 (21.6)	12, 602.1 (16.4)
$t_{1/2,}$ h	4.99 (4.75; 6.37)	6.26 (4.83; 7.52)	5.48 (4.74; 6.96)
TAF			
C_{max}, ng/mL	328.3 (30.5)	344.1 (27.3)	130.7 (39.2)
t_{max}, h	0.50 (0.50; 1.00)	0.50 (0.50; 0.50)	0.50 (0.50; 1.00)
AUC_{last}, ng.h/mL	314.6 (26.9)	326.6 (20.0)	116.4 (26.0)
$t_{1/2,}$ h	0.41 (0.37; 0.43)	0.39 (0.37; 0.51)	0.41 (0.33; 0.51)
TFV			
C_{max}, ng/mL	51.3 (25.3)	54.6 (21.5)	20.7 (14.5)
t_{max}, h	1.50 (1.00; 3.00)	2.00 (1.00; 3.00)	2.00 (1.00; 2.00)
AUC_{tau}, ng.h/mL	903.4 (16.7)	1020.6 (22.3)	359.1 (11.2)
$t_{1/2,}$ h	35.10 (25.42; 45.20)	47.41 (43.57; 63.85)	28.19 (25.28; 36.80)

[a] N=maximum number of subjects with data

AUC_{last}=area under the plasma concentration-time curve from time zero to the last quantifiable (non- below quantification limit) concentration after dosing; AUC_{tau}=area under the plasma concentration-time curve from 0h to the time of next dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; SD=standard deviation; t_{max}=actual sampling time to reach the maximum plasma concentration; t_{max}=time to reach maximum plasma concentration; $t_{1/2}$=terminal half-life

Source: Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-1, Tab10-2, Tab10-4, Tab10-5 and Tab10-6

Table 15: Statistical Comparisons of Multiple-dose Pharmacokinetic Parameters of DRV, COBI, FTC and TAF and TFV, Between 3 Formulations, Part 1, Day 12 (Study GS-US-299-0101)

Parameter	Test versus Reference LS Mean Ratio (90% CI)		
	Formulation 2 versus Formulation 1 (N=10)[a]	Formulation 3 versus Formulation 1 (N=10)[a]	Formulation 3 versus Formulation 2 (N=10)[a]
DRV			
C_{max}, ng/mL	95.98 (83.28; 110.61)	102.55 (88.98; 118.18)	106.84 (92.71; 123.13)
AUC_{tau}, ng.h/mL	92.34 (75.32; 113.21)	102.90 (83.93; 126.16)	111.43 (90.89; 136.62)
COBI			
C_{max}, ng/mL	111.81 (93.87; 133.18)	108.73 (91.28; 129.51)	97.24 (81.64; 115.83)
AUC_{tau}, ng.h/mL	114.74 (91.03; 144.63)	104.16 (82.64; 131.29)	90.78 (72.02; 114.42)
FTC			
C_{max}, ng/mL	112.35 (96.67; 130.59)	104.89 (90.25; 121.92)	93.36 (80.32; 108.51)
AUC_{tau}, ng.h/mL	108.07 (93.79; 124.52)	102.09 (88.61; 117.63)	94.47 (81.99; 108.85)
TAF			
C_{max}, ng/mL	106.38 (81.71; 138.49)	36.93 (31.13; 43.82)	36.81 (28.27; 47.92)
AUC_{last}, ng.h/mL	104.63 (88.19; 124.14)	39.15 (30.08; 50.97)	35.30 (29.75; 41.88)
TFV			
C_{max}, ng/mL	106.82 (91.47; 124.74)	40.98 (35.09; 47.86)	38.37 (32.85; 44.81)
AUC_{tau}, ng.h/mL	111.71 (97.70; 127.74)	40.01 (34.99; 45.75)	35.82 (31.32; 40.96)

[a] N=maximum number of subjects with data

AUC_{last}=area under the plasma concentration-time curve from time zero to the last quantifiable (non- below quantification limit) concentration after dosing; AUC_{tau}= area under the plasma concentration-time curve from 0h to the time of next dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; t_{max}=actual sampling time to reach the maximum plasma concentration

Source: Mod5.3.1.1/GS-US-299-0101_CSR/SupplTab5.1

2.1.1.2.3.2. Results - Part 2 of Study GS-US-299-0101

Darunavir and COBI exposures were comparable across treatments (DRV/COBI + F/TDF versus DRV/COBI dosed alone); the LS mean ratio 90% CIs for C_{max} and AUC were within the 80.00% to 125.00% bounds (Table 16).

Tenofovir and FTC exposures were modestly higher following DRV/COBI + F/TDF, as compared with F/TDF dosed alone. The area under the plasma concentration-time curves from 0h to the time of next dosing (AUC_{tau}) for TFV and FTC were 17% and 16% higher, respectively, following administration of DRV/COBI + F/TDF versus administration of F/TDF alone.

Table 16: Multiple-dose Pharmacokinetic Parameters Including Statistical Analysis of DRV, COBI, FTC and TFV, Part 2, (Study GS-US-299-0101)

Parameter	Mean (SD); t_{max}: Median (Range)		
	Test DRV/COBI + F/TDF N=20[a]	**Reference DRV/COBI N=20[a]**	**Test versus Reference LS Mean Ratio, % (90% CI)**
DRV			
C_{max}, ng/mL	9536 (10.6)	9577 (7.7)	99.29 (96.01; 102.67)
t_{max}, h	3.00 (2.00; 4.00)	4.00 (2.50; 4.00)	-
AUC_{tau}, ng.h/mL	108,767 (16.3)	109,388 (17.6)	99.56 (94.06; 105.39)
$t_{1/2,}$ h	6.44 (5.19; 7.73)	7.23 (5.57; 9.74)	-
COBI			
C_{max}, ng/mL	1427 (23.8)	1423 (19.7)	99.55 (95.41; 103.88)
t_{max}, h	3.50 (2.50; 4.00)	4.00 (2.00; 4.00)	-
AUC_{tau}, ng.h/mL	10,853 (24.2)	11,038 (22.6)	98.04 (94.40; 101.81)
$t_{1/2,}$ h	3.13 (2.87; 3.61)	3.17 (3.03; 3.41)	-
	Test DRV/COBI + F/TDF N=20[a]	**Reference F/TDF N=20[a]**	**Test versus Reference LS Mean Ratio, % (90% CI)**
FTC			
C_{max}, ng/mL	1989 (19.1)	1832 (21.4)	108.94 (100.54; 118.04)
t_{max}, h	3.00 (2.00; 3.00)	1.75 (1.50; 2.00)	-
AUC_{tau}, ng.h/mL	11,174 (12.7)	9575 (10.2)	116.38 (111.62; 121.34)
$t_{1/2,}$ h	7.21 (5.81; 8.08)	9.29 (8.85; 10.14)	-
TFV			
C_{max}, ng/mL	356.8 (33.2)	323.0 (28.0)	109.29 (93.36; 127.94)
t_{max}, h	2.00 (1.50; 2.00)	1.50 (1.00; 2.00)	-
AUC_{tau}, ng.h/mL	3402 (17.5)	2888 (15.7)	117.36 (111.23; 123.81)
$t_{1/2,}$ h	12.29 (10.90; 13.72)	12.13 (10.82; 13.26)	-

[a] N=maximum number of subjects with data

AUC_{last}=area under the plasma concentration-time curve from time zero to the last quantifiable(non- below quantification limit) concentration after dosing; AUC_{tau}= area under the plasma concentration-time curve from 0h to the time of next dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; SD=standard deviation; t_{max}=actual sampling time to reach the maximum plasma concentration; $t_{1/2}$=terminal half-life

Source: Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-7, Tab10-8, Tab10-9, Tab10-10, Tab10-11, Tab10-12, Tab10-13, and Tab10-14

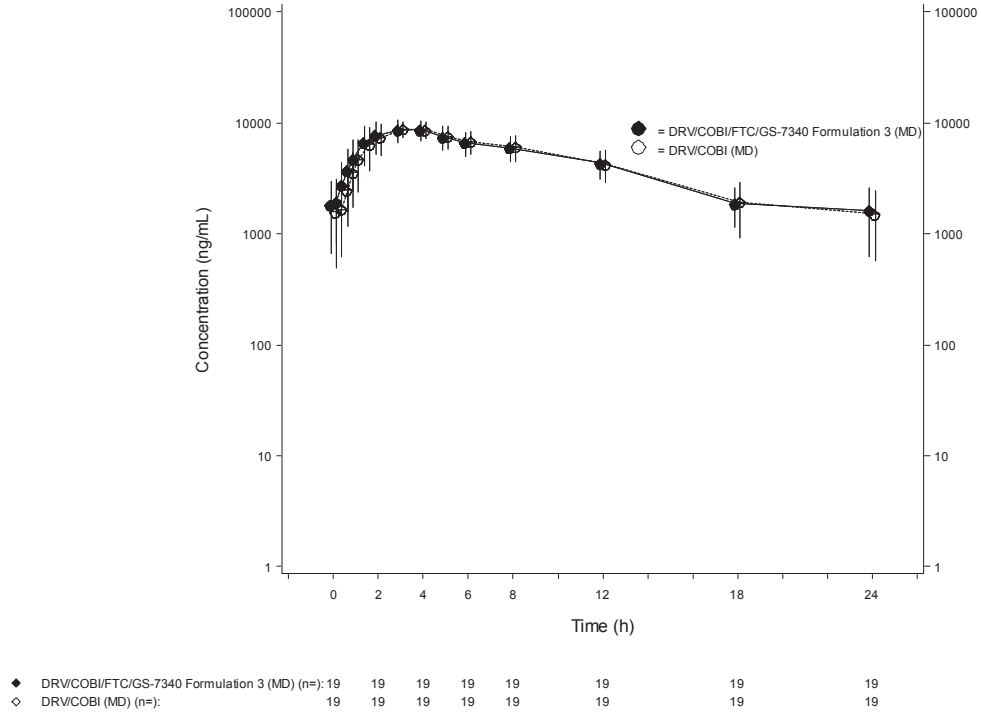
2.1.1.2.3.3. Results - Part 3 of Study GS-US-299-0101

The mean (standard deviation [SD]) multiple-dose plasma concentration-time profiles and PK parameters for DRV and COBI were comparable between treatments (D/C/F/TAF [Formulation 3] versus DRV/COBI dosed alone) (Figure 16, Figure 17, Figure 18, Figure 19, Figure 20).

Tenofovir and FTC plasma concentrations were modestly higher following multiple-dose administration of D/C/F/TAF FDC (with TAF 10 mg) as compared with FTC + TAF (25 mg),

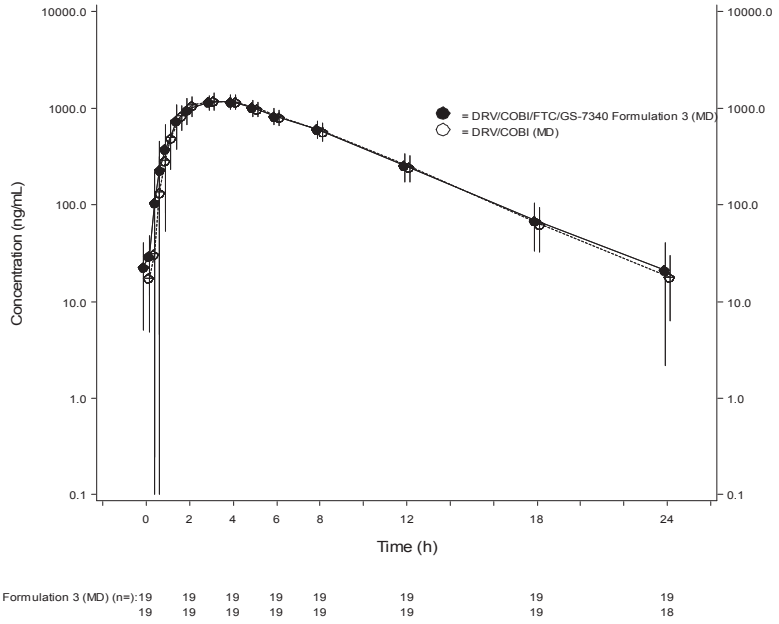
whereas TAF plasma concentrations were lower following administration of the D/C/F/TAF FDC (Table 17).

Figure 16: Mean (SD) DRV Plasma Concentration-time Profiles, Comparison of D/C/F/TAF FDC (Formulation 3; TAF 10 mg) versus DRV/COBI; Study GS-US-299-0101 (Part 3)



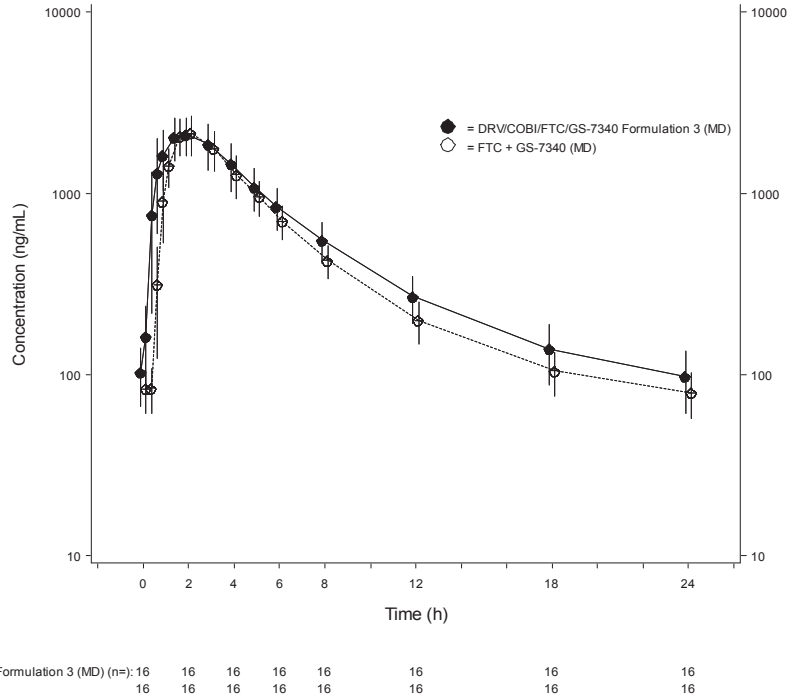
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-12

Figure 17: Mean (SD) COBI Plasma Concentration-time Profiles, Comparison of D/C/F/TAF FDC (Formulation 3; TAF 10 mg) versus DRV/COBI; Study GS-US-299-0101 (Part 3)



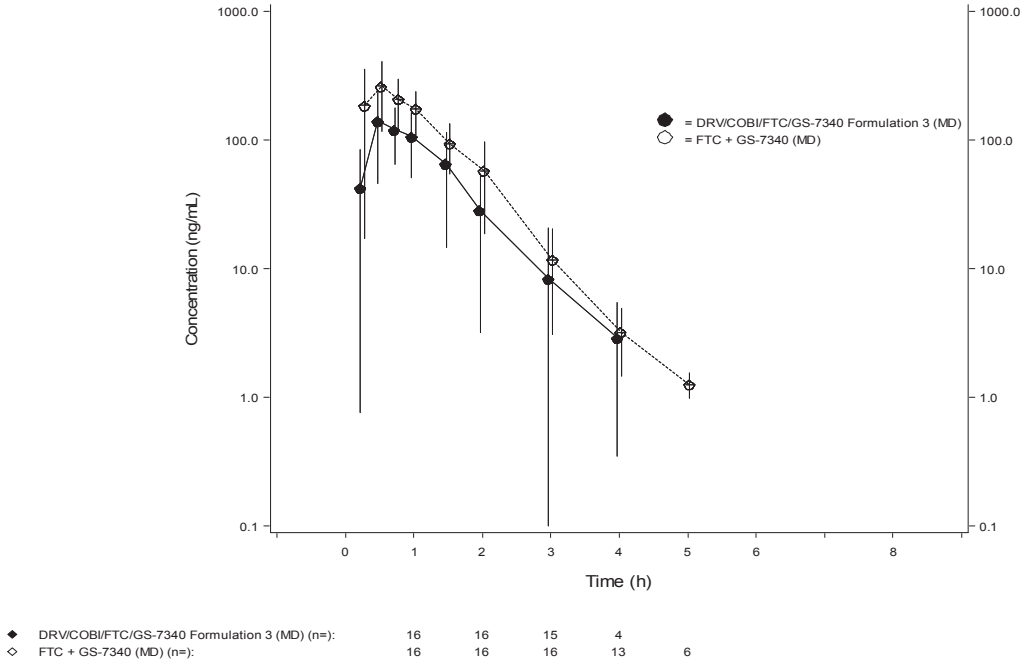
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-13

Figure 18: Mean (SD) FTC Plasma Concentration-time Profiles, Comparison of D/C/F/TAF FDC (Formulation 3; TAF 10 mg) versus FTC + TAF (25 mg); Study GS-US-299-0101 (Part 3)



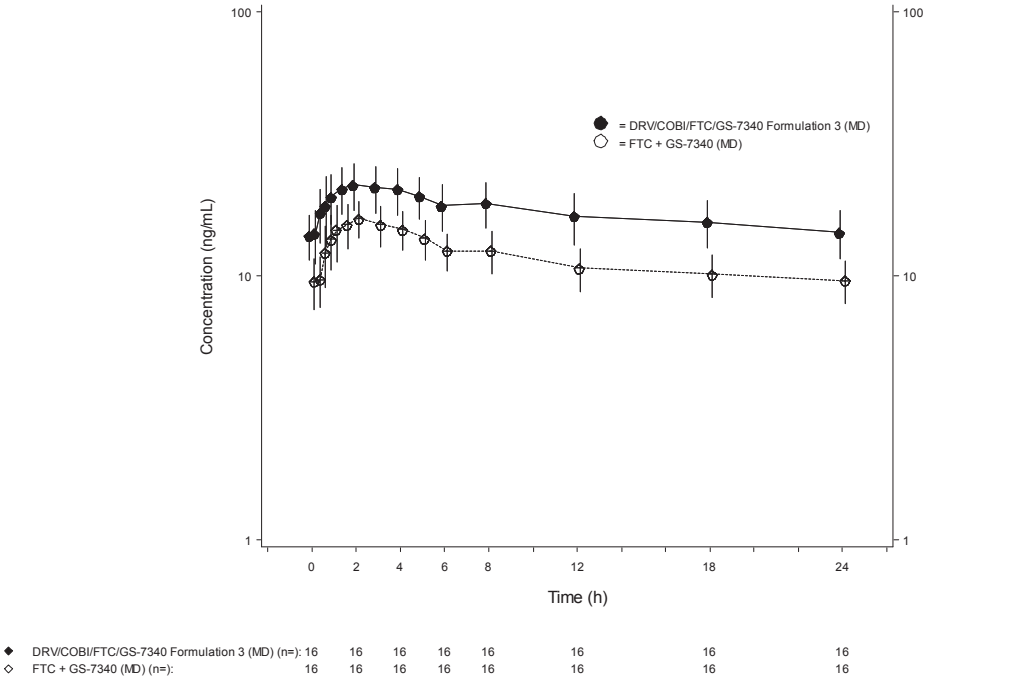
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-14

Figure 19: Mean (SD) TAF Plasma Concentration-time Profiles, Comparison of D/C/F/TAF FDC (Formulation 3; TAF 10 mg) versus FTC + TAF (25 mg); Study GS-US-299-0101 (Part 3)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-10

Figure 20: Mean (SD) TFV Plasma Concentration-time Profiles, Comparison of D/C/F/TAF FDC (Formulation 3; TAF 10 mg) versus FTC + TAF (25 mg); Study GS-US-299-0101 (Part 3)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Fig10-11

Based on C_{max} and AUC, single dose TAF exposures were lower and TFV exposures were similar following once-daily administration of D/C/F/TAF FDC Formulation 3 (TAF 10 mg) compared with FTC + TAF (25 mg) (Table 16).

Table 17: Single-dose Pharmacokinetic Parameters of TAF and TFV (Part 3, Study GS-US-299-0101)

Parameter	Mean (SD); t_{max}: Median (Range)	
	D/C/F/TAF FDC 800/150/200/10 mg Formulation 3 (Test) N=16[a]	FTC + TAF 200/25 mg (Reference) N=16[a]
TAF		
C_{max}, ng/mL	181.1 (18.9)	278.4 (28.5)
t_{max}, h	1.00 (0.75; 1.00)	0.75 (0.50; 1.00)
AUC_{last}, ng.h/mL	183.6 (27.5)	361.0 (27.3)
$t_{1/2,}$ h	0.37 (0.35; 0.41)	0.45 (0.41; 0.54)
TFV		
C_{max}, ng/mL	7.9 (23.5)	9.0 (19.3)
t_{max}, h	2.00 (1.50; 2.50)	2.00 (1.75; 2.00)
AUC_{last}, ng.h/mL	103.5 (20.0)	112.0 (17.1)

[a] N=maximum number of subjects with data
AUC_{last}=area under the plasma concentration-time curve from time zero to the last quantifiable (non- below quantification limit) concentration after dosing; C_{max}=maximum plasma concentration; SD=standard deviation; t_{max}=actual sampling time to reach the maximum plasma concentration
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-15 and Tab10-18

For FTC the 90% CI of the LS mean ratio for C_{max} and AUC were within the 80.00% to 125.00% interval after intake of the D/C/F/TAF FDC (TAF 10 mg) compared with intake of FTC + TAF (25 mg).

Multiple-dose TAF exposures based on C_{max} and AUC were lower following D/C/F/TAF FDC (TAF 10 mg) compared with FTC + TAF (25 mg). Based on the LS mean ratios, TAF C_{max} was approximately 41% and AUCtau was approximately 48% lower; the 90% CI of the LS mean ratio were outside the bounds of the 80.00% to 125.00% interval. Tenofovir exposures based on C_{max} and AUC were higher following once-daily administration of D/C/F/TAF FDC (TAF 10 mg) compared with FTC + TAF (25 mg). Tenofovir C_{max} was 41% and AUC_{tau} was 50% higher; the 90% CI of the LS mean ratio were outside the bounds of the 80.00% to 125.00% interval.

Table 18: Multiple-dose Pharmacokinetic Parameters of DRV, COBI, FTC, TAF and TFV (Part 3; Study GS-US-299-0101)

Parameter	Mean (SD); t_{max}: Median (Range)		
	D/C/F/TAF FDC 800/150/200/10 mg Formulation 3 (Test) N=19[a]	**DRV/COBI 800/150 mg (Reference) N=19[a]**	**Test versus Reference LS Mean Ratio, % (90% CI)**
DRV			
C_{max}, ng/mL	9233.0 (20.2)	9320.8 (13.5)	98.29 (94.21; 102.54)
t_{max}, h	3.00 (3.00; 4.00)	3.00 (2.00; 4.00)	
AUC_{tau}, ng.h/mL	102,288.7 (26.3)	102,149.3 (28.5)	100.47 (95.65; 105.53)
$t_{1/2,}$ h	6.84 (6.05; 8.66)	6.48 (5.41; 7.92)	
COBI			
C_{max}, ng/mL	1237.3 (15.4)	1245.8 (16.9)	99.47 (95.18; 103.95)
t_{max}, h	3.00 (3.00; 4.00)	3.00 (2.00; 4.00)	
AUC_{tau}, ng.h/mL	9229.9 (18.9)	9229.0 (18.9)	99.97 (94.83; 105.39)
$t_{1/2,}$ h	3.11 (2.79; 3.31)	2.92 (2.73; 3.44)	
	D/C/F/TAF FDC 800/150/200/10 mg Formulation 3 (Test) N=16[a]	**FTC + TAF 200/25 mg (Reference) N=16[a]**	**Test versus Reference LS Mean Ratio, % (90% CI)**
FTC			
C_{max}, ng/mL	2362.8 (17.4)	2207.3 (23.1)	108.22 (103.06; 113.64)
t_{max}, h	1.50 (1.50; 2.00)	2.00 (1.50; 2.00)	
AUC_{tau}, ng.h/mL	13,444.1 (20.6)	11,556.9 (18.6)	115.96 (112.94; 119.07)
$t_{1/2,}$ h	13.22 (6.87; 21.81)	15.90 (8.48; 22.88)	
TAF			
C_{max}, ng/mL	184.0 (35.8)	317.2 (41.6)	58.95 (48.30, 71.95)
t_{max}, h	0.75 (0.50, 1.00)	0.50 (0.50, 0.75)	
AUC_{last}, ng.h/mL	166.7 (30.0)	320.0 (30.8)	52.10 (46.53; 58.33)
$t_{1/2,}$ h	0.37 (0.32, 0.44)	0.45 (0.42, 0.54)	
TFV			
C_{max}, ng/mL	24.2 (17.4)	17.2 (16.9)	141.21 (134.20; 148.59)
t_{max}, h	2.00 (0.88; 3.00)	2.00 (1.00; 2.00)	
AUC_{tau}, ng.h/mL	421.1 (19.3)	280.2 (17.2)	149.81 (143.48; 156.43)
$t_{1/2,}$ h	43.53 (39.87; 74.20)	41.07 (36.15; 49.49)	

[a] N=maximum number of subjects with data

AUC_{last}=area under the plasma concentration-time curve from time zero to the last quantifiable (non- below quantification limit) concentration after dosing; AUC_{tau}=area under the plasma concentration-time curve from 0h to the time of next dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; SD=standard deviation; t_{max}=actual sampling time to reach the maximum plasma concentration; $t_{1/2}$=terminal half-life

Source: Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-16, Tab10-17, Tab10-19, Tab10-20, Tab10-21, Tab10-23, Tab10-22, Tab10-23, and Tab10-24

2.1.1.2.4. Conclusion

Part 1: Formulations 1 (monolayer; 25 mg TAF), 2 (bilayer; 25 mg TAF) or 3 (monolayer, 10 mg TAF) were administered over 21 days. Systemic exposures of DRV, COBI, and FTC were consistent with historical data, for all formulations. The TAF exposures were in a range associated with potent antiviral activity, for all formulations (ie, similar to those observed in a previous proof-of-concept study [GS-US-120-0104]). Tenofovir alafenamide exposures were between 30 and 50% higher after single dose compared with multiple doses consistent with a mixed inhibitory/inductive effect on TAF absorption.[10] Steady-state TFV plasma levels following administration of the D/C/F/TAF FDC formulation containing 10 mg TAF were proportionally lower compared with the FDC formulations containing 25 mg TAF. The resulting TFV plasma levels from the FDC with 10 mg TAF were approximately 90% lower than levels following administration of an FDC containing E/C/FTDF or following administration of TDF with boosted PIs. Subsequently, Formulation 3 was chosen for Part 3 of this study and for further development.

Part 2: Following the administration of DRV/COBI + F/TDF, the 90% CIs of the LS mean ratio for DRV AUC_{tau} and C_{max} were contained within the protocol-defined no-effect boundary of 80.00% to 125.00% relative to DRV/COBI, while the 90% CI of the LS mean ratio for DRV C_{tau} was slightly below the lower limit. The 90% CIs of the LS mean ratios for COBI, FTC, and TFV were within the wider protocol-defined, 70.00% to 143.00% no-effect boundary relative to DRV/COBI or F/TDF, indicating no clinically relevant differences. The stricter 80.00% to 125.00% boundary was also met for the relevant exposure parameters of COBI and FTC. Exposures of DRV, COBI, FTC, and TFV were consistent with historical data.

Part 3: Following the administration of D/C/F/TAF FDC Formulation 3 containing 10 mg TAF , the TAF exposure was lower compared to FTC + TAF (with 25 mg TAF; reference treatment), with the 90% CIs of the LS mean ratios for exposure parameters below the protocol-defined no-effect boundary. However, observed TAF exposures were in a range associated with antiviral activity of TAF administered as a single agent (See the Summary of Clinical Pharmacology in Mod2.7.2/Sec3.5.1). Tenofovir exposures following the FDC with 10 mg TAF were 41% to 50% higher relative to FTC + TAF 25 mg (reference treatment). However, these levels are still substantially lower than TFV levels following TDF-containing regimens. Tenofovir exposures following the D/C/F/TAF FDC with 10 mg TAF were approximately 88% lower than TFV exposures observed following DRV/COBI + F/TDF in Part 2. Following the administration of FDC Formulation 3, the 90% CIs of the LS mean ratios for DRV exposure parameters AUC_{tau} and C_{max} were within the no-effect boundary of 80.00% to 125.00%, while the 90% CI of the LS mean ratios for DRV C_{tau} was slightly above the upper limit. Cobicistat and FTC exposures were comparable relative to DRV/COBI or FTC + TAF, indicating no clinically relevant differences.

2.1.1.3. Study TMC114FD2HTX1004: Relative Bioavailability of the D/C/F/TAF Fixed-dose Combination Tablet Administered Orally as a Whole Tablet, as a Split Tablet, and as a Crushed Tablet

Mod5.3.1.1/TMC114FD2HTX1004_CSR

2.1.1.3.1. Objective

To evaluate:

- The single-dose pharmacokinetics and relative bioavailability of DRV, COBI, FTC, and TAF when administered either as a whole D/C/F/TAF FDC tablet, as a split tablet, or as a crushed tablet mixed in applesauce, under fed conditions.

2.1.1.3.2. Subjects and Methods

This was a Phase 1, open-label, 3-way crossover study in healthy subjects. During 3 subsequent sessions, each subject received 3 treatments randomized according to a classical 3-period, 3-treatment Williams design.

The study population comprised 30 healthy volunteers.

The treatments were as follows:

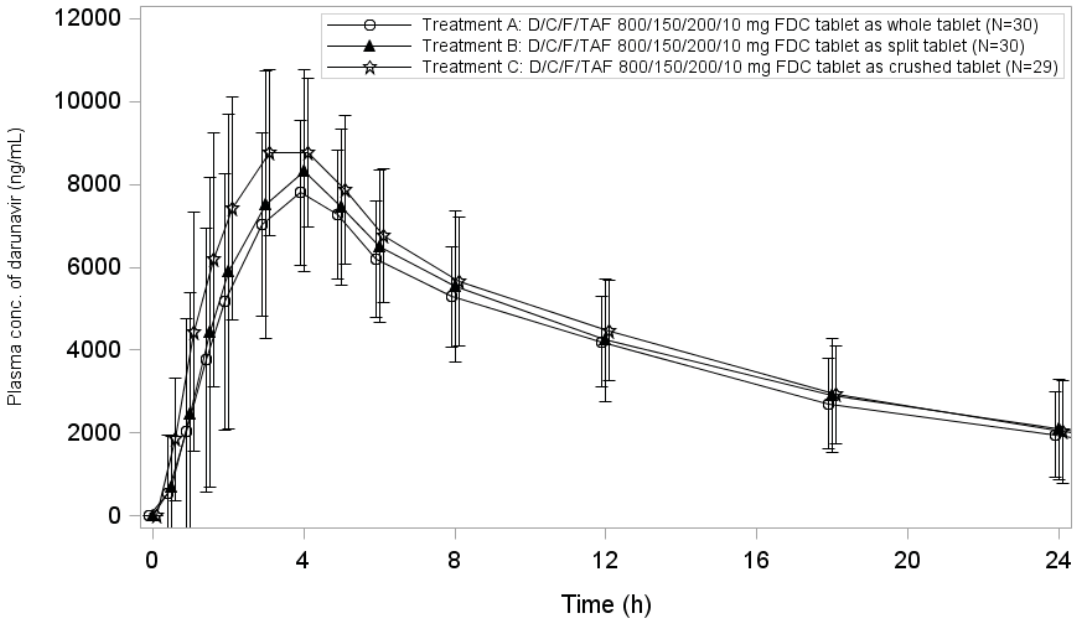
- Treatment A: a single dose of D/C/F/TAF (800/150/200/10 mg) FDC tablet swallowed as a whole, intact tablet with 240 mL of noncarbonated water (reference).
- Treatment B: a single dose of D/C/F/TAF (800/150/200/10 mg) FDC tablet as a split tablet swallowed with 240 mL of noncarbonated water (test). The tablet was split in half using a tablet cutter.
- Treatment C: a single dose of D/C/F/TAF (800/150/200/10 mg) FDC tablet as a crushed tablet (mortar and pestle) mixed in 4 oz. of applesauce (test).

All treatments were administered under fed conditions, ie, no more than 30 minutes after the start and within 10 minutes after completion of a regular-fat standard breakfast.

2.1.1.3.3. Results

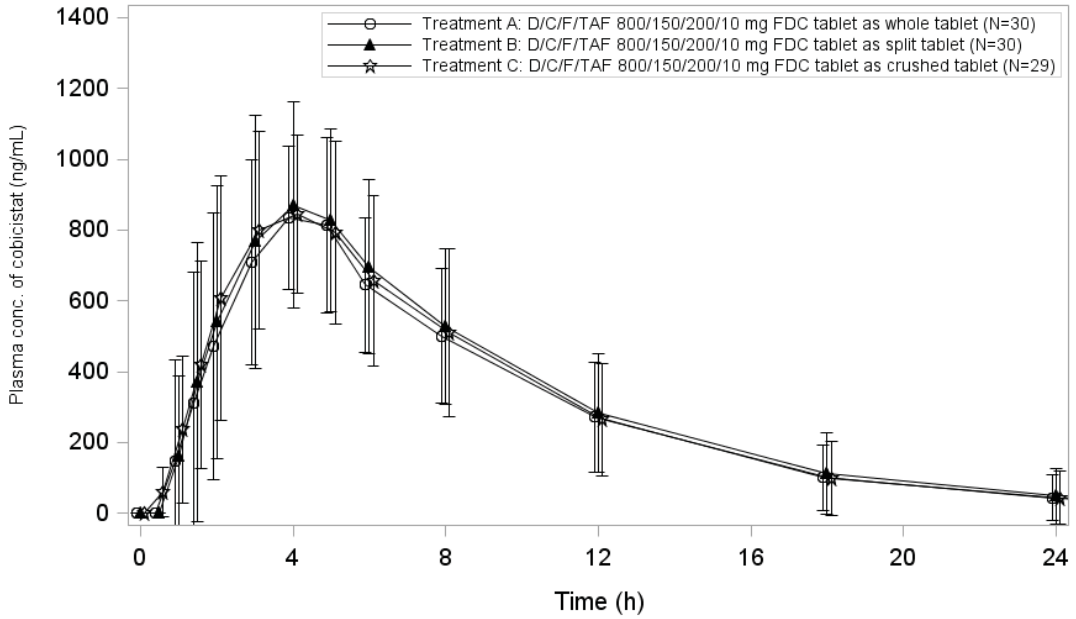
Darunavir, COBI, FTC and TAF mean plasma concentrations over time were largely comparable after intake as the D/C/F/TAF FDC tablet swallowed whole, as a split tablet and as a crushed tablet (Figure 21, Figure 22, Figure 23, and Figure 24). For DRV, slightly higher mean plasma concentrations were observed until approximately 4-5 hours after dosing for the crushed tablet, although the standard deviations largely overlapped. For FTC, the mean plasma concentrations were slightly lower between approximately 2 and 4 hours after dosing as a crushed tablet, although the standard deviations largely overlapped. For TAF, there was a very large variability in the plasma concentrations for all treatments, especially during the absorption phase.

Figure 21: Mean (SD) Plasma Concentration-time Profiles of DRV After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet (Treatment A), a Split Tablet (Treatment B), and a Crushed Tablet (Treatment C), Under Fed Conditions (Study TMC114FD2HTX1004)



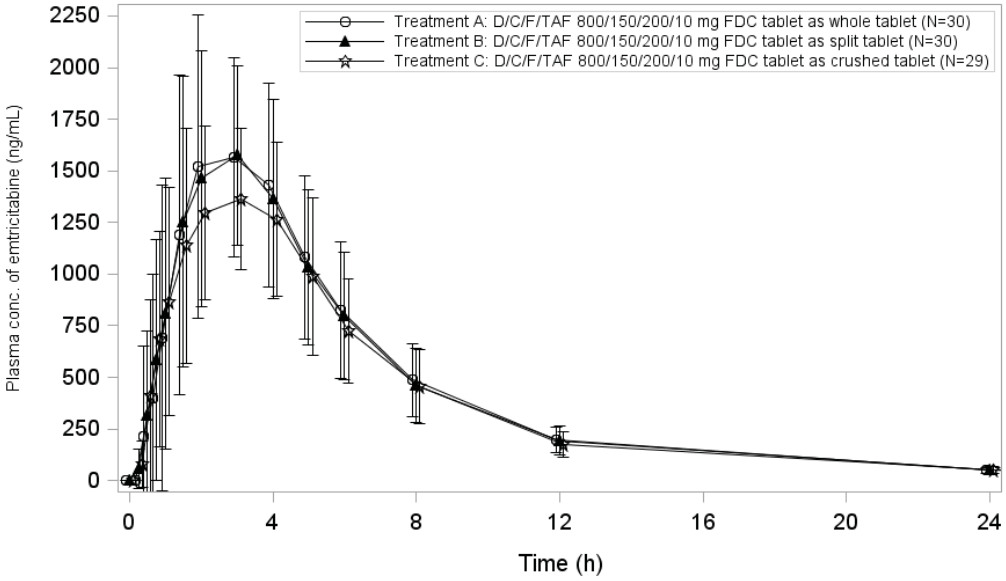
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Fig3

Figure 22: Mean (SD) Plasma Concentration-time Profiles of COBI After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet (Treatment A), a Split Tablet (Treatment B), and a Crushed Tablet (Treatment C), Under Fed Conditions (Study TMC114FD2HTX1004)



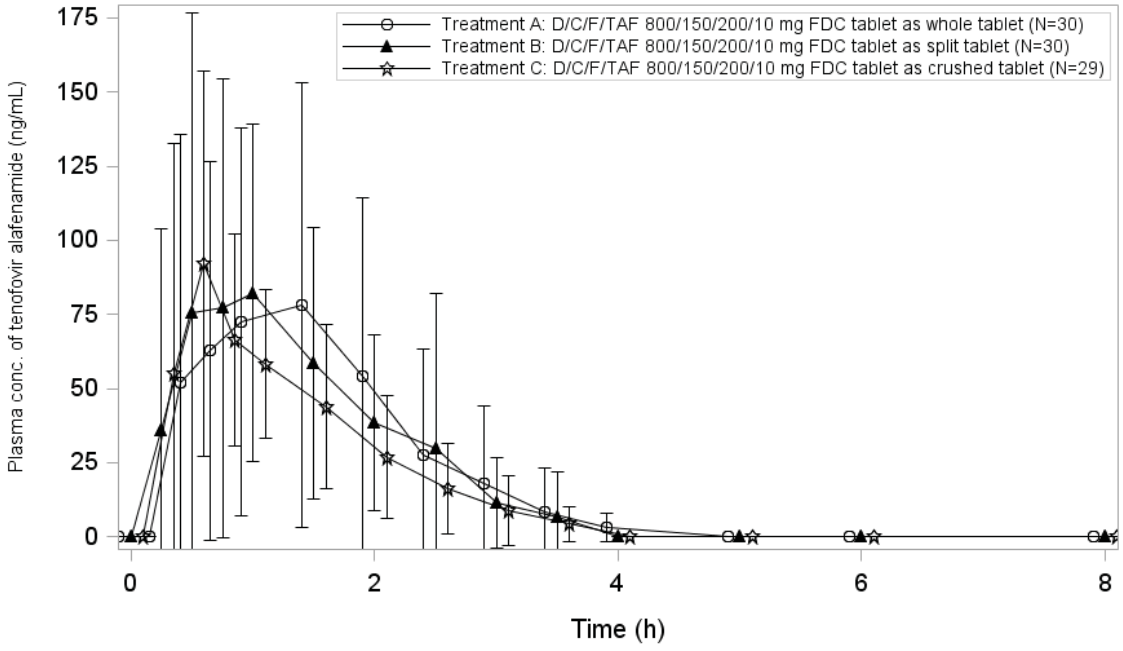
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Fig4

Figure 23: Mean (SD) Plasma Concentration-time Profiles of FTC Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet (Treatment A), a Split Tablet (Treatment B), and a Crushed Tablet (Treatment C), Under Fed Conditions (Study TMC114FD2HTX1004)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Fig5

Figure 24: Mean (SD) Plasma Concentration-time Profiles of TAF After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet (Treatment A), a Split Tablet (Treatment B), and a Crushed Tablet (Treatment C), Under Fed Conditions (Study TMC114FD2HTX1004)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Fig6

The exposures of DRV, COBI and FTC were comparable following intake of the D/C/F/TAF FDC tablet swallowed whole, as a split tablet or as a crushed tablet. The 90% CIs of the LS mean ratios for the main PK parameters (C_{max}, AUC_{last} and AUC_{∞}) were all within the 80.00% to 125.00% interval, except for the FTC C_{max} when administered as a crushed tablet (17% lower C_{max}).

For TAF, the AUC_{last} and AUC_{∞} were similar when administered as a split tablet compared to a whole tablet, with the 90% CIs of the LSmeans ratios within the 80.00% - 125.00% boundaries of no effect. The C_{max} of TAF was decreased by 11% for a split tablet compared to a whole tablet. The C_{max}, AUC_{last}, and AUC_{∞} of TAF were decreased by 29%, 19%, and 18%, respectively, when administered as a crushed tablet compared to a tablet swallowed whole.

The median t_{max} and terminal elimination half-life ($t_{1/2}$) were comparable between treatments for all components. For TAF there was some difference in the median t_{max} between treatments, but the ranges overlapped.

Table 19: Pharmacokinetic Parameters and Statistical Analysis of DRV After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet, a Split Tablet, and a Crushed Tablet, Under Fed Conditions (Study TMC114FD2HTX1004)

Pharmacokinetics of DRV (mean [SD], t_{max}: median [range])	**D/C/F/TAF FDC swallowed whole (reference)**	**D/C/F/TAF FDC split tablet (test1)**	**D/C/F/TAF FDC crushed tablet (test2)**
n	30	30	29
C_{max} (ng/mL)	8,437 (1,674)	8,963 (2,366)	9,484 (1,867)
t_{max} (h)	4.00 (1.00 – 8.00)	4.00 (1.50 – 6.00)	3.02 (1.50 – 5.03)
AUC_{last} (ng.h/mL)	116,139 (38,309)	123,917 (53,827)	130,532 (48,649)
AUC_{∞} (ng.h/mL)	116,422 (38,652)	124,469 (54,875)	130,940 (49,458)
$t_{1/2term}$ (h)	5.5 (2.3)	5.3 (2.0)	5.0 (1.7)
		LSmeans Ratio (90%CI), %	
		Test1 vs Reference	**Test2 vs Reference**
n		30 vs 30	29 vs 30
C_{max}		104.75 (100.02 – 109.71)	113.38 (108.20 – 118.81)
AUC_{last}		102.96 (97.46 – 108.78)	111.16 (105.15 – 117.53)
AUC_{∞}		103.10 (97.59 – 108.92)	111.18 (105.17 – 117.54)

Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Tab4-6

Table 20: Pharmacokinetic Parameters and Statistical Analysis of COBI After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet, a Split Tablet, and a Crushed Tablet, Under Fed Conditions (Study TMC114FD2HTX1004)

Pharmacokinetics of COBI (mean [SD], t_{max}: median [range])	**D/C/F/TAF FDC swallowed whole (reference)**	**D/C/F/TAF FDC split tablet (test1)**	**D/C/F/TAF FDC crushed tablet (test2)**
n	30	30	29
C_{max} (ng/mL)	931 (231)	985 (241)	937 (242)
t_{max} (h)	4.00 (1.00 – 5.02)	3.59 (1.50 – 6.00)	3.03 (2.00 – 6.00)
AUC_{last} (ng.h/mL)	7,785 (3,433)	8,297 (4,076)	8,062 (3,786)
AUC_{∞} (ng.h/mL)	7,883 (3,497)	8,391 (4,144)	8,180 (3,898)
$t_{1/2term}$ (h)	3.8 (1.0)	3.8 (1.0)	3.8 (1.3)
		LSmeans Ratio (90%CI), %	
		Test1 vs Reference	**Test2 vs Reference**
n		30 vs 30	29 vs 30
C_{max}		105.81 (101.41 – 110.40)	99.79 (95.59 – 104.18)
AUC_{last}		104.56 (99.05 – 110.39)	101.24 (95.83 – 106.95)
AUC_{∞}		104.45 (99.00 – 110.20)	101.33 (95.97 -106.99)

Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Tab7-9

Table 21: Pharmacokinetic Parameters and Statistical Analysis of FTC After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet, a Split Tablet, and a Crushed Tablet, Under Fed Conditions (Study TMC114FD2HTX1004)

Pharmacokinetics of FTC (mean [SD], t_{max}: median [range])	**D/C/F/TAF FDC swallowed whole (reference)**	**D/C/F/TAF FDC split tablet (test1)**	**D/C/F/TAF FDC crushed tablet (test2)**
n	30[a]	30[b]	29[c]
C_{max} (ng/mL)	1,915 (565)	1,892 (537)	1,599 (472)
t_{max} (h)	2.00 (0.75 – 4.02)	2.51 (0.75 – 5.00)	2.02 (1.00 – 4.00)
AUC_{last} (ng.h/mL)	11,830 (2,737)	11,742 (2,728)	11,013 (2,690)
AUC_{∞} (ng.h/mL)	11,975 (2,806)	12,202 (2,809)	10,956 (2,682)
$t_{1/2term}$ (h)	16.7 (4.3)	16.2 (3.4)	16.0 (3.7)
		LSmeans Ratio (90%CI), %	
		Test1 vs Reference	**Test2 vs Reference**
n		30[b] vs 30[a]	29[c] vs 30[a]
C_{max}		100.38 (92.72 – 108.68)	83.24 (76.81 – 90.21)
AUC_{last}		98.96 (94.76 – 103.34)	92.22 (88.25 – 96.36)
AUC_{∞}		99.24 (94.49 – 104.22)	92.52 (88.13 – 97.13)

[a] n=29 for AUC_{∞} and $t_{1/2term}$
[b] n=26 for AUC_{∞} and $t_{1/2term}$
[c] n=27 for AUC_{∞} and $t_{1/2term}$

Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Tab10-12

Table 22: Pharmacokinetic Parameters and Statistical Analysis of TAF After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg FDC Tablet Swallowed as a Whole Tablet, a Split Tablet, and a Crushed Tablet, Under Fed Conditions (Study TMC114FD2HTX1004)

Pharmacokinetics of TAF (mean [SD], t_{max}: median [range])	**D/C/F/TAF FDC swallowed whole (reference)**	**D/C/F/TAF FDC split tablet (test1)**	**D/C/F/TAF FDC crushed tablet (test2)**
n	30	30[a]	29
C_{max} (ng/mL)	163 (71.6)	155 (90.4)	121 (69.9)
t_{max} (h)	1.25 (0.25 – 2.50)	1.00 (0.25 – 2.50)	0.57 (0.25 – 2.00)
AUC_{last} (ng.h/mL)	155 (43.2)	153 (51.3)	126 (37.5)
AUC_{∞} (ng.h/mL)	156 (43.2)	156 (52.1)	128 (37.4)
$t_{1/2term}$ (h)	0.4 (0.1)	0.4 (0.2)	0.5 (0.2)
	LSmeans Ratio (90%CI), %		
		Test1 vs Reference	**Test2 vs Reference**
n		30[a] vs 30	29 vs 30
C_{max}		89.25 (74.53 – 106.88)	71.32 (59.43 – 85.59)
AUC_{last}		97.08 (89.61 – 105.18)	80.93 (74.63 – 87.77)
AUC_{∞}		97.69 (90.19 – 105.81)	81.63 (75.44 – 88.33)

[a] n=28 for AUC_{∞}

Source: Mod5.3.1.1/TMC114FD2HTX1004_CSR/Tab13-15

2.1.1.3.4. Conclusion

Intake of the D/C/F/TAF FDC as a split tablet compared to as a whole tablet did not impact the relative bioavailability (C_{max}, AUC_{last}, and AUC_{∞}) of the different components (DRV, COBI, FTC, and TAF), except for an 11% decrease in the TAF C_{max}.

Intake of the D/C/F/TAF FDC as a crushed tablet compared to as a whole tablet did not impact the relative bioavailability (C_{max}, AUC_{last}, and AUC_{∞}) of DRV, COBI, and FTC, except for a 17% decrease in the FTC C_{max}; the relative bioavailability of TAF decreased by 29%, 19%, and 18% for C_{max}, AUC_{last}, and AUC_{∞}, respectively.

2.2. Comparative Bioequivalence

2.2.1. D/C/F/TAF FDC

2.2.1.1. Study TMC114FD2HTX1001: A Single-dose Bioequivalence Study of Darunavir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide Administered as a Fixed-dose Combination Tablet or as Separate Agents

Mod5.3.1.2/TMC114FD2HTX1001_CSR

2.2.1.1.1. Objective

To evaluate the single-dose PK and 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, in healthy subjects.

2.2.1.1.2. Subjects and Methods

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; Mod5.3.1.2/TMC114FD2HTX1001_CSR/Sec3.8.3.2). The results of this sample size reestimation indicated no additional subjects were to be recruited, and recruitment was halted at 96 subjects.

The treatments were as follows:

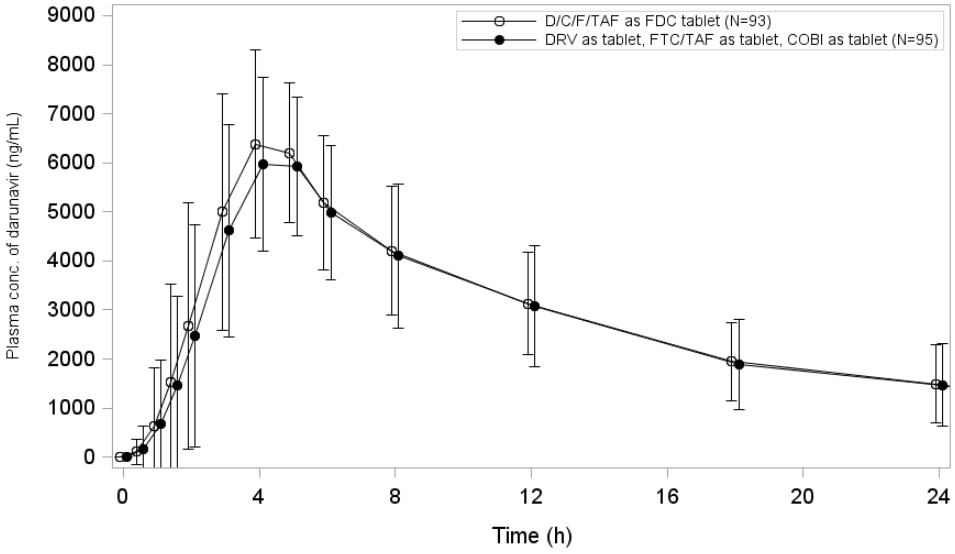
- Treatment A (test): a single oral dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet, under fed conditions.
- Treatment B (reference): a single oral dose of DRV as 1 x 800 mg tablet, F/TAF as 1 x 200/10 mg FDC tablet, and COBI 150 mg as 1 x 150 mg tablet, under fed conditions.

2.2.1.1.3. Results

All data presented in this section is under fed conditions (standardized regular-fat breakfast) and compares D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet (Treatment A; test) with combined intake of single oral dose of DRV as 1 x 800 mg tablet, F/TAF as 1 x 200/10 mg FDC tablet, and COBI 150 mg as 1 x 150 mg tablet (Treatment B; reference).

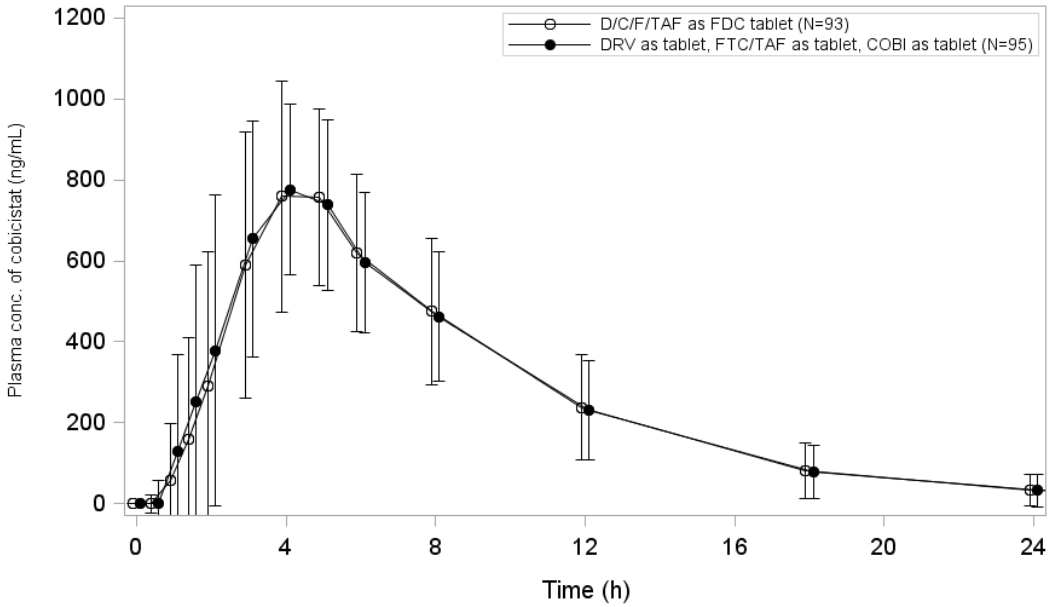
No major differences were observed regarding the shape of the DRV (Figure 25), COBI (Figure 26), FTC (Figure 27), and TAF (Figure 28) mean PK profiles between the FDC or the single agents. A summary of the PK parameters is presented in Table 23. The 90% CIs of the LS mean ratios of all main PK parameters were within the 80.00% to 125.00% bioequivalence limits for all 4 compounds (DRV, COBI, FTC, and TAF). 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 this statistical analysis.

Figure 25: Mean Plasma Concentration-time Profiles of DRV (Including SD Bars) After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg as FDC Tablet (Treatment A) and as Separate Agents DRV 800 mg, F/TAF 200/10 mg FDC, and COBI 150 mg Tablets (Treatment B) Under Fed Conditions (Study TMC114FD2HTX1001)



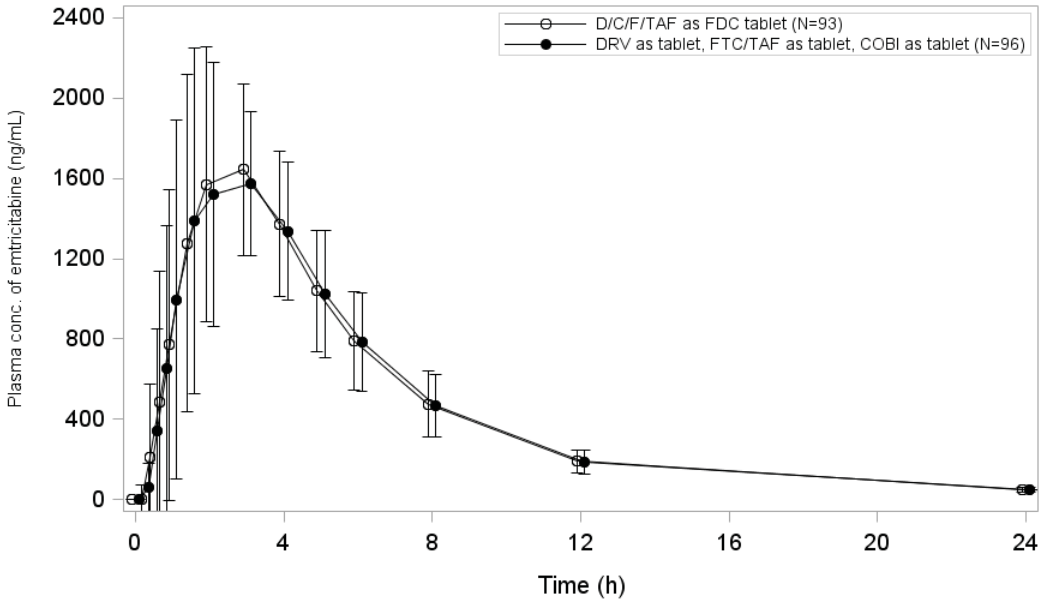
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.2/TMC114FD2HTX1001_CSR/Fig3

Figure 26: Mean Plasma Concentration-time Profiles of COBI (Including SD Bars) After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg as FDC Tablet (Treatment A) and as Separate Agents DRV 800 mg, F/TAF 200/10 mg FDC, and COBI 150 mg Tablets (Treatment B), Under Fed Conditions (Study TMC114FD2HTX1001)



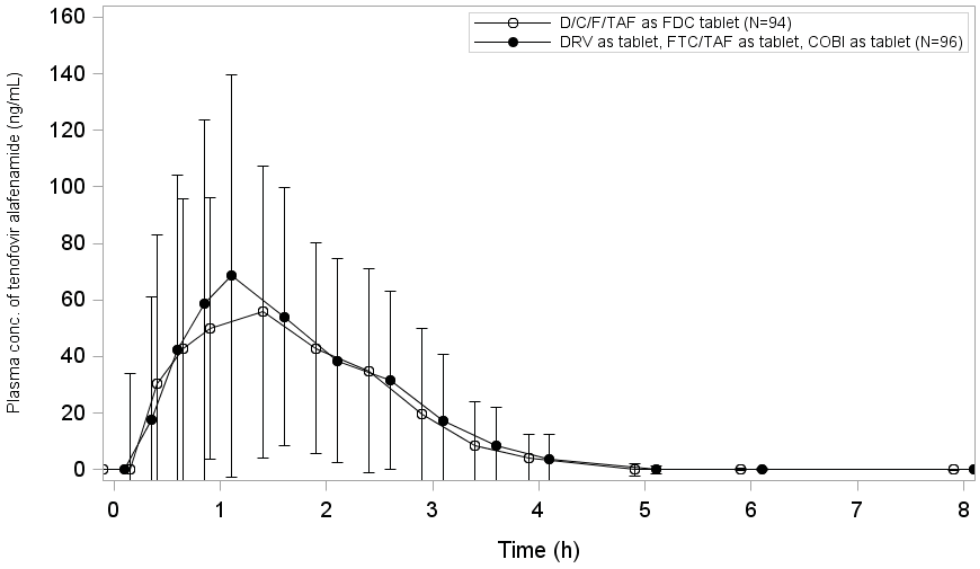
FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.2/TMC114FD2HTX1001_CSR/Fig6

Figure 27: Mean Plasma Concentration-time Profiles of FTC (Including SD Bars) After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg as FDC Tablet (Treatment A) and as Separate Agents DRV 800 mg, F/TAF 200/10 mg FDC, and COBI 150 mg Tablets (Treatment B), Under Fed Conditions (Study TMC114FD2HTX1001)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.2/TMC114FD2HTX1001_CSR/Fig4

Figure 28: Mean Plasma Concentration-time Profiles of TAF (Including SD Bars) After Single Dose Administration of D/C/F/TAF 800/150/200/10 mg as FDC Tablet (Treatment A) and as Separate Agents DRV 800 mg, F/TAF 200/10 mg FDC, and COBI 150 mg Tablets (Treatment B), Under Fed Conditions (Study TMC114FD2HTX1001)



FDC=fixed-dose combination; SD=standard deviation
Source: Mod5.3.1.2/TMC114FD2HTX1001_CSR/Fig5

Table 23: Single-dose Pharmacokinetic Parameters Including Statistical Analysis of DRV, COBI, FTC and TAF (Study TMC114FD2HTX1001)

Parameter	Mean (SD); t_{max}: Median (Range)		
	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.

AUC_{∞}=area under the plasma concentration-time curve (AUC) measured from time zero and extrapolated to infinity; AUC_{last}=AUC from 0h up to the time of the last measurable concentration after dosing; CI=confidence interval; C_{max}=maximum plasma concentration; LS=least square; SD=standard deviation; t_{max}=time to reach C_{max}
Source: Mod5.3.1.2/TMC114FD2HTX1001_CSR/Tab6, Tab7, Tab8, Tab9, Tab10, Tab11, Tab12, and Tab13

2.2.1.1.4. Conclusion

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. 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. The 90% CIs of the LS mean ratios of all main PK parameters for all

4 compounds (DRV, COBI, FTC, TAF) were within the 80.00% to 125.00% bioequivalence limits.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

An overview table of all bioavailability parameters across biopharmaceutic and clinical pharmacology studies in which DRV, COBI, FTC and TAF were coadministered is provided in Mod2.7.2/Appendix 2. A discussion and comparison of PK parameters for the different components across studies and across populations is presented in Mod2.7.2/Sec3.2.

3.1. Relative Bioavailability – Impact of Formulation

3.1.1. Formulations Used in Clinical Studies

In study GS-US-299-0101, 3 formulations of the D/C/F/TAF FDC were compared (single- and multiple-dose PK). Formulations 1 and 2 were a monolayer and bilayer formulation, respectively, each containing 25 mg TAF, while Formulation 3 was a monolayer formulation containing 10 mg TAF; all formulations contained D/C/F 800/150/200 mg (see Section 1.1.1). Formulation 3 (also denoted monolayer formulation A) was selected as the proposed Phase 2 formulation also to be administered in Part 3 of this same study, where the bioavailability of DRV, COBI, FTC, TAF and TFV administered as this D/C/F/TAF FDC (800/150/200/10 mg) relative to administration of the individual components: DRV/COBI 800/150 mg or FTC 200 mg + TAF 25 mg was examined.

An optimized form of the D/C/F/TAF 800/150/200/10 mg Phase 2 formulation was used in the Phase 3 studies TMC114IFD3013 and TMC114FD2HTX3001 (G001).

The single-dose exposures of DRV, COBI, FTC and TAF when administered as the intended commercial FDC tablet (G001, D/C/F/TAF 800/150/200/10 mg) was compared with the respective exposures when coadministered as formulations of the separate agents at the same dose (single oral dose of DRV as 1 x 800 mg tablet, F/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet) in panel 2 of Study TMC114FD2HTX1002 and in bioequivalence Study TMC114FD2HTX1001.

3.1.1.1. Monolayer Versus Bilayer Formulation of D/C/F/TAF FDC

Part 1 of Study GS-US-299-0101 evaluated the PK of DRV, COBI, FTC and TAF when administered as 3 different formulations of D/C/F/TAF in order to select the formulation for further development.

Formulations 1 (monolayer) and 2 (bilayer) each contained 25 mg TAF, whereas Formulation 3 (monolayer) contained 10 mg TAF.

Single-dose exposures for TAF and TFV were comparable between Formulation 1 and Formulation 2 (each containing 25 mg TAF); both after single dose and after multiple dose (Section 2.1.1.2.3.1, Table 13, Table 14, Table 15, and Table 16). Also, DRV, COBI and FTC multiple-dose exposures were generally comparable between these formulations.

Administration of lower TAF dose formulation (Formulation 3; 10 mg TAF) led to proportionally lower exposures of TAF and TFV (Section 2.1.1.2.3.1, Table 13, Table 14, Table 15, and Table 16), as expected. The observed TAF exposures were, however, in a range associated with antiviral activity of TAF administered as a single agent (see Mod2.7.2/Sec3.5.1)

and were consistent with historical data from supportive studies. Formulation 3 was selected for Phase 2 and further development.

3.1.1.2. Fixed Dose Combination Versus Single Agent Coadministration

The D/C/F/TAF FDC was shown to be bioequivalent to combined administration of the separate formulations, for all components, in study TMC114FD2HTX1001. Also in the smaller size study, TMC114FD2HTX1002 (panel 2), similar results were obtained. Only the C_{max} for TAF was 9% lower with the D/C/F/TAF FDC in that study, but this may be related to the large inter- and intrasubject variability of TAF and this study was not powered to show bioequivalence.

An overview of the PK parameters for the different components administered as the D/C/F/TAF FDC across studies is shown in Table 24. The PK parameters are generally comparable across studies. The somewhat larger across-study variability for TAF is reflective of the larger PK variability for TAF.

It has previously been shown for the development of the DRV/COBI FDC (NDA 205395), that the exposure for DRV when boosted with COBI or rtv is equivalent, and this allows also extrapolation of relevant data from the historical DRV/rtv and DRV/COBI development programs, where applicable. In addition, the F/TAF FDC administered with EVG/COBI was shown to be bioequivalent to the E/C/F/TAF FDC for the TAF and FTC components (NDA208215), which allows further extrapolation of relevant data from the E/C/F/TAF development program, where applicable. This is further discussed in more detail in Mod2.7.2.

3.1.2. Manufacturing Changes

Following the decision to use formulation 3 from GS-US-299-0101 for further development, some minor changes were introduced to this D/C/F/TAF FDC formulation (G001) intended for commercialisation: [redacted] has been added to the tablet and the non-functional film-coating agent was changed from [redacted] This is not expected to have altered the relative bioavailability of the D/C/F/TAF FDC G001 formulation. The G001 formulation including [redacted] and non-functional film-coating [redacted] was used in the D/C/F/TAF bioequivalence and pivotal Phase 3 studies.

In the bioequivalence study (TMC114FD2HTX1001) the D/C/F/TAF FDC intended commercial formulation (G001) was shown to be bioequivalent to the combined administration of the separate formulations (DRV, F/TAF FDC, and COBI). The 90% CIs of the LS mean ratios of all main PK parameters for all 4 components (DRV, COBI, FTC, and TAF) were within the 80.00% to 125.00% bioequivalence limits.

3.1.3. Administration Mode

To accommodate subjects that have difficulty swallowing, the impact of splitting or crushing the D/C/F/TAF FDC on the oral bioavailability of DRV, COBI, FTC and TAF was investigated in study TMC114FD2HTX1004 (Section 2.1.1.3).

Intake of the D/C/F/TAF FDC as a split tablet compared to as a whole tablet did not impact the relative bioavailability (C_{max}, AUC_{last}, and AUC_{∞}) of the different components (DRV, COBI, FTC, and TAF), except for an 11% decrease in the TAF C_{max}. The latter is not considered clinically relevant. Therefore, for patients who are unable to swallow, the D/C/F/TAF FDC may be split.

Intake of the D/C/F/TAF FDC as a crushed tablet compared to as a whole tablet did not impact the relative bioavailability (C_{max}, AUC_{last}, and AUC_{∞}) of DRV, COBI, and FTC, except for a 17% decrease in the FTC C_{max}; the relative bioavailability of TAF decreased by 29%, 19%, and 18% for C_{max}, AUC_{last}, and AUC_{∞}, respectively. The clinical relevance of a potential decrease in TAF exposure is further discussed in Mod2.7.2/Sec3.5.1.4.

3.2. Effect of Concomitant Food Intake

The effect of food on the oral bioavailability of DRV, COBI, FTC and TAF when administered as the D/C/F/TAF FDC tablet was investigated in study TMC114FD2HTX1002; panel 3 (Section 2.1.1.1.3.3, Table 11). The 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 the AUC_{last} for both FTC and TAF were comparable for both conditions. The C_{max}, AUC_{last}, and AUC_{∞} were lower under fasted compared to fed condition for both DRV (30% to 45% lower) and COBI (16% to 29% lower).

The D/C/F/TAF FDC was administered under fed conditions as well in Phase 1 studies GS-US-299-0101, TMC114FD2HTX1001 and TMC114FD2HTX1004. For comparison, the PK parameters (AUC and C_{max}) for DRV, COBI, FTC and TAF are presented with those from the food effect study TMC114FD2HTX1002 in Table 24.

The food effect for DRV with the D/C/F/TAF FDC was also comparable to that previously observed with other DRV formulations. In a previous food effect evaluation for the DRV/COBI FDC (TMC114IFD1003, NDA205395/Mod5.3.1.1/TMC114IFD1003-CSR), the exposure of DRV decreased by approximately 40% to 50% when administered under fasted conditions compared with a high-fat breakfast, while the exposure of COBI was unaltered in fasted versus fed conditions.[8] In a previous food effect study with DRV/rtv (TMC114-C143, NDA021976/Mod5.3.1.1/TMC114-C143-CSR), the exposure (C_{max} and AUC_{last}) of DRV decreased by approximately 30% when administered under fasted conditions compared with a standard breakfast. Moreover, between different meal types (standard breakfast, high-fat breakfast, nutritional protein-rich drink, and croissant and coffee) the exposure of DRV was shown to be comparable.[9]

The effect of food on COBI exposure was further comparable to that in a previous food effect study for E/C/F/TDF, where it was shown that different types of meals did not impact the ability of COBI as a PK enhancer (study GS-US-236-0105).[13] The food effect for COBI is as such not considered clinically relevant.

The effect of food on TAF and FTC exposure in the absence of a boosting agent was evaluated previously in Study GS-US-311-1386 using the F/TAF (200/25 mg) FDC.[6] Overall, FTC exposure (AUC_{inf}) decreased by 9% when F/TAF (200/25 mg) was administered under fed conditions compared with fasted conditions. These findings are consistent with those from previous studies (FTC-111 and GS-US-236-0105), which supports the current recommendation that FTC can be administered without regard to food. Overall, TAF exposure (AUC_{inf}) increased by 75% when F/TAF (200/25 mg) was administered under fed conditions compared with fasted conditions. The wide range of TAF exposure associated with potent antiviral activity demonstrated in a previous proof-of-concept study (GS-US-120-0104) and with safety and efficacy data for F/TAF containing regimens (Mod2.7.2/Sec3.5) indicate that the differences in TAF PK upon F/TAF administration with or without food are not clinically relevant. In general, food increases the exposure to TAF to some extent, either via an impact on C_{max} or AUC, or both. The impact of food on the TAF PK was less pronounced in the presence of a booster, as shown with the D/C/F/TAF FDC (TMC114FD2HTX1002; Section 2.1.1.1.3.3) and also with E/C/F/TAF (GS-US-292-0110).[4] The recommended intake for the D/C/F/TAF FDC is with food, and this was also the recommended intake in the D/C/F/TAF Phase 3 studies.

In summary, the impact of food on the PK of COBI, FTC and TAF is not considered to be clinically relevant. However, 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 is administered with food. The type of food does not affect the exposure to DRV.

3.3. Inter- and Intrasubject Variability

The %CV for the PK parameters of the components of D/C/F/TAF administered as the D/C/F/TAF FDC, in fed and fasted conditions, is shown in Table 24 and is also further discussed in Mod2.7.2/Sec3.2.6.

Overall conclusions based on the data presented in this summary are provided at the beginning of this document, just prior to Section 1.

Table 24: Pharmacokinetic Parameters of DRV, COBI, FTC and TAF After Administration of a Single-dose of the D/C/F/TAF FDC under Standardized Fed Conditions (Studies TMC114FD2HTX1002 [Panel 1,2 and 3], GS-US-299-0101, TMC114FD2HTX1001 and TMC114FD2HTX1004) and Fasted Conditions (Study TMC114FD2HTX1002 [Panel 3])

Study	C_{max}, AUC: Mean (SD; %CV) and Median (range); t_{max}, $t_{1/2}$: Median (range)							
	TMC114 FD2HTX1001	TMC114 FD2HTX1002				GS-US-299-0101 (Day 1, single dose)		TMC114 FD2HTX1004
		Panel 1	Panel 2	Panel 3		Part 1	Part 3	Swallowed whole
Component / Parameter	(Fed - regular-fat breakfast) N=96[a]	(Fed- regular-fat breakfast) N=24[a]	(Fed - regular-fat breakfast) N=24[a]	(Fed - high-fat breakfast N=24[a]	(Fasted) N=24[a]	(Formulation 3) (Fed- regular-fat breakfast) N=10	(Fed- regular-fat breakfast) N=19[a]	(Fed - regular-fat breakfast) N=30
DRV								
C_{max}, ng/mL	7042 (1481; 21.0)	-	6670 (1521; 22.8)	6629 (1543; 23.3)	4089 (1846; 45.1)	-	-	8437 (1674; 19.8)
	7100 (4350 - 11300)	-	6430 (4700 - 10700)	6790 (3930 - 9100)	4310 (437 - 8030)	-	-	8475 (5410 - 11500)
AUC_{last}, ng.h/mL	87200 (27385; 31.4)	-	90809 (44208; 48.7)	93541 (39730; 42.5)	67504 (35642; 52.8)	-	-	116139 (38309; 33.0)
	83956 (39423 - 166145)	-	76164 (43840 - 249447)	89528 (40067 - 181446)	56823 (6777 - 142318)	-	-	109420 (67406 - 260193)
AUC_{∞}, ng.h/mL	87280 (28097; 32.2)	-	93308 (44140; 47.3)	94686 (40882; 43.2)	72147 (36009; 49.9)	-	-	116422 (38652; 33.2)
t_{max}, h	4.00 (1.50 - 8.00)	-	5.00 (2.00 - 8.00)	5.00 (1.50 - 8.00)	3.00 (1.00 - 8.02)	-	-	4.00 (1.00 - 8.00)
$t_{1/2}$, h	5.5 (3.1 - 13.4)	-	6.4 (3.9 - 10.8)	6.8 (4.1 - 16.2)	6.4 (4.2 - 12.8)	-	-	5.0 (2.8 - 12.6)
COBI								
C_{max}, ng/mL	894 (254; 28.5)	-	801 (159; 19.8)	711 (164; 23.1)	704 (368; 52.3)	-	-	931 (231; 24.8)
	866 (240 - 2160)	-	799 (505 - 1140)	699 (372 - 1040)	619 (15.3 - 1360)	-	-	907 (509- 1420)
AUC_{last}, ng.h/mL	6681 (2486; 37.2)	-	6224 (1886; 30.3)	6168 (2260; 36.6)	5771 (3206; 55.6)	-	-	7785 (3433; 44.1)
	6507 (1348 - 14976)	-	5769 (3395 - 10743)	6420 (2829 - 11693)	4910 (76.9 - 11205)	-	-	6985 (3098- 21515)
AUC_{∞}, ng.h/mL	6785 (2518; 37.1)	-	6301 (1903; 30.2)	6258 (2268; 36.2)	6136 (3064; 49.9)	-	-	7883 (3497; 44.4)
t_{max}, h	4.00 (1.50 - 6.00)	-	4.00 (1.50 - 6.00)	5.00 (2.00 - 6.10)	3.00 (1.00 - 6.00)	-	-	4.00 (1.00 - 5.02)
$t_{1/2}$, h	3.6 (2.2 - 6.6)	-	3.4 (2.6 - 5.5)	3.9 (2.6 - 4.6)	4.2 (1.7 - 5.8)	-	-	3.6 (2.4 – 8.0)

Table 24 continued: Pharmacokinetic Parameters of DRV, COBI, FTC and TAF After Administration of a Single-dose of the D/C/F/TAF FDC under Fed Conditions (Studies TMC114FD2HTX1002 [Panel 1,2 and 3], GS-US-299-0101, TMC114FD2HTX1001 and TMC114FD2HTX1004) and Fasted Conditions (Study TMC114FD2HTX1002 [Panel 3])

Study	C_{max}, AUC_{last}: Mean (SD; %CV) and Median (range); t_{max}, $t_{1/2}$: Median (range)							
	TMC114 FD2HTX1001	TMC114 FD2HTX1002				GS-US-299-0101 (Day 1, single dose)		TMC114 FD2HTX1004
		Panel 1	Panel 2	Panel 3		Part 1	Part 3	Swallowed whole
Component / Parameter	(Fed - regular-fat breakfast) N=96[a]	(Fed- regular-fat breakfast) N=24[a]	(Fed - regular-fat breakfast) N=24[a]	(Fed - high-fat breakfast) N=24[a]	(Fasted) N=24[a]	(Formulation 3) (Fed- regular-fat breakfast) N=10	(Fed- regular-fat breakfast) N=19[a]	(Fed - regular-fat breakfast) N=30
FTC								
C_{max}, ng/mL	2053 (469; 22.8)	1691 (414; 24.5)	1677 (411; 24.5)	1785 (486; 27.2)	2247 (573; 25.5)	-	-	1915 (565; 29.5)
	1960 (1140 - 3730)	1655 (1180 - 3020)	1580 (990 - 2560)	1635 (1270 - 3060)	2055 (1290 - 3640)	-	-	1805 (435 - 3100)
AUC_{last}, ng.h/mL	11746 (1868; 15.9)	10595 (1777; 16.8)	10365 (1753; 16.9)	11499 (2055; 17.9)	11593 (2573; 22.2)	-	-	11830 (2737; 23.1)
	11630	10605	10132	11166	10936	-	-	11443
	(7656 - 16312)	(7540 - 13852)	(7532 - 14539)	(8523 - 15993)	(8567 - 18984)			(6101 - 18887)
AUC_{∞}, ng.h/mL	11927 (1935; 16.2)	10223 (1693; 16.6)	10135 (1650; 16.3)	10029 (1079; 10.8)	12286 (2729; 22.2)	-	-	11975 (2806; 23.4)
t_{max}, h	2.00 (0.50 - 5.00)	2.50 (1.00 - 5.00)	3.00 (1.00 - 4.98)	2.00 (0.75 - 5.00)	1.00 (0.50 - 2.00)	-	-	2.00 (0.75 - 4.02)
$t_{1/2}$, h	17.7 (7.5 - 22.8)	10.3 (9.3 - 12.0)	10.1 (9.2 - 10.9)	10.6 (9.4 - 12.9)	10.5 (8.6 - 13.8)	-	-	17.3 (7.4 – 24.7)
TAF								
C_{max}, ng/mL	110 (54.1; 49.0)	102 (62.0; 60.7)	105 (94.9; 90.3)	107 (65.2; 61.0)	180 (90.6; 50.3)	171.7 (63.46; 37.0)	181.1 (34.17; 18.9)	163 (71.6; 43.8)
	97.2 (31.1 - 253)	87.6 (25.5 - 228)	66.8 (30.1 - 460)	105 (23.2 - 307)	144 (67.4 - 419)	144 (117 - 288)	186.8 (136.9 - 221.9)	149 (58.0 - 312)
AUC_{last}, ng.h/mL	123 (42.0; 34.2)	114 (55.8; 49.1)	123 (67.8; 55.3)	177 (51.5; 44.1)	106 (44.7; 42.2)	166 (41.46; 25.0)	183.6 (50.54; 27.5)	155 (43.2; 28.0)
	117 (52.7 - 261)	98.9 (39.8 - 264)	93.1 (45.5 - 305)	107 (64.1 - 298)	100 (45.5 - 209)	165 (94.3 - 263)	178.4 (119.2 - 270.8)	149 (66.1 - 223)
AUC_{∞}, ng.h/mL	127 (39.4;31.1)	138 (72.2; 52.2)	119 (42.0; 35.3)	125 (57.3; 45.9)	109 (47.7; 43.8)	168.5 (40.33; 23.9)	184.5 (53.7; 29.1)	156 (43.2; 27.8)
t_{max}, h	1.50 (0.25 - 3.50)	1.50 (0.50 - 5.00)	1.28 (0.50 - 3.00)	0.88 (0.25 - 5.00)	0.50 (0.25 - 0.75)	0.75 (0.50 - 1.00)	1.00 (0.50 - 1.50)	1.25 (0.25 – 2.50)
$t_{1/2}$, h	0.3 (0.2 - 0.9)	0.5 (0.2 - 0.9)	0.4 (0.3 - 0.7)	0.5 (0.2 - 0.8)	0.3 (0.2 - 1.0)	0.42 (0.27 - 1.06)	0.37 (0.34 - 0.64)	0.3 (0.2 - 0.7)

[a] N=maximum number of subjects with data

AUC_{last}=area under the plasma concentration-time curve from 0h up to the time of the last quantifiable (non-below quantification limit) concentration after dosing; AUC_{∞}=area under the plasma concentration-time curve measured from time zero and extrapolated to infinity; C_{max}=maximum plasma concentration; CV=coefficient of variation; t_{max}= time to reach the maximum plasma concentration; $t_{1/2}$=terminal half-life

Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/TABPK11, 17, 23, 29, 35, 41, 47, 53, 59, and 65; Mod5.3.1.2/TMC114FD2HTX1001_CSR/TABPK4, 10, 16, and 22; Mod5.3.1.1/GS-US-299-0101_CSR/Tab4.1.4 and Tab4.3.14; Mod5.3.1.1/TMC114FD2HTX1004_CSR/TABPK07, TABPK13, TABPK19, TABPK25

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APPENDICES

Appendix 1: In Vitro Dissolution Data for the D/C/F/TAF Formulation (G001) Used in Biopharmaceutic Studies, Measured With the Proposed Dissolution Method

Dosage Form	Formulation Number	Dissolution Apparatus	Media Temperature Units	Collection Times (min), Mean % Dissolved (SD)								
				5	10	15	20	30	45	60	90	120
[redacted]												

Appendix 2: Clinical Studies With D/C/F/TAF

Study ID	Objective(s)	Population	Dose	Route	Formulation or Lot	Location of Report	Study Previously Included in an Approved Marketing Authorization
Biopharmaceutic Studies							
GS-US-299-0101	Bioavailability	Healthy Subjects	800/150/200/25 mg (D/C/F/TAF) 800/150/200/25 mg (D/C/F/TAF) 800/150/200/10 mg (D/C/F/TAF) 800/150 mg (DRV/COBI) 200 + 25 mg (FTC + TAF)	oral oral oral	Formulation 1 (monolayer) Formulation 2 (bilayer) Formulation 3 (monolayer)	5.3.1.1	F/TAF (NDA208215)
TMC114FD2HTX1001	Bioequivalence	Healthy Subjects	800/150/200/10 mg (D/C/F/TAF) 800/150/200/10 mg DRV + COBI + F/TAF)	oral	G001	5.3.1.2	-
TMC114FD2HTX1002	Bioavailability/ Food Effect	Healthy Subjects	800/150/200/10 mg (D/C/F/TAF) 800/150/200/10 mg (DRV + COBI + F/TAF) 150/150/200/10 mg (E/C/F/TAF)	oral	G001	5.3.1.1	-
TMC114FD2HTX1004	Bioavailability	Healthy Subjects	800/150/200/10 mg (D/C/F/TAF)	oral	G001	5.3.1.1	-
Efficacy and Safety Studies in HIV-1 Infected Patients							
GS-US-299-0102	Safety, Efficacy Phase 2	ART naïve HIV-1 Infected Patients	800/150/200/10 mg (D/C/F/TAF) 800+150+200+300 mg (DRV + COBI + F/TDF)	oral	G001	5.3.5.1	F/TAF (NDA208215)
TMC114FD2HTX3001	Safety, Efficacy	ART naïve	800/150/200/10 mg (D/C/F/TAF)	oral	G001	5.3.5.1	-

Study ID	Objective(s)	Population	Dose	Route	Formulation or Lot	Location of Report	Study Previously Included in an Approved Marketing Authorization
	Phase 3	HIV-1 Infected Patients	800/150 + 200/300 mg (DRV/COBI + F/TDF)				
TMC114IFD3013	Safety, Efficacy Phase 3	ART experienced, virologically suppressed HIV-1 Infected Patients	800/150/200/10 mg (D/C/F/TAF) Boosted PI + F/TDF	oral	G001	5.3.5.1	-

Mod5.3.1.1/GS-US-299-0101_CSR; Mod5.3.1.2/TMC114FD2HTX1001_CSR; Mod5.3.1.1/TMC114FD2HTX1002_CSR; Mod5.3.1.1/TMC114FD2HTX1004_CSR; Mod5.3.5.1/GS-US-299-0102 Final CSR; Mod5.3.5.1/TMC114FD2HTX3001_W48_CSR; Mod5.3.5.1/TMC114IFD3013_W48_CSR

Appendix 3: Bioanalytical Method: Validation Parameters, D/C/F/TAF Biopharmaceutic Studies

Method	LC-MS/MS BA10833, Full Validation (Mod5.3.1.4)	LC-MS/MS BA10833, Full Validation (Mod5.3.1.4)	LC-MS/MS BA10878, Partial Validation (Mod5.3.1.4)
Analyte	DRV	COBI	FTC
Matrix	Plasma	Plasma	Plasma
Validated concentration range	5 to 10,000 ng/mL	5 to 5,000 ng/mL	5 to 5,000 ng/mL
Inter-run accuracy (%RE)	-3.8 to 0.6	-6.0 to -0.3	N/A
Inter-run precision (%CV)	2.7 to 5.1	1.3 to 5.8	N/A
Intra-run accuracy (%)	-5.4 to 2.4	-10.6 to 0.6	-4.0 to 4.4
Intra-run precision (%CV)	1.3 to 3.9	0.5 to 5.2	2.2 to 5.4
Intra-run accuracy (dilution) (%)	-2.0 (10× dilution)	-6.7 (10× dilution)	-3.7 (10× dilution)
Intra-run precision (dilution) (%CV)	3.1 (10× dilution)	3.0 (10× dilution)	5.9 (10× dilution)
Incurred sample reproducibility	Study TMC114FD2HTX1001: 202/204 samples within 20% Study TMC114FD2HTX1002: 128/128 samples within 20%	Study TMC114FD2HTX1001: 200/204 samples within 20% Study TMC114FD2HTX1002: 128/128 samples within 20%	Study TMC114FD2HTX1001: 204/204 samples within 20% Study TMC114FD2HTX1002: 146/160 samples within 20%
Selectivity	No relevant interferences	No relevant interferences	No relevant interferences
Matrix effect	Within criteria	Within criteria	Within criteria
Matrix effect in haemolyzed plasma	Within criteria	Within criteria	Within criteria
Matrix effect in lipemic plasma	Within criteria	Within criteria	Within criteria
Stability in stock solution	27 hours at room temperature 43 days at -20°C	25 hours at room temperature 42 days at -20°C	72 hours at room temperature 46 days at -20°C
Stability in plasma	5 F/T cycles at -20°C and -70°C 27 hours at room temperature	5 F/T cycles at -20°C and -70°C 27 hours at room temperature	5 F/T cycles at -20°C and -70°C 24 hours at room temperature
Processed sample stability	144 hours at 10ºC	144 hours at 10ºC	120 hours at 10ºC
Stability in frozen matrix	526 days at -20°C and -70°C	526 days at -20°C and -70°C	392 days at -20°C and -70°C

Appendix 3: Bioanalytical Methods: Validation Parameters (continued)

Method	LC-MS/MS [redacted] 60-1115, Full Validation (Mod5.3.1.4)	LC-MS/MS [redacted] 60-1578, Full Validation (Mod5.3.1.4)
Analyte	TAF	TAF
Matrix	Plasma	Plasma
Validated concentration range	1 to 1,000 ng/mL	1 to 1,000 ng/mL
Inter-run accuracy (%RE)	-3.7 to 6.5	-7.3 to -5.6
Inter-run precision (%CV)	1.8 to 7.3	3.8 to 6.3
Intra-run accuracy (%)	-4.5 to 7.8	-9.0 to -2.8
Intra-run precision (%CV)	1.2 to 9.5	2.4 to 7.9
Dilution	20 fold dilution validated	20 fold dilution validated
Incurred sample reproducibility	Study TMC114FD2HTX1002: 127/138 samples within 20%	Study TMC114FD2HTX1001: 186/193 samples within 20%
Selectivity	No relevant interferences	No relevant interferences
Stability in blood	4 hours at room temperature and in ice bath	4 hours at room temperature and in ice bath
Stability in stock solution	18 hours at room temperature 133 days at -20°C	18 hours at room temperature 133 days at -20°C
Stability in plasma	5 F/T cycles at -20°C and -70°C 6.5 hours in ice bath	5 F/T cycles at -20°C and -70°C 6.5 hours in ice bath
Processed sample stability	164 hours at 4ºC	154 hours at 4ºC
Stability in frozen matrix	520 days at -70°C	520 days at -70°C
Matrix effect in haemolyzed plasma		Within criteria
Matrix effect in lipemic plasma		Within criteria

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

Appendix 4: Bioanalytical Methods Used for Completed D/C/F/TAF Clinical Studies With Pharmacokinetic Sampling

Study ID (Location)	Matrix	Analyte	Concentration Range (LLOQ is lower end of the concentration range)	Method	Method Validation Report	Study Previously Included in an Approved Marketing Authorization
Phase 1 Studies						
TMC114FD2HTX1001	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA10833	-
(Mod5.3.1.2)		COBI	5 to 5,000 ng/mL	LC-MS/MS	BA10833	
		FTC	5 to 5,000 ng/mL	LC-MS/MS	BA10878	
		TAF	1 to 1,000 ng/mL	LC-MS/MS	[redacted] 60-1578	
TMC114FD2HTX1002	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA10833	-
(Mod5.3.1.1)		COBI	5 to 5,000 ng/mL	LC-MS/MS	BA10833	
		FTC	5 to 5,000 ng/mL	LC-MS/MS	BA10878	
		TAF	1 to 1,000 ng/mL	LC-MS/MS	[redacted]60-1115	
TMC114FD2HTX1004	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA10833	-
(Mod5.3.1.1)		COBI	5 to 5,000 ng/mL	LC-MS/MS	BA10833	
		FTC	5 to 5,000 ng/mL	LC-MS/MS	BA10878	
		TAF	1 to 1,000 ng/mL	LC-MS/MS	[redacted] 60-1578	
GS-US-299-0101	Plasma	DRV	20 to 10,000 ng/mL	LC-MS/MS	[redacted] 42-0902	F/TAF (NDA208215)
(Mod5.3.1.1)		COBI	5 to 5,000 ng/mL	LC-MS/MS	[redacted] 60-0949	
		FTC	5 to 3,000 ng/mL	LC-MS/MS	[redacted] 42-0831	
		TAF	1 to 1,000 ng/mL	LC-MS/MS	[redacted]60-1115	
		TFV	0.3 to 300 ng/mL	LC-MS/MS	[redacted] 60-1116	
Phase 2/3 Studies						
GS-US-299-0102	Plasma	DRV	20 to 10,000 ng/mL	LC-MS/MS	[redacted]42-0902	F/TAF (NDA208215)
(Mod5.3.5.1)		COBI	5 to 5,000 ng/mL	LC-MS/MS	[redacted] 60-0949	
		FTC	5 to 3,000 ng/mL	LC-MS/MS	[redacted] 42-0831	
		TAF	1 to 1,000 ng/mL	LC-MS/MS	[redacted] 60-1115	
		TFV	0.3 to 300 ng/mL	LC-MS/MS	[redacted] 60-1116	
TMC114IFD3013	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA10833	-
(Mod5.3.5.1)		COBI	5 to 5,000 ng/mL	LC-MS/MS	BA10833	
TMC114FD2HTX3001	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA10833	-
(Mod5.3.5.1)		COBI	5 to 5,000 ng/mL	LC-MS/MS	BA10833	
		TAF	1 to 1,000 ng/mL	LC-MS/MS	[redacted] 60-1578	

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

Janssen Research & Development

Summary of Clinical Pharmacology Studies

Darunavir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults and Adolescents

D/C/F/TAF (Darunavir/ Cobicistat/ Emtricitabine/ Tenofovir Alafenamide)

Status:	Approved
Date:	11 September 2017
Prepared by:	Janssen Research & Development, a division of Janssen Pharmaceutica NV
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ABBREVIATIONS

AAG	alpha-1 acid glycoprotein
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALAG	absorption lag time
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{24h}	area under the plasma concentration-time curve over 24 hours
AUC_{∞}	area under the plasma concentration-time curve measured from time zero to the last quantifiable concentration, and extrapolated to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
$AUC_{\tau au}$ [a]	area under the plasma concentration-time curve over the dosing interval (tau, from time zero to the time of next dosing) – same as AUC_{24h} for qd dosing
BCRP	breast cancer resistance protein
BMD	bone mineral density
BOV	between occasion variability
BSV	between subject variability
C_{0h}	predose plasma concentration
C_{tau}	plasma concentration at the end of the dosing interval tau
CI	confidence interval
CL/F	apparent clearance
CL_p/F	apparent intercompartmental clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COBI	cobicistat
CPT	Child-Pugh-Turcotte
CSR	clinical study report
$C_{ss,av}$	average plasma concentration at steady-state
CV	coefficient of variability
CYP	cytochrome P450
D1	duration of zero-order input into the depot compartment
ddI	didanosine
DHA	dihydroartemisinin
DNA	deoxyribonucleic acid
DRV	darunavir
DRV/COBI	darunavir/cobicistat
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DRV/rtv	darunavir/low-dose ritonavir
DTG	dolutegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
EC_{50}	median 50% effective concentration
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft Gault equation
EVG	elvitegravir
EVG/COBI	elvitegravir/cobicistat
FDA	Food and Drug Administration

FDC	fixed-dose combination
F/TAF	emtricitabine/tenofovir alafenamide
F/TDF	emtricitabine/tenofovir disoproxil fumarate
FR_{SLOW}	fraction of the (TAF) dose absorbed via the slow pathway
FTC	emtricitabine
FTC/RPV/TAF	emtricitabine/rilpivirine/tenofovir alafenamide
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate
GAM	generalized additive model
GFR	glomerular filtration rate
GSI	Gilead Sciences, Inc.
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus type 1
HMG-CoA	3-hydroxy-3-methylglutary coenzyme A
ICH	International Conference on Harmonisation
IC_{50}	50% inhibitory concentration
IQR	interquartile range
ISV	intersubject variability (synonymous with between subject variability)
IV	intravenous
KA	first-order absorption rate constant
KTR	absorption transit rate constant
LBW	lean body weight
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LPV	lopinavir
LPV/rtv	lopinavir/low-dose ritonavir
LS	least square
MAP	maximum a posteriori
MATE1	multidrug and toxin extrusion protein 1
MDZ	midazolam
MRP	multidrug resistance-associated protein
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OAT	organic anion transporter
OATP	organic anion transporter protein
OCT2	organic cation transporter 2
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PXR	pregnane X receptor
QTcF	QT interval corrected by Fridericia's formula
RAM	resistance associated mutation
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
rtv	low-dose ritonavir
RUV	residual unexplained variability
SD	standard deviation
SE	standard error
SOC	system organ class
SQR	square root
SSRI	selective serotonin reuptake inhibitor
STR	single-tablet regimen
$t_{1/2}$	terminal half-life

TAF	tenofovir alafenamide
TDD	total daily dose
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
t_{max}	time to reach maximum plasma concentration
UGT	uridine diphosphate glucuronosyltransferase
V_c/F	apparent volume of distribution for the central compartment
V_p/F	apparent volume of distribution for the peripheral compartment
WT	total body weight

[a.] Unless specified in the text, $AUC_{tau}=AUC_{24h}$

SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF) fixed-dose combination (FDC) tablet - hereafter referred to as the D/C/F/TAF FDC - combines 4 agents for oral once daily use for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. Thus, a complete protease inhibitor (PI)-based HIV-1 treatment regimen is combined into 1 pill, containing a PI darunavir (DRV) (800 mg), a pharmacokinetic (PK) enhancer cobicistat (COBI) (150 mg), a nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC) (200 mg), and a tenofovir (TFV) prodrug, tenofovir alafenamide (TAF) (10 mg).

Darunavir is an approved HIV-1 PI with a high genetic barrier to resistance. It is also a cytochrome P450 (CYP)3A substrate. Cobicistat is a potent mechanism-based inhibitor of CYP3A, and is an approved PK enhancer that boosts systemic exposures of e.g. the HIV-1 PIs atazanavir (ATV) and DRV. Cobicistat has no intrinsic antiviral activity. Emtricitabine is an approved NRTI that is generally well tolerated. Tenofovir alafenamide is an oral prodrug of TFV, a nucleotide analog that inhibits HIV- 1 reverse transcription. Tenofovir alafenamide is more stable in plasma than tenofovir disoproxil fumarate (TDF; another widely used oral prodrug of TFV) and is predominantly hydrolyzed to TFV intracellularly by cathepsin A, resulting in higher intracellular levels of the active phosphorylated metabolite TFV-diphosphate (TFV-DP) and lower circulating levels of TFV relative to TDF.[1,2] This distinct metabolism of TAF is intended to both maximize antiviral potency and improve clinical safety compared with TDF.

The clinical development program for the D/C/F/TAF 800/150/200/10 mg FDC tablet is based on two pivotal Phase 3 studies, TMC114FD2HTX3001 and TMC114IFD3013, complemented with biopharmaceutic studies further characterizing the D/C/F/TAF FDC formulation. In addition, relevant clinical pharmacology data have been gathered in the clinical development programs for the DRV, COBI, FTC and TAF single agents and combinations thereof (darunavir/cobicistat [DRV/COBI] and emtricitabine/tenofovir alafenamide [F/TAF]).

This Summary of Clinical Pharmacology Studies presents an overview of the clinical pharmacology data for the components of the D/C/F/TAF FDC, separately or in combination, that support the use of the D/C/F/TAF FDC for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Pharmacokinetic data are discussed from 2 pivotal Phase 3 Studies and 1 Phase 2 Study in HIV-I infected antiretroviral therapy (ART)-naïve subjects, 3 relative bioavailability studies and 1 bioequivalence study conducted with the D/C/F/TAF FDC. Additionally, relevant PK data and PK/PD evaluations forming the basis for approval of the applications for DRV/COBI and F/TAF are referenced within this current application.

The comparable exposure (ie, area under the plasma concentration-time curve [AUC] and maximum plasma concentration [C_{max}]) for DRV, COBI, FTC, and TAF when administered as single agents or as the D/C/F/TAF FDC in healthy subjects (studies GS-US-299-0101, TMC114FD2HTX1002, TMC114FD2HTX1001, and TMC114FD2HTX1004) and in HIV-1 infected ART-naïve subjects (study GS-US-299-0102, TMC114FD2HTX3001, TMC114IFD3013) 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.

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

Pharmacokinetics

Absorption and Distribution

- Darunavir, COBI, FTC and TAF are all orally available when coadministered as the D/C/F/TAF FDC tablet. Darunavir has an absolute bioavailability of 82% when coadministered 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 coadministration with COBI, such that DRV exposures (AUC_{24h} and C_{max}) comparable to DRV coadministered with rtv are achieved.
- The D/C/F/TAF FDC is bioequivalent to coadministration of formulations of the separate agents DRV, COBI, and F/TAF. The D/C/F/TAF FDC can be split without clinically relevant impact on the bioavailability of DRV, COBI, FTC or TAF.
- 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.

Metabolism and 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 (AUC_{24h} and C_{max}) comparable to DRV coadministered 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 [IV] dose). Emtricitabine undergoes little metabolism; therefore, metabolism is a minor route of FTC elimination.
- Tenofovir alafenamide has a distinct metabolic profile designed to maximize both antiviral potency and clinical safety. Inside cells, TAF 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 monomuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages, which results in greater concentrations of TFV-DP in PBMCs and lower exposure of TFV in the systemic circulation (approximately 90% lower) and undesired tissues, including the kidney and bone. Tenofovir alafenamide is thus extensively metabolized, and predominantly excreted as TFV. There is very minimal renal excretion for TAF.

Special populations

The information and guidance for special populations for the D/C/F/TAF FDC is predominantly derived from that for the separate agents, DRV, COBI and F/TAF; and confirmed, where applicable, with D/C/F/TAF Phase 3 data

- Age was not a clinically relevant covariate for the PK of any of the components of the D/C/F/TAF FDC. There are limited data in elderly subjects.
- Adult doses for DRV, COBI, and F/TAF have shown to provide systemic exposures in pediatric subjects aged ≥12 and <18 years that is comparable to that in adults.
- Sex was not a clinically relevant 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.
- 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.
- 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 [$eGFR_{CG}$] ≥30 mL/min). The D/C/F/TAF FDC should not be initiated in patients who have an $eGFR_{CG}$ <30 ml/min.

Drug-drug Interactions

- The drug-drug interaction profile of the D/C/F/TAF FDC is primarily driven by the drug-drug interaction profile of DRV/COBI.
    - COBI-boosted darunavir mainly inhibits CYP3A, CYP2D6 and P-glycoprotein (P-gp). Coadministration 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. Coadministration 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-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-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. Coadministration of TAF with drugs that inhibit P-gp may increase the absorption and plasma concentrations of TAF.

1. BACKGROUND AND OVERVIEW

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 analog of low-dose ritonavir (rtv), and a potent mechanism-based CYP3A inhibitor that increases the systemic exposure of other coadministered drugs metabolized by CYP3A. Cobicistat has no intrinsic anti-HIV-1 activity but is licensed as a PK enhancer ("booster") of antiretroviral (ARV) agents, such as DRV 800 mg once daily as part of ARV combination therapy in HIV-1 infected adults. Cobicistat 150 mg once daily is currently approved as a single agent (Tybost®; Gilead Sciences Inc. [GSI]) or as part of fixed dose combinations (FDCs) containing atazanavir (ATV) and COBI (Evotaz®) for the treatment of HIV-1 infection in adults; and containing the integrase strand transfer inhibitor (INI) elvitegravir (EVG), emtricitabine (FTC), tenofovir disoproxyl fumarate (TDF) or tenofovir alafenamide (TAF), and COBI (Stribild®/Genvoya®; GSI) for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older.

Darunavir with COBI (DRV/COBI) as an FDC tablet (800/150 mg; PREZCOBIX®/REZOLSTA®) is also licensed and is currently indicated in combination with other ARV medicinal products for the treatment of HIV-1 infection.

Emtricitabine (Emtriva®) at a dose of 200 mg once daily is an approved nucleoside reverse transcriptase inhibitor (NRTI), indicated in combination with other ARV medicinal products for the treatment of HIV-1 infected adults and children aged at least 4 months. Emtricitabine is also approved as part of a number of FDC drugs, including emtricitabine/tenofovir disproxil fumarate (FTC/TDF) (Truvada® hereafter called F/TDF) and others (see elsewhere in this Section).

Tenofovir (TFV) is a nucleotide analog 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 (TDF, Viread®) is an oral prodrug of TFV and has been the preferred nucleotide analog reverse-transcriptase inhibitor. However, nephrotoxicity and reduced bone mineral density (BMD) may occur, including elevated risks of reduced kidney function, proteinuria and proximal tubular dysfunction in some patients.[5,14,35]

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 (approximately 90% lower) circulating plasma levels of TFV relative to TDF.[1,2,32] 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®; GSI) is licensed as an FDC tablet indicated for the treatment of HIV-1 in combination with other ARV agents in adults and adolescents aged

12 years and older. A TAF dose of 10 mg once daily is being evaluated in the D/C/F/TAF Phase 3 studies.

Once-daily combined antiretroviral therapy (ART) regimens are aimed at reducing the pill burden for patients with HIV-1. Currently, there are only 6 effective once-daily non-nucleoside reverse transcriptase inhibitor (NNRTI) or INI-based FDC tablets approved as a complete regimen for the treatment of HIV-1 infection: Atripla® (efavirenz/FTC/TDF), Complera®/Eviplera® (FTC/rilpivirine [RPV]/TDF), Stribild® (EVG/COBI/FTC/TDF, hereafter referred to as E/C/F/TDF), Genvoya® (EVG/COBI/FTC/TAF, hereafter referred to as E/C/F/TAF), Triumeq® (dolutegravir/abacavir/lamivudine) and Odefsey® (FTC/RPV/TAF). There remains a need for simplified PI-based ART that combines potent and sustained efficacy, favorable tolerability, and minimal long-term toxicity, with practical, convenient dosing.

To reduce the pill burden for DRV-containing ARV regimens, the darunavir/cobicistat (DRV/COBI) FDC (REZOLSTA/PREZCOBIX) was developed. The Applicant and GSI have subsequently coformulated DRV and COBI with FTC and TAF to form the first PI-based FDC single-tablet option (D/C/F/TAF FDC). GSI has transferred further development of the regimen to the Applicant and, subject to regulatory approval, the manufacturing, registration, distribution and commercialization of the product worldwide. The D/C/F/TAF FDC is intended to be marketed for use in the same population of HIV-1 infected subjects for which DRV/COBI 800/150 mg once daily in combination with other ARVs is registered, and extended to adolescents aged as of 12 years and weighing at least 40 kg.

Clinical pharmacology data from the clinical studies in HIV-1 infected subjects conducted with the D/C/F/TAF FDC (mainly 2 pivotal Phase 3 studies and 1 Phase 2 study) are summarized in this document. 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 as outlined in the sections below. Data from the development of the individual components is presented or referenced where warranted.

1.1. General Attributes of the Drug

1.1.1. Drug/Drug Product Information

Dosage form/strengths: Oral immediate-release FDC tablet containing a fixed ratio of 800 mg DRV, supplied as DRV ethanolate, 150 mg COBI adsorbed on silicon dioxide, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of the hemifumarate co-crystal, TAF hemifumarate).

Pharmacologic class: DRV is a PI registered for the treatment of HIV-1 infection when coadministered with a PK enhancer. Cobicistat is a PK enhancer used to increase systemic exposure of certain coadministered ARV drugs metabolized by CYP3A enzymes. Emtricitabine is an NRTI. Tenofovir alafenamide is an oral prodrug of TFV, an NtRTI.

Chemical Name: DRV: [(1S,2R)-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b] furan-3-yl ester

ethanolate; COBI: 1,3-thiazol-5-ylmethyl (2R,5R)-(5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-2-yl)carbamate. FTC: 5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. TAF: 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).

Physical Characteristics: Darunavir and COBI differ in their pKa and solubility profiles. Darunavir is very slightly soluble at a pH range of 1 to 12 (<1 mg/100 mL). The solubility of COBI varies from soluble to practically insoluble depending on pH, with high solubility at low pH (>40 mg/mL at a pH of 1.1) and low solubility at moderate pH (0.04 mg/mL at a pH of 7.5 and 8.2). The aqueous solubility of TAF is pH-dependent with solubility decreasing with increasing basicity; TAF is soluble at low pH (pH 2.0), sparingly soluble at pH 3.8, and slightly soluble at pH values up to 8.0. Emtricitabine has a high aqueous solubility across the physiological pH range.

Formulation: The D/C/F/TAF FDC tablets are yellow to yellowish-brown capsule-shaped, film-coated tablets, debossed with "JG" on one side and "8121" on the other side, containing 800 mg of DRV (as 867 mg of DRV ethanolate), 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of the hemifumarate co-crystal, TAF hemifumarate). The D/C/F/TAF FDC tablet core contains silicon dioxide, croscarmellose sodium, microcrystalline cellulose, and magnesium stearate as inactive ingredients and tablets are film-coated with polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and yellow ferric oxide. The quantitative formula is provided in Mod3.2.P.2.2.1/Tab1.

1.1.2. Proposed Mechanism(s) of Action and Indication

Darunavir is an HIV-1 PI with potent *in vitro* activity against wild-type and multi-drug resistant HIV-1 strains. It is an inhibitor of the dimerization and catalytic activity of the HIV-1 protease (K_D of 4.5 x 10^{-12} M), whereby it selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in virus infected cells, hence preventing the formation of mature infectious virus particles.

Cobicistat, a structural analogue of ritonavir (RTV), was found to be a potent mechanism-based inhibitor of human hepatic microsomal CYP3A activity with *in vitro* kinetic parameters similar to those of RTV, but devoid of anti-HIV-1 activity.[21]

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.

Tenofovir alafenamide is a phosphonoamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide readily permeates the cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading TFV into PBMCs (including lymphocytes and other HIV-1 target cells) and macrophages. Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite

TFV-DP. Tenofovir-DP inhibits HIV-1 replication through incorporation into viral DNA by the HIV-1 RT, which results in DNA chain-termination.

The D/C/F/TAF FDC is intended for indication as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg).

1.1.3. Proposed Dosage and Route of Administration

The recommended dose of the D/C/F/TAF FDC is 800/150/200/10 mg once daily (ie, a single tablet), to be taken orally, with food.

1.2. Human Biomaterial Studies

Nonclinical studies have not been conducted with DRV, COBI, FTC, and TAF in combination (D/C/F/TAF) or with DRV/COBI in combination. The overall nonclinical program conducted separately for each agent is considered adequate to support the safety of the FDC tablet. The D/C/F/TAF combination is not expected to induce clinically relevant additive or synergistic effects (Nonclinical Overview in Mod2.4).

The nonclinical pharmacology, PK, metabolism, and toxicology of DRV, COBI, FTC and TAF have been established in support of the respective marketing authorizations for these individual licensed drugs (as separate agents or as FDC). Pertinent information from human biomaterial studies conducted with DRV, COBI, FTC and TAF relating to the general absorption, distribution, metabolism, and excretion (ADME) characteristics of the D/C/F/TAF FDC components is summarized in the Nonclinical Overview (Mod2.4) and is included, where appropriate, in this summary (Section 3.1).

1.3. Clinical Pharmacology Studies

1.3.1. Overview

1.3.1.1. Overview of Studies - D/C/F/TAF FDC

The PK and/or PD properties of D/C/F/TAF as a combination were studied in four Phase 1 studies, one Phase 2 study and 2 Phase 3 studies (Table 1). An overview of all biopharmaceutic studies is presented in Mod2.7.1/Appendix 2. An overview of all clinical pharmacology studies is presented in Appendix 1. More details per study are given in Section 2, in the tabular listing of all clinical studies (Mod5.2) and in the individual study reports (Mod5.3).

Table 1: Number of Studies and Subjects – D/C/F/TAF FDC

Type of Study	Number of Studies	Population	Number of Subjects
Phase 1			
Single dose	3 (TMC114FD2HTX1002, TMC114FD2HTX1001 and TMC114FD2HTX1004)	Healthy subjects	198 (72, 96 and 30)
Repeated-dose	1 (GS-US-299-0101)	Healthy subjects	102
Phase 2			
Efficacy and Safety	1 (GS-US-299-0102)	ART-naïve HIV-1 infected subjects	153[a]
Pivotal Phase 3			
Efficacy and Safety	1 (TMC114FD2HTX3001)	ART-naïve HIV-1 infected subjects	725[b]
Efficacy and Safety	1 (TMC114IFD3013)	Virologically-suppressed HIV-1 infected subjects	1141[c]
Total	7	-	2319

[a] 103 subjects in the D/C/F/TAF FDC group and 50 subjects in the DRV plus COBI plus F/TDF group
[b] 362 subjects in the D/C/F/TAF FDC group and 363 subjects in the DRV/COBI plus F/TDF group
[c] 763 subjects in the D/C/F/TAF FDC group and 378 subjects in the boosted PI plus F/TDF group
Number of subjects includes all subjects that were treated in studies.
ART=antiretroviral therapy; HIV=human immunodeficiency virus
Source: Mod5.3.1.2/TMC114FD2HTX1001_CSR; Mod5.3.1.1/TMC114FD2HTX1002_CSR; Mod5.3.1.1/GS-US-299-0101_CSR; Mod5.3.1.1/TMC114FD2HTX1004_CSR; Mod5.3.5.1/GS-US-299-0102_CSR; Mod5.3.5.1/TMC114FD2HTX3001_CSR and Mod5.3.5.1/TMC114IFD3013_CSR

Single oral doses of D/C/F/TAF were administered as 1 x FDC tablet or as a combination of the separate agents, with food (except when the food effect was evaluated) and repeated oral doses were taken as 1 x FDC tablet once daily or as a combination of the separate agents once daily, with food.

- Study GS-US-299-0101 compared 3 candidate D/C/F/TAF FDC tablet formulations 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 D/C/F/TAF FDC relative to the administration of the individual components: DRV plus COBI or FTC plus TAF (summarized in Mod2.7.1/Sec2.1.1.2).

Based on the results of Study GS-US-299-0101, a monolayer D/C/F/TAF FDC containing 10 mg TAF (see Section 3.6 for the rationale on dose selection) was selected for further development; G001. The non-functional film-coating agent was changed from Opadry II® White 85F18422 to Opadry II® Yellow 85F120020. A deboss code, "8121" on one side and "JG" on the other side, was added to the tablet (refer to Mod2.7.1/Sec1.1).

- Study TMC114FD2HTX1002 compared the PK of DRV, COBI, FTC, and TAF after single-dose administration as the D/C/F/TAF FDC (G001) to the separate agents (DRV plus COBI plus F/TAF) under fed conditions; evaluated the relative bioavailability of TAF and FTC after single-dose administration of the D/C/F/TAF FDC (G001) compared to an FDC with EVG, COBI, and F/TAF (E/C/F/TAF); and investigated the effect of food on the single-dose PK of the D/C/F/TAF FDC (summarized in Mod2.7.1/Sec2.1.1.1).

- Study TMC114FD2HTX1001 evaluated the single-dose PK and bioequivalence of the D/C/F/TAF FDC (G001) relative to combined administration of formulations of the separate agents (DRV 800 mg tablet and FTC/TAF 200/10 mg FDC in the presence of COBI 150 mg tablet), under fed conditions, in healthy subjects (summarized in Mod2.7.1/Sec2.2.1.1).
- Study TMC114FD2HTX1004 evaluated the impact of splitting or crushing of the D/C/F/TAF FDC (G001) on the relative bioavailability of DRV; COBI, FTC and TAF, under fed conditions, in healthy subjects (summarized in Mod2.7.1/Sec2.1.1.3).
- Phase 2 study GS-US-299-0102 evaluated the safety and efficacy of the D/C/F/TAF FDC (G001) versus COBI-boosted DRV (DRV plus COBI) plus F/TDF in HIV-1 infected ART-naïve adult subjects (summarized in Section 2.2.2.1). This study also included a PK substudy.
- Pivotal Phase 3 study TMC114FD2HTX3001 evaluated the efficacy and safety of the D/C/F/TAF FDC (G001) versus COBI-boosted DRV (DRV/COBI FDC) plus F/TDF in HIV-1 infected ART-naïve adult subjects (summarized in Section 2.2.2.2). In this study, also the DRV, COBI and TAF pharmacokinetics were evaluated (for subjects in the D/C/F/TAF treatment arm).
- Pivotal Phase 3 study TMC114IFD3013 evaluated the efficacy and safety of the D/C/F/TAF FDC (G001) versus a boosted PI plus F/TDF in virologically suppressed HIV-1 infected adult subjects (summarized in Section 2.2.2.3). In this study, also the DRV and COBI pharmacokinetics were evaluated (for subjects in the D/C/F/TAF treatment arm).

1.3.1.2. Overview of Historical Studies With Separate Agents

Completed studies that formed the basis of the marketing authorization for DRV/COBI (PREZCOBIX/REZOLSTA) and F/TAF (Descovy) and relevant for the current submission for the D/C/F/TAF FDC are presented here, and referenced, where relevant, in Section 3 of this document.

1.3.1.2.1. DRV/COBI

The data that supported the registration of the DRV/COBI 800/150 mg FDC (NDA205395) were 2 relative oral bioavailability studies (bridging DRV/COBI with established data from single agent DRV boosted with rtv), 1 bioequivalence study, and 1 Phase 3b, open-label study:

- Study GS-US-216-0115 compared darunavir/low-dose ritonavir (DRV/rtv) 800/100 mg coadministered as single agents with DRV/COBI 800/150 mg coadministered as single agents in healthy subjects following repeated once daily dosing under fed conditions (NDA203094/Mod5.3.1.2/GS-US-216-0115_CSR).
- Study TMC114IFD1001 compared DRV/COBI 800/150 mg FDC tablet formulations versus DRV/rtv 800/100 mg coadministered as single agents in healthy subjects following repeated once daily dosing under fed conditions (NDA205395/Mod5.3.1.1/TMC114IFD1001_CSR).
- 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 (NDA205395/Mod5.3.1.2/TMC114IFD1003_CSR).
- Study GS-US-216-0130 assessed the safety and efficacy of the combined use of DRV and COBI, coadministered as separate agents in HIV-1 infected subjects and included an intensive PK

substudy (N=60) and sparse PK sampling for population PK purposes (NDA205395/Mod5.3.5.2/GS-US-216-0130_CSR).

In addition, several studies conducted with DRV alone, DRV coadministered with rtv, or with COBI alone further support this application. For DRV, these included a mass-balance study, a hepatic impairment study, 24 drug-drug interaction studies, a thorough QT/QTc study, and a food effect study evaluating different types of food (Table 2).

For COBI, additional studies were conducted in the absence of DRV, including a mass-balance study, 1 hepatic impairment study, 2 renal impairment studies, 6 drug-drug interaction studies, and 1 thorough QT/QTc study (Table 2).

Table 2: Number of Studies and Subjects – Submission DRV/COBI

Type of Study	Number of Studies	Population	Number of Subjects
DRV (NDA021976) and DRV/COBI (NDA205395)			
Phase 1:			
Mass-balance	1 (TMC114-C109)	Healthy subjects	8
Renal impairment	1 (GS-US-216-0121)	Healthy subjects and subjects with renal-impairment	54
Hepatic impairment	1 (TMC114-C134)	Healthy subjects and subjects with hepatic-impairment	32
Drug-drug interaction	24 (TMC114-C123, TMC114-C124, TMC114-C111, TMC114-C119, TMC125-C176, TMC278-C112, TMC114-MK0518, TMC114-A4001052, TMC114-C122, TMC114-C150, TMC114-C142, TMC114-C172, TMC114-C121, TMC114-C129, TMC125VIR1001, TMC114-C107, TMC114-C163, TMC114-C131, VX950-C124 TMC114-C133, TMC114-C120, TMC114-C171, TMC114-C127, TMC114-C128);	Healthy subjects, HIV-negative subjects on stable methadone therapy (C127), HIV-negative subjects on buprenorphine/naloxone maintenance therapy (C171), HIV-1 infected subjects on stable nevirapine (C119)	485 (18+13+12+19+32+16+18+16+18+17+18+32+36+26+33+16+27+19+20+16+14+17+16+16)
QT/QTc	1 (TMC114-C153)	Healthy subjects	40
Phase 3:			
Safety/Efficacy	1 (GS-US-216-0130)	HIV-1 infected subjects	313
	29		**932**
COBI (NDA203094) and DRV/COBI (NDA205395)			
Phase 1:			
Mass-balance	1 (GS-US-216-0111)	Healthy subjects	8
Renal impairment	1 (GS-US-216-0124)	Healthy subjects and subjects with renal-impairment	24
Hepatic impairment	1 (GS-US-183-0133)	Healthy subjects and subjects with hepatic-impairment	20
Drug-drug interaction	6 (GS-US-216-0112, GS-US-201-0104, GS-US-216-0120, GS-US-216-0122, GS-US-216-0123, GS-US-236-0106)	Healthy subjects	175 (53+18+33+16+34+21)
QT/QTc	1 (GS-US-216-0107)	Healthy subjects	48
	10		**275**
Overall Total	**39**		**1207**

Number of subjects includes all subjects that were treated in studies referenced in this document.
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, which are not included for this application. Source: Clinical Study Reports

1.3.1.2.2. 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 an ARV regimen, 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).

Where appropriate, with respect to the discussion of PK and PK/PD for TAF and the dose selection of TAF for the D/C/F/TAF FDC, reference to Phase 3 studies with F/TAF in other combinations than D/C/F/TAF are discussed. This reference to F/TAF in other fixed dose combinations pertains to studies from a development partner, and therefore, the reference to prior NDAs may not be the original submission for such studies.

Table 3: Number of Studies and Subjects – Submission F/TAF

Type of Study[a]	Number of Studies[a]	Population	Number of Subjects
F/TAF (NDA208215)			
Phase 1			
Mass-balance	2 (GS-US-120-0109, FTC-106)	Healthy Subject	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
Drug-drug interaction	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 PK/PD	5 (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	1,287 (40+435+431+333 +50[b])
		HIV-infected with renal impairment	248
Total	19		1,988

[a] Only studies for which pharmacokinetic data are referenced in this application are listed.
[b] N=24 in the intensive PK part of the study.
Number of subjects includes all subjects that were treated in studies.
HIV=human immunodeficiency virus; PD=pharmacodynamic; PK=pharmacokinetic
Source: Clinical Study Reports and Gaur et al, 2016[15]

1.3.2. Noncompartmental Pharmacokinetics

The noncompartmental PK of DRV, COBI, FTC and TAF when coadministered as the D/C/F/TAF 800/150/200/10 mg FDC tablet were evaluated in healthy subjects in 3 relative bioavailability studies (TMC114FD2HTX1002 and TMC114FD2HTX1004; single doses and GS-US-299-0101; single- and multiple doses) and in a bioequivalence study (TMC114FD2HTX1001; single doses), which are described in Mod2.7.1/Sec2. In HIV-1 infected subjects, the steady-state noncompartmental PK of DRV, COBI, FTC, TAF and TFV when DRV, COBI, FTC and TAF were coadministered as the D/C/F/TAF FDC or as a combination of DRV 800 mg, COBI 150 mg and the FDC FTC 200 mg/TDF 300 mg (hereafter F/TDF), once daily, were compared (GS-US-299-0102, Section 2.2.2.1).

1.3.3. Population Pharmacokinetic Analysis

Based on an update of a previously developed population PK model for DRV, a population PK analysis of DRV 800 mg once daily administered as part of the D/C/F/TAF FDC tablet was conducted for subjects in the D/C/F/TAF arms of the Phase 3 studies TMC114FD2HTX3001 (Section 2.2.2.2) and TMC114IFD3013 (Section 2.2.2.3). A population PK model was developed for TAF when administered in combination with DRV, COBI and FTC. This model was used to determine individual exposure metrics for TAF for subjects in the D/C/F/TAF arm of the Phase 3 study TMC114FD2HTX3001 (Section 2.2.2.2). In addition, individual exposure metrics from the TAF population PK analysis are available for a limited number of subjects in the GS-US-299-0102 study (Section 2.2.2.1). Additional data pertinent to this marketing authorization from population PK analyses for the individual components DRV, COBI, FTC and TAF are referenced for comparison, as applicable, in Section 3.

1.3.4. Drug-drug Interactions

No drug-drug interaction studies have been performed with the D/C/F/TAF combination. The drug-drug interaction potential of D/C/F/TAF has been evaluated on the basis of interactions observed with each of the single components and, in the case of DRV, also when coadministered with rtv. A tabular overview of studies pertinent to evaluation of the drug-drug interaction potential of D/C/F/TAF based on the individual components is presented in Section 2.1.5.2 and Section 2.1.5.3, with a reference to the NDA in which these studies have been previously submitted and an overall evaluation of the drug-drug interactions is discussed in Section 3.4.2.

1.3.5. Pharmacodynamics and Pharmacokinetics/Pharmacodynamics

The efficacy and safety of the D/C/F/TAF FDC was investigated in Phase 2 study GS-US-299-0102 (Section 2.2.2.1) and 2 pivotal Phase 3 studies, TMC114FD2HTX3001 (Section 2.2.2.2) and TMC114IFD3013 (Section 2.2.2.3). Efficacy and safety data from these studies are detailed in Mod2.7.3 and Mod2.7.4. Pharmacokinetic/PD analyses are presented in Section 3.5.1.1.

Where relevant, further PK/PD data is presented from studies with separate components in this submission.

Specifically, for TAF (NDA208215), the PK/PD relationship was evaluated in the proof-of-concept study (GS-US-120-0104, Section 2.2.3.2), in the pooled Phase 3 studies (GS-US-292-0104 and GS-US-292-0111, Section 2.2.3.3) and also in the Phase 3 switch study GS-US-311-1089 (Section 2.2.3.4) with F/TAF in combination with various third agents. Pharmacokinetic results of these analyses evaluating potential relationships with efficacy or safety parameters in HIV-1 infected subjects are presented in Section 3.5.1 (efficacy) and Section 3.5.2 (safety).

1.3.6. Selection of Response Endpoints and Biomarkers

The PD parameters for antiviral activity used in PK/PD analyses included virologic outcome, ie, virologic success: plasma viral load <50 HIV-1 ribonucleic acid [RNA] copies/mL; virologic rebound; virologic failure). These are standard measures of virologic response in studies in HIV-1 infected subjects.

The PD parameters for safety included the occurrence of certain prespecified adverse events (AEs) of interest (eg, bone, renal, skin) and the worst laboratory abnormality for selected laboratory parameters (eg, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides, glucose, amylase, or lipase). These are standard measures of safety in studies in HIV-1 infected subjects.

1.3.7. Rationale for Studies

The development program for D/C/F/TAF was based on 2 pivotal Phase 3 studies establishing the efficacy and safety of D/C/F/TAF in HIV-1 infected patients. In these studies, the D/C/F/TAF FDC tablet combining 4 components into a single tablet was used. To further characterize the FDC tablet, 4 biopharmaceutic studies evaluated the relative bioavailability or bioequivalence of DRV, COBI, FTC, and TAF coadministered 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, where applicable.

1.4. Critical Aspects of Methods Used

1.4.1. Study Design

In all studies with the D/C/F/TAF FDC summarized in this application, randomization was used to minimize bias in the assignment of subjects to treatment groups, thereby enhancing the validity of statistical comparisons across treatment groups. All studies had an open-label or double-blind, randomized design, which is a widely accepted means of comparing the PK of different formulations or different combinations of drugs.

All Phase 1 biopharmaceutic and clinical pharmacology studies with the D/C/F/TAF FDC were conducted as open-label, crossover studies.

1.4.2. Bioanalytical Methods

An overview of the bioanalytical methods used in studies in which D/C/F/TAF was administered is provided in Mod2.7.1/Sec1.3. An overview of method validation parameters used in these studies is provided in Mod2.7.1/Appendix 3 and a tabulated listing of the bioanalytical methods that were used for each clinical study is provided in Mod2.7.1/Appendix 4, including an indication of whether that study was previously included for an approved marketing authorization.

1.4.3. Choice of the Dose Levels

For DRV, COBI and FTC, the dose used for the D/C/F/TAF FDC is the dose approved for use when coadministered with the other agents. For TAF, a 10-mg dose was selected for the D/C/F/TAF FDC. This is supported by the totality of data from biopharmaceutic and drug-drug interaction studies and the wide range of safe and efficacious TAF plasma exposures as established in historical studies with other ARV agents. It was aimed to ensure that patients would have a TAF systemic exposure that is within the range of TAF exposures for which antiviral activity was shown and for which no PK/PD relationship was established, and the TFV systemic exposure was aimed to be as low as possible, to enhance the safety profile.

An extensive discussion of the rationale for dose selection is presented in Section 3.6.

1.4.4. Study Population

All Phase 1 studies with the D/C/F/TAF FDC or with the separate agents were conducted in healthy subjects. The Phase 2 and 3 studies with the D/C/F/TAF FDC were conducted in ART-naïve or virologically suppressed HIV-1 infected adults. Supportive efficacy and safety studies with the separate agents were conducted in HIV-1 infected adults or adolescents.

1.4.5. Pharmacokinetic Analysis Methods

PK parameters were calculated with conventional non-compartmental methods using actual times of blood sampling, unless otherwise stated in the clinical study report. In addition, for the population PK analysis for the pivotal Phase 3 studies and GS-US-299-0102, a nonlinear mixed-effects approach was used to generate the PK parameters.

1.4.6. Statistical Methods

Mostly, values presented in the tables in this module represent arithmetic mean ± standard deviation (SD) or mean (% coefficient variation [CV]) for the individual treatments; time to reach maximum plasma concentration (t_{max}) values are presented as median (range). Pair-wise comparisons between 2 treatments for C_{max} and AUC values are based on log-transformed data, unless otherwise stated in the clinical study report. Ratios and 90% confidence intervals (CI) represent the ratio of point estimates of the geometric mean or least square (LS) mean and associated CIs.

Bioequivalence between treatments or absence of food or administration mode 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%.[6] For TAF PK, given its high within-subject variability, broader limits of 70.00% to 143.00% were sometimes used, as indicated in the respective clinical study reports.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

The clinical pharmacology studies that support the indication for which marketing authorization is requested are summarized in this section and listed in Appendix 1. Supplementary information about the D/C/F/TAF studies is provided in the tabular listing of all clinical studies (Mod5.2) and in the individual study reports (Mod5.3).

Apart from the biopharmaceutic studies discussed in more detail in Module 2.7.1, clinical pharmacology studies performed with the D/C/F/TAF FDC are limited to the Phase 2 (GS-US-299-0102) and Phase 3 efficacy and safety studies (TMC114FD2HTX3001 and TMC114IFD3013). Further clinical pharmacology data are derived from the development programs of the individual components of D/C/F/TAF. Those data are only briefly referenced or summarized here, with an indication of the respective marketing authorizations for the individual components, as single agents or in combination, where these studies were previously submitted.

Data for compounds other than the components of the D/C/F/TAF FDC, except for rtv as a booster for DRV where applicable, will not be discussed as they are not considered pertinent to this marketing authorization for D/C/F/TAF, unless otherwise indicated (eg, when discussing drug-drug interactions).

2.1. Human Pharmacokinetic Studies

2.1.1. Mass-balance

2.1.1.1. D/C/F/TAF FDC

Studies were not performed with the D/C/F/TAF FDC. With regard to mass-balance studies, information in the marketing authorization is based on the development programs of the individual components, discussed in Section 3.2.2 and briefly presented in Sections 2.1.1.2 and 2.1.1.3 for the separate agents, and derived from their respective marketing authorizations.

2.1.1.2. DRV/COBI

Mass-balance studies with DRV or COBI as single components, supporting the marketing authorization for the D/C/F/TAF FDC, are described briefly below.

The mass-balance study for DRV (NDA021976/Mod5.3.3.1/TMC114-C109_CSR) characterized the excretion and overall metabolic profile of DRV in healthy subjects, with and without coadministration of rtv. DRV was rapidly absorbed with and without rtv; however, when coadministered with rtv, the mean C_{max} of unchanged DRV increased approximately 2-fold and the mean AUC_{∞} increased approximately 11-fold. Unchanged drug accounted for the largest fraction of the radioactivity in plasma samples obtained after administration of DRV in the absence or presence of rtv, with a higher percentage in the presence of rtv (eg, 48.5% and 79.4% at 1 hour after administration, in the absence and presence of rtv, respectively). The administered radioactivity was predominantly excreted in feces, amounting on average to 81.7% and 79.5% of the dose at 168 hours after dosing in the absence and presence of rtv, respectively. An average of 12.2% and 13.9% of the

administered radioactivity was recovered in urine in the absence and presence of rtv, respectively. At 168 hours after dosing, approximately 93% of the dose had been recovered irrespective of whether rtv was coadministered or not. Coadminstration with rtv reduced the DRV metabolism, with an approximately 7-fold increase in excreted unchanged DRV; unchanged DRV was mainly excreted via the feces in the absence (6.8%) or presence (41.2%) of rtv. The mean excretion of unchanged DRV in urine was 1.2% and 7.7%, respectively.

The mass-balance of COBI was characterized at steady-state in healthy subjects (NDA203094/Mod5.3.3.1/GS-US-216-0111_CSR). COBI was extensively metabolized. The combined mean (SD) recovery of 14C-radioactivity from urine and feces was 94.4% (3.75%), with most of the radioactive dose recovered in feces (86.2% [3.95%]). The predominant species circulating in plasma was COBI, which accounted for 98.6% of the total 14C-radioactivity over 24 hours, with levels undetectable in most subjects 32 hours post-dose. There were no quantifiable metabolites in plasma; the major species in feces was unchanged COBI (27%), the rest were mainly oxidative metabolites. Renal excretion of COBI was a minor pathway for elimination (<10% of the administered dose was present in urine as parent drug plus metabolites).

2.1.1.3. F/TAF

Mass-balance studies with FTC or TAF as single components, supporting the marketing authorization for the D/C/F/TAF FDC, are described briefly below.

Study GS-US-120-0109 (NDA208215/Mod5.3.3.1/GS-US-120-0109_CSR) evaluated the mass-balance, PK, metabolism and excretion of a single dose of [^{14}C]TAF in healthy subjects. Tenofovir alafenamide was shown to be extensively metabolized in urine and feces. The mean (SD) cumulative urinary and fecal recovery was 83.4% (2.45%). The mean (SD) recovery from feces was 47.2% (4.62%), and the mean (SD) recovery from urine was 36.2% (5.62%). The predominant excreted species was TFV, renal excretion of the TAF parent drug was minor. The predominant species circulating in plasma was uric acid, which accounted for 73.9% of the total [^{14}C]-radioactivity AUC over the 96-hour period. At the first maximal plasma radioactivity concentration around 2 hours postdose, the predominant species was TAF. At the second maximal plasma radioactivity concentration around 24 to 48 hours postdose, the predominant species was uric acid. Additional low quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine, which were identical to the endogenous products of purine metabolism.

Study FTC-106 (NDA021752/Mod5.3.3.1/FTC-106_CSR) evaluated the mass-balance and ADME of [^{14}C]FTC. Emtricitabine was primarily eliminated from the plasma via renal excretion as unchanged drug. The majority of FTC (85.8%) was excreted in the urine, with 13.7% recovered from the urine and feces as metabolites.

2.1.2. Healthy Subject Pharmacokinetics

Data from a bioequivalence study comparing the intended commercial D/C/F/TAF FDC with DRV (800 mg), COBI (150 mg), and F/TAF (200/10 mg) coadministered as formulations of the separate agents (TMC114FD2HTX1001), and relative bioavailability studies comparing D/C/F/TAF

800/150/200/10 mg administered as an FDC tablet with the coadministration of formulations of the separate agents, and including a comparison of 3 candidate D/C/F/TAF FDC tablet formulations, and food effect and different administration modes (GS-US-299-0101, TMC114FD2HTX1002 and TMC114FD2HTX1004) are summarized in Mod2.7.1/Sec2. Where applicable, data from these studies are included in the comparison of data across studies in Section 3 of this Summary of Clinical Pharmacology Studies.

2.1.3. Patient Pharmacokinetics

Pharmacokinetic data for the D/C/F/TAF FDC in HIV-1 infected patients is presented from studies GS-US-299-0102 in Section 2.2.2.1, TMC114FD2HTX3001 in Section 2.2.2.2 and TMC114IFD3013 in Section 2.2.2.3. Patient PK data are also briefly presented for relevant historical studies with TAF in Sections 2.2.3.

2.1.4. Intrinsic Factor Pharmacokinetics

2.1.4.1. Hepatic Impairment

D/C/F/TAF FDC

Studies were not performed with the D/C/F/TAF FDC. With regard to hepatic impairment, the information in the marketing authorization is based on the development programs of the individual components, discussed in Section 3.3.4, with studies for the separate agents briefly presented below, and derived from their respective marketing authorizations.

DRV/COBI

Studies with DRV and COBI as single agents in subjects with hepatic impairment, supporting the marketing authorization for the D/C/F/TAF FDC, are described briefly below.

Study TMC114-C134 (NDA021976/Mod5.3.3.3/TMC114-C134_CSR) assessed the single-dose and steady-state PK of DRV with rtv in subjects with mild or moderate hepatic impairment compared with healthy control subjects. The mean exposure (C_{max} and AUC_{12h}) of DRV was slightly lower in subjects with mild hepatic impairment (LS mean ratio DRV C_{max} and AUC_{12h} 80% and 86% after single dose and 88% and 94% after multiple dose) and slightly higher in subjects with moderate hepatic impairment (LS mean ratio DRV C_{max} and AUC_{12h} 102% and 110% after single dose and 122% and 120% after multiple dose) compared with healthy subjects. The exposure to rtv was comparable in healthy subjects and subjects with mild hepatic impairment and approximately 1.5 -fold higher in subjects with moderate hepatic impairment. Higher percentages of unbound plasma DRV and lower plasma alpha-1 acid glycoprotein (AAG) concentrations were seen in subjects with hepatic impairment (12 and 16% in subjects with mild and moderate hepatic impairment versus ~7.5% in healthy subjects), with an inverse relationship between plasma concentrations of AAG and percentages of unbound DRV.

Study GS-US-183-0133 (NDA203094/Mod5.3.3.3/GS-US-183-0133_CSR) assessed the PK and safety of coadministered COBI and EVG in subjects with moderate hepatic impairment compared

with healthy control subjects. The exposure of COBI was similar in subjects with moderate hepatic impairment compared with healthy subjects following once-daily administration of COBI/EVG, for AUC_{24h} (LS mean ratio 100%), while the C_{24h} was increased (LS mean ratio 208%); however, these changes were not considered clinically significant. No clinically relevant correlations between COBI exposure and Child-Pugh-Turcotte (CPT) score or individual liver function laboratory parameters were observed.

F/TAF

FTC PK has not been evaluated in subjects with hepatic impairment.

Studies with TAF in subjects with hepatic impairment, supporting the marketing authorization for the D/C/F/TAF FDC, are described briefly below.

Study GS-US-120-0114 (NDA208215/Mod5.3.3.3/GS-US-120-0114_CSR) evaluated the PK and safety of single doses of TAF in subjects with mild or moderate hepatic impairment. In non−HIV-1 infected subjects with mild or moderate hepatic impairment, TAF plasma exposure parameters were comparable with those in subjects with normal hepatic function. In subjects with mild hepatic impairment (CPT Class A score of 5 to 6), AUC_{∞}, AUC_{last}, and C_{max} were 7.52%, 8.17%, and 10.99% lower, respectively, than those of subjects with normal hepatic function. In subjects with moderate hepatic impairment (CPT Class B score of 7 to 9), AUC_{∞}, AUC_{last}, and C_{max} were 12.69%, 15.06%, and 18.70% higher, respectively, than those of subjects with normal hepatic function. The upper bounds of the 90% CIs for the TAF AUC_{∞}, AUC_{last}, or C_{max} LS mean ratios were below the protocol-defined clinically significant increase of 100% and the observed increases were not considered clinically relevant. Tenofovir plasma exposure parameters were comparable with those in subjects with normal hepatic function. In subjects with mild hepatic impairment, AUC_{∞}, AUC_{last}, and C_{max} were 10.84%, 10.69%, and 2.97% lower, respectively, than those of subjects with normal hepatic function. In subjects with moderate hepatic impairment, AUC_{∞}, AUC_{last}, and C_{max} were 2.78%, 4.45%, and 12.44% lower, respectively, than those in subjects with normal hepatic function. The upper bounds of the 90% CIs for the TFV AUC_{∞}, AUC_{last}, and C_{max} LS mean ratios were below the protocol-defined clinically significant increase of 100% and the observed decreases were not considered clinically relevant.

2.1.4.2. Renal Impairment

D/C/F/TAF FDC

Studies were not performed with the D/C/F/TAF FDC. With regard to renal impairment, the marketing authorization is based on the development programs of the individual components or DRV/COBI and F/TAF FDCs, discussed in Section 3.3.5, with studies for the separate agents briefly presented below, and derived from their respective marketing authorizations.

DRV/COBI

Darunavir PK has not been evaluated in subjects with renal impairment.

Studies with COBI in subjects with renal impairment, supporting the marketing authorization for the D/C/F/TAF FDC, are described briefly below.

Study GS-US-216-0121 (NDA203094/Mod5.3.3.3/GS-US-216-0121_CSR) assessed renal function 1) in healthy subjects before, during and after COBI or rtv administration and 2) in subjects with mild to moderate renal impairment before, during and after COBI administration. Higher COBI exposure (mean AUC_{24h} ~43% higher) was observed in subjects with mild to moderate renal impairment compared with subjects with normal renal function. Significant decreases in estimated glomerular filtration rate (eGFR) were seen in all subjects at Day 7, but these were reversible. In contrast, actual glomerular filtration rate (GFR) (measured by the IV probe drug iohexol) was unchanged in all subjects.

Study GS-US-216-0124 (NDA203094/Mod5.3.3.3/GS-US-216-0124_CSR) assessed the PK of EVG and COBI in subjects with severe renal impairment (not on dialysis) compared with healthy subjects. No clinically relevant changes in EVG or COBI PK (LS mean ratio COBI C_{24h}, C_{max}, and AUC_{24h} 113%, 122%, and 125%, respectively) were observed in subjects with severe renal impairment compared with matched healthy control subjects with normal renal function. Decreases in eGFR were seen in all subjects at Day 7, were comparable between subjects with severe renal impairment and healthy subjects, and were reversible.

F/TAF

Studies with TAF or FTC, investigating the impact of renal impairment, and supporting the marketing authorization for the D/C/F/TAF FDC, are briefly described below.

Study FTC-107 (NDA021752/Mod5.3.3.3/FTC-107_CSR) was an open-label, parallel group study with up to 6 subjects in each of the 5 groups with varying degrees of renal impairment as determined by estimated $eGFR_{CG}$ values (>80 mL/min as normal function; 50 to 80 mL/min as mild impairment; 30 to 49 mL/min as moderate impairment; <30 mL/min as severe impairment; or functional anephric requiring hemodialysis).

This study showed that the percentage of the dose excreted as unchanged FTC in urine for subjects with normal renal function and those with mild renal impairment ($eGFR_{CG}$ 50 to 80 mL/min) was similar. The percentage of the dose excreted was also similar to that observed in previous studies with healthy subjects (NDA021752/Mod5.3.3.1/FTC-106_CSR) and HIV-1 infected subjects with normal renal function (NDA021752/Mod5.3.3.2/FTC-101_CSR). However, in subjects with moderate and severe renal impairment ($eGFR_{CG}$ <50 mL/min), the urinary recovery was lower (approximately 30% to 50% of the dose) over a 72-hour collection period, primarily due to slower excretion of FTC by the impaired kidneys.

Study GS-US-120-0108 (NDA208215/Mod5.3.3.3/GS-US-120-0108_CSR) evaluated the PK (TAF and TFV) and safety of single doses of TAF in subjects with severe renal impairment.

A 1.9-fold higher TAF systemic exposure (as assessed by AUC_{∞}) was observed in subjects with severe renal impairment relative to age- and sex-matched subjects with normal renal function (Table 4). Plasma TFV exposure was higher in subjects with severe renal impairment compared to that in subjects with normal renal function, but still within expected ranges (refer to Section 3.3.5). TAF was generally well tolerated in all subjects.

Table 4: Statistical Comparisons of TAF PK Parameter Estimates in Non–HIV-Infected Between Subjects With Severe Renal Impairment and Subjects With Normal Renal Function (Study GS-US-120-0108)

	Mean (%CV)		
TAF PK Parameter	Test Severe Renal Impairment (N=14)	Reference Normal Renal Function (N=13)	LS Mean Ratio % (90% CI)
AUC_{∞}, ng.h/mL	513.2 (47.3)	267.3 (49.2)	191.89 (137.81, 267.18)
AUC_{last}, ng.h/mL	510.6 (47.4)	265.9 (49.5)	192.26 (137.81, 268.21)
C_{max}, ng/mL	363.7 (65.7)	198.8 (62.1)	179.43 (123.73, 260.20)

Study GS-US-292-0112 (NDA207561/Mod5.3.5.2/GS-US-292-0112_CSR) is a Phase 3, open-label, multi-center, multiple-cohort study to evaluate the efficacy, safety, and tolerability of E/C/F/TAF in HIV-1 infected adult subjects with stable, mild to moderate renal impairment (subjects with eGFR CG 30 to 69 mL/min, inclusive). In this study, 248 subjects switched from their current treatment to E/C/F/TAF (see also Section 3.3.5).

2.1.5. Extrinsic Factor Pharmacokinetics

2.1.5.1. D/C/F/TAF FDC

The food effect for the D/C/F/TAF FDC was evaluated in study TMC114FD2HTX1002, and is described in Mod2.7.1/Sec2.1.1.1. The effect of food on drug absorption for the different components of the D/C/F/TAF FDC is further described in detail in Mod2.7.1/Sec3.2. The impact of different administration modes (splitting or crushing the D/C/F/TAF FDC tablet) was evaluated in study TMC114FD2HTX1004, and is described in Mod2.7.1/Sec2.1.1.3.

Drug-drug interaction studies were not performed with the D/C/F/TAF FDC. As the D/C/F/TAF FDC contains DRV, COBI, FTC, and TAF, interactions that have been identified with the individual components determine the interactions that may occur with the D/C/F/TAF FDC. An extensive evaluation of the recommendations for use with coadministered drugs, including an extensive package of drug-drug interaction studies, has been performed with the individual components for the respective DRV, DRV/COBI and F/TAF marketing authorizations as presented in the respective prescribing information for these products. The recommendations for the D/C/F/TAF FDC are based on the combination of recommendations for DRV/COBI and F/TAF, with a further evaluation of the appropriateness of each recommendation for the D/C/F/TAF combination.

The D/C/F/TAF FDC is intended as a complete treatment regimen and, therefore, drug interactions with other ARVs are not presented in the proposed prescribing information. A reference to these

studies is however included in this document, for a complete overview of the drug interaction profile of the D/C/F/TAF components.

The relevant drug-drug interaction studies from the respective DRV/COBI and F/TAF marketing authorizations are listed in Section 2.1.5.2 and Section 2.1.5.3. The individual study data are not described in detail, as these have been previously assessed. An overall evaluation of drug-drug interactions, both between the components of the D/C/F/TAF FDC as well as with other agents, is further discussed in Section 3.4.2.

2.1.5.2. DRV/COBI

Table 5 lists an overview of drug-drug interaction studies that have been previously presented for the marketing authorization for DRV/COBI (PREZCOBIX/REZOLSTA) and that are also considered pertinent to this D/C/F/TAF FDC marketing authorization.

In addition to the drug interaction studies presented here, the drug interaction between DRV/COBI and F/TDF was evaluated in study GS-US-299-0101 (Panel 2), discussed in Mod2.7.1/Sec2.1.1.2.

Table 5: Overview Drug-Drug Interaction Studies for DRV (boosted with rtv or COBI)

Study	Component of D/C/F/TAF	Coadministered drug	Prior NDA
HIV Antiretrovirals			
TMC114-C123	DRV/rtv 600/100 mg bid	didanosine 400 mg qd	NDA021976/Mod5.3.3.4
TMC114-C124	DRV/rtv 300/100 mg bid	tenofovir disoproxil fumarate 300 mg qd	NDA021976/Mod5.3.3.4
TMC114-C111	DRV/rtv 300/100 mg bid	efavirenz 600 mg qd	NDA021976/Mod5.3.3.4
TMC114-C119*	DRV/rtv 300/100 mg bid or 400/100 bid	nevirapine 200 mg bid	NDA021976/Mod5.3.3.4
TMC125-C176	DRV/rtv 600/100 mg bid	etravirine 100 mg bid or 200 mg bid	NDA021976/Mod5.3.3.4
TMC278-C112	DRV/rtv 800/100 qd	rilpivirine 150 mg qd	NDA021976/Mod5.3.3.4
TMC114-A4001052	DRV/rtv 600/100 mg bid	maraviroc 150 mg bid	-[24]
GS-US-216-0112	COBI 150 mg qd	efavirenz 600 mg single dose	NDA203094/Mod5.3.3.4
GS-US-201-0104	COBI 150 mg qd or DRV+COBI 800+150 mg qd	elvitegravir 150 mg qd	NDA203094/Mod5.3.3.4
GS-US-216-0123	COBI 150 mg qd[b]	atazanavir 300 mg qd	NDA203094/Mod5.3.3.4
Other (non-antiretroviral) drugs			
TMC114-C122	DRV/rtv 400/100 mg bid	ranitidine 150 mg bid omeprazole 20 mg qd	NDA021976/Mod5.3.3.4
TMC114-C150	DRV/rtv 600/100 mg bid	digoxin 0.4 mg single dose	NDA021976/Mod5.3.3.4
TMC114-C142	DRV/rtv 400/100 mg bid	clarithromycin 500 mg bid	NDA021976/Mod5.3.3.4
TMC114-C172	DRV/rtv 600/100 mg bid	carbamazepine 200 mg bid	NDA021976/Mod5.3.3.4
TMC114-C121	DRV/rtv 400/100 mg bid	paroxetine 20 mg qd sertraline 50 mg qd	NDA021976/Mod5.3.3.4
TMC114-C129	DRV 400 mg bid or DRV/rtv 400/100 mg bid	ketoconazole 200 mg bid	NDA021976/Mod5.3.3.4
TMC125VIR1001	DRV/rtv 600/100 mg bid	artemether/lumefantrine 80/480 mg (6 doses at 0, 8, 24, 36, 48, and 60 hours)	NDA021976/Mod5.3.3.4
TMC114-C107	DRV/rtv 400/100 mg bid	rifabutin 150 mg qd (compared to rifabutin 300 mg qd alone)	NDA021976/Mod5.3.3.4
TMC114-C163	DRV/rtv 600/100 mg bid	rifabutin 150 mg qod (compared to rifabutin 300 mg qd alone)	NDA021976/Mod5.3.3.4
TMC114-C131	DRV/rtv 600/100 mg bid	ethinyl estradiol/norethindrone 35 µg/1 mg qd	NDA021976/Mod5.3.3.4

Study	Component of D/C/F/TAF	Coadministered drug	Prior NDA
VX950-C124	DRV/rtv 600/100 mg bid	telaprevir 750 mg q8h	-[41]
TMC114-C133	DRV/rtv 300/100 mg bid	atorvastatin 10 mg qd (compared to 40 mg qd administered alone)	NDA021976/Mod5.3.3.4
TMC114-C120	DRV/rtv 600/100 mg bid	pravastatin 40 mg single dose	NDA021976/Mod5.3.3.4
TMC114-C171	DRV/rtv 600/100 mg bid	buprenorphine/naloxone maintenance therapy (maximum 24/6 mg qd)	NDA021976/Mod5.3.3.4
TMC114-C127	DRV/rtv 600/100 mg bid	methadone (maintenance therapy: 55 to 150 mg qd)	NDA021976/Mod5.3.3.4
TMC114-C128	DRV/rtv 400/100 mg bid	sildenafil 25 mg single dose	NDA021976/Mod5.3.3.4
GS-US-216-0112	COBI 150 mg qd	desipramine 50 mg single dose digoxin 0.5 mg single dose	NDA203094/Mod5.3.3.4
GS-US-216-0120	COBI 150 mg qd[a]	famotidine 40 mg qd (12 h after COBI) omeprazole 20 mg qd	NDA203094/Mod5.3.3.4
GS-US-216-0122	COBI 150 mg qd[a]	famotidine 40 mg qd (at same time as COBI)	NDA203094/Mod5.3.3.4
GS-US-216-0123	COBI 150 mg qd[a]	rosuvastatin 10 mg single dose rifabutin 150 mg qod (compared to rifabutin 300 mg qd alone)	NDA203094/Mod5.3.3.4
GS-US-236-0106	COBI 150 mg qd[c]	ethinyl estradiol 0.025 mg/ norgestimate 0.180/0.215/0.250 mg qd	NDA203094/Mod5.3.3.4

bid=twice daily; COBI=cobicistat; DRV=darunavir; EVG= elvitegravir; q8h=every 8 hours; q12h=every 12 hours; qd=once daily; qod=every other day; rtv=ritonavir.
* Study performed in HIV-1 infected subjects
[a] Coadministered with EVG 150 mg qd
[b] Coadministered with EVG 85 mg qd
[c] Admistered as E/C/F/TDF 150/150/200/300 mg qd

2.1.5.3. FTC/TAF

Table 6 lists an overview of drug-drug interaction studies that have been previously presented for the marketing authorization for FTC/TAF (Descovy) and that are also considered pertinent to this D/C/F/TAF FDC marketing authorization.

Table 6: Overview Drug-Drug Interaction Studies for TAF

Study	Component of D/C/F/TAF	Coadministered drug	Prior NDA
HIV Antiretrovirals			
GS-US-311-0101	F/TAF 200/40 mg qd F/TAF 200/25 mg qd TAF 8 mg single dose	efavirenz 600 mg qd DRV/COBI 800/150 mg qd COBI 150 mg qd	NDA208215/Mod5.3.3.4
GS-US-120-0117	TAF 25 mg single dose	rilpivirine 25 mg single dose	NDA208215/Mod5.3.3.4
GS-US-120-1554	TAF 25 mg qd	rilpivirine 25 mg qd	NDA208215/Mod5.3.3.4
GS-US-120-0118	F/TAF 200/10 mg single dose	ATV/rtv 300/100 mg qd DRV/rtv 800/100 mg dq LPV/rtv 200/50 mg qd DTG 50 qd	NDA208215/Mod5.3.3.4
Other (non-antiretroviral) drugs			
GS-US-120-1538	TAF 25 mg qd	Midazolam 1 mg (IV) or 2.5 mg (oral) single dose	NDA208215/Mod5.3.3.4
GS-US-292-1316	C/F/TAF 150/200/10 mg[a] single dose	sertraline 50 mg single dose	NDA207561/Mod5.3.3.4

ATV=atazanavir; COBI=cobicistat; GDT=dolutegravir; DRV=darunavir; F=emtricitabine; LPV=lopinavir; qd=once daily; TAF= tenofovir alafenamide.
[a] Administered as E/C/F/TAF 150/150/200/10 mg

2.2. Human Pharmacodynamic Studies

2.2.1. Healthy Subject Pharmacodynamics and Pharmacokinetics/Pharmacodynamics

There were no studies with pharmacodynamic measures in healthy subjects with the D/C/F/TAF FDC. Apart from the thorough QT studies with individual agents, such studies are also not applicable for DRV/COBI or F/TAF.

2.2.1.1. Thorough QT Studies

D/C/F/TAF FDC

Studies not performed with the D/C/F/TAF FDC. With regard to the effect on QT prolongation, information in the D/C/F/TAF FDC marketing authorization is based on the thorough QT studies performed in the development programs of the individual components DRV, COBI and F/TAF, further discussed in Section 3.5.2 and individual studies presented briefly below.

DRV/COBI

Thorough QT studies with DRV or COBI as single components, supporting the marketing authorization for the D/C/F/TAF FDC, are described briefly below.

Study TMC114-C153 (NDA021976/Mod5.3.4.1/TMC114-C153_CSR) assessed the PK and cardiac safety of DRV coadminstered with rtv (DRV/rtv 1600/100 mg once daily, DRV/rtv 800/100 mg twice daily), with particular attention to the QT/ QT interval corrected by Fridericia's formula (QTcF) interval, in healthy subjects (including also positive control moxifloxacin and placebo). The PK for the different components was as anticipated. There was no clinically relevant prolongation of the QTc interval by DRV/rtv (see also Section 3.5.2.2.1).

Study GS-US-216-0107 (NDA203094/Mod5.3.4.1/GS-US-216-0107_CSR) assessed the effects of COBI (250 mg, 400 mg) on time-matched, baseline-adjusted, placebo-corrected QTcF in healthy subjects (including also positive control moxifloxacin). The COBI PK was as anticipated. There was no clinically relevant prolongation of QTcF interval at therapeutic and supratherapeutic COBI doses (see also Section 3.5.2.2.1).

F/TAF

Study GS-US-120-0107 (NDA208215/Mod5.3.4.1/GS-US-120-0107_CSR) was a thorough QT study with single component TAF, and supports the marketing authorization for the D/C/F/TAF FDC. This study evaluated the safety and effect of therapeutic (25 mg) and supratherapeutic (125 mg) doses of TAF (and TFV) on baseline-adjusted, placebo-corrected QTcF, QTcB and QTcN and determined the PK of TAF and TFV and their effect on ECG, in healthy subjects (including moxofloxacin as positive control). No TAF-treated subject experienced an absolute QTc interval >500 msec, or change from predose baseline QTc >60 msec with any correction factor at any TAF dose. The TAF exposures were

approximately dose-proportional and there were no meaningful relationships between QTcF and TAF or TFV plasma concentrations. TAF and TFV were well tolerated.

2.2.2. Patient Pharmacodynamics and Pharmacokinetics/Pharmacodynamics – D/C/F/TAF

2.2.2.1. A Phase 2, Randomized, Double-Blind Study of the Safety and Efficacy of the D/C/F/TAF Single Tablet Regimen Versus Cobicistat-boosted Darunavir plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults (Study GS-US-299-0102)

Mod5.3.5.1/GS-US-299-0102_CSR

2.2.2.1.1. Objectives

To evaluate the safety and efficacy of a D/C/F/TAF FDC versus COBI-boosted DRV (DRV plus COBI) plus F/TDF (Truvada) in HIV-1 infected ART-naïve adult subjects. The PK of the components was also assessed.

2.2.2.1.2. Subjects and Methods

This was a Phase 2, randomized, double-blind, multicenter, active-controlled study. Subjects were randomized 2:1 (D/C/F/TAF FDC: DRV plus COBI plus F/TDF):

- Treatment Group 1: D/C/F/TAF FDC 800/150/200/10 mg tablet plus matching placebos for individual drugs, once daily for 48 weeks.
- Treatment Group 2: DRV 800 mg (400 mg tablet x 2) plus COBI 150 mg tablet plus FDC FTC 200 mg/TDF 300mg plus matching placebo for the D/C/F/TAF FDC, once daily for 48 weeks.

The study population comprised 153 subjects (103 in the D/C/F/TAF FDC group and 50 in the DRV plus COBI plus F/TDF group). Of the 153 subjects, 142 (92.8%) were male; 92 (60.1%) were white and 53 (34.6%) were black; and the mean age was 35 years (range: 18 to 68 years). Demographic and baseline disease characteristics were similar between the 2 treatment groups.

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.

At 48 weeks, a similar percentage of subjects in the D/C/F/TAF FDC group compared with the DRV plus COBI plus F/TDF group had prematurely discontinued study drug (18.4% [19 subjects] versus 16.0% [8 subjects]).

2.2.2.1.3. Results

2.2.2.1.3.1. Pharmacokinetics

The mean (SD) plasma concentration-time profile of DRV, COBI, FTC and TAF at steady-state following administration of the D/C/F/TAF FDC in treatment-naïve HIV-1 infected subjects are shown in Figure 1, Figure 2, Figure 3 and Figure 4, respectively.

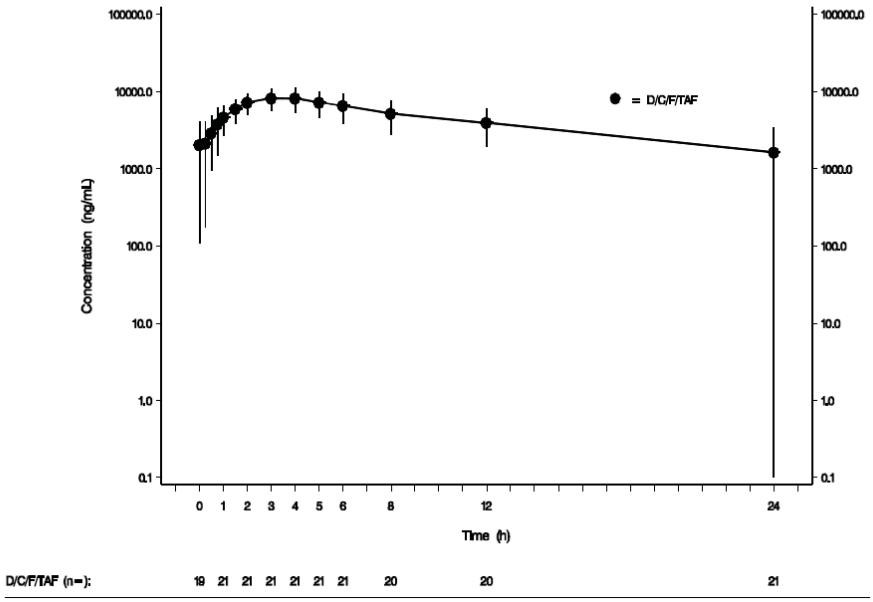
The DRV, COBI, and FTC plasma exposures were consistent with historical data (Table 7).

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; Table 7) was consistent with historical data for subjects receiving the D/C/F/TAF FDC or TAF 25 mg single agent in the proof-of-concept study (mean AUC_{last} 115.2 ng.h/mL, Table 30).

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 TFV AUC from time of administration up to the end of the dosing interval (AUC_{tau}, 339.0 [37.1] ng.h/mL) versus administration of DRV plus COBI plus F/TDF (3737.0 [26.8] ng.h/mL) (Table 8).

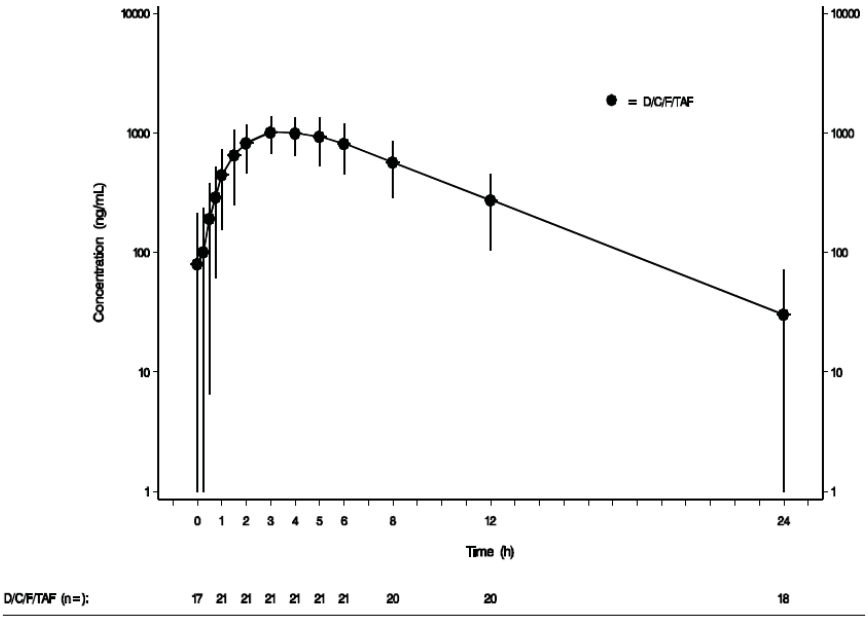
The PBMC intracellular TFV-DP AUC_{tau} was markedly higher in the D/C/F/TAF FDC group than in the DRV plus COBI plus F/TDF group. The TFV-DP AUC_{tau} LS Mean ratio (TAF vs TDF) of 652.09% (Table 9) was consistent with the approximate 5- to 7-fold increase in TFV-DP exposure observed following administration of TAF 25 mg versus TDF 300 mg (GS-US-120-0104; see Section 2.2.3.2).

Figure 1: Mean Plasma Concentration-time Curves of DRV (including SD bars) After a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (PK Substudy, GS-US-299-0102)



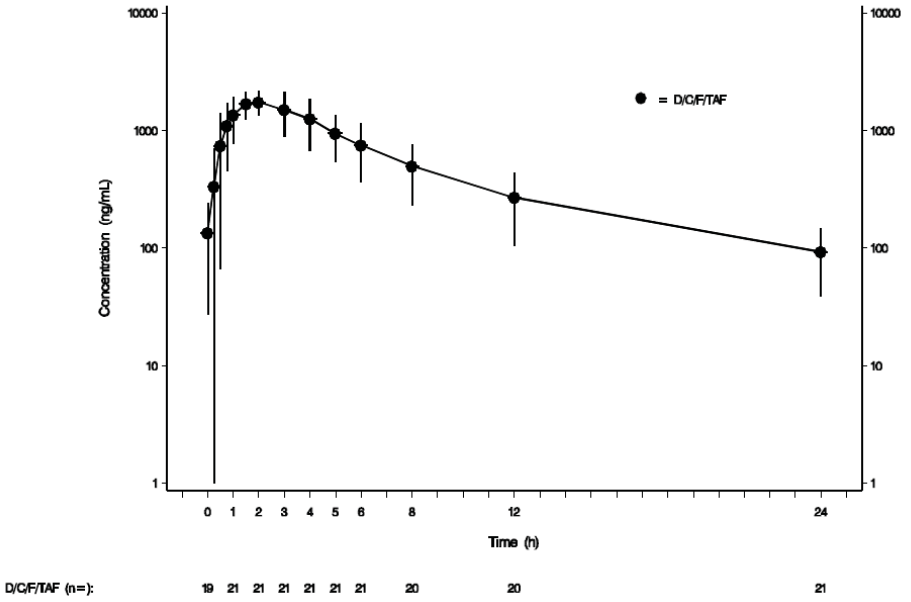
Source: Mod5.3.5.1/GS-US-299-0102_CSR/Fig 18.1

Figure 2: Mean Plasma Concentration-time Curves of COBI (including SD bars) After a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (PK Substudy, GS-US-299-0102)



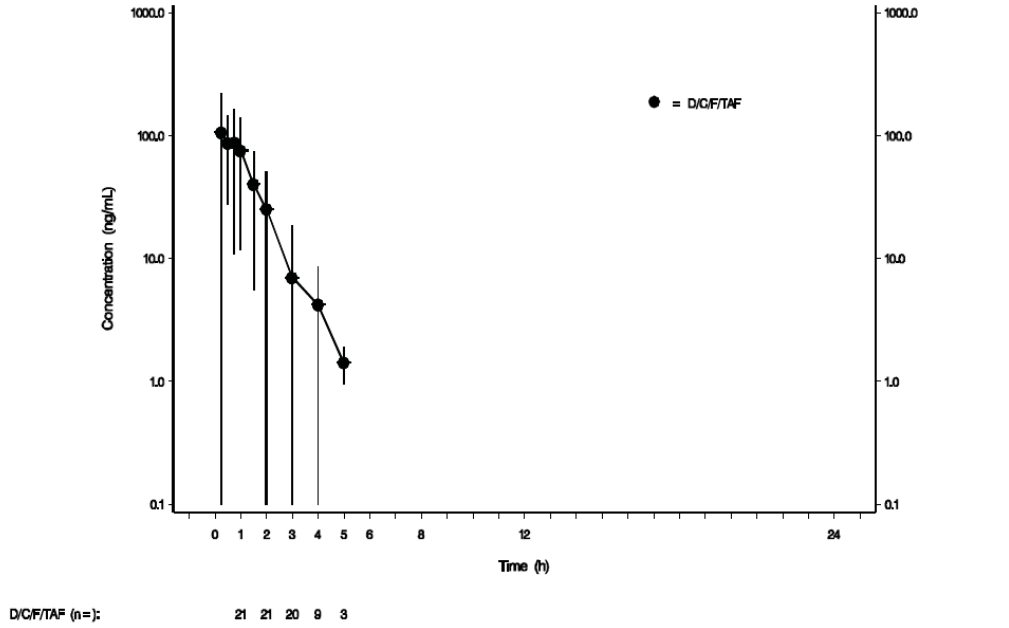
Source: Mod5.3.5.1/GS-US-299-0102_CSR/Fig 18.2

Figure 3: Mean Plasma Concentration-time Curves of FTC (including SD bars) After a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (PK Substudy, GS-US-299-0102)



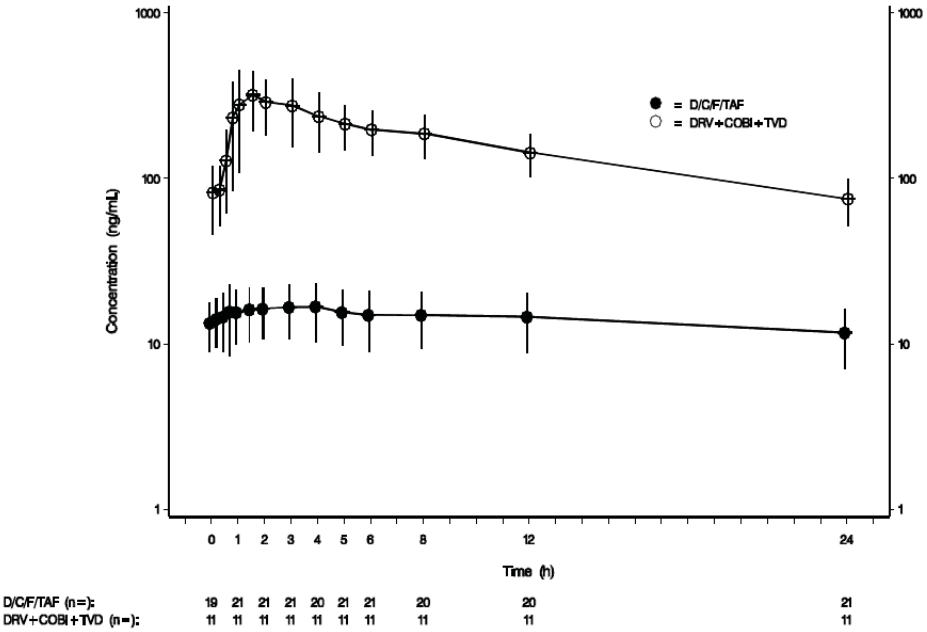
Source: Mod5.3.5.1/GS-US-299-0102_CSR/Fig18.3

Figure 4: Mean Plasma Concentration-time Curves of TAF (including SD bars) After a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (PK Substudy, GS-US-299-0102)



Source: Mod5.3.5.1/GS-US-299-0102_CSR/Fig18.3

Figure 5: Mean Plasma Concentration-time Curves of TFV(including SD bars) After a Single Oral Dose of D/C/F/TAF 800/150/200/10 mg as 1 x FDC Tablet (PK Substudy, GS-US-299-0102)



Source: Mod5.3.5.1/GS-US-299-0102_CSR/Fig18.5

Table 7: Pharmacokinetic Parameters of DRV, COBI, TAF and FTC (PK Substudy Analysis Set; D/C/F/TAF treatment arm; GS-US-299-0102)

Parameter	Mean (SD); t_{max}, $t_{1/2}$: Median (Range)			
	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)

AUC_{last}=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; AUC_{tau}=AUC from time of administration up to the end of the dosing interval; CI=confidence interval; C_{max}=maximum observed analyte concentration; C_{tau}=plasma concentration at the end of the dosing interval; N=number of subjects; SD=standard deviation; $t_{1/2}$=apparent elimination half-life; t_{max}=actual sampling time to reach the maximum observed analyte concentration.
Source: Mod5.3.5.1/GS-US-299-0102_CSR/Tab55.1, Tab55.2, Tab55.3, 55.4

Table 8: Statistical Comparisons of TFV Pharmacokinetic Parameter Estimates Between Test and Reference Treatments (All Substudy PK Analysis Set; 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)

AUC_{tau}=AUC from time of administration up to the end of the dosing interval; CI=confidence interval; C_{max}=maximum observed analyte concentration; C_{tau}=plasma concentration at the end of the dosing interval; COBI=cobicistat; DRV=darunavir; LS=least square; N=number of subjects SD=standard deviation; vs=versus
Source: Mod5.3.5.1/GS-US-299-0102_CSR/Tab10-2 and Tab10-3

Table 9: Statistical Comparisons of AUC_{tau} Between Test and Reference Treatments (All Substudy PK Analysis Set; GS-US-299-0102)

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

AUC: area under the plasma concentration-time curve; LS: least square
Source: Mod5.3.5.1/GS-US-299-0102/Sec15.1/Tab56.

Population Pharmacokinetics

TAF AUCs from Study GS-US-299-0102 were estimated using a TAF population PK model developed by GSI; TAF exposures were estimable for 52 subjects in Study GS-US-299-0102. The mean (SD, %CV, range) TAF AUC_{tau} was 101.7 ng.h/mL (50.52, 49.8, 38.3 to 295.6) (Mod5.3.5.1/GS-US-299-0102_CSR).

The PK for the different components in the D/C/F/TAF FDC in study GS-US-299-0102 is further compared with that from historical data in Section 3.2.1.3.

2.2.2.1.3.2. Efficacy

Virologic outcomes at Week 24 were similar between the 2 treatment groups for the primary endpoint analysis for the full analysis set (FAS). Virologic success rates were as follows: D/C/F/TAF 74.8%, DRV+COBI+F/TDF 74.0%; difference (95% CI) in percentages: 3.3% (-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 versus DRV+COBI+F/TDF) was greater than the prespecified –12% noninferiority margin, D/C/F/TAF was determined to be noninferior to DRV + COBI + F/TDF. Virologic success rates for the Week 24 per protocol (PP) Analysis Set (defined as the FAS minus subjects with major protocol violations) were similar between the 2 treatment groups, as follows: D/C/F/TAF 84.6%, 77 of 91 subjects, DRV+COBI+F/TDF 78.7%, 37 of 47 subjects. The difference (95% CI) in percentages was 8.3% (-5.3% to 22%).

The rates of virologic success through Week 48 when assessed using the Food and Drug Administration (FDA)-defined snapshot algorithm (HIV-1 RNA <50 copies/mL) using the FAS were:

D/C/F/TAF 76.7%, DRV + COBI + F/TDF 84.0%; difference (95% CI) in percentages: -6.2% (-19.9% to 7.4%). The difference in rates of virologic success between treatment arms was primarily due to a difference in the numbers of subjects who discontinued study drug due to other reasons and had the last available HIV-1 RNA ≥50 copies/mL (D/C/F/TAF: 8.7%, 9 subjects; DRV + COBI + F/TDF: 4.0%, 2 subjects). The percentage of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups (D/C/F/TAF 15.5%, %, DRV + COBI + F/TDF 12.0%). Virologic success rates for the Week 48 PP Analysis Set (defined as the FAS minus subjects with major protocol violations) were however similar between the 2 treatment groups, as follows: D/C/F/TAF 92.9%, 79 of 85 subjects, DRV+COBI+F/TDF 91.3%, 42 of 46 subjects. Further details on the efficacy in study GS-US-299-0102 are described in Mod2.7.3/Sec3.1.2.

2.2.2.1.3.3. Safety

The D/C/F/TAF FDC and DRV+COBI+F/TDF were generally well tolerated, low percentages of subjects had SAEs or discontinued study drug due to AEs in both groups.

Further details on the safety in study GS-US-299-0102 are described in Mod2.7.4/Sec3.1.1.3.

2.2.2.1.4. Conclusion (Pharmacokinetics)

The pharmacokinetics of the components of the D/C/F/TAF FDC were in line with those in previous studies. Subjects who received the D/C/F/TAF FDC had intracellular TFV-DP concentrations 6.5-fold higher than subjects who received DRV+COBI+F/TDF. Conversely, subjects who received the D/C/F/TAF FDC had circulating plasma TFV levels 91% lower than those who received DRV+COBI+F/TDF. There were no PK/PD analyses in this study.

2.2.2.2. A Phase 3, Randomized, Active-controlled, Double-blind Study to Evaluate Efficacy and Safety of D/C/F/TAF Once daily FDC Regimen Versus a Regimen Consisting of DRV/COBI FDC Coadministered With FTC/TDF FDC in Antiretroviral Treatment-naïve HIV-1 Infected Subjects (Study TMC114FD2HTX3001)

Mod5.3.5.1/TMC114FD2HTX3001_CSR

2.2.2.2.1. Objectives

To evaluate the efficacy and safety of a D/C/F/TAF FDC versus COBI-boosted DRV (DRV/COBI FDC, PREZCOBIX) plus F/TDF (Truvada) in HIV-1 infected ART-naïve adult subjects. The PK of DRV, COBI and TAF were also assessed.

2.2.2.2.2. Subjects and Methods

This is a randomized, active-controlled, double-blind, multicenter, Phase 3 study. The primary endpoint was at Week 48. Subjects were randomized 1:1 (D/C/F/TAF FDC: DRV/COBI plus F/TDF):

- Treatment Group 1: D/C/F/TAF 800/150/200/10 mg FDC tablet once daily (D/C/F/TAF group).

- Treatment Group 2: DRV/COBI 800/150 mg FDC tablet plus F/TDF 200/300 mg FDC tablet once daily (control group).

The study population comprised 725 subjects (362 subjects in the D/C/F/TAF group and 363 subjects in the control group). Of the 725 subjects, 640 (88.3%) were male; 600 (83.2%) were white and 80 (11.1%) were black; and the mean age was 35 years (range: 18 to 71 years). Demographic and baseline disease characteristics were similar between the 2 treatment groups.

Sparse pharmacokinetic sampling was performed for all subjects (only samples from subjects randomized to the D/C/F/TAF group were analysed) to evaluate the pharmacokinetics of DRV and TAF. Also, plasma concentrations of COBI were measured as this is done in a single bioanalytical assay with DRV. The plasma concentrations of FTC and TFV were not evaluated.

Pharmacokinetic parameters of DRV (AUC_{24h}, C_{0h}) and TAF ($AUC_{tau,}$ C_{2h}) were derived using population pharmacokinetic modeling. In addition, observed DRV and COBI plasma concentrations (taken within 20 to 28 hours after the last dose of D/C/F/TAF) were summarized with descriptive statistics.

At Week 48 week, a similar percentage of subjects in the D/C/F/TAF group compared with the control group had prematurely discontinued study drug (6.4% [23 subjects] versus 7.7% [28 subjects]).

2.2.2.2.3. Results

2.2.2.2.3.1. Pharmacokinetics

DRV/COBI

The population PK analysis of DRV in study TMC114FD2HTX3001 is described in a separate report (Mod5.3.3.5/DCFTAF Phase 3-DRV PopPK-report) and is summarized in Section 2.2.2.4.1.

The DRV PK parameters in the D/C/F/TAF arm of study TMC114FD2HTX3001 are summarized in Table 10. These results are in line with data from other D/C/F/TAF studies and historical studies with DRV/COBI, as discussed in Section 3.2.2.1.

Table 10: Population PK Parameter Estimates for DRV Following Multiple-Dose Administration of the D/C/F/TAF FDC 800/150/200/10 mg Once Daily in HIV-1 Infected Subjects (Study TMC114FD2HTX3001, D/C/F/TAF arm)

Parameter	Mean (SD); Median (Range)
N	355
C_{0h}, ng/mL	1899 (759)
	1783 (418 - 5895)
AUC_{24h}, ng.h/mL	87909 (20232)
	84248 (40697 - 188760)

N=maximum number of subjects with data.
Source: Module 5.3.5.1/TMC114FD2HTX3001-CSR/Att-TPK03_EXT

Subjects were instructed to take their ARV medication in the morning, to facilitate the PK sampling for TAF, which is a prodrug with a very short elimination half-life. As such, pharmacokinetic samples were taken mostly within ~4 hours after a D/C/F/TAF dose. Consequently, there were only very few subjects with pharmacokinetic samples taken within 20-28 hours after the previous D/C/F/TAF dose. Therefore, the summary of observed predose plasma concentrations for DRV and COBI should be interpreted with caution (Module 5.3.5.1/TMC114FD2HTX3001-CSR/Att-TPK01_EXT).

There were no relevant differences in the DRV pharmacokinetics between visits over time (Module 5.3.3.5/DCFTAF Phase 3-DRV PopPK-report).

There were no significant differences in the DRV PK parameters between the different subgroups (age category, eGFR category, treatment adherence) (Module 5.3.5.1/TMC114FD2HTX3001-CSR/Sec7).

TAF

The population PK analysis of TAF in study TMC114FD2HTX3001 is described in a separate report (Mod5.3.3.5/TMC114FD2HTX3001-TAF PopPK-report) and is summarized in Section 2.2.2.4.2.

The TAF PK parameters in the D/C/F/TAF arm of study TMC114FD2HTX3001 are summarized in Table 11. These results are in line with data from historical studies with TAF, as discussed in Section 3.2.2.3.

Table 11: Population PK Parameter Estimates for TAF Following Multiple-Dose Administration of the D/C/F/TAF FDC 800/150/200/10 mg Once Daily in HIV-1 Infected Subjects (Study TMC114FD2HTX3001, D/C/F/TAF arm)

Parameter	Mean (SD); Median (Range)
N	355
C_{2h}, ng/mL	12.0 (11.9)
	7.91 (0.08 – 73.0)
AUC_{tau}, ng.h/mL	132 (41)
	124 (71 - 400)

N=maximum number of subjects with data.
Source: Module 5.3.5.1/TMC114FD2HTX3001-CSR/Att-TPK04_EXT

There were no relevant differences in the TAF pharmacokinetics between visits over time (Mod5.3.3.5/TMC114FD2HTX3001-TAF PopPK-report).

There were no significant differences in the TAF PK parameters between the different subgroups (age category, eGFR category, treatment adherence) (Mod5.3.5.1/TMC114FD2HTX3001-CSR/Sec7).

2.2.2.2.3.2. Efficacy

An extensive evaluation of the efficacy in study TMC114FD2HTX3001 is described in the clinical study report (Mod5.3.5.1/TMC114FD2HTX3001-CSR/Sec5) and in Mod2.7.3/Sec3.1.1.

In both treatment groups, comparable virologic response rates (FDA Snapshot approach) at Week 48 were observed in the ITT analysis set: 91.4% vs 88.4% in the D/C/F/TAF and control group, respectively. D/C/F/TAF was noninferior compared to the control treatment with a difference between the treatment groups of 2.7% (95% CI: -1.6; 7.1).

The results for virologic response were consistent across the sensitivity analyses and the subgroups analyses (by baseline disease and demographic characteristics) and were consistent with the immunologic response.

There was no development of resistance to DRV or TAF (no DRV, primary PI or NRTI RAMs). Only one subject in the D/C/F/TAF group developed a M184I/V mutation conferring FTC resistance.

2.2.2.2.3.3. Safety

An extensive evaluation of the safety in study TMC114FD2HTX3001 is described in the clinical study report (Mod5.3.5.1/TMC114FD2HTX3001-CSR/Sec6) and in Mod2.7.4/Sec3.1.1.1.

Based on AEs and other safety assessments, no safety concerns were identified.

Rash occurred in a similar proportion of subjects in each treatment group and led to early discontinuation of treatment in, respectively, 1.7% and 1.4% of subjects. No severe skin reactions occurred in the D/C/F/TAF group; in the control group, 0.8% of subjects experienced a severe skin reaction which led to treatment discontinuation.

Due to the absence of lipid-protective effect of a TDF-based regimen compared to a TAF-based regimen, lipids increased at Week 48 vs baseline in the D/C/F/TAF group, but these were not reflected in clinically relevant changes in the TC/HDL ratio. Lipid-lowering treatment was initiated by 1.7% vs 0.6% subjects during the treatment phase.

At Week 48, the subjects showed a better renal and bone safety profile when using a TAF-based regimen compared to a TDF-based regimen. In the D/C/F/TAF group versus control, there were:

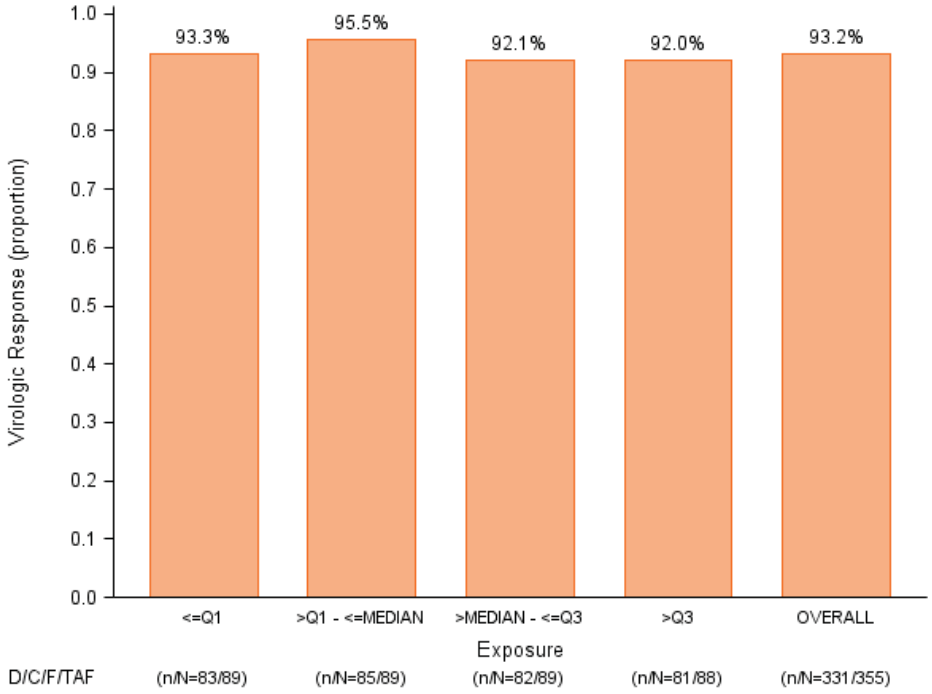
- Greater increases in $eGFR_{cyst}$, a lower incidence of proteinuria, and a lower incidence of increases in markers of potential proximal renal tubulopathy.
- Stable hip and spine bone mineral density compared to decreases in the control group.

2.2.2.2.3.4. Pharmacokinetic/Pharmacodynamic Relationships

Efficacy

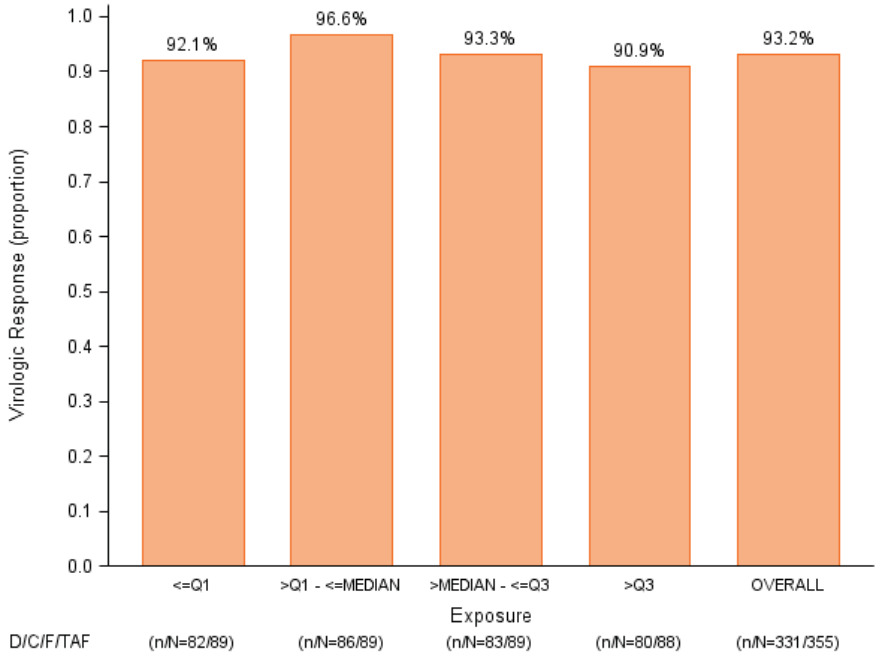
There were no apparent relationships (graphically, and via logistic regression) between the pharmacokinetics of DRV or TAF and efficacy (both overall, and when excluding subjects that discontinued prematurely for non-efficacy reasons. The virologic response (<50 copies/mL; FDA snapshot approach, Week 48) was similar across quartiles of DRV (AUC_{24h} or C_{0h}) or TAF (AUC_{tau}) exposure (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7).

Figure 6: Bar Chart of the Proportion of Virologic Response (<50 Copies/mL) According to FDA Snapshot Approach at Week 48, overall and by DRV AUC_{24h} quartiles (Study TMC114FD2HTX3001)



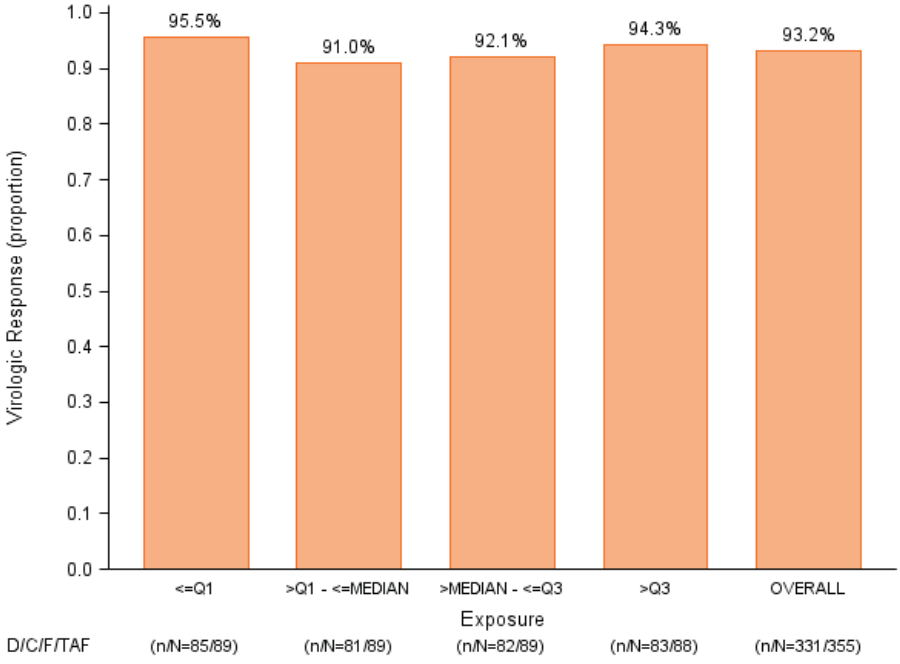
DRV AUC_{24h} (h*ng/mL): Q1=74086; median=84248; Q3=98877
Source: Module 5.3.5.1/TMC114FD2HTX3001-CSR/Fig19

Figure 7: Bar Chart of the Proportion of Virologic Response (<50 Copies/mL) According to FDA Snapshot Approach at Week 48, overall and by DRV C_{0h} quartiles (Study TMC114FD2HTX3001)



DRV C_{0h} (h*ng/mL): Q1=1363; median=1783; Q3=2274
Source: Module 5.3.5.1/TMC114FD2HTX3001-CSR/Fig19

Figure 8: Bar Chart of the Proportion of Virologic Response (<50 Copies/mL) According to FDA Snapshot Approach at Week 48, overall and by TAF AUC_{tau} quartiles (Study TMC114FD2HTX3001)



TAF AUC_{tau} (h*ng/mL): Q1=103.02; median=123.85; Q3=148.52
Source: Module 5.3.5.1/TMC114FD2HTX3001-CSR/Fig20

Safety

There were no apparent clinically relevant relationships (graphically) between DRV (AUC_{24h}) or TAF pharmacokinetics (AUC_{tau}) and the occurrence of AEOIs (bone, cardiac conduction, convulsions, coronary artery, lipids, lipodystrophy, liver, ocular, pancreas, rash, renal, skin), or graded laboratory abnormalities or changes in the selected laboratory parameters of interest (amylase, ALT/AST, alkaline phosphatase, total bilirubin, cholesterol, LDL, triglycerides, glucose, creatinine, eGFR laboratory parameters, urine albumin to creatinin ratio, urine protein to creatinin ratio). For some of the parameters, the number of subjects was very low, and the analyses should be interpreted with caution (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7).

Note the following:

- There were only 2 subjects with convulsion AEOIs (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.11.4).
  - One subject had a DRV AUC_{24h} (median AUC_{24h} across visits 91,882 ng.h/mL) around the mean value across subjects (mean AUC_{24h} 87,909 ng.h/mL, range: 40,697; 188,760 ng.h/mL). The other subject had almost the highest DRV AUC_{24h} (median AUC_{24h} across visits 180,510 ng.h/mL, and AUC_{24h} at Week 24 for this subject, around the time of the AE 272,200 ng.h/mL).
  - One subject had a TAF AUC_{tau} (194 ng.h/mL) which is above the mean value across subjects but not at the high end of the range (mean 132 ng.h/mL, range 71; 400 ng.h/mL). The other subject had a TAF AUC_{tau} above the mean value across subjects but not at high end of the range (median AUC_{tau} across visits 212 ng.h/mL, and AUC_{tau} at Week 24 for this subject, around the time of the AE 286 ng.h/mL).

  There were no concomitant medications reported that would be expected to increase the DRV or TAF exposure. Based on these 2 cases, no conclusions can be drawn on the relationship between DRV or TAF exposure and convulsion AEOIs.
- The median DRV AUC_{24h} was higher in the small subgroup of subjects with a laboratory abnormality in UACR (≥30mg/g; n=28) or in UPCR (≥200mg/g; n=23) compared to the median AUC_{24h} in subjects without such laboratory abnormalities, but the AUC_{24h} ranges largely overlapped. For the TAF AUC_{tau}, such a difference was less pronounced. These findings were not clinically relevant (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7).

2.2.2.2.4. Conclusion (Pharmacokinetics, Pharmacokinetic/Pharmacodynamic)

The DRV pharmacokinetics were in line with those in other studies with COBI-boosted DRV (see also Section 3.2.2.1). The TAF pharmacokinetics were in line with those in previous studies with TAF (see also Section 3.2.2.3). There were no relevant differences in DRV or TAF pharmacokinetics between subgroups.

There were no apparent relationships between the DRV or TAF pharmacokinetics and virologic response.

There were no apparent relationships between the pharmacokinetics of DRV or TAF and safety parameters of interest.

2.2.2.3. A Phase 3, Randomized, Active-controlled, Open-label Study to Evaluate Efficacy, Safety and Tolerability of Switching to a D/C/F/TAF Once Daily Single-tablet Regimen Versus Continuing the Current Regimen Consisting of a Boosted PI Combined With FTC/TDF in Virologically Suppressed HIV-1 Infected Subjects (Study TMC114IFD3013)

Mod5.3.5.1/TMC114IFD3013_CSR

2.2.2.3.1. Objectives

To evaluate the efficacy and safety of switching to a D/C/F/TAF FDC relative to continuing the current boosted PI plus F/TDF in virologically suppressed HIV-1 infected adult subjects. The PK of DRV and COBI were also assessed.

2.2.2.3.2. Subjects and Methods

This is a randomized, active-controlled, open-label, multicenter, Phase 3 study. The primary endpoint was at Week 48. Subjects were randomized 2:1 (D/C/F/TAF FDC: boosted PI plus F/TDF):

- Treatment Group 1: D/C/F/TAF 800/150/200/10 mg FDC tablet once daily (D/C/F/TAF group).
- Treatment Group 2: continue current boosted PI combined with F/TDF (control group).

The study population comprised 1141 subjects (763 subjects in the D/C/F/TAF group and 378 subjects in the control group). Of the 1141 subjects, 936 (82.0%) were male; 855 (75.5%) were white and 237 (20.9%) were black; and the mean age was 45 years (range: 19 to 78 years). Demographic and baseline disease characteristics were similar between the 2 treatment groups.

Sparse pharmacokinetic sampling was performed for all subjects randomized to the D/C/F/TAF group to evaluate the pharmacokinetics of DRV. Also, plasma concentrations of COBI were measured as this is included in a single bioanalytical assay together with DRV. The plasma concentrations of FTC, TAF, and/or TFV were not evaluated. Single sparse blood samples were to be taken at least 15 minutes postdose if the regular dosing time coincided with the study visit or at any time during the visit if the dosing time did not co-incide with the scheduled study visit.

DRV pharmacokinetic parameters (AUC_{24h}, C_{0h}) were derived using population pharmacokinetic modeling. In addition, observed DRV and COBI plasma concentrations (taken within 20 to 28 hours after the last dose of D/C/F/TAF) were summarized with descriptive statistics.

At Week 48 week, a similar percentage of subjects in the D/C/F/TAF group compared with the control group had prematurely discontinued study drug (4.5% [34 subjects] versus 5.3% [20 subjects]).

2.2.2.3.3. Results

2.2.2.3.3.1. Pharmacokinetics

The population PK analysis of DRV in study TMC114IFD3013 is described in a separate report (Mod5.3.3.5/DCFTAF Phase 3-DRV PopPK-report) and is summarized in Section 2.2.2.4.1.

The DRV PK parameters in the D/C/F/TAF arm of study TMC114IFD3013 are summarized in Table 12. These results are in line with data from other D/C/F/TAF studies and historical studies with DRV/COBI, as discussed in Section 3.2.2.1.

Table 12: Population PK Parameter Estimates for DRV Following Multiple-Dose Administration of the D/C/F/TAF FDC 800/150/200/10 mg Once Daily in HIV-1 Infected Subjects (Study TMC114IFD3013, D/C/F/TAF arm)

Parameter	Mean (SD); Median (Range)
N	750
C_{0h}, ng/mL	1813 (859)
	1679 (231 - 6757)
AUC_{24h}, ng.h/mL	85972 (22413)
	82529 (41920 - 209490)

N=maximum number of subjects with data.
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TPK03_EXT

The mean estimated DRV C_{0h} from the population PK analysis is also in line with the descriptive analysis based on observed DRV predose (trough) plasma concentrations (limited to samples taken within 20-28 hours after the prior D/C/F/TAF dose): mean (SD) DRV $C_{predose}$ 1956 ng/mL (1574; n=242) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TPK01_EXT).

A similar analysis was done for observed COBI predose (trough) plasma concentrations (limited to samples taken within 20-28 hours after the prior D/C/F/TAF dose): mean (SD) COBI $C_{predose}$ 124 ng/mL (229; n=242) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TPK01_EXT).

There were no relevant differences in the DRV or COBI pharmacokinetics between visits over time (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TPK01_EXT).

There were no significant differences in the DRV PK parameters between the different subgroups (age category, eGFR category, treatment adherence) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7).

2.2.2.3.3.2. Efficacy

An extensive evaluation of the efficacy in study TMC114IFD3013 is described in the clinical study report (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5) and in Mod2.7.3/Sec3.1.3.

In HIV-1 infected, treatment-experienced, virologically suppressed adults, switching to once-daily D/C/F/TAF resulted in similar low protocol-defined virologic rebound rate cumulative through Week 48 vs continuing TDF-based bPI regimen (2.5% vs 2.1%) in the ITT analysis set inferring

noninferiority (95% CI: -1.5; 2.2), and a high virologic suppression rate (94.9% vs 93.7%) in the Week-48 analysis.

Results were consistent across the analyses in the PP population, and various subgroups, such as bPI, adherence, and demographic characteristics.

No resistance associated with any of the study drugs was observed post-baseline.

2.2.2.3.3.3. Safety

An extensive evaluation of the safety in study TMC114IFD3013 is described in the clinical study report (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6) and in Mod2.7.4/Sec3.1.1.2.

Based on AEs and other safety assessments, no safety concerns were identified.

In the D/C/F/TAF group, there was a higher incidence of AEs at least possibly related and of AEOIs. These findings were expected as, similar to what has been observed in other 'switch' studies, subjects in the switch group have a higher risk of developing an ADR as they are exposed to a new drug, compared to the control group who continues an existing treatment. The higher incidence of AEOIs in the D/C/F/TAF group was mainly driven by a higher frequency of rash AEOIs and lipid-related AEOIs, which are known ADRs to DRV/COBI. The fact that this was an open-label study may have affected the causality assessment of these events.

The higher incidence of rash AEOIs in the D/C/F/TAF group compared to the control group was mainly due to the high incidence of rash in subjects who switch from another PI to DRV or who switch from rtv to COBI as booster at baseline. None of the rash AEOIs were of clinical concern as all rash AEOIs were transient and nonserious and all drug-related rash AEOIs were grade 1.

Due to the loss of lipid-protective effect of a TDF-based regimen after a switch to a TAF-based regimen, lipids increased at Week 48 vs baseline, but these were not reflected in clinically relevant changes in the TC/HDL ratio. Lipid-lowering treatment was initiated by 2.5% vs 1.9% subjects during the treatment phase.

At Week 48, the subjects showed a better renal and bone safety profile when switching from a TDF-based regimen to a TAF-based regimen. In the D/C/F/TAF group vs the control group, there was:

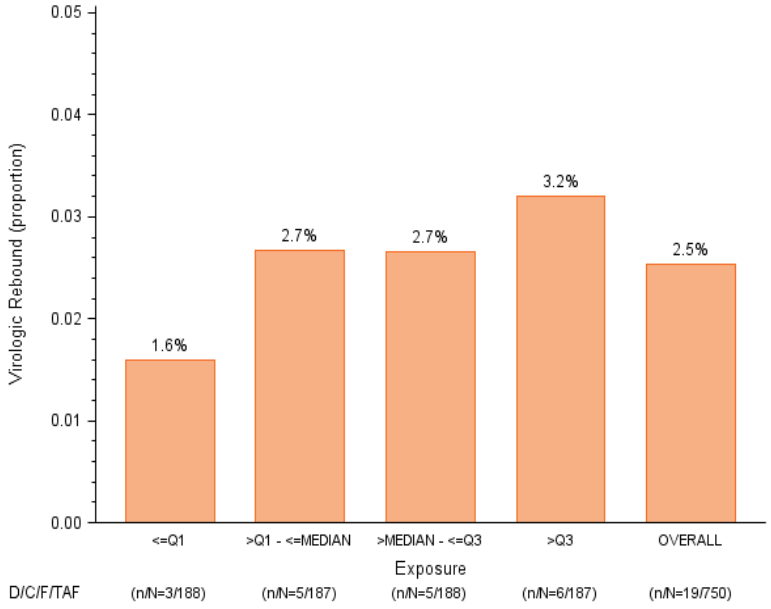
- A preservation of the GFR (as assessed by $eGFR_{cyst}$).
- A lower incidence of tubular proteinuria and a trend towards a lower incidence of increases in markers of potential proximal renal tubulopathy.
- Increases in hip and spine BMD compared to decreases in the control group.

2.2.2.3.3.4. Pharmacokinetic/Pharmacodynamic Relationships

Efficacy

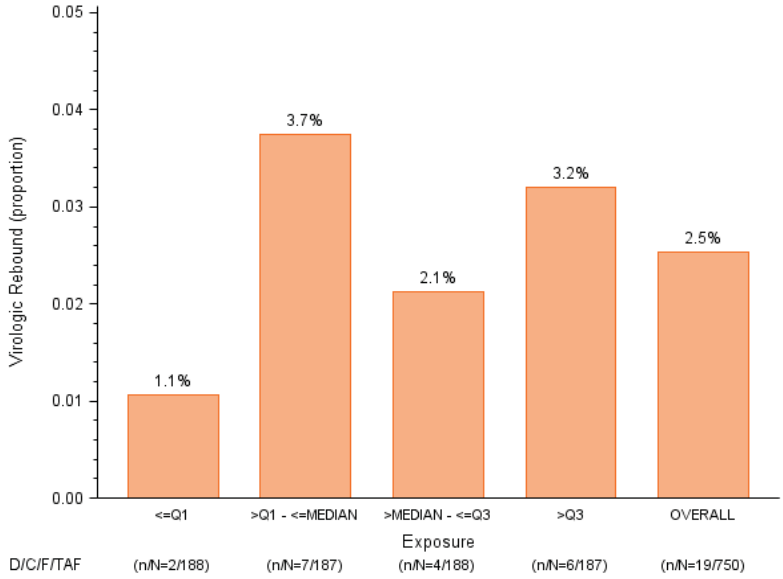
There were no apparent relationships (graphically, and via logistic regression) between the pharmacokinetics of DRV (AUC_{24h} and C_{0h}) and virologic rebound or virologic failure. The proportion of virologic rebounders through Week 48 and the proportion of virologic failures (Week 48 FDA snapshot approach) were similar across quartiles of DRV exposure (AUC_{24h} or C_{0h}) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7).

Figure 9: Bar Chart of the Proportion of Protocol-defined Virologic Rebound Through Week 48 (HIV-1 RNA >=50 Copies/mL), Overall and by DRV AUC_{24h} Quartiles (Study TMC114IFD3013)



DRV AUC_{24h} (h*ng/mL): Q1=69885; median=82528.5; Q3=98943
Source: Module 5.3.5.1/TMC114FD2HTX3001-CSR/Fig25

Figure 10: Bar Chart of the Proportion of Protocol-defined Virologic Rebound Through Week 48 (HIV-1 RNA >=50 Copies/mL), Overall and by DRV C_{0h} Quartiles (Study TMC114IFD3013)



DRV C_{0h} (ng/mL): Q1=1208.8; median=1679.05; Q3=2278.9
Source: Module 5.3.5.1/TMC114FD2HTX3001-CSR/Fig25

Safety

There were no apparent clinically relevant relationships (graphically) between DRV AUC_{24h} and the occurrence of AEOIs (bone, cardiac conduction, convulsions, coronary artery, lipids, lipodystrophy, liver, ocular, pancreas, rash, renal, skin), or graded laboratory abnormalities or changes in the selected laboratory parameters of interest (amylase, ALT/AST, alkaline phosphatase, total bilirubin, cholesterol, LDL, triglycerides, glucose, creatinine, eGFR laboratory parameters, urine albumin to creatinin ratio, urine protein to creatinin ratio) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7). For some of the parameters, the number of subjects was very low, and the analyses should be interpreted with caution.

2.2.2.3.4. Conclusions (Pharmacokinetics, Pharmacokinetic/Pharmacodynamic)

The DRV pharmacokinetics were in line with those in other studies with COBI-boosted DRV (see also Section 3.2.2.1). There were no relevant differences in DRV pharmacokinetics between subgroups.

There were no apparent relationships between the DRV pharmacokinetics and virologic rebound or virologic failure.

There were no apparent relationships between the pharmacokinetics of DRV and safety parameters of interest.

2.2.2.4. Population Pharmacokinetic Analysis

2.2.2.4.1. Darunavir

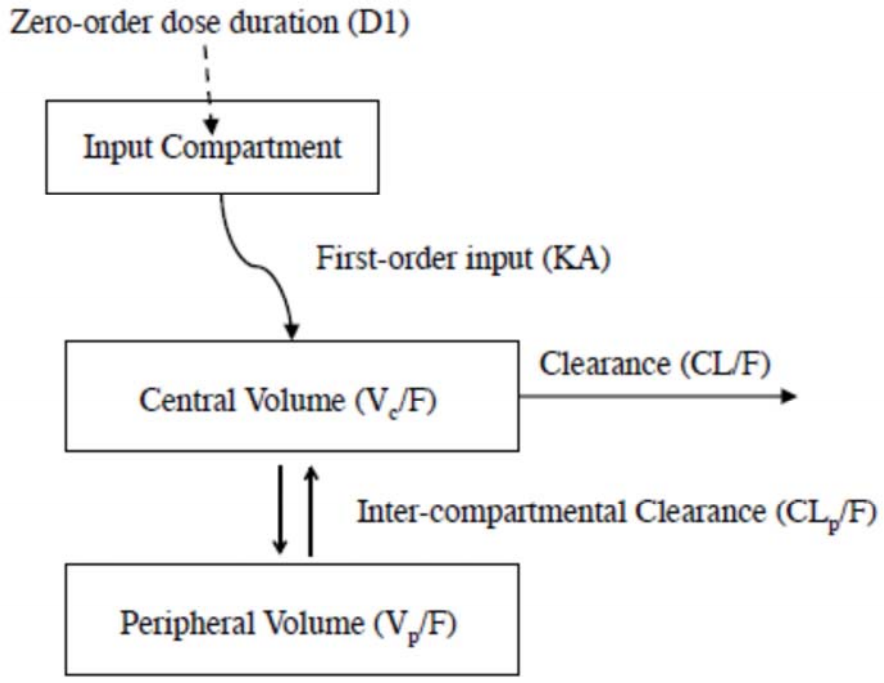
Population pharmacokinetic analysis for DRV administered as the D/C/F/TAF FDC is available for the pivotal Phase 3 studies TMC114FD2HTX3001 and TMC114IFD3013. The DRV pharmacokinetic data obtained in the individual studies are summarized in the respective study sections (TMC114FD2HTX3001, see Section 2.2.2.2.3.1; TMC114IFD3013, see Section 2.2.2.3.3.1).

The model development and analysis is described in a separate report (Mod5.3.3.5/DCFTAF Phase 3-DRV PopPK-report), with a high-level summary below.

Population PK Model Building

The previously available population PK model for DRV was developed from richly sampled PK data collected in phase 1 and 2 studies where DRV was co-administered with ritonavir, and subsequently updated using richly sampled PK data from the phase 3 study GS-US-216-0130 where DRV was co-administered with COBI. The model consists of a 2-compartment disposition model with a sequential zero-order input into the depot compartment followed by a first-order absorption. Effects of total daily dose (TDD) and α1-acid glycoprotein (AAG) on apparent clearance (CL/F) were included. Between-subject variability (BSV) terms were included on CL/F, apparent volume of distribution for the central compartment (Vc/F), apparent volume of distribution for the peripheral compartment (Vp/F), apparent intercompartmental clearance (CLp/F), and the duration of zero-order input into the depot compartment (D1). The residual unexplained variability (RUV) was explained by a proportional term (Figure 11).

Figure 11: DRV Structural Population PK Model

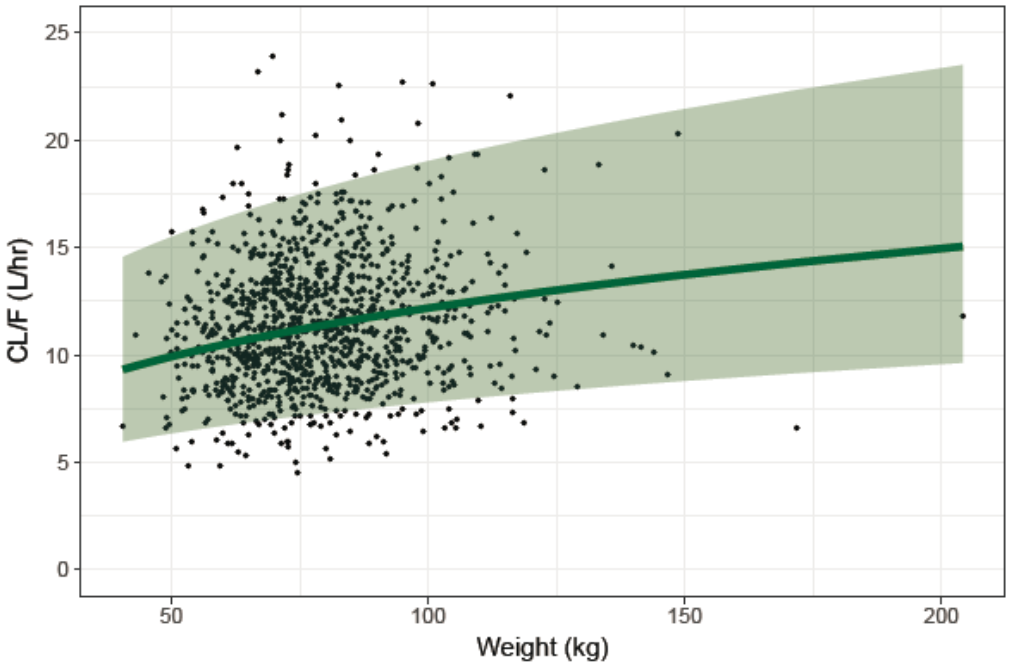


This model was now updated with DRV data from sparse sampling in subjects in the D/C/F/TAF arm of Phase 3 studies TMC114FD2HTX3001 and TMC114IFD3013.

The prior structural model (Figure 11) was retained, while several parameters were re-estimated, including CL/F, V_c/F, D1, BSV on CL/F and the proportional RUV. Additionally, total body weight (WT) was included as a covariate on CL/F (Figure 12). The model predicts a CL/F of 10.9 L/hr, 11.3 L/hr, and 11.7 L/hr for subjects with a WT of 67.8 kg (25th percentile), 76.5 kg (50th percentile) and 87.5 kg (75th percentile), respectively. This translates in a model-predicted decrease of 13% and 22.4% in mean AUC_{24h} and C_{0h}, respectively, between the 1st and 4th quartiles of WT. This is not considered clinically relevant.

Parameter estimates for the updated final model are shown in Table 13.

Figure 12: Model-predicted effect of bodyweight on DRV CL/F



Dots = individual MAP estimates of CL/F, dashed green line = model predicted effect for subject with AAG of 68 mg/dL; shaded area = 95% prediction interval incorating BSV on CL/F

Exposure Metric Estimation For Darunavir

Individual exposure metrics (C_{0h}, AUC_{24h}, and $C_{ss,ave}$) for DRV, for subjects recruited in the D/C/F/TAF arm in studies TMC114FD2HTX3001 and TMC114IFD3013, were successfully derived for each individual at each visit. The individual median value across visits for C_{0h} and AUC_{24h} was used for overall data summaries and for PK/PD evaluations.

Graphical Covariate Analysis

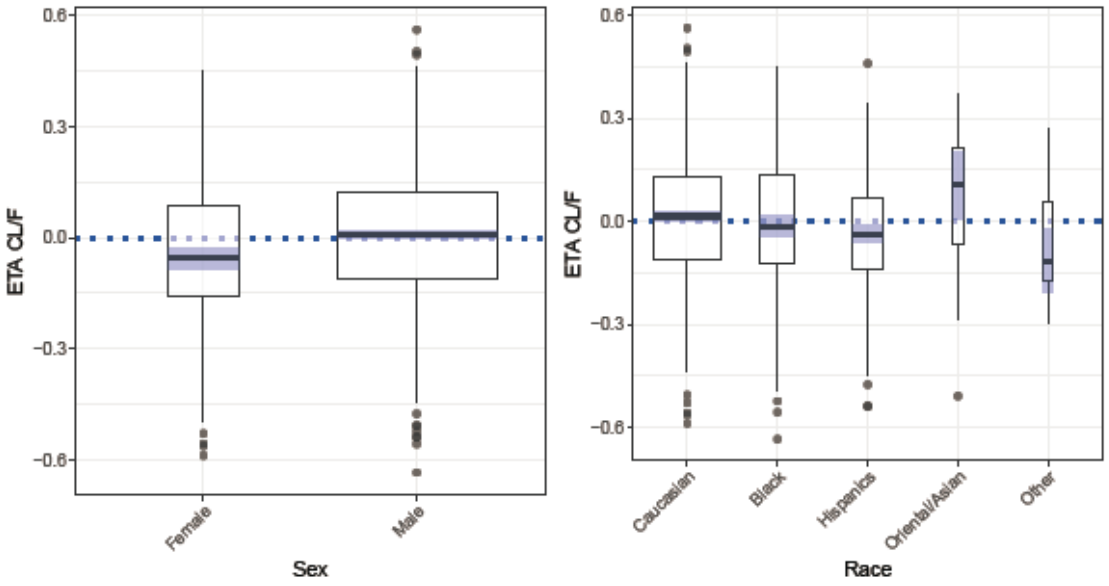
As discussed above, AAG and total body weight were included as covariate on CL/F in the final model and no effect of these covariates remained after that. From the η-covariate plots (Figure 13, Figure 14) for CL/F a marginally lower CL/F in female subjects compared to male subjects was suggested; but this is not considered clinically relevant. No other relationships were evident.

Table 13: Final Population PK Model Parameter Estimates of DRV Following Multiple-Dose Administration of D/C/F/TAF 800/150/200/10 mg Once Daily

Parameter	Rerun Updated Model Estimate (CV%)
*Apparent clearance (CL_r/F, L/hr)	44.07 (1.2)
Effect of TDD on CL_r/F	0.388 FIX
Effect of AAG on CL_r/F (dL/mg)	0.0304 FIX
Exponent of WT on CL_r/F	0.307 (16.1)
Apparent volume of distribution for the central compartment (V_c/F, L)	88.2 (5.8)
Apparent inter-compartmental clearance (CL_p/F, L/hr)	24.0 FIX
Apparent volume of distribution for the peripheral compartment (V_p/F, L)	90.0 FIX
First-order absorption rate constant (KA, hr^{-1})	0.393 FIX
Relative bioavailability (F_{REL})	1.18 FIX
Duration of zero-order input into the depot compartment (D1, hr)	0.290 (13.3)
Between-subject variability on CL_r/F (CV%)	23.0 (3.3)
Between-subject variability on V_c/F (CV%)	15.6 FIX
Between-subject variability on CL_p/F (CV%)	51.0 FIX
Between-subject variability on V_p/F (CV%)	55.7 FIX
Between-subject variability on D1 (CV%)	88.4 FIX
Residual unexplained variability (Proportional RUV, CV%)	43.2 (1.4)

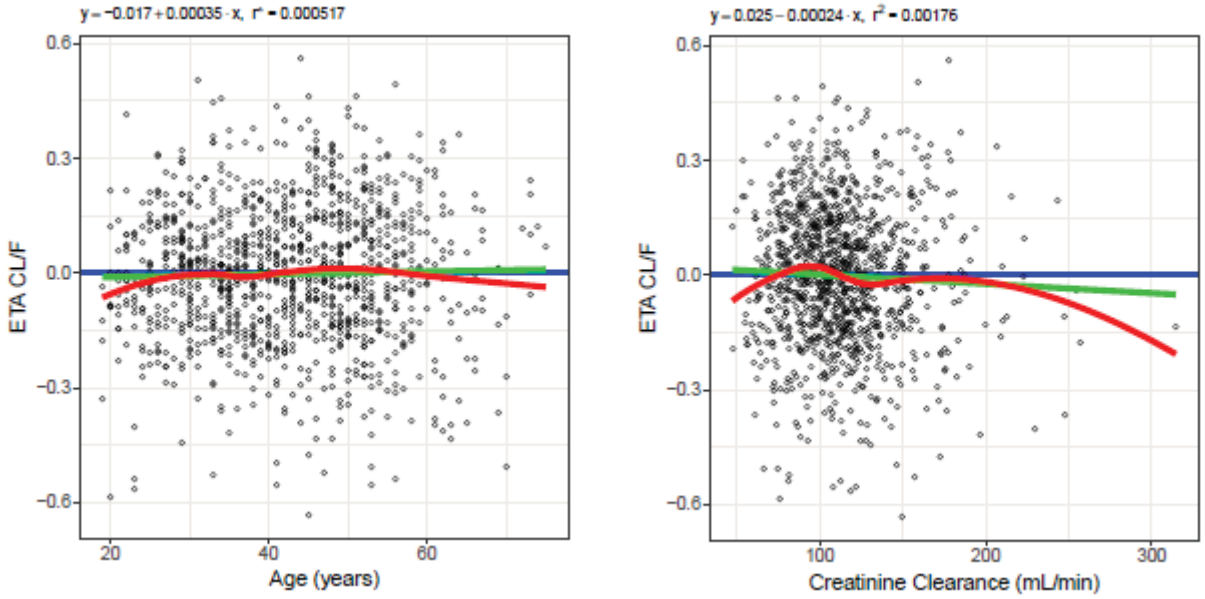
CV% = percent coefficient of variation, AAG = α1-acid glycoprotein, TDD = total daily dose, WT = total body weight.
*$CL/F = 44.07*(1/(1 + 0.0304*AAG))*(TDD/1200)^{0.388} *(WT/70)^{0.307}$

Figure 13: Relationship Between ETA on DRV CL/F and Categorical Potential Covariates



dotted blue lines represent zero, thick solid black lines represent the median of the data, hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5*IQR of the hinges respectively, and values outside the whiskers are represented with dots. The shaded region is the approximate 95%CI for the median, calculated as ±1.58*IQR/SQR(n). (SQR=square root)

Figure 14: Relationship Between ETA on DRV CL/F and Continuous Potential Covariates



solid blue line represents zero, solid red line represents the trend in the data (Loess smooth), solid green line represents a linear regression with the corresponding regression model shown above each panel.

Conclusions

- The PK of DRV when administered as the D/C/F/TAF FDC were described using a 2-compartment disposition model with a sequential zero-order input into the depot compartment followed by a first-order absorption.

- Total daily dose and AAG were included in the model, as as the case for the previously available population PK model. In addition, total body weight was included in the final model as it explained part of the DRV variability. The estimated effect translated in a 13% difference in AUC_{24h} between the 1st and 4th weight quartiles. This is not considered clinically relevant, given the wide therapeutic window for DRV at the recommended dose. Graphical analyses between individual parameters and covariates suggested no other clinically relevant covariates for inclusion in the model.

- The individual DRV steady-state exposure metrics (C_{0h}, AUC_{24h}, and $C_{ss,ave}$) for subjects in the D/C/F/TAF arms of Phase 3 studies TMC114FD2HTX3001 and TMC114IFD3013 in HIV-infected subjects were successfully determined.

2.2.2.4.2. TAF

Population pharmacokinetic analysis for TAF administered as the D/C/F/TAF FDC is available for the pivotal Phase 3 study TMC114FD2HTX3001. The TAF pharmacokinetic data in TMC114FD2HTX3001 are summarized in Section 2.2.2.2.3.1.

The model development and analysis is described in a separate report (Mod5.3.3.5/TMC114FD2HTX3001-TAF PopPK-report), with a high-level summary below.

Population PK Model Building

During the model building, data from two Phase 1 studies in healthy volunteers (TMC114FD2HTX1001 and TMC114FD2HTX1002, rich PK sampling) and one Phase 2 study in HIV- 1 infected subjects (GS-US-299-0102, rich PK sampling in a subgroup, sparse sampling in all subjects) with D/C/F/TAF as a FDC tablet and coadministered as separate agents (where applicable) were included.

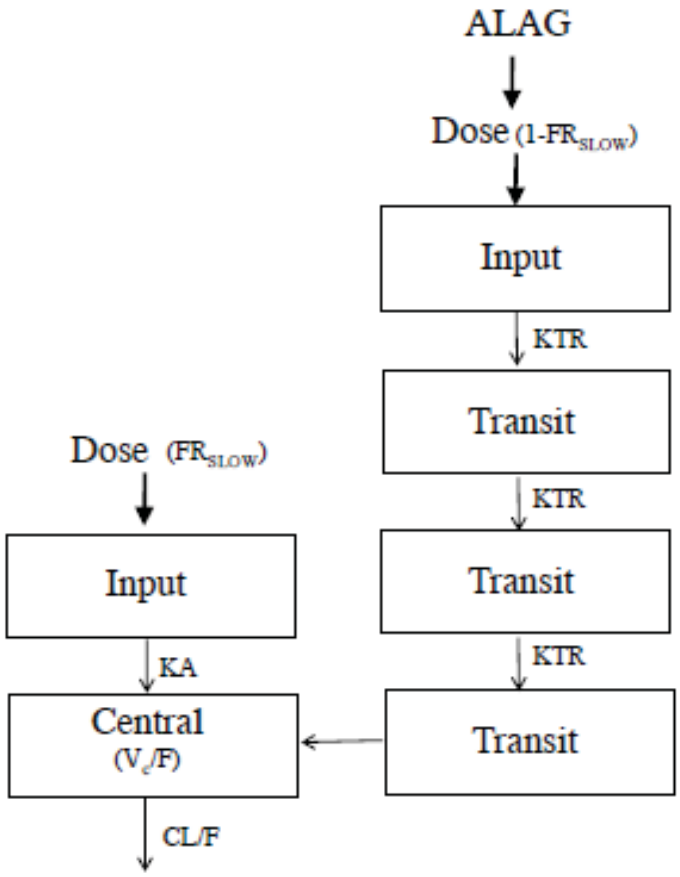
The model that most adequately described the data was a one-compartment disposition model with absorption described by a dual input (slow and fast pathway), where the fraction of the dose absorbed via the slow pathway (FR_{SLOW}) was estimated. Absorption via the slow pathway was described by a first-order absorption rate constant (KA), while absorption via the fast pathway was described by a series of transit compartments following an absorption lag time (ALAG). Due to large within-subject variability in absorption across occasions, a mixture model was implemented for ALAG by occasion. Between-subject variability (BSV) was included on apparent clearance (CL/F), apparent volume of distribution for the central compartment (Vc/F), KA, the absorption transit rate constant (KTR), and FR_{SLOW}. Between-occasion variability (BOV) was included on ALAG, with residual unexplained variability (RUV) characterised by a proportional term.

A schematic of the final model and parameter estimates are shown in Figure 15 and Table 14 below.

Lean body weight (LBW)[1] and AAG were found to describe part of the variability on TAF CL/F and were included in the model. The model-predicted effects of LBW and AAG on CL/F are displayed in Figure 16 and Figure 17. The model predicts a CL/F of 80.4 L/hr, 91.4 L/hr, and 97.5 L/hr for subjects with a LBW of 47.6 kg (25th percentile), 57.1 kg (50th percentile) and 62.7 kg (75th percentile), respectively. This translates in a model-predicted decrease of 29% in the mean AUC_{tau} between the 1st and 4th quartiles of LBW. The model predicts a CL/F of 96.3 L/hr, 84.4 L/hr, and 74.6 L/hr for subjects with a AAG of 60 mg/dL (25th percentile), 74 mg/dL (50th percentile) and 90 mg/dL (75th percentile), respectively. This translates in a model-predicted decrease of 38% in the mean AUC_{tau} between the 4th and 1st quartiles of AAG.

This model was then updated with TAF data from sparse sampling in subjects in the D/C/F/TAF arm of Phase 3 study TMC114FD2HTX3001. The prior structural model was retained, while the absorption parameter KTR and the ALAG were re-estimated.

Figure 15: TAF Structural Population PK Model



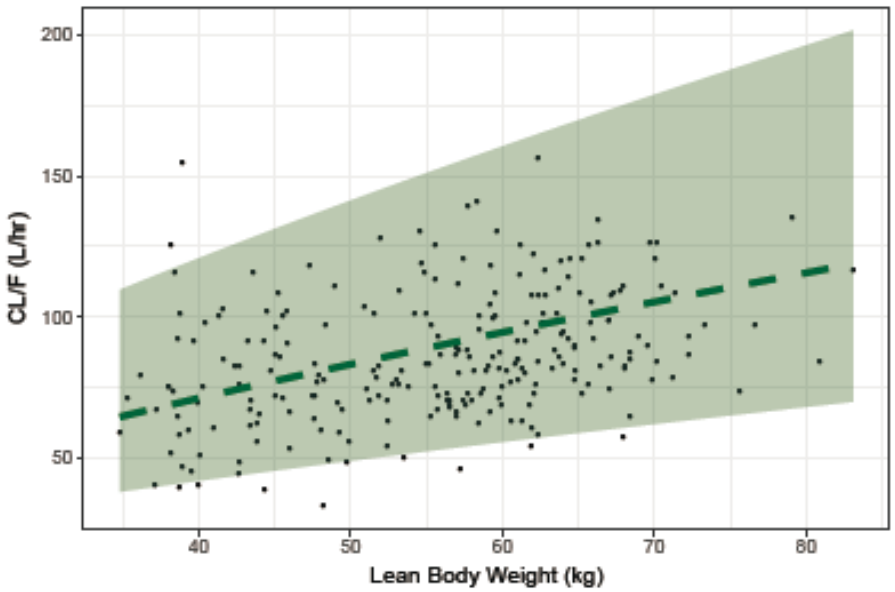
[1] LBW (male) = (9270*WT)/(6680+216*BMI); LBW (female) = (9270*WT)/(8780+244*BMI)

Table 14: Final Population PK Model Parameter Estimates of TAF Following Multiple-Dose Administration of D/C/F/TAF 800/150/200/10 mg Once Daily

Parameter	Estimated Value (%SE)	
	Re-run of Phase III Model	Phase III Model
*Apparent clearance (CL/F, L/hr)	89.0 FIX	89.0 FIX
Exponent for LBW on CL	0.70 FIX	0.70 FIX
Exponent for AAG on CL	-0.63 FIX	-0.63 FIX
Apparent central volume of distribution (V_c/F, L)	36.3 FIX	36.3 FIX
First order absorption rate constant for pathway one (KA, hr^{-1})	0.67 FIX	0.67 FIX
Absorption transit rate constant for pathway two (KTR, hr^{-1})	38.5 (24.4)	38.3 (30.6)
Fraction of dose via the slow pathway (FR_{SLOW})	0.135 FIX	0.135 FIX
Probability of subpopulation one (MIX_1), two (MIX_2), three (MIX_3)**	0.21 FIX	0.21 FIX
Lag-time for second pathway (ALAG, hrs)	0 FIX	0 FIX
Between subject variability for CL/F (%CV)	27.0 FIX	27.0 FIX
Between subject variability for V_c/F (%CV)	37.3 FIX	37.3 FIX
Between subject variability for KA (%CV)	55.6 FIX	55.6 FIX
Between subject variability for KTR (%CV)	66.8 FIX	66.8 FIX
Between subject variability for FR_{SLOW} (%CV)	78.9 FIX	78.9 FIX
Between occasion variability for ALAG (%CV)	NA	NA
Residual unexplained variability Rich (%CV)	NA	NA
Residual unexplained variability Sparse (%CV)	75.9 FIX	75.9 FIX

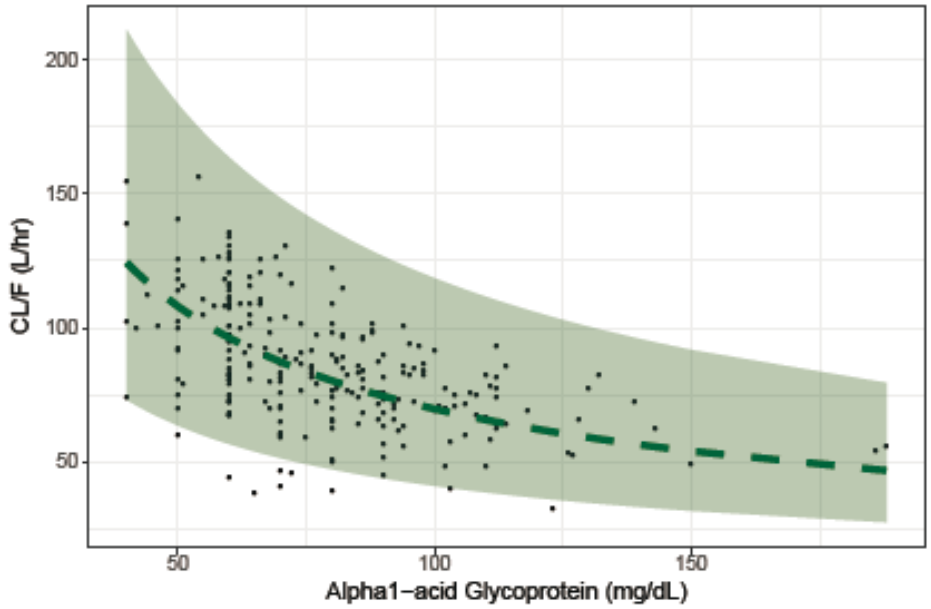
CV% = percent coeffcient of variation, LBW = lean body weight, AAG = α1-acid glycoprotein.
*$CL/F = 89.0*(LBW/55)^{0.70} *(AAG/68)^{-0:63}$; **Subpopulation 4 = 0.37 [i.e. 1 - 0.21 - 0.21 - 0.21]

Figure 16: Impact of Lean Body Weight on TAF CL/F



Dots = individual MAP estimates of CL/F, dashed green line = model predicted effect for a subject with AAG 68 mg/dL, shaded area = 95% predictions interval incorporating BSV on CL/F

Figure 17: Impact of AAG on TAF CL/F



Dots = individual MAP estimates of CL/F, dashed green line = model predicted effect for a subject with LBW of 55 kg, shaded area = 95% predictions interval incorporating BSV on CL/F

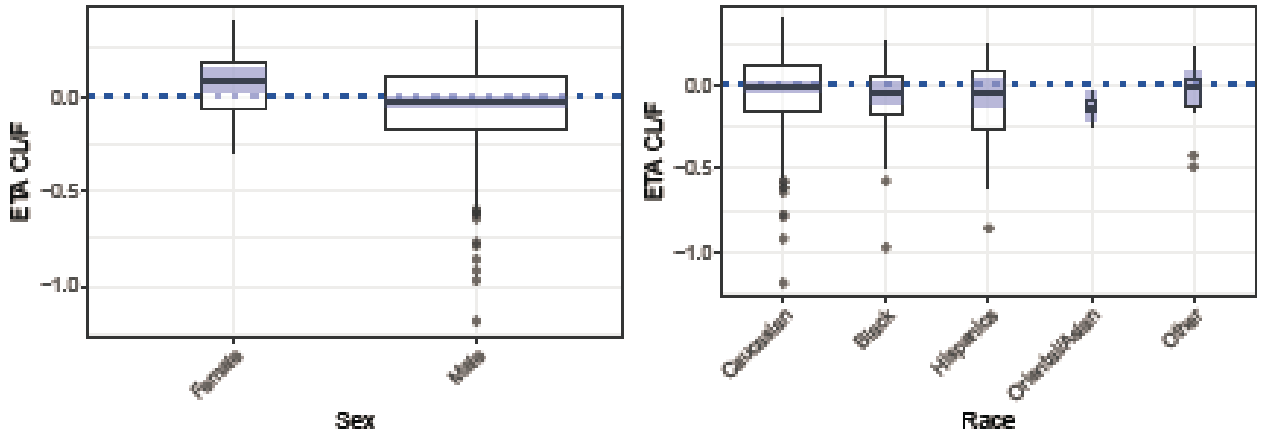
Exposure Metric Estimation For TAF

Using the above described model, individual exposure metrics (C_{2h}, AUC_{tau}, and $C_{ss,ave}$) for TAF, for subjects recruited in the D/C/F/TAF arm of study TMC114FD2HTX3001 were successfully derived for each individual at each visit. The individual median value across visits (mainly AUC_{tau}) was used for overall data summaries and for PK/PD evaluations.

Graphical Covariate Analysis

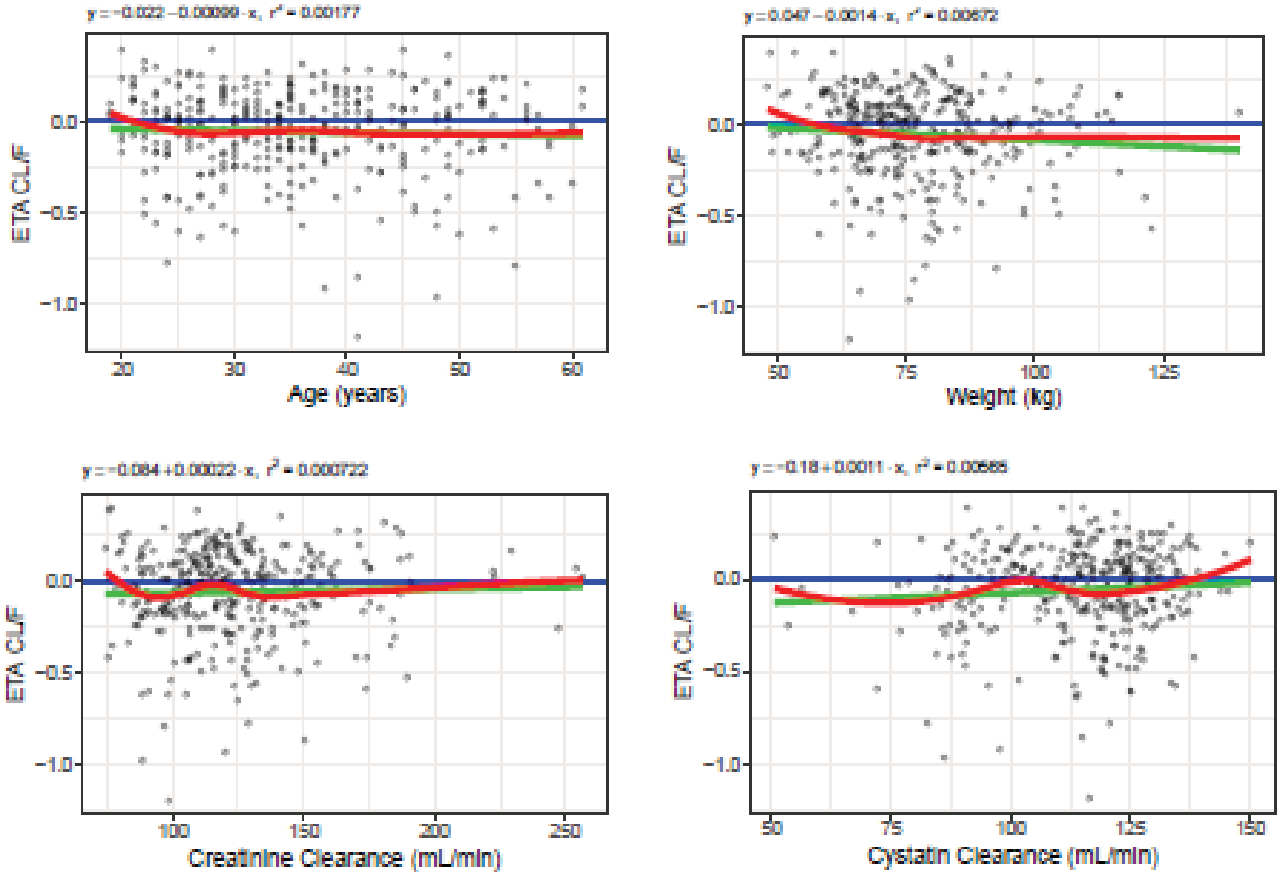
As discussed above, LBW and AAG were included as covariates on CL/F in the final model and no effect of these covariates remained after that. From the η-covariate plots no clear relationships were evident between any of the other potential covariates and TAF CL/F (Figure 18, Figure 19) or Vc/F (Mod5.3.3.5/TMC114FD2HTX3001-TAF PopPK-report).

Figure 18: Relationship Between ETA on TAF CL/F and Categorical Potential Covariates



dotted blue lines represent zero, thick solid black lines represent the median of the data, hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots. The shaded region is the approximate 95%CI for the median, calculated as ±1.58*IQR/SQR(n). (SQR=square root)

Figure 19: Relationship Between ETA on TAF CL/F and Continuous Potential Covariates



The solid blue line represents zero, the solid red line represents the trend in the data (Loess smooth), the solid green line represents a linear regression with the corresponding regression model shown above each panel.

Conclusions

- The TAF PK when administered as the D/C/F/TAF regimen were described by a one-compartment disposition model with absorption described by a dual input (slow and fast pathway), where the fraction of the dose absorbed via the slow pathway (FR_{SLOW}) was estimated.

- Lean body weight and AAG were included in the model, as they explained part of the TAF variability. The estimated effect translated in a model-predicted decrease of 29% in the mean AUC_{tau} between the 1st and 4th quartiles of LBW, and a model-predicted decrease of 38% in the mean AUC_{tau} between the 4th and 1st quartiles of AAG. These differences are not considered clinically relevant, given the wide therapeutic window for TAF at the recommended dose. Graphical analyses between individual parameters and covariates suggested no other clinically relevant covariates for inclusion in the model.

- The individual TAF PK parameters and exposure metrics for subjects in the D/C/F/TAF arm of study TMC114FD2HTX3001 were successfully determined.

2.2.3. Patient Pharmacodynamics and Pharmacokinetics/Pharmacodynamics - F/TAF

TAF is a relatively new antiretroviral, especially in combination with boosted DRV. Therefore, pharmacokinetic data from other studies conducted using TAF or a TAF-containing FDC that contribute additional information to this Summary of Clinical Pharmacology are summarized here, for comparison with TAF pharmacokinetics for the D/C/F/TAF FDC.

The TAF PK/PD analysis including the following studies is described in Section 2.2.3.6 and discussed in Section 3.5.1 (efficacy) and Section 3.5.2 (safety). Other aspects of these historical TAF studies are not discussed anywhere in this submission, except for study GS-US-292-0106 in adolescents, which is briefly discussed in Mod2.7.3/Sec3.2 and Mod2.7.4/Sec3.2.2.

2.2.3.1. Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1 Infected Antiretroviral Treatment-Naïve Adolescents (Study GS-US-292-0106)

Source document: Gaur et al, 2016[15]

2.2.3.1.1. Objectives

Study GS-US-292-0106 is a Phase 2/3, open-label study of the PK, safety, and antiviral activity of the E/C/F/TAF FDC in HIV-1 infected ART-naïve adolescents. The primary objectives of this study were to determine the steady-state PK of the components of E/C/F/TAF in order to confirm the dose of the E/C/F/TAF FDC, and to evaluate the safety and tolerability through 48 weeks of treatment.

The steady-state PK (intensive PK visit) of EVG, TAF, TFV, COBI, and FTC were evaluated in 24 adolescent subjects (aged 12 to 18 years) enrolled in part A of the study. The PK data from adolescents who received E/C/F/TAF in this study were compared to combined available PK data from HIV-1 infected adult subjects (adult comparator).

2.2.3.1.2. Results

2.2.3.1.3. Pharmacokinetics

Pharmacokinetic parameters for all components are presented in Table 15.

The EVG, TAF, TFV, COBI and FTC exposure in adolescents receiving E/C/F/TAF was consistent with exposures observed in adults (Table 16).

The COBI exposures were consistent with the totality of historical data for COBI and in the range of exposure associated with a robust PD effect (boosting), which is the function of COBI in E/C/F/TAF , as also evidenced by the comparable EVG exposure in adolescents and adults in this study.

2.2.3.1.4. Pharmacokinetic Conclusions

Overall, the PK profile of the E/C/F/TAF components in adolescents was comparable to that in adults and was within clinically efficacious ranges for all components, indicating that the E/C/F/TAF 150/150/200/10 mg dose is appropriate for use in adolescents who weigh at least 35 kg (77 lbs).

Table 15: Pharmacokinetic Parameters of EVG, COBI, FTC, TAF and TFV in HIV-1 Infected ART Naïve Adolescents (Study GS-US-292-0106, Part A)

Parameter	Mean (%CV) (N=24)				
	EVG	**COBI**	**FTC**	**TAF**	**TFV**
C_{max}, ng/mL	2230 (19.2)	1202 (35.0)	2265 (22.5)	167 (64.4)	18 (23.7)
C_{tau}, ng/mL	301 (81.0)	25 (180.0)	102 (38.9)	-	10 (21.4)
AUC_{tau}, ng.h/mL	23,840 (25.5)	8241 (36.1)	14,424 (23.9)	-	288 (18.8)
AUC_{last}, ng.h/mL	-	-	-	189 (55.8)	-

AUC_{last}=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; AUC_{tau}=AUC from time of administration up to the end of the dosing interval; CV=coefficient of variation; C_{max}=maximum observed analyte concentration; C_{tau}=plasma concentration at the end of the dosing interval; N=number of subjects.

Table 16: Comparison of EVG, TAF, TFV, COBI and FTC Pharmacokinetic Parameter Estimates Between Adolescents and Adults (Studies GS-US-292-0106, GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111)

Parameter	Mean	
	Study GS-US-292-0106 (Adolescents) N=24	**Studies GS-US-292-0102, GS-US-292-0104 and GS-US-292-0111 (Adults)[a]**
EVG		
AUC_{tau}, ng.h/mL	23840	22800
C_{tau}, ng/mL	301	290
C_{max}, ng/mL	2230	2100
TAF		
AUC_{last}, ng.h/mL	189	AUC_{tau}: 206
C_{max}, ng/mL	167	162
TFV		
AUC_{tau}, ng.h/mL	288	293
C_{tau}, ng/mL	10	11
C_{max}, ng/mL	18	15
COBI		
AUC_{tau}, ng.h/mL	8241	9500
C_{tau}, ng/mL	25	20
C_{max}, ng/mL	1202	1500
FTC		
AUC_{tau}, ng.h/mL	14424	11714
C_{tau}, ng/mL	102	95
C_{max}, ng/mL	2265	2056

AUC_{last}=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; AUC_{tau}=AUC from time of administration up to the end of the dosing interval; C_{max}=maximum observed analyte concentration; C_{tau}=plasma concentration at the end of the dosing interval; EGV=elvitegravir; N=number of subjects.

[a] Adult pharmacokinetic parameters for COBI, EVG, and FTC derived from intensive analysis in E/C/F/TAF Study GS-US-292-102 (N=19); parameters TAF (N=539), and TFV (N=841) from population pharmacokinetic analysis in E/C/F/TAF Studies GS-US-292-104 and GS-US-292-111.

2.2.3.2. A Randomized, Partially-Blinded, Active and Placebo-Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of TAF Monotherapy in Subjects with HIV-1 (Study GS-US-120-0104)

NDA208215/Mod5.3.4.2/GS-US-120-0104_CSR

2.2.3.2.1. Objectives

Study GS-US-120-0104 was the proof-of-concept study with single component TAF in subjects with HIV-1.

The primary objective was:

- To evaluate the short-term antiviral potency of TAF 8 mg, 25 mg, and 40 mg as compared with placebo-to-match TAF or TDF 300 mg, each administered once daily as monotherapy for 10 days, with respect to the time-weighted average change from baseline at Day 11 ($DAVG_{11}$) in plasma HIV-1 RNA (log_{10} copies/mL).

The key secondary PK objective was:

- To investigate the plasma and intracellular PK of TAF and/or TFV following single and multiple doses of TAF or TDF.

Additionally, the correlation between the intracellular concentrations of TFV in PBMCs and the antiviral effect was investigated.

2.2.3.2.2. Study Design

This was a randomized, partially-blinded, active- and placebo-controlled study to evaluate the safety, PK, and antiviral activity of TAF monotherapy in HIV-1 infected subjects. Subjects were randomized in a 2:2:2:1:2 ratio to one of the following 5 treatment groups:

- Treatment Group 1: TAF 8 mg once daily
- Treatment Group 2: TAF 25 mg once daily.
- Treatment Group 3: TAF 40 mg once daily.
- Treatment Group 4: TDF 300 mg once daily.
- Treatment Group 5: Placebo-to-match TAF tablet once daily.

Treatments 1, 2, 3 and 5 (TAF and matched placebo) were blinded, while Treatment 4 (TDF) was open-label. All study medications were administered in the fasted state.

2.2.3.2.3. Results

The antiviral effect of TAF 8 mg was comparable with TDF 300 mg, and increased with higher doses of TAF, with significantly lower plasma HIV-1 RNA levels from baseline to Day 11 at TAF doses of 25 mg and 40 mg.

2.2.3.2.4. Pharmacokinetics

The PK of TAF was stable in plasma, with detectable levels after 0.25 hours and a $t_{1/2}$ of approximately 0.40 hours (see Table 30 and Table 31 in Section 3.5.1.4.1). The steady-state AUC_{tau} was lower for TAF than TFV dosed as TDF. Pharmacokinetic parameters of TAF were similar following single- and multiple-dose administration, within each dose group, as expected given the short plasma $t_{1/2}$ of TAF. Intracellular TFV-DP is presented in Table 17. Following multiple-dose administration of TAF 25 mg and 40 mg, mean intracellular TFV-DP AUC_{tau} values were approximately 7-fold and approximately 25-fold higher, respectively, relative to TDF 300 mg.

Table 17: Summary of Steady-state PK Parameter Estimates for Intracellular TFV-DP Following Once Daily Dosing of TAF; Multiple Dose Day 10 (TAF PK Analysis Set) (Study GS-US-120-0104)

Parameter	Mean (%CV); Median (Range [Q1, Q3]);			
	TAF Dose			TDF Dose
	8 mg N=6	25 mg N=4	40 mg N=7	300 mg N=4
AUC_{tau}, ng.h/mL	3.5 (77.1)	21.4 (76.9)	74.5 (92.7)	3.0 (119.6)
	2.5 (1.6, 5.8)	15.8 (9.6, 33.2)	53.4 (28.3, 104.7)	1.6 (1.0, 4.9)

To account for the variability in the data, the mean and median AUC_{tau} are presented.

2.2.3.2.5. Conclusion (Pharmacokinetics)

In comparison to TDF, which is undetectable in plasma, plasma PK of TAF in this study support the existing evidence that TAF is more stable in plasma. TAF was rapidly absorbed with detectable levels by 0.25 hours postdose, and with a $t_{1/2}$ of approximately 0.40 hours. TFV plasma concentrations were substantially higher when given as TDF. At steady-state, following multiple-dose administration of TAF 8 mg, 25 mg, and 40 mg, the mean TFV AUC_{tau} values were 97%, 86%, and 79% lower, respectively, as compared with the mean TFV AUC_{tau} observed when dosed as TDF 300 mg. Intracellular PBMC TFV-DP AUC_{tau} was similar when given as TAF 8 mg or TDF 300 mg, whereas for TAF 25 mg and 40 mg, the mean intracellular TFV-DP AUC_{tau} values were approximately 7-fold and approximately 25-fold higher, relative to TDF 300 mg.

The PK/PD evaluation for this study is further presented in Section 3.5.1.4.1.

2.2.3.3. Phase 3 Randomized, Double-Blind Studies Evaluating the Efficacy and Safety of E/C/F/TAF in Treatment-naïve HIV-1 Infected Subjects (Studies GS-US-292-0104 and GS-US-292-0111)

NDA207561/Mod5.3.5.1/GS-US-292-0104_CSR

NDA207561/Mod5.3.5.1/GS-US-292-0111_CSR

Studies GS-US-292-0104 and GS-US-292-0111 were randomized, double-blind, multicenter, active controlled Phase 3 studies to evaluate the efficacy and safety and tolerability of EVG 150 mg, COBI 150 mg, FTC 200 mg and TAF 10 mg once daily, administered as the E/C/F/TAF FDC compared with EVG 150 mg, COBI 150 mg, FTC 200 mg and TDF 300 mg once daily administered as the E/C/F/TDF FDC for the treatment of HIV-1 infection in treatment-naïve adults.

The non-compartmental PK parameters for TAF and TFV from the PK substudies from studies GS-US-292-0104 and GS-US-292-0111 are presented in Table 18. The population PK data from the pooled GS-US-292-0104 and GS-US-292-0111 studies is discussed in Section 3.2.2.3. Pharmacokinetic/PD analysis was also performed on pooled data from these 2 Phase 3 studies (Section 2.2.3.6 and Section 3.5.1.4.2).

In Study GS-US-292-0104, the primary TFV PK parameters were compared in subjects administered E/C/F/TAF versus those administered E/C/F/TDF (Table 19). Administration of E/C/F/TAF led to 89.58% lower mean systemic TFV AUC_{tau}. These results were consistent with those observed in GS-US-292-0111, where administration of E/C/F/TAF led to 92.43% lower mean systemic TFV AUC_{tau} versus administration of E/C/F/TDF (Table 19). These data were also consistent with those from the proof-of-concept study (GS-US-120-0104, Section 2.2.3.2) and the D/C/F/TAF Phase 2 study (GS-US-299-0102, Section 2.2.2.1).

Table 18: Pharmacokinetic Parameters of TAF and TFV in HIV-1 Infected ART Naïve Subjects following E/C/F/TAF Administration (PK Substudy Analysis Set; Study GS-US-292-0104 and GS-US-292-0111)

Parameter	Mean (%CV); t_{max} / $t_{1/2}$: Median (Range)			
	Study GS-US-292-0104 N=15		Study GS-US-292-0111 N=21	
	TAF	TFV	TAF	TFV
AUC_{last}, ng.h/mL	229.8 (33.7)	-	259.0 (71.6)	
AUC_{tau}, ng.h/mL	-	311.8 (17.1)		286.2 (22.5)
C_{max}, ng/mL	259.2 (43.8)	17.3 (16.0)	201.6 (72.6)	16.7 (26.2)
t_{max}, h	0.75 (0.50, 1.50)	2.00 (1.50, 3.00)	1.00 (0.50, 2.05)	3.00 (1.00, 4.00)
$t_{1/2}$, h	0.42 (0.36, 0.57)	34.95 (28.57, 48.50)	0.48 (0.39, 0.68)	35.77 (26.69, 65.29)

AUC_{last}=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration; AUC_{tau}=AUC from time of administration up to the end of the dosing interval; CI=confidence interval; C_{max}=maximum observed analyte concentration; C_{tau}=plasma concentration at the end of the dosing interval; N=maximum number of subjects SD=standard deviation; t_{max}=actual sampling time to reach the maximum observed analyte concentration.

Table 19: Statistical Comparisons of TFV PK Parameters Estimates Between E/C/F/TDF and E/C/F/TAF (PK Substudy Analysis Set; Study GS-US-292-0104)

Parameter	LS Mean		LS Mean Ratio % (90% CI)
	E/C/F/TAF	E/C/F/TDF	
Study GS-US-292-0104	**N=15**	**N=15**	
$AUC_{tau,}$ ng.h/mL	307.17	2948.64	10.42 (9.13, 11.89)
C_{max}, ng/mL	17.05	357.14	4.77 (4.10, 5.56)
C_{tau}, ng/mL	10.27	57.62	17.83 (15.07, 21.08)
Study GS-US-292-0111	**N=21**	**N=15**	
AUC_{tau}, ng.h/mL	278.73	3682.91	7.57 (6.62, 8.65)
C_{max}, ng/mL	16.14	442.74	3.65 (3.12, 4.26)
C_{tau}, ng/mL	9.34	74.69	12.51 (10.59, 14.78)

AUC_{tau}=AUC from time of administration up to the end of the dosing interval; CI=confidence interval; C_{max}=maximum observed analyte concentration; C_{tau}=plasma concentration at the end of the dosing interval; LS=least square; N=maximum number of subjects

2.2.3.4. A Phase 3, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects Who are Virologically Suppressed on Regimens Containing F/TDF (Study GS-US-311-1089)

NDA208215/mod5.3.5.1/GS-US-311-1089_CSR

Study GS-US-311-1089 is a Phase 3 randomized, double-blind, multicenter, active controlled study to evaluate the efficacy and safety of FDC F/TAF versus F/TDF in combination with a third agent for the treatment of HIV-1 infection in virologically suppressed adults who either switched to F/TAF, or continued treatment with F/TDF.

The TAF PK parameters, overall and by subgroup are summarized in Table 20. Estimated TAF exposures (AUC_{tau} and C_{max}) were available from 292 subjects.

This study also allows for a direct comparison of intracellular concentrations of the active phosphorylated metabolite TFV-DP between F/TAF and F/TDF in combination with various third agents (boosted by rtv or unboosted). Intracellular PBMC TFV-DP concentrations were more than 4-fold higher in the subjects who received F/TAF than in those who received F/TDF (LS mean [95% CI] 114.001 [100.899, 128.804] pg/10^6 cells for the F/TAF group and 27.781 [24.799, 31.122] pg/10^6 cells for the F/TDF group; LS mean ratio of 416.1%). In the analysis of intracellular PBMC TFV-DP concentration by third agent (boosted by rtv or unboosted), LS mean concentrations in subjects receiving F/TAF ranged from 54.224 to 268.000 pg/10^6 cells, with the number of subjects in each subgroup varying from n=1 to n=82. Although the sample sizes are small, concentrations of intracellular TFV-DP appear to track with the changes in TAF plasma exposure observed upon coadministration with various third agents in clinical studies.

Table 20: Summary of Estimate TAF Exposures (Study GS-US-311-1089)

TAF Exposures Mean (%CV)	N	AUC_{tau}, ng.h/mL	C_{max}, ng/mL
All	292	137.2 (48.1)	140.5 (54.0)
By third agent			
ATV/r	44	149.6 (50.8)	127.1 (60.3)
DRV/r	72	73.5 (41.0)	74.0 (44.2)
DTG	25	155.6 (18.5)	166.3 (36.9)
EFV	6	141.6 (18.7)	126.9 (52.8)
LPV/r	15	89.8 (25.0)	97.1 (42.4)
MVC	1	191.3 (N/A)	249.8 (N/A)
NVP	67	167.4 (32.1)	178.1 (30.2)
RAL	61	170.8 (37.2)	185.4 (44.4)
RPV	1	273.1 (N/A)	238.5 (N/A)

AUC=area under the plasma concentration-time curve; ATV=atazanavir; C_{max}=maximum plasma concentration; DTG=dolutegravir; EFV=efavirenz; LPV=lopinavir; MVC=maraviroc; N/A=not available; NVP=nevirapine; RAL=Raltegravir; RPV=rilpivirine

Table 21 presents the virologic success and virologic failure rates in study GS-US-311-1089 by third agent, again indicating that the virologic response rate is high for all subgroups and independent of third agent or TAF exposure. Further PK/PD analysis is described in Section 2.2.3.6 and Section 3.5.1.4.3.

Table 21: TAF Exposure and Virologic Outcome at Week 48 Using Snapshot Algorithm and HIV-1 RNA <50 copies/mL by Third Agent (Full Analysis Set) (Study GS-US-311-1089)

	F/TAF + 3rd Agent with Available PK Data		F/TAF + 3rd Agent (N=333)			F/TDF + 3rd Agent (N=330)		
Third Agent	N	Mean (%CV) TAF AUC_{tau} (ng*h/mL)	N	Percent of Virologic Success at Week 48 (HIV-1 RNA <50 copies/mL)	Percent of Virologic Failure at Week 48 (HIV-1 RNA ≥50 copies/mL)	N	Percent of Virologic Success at Week 48 (HIV-1 RNA <50 copies/mL)	Percent of Virologic Failure at Week 48 (HIV-1 RNA ≥50 copies/mL)
ATV/r	44	149.6 (50.8)	53	90.6	0	50	94.0	2.0
DRV/r	72	73.5 (41.0)	84	90.5	1.2[a]	82	91.5	2.4
DTG	25	155.6 (18.5)	26	96.2	0	23	91.3	0
EFV	6	141.6 (18.7)	8	100	0	6	83.3	16.7
LPV/r	15	89.8 (25.0)	18	100	0	18	100	0
MVC	1	191.3 (NA)	1	100	0	6	100	0
NVP	67	167.4 (32.1)	74	97.3	0	66	98.5	0
RAL	61	170.8 (37.2)	66	95.5	0	73	89.0	0
RPV	1	273.1 (NA)	3	100	0	6	83.3	16.7

a Subject had TAF AUC of 197.3 ng.h/mL
AUC=area under the plasma concentration-time curve; ATV=atazanavir; C_{max}=maximum plasma concentration; DTG=dolutegravir; EFV= efavirenz HIV=human immunodeficiency virus; LPV=lopinavir; N/A=not applicable; NVP=nevirapine; RAL=Raltegravir; RPV=rilpivirine

2.2.3.5. Integrated Ad Hoc Pharmacokinetic Analysis of TAF 25 mg and TAF 10 mg Plus COBI

In support of the TAF population PK analyses by GSI and to further characterize TAF single- and multiple-dose PK and the effect of covariates on TAF exposure, an integrated ad hoc PK analysis was performed by GSI using data from studies conducted with TAF 25 mg or TAF 10 mg + COBI. For these analyses, data were pooled from studies conducted in healthy or HIV-infected subjects who were administered single-agent TAF 25 mg, F/TAF 200/25 mg, E/C/F/TAF, or F/TAF 200/10 mg + COBI and who had at least 1 non-missing PK parameter (ie, AUC or C_{max}) for the respective analyte. Studies used in the population PK analysis are presented in NDA208215/Mod5.3.5.3/Integrated Ad Hoc PK Analysis for TAF/Tab1.1. A mixed-effect modeling approach using stepwise model selection was applied for each of the PK parameters of interest. Covariates were entered into a multivariate model in a forward stepwise fashion based on the Akaike information criterion (AIC) fit statistic.

Findings from these supportive analyses are included in the discussion of the effect of intrinsic factors (Section 3.3).

2.2.3.6. TAF – HIV-infected subject Pharmacokinetic/Pharmacodynamic Analyses

During the TAF development, PK/PD analyses were performed for TAF and TFV, by GSI. Firstly, the PK/PD relationship between TAF exposure and antiviral activity was explored in the proof-of-concept study, GS-US-120-0104, which established the antiviral effect of TAF in a dose range of 8 to 40 mg once daily. The PK/PD analyses are extensively discussed in Section 3.5, and the proof-of-concept study is briefly described in Section 2.2.3.2.

TAF PK/PD analysis was also performed, by GSI, on pooled data from 2 Phase 3 studies with E/C/F/TAF in which the efficacy and safety of TAF versus TDF was investigated (GS-US-292-0104 and GS-US-292-0111). Subjects included in the PK/PD analysis sets had received at least 1 dose of the E/C/F/TAF FDC and had at least 1 non-missing parameter estimated from the TAF or TFV population PK analysis. A brief overview of the pharmacokinetic data in these studies is provided in Section 2.2.3.3 and PK/PD analyses are discussed in Section 3.5

In addition, PK/PD analysis was also performed, by GSI, on data from a Phase 3 study with the F/TAF FDC in which the efficacy and safety of F/TAF with a variety of 3rd agents was investigated (GS-US-311-1089). Subjects included in the PK/PD analysis set had received at least 1 dose of the F/TAF FDC and had at least 1 non-missing parameter estimated from the TAF or TFV population PK analysis. A brief overview of the pharmacokinetic data in the study is provided in Section 2.2.3.4 and PK/PD analyses are discussed in Section 3.5.

Finally, PK/PD data from Phase 2 study GS-US-299-0102 (Section 2.2.2.1) and Phase 3 studies TMC114FD2HTX3001 (Section 2.2.2.2) and TMC114IFD3013 (Section 2.2.2.3) with the D/C/F/TAF FDC are discussed in Section 3.5.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. General Absorption, Distribution, Metabolism, and Excretion Characteristics of the Drug Components

The ADME characteristics of DRV, COBI, FTC and TAF have not been investigated in the context of the current application for the D/C/F/TAF FDC and as such are based on data from the developments of the individual drug components, which have been previously detailed in the applications for DRV (PREZISTA, NDA021976), DRV/COBI (PREZCOBIX, NDA205395) and for F/TAF (Descovy, NDA208215). A summary of the relevant information is provided below.

3.1.1. Absorption

3.1.1.1. Absorption - In Vitro or Non Clinical Studies

Darunavir: Darunavir is classified as a compound with intermediate to high absorptive permeability. Based on a human Caco-2 cell in vitro model (part of the DRV application), DRV exhibits sufficient membrane permeability to obtain adequate intestinal absorption. The ratio of secretory/absorptive transport decreased with DRV concentration, indicative of efflux (eg, P-gp) (Mod2.4/Sec3.1). This was further supported by a drug-drug interaction study indicating that digoxin (a P-gp substrate) exposure increased when digoxin was coadministered with DRV/rtv.

Cobicistat: Monolayers of Caco-2 cells were used as an in vitro model to investigate the bidirectional permeability and polarized transport characteristics of COBI. Cobicistat displayed high forward permeability (7.61×10^{6} cm/s) with little evidence for efflux (efflux ratio of 1.1). The efflux ratio in P-gp-transfected cells and BCRP-transfected cells was higher (16-fold and 1.9-fold, respectively) than in the corresponding wild-type cells, which suggests that COBI can act as a substrate for these transporters. However, given its high permeability, aqueous solubility, and local intestinal concentrations following oral dosing, the absorption potential of COBI is high (Mod2.4/Sec3.1).

Emtricitabine: Emtricitabine is rapidly and extensively absorbed after oral administration in mice, rats, and cynomolgus monkeys, with oral bioavailability ranging from 58% to 97%. Exposure is roughly dose proportional over most of the range explored. Absorption of FTC was also rapid and complete in humans over the clinical dose range. Emtricitabine is not extensively metabolized; therefore, its bioavailability is likely to be governed only by absorption, with little or no first pass metabolism in the intestinal wall or liver (Mod2.4/Sec3.1).

Tenofovir alafenamide: Tenofovir alafenamide showed a dose-dependent increase in forward permeability and a decrease in efflux ratio indicating saturable efflux transport (Caco-2 cells). At 100 μM TAF, the apparent forward permeability rate was 0.63×10^{-6} cm/s and the efflux ratio 13.6. Addition of the efflux transport inhibitor, cyclosporine A diminished the efflux ratio and increased the forward permeability. The PK of TAF has been extensively characterized in vitro and in nonclinical species, and is characterized by rapid absorption across species with a t_{max} of 0.08 hours in mouse and dog and 0.5 hours in monkey. In all rat plasma samples, TAF was undetectable. Following oral administration in dogs and monkeys, TAF plasma concentrations decline rapidly, with a $t_{1/2}$ of

<1 hour and concentrations undetectable in plasma by 5 hours postdose. Concomitant with the rapid decline in TAF concentrations in plasma, the predominant metabolite TFV was formed and persisted in plasma over the dosing interval. Consistent with the dose-dependent permeability observed in vitro, the oral bioavailability of TAF increased with increasing dose in dogs and the observed oral bioavailability was 14.3% at the 10 mg/kg dose.[1] Following a 15 mg/kg oral dose of [^{14}C]TAF to bile duct cannulated dogs, the fraction absorbed was at least 41% based on excretion in urine and bile. Therefore, hepatic extraction was calculated to be approximately 65% (Mod2.4/Sec3.1).

3.1.1.2. Bioavailability

An overview table of bioavailability parameters across D/C/F/TAF studies in healthy volunteers is provided in Appendix 2.

The absolute bioavailability of DRV, COBI, FTC and TAF has not been investigated in support of the marketing authorization of the D/C/F/TAF FDC. Relative bioavailability and bioequivalence studies (TMC114FD2HTX1001, TMC114FD2HTX1002, and GS-US-299-0101) have been conducted to compare the systemic exposure of DRV, COBI, FTC and TAF following different D/C/F/TAF FDC tablet formulations, and following D/C/F/TAF FDC administration versus coadministration of the separate agents (refer to Mod2.7.1/Sec2). The effect of food on the bioavailability of DRV, COBI, FTC, and TAF with the intended commercial D/C/F/TAF FDC tablet formulation was investigated in study TMC114FD2HTX1002 (refer to Mod2.7.1/Sec2.1.1.1). The impact of splitting or crushing of the D/C/F/TAF FDC on the bioavailability of DRV, COBI, FTC, and TAF was investigated in study TMC114FD2HTX1004 (refer to Mod2.7.1/Sec2.1.1.3).

Further data are available from the developments of the individual drug components, and have been previously detailed in the respective applications for those products.

Darunavir: The absolute bioavailability of a single 600 mg dose of DRV alone is approximately 37% and increases to approximately 82% in the presence of 100 mg twice daily of the PK enhancer, rtv (NDA021976/Mod5.3.1.1/TMC114-C114_CSR). The overall pharmacokinetic enhancement effect by rtv was an approximate 14-fold increase in the systemic exposure of DRV when a single dose of 600 mg darunavir was given orally in combination with rtv at 100 mg twice daily.

Cobicistat: The absolute bioavailability of COBI has not been evaluated. Cobicistat displays greater than dose-proportional increases in plasma exposure due to a combination of reduced systemic CL/F and higher bioavailability via autoinhibition of its own metabolism by CYP3A, which is the desired PD effect for a PK enhancer. The bioavailability of COBI increases with dose following both single- and multiple-dose administration (before reaching a plateau at >150 to 200 mg) which is consistent with its metabolic autoinhibition properties and reduction in first pass effect, and results in a low CL/F (approximately 10% to 15% of hepatic blood flow) (NDA203094/Mod5.3.4.1/GS-US-216-0101_CSR; NDA203094/Mod5.3.3.1/GS-US-216-0113_CSR). At doses greater than 150 to 200 mg, increases in COBI exposure following multiple dose administration corresponded to proportional increases in plasma $t_{1/2,term}$ and reduction in CL/F,

rather than to substantial changes in bioavailability. Accordingly, the bioavailability of COBI is considered to be high.

Cobicistat has 3 basic ionizable groups with pKa of 6.4, 2.5, and 1.8. The intrinsic aqueous solubility of COBI free base (0.075 mg/mL, pH approximately 7) is significantly enhanced under acidic conditions at pH 2 (70 mg/mL). Being a mechanism based inhibitor of CYP3A, COBI exhibits both dose/concentration and time-dependent inhibition of CYP3A; its ability to effectively boost CYP3A substrates is dependent on the concentrations that are achieved pre-systemically and/or systemically. Accordingly, clinical studies were conducted to examine the relative bioavailability and disposition of COBI (in combination with the HIV-integrase inhibitor and CYP3A substrate, EVG) when coadministered with acid reducing agents (Studies GS-US-216-0120; GS-US-216-0122, Table 5). Cobicistat absorption was unaffected upon staggered administration (12 hours apart) or coadministration with omeprazole or famotidine; the 90% CIs of the LS mean ratios of COBI exposure parameters were within 80.00% to 125.00%, indicating that changes in gastric pH do not affect COBI PK or its pharmacoenhancing properties.

Emtricitabine: Single- and multiple- dose PK studies have shown that FTC is rapidly and extensively absorbed after oral administration. Plasma FTC concentrations were measurable at the earliest sampling time (15 minutes postdose) and reached a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1200 mg) and then followed an apparent multiexponential decay from the plasma. More than 85% of an oral dose of FTC is absorbed with little first pass elimination prior to reaching the systemic circulation, resulting in a high absolute bioavailability value (93% as shown in study FTC-110, NDA021752/Mod5.3.1.1/FTC-110_CSR).

Urinary excretion data provide evidence that FTC is extensively absorbed after single or repeated oral doses administered. Urinary recovery of unchanged FTC averaged 47% to 74% in studies with capsule or solution formulations following oral administration of 200 mg FTC as a single dose or at steady-state following once-daily administration. Total recovery of unchanged FTC and its metabolites in urine as determined in a [^{14}C]FTC mass balance study (FTC-106) averaged 85.8% of the administered oral dose, providing the evidence of extensive oral absorption. The remainder of the [^{14}C]FTC dose recovered in feces (13.7%) exclusively as unchanged FTC, primarily over the 48- to 96-hour post dose period.

Tenofovir alafenamide (NDA208215)**:** The TAF PK profile following single doses and at steady-state has been characterized in healthy and HIV-infected individuals at doses ranging from 8 to 125 mg. Tenofovir alafenamide PK is characterized by rapid absorption, with a median plasma t_{max} of approximately 0.50 hours.

Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (approximately 40%). TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine.[19,44] Inhibition of P-gp by a boosting agent (eg, COBI or rtv) reduces P-gp mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. TAF exposures following a 10 mg dose (either as a single agent coadministered with COBI 150 mg or as a component of E/C/F/TAF) have

been shown to be comparable with the exposure achieved following administration of TAF 25 mg either as a single agent or as a component of F/TAF in the absence of a booster. For D/C/F/TAF 800/150/200/10 mg, the TAF exposures are also in the same range as those observed with other combinations, albeit on the lower end of the range.

3.1.1.3. Influence of food

The influence of food on drug absorption for the components of the D/C/F/TAF FDC is described in Section 3.4.1 and in detail in Mod2.7.1/Sec3.2.

3.1.1.4. Influence of administration mode

The influence of splitting or crushing of the D/C/F/TAF FDC on the bioavailability of its components is described in Mod2.7.1/Sec3.1.3.

3.1.2. Distribution

Darunavir (NDA021976**):** The in vitro plasma binding of DRV was investigated in studies TMC114-NC113 and TMC114-NC215 (Mod2.4/Sec3.2). Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α1-acid glycoprotein, and plasma protein binding was concentration dependent. The blood-to-plasma concentration ratio for DRV in humans was 0.64 at DRV 0.5 µg/mL (Mod2.4/Sec3.2.1). Following IV administration, the (mean ± SD) volume of distribution of DRV alone was 88.1 ± 59.01 L and increased to 131 ± 49.91 L in the presence of 100 mg twice-daily rtv.

Cobicistat (NDA203094**):** The plasma protein binding of COBI in nonclinical species ranged from 90.9% to 97.7%, and was 97.3% in samples from clinical studies with healthy human subjects (on average 97% to 98%). Plasma protein binding was concentration independent. After an oral 150 mg dose of [^{14}C]COBI in healthy subjects, the plasma-to-blood ratio of ^{14}C-radioactivity was approximately 2 and was time-independent, indicating that COBI and its metabolites are excluded from the cellular components of the blood (Mod2.4/Sec3.2). The distribution of COBI into compartments other than plasma (eg, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated.

Emtricitabine (NDA021752): In vitro binding of FTC to human plasma proteins is estimated to be <4% and independent of concentration over the range of 0.02 to 200 µg/ml (Mod2.4/Sec3.2). The mean plasma-to-blood concentration ratio is approximately 1.0 and the mean semen-to-plasma concentration ratio is approximately 4.0. The apparent volume of distribution after IV administration of FTC is 1.4 ± 0.3 l/kg, indicating that FTC is widely distributed throughout the body to both intracellular and extracellular fluid spaces.

Tenofovir Alafenamide (NDA208215)**:** Protein binding of TAF was moderate in dog and human plasma with percentage unbound values of 48.0% and 46.8%, respectively. These in vitro values were higher than those observed in multiple human ex vivo studies with the mean percentage unbound TAF ranging from 14% to 23% in all subjects (Mod2.4/Sec3.2). Following oral administration of [^{14}C]TAF to rat, mouse, and dog, [^{14}C]TAF derived radioactivity was widely distributed to most of

the tissues in all species. Distribution studies in dogs showed 5.7 to 15 fold higher ^{14}C radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [^{14}C]TAF relative to [^{14}C]TDF.[27] The distribution of TAF into compartments other than plasma (eg, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated.

3.1.3. Metabolism and Excretion

In vitro metabolism and clinical mass-balance studies were performed with the separate agents DRV, COBI, FTC and TAF in support of their respective marketing authorizations as also detailed in the applications for DRV/COBI and for F/TAF.

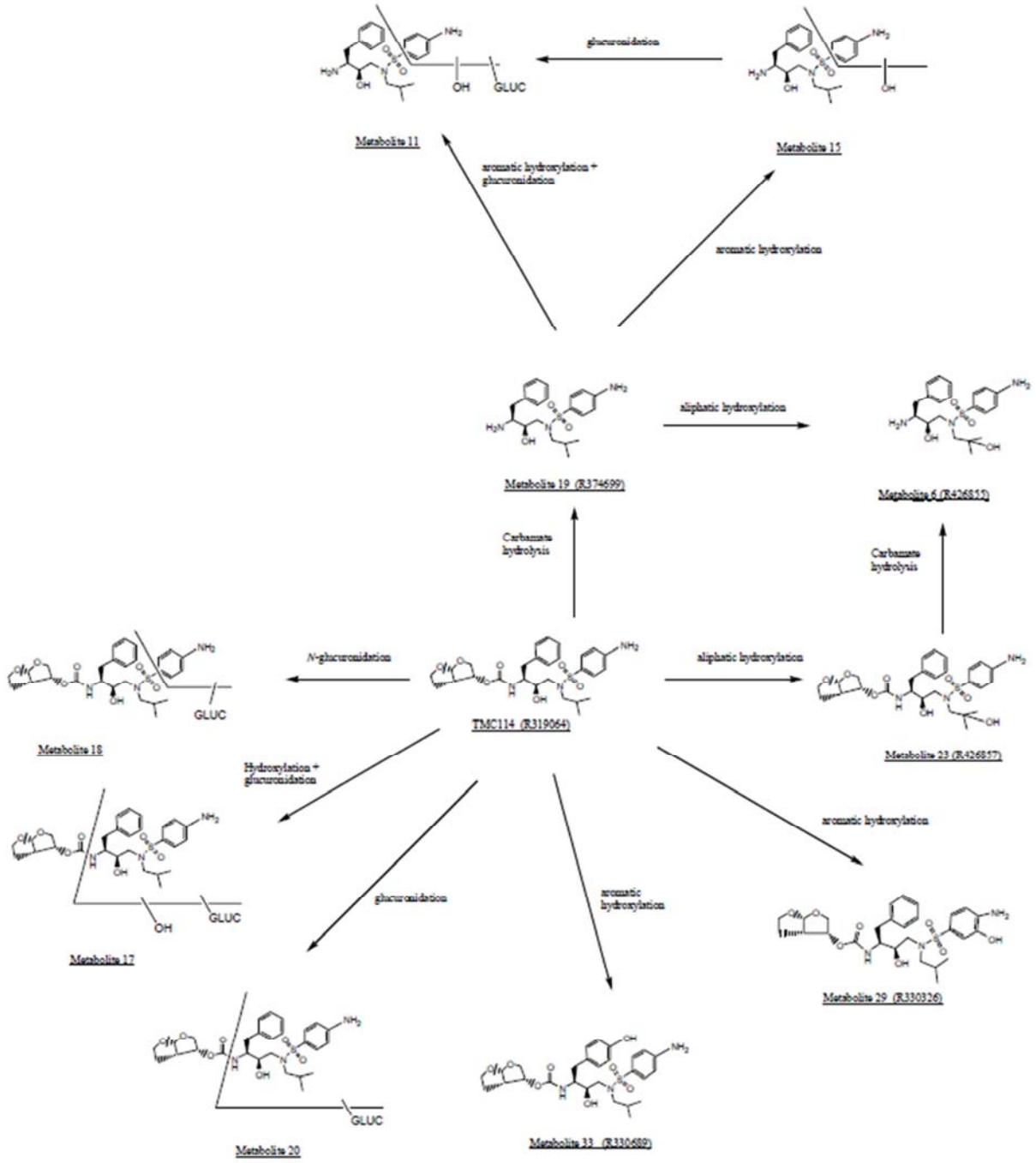
3.1.3.1. In Vitro Metabolism

Darunavir (NDA021976)**:** A nonclinical study in human liver subcellular fractions and/or hepatocytes detected a relatively large number of metabolites for DRV (study TMC114-NC154, Mod2.4/Sec3.3). Major metabolic pathways identified were aliphatic (M21, M23), aromatic (M24, M29), alicyclic hydroxylation (M12, M27, and M28), and carbamate hydrolysis (M19, which was then metabolized further via various pathways to M2, M6, M15, M1, M11, and M3). Minor pathways included glucuronidation (M18, M20, and M17), N dealkylation (M14), and N acetylation (M30). In a nonclinical study (TMC114-NC213, Mod2.4/Sec3.3) using samples from the clinical mass-balance study TMC114-C109, in the absence of rtv, biotransformation of DRV occurred through aliphatic and aromatic hydroxylation, carbamate hydrolysis, and glucuronidation (Figure 20). The predominant metabolic pathway was carbamate hydrolysis, accounting for 13.2% of the dose. Aliphatic hydroxylation at the isobutyl moiety towards the tertiary alcohol function (9.8%) and aromatic hydroxylation at the aniline moiety (4.5%) were other major pathways. In the presence of rtv, the carbamate hydrolysis, isobutyl aliphatic hydroxylation, and aniline aromatic hydroxylation pathways were significantly inhibited, accounting for 0.67%, 2.26%, and 1.42% of the dose, respectively.

In human liver microsomes, the oxidative metabolism of DRV or [^{14}C]DRV was primarily catalyzed by CYP3A enzymes (studies TMC114-NC112 and TMC114-NC202, Mod2.4/Sec3.3). All of the metabolites of DRV identified in human matrices showed activity that was at least 10 fold less than the activity of DRV against wild-type HIV.

A study of CYP interaction potential using CYP probe substrates found that DRV strongly inhibited CYP3A (inhibition constant=0.40 μM), indicating that drug-drug interactions due to CYP3A inhibition are likely (study TMC114-NC123, Mod2.4/Sec3.3). A slight induction by DRV of CYP3A in human hepatocyte cultures was also observed.

Figure 20: Metabolic Pathways of [^{14}C]DRV in Humans After Single-Dose Oral Administration of 400 mg [^{14}C]DRV

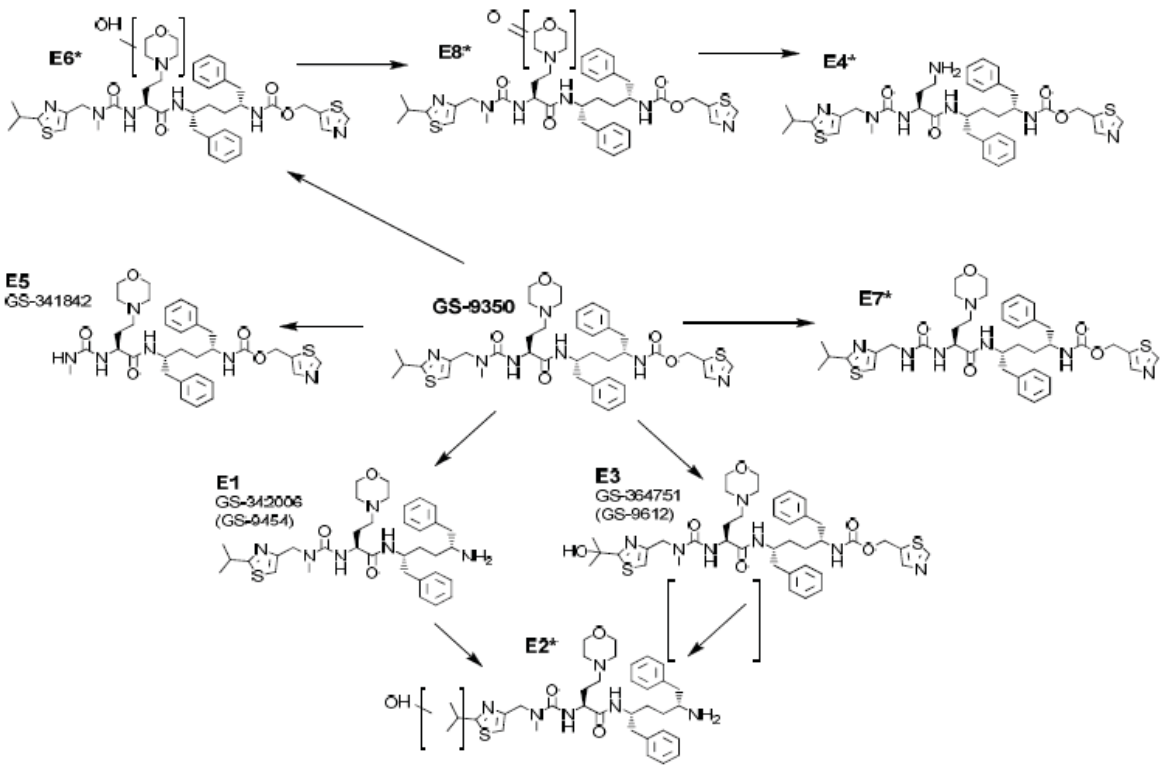


Cobicistat (NDA203094)**:** The metabolism of COBI is mediated primarily via oxidative processes. Preliminary identification of COBI metabolites was performed in vitro using human hepatocytes and in nonclinical and human hepatic microsomal fractions. In all species apart from dog, COBI metabolism could be accounted for by the generation of 3 metabolites: M21, M31, and M26.

Metabolite identification was performed with samples from in vivo studies with [^{14}C]COBI in nonclinical species and in humans (Figure 21). No direct conjugates of COBI were detected, and the 3 primary metabolites (M21, M26, and M31) were common to all species in vivo and in vitro.

The intended pharmacological effect of COBI is inhibition of human CYP3A enzyme activity. Assessment of CYP3A inhibitions in human hepatic microsomal fractions demonstrated that COBI is a potent mechanism-based inhibitor of human CYP3A. COBI had relatively minimal off target inhibitory effects on other CYP isoforms in vitro and did not significantly inhibit UGT1A1 in vitro (Mod2.4/Sec3.3).

Figure 21: Proposed Biotransformation Pathway of COBI in Humans



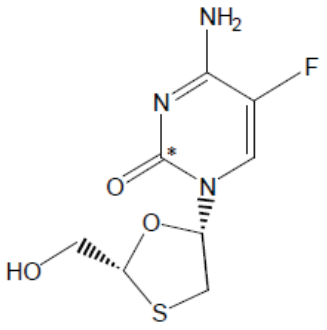
E1=M21; E3=M31; E5=M26. E1, E3, and E5 were generated by humans, mice, rats, and dogs; E2, E4, E6, E7, and E8 were generated exclusively by dogs.

Emtricitabine (NDA021752)**:** In radiolabel studies in mice, rats, and cynomolgus monkeys, it was shown that metabolism accounts for only a minor percentage of FTC elimination. Only trace levels of metabolites were found in feces. Over 90% of the radioactivity in mouse and rat urine, and 64% of the radioactivity in monkey urine was unchanged drug. In humans, unchanged FTC with 3 minor metabolites in urine accounted for essentially the entire dose recovered in urine (approximately 86%) (Figure 22). The 3 putative metabolites were 2 sulfoxides (M1 and M2) and a glucuronide (M3) and they were also identified in other nonclinical species. Thus, FTC is not extensively metabolized and is eliminated primarily as unchanged drug by renal excretion. Based on these observations, it is unlikely

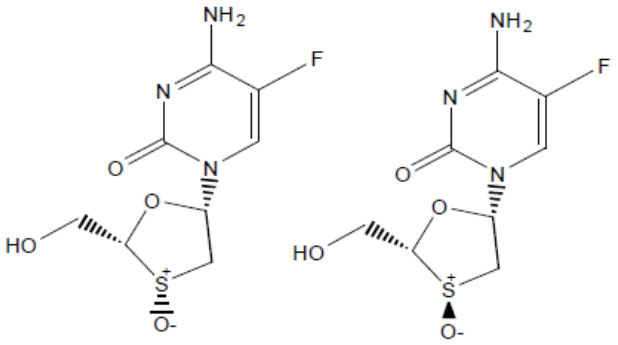
that FTC will be subject to significant first pass metabolism, or to changes in CL/F due to hepatic disease or metabolic drug interactions (Mod2.4/Sec3.3).

FTC and TAF are analogs of 2 different nucleosides, cytidine and adenosine, respectively, and do not share a common intracellular metabolism pathway for pharmacological activation through phosphorylation.

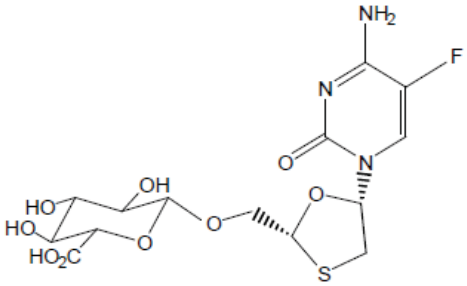
Figure 22: Putative Metabolites of FTC



Emtricitabine (FTC)
*:indicates the site of ^{14}C label



M1 and M2 (3′-Sulfoxide Diastereomers of Emtricitabine)

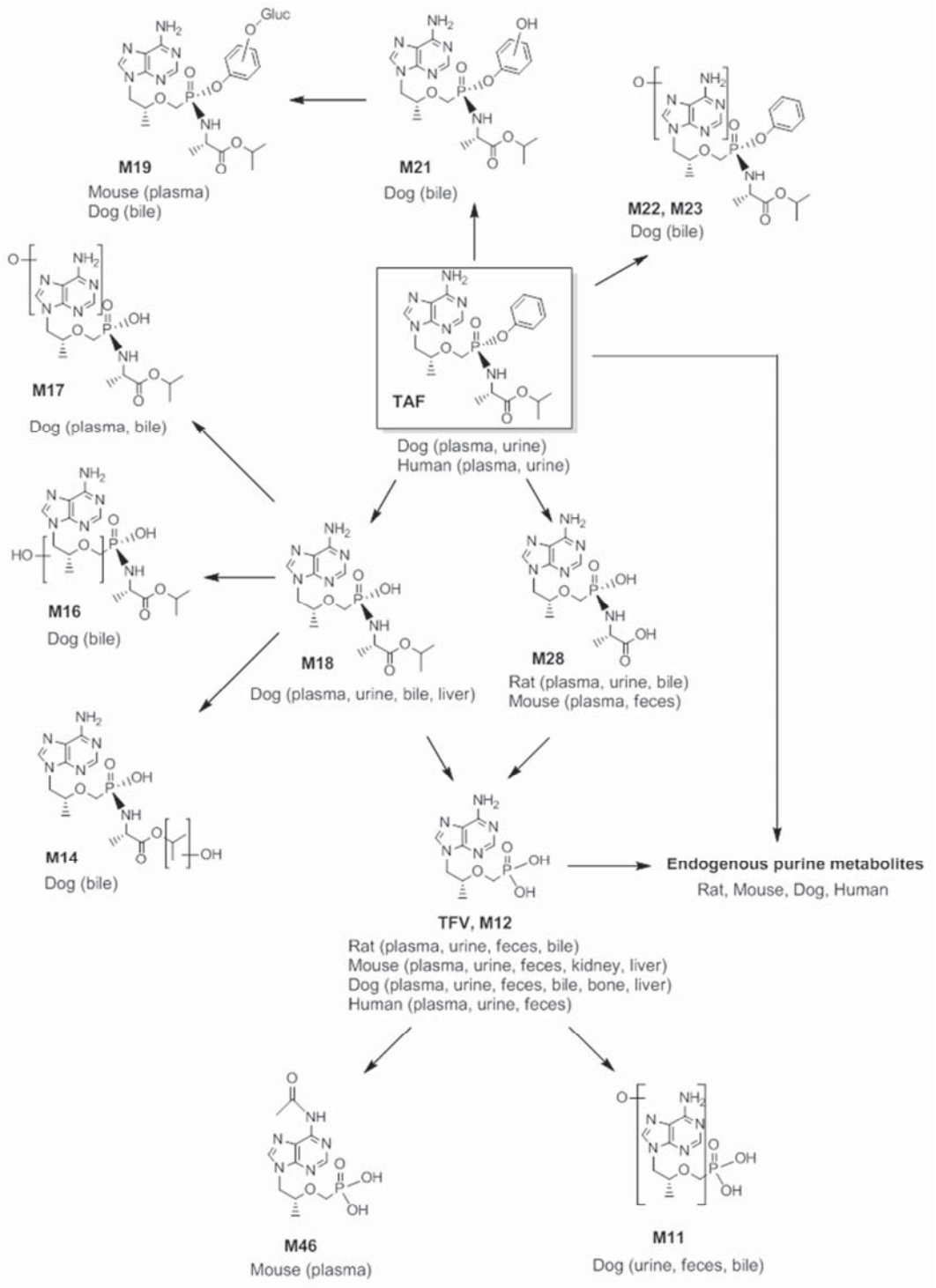


M3 (2′-O-Glucuronide of Emtricitabine)

Tenofovir alafenamide (NDA208215)**:** The biotransformation of TAF was studied in mice, rats, dogs, and humans (Figure 23). Endogenous purine metabolites including hypoxanthine, xanthine, allantoin, and uric acid were observed in all species, including humans. TFV accounted for a majority of drug related material in plasma, urine, and feces from all species, except for human plasma in which uric acid was the predominant metabolite, accounting for 73.9% of the total AUC over 96 hours. The major metabolite in rat bile was M18, which accounted for 63% of total radioactivity recovered in bile. M18 and its oxidized metabolite, M16, were the major metabolites in dog bile accounted for 29% and 38% of total radioactivity recovered in bile. Various oxidative metabolites were found in dog bile. No metabolites unique to human were observed. Following oral dosing of mice, rats, and dogs with [^{14}C]TAF, the majority of radiolabel was recovered in the feces or urine in all species. The elimination of a large amount of radioactivity in bile of bile duct cannulated dogs indicates that biliary excretion is a major route of elimination of [^{14}C]TAF derived radioactivity in dogs. Total recovery of radiolabel was high for all species.

The major enzyme involved in intracellular (PBMCs) conversion of TAF to TFV is cathepsin A, which is a high capacity and low affinity pathway not readily inhibited by other xenobiotics (Mod2.4/Sec3.3).

Figure 23: Biotransformation Pathway of TAF



3.1.3.2. Mass-balance and In Vivo Metabolism

A mass-balance study with the D/C/F/TAF FDC has not been conducted. Data from mass-balance studies with the individual components are summarized below.

Darunavir and COBI are primarily metabolized by CYP3A. Cobicistat is a mechanism based inhibitor of CYP3A and increases the exposure to DRV such that DRV exposures (AUC_{24h} and C_{max}) comparable to DRV coadministered with rtv are achieved. Darunavir is predominantly excreted in feces, with minimal renal excretion, when coadministered with COBI. The renal excretion of COBI is also low. Emtricitabine is primarily eliminated from the plasma via renal excretion, with minimal metabolism. Tenofovir alafenamide is extensively metabolized and excreted in feces and urine as its major metabolite, TFV.

Darunavir (NDA021976)**:** In a clinical mass-balance study (study TMC114-C109, Section 2.1.1.2), the majority of [^{14}C]DRV-related radioactivity was excreted in feces (81.7% and 79.5% at 168 hours in the absence and presence of rtv, respectively); 12.2% and 13.9% of the radioactivity was recovered in urine in the absence and presence of rtv, respectively, including 1.2% and 7.7% as unchanged drug. Darunavir was extensively metabolized in the absence of rtv (only 8% of the dose was excreted unchanged after 48 hours), while coadministration of rtv markedly reduced metabolism (48.8% of the dose excreted unchanged after 48 hours). Unchanged drug was mainly excreted in feces, both with and without rtv coadministration.

Cobicistat (NDA203094)**:** In a clinical mass-balance, PK, and metabolite profile study of COBI following administration of an oral dose of [^{14}C]COBI in healthy subjects (study GS-US-216-0111, Section 2.1.1.2), quantifiable levels of [^{14}C] radioactivity in whole blood and plasma were observed for up to 28 and 32 hours after dosing, respectively. Following oral administration of [^{14}C]COBI, COBI was extensively metabolized, primarily via CYP3A and/or CYP2D6 mediated oxidation, with no evidence of Phase 2 metabolism. The total combined recovery of [^{14}C] radioactivity in feces and urine was 94.4%, with most of the radioactive dose recovered from the feces (86.2%), consistent with the hepatobiliary excretion of COBI. The dose was primarily recovered as parent drug or metabolites M21 or M31; 8.2% of the administered dose was recovered in urine, primarily as unchanged parent drug, with low levels of metabolites M21 and M31. The predominant species circulating in plasma was COBI, which accounted for 98.6% of the total radioactivity over 24 hours. In some instances, at individual timepoints (≤2 timepoints), low levels of radioactive metabolite(s) were detected in pooled plasma samples; however, composite concentration time profiles could not be drawn, precluding quantification of these metabolites.

In feces, COBI was the major species present (27%), followed by known oxidative metabolites, M31 (14%), which results from hydroxylation of isopropyl thiazole, and M21 (5.5%), which results from carbamate cleavage. All other metabolites detected in the feces were in trace amounts, with no values exceeding 3% of the administered dose. Renal excretion of COBI was a minor pathway for elimination (representing 6.31% of the total radioactive dose) and was comprised primarily of COBI. Metabolites M21 and M31 were present in very low amounts in urine.

Emtricitabine (NDA021752)**:** Emtricitabine is primarily eliminated from the plasma via renal excretion as unchanged drug (approximately 65% of an oral dose and approximately 73% of an IV dose). Studies in animals and humans have shown that FTC undergoes little metabolism; metabolism is a minor route of elimination and coadministered drugs known to affect drug metabolism, especially pathways mediated by CYP, would not be expected to have a significant effect on the metabolism of FTC. Furthermore it is unlikely that FTC is an inducer or inhibitor of CYP as other structurally related nucleoside analogs, such as lamivudine (3TC), are not known to affect drug metabolism of coadministered agents. Two clinical studies (FTC-101 and FTC-106) showed that FTC is metabolized intracellularly in PBMCs (the active site for the anti HIV action) to form its active metabolite, FTC-TP. In a mass balance study with [^{14}C]FTC (study FTC-106, Section 2.1.1.3), 99.6% of the total radioactive dose was recovered in urine and feces, and 91.5% of the dose was accounted for as FTC and 3 putative metabolites with structures tentatively identified by mass spectrometry. An average of 65% to 70% of the oral FTC dose was excreted in urine as unchanged drug, accounting for approximately 80% of the total radioactivity present in urine.

Tenofovir alafenamide (NDA208215): Tenofovir alafenamide has a distinct metabolism profile designed to maximize both antiviral potency and clinical safety. Inside cells, TAF is converted by intracellular enzymes to form the pharmacologically active metabolite TFV-DP. Due to increased plasma stability and activation by cathepsin A, as compared with TDF, TAF is more efficiently loaded into PBMCs (including lymphocytes and other HIV target cells) and macrophages, which results in greater concentrations of TFV-DP in PBMCs and much lower exposure of TFV to the systemic circulation and undesired tissues, including the kidney and bone. In Phase 2 clinical trial GS-US-299-0102 (Section 2.2.2.1), D/C/F/TAF demonstrated 6.5-fold higher TFV-DP concentrations in peripheral blood mononuclear cells (PBMCs) and approximately 90% reduction in systemic TFV, compared to the TDF-containing regimen.

Study GS-US-120-0109 (Section 2.1.1.3) evaluated the mass balance and PK of TAF following an oral dose of [^{14}C]TAF to healthy subjects. Tenofovir alafenamide was extensively metabolized (>80% of an oral dose) and excreted in feces and urine as the major metabolite, TFV. Metabolism of TAF to TFV was rapid, with median TAF plasma $t_{1/2}$ of 0.51 hours and a median TFV t_{max} of 3.25 hours postdose. TFV had a median plasma $t_{1/2}$ of 32.37 hours. The predominant species detected in feces was TFV, with all other metabolites detected in trace amounts (no value exceeding 2% of the administered radioactive dose). Renal excretion of TAF as parent drug was a minor pathway (≤2%) (see also GS-US-120-0108, Section 2.1.4.2 and refer to Section 3.3.5).

3.2. Pharmacokinetic Characteristics

The PK parameters of DRV, COBI, FTC and TAF from noncompartmental PK analysis and population PK analysis (DRV and TAF only) for D/C/F/TAF FDC studies are discussed in the sections that follow. In addition, data from historical studies that further support the marketing authorization are briefly discussed below, where applicable.

The PK characteristics of DRV and COBI have previously been reported in the DRV/COBI marketing authorization.

Darunavir/COBI: The noncompartmental PK of DRV and COBI following multiple-dose administration of DRV/COBI 800/150 mg as single agents or as FDC tablet formulations were compared with DRV/rtv 800/100 mg coadministered as single agents, in two studies in healthy subjects (NDA205395/Mod5.3.1.1/TMC114IFD1001CSR; NDA205395/Mod5.3.1.2/GS-US-216-0115_CSR). Within these studies, exposure (C_{max} and AUC_{24h}) to DRV following coadministration of DRV/COBI 800/150 mg once daily was comparable to the exposure to DRV following coadministration of DRV/rtv 800/100 mg once daily. Darunavir exposure was also generally comparable to historical data for DRV exposure following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents. The rate of absorption of DRV was generally similar for DRV/COBI and DRV/rtv combinations; median t_{max} generally ranged from 3.0 to 5.0 hours. Exposure (C_{max} and AUC_{24h}) to COBI following administration of DRV/COBI 800/150 mg once daily FDC tablet formulations was generally comparable to the exposure to COBI following coadministration of DRV/COBI 800/150 mg once daily as single agents and was also comparable to historical data for COBI 150 mg when administered as part of the E/C/F/TDF FDC 150/150/200/300 mg.

In general, the DRV exposure when coadministered with COBI was also comparable to historical data for rtv-boosted DRV in HIV-1 infected subjects, which formed the basis for the approval of the DRV/COBI FDC.

The PK parameters of FTC and TAF in different combinations have previously been reported in the F/TAF marketing authorization.

Emtricitabine (NDA208215)**:** Single- and multiple- dose PK studies have shown that FTC is rapidly and extensively absorbed after oral administration. Plasma FTC concentrations were measurable at the earliest sampling time (15 minutes postdose) and reached a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1,200 mg) and then followed an apparent multiexponential decay from the plasma.

At the therapeutic dose (200 mg once daily), the steady-state maximum plasma FTC concentration averaged approximately 2 µg/mL (FTC capsule formulation). The FTC disposition follows linear, first order kinetics, with steady-state plasma FTC concentration time profiles predictable based on single dose data. The steady-state plasma AUC_{24h} following FTC 200 mg once daily averaged 10 µg.h/mL, which was comparable with the AUC_{∞} value following a single FTC dose administration.

Tenofovir alafenamide (NDA208215)**:** The TAF plasma PK profile has been characterized following single doses and at steady-state in healthy and HIV-1 infected individuals at doses ranging from 8 to 125 mg. Overall, TAF behaved dose proportionally and in a linear manner across the range of doses studied. The TAF plasma PK profile is characterized by rapid absorption, with a median plasma t_{max} of approximately 0.50 hours, and rapid elimination, with a median plasma $t_{1/2}$ of approximately 0.40 hours. Tenofovir alafenamide plasma concentrations are typically undetectable by approximately 5 to 6 hours postdose (eg, studies GS-US-120-0104, TMC114FD2HTX1001 and the Phase 2/3 D/C/F/TAF FDC studies). Due to the short plasma $t_{1/2}$, TAF does not accumulate in plasma.

Tenofovir: The plasma PK profile of TFV, the major metabolite of TAF, has been evaluated in some of the studies with TAF-containing regimens, including the D/C/F/TAF Phase 2 study GS-US-299-0102. The TFV PK profile is typically characterized by rapid emergence in plasma following TAF dosing, with a median plasma t_{max} ranging from 0.25 to 3 hours post dose, and slow elimination, with a median plasma $t_{1/2}$ of 32.37 hours. Importantly, the circulating TFV plasma concentrations with TAF-containing regimens, including also D/C/F/TAF (GS-US-299-0102), are much lower (~90%) compared to those with TDF-containing regimens.

Intracellular TFV-DP: The pharmacologically active form of TFV is the intracellular TFV-DP. Intracellular levels of TFV-DP in PBMCs were evaluated in the TAF proof-of-concept study (GS-US-120-0104), and in several substudies of studies with TAF-containing regimens, including the D/C/F/TAF Phase 2 study GS-US-299-0102 and Phase 3 study GS-US-311-1089. F/TAF administration resulted in intracellular TFV-DP concentrations that were >4-fold (GS-US-311-1089) to 6.5-fold (GS-US-299-0102 with D/C/F/TAF) higher relative to F/TDF administration. This finding is consistent with results from E/C/F/TAF studies. Further details are discussed in Section 3.5.1.4.

3.2.1. Single- and Multiple-Dose Pharmacokinetic Characteristics – Non-Compartmental Analysis

An overview table of the PK parameters across D/C/F/TAF studies is provided in Appendix 2.

3.2.1.1. Single-Dose Pharmacokinetics in Healthy Subjects

3.2.1.1.1. D/C/F/TAF FDC

The PK parameters of DRV, COBI, FTC, TAF and (for some studies) TFV following single-dose administration of D/C/F/TAF administered as the intended FDC tablet or coadministered as separate agents were assessed (noncompartmental PK) in healthy subjects in studies GS-US-299-0101 (single-dose PK parameters assessed only for TAF and TFV), TMC114FD2HTX1001, TMC114FD2HTX1002 and TMC114FD2HTX1004 (Mod 2.7.1/Sec2.1, Sec2.2). In the bioequivalence study TMC114FD2HTX1001, the D/C/F/TAF FDC was shown to be bioequivalent to combined intake of formulations of the separate agents DRV, COBI, and FTC/TAF for all primary PK parameters. Similar results were observed in Panel 2 of relative bioavailability study TMC114FD2HTX1002.

Table 22 summarizes the main single dose PK parameters for DRV, COBI, FTC and TAF when administered as the D/C/FTAF FDC or combined intake of the separate agents.

Table 22: Across-Study Comparison of Single-Dose PK Parameters of DRV, COBI, FTC and TAF in Healthy Subjects After Administration of D/C/F/TAF 800/150/200/10 mg as an FDC tablet or Coadministered as Separate Agents (Studies TMC114FD2HTX1002, TMC114FD2HTX1001 and TMC114FD2HTX1004)

Component Parameter	LS Mean				
	FDC			Separate Agents	
	D/C/F/TAF FDC 800/150/200/10 mg			DRV+COBI+F/TAF 800+150+200/10 mg	
	Study 1002	Study 1001	Study 1004	Study 1002	Study 1001
DRV					
N	23	93	30	24	95
C_{max}, ng/mL	6478	6920	8273	6210	6483
AUC_{last}, ng.h/mL	83074	83575	111271	80664	79714
AUC_{∞}, ng.h/mL	83099	83249	111510	80984	80250
COBI					
N	24	93	30	24	95
C_{max}, ng/mL	786	862	903	853	856
AUC_{last}, ng.h/mL	5961	6274	7233	6344	6352
AUC_{∞}, ng.h/mL	6037	6372	7323	6427	6452
FTC					
N	24	93	30	24	96
C_{max}, ng/mL	1631	1989	1816	1769	2003
AUC_{last}, ng.h/mL	10231	11602	11520	10241	11597
AUC_{∞}, ng.h/mL	-[b]	11816	11702	-	11801
TAF					
N	24	94	30	24	96
C_{max}, ng/mL	87.2	98.9	148	79.7	102
AUC_{last}, ng.h/mL	101	118	148	109	122
AUC_{∞}, ng.h/mL	-[b]	123	149	-	129

[a] N=maximum number of subjects with data
[b] Data unavailable for >50% of subjects.

AUC_{last}=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; AUC_{tau}=AUC from 0h to the time of next dosing; CI=confidence interval; C_{max}=maximum observed analyte concentration; LS=least square; SD=standard deviation; tmax=actual sampling time to reach the maximum observed analyte concentration; vs=versus
Source: Mod5.3.1.1/TMC114FD2HTX1002_CSR/Tab10, Tab16, Tab20 and Tab24;
Mod5.3.1.2/TMC114FD2HTX1001_CSR/Tab7, Tab9, Tab11 and Tab13;
Mod5.3.1.1/TMC114FD2HTX1004_CSR/Tab5, Tab8, Tab11 and Tab14

Single dose PK data for TAF and TFV when administered as the D/C/F/TAF FDC are also available from part 1 (Formulation 3, Day 1 data) and part 3 (Day 1 data) in study GS-US-299-0101 (Mod2.7.1/Tab12 and Tab17). The mean (SD) C_{max}, AUC_{last}, and median (range) t_{max} for TAF were 171.7 (37.0), 165.6 (25.0), and 0.75 (0.50, 1.00), respectively, in part 1 and 181.1 (18.9), 183.6 (27.5), and 1.00 (0.75, 1.00), respectively, in part 3. The mean (SD) C_{max}, AUC_{last}, AUC_{∞} and median (range) t_{max} for TFV were 10.1 (32.6), 110.5 (20.1), and 1.50 (1.00, 2.00), respectively, in part 1 and 7.9 (23.5), 103.5 (20.0), and 2.00 (1.50, 2.50), respectively, in part 3.

In general, the PK parameters for DRV, COBI and FTC were similar across studies with D/C/F/TAF. There was some more difference in the single dose PK of TAF across studies, which is consistent with the larger inter-subject variability for TAF (see Section 3.2.5), but these differences are not considered to be clinically relevant.

3.2.1.2. Multiple-Dose Pharmacokinetics in Healthy Subjects

3.2.1.2.1. D/C/F/TAF FDC

The noncompartmental PK of DRV, COBI, FTC, TAF and TFV following multiple-dose administration of the D/C/F/TAF FDC in healthy subjects was evaluated in study GS-US-299-0101, Mod2.7.1/Sec2.1.1.2.

In part 1 of GS-US-299-0101, the PK for different D/C/F/TAF formulations containing either TAF 25 mg or TAF 10 mg was evaluated (Mod2.7.1/Sec2.1.1.2.3.1/Tab14). The TAF exposures were comparable between the formulations containing TAF 25 mg, and were proportionally lower with the D/C/F/TAF FDC containing TAF 10 mg. Nevertheless, the TAF exposures following repeated administration of all D/C/F/TAF FDC formulations were in a range associated with potent antiviral activity of TAF administered as a single agent in the proof-of-concept study GS-US-120-0104 (Section 2.2.3.2). The TAF exposures (AUC_{last} and C_{max}) were higher (~30% to 50%) following a single dose of each D/C/F/TAF formulation as compared with exposures following multiple doses, consistent with a mixed inhibitory/inductive effect of the other components on TAF absorption (see Section 3.4.2). The exposures for DRV, COBI, and FTC were consistent with historical data.

Tenofovir-DP levels following administration of all the D/C/F/TAF formulations (containing 10 or 25 mg TAF) were also in a range associated with antiviral activity from TAF administered as a single agent (proof-of-concept study GS-US-120-0104, Section 2.2.3.2).

Exposures (C_{max} and AUC_{tau}) to TAF were lower following D/C/F/TAF FDC (800/150/200/10 mg) once daily compared with FTC+TAF (200 mg+25 mg) once daily (GS-US-299-0101, part 3). The TAF C_{max} was approximately 41% and AUC_{tau} was approximately 48% lower after intake of the D/C/F/TAF (10 mg) FDC tablet compared with the combined intake of FTC and TAF 25 mg in the absence of a booster. The TFV plasma exposure was on the other hand 41% to 51% higher after intake of the D/C/F/TAF (10 mg) FDC tablet compared with the combined intake of FTC and TAF 25 mg in the absence of a booster, but was still approximately 90% lower than TFV exposures observed following DRV+COBI+F/TDF in part 2 of GS-US-299-0101. This indicates that the impact of the combination DRV/COBI on the TAF exposure is different from that of COBI alone. The substantial increase in TFV exposures without a change in TAF exposures upon multiple-dose coadministration is indicative of a mixed inhibitory/inductive effect on P-gp influencing TAF absorption (see Section 3.4.2.1).

The D/C/F/TAF FDC containing 10 mg TAF was selected for further clinical development due to achieving TAF and TFV-DP exposures associated with potent antiviral activity (GS-US-120-0104) as well as keeping substantially lower systemic TFV plasma levels, as compared with TDF administered as a single agent or as part of other FDCs, or compared with TDF coadministered with boosted PIs (eg, as observed in part 2 of GS-US-299-0101). The efficacy of the D/C/F/TAF 800/150/200/10 mg regimen was confirmed in the Phase 3 studies TMC114FD2HTX3001 and TMC114IFD3013.

The exposures (C_{max} and AUC_{tau}) of DRV and COBI following administration of the D/C/F/TAF FDC (800/150/200/10 mg) once daily were comparable to the exposures of DRV and COBI following coadministration of DRV and COBI (800 mg + 150 mg) alone, once daily (Mod2.7.1/Tab18). The DRV exposure was also generally comparable to historical data for DRV following multiple-dose administration of DRV/rtv 800/100 mg once daily. The COBI exposure was also generally comparable to historical data for COBI following multiple-dose administration of DRV/COBI 800/150 mg once daily. The rate of absorption of DRV and COBI was similar for the D/C/F/TAF FDC tablet formulation and DRV+COBI coadministered as single agents; the t_{max} for DRV ranged from 2.7 to 3.5 hours and for COBI from 3.0 to 4.0 hours.

Exposure (C_{max} and AUC_{tau}) to FTC following administration of the D/C/F/TAF FDC (800/150/200/10 mg) once daily was modestly higher when compared with exposure to FTC following coadministration of FTC and TAF (200 mg + 25 mg) once daily (GS-US-299-0101, part 3), but within the protocol-defined boundary of 70% to 143% and thus not considered clinically relevant. The rate of absorption of FTC was similar for the D/C/F/TAF FDC tablet formulation and FTC + TAF coadministered as single agents; the t_{max} for FTC ranged between 1.5 and 2.0 hours following both treatments (Mod2.7.1/Tab18).

3.2.1.3. Multiple-Dose Pharmacokinetics in HIV-1 Infected Subjects

3.2.1.3.1. D/C/F/TAF FDC

The noncompartmental 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. 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 in GS-US-299-0102, of which 21 and 11, respectively, participated in the PK substudy (Section 2.2.2.1).

The PK parameters from study GS-US-299-0102 are presented in Table 7 in Section 2.2.2.1.

The mean DRV, COBI and FTC exposures (C_{max} and AUC_{tau}) were consistent with historical data for these agents.

No TAF was detectable 8 hours after administration, and the mean TAF AUC_{last} (130.5 ng.h/mL) was consistent with historical data for subjects receiving D/C/F/TAF (healthy subjects) or TAF 25 mg as single agent in the proof-of-concept study (115.2 ng.h/mL, GS-US-120-0104, Table 30, Section 3.5.1.4.1).

The mean TFV (C_{max} and AUC_{tau}) exposure in plasma was substantially lower (approximately 90%) following administration of the D/C/F/TAF FDC compared with DRV plus COBI plus F/TDF, as was anticipated and intended by the development of TAF as a new prodrug for TFV.

The intracellular TFV-DP AUC_{tau} was markedly higher (6.5-fold) in subjects who received D/C/F/TAF compared with subjects who received DRV + COBI + F/TDF. This was consistent with

the previously observed approximately 5 to 7-fold increase in TFV-DP exposures observed following TAF 25 mg versus TDF 300 mg (GS-US-120-0104, Section 2.2.3.2).

3.2.2. Multiple-Dose Pharmacokinetic Characteristics - Population Pharmacokinetics

3.2.2.1. DRV/COBI

Pharmacokinetic parameters for DRV when administered as the D/C/F/TAF FDC were derived using a population PK model. Details of the population PK model development and analysis are described in a separate report (Module 5.3.3.5/DCFTAF Phase 3-DRV PopPK) and summarized in Section 2.2.2.4.1.

The estimated mean DRV C_{0h} and AUC_{24h} values following multiple-dose administration of D/C/F/TAF 800/150/200/10 mg once daily in HIV-1 infected subjects were generally comparable to values for DRV exposure following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents in mostly ART naïve HIV-1 infected subjects and DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve and ART-experienced HIV-1 infected subjects (Table 23).

Table 23: Across-Study Comparison of Population PK Parameter Estimates for DRV in HIV-1 Infected Subjects Following Multiple-Dose Administration of D/C/F/TAF 800/15/200/10 mg Once Daily, DRV/COBI 800/150 mg Once Daily or DRV/rtv 800/100 mg Once Daily Coadministered as Single Agents (Studies TMC114FD2HTX3001, TMC114IFD3013, GS-US-216-0130, TMC114-C211, TMC114-C229, TMC114-C202, and TMC114-C213)

	Mean (SD); Median (Range)					
	D/C/F/TAF 800/150/200/10 mg qd (ART Naïve)	D/C/F/TAF 800/150/200/10 mg qd (ART Experienced)	DRV/COBI Single Agents 800/150 mg qd (ART Naïve and Experienced [a])	DRV/rtv Single Agents 800/100 mg qd (ART-Naïve)	DRV/rtv Single Agents 800/100 mg qd (ART Experienced)	
Parameter	Week 48 TMC114 FD2HTX3001	Week 48 TMC114 IFD3013	Week 24 GS-US-216-0130	Week 48 TMC114-C211	Week 48 TMC114-C229	Week 24 TMC114-C202 + TMC114-C213
N	355	750	298	335	280	118
C_{0h}, ng/mL	1,899 (759)	1,813 (859)	2,043 (1,257)	2,281 (1,168)	2,160 (1201)	1,963 (1,003)
	1,783	1,679	1,875	2,041	1,896	1,840
	(418 – 5,895)	(231 – 6,757)	(70-6,890)	(368-7,242)	(184-7,881)	(256-5,868)
AUC_{24h}, ng.h/mL	87,909 (20,232)	85,972 (22,413)	100,152 (32,043)	93,026 (27,050)	93,334 (28,626)	92,670 (33,711)
	84,248	82,529	96,900	87,854	87,788	89,845
	(40,697 – 188,760)	(41,920 – 209,490)	(34,500-224,000)	(45,000-219,240)	(45,456-236,920)	(25,828-214,040)

N=maximum number of subjects with data; NA=not available.
[a] 3 subjects with PK data were ART-experienced.

3.2.2.2. FTC

Population PK analyses for FTC were previously performed throughout its development, by GSI. As expected from the renal elimination pathway of FTC and based on simple linear regression analysis and ANOVA, followed by stepwise multiple linear regression analysis, $eGFR_{CG}$ was the most

important covariate affecting the overall plasma exposure to FTC. The effect of renal impairment on FTC PK is discussed in Section 3.3.5. Additional covariates involved in the calculation of $eGFR_{CG}$ value, including age, sex, and body weight, were secondarily important in influencing FTC exposures due to their effect on $eGFR_{CG}$ and consequently overall CL/F. No other clinically relevant effects of intrinsic or extrinsic factors were observed on FTC PK.

3.2.2.3. TAF and TFV

Pharmacokinetic parameters for TAF when administered as the D/C/F/TAF FDC in the Phase 3 studies were derived using a population PK model. Details of the population PK model development and analysis are described in a separate report (Module 5.3.3.5/TMC114FD2HTX3001-TAF PopPK) and summarized in section 2.2.2.4.2. In addition, individual TAF AUC_{tau} values were previously estimated for 52 subjects in the D/C/F/TAF treatment arm of Study GS-US-299-0102 based on sparse sampling, which was done by GSI.

TAF and TFV pharmacokinetic parameters for the E/C/F/TAF and F/TAF studies in HIV-infected subjects were derived using population PK models developed by GSI (ND208215) and are referenced as well here to compare TAF pharmacokinetic data for the D/C/F/TAF FDC and for the TAF dose recommendation (see also Section 3.6).

Based on population PK analyses for the D/C/F/TAF Phase 2/3 studies and historical studies with other TAF combinations, the mean TAF AUC_{tau} values following multiple-dose administration of D/C/F/TAF 800/150/200/10 mg once daily in HIV-1 infected subjects were in range with values for TAF exposure following multiple-dose administration of TAF 25 mg once daily alone or TAF 10 mg once daily in other combinations in HIV-1 infected subjects (Table 24).

Table 24: Across-Study Comparison of Population PK Parameter Estimates for TAF in HIV-1 Infected Subjects Following Multiple-Dose Administration of D/C/F/TAF 800/15/200/10 mg Once Daily, E/C/F/TAF 300/15/200/10 mg Once Daily TAF 25 mg once daily alone or F/TAF 200/10-25 mg once daily with Other ARVs (Studies TMC114FD2HTX3001, GS-US-299-0102, GS-US-120-0104, GS-US-292-0104, GS-US-292-0111, and GS-US-311-1089)

	Mean (SD); Median (Range)				
	D/C/F/TAF 800/150/200/10 mg qd (ART Naïve)	D/C/F/TAF 800/150/200/10 mg qd (ART Naïve)	TAF 25 mg qd (ART Naïve)	E/C/F/TAF 300/150/200/10 mg qd (ART Naïve)	F/TAF 200/10 mg qd or 200/25 mg qd[a] (ART Experienced)
Parameter	Week 48 TMC114 FD2HTX3001	Week 48 GS-US-299-0102	Week 24 GS-US-120-0104	Week 48 GS-US-292-0104 and GS-US-292-0111 (pooled)	Week 48 GS-US-311-1089[b,c]
N	355	52	8	539	292
AUC_{tau}, ng.h/mL	132 (41)	102 (51)	115 (33)	206 (148)	137 (66)
	124 (71 - 400)	87 (38 - 296)	109 (101-133)	NA (47 - 1,869)	NA (30 to 467)

N=maximum number of subjects with data. NA: not available
[a] TAF dose depending on third agent
[b] data pooled across 3rd agent subgroups
[c] for the DRV/rtv subgroup (with F/TAF 200/10mg qd), the mean (SD) AUC_{tau} was 74 (30) ng/mL (n=72)

3.2.3. Comparison of Pharmacokinetics Between Healthy Subjects and Target Patient Population

Overall, the plasma exposures of TAF, DRV, COBI, and FTC in the D/C/F/TAF FDC studies in HIV-1 infected subjects (study GS-US-299-0102, TMC114FD2HTX3001 and TMC114IFD3013) 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 (Table 25).

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 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 115.2 ng.h/mL). Also the TAF exposure in Phase 3 study TMC114FD2HTX3001 was similar (mean (%CV) AUC of 132.4 (30.9) ng.h/mL).

The TAF PK parameters for D/C/F/TAF (TAF 10 mg) from study GS-US-299-0101 in healthy volunteers were also consistent with these historical data from study GS-US-120-0104 with TAF 25 mg single agent.

Table 25: 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 an FDC Tablet or as Separate Agents in Healthy Subjects or in HIV-1 Infected Subjects (Fed Conditions) (Studies GS-US-299-0101 [Parts 1 and 3; Formulation 3] and GS-US-299-0102, non-compartmental analysis)

	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**
Parameter	**Day 12** GS-US-299-0101 (part 1; formulation 3)	**Day 12** GS-US-299-0101 (part 3)	**Day 12** GS-US-299-0101 (part 3)	**Weeks 4-8** 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] AUC_{last} 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.

AUC_{last}=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; AUC_{tau}=AUC from time of administration up to the end of the dosing interval; CI=confidence interval; C_{max}=maximum observed analyte concentration; C_{tau}=trough concentration; LS=least square; N=number of subjects; qd=once daily; SD=standard deviation; $t_{1/2}$=apparent elimination half-life; tmax=actual sampling time to reach the maximum observed analyte concentration; vs=versus.

Source: Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-16, Tab10-17, Tab10-19, Tab10-20, Tab10-21, Tab10-22, Tab10-23 and Tab10-24; Mod5.3.5.1/GS-US-299-0102_CSR/Tab10-5 and Tab55.1, Tab 55.2, Tab 55.3, 55.4

3.2.4. Dose Proportionality and Time Dependency

3.2.4.1. Dose Proportionality

The dose proportionality of exposure to the individual components of the D/C/F/TAF FDC has not been investigated upon coadministration, but has been discussed in detail in the marketing authorizations for the respective separate components.

When DRV was coadministered with rtv as single agents in healthy subjects, the systemic exposure to DRV increased dose proportionally across the DRV/rtv doses of 400/100 mg, 800/100 mg, and 1,200/100 mg once daily. In ART-experienced HIV-1 infected subjects, the systemic exposure to DRV increased less than dose proportionally across the DRV/rtv doses of 400/100 and 800/100 mg once daily.

Cobicistat exhibits nonlinear PK with respect to dose and time, consistent with the properties of a mechanism-based inhibitor. When COBI was administered as a single agent in healthy subjects at single and multiple doses of 50, 100, and 200 mg, the systemic exposure to COBI increased more than dose proportionally and dramatic decreases in CL/F were observed with increases in dose (study GS-US-216-0101). Following single-dose administration, the AUC_{∞} of COBI increased 6.8-fold for the dose increase from 50 to 100 mg COBI and 5.1-fold for the dose increase from 100 to 200 mg. Similar results were observed for single-dose administration of COBI 300 and 400 mg, where a 1.9-fold increase in AUC_{∞} was observed following single-dose administration of 400 mg COBI relative to 300 mg COBI. Cobicistat exposure following multiple-dose administration also increased more than dose proportionally, with a 4.2-fold increase in AUC_{24h} for the dose increase from 50 to 100 mg and a 4.7-fold increase for the dose increase from 100 to 200 mg.

Overall, both FTC and TAF behaved dose proportionally and in a linear manner across the range of doses studied.

In study FTC-101, plasma concentrations of FTC (C_{max}, AUC, and C_{min}) increased in a dose proportional manner following both single and multiple dose administration over the dose range of 25 to 200 mg given once or twice daily.

The TAF PK profile has been characterized following single doses and at steady-state in healthy and HIV-1 infected individuals at doses ranging from 8 to 125 mg. Pharmacokinetic parameters for TAF and TFV following single oral doses of TAF 25 or 125 mg were approximately proportional to dose.

3.2.4.2. Time Dependency

The time dependency of DRV, COBI, FTC or TAF exposure when coadministered as the D/C/F/TAF FDC has not been investigated within a single study, but has been explained in detail in the marketing authorizations for the respective separate agents.

Cross-study comparisons for historical studies with DRV/COBI in healthy subjects (TMC114IFD1001 and TMC114IFD1003) suggested that DRV does not accumulate over time, while COBI exhibited a 1.5- to 1.7-fold increase in exposure following multiple-dose administration relative to single-dose administration.

The FTC disposition follows linear, first order kinetics, with steady-state plasma FTC concentration time profiles predictable based on single dose data. The steady-state plasma AUC_{24h} following FTC 200 mg once daily was comparable with the AUC_{∞} value following a single FTC dose administration.

In healthy subjects, a comparison of TAF and TFV exposure (C_{max} and AUC) after single-dose administration of D/C/F/TAF FDC tablets in study GS-US-299-0101 and multiple-dose (once daily) administration in the same study suggested that TAF did not accumulate over time while there was a 2- to 3-fold increase in plasma TFV after multiple dose compared to single dose administration (Table 26).

Table 26: Comparison of PK Parameters of TAF and TFV After Single- and Multiple-Dose (Once Daily) Administration of the D/C/F/TAF 800/150/200/10 mg FDC tablet (Study GS-US-299-0101)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Single Dose D/C/F/TAF FDC 800/150/200/10 mg (Formulation 3) N=10[a]	Multiple Dose D/C/F/TAF FDC 800/150/200/10 mg qd (Formulation 3) N=10[a]
	Day 1	Day 12
TAF		
C_{max}, ng/mL	171.7 (37.0)	130.7 (39.2)
t_{max}, h	0.75 (0.50, 1.00)	0.50 (0.50, 1.00)
AUC_{tau}, ng.h/mL	165.6 (25.0)	116.4 (26.0)
$t_{1/2}$, h	0.42 (0.36, 0.58)	0.41 (0.33, 0.51)
TFV		
C_{max}, ng/mL	10.1 (32.6)	20.7 (14.5)
t_{max}, h	1.50 (1.00, 2.00)	2.00 (1.00, 2.00)
AUC_{tau}, ng.h/mL	110.5 (20.1)	359.1 (11.2)
$t_{1/2}$, h	32.39 (26.23, 42.27)	28.19 (25.28, 36.80)

[a] N=maximum number of subjects with data

AUC_{last}=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; AUC_{tau}=AUC from time of administration up to the end of the dosing interval; CI=confidence interval; C_{max}=maximum observed concentration; C_{tau}=trough concentration; LS=least square; N=number of subjects; qd=once daily; SD=standard deviation; $t_{1/2}$=apparent elimination half-life; t_{max}=actual sampling time to reach the maximum observed concentration
Source: Mod5.3.1.1/GS-US-299-0101_CSR/Tab10-1 and 10-2

3.2.5. Intersubject Variability in Pharmacokinetic Parameters

The ISV, based on %CV for the AUC and C_{max} is discussed below for the D/C/F/TAF components administered as the D/C/F/TAF FDC or as separate agents (study TMC114FD2HTX1001, Panel 2/3 of study TMC114FD2HTX1002 and study TMC114FD2HTX1004 [reference treatment]).

Darunavir: Low to moderate variability based on the %CV for C_{max} and AUC, ranging between 21% and 32% for the D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet and between 22% and

35% for combined intake of DRV as 1x 800 mg tablet, FTC/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet was observed in the bioequivalence study TMC114FD2HTX1001 (Mod2.7.1/Sec2.1.2.2). Similar results were observed in Panel 2 of study TMC114FD2HTX1002 (Mod2.7.1/Sec2.1.1.1); ranging between 23% and 49% for D/C/F/TAF FDC tablet, and between 39% and 63% following coadministration of the single agents. Also in study TMC114FD2HTX1004 (Mod2.7.1/Sec2.1.1.3) similar results were observed for the D/C/F/TAF FDC tablet swallowed whole, with %CV for DRV C_{max} and AUC ranging between 19% and 33%. Intersubject variability in DRV PK parameters was larger in fasted conditions, and ranged between 45% and 53% for the D/C/F/TAF FDC tablet under fasted conditions and between 23% and 43% under fed conditions (Panel 3 of study TMC114FD2HTX1002).

Cobicistat: Low to moderate variability in COBI PK parameters**,** ranging between 29% and 37% for the D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet and between 24% and 36% for combined intake of DRV as 1x 800 mg tablet, FTC/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet was observed in the bioequivalence study TMC114FD2HTX1001 (Mod2.7.1/Sec2.2.1.1). Similar results were observed in Panel 2 of study TMC114FD2HTX1002 (Mod2.7.1/Sec2.1.1.1), ranging between 20% and 30% for D/C/F/TAF FDC tablet, and between 23% and 35% following coadministration of the single agents. Also in study TMC114FD2HTX1004 (Mod2.7.1/Sec2.1.1.3) similar results were observed for the D/C/F/TAF FDC tablet swallowed whole, with %CV for COBI C_{max} and AUC ranging between 25% and 44%. Intersubject variability in COBI PK parameters was larger under fasted conditions, and ranged between 50% and 56% for D/C/F/TAF FDC tablet under fasted conditions and between 23% and 37% under fed conditions (Panel 3 of study TMC114FD2HTX1002).

Emtricitabine: Low to moderate variability in FTC PK parameters**,** ranging between 17% and 24% for the D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet and between 16% and 23% for combined intake of DRV as 1x 800 mg tablet, FTC/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet was observed in the bioequivalence study TMC114FD2HTX1001 (Mod2.7.1/Sec2.2.1.1). Similar results were observed in Panel 2 of study TMC114FD2HTX1002 (Mod2.7.1/Sec2.1.1.1), ranging between 16% and 25% for D/C/F/TAF FDC tablet and between 14% and 26% following coadministration of the single agents. Also in study TMC114FD2HTX1004 (Mod2.7.1/Sec2.1.1.3) similar results were observed for the D/C/F/TAF FDC tablet swallowed whole, with %CV for FTC C_{max} and AUC ranging between 23% and 30%. Intersubject variability in FTC PK parameters ranged between 22% and 26% for D/C/F/TAF FDC tablet under fasted conditions and between 11% and 27% under fed conditions (Panel 3 of study TMC114FD2HTX1002).

Tenofovir Alafenamide: A large variability in TAF plasma concentrations was observed for both treatments in study TMC114FD2HTX1001, with variability in PK parameters ranging between 31% and 49% for D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet and between 43% and 62% for combined intake of the separate agents DRV as 1 x 800 mg tablet, FTC/TAF as 1x 200/10 mg tablet and COBI as 1 x 150 mg tablet (Mod2.7.1/Sec2.2.1.1). A large variability in TAF plasma concentrations was also observed for both treatments in Panel 2 of study TMC114FD2HTX1002 (Mod2.7.1/Sec2.1.1.1), especially during the absorption phase. In Panel

2 of study TMC114FD2HTX1002, ISV based on the %CV of C_{max} and AUC ranged between 35% and 90% for D/C/F/TAF FDC tablet and between 83% and 94% following coadministration of the single agents. In Panel 3, ISV for TAF PK parameters ranged between 42% and 50% for the D/C/F/TAF FDC tablet under fasted conditions, and between 44% and 61% under fed conditions. Similar variability for TAF was observed in study TMC114FD2HTX1004 (Mod2.7.1/Sec2.1.1.3) with %CV for TAF C_{max} and AUC ranging between 28% and 44% for the D/C/F/TAF FDC tablet swallowed whole.

3.3. Effect of Intrinsic Factors

3.3.1. Age

In the DRV and TAF population PK covariate analysis for the D/C/F/TAF Phase 3 studies, age was not found to have a relevant impact on the DRV or TAF PK (Section 2.2.2.4). Furthermore, pharmacokinetic subgroup analysis showed no considerable differences in DRV pharmacokinetics for ages below or equal to 65 years (N=725) or ages greater than 65 years (N=25). For TAF, the pharmacokinetic subgroup analysis showed no considerable differences in TAF pharmacokinetics for ages below or equal to 50 years (N=321) or ages greater than 50 years (N=36). This is in line with earlier data for these compounds, as described below.

The effect of age for the other components in the D/C/F/TAF FDC can also be further derived from data for the individual components.

Data supporting the use of the D/C/F/TAF FDC in adolescents (≥12 years to <18 years) are described in Section 3.3.1.2.

Based on historical studies, age is not considered to have a clinically relevant effect on the exposure to DRV. In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, age was assessed as a potential covariate that could explain variability in the PK of DRV. A graphical analysis suggested that age could explain some of the variability in DRV CL/F and V_p/F, but age was found not to be a significant covariate in the DRV population PK model. This was also consistent with data previously obtained with rtv-boosted DRV where age (range 18 to 75 years; n=12, age ≥65 years) was not found to be a significant covariate for DRV PK.[22,23]

Based on historical studies, using population PK modeling, age was found not to have a clinically relevant effect on COBI exposure.[7,8] The PK of COBI have not been fully evaluated in older subjects (>65 years).

Based on historical studies, no clinically relevant PK differences due to age have been identified for FTC. The difference in mean/median AUC and C_{max} between subjects >40 years and subjects ≤ 40 years of age was <10%. Subjects >40 years of age had a longer mean or median $t_{1/2}$ than subjects ≤40 years by 26% or 30% but there were no major differences in the overall range and distribution of $t_{1/2}$ values between the 2 age groups.

Based on historical studies, no clinically relevant PK differences due to age have been identified for TAF. Using population PK modeling, age (range studied: 12 to 82 years) was found not to have an effect on TAF exposure in HIV-1 infected subjects and was not a statistically significant or clinically relevant covariate.[9]

3.3.1.1. Elderly

In general, caution is recommended when administering D/C/F/TAF in older patients due to the greater frequency of decreased hepatic function, concomitant disease(s), and/or polypharmacy.

3.3.1.2. Pediatrics

There are no data with the D/C/F/TAF combination in pediatric subjects.

Darunavir is indicated for use in pediatric patients of 3 years of age and above. A DRV 800 mg once daily dose is indicated for adolescents aged ≥12 years and weighing at least 40 kg.[29,30]

Emtricitabine is indicated for use in the pediatric population as of birth (US) or 4 months (EU) of age and above. A FTC 200 mg once daily dose is indicated for children weighing at least 33 kg.[10,11]

The doses for COBI and TAF for use in adolescents are derived from the clinical development of another FDC, E/C/F/TAF, containing the components COBI, FTC and TAF at doses of 150 mg, 200 mg and 10 mg, respectively. The E/C/F/TAF FDC, was administered to HIV-1 infected, ART-naïve adolescent in study GS-US-292-0106 (see Section 2.2.3.1) and the PK of the different components were compared to those in adults. This study showed that the COBI, FTC and TAF exposures, coadministered at doses of 150 mg, 200 mg and 10 mg, in adolescents were similar to exposures achieved in adults. Also the EVG exposure was similar in adults and adolescents, confirming that the boosting effect of COBI is similar in adolescents and adults This study also confirmed that these doses were safe and well tolerated in the adolescent population, and led to the approval of the E/C/F/TAF FDC as well as the F/TAF FDC for use in adolescents as of 12 years of age.[12,13]

Based on the above, the D/C/F/TAF FDC combining DRV, COBI, FTC and TAF at doses of 800 mg, 150 mg, 200 mg and 10 mg given once daily is also considered appropriate for use in adolescents aged ≥12 years and weighing at least 40 kg.

Data and doses for coadministration of the components of the D/C/F/TAF FDC in children <12 years are currently not available. The D/C/F/TAF FDC is therefore not recommended for use in pediatric patients ≥3 to <12 years of age. The D/C/F/TAF FDC should not be used in pediatric patients <3 years of age, in view of the toxicity observed in juvenile rats dosed with DRV.

3.3.2. Sex

Overall, sex is not considered to have a clinically relevant effect on the exposure of the D/C/F/TAF components.

In the DRV population PK analysis of the D/C/F/TAF Phase 3 studies, a marginally lower CL/F was observed in female subjects compared to male subjects. This could, however, explain only a small part of the DRV variability and sex was not included in the DRV population PK model (Section 2.2.2.4.1). For TAF, sex was not found to have a relevant impact on the TAF PK in the D/C/F/TAF Phase 3 studies (Section 2.2.2.4.2). This is in line with earlier data for these compounds, as described below.

The effect of sex for the other components in the D/C/F/TAF FDC can also be further derived from data for the individual components.

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, sex was assessed as a potential covariate that could explain variability in the PK of DRV. Similar to the observations for D/C/F/TAF, a graphical analysis suggested that sex could explain some of the variability in DRV CL/F and V_p/F, but sex was found not to be a significant covariate for the DRV population PK model, and thus not clinically relevant. This was also consistent with data previously obtained for rtv-boosted DRV where a trend towards a higher (1.10-fold) mean exposure to DRV in females compared with males was observed, which was not considered to be clinically relevant.[22,23]

Based on historical studies, no clinically relevant differences between males and females have been identified for the COBI PK.[7,8]

Based on historical studies, no clinically relevant PK differences due to sex have been identified for FTC. There were no major differences with respect to range and distribution of AUC values between males and females. The 16% higher mean AUC and the ~20% higher C_{max} in female subjects as compared with males are not considered clinically relevant. In addition, all C_{max} data points in female subjects were within the C_{max} data range of male subjects. There were no major differences in the overall range and distribution of $t_{1/2}$ values between male and female subjects. However, female subjects tended to have a shorter mean or median $t_{1/2}$ than male subjects by 12% or 17%.

Based on historical studies, no clinically relevant PK differences due to sex have been identified for TAF. Using population PK modeling, sex did not have an effect on TAF exposure in HIV-1 infected subjects and was not a statistically significant or clinically relevant covariate.[9]

3.3.3. Body Weight and Related Measures of Body Size

Overall, bodyweight or related factors are not considered to have a clinically relevant effect on the exposure of the D/C/F/TAF components.

In the DRV population PK analysis of the D/C/F/TAF Phase 3 studies (Section 2.2.2.4.1), total body weight was found to explain part of the variability for DRV CL/F and was included in the final DRV population PK model. The impact of body weight on the DRV exposure metrics is, however, limited (a predicted decrease of 13% and 22.4% in the mean AUC_{24h} and C_{0h},

respectively between the 1st and 4th quartiles of body weight), and this difference is not considered clinically relevant.

In the TAF population PK analysis of the D/C/F/TAF Phase 3 study TMC114FD2HTX3001 (Section 2.2.2.4.2), lean body weight was found to explain part of the variability for TAF CL/F and was included in the final TAF population PK model. The impact of this body weight measure on the TAF exposure metrics is however limited (a predicted decrease of 29% in the mean AUC_{tau} between the 1st and 4th quartiles of body weight), and the difference is not considered clinically relevant.

The effect of body weight measures for the other components in the D/C/F/TAF FDC can also be further derived from data for the individual components.

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, body weight, height, body surface area, and body mass index were assessed as potential covariates that could explain variability in the PK of DRV. At that time, body weight was found to have a similar effect on DRV CL/F as described above for D/C/F/TAF; however, body weight was not included in the DRV population PK model at that time due to the absence of clinical significance. This was also consistent with data previously obtained for rtv-boosted DRV where body weight was found to have no clinically relevant effect on DRV PK.[22]

Based on historical studies, no clinically relevant effect of bodyweight was observed for COBI.[7,8]

Based on historical studies for FTC, the summary data of AUC and C_{max} values distinguishing body weight groups showed that there were no major differences in the overall range and distribution of AUC and C_{max} values between the two body weight groups. However, subjects with a body weight ≤75 kg had about 10% to 15% higher mean/median AUC and C_{max} values than subjects with a body weight >75 kg. There were no major differences in the overall range and distribution of $t_{1/2}$ values between the 2 weight groups. Subjects with a body weight ≤75 kg tended to have slightly shorter (<10%) median $t_{1/2}$ than subjects with a body weight >75 kg.

Based on historical studies, the effect of body weight on the TAF PK was considered during covariate assessment in the pooled Phase 2 and Phase 3 study populations used for TAF population PK analyses. The median (Q1, Q3) body weight was 75 (66, 86) kg, with a range of 35 to 219 kg. The mean TAF AUC was lower for subjects with body weight >75 kg, but the ranges largely overlapped and the difference was not considered clinically relevant (Table 27).

Table 27: Integrated Ad Hoc PK Analysis: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF 25 mg or TAF 10 mg + COBI in Healthy or HIV-Infected Subjects by Weight Range (TAF PK Analysis Set)

	Mean (%CV)			
	TAF 25 mg		TAF 10 mg + COBI	
Parameter	Weight ≤75 kg (N=200)	Weight >75 kg (N=240)	Weight ≤75 kg (N=205)	Weight >75 kg (N=179)
AUC_{last}, ng.h/mL	298.4 (50.37)	239.4 (46.16)	327.6 (41.61)	275.6 (39.45)
C_{max}, ng/mL	241.3 (61.09)	203.8 (54.31)	280.4 (54.59)	266.5 (52.09)

3.3.4. 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 presented in this marketing authorization is based on data derived during the development programs of the individual components and has previously been presented in their respective marketing authorizations.

Darunavir: In non-HIV-1 infected subjects treated with DRV/rtv 600/100 mg twice daily, the mean C_{max} and AUC_{12h} of DRV were decreased by 12% and 6%, respectively, in subjects with mild hepatic impairment relative to healthy matched control subjects; these parameters were increased approximately 1.20-fold in subjects with moderate hepatic impairment relative to healthy matched control subjects (TMC114-C134, Section 2.1.4.1). Higher percentages of unbound plasma DRV (12% and 16% in subjects with mild and moderate hepatic impairment vs ~7.5% in healthy subjects) and lower plasma α1-acid glycoprotein (AAG) concentrations were seen in subjects with hepatic impairment, with an inverse relationship between plasma concentrations of AAG and percentages of unbound DRV (see also Section 3.3.9). These differences are not considered clinically relevant. The effect of severe hepatic impairment on the PK of DRV has not been studied.

Cobicistat: Overall, no clinically relevant differences in COBI PK were observed between non-HIV-1 infected subjects with moderate hepatic impairment and non-HIV-1 infected subjects with normal hepatic function (GS-US-183-0133, Section 2.1.4.1). The AUC_{24h} and C_{max} of COBI were generally comparable in subjects with moderate hepatic impairment relative to healthy matched control subjects; the C_{24h} was increased 2.08-fold, which was not considered to be clinically relevant. Exploratory analyses indicated no clinically relevant correlations between COBI exposures and Child-Pugh-Turcotte (CPT) scores or individual liver function laboratory parameters. The effect of severe hepatic impairment on the PK of COBI has not been studied.

Emtricitabine: The PK of FTC has not been studied in subjects with hepatic impairment. Renal excretion of unchanged drug is the major route of elimination of FTC in man with metabolism representing only a minor pathway for the elimination (<13% of oral dose) (study FTC-106). Therefore, in patients with various degrees of hepatic dysfunction, little change in FTC CL/F is expected.

Tenofovir Alafenamide/Tenofovir: The PK of TAF and its metabolite TFV was evaluated in non–HIV-infected subjects with mild or moderate hepatic impairment (CPT Class A or B) and in healthy matched subjects with normal hepatic function following a single dose of TAF (study GS-US-120-0114, Section 2.1.4.1). There were no clinically relevant changes in TAF or TFV PK in subjects with hepatic impairment compared with healthy subjects and no clinically relevant correlation between exposure and baseline hepatic impairment. The effect of severe hepatic impairment on the PK of TAF has not been studied.

Hepatitis B and/or Hepatitis C Virus Coinfection

In the D/C/F/TAF FDC Phase 3 studies, there were no subjects with pharmacokinetic sampling and Hepatitis B/C coinfection. The effect of Hepatitis B/C coinfection for the components in the D/C/F/TAF FDC can be derived from data for the individual components.

In HIV-1 infected subjects taking DRV/rtv, the population PK analysis (48 week) of data from Phase 3 clinical studies indicated that HBV and/or hepatitis C virus co-infection status had no apparent effect on the exposure of DRV.[22]

The PK of FTC has been evaluated in a Phase 1 study in subjects with chronic HBV (study FTC-101). The mean C_{max} and AUC_{tau} values of FTC in HBV-infected subjects (receiving 200 mg dose in capsule) appeared to be comparable with those in healthy subjects (receiving 200 mg dose in solution). The mean C_{max} and AUC_{tau} values of FTC in HBV-infected subjects were slightly higher than those in the HIV-1 infected subjects; however, the small differences were not thought to be clinically significant.

Study GS-US-292-1249 is a Phase 3b open-label study to evaluate the efficacy and safety of switching to an FDC of E/C/F/TAF 150/150/200/10 mg in HIV-1/HBV coinfected adults. This study is briefly discussed in Mod2.7.4/Sec6.1.5. There are no PK evaluations in this study.

3.3.5. Renal Impairment

The effect of renal impairment on the PK of DRV, COBI, FTC and TAF when coadministered as the D/C/F/TAF FDC has not been evaluated in specific studies. In the D/C/F/TAF Phase 3 studies (covariate analyses population PK and subgroup analyses), creatinine clearance (eGFR) was not found to have a relevant impact on the DRV or TAF PK (Section 2.2.2.4). This is in line with earlier data for these compounds, as described below

The effect of renal impairment for the components in the D/C/F/TAF FDC can also be further derived from data for the individual components, as previously presented in their respective marketing authorizations.

Since DRV and COBI are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Emtricitabine can be removed by hemodialysis, which removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing. Tenofovir is efficiently removed by

hemodialysis with an extraction coefficient of approximately 54%. It is not known whether FTC or TFV can be removed by peritoneal dialysis

Darunavir: The renal CL/F of DRV is limited, and therefore a decrease in total body CL/F is not expected in patients with renal impairment. A mass-balance study with [^{14}C]DRV/rtv showed that only approximately 7.7% of the administered dose of DRV is excreted in the urine as unchanged drug (Section 2.1.4.2).

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, creatinine clearance as a measure of renal function was assessed as a potential covariate that could explain variability in the PK of DRV. A graphical analysis indicated that creatinine clearance did not explain any of the variability in DRV CL/F and V_p/F. This was also consistent with data previously obtained for rtv-boosted DRV where creatinine clearance was found to not have a clinically relevant effect on DRV pharmacokinetics.[21] No PK data for DRV are available in HIV-1-infected patients with severe renal impairment or end stage renal disease.

Cobicistat: In a study evaluating COBI PK in non-HIV infected subjects with severe renal impairment ($eGFR_{CG}$ <30. mL/min), no clinically relevant differences in COBI PK (LS mean AUC_{24h} ratio 1.25) were observed between subjects with severe renal impairment and healthy subjects ($eGFR_{CG}$ ≥90 mL/min), consistent with the low renal clearance of COBI (GS-US-216-0124, Section 2.1.4.2). In a study comparing COBI PK in non-HIV infected subjects with mild to moderate renal impairment (eGFR 50 to 79 mL/min) with that in healthy subjects (eGFR ≥80 mL/min), higher COBI exposures (mean AUC_{24h} ~43% increased) were observed in subjects with mild to moderate renal impairment relative to subjects with normal renal function (GS-US-216-0121, Section 2.1.4.2), which suggests a change in COBI CL/F with or without a change in bioavailability. These changes are not considered clinically relevant.

Cobicistat has been shown to decrease the estimated creatinine clearance due to inhibition of active tubular secretion of creatinine via the organic cation transporter 2 (OCT2) renal transporter, without an effect on GFR.

Emtricitabine: Because renal excretion of the unchanged drug is the principal route of elimination for FTC, it can be anticipated that the PK profiles of FTC in subjects with altered or deficient renal function may vary or deviate from those in subjects with normal renal function, which was evaluated in study FTC-107 (Section 2.1.4.2).

Tenofovir alafenamide: Study GS-US-120-0108 was performed to evaluate the PK of TAF and its metabolite TFV following a single dose of TAF in non−HIV-1 infected subjects with severe renal impairment (defined as subjects with $eGFR_{CG}$ between 15 mL/min and 29 mL/min [inclusive] who were not on dialysis) compared with age- and sex-matched non−HIV-infected subjects with normal renal function ($eGFR_{CG}$ ≥90 mL/min) (study GS-US-120-0108; Section 2.1.4.2).

Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure (as assessed by AUC_{∞}) relative to age- and sex-matched subjects with normal renal function. Given that the plasma TAF exposures in subjects with renal impairment were within or below the range of TFV exposures achieved as part of a TDF-containing regimen in subjects with normal renal function, these data supported the conduct of a Phase 3 clinical study to evaluate the safety and efficacy of E/C/F/TAF in ART-naïve and ART-experienced HIV-1 infected subjects with mild to moderate renal impairment (stable $eGFR_{CG}$ of 30 to 69 mL/min, study GS-US-292-0112, Section 2.1.4.2).

A PK substudy (n=30) of GS-US-292-0112 showed mean (%CV) TAF exposure (AUC) of 254.2 (54.1) ng.h/mL (n=29 for this parameter). The TAF exposure was numerically higher in subjects with baseline $eGFR_{CG}$ <50 versus ≥50 mL/min. These Phase 3 data are consistent with results from the renal impairment study, GS-US-120-0108.

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-1 infected subjects, baseline $eGFR_{CG}$ was not a statistically significant or clinically relevant covariate influencing TAF PK.[9] Although TAF exposure was higher in HIV-1 infected subjects with lower baseline $eGFR_{CG}$ relative to those with normal renal function (>90 mL/min), the difference between those with moderate renal impairment (30 ≤$eGFR_{CG}$ <60 mL/min; mean [%CV] AUC 305.0 [112.5] ng.h/mL; C_{max} 208.6 [53.0] ng/mL) and those with normal renal function was less than 50% (mean [%CV] AUC 210.4 [94.1] ng.h/mL; C_{max}158.9 [57.1] ng/mL

Following a single dose of TAF, non–HIV-1 infected subjects with severe renal impairment (study GS-US-120-0108) had a 5.74-fold mean increase in systemic TFV exposure (as assessed by AUC_{∞}) relative to age- and sex-matched non–HIV-1 infected subjects with normal renal function (Table 28). The plasma TFV exposure observed in this study in subjects with severe renal impairment was within or below the ranges of exposure observed in historical studies after administration of TDF 300 mg in both HIV-1 infected and non–HIV-1 infected subjects with normal renal function (TFV AUC 3,300 ng.h/mL).

Table 28: Statistical Comparisons of TFV PK Parameter Estimates in Non−HIV-Infected Between Subjects With Severe Renal Impairment and Subjects With Normal Renal Function (Study GS-US-120-0108)

	Mean (%CV)		
TFV PK Parameter	Test Severe Renal Impairment (N=14)	Reference Normal Renal Function (N=13)	LS Mean Ratio % (90% CI)
AUC_{∞}(ng.h/mL)	2073.8 (47.1)	342.6 (27.2)	573.76 (457.21, 720.01)
AUC_{last}, ng.h/mL	1694.9 (43.1)	298.0 (26.1)	545.91 (442.82, 672.99)
C_{max}, ng/mL	26.4 (32.4)	9.5 (36.5)	279.31 (231.48, 337.02)

Source: NDA208215/Mod5.3.3.3/GS-US-120-0108_CSR/Sec15.1/Tab4.2 and Tab6.1

3.3.6. Race/Ethnicity

Overall, there were no clinically relevant differences in the exposure of the D/C/F/TAF FDC components based on race/ethnicity.

In the D/C/F/TAF Phase 3 studies, race was not found to have a relevant impact on the DRV or TAF PK (covariate analyses population PK, Section 2.2.2.4). This is in line with earlier data for these compounds, as described below.

Darunavir: In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, race was assessed as a potential covariate that could explain variability in the PK of DRV. A graphical analysis indicated that race did not explain any of the variability in DRV CL/F and V_p/F. This was also consistent with data previously obtained for rtv-boosted DRV. Although there was a trend towards a lower exposure in Asian subjects (13 to 15%) compared to Caucasian subjects in studies with DRV/rtv, this difference is not considered clinically relevant.[21,22,23]

Cobicistat: Based on historical studies, there were no clinically relevant PK differences for COBI by race or ethnicity.[7,8]

Emtricitabine: Based on historical studies, no clinically relevant PK differences due to race or ethnicity have been identified for FTC. There were no major differences in the overall range and distribution or in the mean/median values for any of the key FTC PK parameter estimates (AUC, C_{max} and $t_{1/2}$) between the Caucasian and non-Caucasian groups.

Tenofovir Alafenamide: Based on historical studies, no clinically relevant PK differences due to race or ethnicity have been identified for TAF. Using population PK modeling, race did not have an effect on TAF exposure in HIV-infected subjects and was not a statistically significant or clinically relevant covariate).[9]

3.3.7. Pregnancy or Lactation

No information is available for the D/C/F/TAF combination.

3.3.8. Genetic Differences

Darunavir and COBI are primarily metabolized by CYP3A. The effect of genetic polymorphisms in CYP enzymes on the PK of DRV and/or COBI has not been evaluated. However, typically, genetic variations do not result in clinically relevant differences in the PK of drugs primarily metabolized by CYP3A. Indeed, the ISV in the PK of DRV and COBI is only low to moderate, suggesting no important role for genetic or demographic factors impacting the PK to a clinically relevant extent. This is further substantiated by the fact that there were no clinically relevant differences in the PK of DRV or COBI by race/ethnicity (see Section 3.3.6).

Because TAF is a substrate for hepatic transporters OATP1B1 and OATP1B3 exposure to TAF may be affected by inhibitors of OATP1B1 and OATP1B3 or by genetic polymorphisms affecting their transport activities. The effects of differences in OATP1B1 and OATP1B3 activity are, however, not expected to lead to clinically relevant changes in TAF PK given the high passive permeability of TAF.

3.3.9. Plasma AAG Concentration

Darunavir is approximately 95% bound to plasma proteins and binds primarily to plasma AAG. Plasma AAG is included as a significant covariate in the population PK model for DRV (for DRV/rtv and for DRV/COBI), with higher plasma AAG levels resulting in higher DRV exposure.[22,43] This was also confirmed in the current DRV population PK analysis for the D/C/F/TAF Phase 3 studies, and plasma AAG was retained in the final DRV model (see Section 2.2.2.4.1).

Tenofovir alafenamide is approximately 80% bound to plasma protein, and it is not known which plasma proteins. In the TAF population PK analysis for TMC114FD2HTX3001, plasma AAG was found to be a statistically significant covariate for the TAF CL/F, with higher plasma AAG levels resulting in lower TAF CL/F (and thus higher TAF exposure). Plasma AAG was therefore included in the final TAF population PK model (see Section 2.2.2.4.2).

Plasma AAG levels are not anticipated to have a clinically relevant impact on the PK of the other components of the D/C/F/TAF FDC.

3.4. Effect of Extrinsic Factors

3.4.1. Food

The effect of food on drug absorption for the different components of the D/C/F/TAF FDC is described in detail in Mod2.7.1/Sec3.1.3.

The C_{max} of FTC and TAF was 1.26- and 1.82-fold higher, respectively, after administration of the D/C/F/TAF FDC under fasted compared to fed conditions, and the AUC_{last} for both FTC and TAF were comparable for test and reference. The C_{max}, AUC_{last}, and AUC_{∞} were lower under fasted compared to fed conditions for both DRV (30% to 45% lower) and COBI (16% to 29% lower). These results are consistent with historical data of food effect studies with the components of the D/C/F/TAF FDC.

In summary, 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. The type of food does not affect the exposure of DRV. Intake with food was also recommended for subjects in all studies with the D/C/F/TAF FDC (except when evaluating the food effect) or studies with other DRV-containing regimens.

3.4.2. Drug-drug Interactions

3.4.2.1. Drug-drug Interaction Between the Components of the D/C/F/TAF FDC

The DCFTAF FDC tablet combines 4 components in a single tablet. The drug interactions between the different components have been taken into account for the combination of these drugs at the doses selected (see also Section 3.6).

Darunavir is a CYP3A substrate with, in itself, limited bioavailability and an elimination half-life that is shortened by CYP3A-dependent metabolism. Cobicistat is a potent, selective, mechanism-based inhibitor of CYP3A and as such developed as a PK enhancer. The inhibition of the CYP3A mediated metabolism of DRV by COBI enhances the systemic exposure to DRV and is therefore the intended pharmacological effect for the DRV/COBI combination. The DRV exposure when combined with COBI is similar to that when rtv was used as a PK enhancer, as previously established through the DRV/COBI development program.

Emtricitabine is mostly eliminated via renal excretion and there is no clinically relevant impact on its exposure by DRV, COBI or TAF or vice versa. Moreover, FTC has already been used very widely and for a substantial amount of time in combination with boosted DRV-based HIV-1 treatment regimens.

Tenofovir alafenamide has no impact on the PK of DRV, COBI or FTC.

When COBI alone is coadministered with TAF, TAF and TFV exposures (AUC) increased 2.65-fold and 3.30-fold, respectively (NDA208215/Mod5.3.3.4/GS-US-311-0101_CSR, Cohort 4). In the presence of DRV/COBI however, TAF exposures were unaltered (LSmean AUC ratio 0.98, 90%CI 0.80, 1.19) while the TFV exposure was 3.24-fold increased (NDA208215/Mod5.3.3.4/GS-US-311-0101_CSR, Cohort 2), albeit still leading to TFV exposures substantially lower (~90%) than with administration of 300 mg TDF. Similar results were observed for DRV/rtv when coadministered with TAF (NDA208215/Mod5.3.3.4/GS-US-120-0118_CSR).

The exact mechanism for the observed TAF and TFV effects when TAF is coadministered with DRV/COBI is unknown. The increase in TFV exposure, without a change in TAF exposure, upon multiple-dose coadministration of TAF with DRV/COBI suggests a mixed inhibitory/inductive effect on P-gp influencing TAF absorption. The increase in TAF exposure (AUC_{last} and C_{max}) following a single dose of F/TAF+DRV/COBI, as compared with a single dose of F/TAF alone, suggested the presence of an inhibitory drug interaction resulting in increased availability of TAF following a single dose. This effect is then ablated following multiple dosing. The comparable exposure of TAF following multiple-dose coadministration with DRV+COBI versus TAF alone may be due to an inductive effect of DRV on P-gp in the presence of COBI, becoming apparent after multiple dosing.

Irrespective of the hypothesized mechanism for interaction, the TAF and TFV exposures have been carefully considered when selecting the TAF dose for the D/C/F/TAF development program. A TAF dose of 10 mg was selected, based on the following:

- Provides TAF exposures (mean AUC ~130 ng.h/mL, Phase 2/3 D/C/F/TAF) similar to those observed with TAF 25 mg which provided near maximal antiviral activity (proof-of-concept study GS-US-120-0104, mean AUC 115.2 ng.h/mL).
- Provides TAF exposures that are well above the protein binding adjusted median 50% effective concentration in cell-based assays (EC_{50}) of TAF (8.4 ng.h/mL).

- Provides TAF exposures within range of those associated with efficacy established in clinical studies with E/C/F/TAF and F/TAF, which yielded uniformly high rates of viral suppression or maintenance of viral suppression (see Section 3.5.1.4). Efficacy of these TAF exposures were also confirmed in the D/C/F/TAF Phase 3 studies TMC114FD2HTX3001 and TMC114IFD3013.
- Absence of PK/PD relationship for TAF exposure across a wide range of TAF exposures which includes TAF exposures observed with boosted DRV (see Section 3.5.1.4). This was also confirmed for the D/C/F/TAF pivotal Phase 3 study TMC114FD2HTX3001.
- Provides TFV-DP levels in a range associated with antiviral activity observed with TAF 25 mg single agent (proof-of-concept study GS-US-120-0104) and 6.5-fold higher compared to similar regimens with TDF and higher compared to E/C/F/TAF regimens (see Section 3.5.1.4.4).
- Provides TFV exposures that are not higher than those observed following TAF 25 mg administered as a single agent, and approximately 90% lower compared to TDF-containing regimens.

Further details on the dose selection for the D/C/F/TAF FDC are discussed in Section 3.6

3.4.2.2. Drug-drug Interactions With Other Co-medications

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

The recommendations for use of the D/C/F/TAF FDC with other agents are based on a combination of the recommendations in the currently approved prescribing information for DRV/COBI and FTC/TAF, respectively, as appropriate.

D/C/F/TAF is intended as a complete regimen for the treatment of HIV-1 infection, and is not expected to be coadministered with other HIV-1 antiviral agents. Data on drug-drug interactions for D/C/F/TAF components with other ARV drugs are as such summarized in this document to describe the overall drug-drug interaction potential for the D/C/F/TAF components, but they are not included in the proposed D/C/F/TAF prescribing information.

D/C/F/TAF is not recommended in combination with ritonavir, and not with other ARVs that require PK enhancement (eg, another protease inhibitor or elvitegravir) since dosing recommendations for such combinations have not been established.

Darunavir/COBI: Drug-drug interaction information for DRV/COBI is largely based on the extensive knowledge of drug-drug interactions for DRV/rtv, extrapolated to DRV/COBI, taking into account the differences between COBI and rtv.

A comprehensive drug-drug interaction program has been conducted with DRV/rtv, including a cocktail study to assess the effects of DRV/rtv coadministered as single agents on the

metabolism of probe substrates (NDA021976/Mod5.3.3.4/TMC114-C173-CSR). Interactions are most likely a result of the rtv component because of its inhibitory effects on CYP2D6, CYP3A, and certain transporters, and/or its induction effects on CYP2C9, CYP2C19, and UGT. A summary of the interactions and recommendations for use of DRV/rtv in combination with various drugs is available in the local prescribing information for DRV.

Upon coadministration of COBI as a booster of DRV, COBI is expected to display a mechanism based CYP3A inhibition profile comparable to that observed with rtv boosting, as the inhibition is near maximal in both instances, and the inhibitory profile towards other CYP enzymes and transporter proteins are qualitatively similar between the 2 boosting agents. In human hepatic microsomal fractions and tests for enzyme-specific activities, COBI showed good specificity as an inhibitor of CYP3A, with no significant inhibition of CYP1A2, CYP2C9, and CYP2C19 and mild inhibition of CYP2B6 (similar to rtv). Cobicistat was a milder inhibitor of CYP2D6, CYP2C8 and UGT1A1 activities than rtv. Cobicistat, like rtv, inhibits the following transporters: P-gp, BCRP, MATE-1, OATP1B1 and OATP1B3.

As COBI also inhibits CYP3A, CYP2D6 and P-gp (both of the the latter albeit mildly and to a lesser extent than rtv), most data generated with DRV/rtv coadministered as single agents related to these enzymes can be extrapolated to D/C/F/TAF FDC. For drugs that are (pure) CYP2D6 or CYP3A substrates, the interaction between DRV/COBI and DRV/rtv is expected to be similar in magnitude. The principal difference in drug interaction potential is that, in contrast to ritonavir, COBI does not add a metabolic enzyme induction. Based on in vitro data, COBI is not expected to induce CYP1A2 or CYP2B6 and based on in vivo data, cobicistat is not expected to induce MDR1 or, in general, CYP3A to a clinically significant extent. The induction effect of COBI on CYP2C9, CYP2C19, or UGT1A1 is unknown, but is expected to be low based on CYP3A in vitro induction data. Though this difference in induction potential with rtv may drive some quantitative differences in drug interactions, the impact thereof is not expected to result in the need for different dosing recommendations for the co-medication between DRV/rtv and DRV/COBI.

Cobicistat-boosted DRV inhibits CYP3A, CYP2D6 and P-gp. Coadministration of D/C/F/TAF with medicinal products primarily metabolized by CYP3A and/or CYP2D6 and/or transported by P-gp may result in increased plasma concentrations of such medicinal products.

Darunavir and COBI are both metabolized by CYP3A. Drugs that induce CYP3A activity are expected to increase the clearance of DRV and COBI, resulting in lower plasma concentrations of DRV and COBI which may lead to loss of efficacy of DRV and development of resistance. Coadministration of D/C/F/TAF and other medicinal products that inhibit CYP3A may increase plasma concentrations of DRV and COBI.

Based on the effect of DRV/COBI, coadministration 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). These drugs include: alfuzosin, some antiarrhythmics (dronedarone), some antihistamines (astemizole,

terfenadine *[both no longer marketed in several countries]*), cisapride, colchicine (in patients with renal or hepatic impairment), ergot derivatives (eg, dihydroergotamine, ergometrine, ergotamine, methylergonovine), elbasvir/grazoprevir, some HMG CoA reductase inhibitors (lovastatin, simvastatin), some antipsychotics/neuroleptics (pimozide, sertindole *[no longer marketed in several countries]*, lurasidone), ranolazine, sildenafil (for treatment of pulmonary arterial hypertension), and sedative/hypnotics (oral MDZ, triazolam).

Because DRV and COBI are metabolized by CYP3A, and TAF is a P-gp substrate (see below), CYP3A and P-gp inducers such as carbamazepine, phenobarbital, phenytoin, rifampin and St John's wort (Hypericum perforatum) are also contraindicated.

Tenofovir alafenamide: The potential for TAF to affect human CYP mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme selective activities (NDA208215/Mod4.2.2.6/AD-120-2003_report). The inhibitory activity of TAF with human liver microsomal CYP isoenzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed at concentrations up to 25 µM. The 50% inhibitory concentration (IC_{50}) values calculated for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were greater than 25 µM. TAF weakly inhibited CYP3A mediated oxidation of MDZ or testosterone in vitro with IC_{50} values of 7.6 and 7.4 µM, respectively. Clinical evaluation of TAF as a CYP3A4 inhibitor or inducer (NDA208215/Mod5.3.3.4/GS-US-120-1538_CSR) showed no clinically relevant differences in MDZ PK relative to MDZ alone following coadministration of MDZ (oral or IV) and TAF; these data indicate that TAF does not exhibit CYP3A inhibition or induction activity, either presystemically or systemically.

The potential for TAF to be a mechanism based inhibitor of the human CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A was assessed at TAF concentration at 50 µM (NDA208215/Mod4.2.2.6/AD-120-2040_report). There was no evidence for time or cofactor dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control.

Tenofovir alafenamide is not an inhibitor of UGT1A1.

Tenofovir alafenamide is a substrate of P-gp, BCRP, OATP1B1 and OATP1B3. Tenofovir alafenamide is transported by P-gp and metabolized by esterases expressed in the intestine.[19,44] Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly affect P-gp activity (inhibition by eg, COBI, rtv, ciclosporin or induction by eg, rifamycin, carbamazepine, phenytoin) may lead to changes in TAF bioavailability. Coadministration with COBI or rtv can lead to near maximum inhibition of P-gp, resulting in an increase in TAF exposure. Notably, however, coadministration with rtv or COBI boosted DRV had almost no effect on TAF plasma exposure (6% increase and 2% decrease in AUC_{last}, respectively).

As TAF is not metabolized by CYP enzymes except for weak metabolism observed for CYP3A4 in vitro, CYP inhibitors or inducers are not expected to have a relevant effect on TAF PK;

however, CYP inducers are often also P-gp inducers, and coadministration with P-gp inducers may decrease the absorption of the P-gp substrate TAF. Coadministration with a modest CYP3A and P-gp inducer (ie, EFV) resulted in slightly lower TAF exposure (14% to 22%), As such, minimal effect on TAF exposure is expected upon coadministration of F/TAF with a modest or weak CYP3A/P-gp inducer. Coadministration of F/TAF with potent CYP3A/P-gp inducers is not recommended but based on the combined information for the different components; use of the D/C/F/TAF FDC is contraindicated with potent P-gp inducers (e.g., the carbamazepine, phenytoin, phenobarbital, rifampin, St John's wort). Effects of differences in OATP1B1 and OATP1B3 activity (by inhibitors or genetic polymorphisms) are not expected to be clinically relevant given the high passive permeability of TAF.

Tenofovir: The potential for TFV to affect human CYP mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme selective activities (NDA021752/Mod5.3.2.2/V990172-104_report). TFV at 100 μM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

Emtricitabine: In vitro and clinical drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low.

Emtricitabine, like tenofovir, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. As such, coadministration with medicinal products that are eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the coadministered medicinal product. Medicinal products that decrease renal function may increase concentrations of FTC or tenofovir.

Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valaciclovir, valganciclovir, aminoglycosides (eg gentamycin), and high-dose or multiple NSAIDs.

An overview of drug interactions (based on observed data with single agents or predicted) and dosing recommendations are summarized in Table 29. This table combines all recommendations for non-ARV concomitant medications from the currently approved prescribing information for DRV/COBI and for FTC/TAF, adjusted with up-to-date information, where applicable.

Table 29: Interactions Between the Individual Components of the D/C/F/TAF FDC and Other Medicinal Products; Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
α1-Adrenoreceptor Antagonists: alfuzosin	↑ alfuzosin	Coadministration of D/C/F/TAF with alfuzosin may increase alfuzosin concentrations (inhibition of CYP3A). Coadministration of D/C/F/TAF with alfuzosin is contraindicated.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Antacids: e.g., aluminium/magnesium, hydroxide, calcium carbonate	↔ darunavir ↔ cobicistat	D/C/F/TAF and antacids can be used concomitantly without dose adjustment.
Antiarrhythmics/anti-angina: e.g., amiodarone, bepridil disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine,	↑ antiarrhythmics	Coadministration of D/C/F/TAF with these antiarrhythmics may increase concentrations of the antiarrhythmic (inhibition of CYP3A), and the combination should thus be used with caution. Clinical monitoring is recommended for antiarrhythmics when coadministered with D/C/F/TAF.
dronedarone ranolazine		Concomitant use of D/C/F/TAF with dronedarone or ranolazine is contraindicated.
digoxin	↑ digoxin	Coadministration of D/C/F/TAF with digoxin may increase concentrations of digoxin (inhibition of P-gp). The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Antibacterial: (ketolide or macrolide antibiotics) clarithromycin, erythromycin, telithromycin	effect on darunavir unknown ↑ cobicistat ↑ antibacterial	Coadministration of D/C/F/TAF with these antibacterials may increase concentrations of darunavir (although no darunavir increase was observed with ritonavir-boosted darunavir and clarithromycin), cobicistat, or the antibacterial (inhibition of CYP3A). Consider alternative antibiotics with concomitant use of D/C/F/TAF and consult local prescribing information for antibacterials.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Anticancer Agents:	↑ anticancer agent	Coadministration of D/C/F/TAF with these anticancer agents may increase concentrations of the anticancer agent (inhibition of CYP3A), resulting in the potential for increased adverse events usually associated with these agents.
dasatinib, nilotinib,		A decrease in the dosage or an adjustment of the dosing interval of dasatinib or nilotinib may be necessary when co-administered with D/C/F/TAF. Consult the dasatinib and nilotinib prescribing information for dosing instructions.
vinblastine, vincristine		For vincristine and vinblastine, consider temporarily withholding the cobicistat-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when D/C/F/TAF is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consider initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
everolimus		Concomitant use of everolimus and D/C/F/TAF is not recommended.
Anticoagulants:	↑ anticoagulant	Coadministration of D/C/F/TAF with these anticoagulants may increase concentrations of the anticoagulant (inhibition of CYP3A and/or P-gp).
apixaban		When used in combination with D/C/F/TAF, the recommended dose of apixaban is 2.5 mg twice daily.
dabigatran etexilate,		The combination of D/C/F/TAF and dabigatran etexilate is not recommended in specific renal impairment groups (depending on indication). Consult the dabigatran etexilate prescribing information for specific recommendations
rivaroxaban		Coadministration of D/C/F/TAF and rivaroxaban is not recommended.
warfarin	effect on warfarin unknown	Coadministration of D/C/F/TAF with warfarin may affect warfarin concentrations. When D/C/F/TAF is coadministered with warfarin, the international normalized ratio (INR) should be monitored and used for titration of warfarin dose to obtain the desired clinical effect.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Anticonvulsants: with CYP3A induction effects: carbamazepine, phenobarbital, phenytoin	↓ darunavir ↓ cobicistat ↓ tenofovir alafenamide	Coadministration of D/C/F/TAF with carbamazepine, phenobarbital, or phenytoin (which are CYP3A and P-gp inducers) decreases plasma concentrations of darunavir, cobicistat, and tenofovir alafenamide which may result in loss of therapeutic effect and development of resistance. Concomitant use of D/C/F/TAF with these anticonvulsants is contraindicated.
eslicarbazepine, oxcarbazepine	darunavir: effect unknown ↓ cobicistat ↓ tenofovir alafenamide	Coadministration of D/C/F/TAF with oxcarbazepine or eslicarbazepine may decrease darunavir, cobicistat, and/or tenofovir alafenamide concentrations (induction of CYP3A and P-gp), which may result in loss of therapeutic effect and development of resistance. Consider alternative anticonvulsant or antiretroviral therapy to avoid potential changes in exposures. If co-administration is necessary, monitor for lack or loss of virologic response.
That are metaolized by CYP3A: e.g., clonazepam, ethosuximide	↑clonazepam ↑ethosuximide	Coadministration of D/C/F/TAF with these anticonvulsants may increase concentrations of the anticonvulsant (inhibition of CYP3A). Clinical monitoring is recommended when coadministering D/C/F/TAF with these anticonvulsants.
Antidepressants: selective serotonin reuptake inhibitors (SSRIs): paroxetine, sertraline	SSRIs: effect unknown	Concomitant use of D/C/F/TAF and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when coadministering D/C/F/TAF with these antidepressants and a dose adjustment of the antidepressant may be needed.
tricyclic antidepressants (TCAs): amitriptyline, desipramine, imipramine, nortriptyline,	↑ TCAs	
other antidepressants: trazodone	↑ trazodone	
Antifungals: itraconazole, clotrimazole fluconazole ketoconazole, posaconazole,	↑ darunavir ↑ cobicistat ↑tenofovir alafenamide ↑ antifungal ↔ posaconazole (not studied)	Coadministration of D/C/F/TAF with these antifungals may increase concentrations of darunavir, cobicistat, tenofovir alafenamide, and/or the antifungal (inhibition of CYP3A and/or P-gp). Clinical monitoring for increased adverse reactions is recommended when coadministering D/C/F/TAF with these antifungals. When used in combination with D/C/F/TAF, the dose of itraconazole or ketoconazole should not exceed 200 mg/day.
voriconazole	voriconazole: effects unknown	Concentrations of voriconazole may increase or decrease when coadministered with D/C/F/TAF. Coadministration with voriconazole is not recommended unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Antihistamines: astemizole, terfenadine	↑ antihistamines	Exposure to these antihistamines may be increased when coadministered with D/C/F/TAF. Concomitant use of D/C/F/TAF with astemizole and terfenadine is contraindicated. *[note these drugs are no longer marketed in several countries]*
Anti-gout: colchicine	↑ colchicine	Concomitant use of D/C/F/TAF with colchicine may increase concentrations of colchicine (inhibition of CYP3A). Coadministration of D/C/F/TAF with colchicine is contraindicated in patients with renal or hepatic impairment. Refer to colchicine product information for dosing recommendations for patients without renal or hepatic impairment: • Treatment of gout flares – co-administration of colchicine: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. • Prophylaxis of gout flares – co-administration of colchicine: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. • Treatment of familial Mediterranean fever – co-administration of colchicine: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimalarial: artemether/lumefantrine	↔ darunavir artemether: effect unknown lumefantrine: effect unknown	Monitor for a potential decrease of antimalarial efficacy or potential QT prolongation.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Antimycobacterial: rifabutin, rifampin, rifapentine	↓ darunavir ↓ cobicistat ↓ tenofovir alafenamide ↑ rifabutin	Coadministration of D/C/F/TAF with rifabutin, rifampin, or rifapentine may decrease darunavir, cobicistat, and/or tenofovir alafenamide concentrations (induction of CYP3A and P-gp), which may result in loss of therapeutic effect and development of resistance. Rifabutin concentrations may be increased when coadministered with D/C/F/TAF. Coadministration of D/C/F/TAF with rifabutin and rifapentine is not recommended. If combination of rifabutin and D/C/F/TAF is required, the recommended dose of rifabutin is 150 mg every other day. Clinical monitoring is recommended when coadministering D/C/F/TAF with rifabutin. Coadministration of D/C/F/TAF with rifampin is contraindicated. This recommendation is different from ritonavir-boosted darunavir. Consult the darunavir product information for further details.
β-Blockers: e.g., carvedilol, metoprolol, timolol	↑ beta-blockers	Coadministration of D/C/F/TAF and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when coadministering D/C/F/TAF with beta-blockers that are metabolized by CYP2D6.
Calcium Channel Blockers: e.g., amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blockers	Coadministration of D/C/F/TAF with calcium channel blockers may increase concentrations of the calcium channel blocker (inhibition of CYP3A). Clinical monitoring is recommended when coadministering D/C/F/TAF with calcium channel blockers metabolized by CYP3A.
Contraceptives: progestin/estrogen	progestin: effects unknown estrogen: effects unknown	No dosing recommendations can be made on the use of D/C/F/TAF with oral or other hormonal contraceptives. Additional or a lternative (non-hormonal) forms of contraception should be considered.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Corticosteroids: **Inhaled/Nasal/Systemic**: dexamethasone	↓ darunavir ↓ cobicistat	Coadministration of D/C/F/TAF with systemic dexamethasone or other corticosteroids that induce CYP3A may decrease darunavir and/or cobicistat concentrations which may result in loss of therapeutic effect of and development of resistance. Coadministration of D/C/F/TAF with (systemic) dexamethasone is not recommended. Alternative corticosteroids should be considered.
betamethasone budesonide fluticasone mometasone prednisone triamcinolone	↑ corticosteroid	Coadministration of D/C/F/TAF with inhaled or nasal fluticasone or other corticorsteroids that are metabolized by CYP3A can increase the risk for corticosteroid adverse events and may result in reduced serum cortisol concentrations. Alternative corticosteroids, including beclomethasone and prednisolone (for which PK and/or PD are less affected by strong CYP3A inhibitors relative to other steroids) should be considered, particularly for long-term use.
Endothelin receptor antagonists: bosentan	↓ darunavir ↓ cobicistat ↑ bosentan	Bosentan concentrations may be increased when coadministered with D/C/F/TAF. Clinical monitoring is recommended when coadministering D/C/F/TAF with bosentan and a dose adjustment of bosentan may be needed: <u>Initiation of bosentan in patients taking D/C/F/TAF:</u> In patients who have been receiving D/C/F/TAF for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Initiation of D/C/F/TAF in patients on bosentan:</u> Discontinue use of bosentan at least 36 hours prior to initiation of D/C/F/TAF. After at least 10 days following the initiation of D/C/F/TAF, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability. <u>Switching from darunavir co-administered with ritonavir to D/C/F/TAF in patients on bosentan</u>: Maintain bosentan dose. Recommendations may need to be aligned with the local prescribing information for bosentan
Ergot Alkaloids e.g., ergotamine, ergonovine, dihydroergotamine, methylergonovine	↑ ergot alkaloids	Exposure to the ergot alkaloids may be increased when coadministered with D/C/F/TAF. Concomitant use of D/C/F/TAF with ergot alkaloids is contraindicated.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Eugeroics armodafinil, modafinil	↓ darunavir ↓ cobicistat	Coadministration of D/C/F/TAF with armodafanil or modafinil may decrease darunavir and/or cobicistat concentrations (induction of CYP3A), which may result in loss of therapeutic effect and development of resistance. Coadministration of D/C/F/TAF and armodafanil or modafinil, which are CYP3A inducers, is not recommended.
GI Motility Agents Cisapride	↑ cisapride	Exposure to cisapride may be increased when coadministered with D/C/F/TAF. Concomitant use of D/C/F/TAF with cisapride is contraindicated.
H_2-Receptor Antagonists: cimetidine, famotidine, nizatidine, ranitidine	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (ie, decreased gastric acidity) no interaction is expected when D/C/F/TAF is coadministered with H_2-receptor antagonists. D/C/F/TAF can be coadministered with H2-receptor antagonists without dose adjustment.
Hepatitis C Virus (HCV) Direct-Acting Agents		
boceprevir,	↓ darunavir ↓ boceprevir	Concomitant administration of D/C/F/TAF with boceprevir may decrease darunavir and/or boceprevir concentrations (mechanism unknown) and has the potential to adversely affect the intracellular activation and antiviral efficacy of tenofovir alafenamide based on in vitro data. Coadministration of D/C/F/TAF with boceprevir is not recommended.
simeprevir	darunavir: effects unknown ↑ simeprevir	No drug interaction data are available. The combination of D/C/F/TAF and simeprevir is not recommended.
elbasvir/grazoprevir	↑ elbasvir ↑ grazoprevir	Concomitant administration of D/C/F/TAF with elbasvir/grazoprevir may increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations (OATP1B1/3 inhibition). Concomitant use of D/C/F/TAF with elbasvir/grazoprevir is contraindicated.
sofosbuvir, ledipasvir, daclatasvir		Based on mechanistic considerations, no clinically relevant interaction is expected when D/C/F/TAF is coadministered with sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir. D/C/F/TAF can be coadministered with sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir without dose adjustment.
Herbal Products: St. John's wort	↓ darunavir ↓ cobicistat ↓ tenofovir alafenamide	Coadministration of D/C/F/TAF with products containing St. John's wort (Hypericum perforatum) may cause significant decreases in darunavir, cobicistat, and/or tenofovir alafenamide concentrations (induction of CYP3A or P-gp), which may result in loss of therapeutic effect and development of resistance. Co administration of D/C/F/TAF with products containing St. John's wort (Hypericum perforatum) is contraindicated.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
HMG-CoA Reductase Inhibitors: e.g., atorvastatin, fluvastatin pitavastatin, pravastatin, rosuvastatin,	pitavastatin: effect unknown ↑ other HMG-CoA reductase inhibitors	Concomitant use of a HMG-CoA reductase inhibitor and D/C/F/TAF may increase plasma concentrations of the lipid lowering agent (inhibition of CYP3A and/or transport), which may lead to adverse events such as myopathy. When coadministering D/C/F/TAF with HMG-CoA reductase inhibitors, start with the lowest recommended dose and titrate while monitoring for safety.
lovastatin, simvastatin		Coadministration of D/C/F/TAF with lovastatin or simvastatin is contraindicated.
Immunosuppressants: cyclosporine, sirolimus, tacrolimus	↑ immunosuppressants	Coadministration of D/C/F/TAF and these immunosuppressants may increase concentrations of the immunosuppressants (inhibition of CYP3A). Co-administration of ciclosporin is expected to increase plasma concentrations of tenofovir alafenamide (P-gp inhibition). Therapeutic drug monitoring is recommended for the immunosuppressant when coadministered with D/C/F/TAF.
everolimus		Concomitant use of everolimus and D/C/F/TAF is not recommended.
Inhaled beta agonist: salmeterol	↑ salmeterol	Coadministration of D/C/F/TAF with salmeterol may increase concentrations of salmeterol (inhibition of CYP3A). The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Coadministration of D/C/F/TAF with salmoterol is not recommended.
Narcotic Analgesics: fentanyl, oxycodone, tramadol	↑ analgesic	Coadministration of D/C/F/TAF with these analgesics may increase concentrations of the analgesic (inhibition of CYP2D6 and/or CYP3A). Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended when coadministering D/C/F/TAF with these analgesics. A dose decrease may be needed for tramadol with concomitant use
Narcotic Analgesic/ Treatment of Opioid Dependence: buprenorphine, buprenorphine/naloxone, naloxone, methadone	↔ buprenorphine ↑ norbuprenorphine ↔ naloxone ↓ methadone (effects observed with DRV/rtv)	No a priori dose adjustment of buprenorphine or methadone is required when coadministering with D/C/F/TAF. However, careful clinical monitoring is recommended as the dose of buprenorphine or methadone may need to be adjusted in some patients.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Neuroleptics/ Antipsychotics: lurasidone, perphenazine, pimozide, risperidone, thioridazine	↑ neuroleptic/ antipsychotic	Coadministration of D/C/F/TAF and these neuroleptics may increase concentrations of the neuroleptic (inhibition of CYP3A or CYP2D6). A lower dose of the neuroleptic may be needed. Coadministration of D/C/F/TAF with lurasidone and pimozide is contraindicated.
quetiapine	↑ quetiapine	Concomitant use of quetiapine and D/C/F/TAF may increase the exposure to quetiapine (inhibition of CYP3A). *Initiation of D/C/F/TAF in patients taking quetiapine:* consider alternative antiretroviral therapy to avoid increases in quetiapine exposure. If coadministration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. *Initiation of quetiapine in patients taking D/C/F/TAF:* refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Phosphodiesterase PDE-5 inhibitors: avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	Coadministration of D/C/F/TAF and PDE-5 inhibitors may increase concentrations of the PDE-5 inhibitor (inhibition of CYP3A), which may lead to adverse events such as hypotension, syncope, visual disturbances and priapism. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): • Coadministration of D/C/F/TAF with sildenafil is contraindicated (see Contraindications). • The following dose adjustments are recommended for use of tadalafil with D/C/F/TAF: Initiation of tadalafil in patients on D/C/F/TAF: In patients receiving D/C/F/TAF for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Initiation of D/C/F/TAF in patients on tadalafil: Avoid use of tadalafil during the initiation of D/C/F/TAF. Stop tadalafil at least 24 hours prior to starting D/C/F/TAF. After at least one week following the initiation of D/C/F/TAF, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Patients switching from darunavir coadministered with ritonavir to D/C/F/TAF: maintain tadalafil dose Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse events. Coadministration of D/C/F/TAF and avanafil is not recommended
Platelet Aggregation Inhibitors: ticagrelor	↑ ticagrelor	Coadministration of D/C/F/TAF with ticagrelor may increase concentrations of ticagrelor (inhibition of CYP3A and/or P-gp). Coadministration of D/C/F/TAF and ticagrelor is not recommended.
Proton Pump Inhibitors: e.g., esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (ie, decreased gastric acidity) no interaction is expected when D/C/F/TAF is coadministered with proton pump inhibitors. D/C/F/TAF and proton pump inhibitors can be coadministered without dose adjustment.

Concomitant Drug Class: Drug Name	**Effect on Concentration of D/C/F/TAF Components or Concomitant Drug**	**Clinical Comment**
Sedatives/Hypnotics: Metabolized by CYP3A e.g., buspirone, clorazepate, diazepam, estazolam, flurazepam, parenterally administered midazolam, zolpidem	↑ sedatives/hypnotics	Coadministration of D/C/F/TAF with these sedatives/hypnotics may increase concentrations of the benzodiazepine (inhibition of CYP3A). When coadministering D/C/F/TAF with these sedatives/ hypnotics metabolized by CYP3A, titration is recommended and a lower dose of the sedatives/hypnotics should be considered with monitoring for increased and prolonged effects or adverse reactions. Coadministration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered.
oral midazolam, triazolam		Coadministration of D/C/F/TAF with oral midazolam or triazolam is contraindicated.

3.4.2.3. Interactions With NRTIs

Nucleoside/nucleotide reverse transcriptase inhibitors for which the interaction with DRV (coadministered with rtv) has been investigated include ddI (Section 3.4.2.3.1) and TDF (Section 3.4.2.3.2). Based on the different elimination pathways of the other NRTIs (eg, abacavir, FTC [see also Section 3.4.2.1], lamivudine, stavudine, or zidovudine) that are primarily renally excreted, no drug interactions are expected. Similar results are anticipated for DRV/COBI and no clinically relevant interactions for any of the components of the D/C/F/TAF are anticipated.

As the D/C/F/TAF FDC is intended as a complete regimen for the treatment of HIV-1, this drug-drug interaction information will not be included in the prescribing information.

3.4.2.3.1. Didanosine

When DRV/rtv 600/100 mg twice daily and ddI 400 mg once daily were coadministered in healthy subjects (TMC114-C123, Table 5), the mean steady-state exposure (AUC_{12h}) to DRV was not affected, and the mean exposure (AUC_{24h}) to ddI was decreased slightly (9%, which was not considered to be clinically relevant), as compared with their administration alone. The mean exposure (AUC_{12h}) to rtv (100 mg twice daily) was decreased by 14% when coadministered with DRV in the presence of ddI, but the mean C_{min} and C_{0h} were slightly increased, 1.05- and 1.32-fold, respectively. These changes in rtv exposure were not considered clinically relevant. There are no metabolic interactions expected between ddI and COBI. Also, COBI solubility is not affected by pH.

3.4.2.3.2. Tenofovir Disoproxil Fumarate

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion, and is not metabolized. In the presence of rtv, tenofovir (administered as the prodrug TDF; TMC114-C124, Table 5) increased DRV exposure 1.21-fold, and DRV/rtv increased tenofovir exposure 1.22-fold. The exposure to rtv (100 mg twice daily), when coadministered with DRV, was not affected to any relevant degree by the presence of tenofovir. When F/TDF was coadministered with DRV/COBI 800/150 mg once daily, the TFV exposure increased 1.17-fold, and the DRV and COBI exposure was not affected (GS-US-299-0101, Mod2.7.1/Sec2.1.1.2.3.2).

In the DRV/COBI Phase 3b study (NDA205395/Mod5.3.5.2/GS-US-216-0130_W24_CSR), DRV/COBI was mostly (97%) combined with TDF/FTC and was, in general, safe and well tolerated. The analysis of integrated data from the primary 24-week analyses of studies TMC114-C202 and TMC114-C213 in HIV-1 infected subjects (NDA021976/Mod5.3.5.1) indicated that concomitant use of TDF had no apparent effect on the exposure to DRV. Thus, taking in account the only modest changes in exposure seen in study TMC114-C124 and GS-US-299-0101 and the apparent lack of any effect seen in studies TMC114-C202 and TMC114-C213, and the wealth of information of combined use of TDF with boosted DRV, any impact on the pharmacokinetics are not considered clinically relevant.

The D/C/F/TAF FDC contains another TFV prodrug and should not be combined with medicinal products containing TDF.

3.4.2.4. Interactions with NNRTIs

Non-nucleoside reverse transcriptase inhibitors for which the interaction with DRV (coadministered with rtv) has been investigated include EFV (Section 3.4.2.4.1), NVP (Section 3.4.2.4.3), etravirine (Section 3.4.2.4.2), and RPV (Section 3.4.2.4.4), all of which are CYP3A inducers with the exception of RPV. Non-nucleoside reverse transcriptase inhibitors for which the interaction with F/TAF has been investigated include EFV and RPV.

As the D/C/F/TAF FDC is intended as a complete regimen for the treatment of HIV-1, this drug-drug interaction information will not be included in the prescribing information.

3.4.2.4.1. Efavirenz

Efavirenz (600 mg once daily) decreased the exposure (AUC) to DRV (oral solution, coadministered with rtv at a dose of 300/100 mg twice daily) by 13%, and DRV coadministration resulted in a 1.21-fold increase in EFV exposure (TMC114-C111, Table 5). The exposure to rtv (100 mg twice daily), when coadministered with DRV, was decreased by 28% in the presence of EFV. Based on the absence of a PK/PD relationship for boosted DRV, the 13% decrease in DRV exposure due to EFV coadministration is not considered clinically relevant. Coadministration of COBI with efavirenz did not affect the AUC_{last} or AUC_{∞} of efavirenz, and the C_{max} of efavirenz was only slightly reduced (13%) (GS-US-216-0112, Table 5). However, because COBI is a CYP3A substrate, EFV may lower COBI exposure and consequently also its boosting activity on DRV.

When EFV was coadministered with F/TAF (GS-US-311-0101, Table 6), the LS mean ratio and 90% CIs for TAF AUC_{last} and TFV AUC_{tau} and C_{tau} were within the protocol-defined lack of interaction boundary. The TAF and TFV C_{max} decreased by 12% and 18%, respectively.

As the D/C/F/TAF FDC is intended as a complete regimen for the treatment of HIV-1, this drug-drug interaction will not be included in the prescribing information.

3.4.2.4.2. Etravirine

Etravirine is a substrate of CYP3A, 2C9, and 2C19. At steady-state, coadministration of DRV/rtv 600/100 mg twice daily with etravirine caused a 37% decrease in exposure to etravirine (AUC_{12h}) when etravirine was administered at 100 mg twice daily and a 1.80-fold increase in exposure to etravirine when etravirine was administered at 200 mg twice daily, in both cases compared with administration of etravirine 100 mg twice daily alone (TMC114-176, Table 5). For DRV exposure, only the mean AUC_{12h} was increased (1.15-fold) after coadministration of etravirine 200 mg twice daily. The mean AUC_{12h} of rtv was decreased by 14% and 11%, respectively, after coadministration of etravirine 100 mg and 200 mg twice daily. As COBI is a CYP3A substrate, etravirine may lower COBI exposure and consequently also its boosting activity on DRV. The interaction with F/TAF has not been evaluated but no significant drug interaction is anticipated.

As the D/C/F/TAF FDC is intended as a complete regimen for the treatment of HIV-1, this drug-drug interaction will not be included in the prescribing information.

3.4.2.4.3. Nevirapine

When compared with historical data, NVP (200 mg twice daily) increased the exposure to DRV (tablet formulation, coadministered with rtv at a dose of 400/100 mg twice daily) 1.24-fold, and DRV induced a 1.27-fold increase in NVP exposure, which may be due to CYP3A inhibition by DRV coadministered with rtv (TMC114-119, Table 5). The exposure to rtv (100 mg twice daily), when coadministered with DRV, was increased 1.10-fold when DRV/rtv was coadministered with NVP. These changes were not considered clinically relevant. As COBI is a CYP3A substrate, NVP may lower COBI exposure (inhibition of CYP3A) and consequently also its boosting activity on DRV.

The interaction with F/TAF has not been evaluated but no significant drug interaction is anticipated.

As the D/C/F/TAF FDC is intended as a complete regimen for the treatment of HIV-1, this drug-drug interaction will not be included in the prescribing information.

3.4.2.4.4. Rilpivirine

Rilpivirine is a CYP3A substrate. In healthy subjects, at steady-state conditions, coadministration of RPV 150 mg once daily with DRV/rtv 800/100 mg once daily caused a 2.30-fold increase in the mean AUC_{24h} of rilpivirine and a 1.79-fold increase in the mean C_{max}, as compared with administration of RPV alone (TMC278-C112, Table 5). The increase in RPV C_{max} was below

85% (1.85-fold) and is not expected to be of clinical relevance or cause safety concerns. There was no clinically relevant effect on the mean exposure to DRV/rtv on coadministration with RPV. Darunavir/rtv and RPV can be coadministered without dose adjustments. The drug interaction between DRV/COBI and RPV has not been evaluated, but is anticipated to not exceed that observed with DRV/rtv.

Coadministration of F/TAF and RPV, evaluated after single dose and at steady-state, did not result in clinically relevant changes in the pharmacokinetics of RPV, FTC or TAF (GS-US-120-0117 and GS-US-120-1554, Table 6).

As the D/C/F/TAF FDC is intended as a complete regimen for the treatment of HIV-1, this drug-drug interaction information will not be included in the prescribing information.

3.4.2.5. Interactions with HIV PIs Other Than DRV

The appropriate dose of boosted DRV for coadministration with other HIV PIs has not been established. Cobicistat is an approved pharmacokinetic enhancer for the HIV PIs ATV and DRV.

The combination of F/TAF with several HIV PIs has been evaluated throughout its development (GS-US-120-0118, Table 6). Coadministration with ATV/rtv or with LPV/rtv increased the TAF exposure (AUC_{last}) by 1.91-fold and 1.46-fold, respectively. The TFV exposure (AUC_{last}) increased by 2.48-fold and 3.22-fold, respectively.

As the D/C/F/TAF FDC is intended as a complete regimen for the treatment of HIV-1, this drug-drug interaction will not be included in the prescribing information.

3.4.2.6. Interactions with CCR5RAs

Maraviroc is a CYP3A substrate. The exposure to maraviroc increased 4.05-fold when maraviroc (150 mg twice daily) was coadministered with DRV/rtv (600/100 mg twice daily), as compared with administration of maraviroc alone (TMC114-A4001052)[24]. There was no apparent effect of maraviroc on DRV/rtv exposure, as the DRV/rtv exposure in the presence of maraviroc was similar to the exposure observed in healthy subjects in other studies. The drug interaction between DRV/COBI and maraviroc has not been evaluated, but is anticipated to not exceed that observed with DRV/rtv. The interaction with F/TAF has not been evaluated but no significant drug interaction is anticipated.

As the D/C/F/TAF FDC is intended as a full regimen for the treatment of HIV-1, this drug-drug interaction information will not be included in the prescribing information.

3.4.2.7. Interactions with Integrase Strand Transfer Inhibitors

As the D/C/F/TAF FDC is intended as a full regimen for the treatment of HIV-1, this drug-drug interaction information will not be included in the prescribing information.

3.4.2.7.1. Dolutegravir

Dolutegravir (DTG) is primarily metabolized by glucuronidation (UGT1A1) with CYP3A having a minor role; it is also substrate of P-gp. Dolutegravir does not appear to inhibit or induce CYP, nor does it inhibit P-gp. An open-label, 2-period, 2-sequence crossover study in 15 healthy volunteers was conducted to assess the effect of DRV/rtv on DTG (1-way interaction).[37] In this study, DTG 30 mg once daily alone was administered for 5 days followed by the addition of DRV/rtv 600/100 mg twice daily for 14 days. Dolutegravir PK was assessed on Day 5 of treatment alone and Day 14 of the coadministered treatments. Coadministration of DRV/rtv to DTG decreased DTG AUC_{24h}, C_{max} and C_{24h} by 22%, 11% and 38%, respectively. The decrease in DTG is not considered to be clinically relevant. The interaction with DRV/COBI has not been evaluated but is anticipated to not exceed that observed with DRV/rtv.

Coadministration of FTC+TAF with DTG did not result in clinically relevant changes for any of the components (GS-US-120-0118, Table 6).

3.4.2.7.2. Elvitegravir

The exposure to DRV when coadministered with EVG/COBI was increased relative to single-dose administration of DRV alone (GS-US-201-0104, Table 5). As EVG is coformulated with COBI (and FTC and TDF or TAF), coadministration of E/C/F/TDF or E/C/F/TAF with the D/C/F/TAF FDC is expected to double the COBI and FTC exposure, slightly increase the TFV exposure, and/or double the TAF exposure.

3.4.2.7.3. Raltegravir

The literature on HIV-infected patients suggests that DRV exposure in plasma may decrease in the presence of raltegravir. This contrasts with the results of a study conducted in healthy subjects by Merck (in collaboration with Janssen). In this study (TMC114-MK0518, data not shown), no signal for an interaction between DRV/rtv and raltegravir could be detected, although no firm PK conclusion could be made due to an insufficient sample size.

The decrease in DRV C_{0h} when DRV/rtv was coadministered with raltegravir, as reported in the literature, ranged from 18% to 39%, for C_{max}, the decrease was approximately 39%, and for AUC, the decrease ranged from 20% to 42%. Intracellular DRV C_{0h} decreased by 31%, with no apparent change in intracellular AUC_{24h} when DRV/rtv 800/100 mg once daily was coadministered with raltegravir 400 mg twice daily in HIV-infected subjects.[20] The mechanism by which raltegravir decreases DRV exposure is unknown.

Raltegravir does not inhibit the major CYP isozymes involved in drug metabolism (CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and 2B6), UGT (UGT1A1 and 2B7), or P-gp, and it does not induce CYP3A.[3] In vitro, raltegravir induced the expression of ABCC1 (gene that encodes MRP1), with 1.7-fold increases in gene expression at concentrations of 1 µmol/L and 2.0-fold increases at 10 µmol/L.[46] The geometric mean steady-state raltegravir C_{max} when administered 400 mg twice daily in healthy subjects under fasted conditions or with food (low-, moderate-, or high-fat)

ranged from 1.31 to 5.32 µmol/L[3], suggesting that induction of ABCC1 by raltegravir may occur in vivo. Darunavir, however, does not appear to be a substrate of MRP1.[26]

Treatment with DRV/rtv when coadministered with raltegravir has been shown to be efficacious in the following clinical studies:

- DRV/rtv 800/100 mg once daily with raltegravir 400 mg twice daily as part of an NRTI-sparing regimen (A5262, ANRS 143/NEAT 001, and RADAR).
- DRV/rtv 600/100 mg twice daily with other ARVs including raltegravir 400 mg twice daily (BENCHMRK and TRIO).
- Subjects on DRV/rtv 600/100 mg twice daily switched from enfuvirtide to raltegravir (EASIER-ANRS 138).

Therefore, the reported decreases in plasma concentrations of DRV do not appear to be clinically relevant. The interaction with DRV/COBI has not been evaluated but is anticipated to not exceed that observed with DRV/rtv.

The interaction with F/TAF has not been evaluated but no significant drug interaction is anticipated.

3.4.2.8. Interactions with Other Drugs

3.4.2.8.1. α_1-Adrenoreceptor Antagonists

Cobicistat and DRV are CYP3A inhibitors, and alfuzosin is a CYP3A substrate that is contraindicated with potent CYP3A inhibitors (eg, rtv).[16] Accordingly, D/C/F/TAF, like DRV/COBI or DRV/rtv, may increase alfuzosin exposures and coadministration with the D/C/F/TAF FDC is contraindicated.

3.4.2.8.2. Acid Suppressing Agents Including Antacids, H_2-Receptor Antagonists, and Proton Pump Inhibitors

The exposure to DRV and rtv was not affected when the H_2-receptor antagonist ranitidine (150 mg twice daily) or the proton pump inhibitor omeprazole (20 mg once daily) was coadministered with DRV/rtv at a dose of 400/100 mg twice daily (TMC114-C122, Table 5). The DRV PK is thus not affected by coadministration with acid suppressing agents.

The solubility of COBI is unaffected by pH, as demonstrated in studies with proton pump inhibitors and H_2-receptor antagonists (GS-US-216-0120 and GS-US-216-0122, Table 5).

The interaction with F/TAF has not been evaluated but no significant drug interaction is anticipated.

No dose adjustment of D/C/F/TAF is required when coadministered with acid suppressing agents such as antacids, H_2-receptor antagonists, or proton pump inhibitors.

3.4.2.8.3. Antiangina/Antiarrhythmics

Antiarrhythmic agents, including but not limited to amiodarone, bepridil, disopyramide, dronedarone, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine, and ranolazine are primarily metabolized by CYP3A and/or CYP2D6 (among other isozymes).[25] DRV/COBI is a strong (mechanism-based, for COBI) CYP3A inhibitor and an inhibitor, albeit mildly, of CYP2D6. Accordingly, exposures of these antiarrhythmic agents are expected to increase with D/C/F/TAF. Caution is warranted when D/C/F/TAF is coadministered with these antiarrhythmics. Coadministration of dronedarone or ranolazine with D/C/F/TAF is contraindicated.

Digoxin is a P-gp substrate and is known as a narrow therapeutic index drug. At steady-state, DRV (tablet formulation, coadministered with rtv at a dose of 600/100 mg twice daily) increased the exposure (AUC_{24h}) to digoxin (single dose of 0.4 mg) 1.35-fold (TMC114-C150, Table 5). Coadministration of COBI 150 mg once daily with a single dose of digoxin 0.5 mg resulted in a 1.41-fold increase in C_{max}, which may have been due to transient inhibition of gut P-gp (GS-US-216-0112, Table 5). Coadministration of D/C/F/TAF with digoxin is expected to increase digoxin to a similar extent as DRV/rtv and COBI. Digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect, while assessing the overall clinical state of the subject.

3.4.2.8.4. Antibacterials

Clarithromycin is a substrate of P-gp and CYP3A. At steady-state, DRV (tablet formulation, coadministered with rtv at a dose of 400/100 mg twice daily) increased the exposure (AUC_{12h}) to clarithromycin (500 mg twice daily) 1.57-fold and inhibited formation of the active metabolite 14-hydroxy clarithromycin (TMC114-C142, Table 5). These changes are not considered to be clinically relevant. The exposure to DRV (AUC_{12h}) was decreased by 13% when combined with clarithromycin (in the presence of rtv), which was not considered to be clinically relevant. The exposure to rtv was not affected to any relevant degree by the presence of clarithromycin. Based on theoretical considerations, coadministration of DRV/COBI with clarithromycin and other antibacterials like erythromycin and telithromycin, may increase concentrations of DRV (though no DRV increase was observed with clarithromycin and DRV/rtv), COBI and/or the antibacterial.

Coadministration of D/C/F/TAF with clarithromycin is expected to increase clarithromycin exposure to a similar magnitude as DRV/rtv. The local prescribing information for clarithromycin should be consulted for specific dosing recommendations, especially for specific subjects with renal impairment.

3.4.2.8.5. Anticancer/Antineoplastic Agents

Dasatinib, nilotinib, vinblastine, everolimus and vincristine are primarily metabolized by CYP3A (vinblastine is also metabolized by CYP2D6 to a minor extent); accordingly, their exposures are expected to increase when coadministered with D/C/F/TAF (based on DRV/COBI), which may result in increased AEs associated with these medicinal products. Clinical monitoring is

recommended when coadministering D/C/F/TAF with these anticancer agents and a dose adjustment may be needed; concomitant use of everolimus is not recommended.

3.4.2.8.6. Anticoagulants

Apixaban, rivaroxaban and ticagrelor are CYP3A and P-gp substrates; dabigatran etexilate is a substrate for P-gp.[34] Coadministration of D/C/F/TAF (based on DRV/COBI) with these anticoagulants may result in increased plasma concentrations of the anticoagulant. Therefore, coadministration of D/C/F/TAF and rivaroxaban or ticagrelor is not recommended. When coadministered with D/C/F/TAF, the recommended dose of apixaban is 2.5 mg twice daily. The combination of D/C/F/TAF and dabigatran etexilate should be used with caution and is not recommended in specific renally impaired subjects (consult the local prescribing information). Warfarin is metabolized primarily by CYP2C9 with a minor component of CYP3A. Coadministration of D/C/F/TAF with warfarin may alter warfarin exposure. The international normalized ratio should be monitored when D/C/F/TAF is coadministered with warfarin.

3.4.2.8.7. Anticonvulsants

Carbamazepine is a substrate and inducer of CYP3A. The coadministration of carbamazepine 200 mg twice daily with DRV/rtv 600/100 mg twice daily (TMC114-C172, Table 5) had no effect on the mean exposure (AUC_{12h}) to DRV, but the mean exposure to carbamazepine (AUC_{12h}) was increased 1.45-fold and the mean exposure to the metabolite carbamazepine epoxide was decreased by 54%; the mean exposure to rtv was decreased by 49%. Although carbamazepine is an inducer of CYP3A, it had no clinically relevant effect on the PK of DRV in this study. The decrease in rtv exposure did not affect exposure to DRV, which is consistent with observations from another drug-drug interaction study (ddI). Ritonavir is a potent inhibitor of CYP3A metabolism and is able to increase exposure to CYP3A substrates, as was observed for carbamazepine in this study. The inhibition of the CYP3A metabolism of carbamazepine to carbamazepine epoxide likely resulted in the lower exposure to carbamazepine epoxide in the presence of DRV/rtv.

The DRV/COBI combination may be more susceptible to interaction with CYP3A inducers, like carbamazepine, which may decrease both COBI and/or DRV concentrations, which may result in loss of therapeutic effect and development of resistance. The effect of lower COBI exposure on DRV exposure has not been established. Like carbamazepine, the anticonvulsants phenobarbital and phenytoin are known inducers of CYP isozymes, including CYP3A. The interaction between these antiepileptics and COBI and/or DRV is not known.

Carbamazepine, phenobarbital, and phenytoin are also P-gp inducers and may as such decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance.

Because of the potential for decreased COBI and/or DRV and/or TAF exposure, coadministration of carbamazepine, phenytoin or phenobarbital and the D/C/F/TAF FDC is contraindicated. Coadministration of oxcarbazepine or eslicarbazepine, less potent CYP3A and P-gp inducers, and D/C/F/TAF is not recommended.

Clonazepam and ethosuximide are CYP3A substrates. Coadministration of D/C/F/TAF (based on DRV/COBI) with these anticonvulsants may result in increased plasma concentrations of the anticoagulant. Clinical monitoring is recommended.

3.4.2.8.8. Antidepressants

Paroxetine is primarily metabolized by CYP2D6 and sertraline is primarily metabolized by CYP3A. The coadministration of paroxetine (20 mg once daily), did not affect the exposure to DRV (coadministered with rtv at a dose of 400/100 mg twice daily), but DRV/rtv coadministration resulted in a 39% decrease in the exposure to paroxetine (TMC114-C121, Table 5). Sertraline (50 mg once daily) did not affect the exposure to DRV (coadministered with rtv at a dose of 400/100 mg twice daily), but DRV coadministration resulted in a 49% decrease in the exposure to sertraline (TMC114-C121, Table 5). The mechanism for the decrease in paroxetine and sertraline exposure is not known. Darunavir, paroxetine, and sertraline are all highly bound (>95%) to plasma AAG, so the decrease in paroxetine and sertraline exposure may be due to a protein-binding interaction, resulting in decreased total plasma concentrations of paroxetine or sertraline in the presence of DRV/rtv. The exposure to rtv was increased 1.34-fold in the presence of paroxetine but unaffected by sertraline. The drug interaction with DRV/COBI has not been evaluated, but is anticipated to not exceed that observed with DRV/rtv. Coadministration of D/C/F/TAF with paroxetine or sertraline is expected to increase paroxetine and sertraline total plasma concentrations via inhibition of CYP2D6 or CYP3A, respectively. However, a protein binding interaction cannot be excluded.

Coadministration with F/TAF (as part of the E/C/F/TAF FDC) did not have a clinically relevant impact on the pharmacokinetics of sertraline, or vice versa (GS-US-292-1316, Table 6).

Desipramine and trazodone are substrates of CYP2D6 and CYP3A, respectively. Accordingly, their exposures may increase with D/C/F/TAF coadministration (through effect of DRV/COBI). When desipramine 50 mg was coadministered with COBI 150 mg once daily alone, C_{max} and AUC_{last} increased 1.24- and 1.58-fold, respectively (GS-US-216-0112, Table 5).

Clinical monitoring is recommended when coadministering D/C/F/TAF with the antidepressants amitriptyline, desipramine, imipramine, paroxetine, nortriptyline, sertraline and trazodone. The combination should be used with caution, and a lower dose of antidepressant should be considered.

3.4.2.8.9. Antidiabetics

Metformin is a substrate of OCT1, OCT2, MATE-1, and MATE-2.[39] Coadministration of D/C/F/TAF (based on COBI) with metformin may alter the renal clearance of metformin and enhance its response.

3.4.2.8.10. Antifungals

Ketoconazole is a substrate and potent inhibitor of CYP3A. Ketoconazole (200 mg twice daily) increased the exposure (AUC_{12h}) to DRV (tablet formulation, coadministered with rtv at a dose of 400/100 mg twice daily) 1.42-fold (TMC114-C129, Table 5). The exposure (AUC_{12h}) to

ketoconazole was also significantly increased (by more than 3-fold) when coadministered with DRV/rtv. Coadministration of D/C/F/TAF with ketoconazole is expected to increase DRV, COBI, and ketoconazole exposure to a similar extent as DRV/rtv. Based on these results, a maximum daily dose of 200 mg ketoconazole is recommended when ketoconazole is coadministered with boosted DRV.

Coadministration of itraconazole, clotrimazole, fluconazole, isavuconazole or ketoconazole, also P-gp inhibitors, may also increase plasma concentrations of TAF. However, no specific dosing recommendations for D/C/F/TAF are needed based on the effect on TAF PK alone.

Itraconazole, clotrimazole and isavuconazole are also substrates of CYP3A; and fluconazole is a substrate of P-gp. Accordingly, their exposures, as well as DRV and/or COBI exposure, may increase with D/C/F/TAF coadministration. Posaconazole may also increase the DRV and/or COBI exposure. Clinical monitoring is recommended when coadministering D/C/F/TAF with itraconazole, clotrimazole, fluconazole, isavuconazole, ketoconazole and posaconazole. As for ketoconazole, when used in combination with D/C/F/TAF, the dose of itraconazole should not exceed 200 mg per day. For voriconazole, the impact of D/C/F/TAF is not known, voriconazole concentrations may decrease or increase. Voriconazole should not be used with the D/C/F/TAF FDC unless the possible benefit is considered to outweigh the risks associated with the unpredictable effect on plasma concentrations.

3.4.2.8.11. Antigout Agents

Colchicine is a substrate of CYP3A and P-gp.[40] Accordingly, colchicine exposure may increase with D/C/F/TAF coadministration (based on DRV/COBI). Coadministration of D/C/F/TAF with colchicine is contraindicated in patients with renal or hepatic impairment.

3.4.2.8.12. Antihistamines

Astemizole and terfenadine are substrates of CYP3A. Accordingly, their exposure may increase with D/C/F/TAF coadministration (based on DRV/COBI). Coadministration of D/C/F/TAF with astemizole or terfenadine is contraindicated.

3.4.2.8.13. Antimalarials

Artemether and lumefantrine are CYP3A substrates; artemether is also metabolized to a lesser extent by CYP2B6, 2C9, and 2C19. After single-dose administration of artemether/lumefantrine 80/480 mg in the presence of DRV/rtv 600/100 mg twice daily, the mean C_{max} and AUC_{8h} of artemether were, respectively, 15% and 9% lower than after single-dose administration of artemether/lumefantrine alone. After multiple-dose administration, the mean C_{max} and AUC_{last} of artemether were decreased by 18% and 16%, respectively, while the C_{min} of artemether was comparable in the presence and absence of DRV/rtv (TMC125VIR1001, Table 5).

After single-dose administration of artemether/lumefantrine in the presence of DRV/rtv, the mean C_{max} and AUC_{8h} of the artemether metabolite DHA were, respectively, increased 1.06- and 1.12-fold compared with after single-dose administration of artemether/lumefantrine alone. After

multiple-dose administration, the mean C_{max} and AUC_{last} of DHA were both decreased by 18%, while the C_{min} of DHA was comparable for in the presence and absence of DRV/rtv.

After intake of artemether/lumefantrine in the presence of DRV/rtv, C_{min}, C_{max}, and AUC_{264h} of lumefantrine were, respectively, 2.26-, 1.65-, and 2.75-fold higher than in the absence of DRV/rtv.

After administration of DRV/rtv alone or in the presence of artemether/lumefantrine, the mean C_{max} and AUC_{12h} of DRV were comparable, while the C_{min} of DRV was decreased by 13% in the presence artemether/lumefantrine. The C_{min} and AUC_{12h} of rtv were comparable in the presence and absence of artemether/lumefantrine, while the mean C_{max} of rtv was decreased by 15% in the presence of artemether/lumefantrine.

Given the complex interplay of interactions, the impact of DRV/COBI on the exposure to artemether/lumefantrine is unknown, no clinically relevant impact on the DRV exposure is anticipated. For FTC/TAF, no impact on the exposure to artemether/lumefantrine or vice versa is anticipated. When coadministering D/C/F/TAF with artemether/lumefantrine, clinical monitoring is recommended.

3.4.2.8.14. Antimycobacterials

Rifabutin is a substrate and inducer of CYP3A. The coadministration of rifabutin 150 mg every other day with DRV/rtv 600/100 mg twice daily increased the mean exposure (AUC_{12h}) to DRV 1.57-fold and to rtv 1.66-fold, compared with DRV/rtv 600/100 mg twice daily alone (TMC114-C163, Table 5). Following coadministration with DRV/rtv, the mean exposure (AUC_{τ}) to rifabutin 150 mg every other day decreased slightly (by 7%), as compared with rifabutin 300 mg once daily alone (ie, when the dose of rifabutin was decreased in the presence of DRV/rtv), and the mean exposure to 25-*O*-desacetylrifabutin was increased 9.81-fold. The combined exposure to 25-*O*-desacetylrifabutin and rifabutin increased 3.13-fold when rifabutin was coadministered with DRV/rtv. When EVG/COBI 150/150 mg once daily was coadministered with rifabutin 300 mg every other day (GS-US-216-0123, Table 5), exposure to rifabutin was unchanged, but the C_{max} and AUC of 25-*O*-desacetylrifabutin were increased 4.84- and 6.25-fold, respectively, relative to administration of rifabutin 300 mg once daily alone.

Based on the safety findings in the study with DRV/rtv and rifabutin, a dose reduction in rifabutin of at least 75% (ie, rifabutin 150 mg every other day) is warranted if rifabutin is coadministered with DRV/rtv; in this case, based on the safety findings for DRV in this study and the overall safety profile of DRV, there are no safety concerns with the impact on DRV exposure.

The DRV/COBI combination may be more susceptible to interaction with CYP3A inducers like rifabutin, which may decrease both COBI and/or DRV concentrations, which may result in loss of therapeutic effect and development of resistance. The effect of lower COBI exposure on DRV exposure has not been established. Like rifabutin, the antimycobacerials rifampin and rifapentin, are known inducers of CYP3A.

Rifabutin, rifampin, and rifapentine are also P-gp inducers and may as such decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance.

Because of the potential for decreased COBI and/or DRV and/or TAF exposure, coadministration of rifampin and the D/C/F/TAF FDC is contraindicated. Coadministration of rifapentin and rifabutin and D/C/F/TAF is not recommended. Coadministration of D/C/F/TAF with rifabutin is expected to increase rifabutin exposure to a similar extent as DRV/rtv. If the combination of D/C/F/TAF and rifabutin is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (eg, Monday-Wednesday-Friday). Increased monitoring for rifabutin−associated adverse reactions, including neutropenia and uveitis, is warranted due to an expected increase in exposure to desacetyl−rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin, thus leading to a risk of rifabutin resistance and treatment failure.

3.4.2.8.15. Antipsychotics

Quetiapine is a substrate of CYP3A. Coadministration of D/C/F/TAF (based on DRV/COBI) with quetiapine may increase quetiapine plasma concentrations and, consequently, quetiapine-related toxicity. When coadministered with D/C/F/TAF, the quetiapine dose may need to be adjusted.[36]

3.4.2.8.16. Beta-Blockers

Carvedilol, metoprolol, and timolol are substrates of CYP2D6.[28] Exposures of these beta-blockers may increase when coadministered with D/C/F/TAF (based on DRV/COBI). Clinical monitoring is recommended when coadministering D/C/F/TAF with beta-blockers.

3.4.2.8.17. Calcium Channel Blockers

Amlodipine, diltiazem, felodipine, nicardipine, nifedipine, and verapamil are substrates of CYP2D6 and/or CYP3A.[28] Accordingly, exposures of these calcium channel blockers may increase with coadministration of D/C/F/TAF (based on DRV/COBI). Clinical monitoring is recommended when coadministering D/C/F/TAF with calcium channel blockers.

3.4.2.8.18. Contraceptives

Ethinyl estradiol is a CYP3A and CYP2C9 substrate and norethindrone is a CYP3A substrate. In healthy women, the mean exposure (AUC_{24h}) to ethinyl estradiol and norethindrone was decreased by 44% and 14%, respectively, when DRV/rtv 600/100 mg twice daily was coadministered with ethinyl estradiol 35 µg and norethindrone 1 mg once daily, as compared with administration of ethinyl estradiol and norethindrone alone (TMC114-C131, Table 5).

Coadministration of ethinyl estradiol and norgestimate with COBI was studied in the context of the E/C/F/TDF 150/150/200/300 mg STR (GS-US-236-0106, Table 5). Coadministration of the E/C/F/TDF STR with ethinyl estradiol/norgestimate resulted in decreased exposure to ethinyl estradiol and increased exposure to the active metabolite of norgestimate, norelgestromin. Serum

progesterone and follicle-stimulating hormone concentrations were comparable with and without the E/C/F/TDF STR, while a greater decrease in serum luteinizing hormone concentrations was observed when ethinyl estradiol/norgestimate was coadministered with the E/C/F/TDF STR relative to administration of ethinyl estradiol/norgestimate alone. These PD results suggest that negative feedback inhibition for the secretion of follicle-stimulating hormone and luteinizing hormone was maintained despite an observed reduction in ethinyl estradiol plasma concentrations.

Given the complex metabolism of estrogen and progesterone derivatives, no dose recommendations can be made on the use of D/C/F/TAF with contraceptives. Alternative methods of nonhormonal contraception are recommended.

3.4.2.8.19. Corticosteroids metabolized by CYP3A

Budesonide, fluticasone, prednisone, betamethasone, mometasone and triamcinolone are substrates of CYP3A, and accordingly, their exposures may increase with coadministration of D/C/F/TAF (based on DRV/COBI). This can increase the risk for corticosteroid adverse events and may result in reduced serum cortisol concentrations; alternatives to these corticosteroids should be considered, particularly for long-term use.

3.4.2.8.20. Corticosteroids that are inducing CYP3A

When administered systemically, dexamethasone is a moderate inducer of CYP3A. Coadministration of D/C/F/TAF with systemic dexamethasone or other corticosteroids that induce CYP3A is expected to decrease COBI and/or DRV exposures. Systemic dexamethasone in combination with D/C/F/TAF is not recommended.

3.4.2.8.21. Endothelin Receptor Antagonists

Bosentan is a substrate and moderate inducer of CYP2C9, CYP2C19, and CYP3A.[42] Coadministration of D/C/F/TAF (based on DRV/COBI) with bosentan is expected to decrease COBI and/or DRV exposures. Bosentan concentrations may be increased when coadministered with D/C/F/TAF. Clinical monitoring is recommended when coadministering D/C/F/TAF with bosentan and a dose adjustment of bosentan may be needed

3.4.2.8.22. Ergot Derivatives

Dihydroergotamine, ergometrine, ergotamine, and methylergonovine are substrates of CYP3A. Accordingly, the exposures of these ergot derivatives may increase with coadministration of D/C/F/TAF (based on DRV/COBI). Coadministration of these ergot derivatives with D/C/F/TAF is contraindicated.

3.4.2.8.23. Eugeroics

Modafinil and armodafinil are inducers of CYP3A. Coadministration of D/C/F/TAF with modafinil or armodafinil is expected to decrease COBI and/or DRV exposures. Modafinil or armodafinil in combination with D/C/F/TAF is not recommended.

3.4.2.8.24. Gastrointestinal Motility Agents

Cisapride is a substrate of CYP3A. Accordingly, cisapride exposure may increase with coadministration of D/C/F/TAF (based on DRV/COBI). Coadministration of cisapride with D/C/F/TAF is contraindicated.

3.4.2.8.25. Hepatitis C Virus Direct-Acting Agents, NS3/4A PIs

Telaprevir is a CYP3A and P-gp substrate and inhibitor. Coadministration of telaprevir 750 mg every 8 hours with DRV/rtv 600/100 mg twice daily in healthy subjects resulted in decreased plasma exposure to DRV (40% to 42%) and telaprevir (32% to 36%), and increased plasma concentrations of rtv (1.37- to 1.48-fold), as compared with administration of telaprevir and DRV/rtv alone (VX950-C124).[41] The mechanism of this interaction is unknown.

Boceprevir is a substrate of CYP3A and a substrate and inhibitor of P-gp. Coadministration of DRV/rtv with boceprevir resulted in decreases in both DRV and boceprevir exposure.[18]

The interaction with F/TAF has not been evaluated but co-administration with boceprevir or telaprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of TAF.

The coadministration of D/C/F/TAF with telaprevir or boceprevir is not recommended.

Simeprevir is a substrate of CYP3A. Accordingly, simeprevir exposure increases with coadministration of D/C/F/TAF (based on DRV/COBI). The coadministration of D/C/F/TAF with simeprevir is not recommended.

No clinically relevant interactions in either direction are anticipated when D/C/F/TAF is coadministered with daclatasvir, ledipasvir and/or sofosbuvir. D/C/F/TAF and sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir can be used concomitantly without dose adjustment.

3.4.2.8.26. Herbal Products

St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A, 2C9, 2C19, and P-gp.[31] Coadministration of D/C/F/TAF with St. John's wort is expected to decrease COBI and/or DRV and/or TAF exposure, which may result in loss of therapeutic effect and development of resistance. Coadministration of D/C/F/TAF with St. John's wort is contraindicated.

3.4.2.8.27. HMG-CoA Reductase Inhibitors

Atorvastatin is metabolized by CYP3A and is transported by OATP. The results of an interaction study with atorvastatin showed that atorvastatin (10 mg once daily) in combination with DRV (oral solution, coadministered with rtv at a dose of 300/100 mg twice daily, TMC114-C133, Table 5) provided exposure to atorvastatin that was comparable to the exposure following administration of atorvastatin alone (40 mg once daily). The interaction is anticipated to be similar for DRV/COBI. When coadministration of atorvastatin and D/C/F/TAF is desired, it is recommended to start with a low dose of atorvastatin and a gradual dose increase may then be tailored to the clinical response. Consult the local prescribing information.

Pravastatin is not metabolized by CYP3A to any clinically relevant extent, as indicated by in vitro and in vivo data. Darunavir (coadministered with rtv at a dose of 600/100 mg twice daily) increased exposure to pravastatin (single 40 mg dose) 1.81-fold, but pravastatin did not impact the PK of DRV (or rtv) (TMC114-C120, Table 5). The increase in pravastatin exposure was, however, not consistently found. A subsequent interaction study suggests polymorphisms in solute carrier OATP1B1 may partly explain the variability in interaction.

Pitavastatin is metabolized primarily by UGT to pitavastatin lactone (inactive) with minor involvement of CYP2C8 and 2C9. Darunavir (coadministered with rtv at a dose of 800/100 mg once daily) decreased pitavastatin (4 mg once daily) exposure 26% and pitavastatin lactone exposure by 32%, most likely as a result of UGT induction; pitavastatin had no effect on the PK of DRV (or rtv).[45]

Cobicistat also has the ability to inhibit P-gp and BCRP at the intestinal level, and OATP1B1 and 1B3 at the hepatic uptake level during first pass. The recommendations for the other agents that are not CYP3A substrates and only substrates for transporters are based on data from a study that showed no clinically relevant changes in rosuvastatin exposures (AUC) and/or expected modest interactions that did not necessitate dose modification. Fluvastatin and pitavastatin are also substrates of OATP1B1 and are not CYP3A substrates. Accordingly, modest increases in their exposures are expected when coadministered with D/C/F/TAF (though not observed for pitavastatin with DRV/rtv), similar to those observed with rosuvastatin.

Lovastatin and simvastatin are substrates of CYP3A. A significant increase in lovastatin and simvastatin exposure is expected when coadministered with D/C/F/TAF (based on DRV/COBI). Therefore, coadministration of D/C/F/TAF with lovastatin or simvastatin is contraindicated.

3.4.2.8.28. Immunosuppressants

Ciclosporin, everolimus, sirolimus, and tacrolimus are substrates of CYP3A. Accordingly, exposures of these immunosuppressants may increase on coadministration with D/C/F/TAF (based on DRV/COBI). Ciclosporin is also an inhibitor of P-gp and is anticipated to increase TAF exposures. Caution is warranted and therapeutic concentration monitoring is recommended for the immunosuppressant when coadministered with D/C/F/TAF; coadministration with everolimus is not recommended.

3.4.2.8.29. Inhaled Beta Agonists

Salmeterol is a substrate of CYP3A. Accordingly, salmeterol exposures may increase with coadministration of D/C/F/TAF (based on DRV/COBI). Coadministration of D/C/F/TAF with salmeterol may result in increased risk of cardiovascular AEs associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. Therefore, coadministration of D/C/F/TAF with salmeterol is not recommended.

3.4.2.8.30. Narcotic Analgesics

Fentanyl, oxycodone, and tramadol are metabolized by CYP2D6 and/or CYP3A.[17] Coadministration of D/C/F/TAF (based on DRV/COBI) with these narcotic analgesics may

increase concentrations of the analgesic. Clinical monitoring is recommended when coadministering D/C/F/TAF with these analgesics.

3.4.2.8.31. Narcotic Analgesics/Treatment of Opioid Dependence

Buprenorphine is metabolized by the CYP3A and 2C, and UGT families. Naloxone is metabolized by UGT2B7 and 1A1, and CYP2C18, and 2C19. Buprenorphine/naloxone exposure (AUC_{24h}) was not affected by coadministration with DRV/rtv 600/100 mg twice daily (TMC114-C171, Table 5). The exposure to the active metabolite norbuprenorphine increased 1.46-fold. Modest increases in buprenorphine and naloxone exposures (1.35-fold and 1.42-fold, respectively) were observed upon coadministration with COBI/EVG.[4] However, these modest changes in exposure did not lead to clinical opiate overdose or withdrawal when assessed with standardized scales and, therefore, are not considered to be clinically relevant.

Methadone is primarily metabolized by CYP2B6 and 2C19. When DRV/rtv 600/100 mg twice daily was added to a stable, individualized methadone maintenance therapy (TMC114-C127, Table 5), the mean C_{min}, C_{max}, and AUC_{24h} values of biologically active R(-) methadone were decreased by 15%, 24%, and 15%, respectively, as compared with methadone alone. The mean C_{min}, C_{max}, and AUC_{24h} values of inactive S(+) methadone were decreased by 40%, 44%, and 36%, respectively. There were no increases in symptoms of opiate withdrawal during the study, and no methadone dose adjustments were needed during the coadministration phase. Cobicistat shows no inductive or inhibitory effects on CYP2B6 and/or 2C19.

No dose adjustment of buprenorphine, methadone, and/or naloxone may be required when coadministering with D/C/F/TAF. However, clinical monitoring is recommended, as the dose of buprenorphine, methadone, and/or naloxone may need to be adjusted in some patients.

3.4.2.8.32. Neuroleptics

Perphenazine, pimozide, risperidone, lurasidone, sertindole, and thioridazine are substrates of CYP2D6 and/or CYP3A. Accordingly, the exposures of these neuroleptics may increase with coadministration of D/C/F/TAF (based on DRV/COBI). Clinical monitoring is recommended when coadministering D/C/F/TAF with perphenazine, risperidone, or thioridazine, and a lower dose of the neuroleptic should be considered. Coadministration of D/C/F/TAF with pimozide, lurasidone or sertindole is contraindicated.

3.4.2.8.33. Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 inhibitors such as avanafil, sildenafil, tadalafil, and vardenafil are primarily metabolized by CYP3A. When sildenafil (single dose of 25 mg) was given with DRV (coadministered with rtv at a dose of 400/100 mg twice daily), the exposure to sildenafil was comparable to administration of sildenafil (single dose of 100 mg) alone (TMC114-C128, Table 5). The metabolite *N*-desmethyl sildenafil, which is 50% less active than the parent compound sildenafil, was hardly formed in the presence of DRV/rtv. This increase in sildenafil exposure is likely due to CYP3A inhibition.

Thus, in the presence of D/C/F/TAF, dose adjustment for sildenafil is required. When coadministered with D/C/F/TAF, no more than 25 mg sildenafil is recommended over a 48-hour period when sildenafil is used for treatment of erectile dysfunction. The findings from this study can be extrapolated to other PDE-5 inhibitors when used for treatment of erectile dysfunction (vardenafil: single dose not exceeding 2.5 mg in 72 hours; tadalafil: single dose not exceeding 10 mg in 72 hours) when coadministered with D/C/F/TAF. Coadministration of D/C/F/TAF with avanafil is not recommended.[38] Coadministration of D/C/F/TAF with sildenafil for pulmonary arterial hypertension is contraindicated because a safe and effective dose of sildenafil in the presence of DRV/rtv for the treatment of pulmonary arterial hypertension has not been established. Coadministration of D/C/F/TAF with tadalafil for pulmonary arterial hypertension may require dose adjustment of tadalafil.

3.4.2.8.34. Sedatives/Hypnotics

Buspirone, clorazepate, diazepam, estazolam, flurazepam, MDZ, triazolam, and zolpidem are all substrates of CYP3A. Accordingly, exposures of these sedative/hypnotic agents may increase with coadministration of D/C/F/TAF (based on DRV/COBI). Clinical monitoring is recommended when coadministering D/C/F/TAF with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Parenteral MDZ should be coadministered with D/C/F/TAF in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral MDZ should be considered, especially if more than a single dose of MDZ is administered. Coadministration of D/C/F/TAF with oral MDZ or triazolam is contraindicated.

The anxiolyticum/sedative benzodiazepine lorazepam is not metabolized via CYP450 enzymes and no clinically relevant drug-drug interactions are anticipated with the D/C/F/TAF components.

3.5. Pharmacodynamics

3.5.1. Pharmacokinetic/Pharmacodynamic Relationship - Efficacy

3.5.1.1. D/C/F/TAF

Prior to the development of the D/C/F/TAF FDC, the PK/PD relationships for the different components of the D/C/F/TAF FDC had been evaluated throughout their respective development programs, the combination of which have led to the dose selection for the different components in the D/C/F/TAF FDC (Section 3.6). The efficacy and PK/PD relationships for boosted DRV and for FTC are well-established through their developments in different combinations (including D/C/F/TAF) and are only briefly discussed. The prodrug TAF is relatively new, and therefore a more thorough evaluation of the TAF PK/PD relationship, leading to and confirming the dose selection of TAF for the D/C/F/TAF FDC, is provided in Section 3.5.1.4.

The efficacy and safety of the D/C/F/TAF FDC was investigated in the 2 pivotal Phase 3 studies (TMC114FD2HTX3001 and TMC114IFD3013, Section 2.2.2.2 and 2.2.2.3) and Phase 2 study GS-US-299-0102 (Section 2.2.2.1). Efficacy data from these studies are further detailed in

Mod2.7.3/Sec3.1. Pharmacokinetic data are available for all components from a PK substudy in GS US-299-0102 (as well as from TAF population PK analysis with data available for 52 subjects in the D/C/F/TAF treatment arm) and in addition, for DRV and COBI from the Phase 3 studies TMC114FD2HTX3001 and TMC114IFD3013 and for TAF from Phase 3 study TMC114FD2HTX3001.

The PK/PD analyses from the D/C/F/TAF Phase 3 studies indicated (both graphically and via logistic regression) that there were no apparent relationships between the pharmacokinetics of DRV and the main efficacy endpoints (virologic response for TMC114FD2HTX3001, Section 2.2.2.2; virologic rebound or virologic failure for TMC114IFD3013, Section 2.2.2.3).

The PK/PD analyses from the D/C/F/TAF Phase 3 study TMC114FD2HTX3001 indicated (both graphically and via logistic regression) that there was no apparent relationship between the pharmacokinetics of TAF and the main efficacy endpoint (virologic response, <50 c/mL FDA Snapshot Week 48, Section 2.2.2.2). Also in the D/C/F/TAF Phase 2 study GS-US-299-0102, no PK/PD relationship was observed; virologic response at Week 48 was similar in all TAF AUC quartiles and there was no trend for a relationship between TAF exposure and virologic failure at Week 48. The TAF PK/PD analysis across studies is further discussed in more detail in Section 3.5.1.4.

3.5.1.2. DRV/COBI

Throughout the development of DRV, in studies with DRV/rtv (NDA021976/Mod5.3.5.1/TMC114-C211 and TMC114-C229 CSRs) and DRV/COBI (NDA205395/Mod5.3.5.2/GS-US-216-0130_W24_CSR) once daily regimens in HIV-1 infected patients, no relevant relationship between DRV AUC_{24h} or C_{0h} and efficacy was observed, ie, there was no indication that a lower DRV exposure would result in lower virologic response. There was a good and comparable virologic response across all exposure quartiles Moreover, further PK/PD analyses using generalized additive modeling (GAM) indicated that a reduction in DRV exposure by up to 50% would not impact the efficacy and would still result in the same predicted mean virologic response. This is related to the fact that DRV plasma concentrations in the presence of a booster are likely to be on the plateau of the concentration-response curve and far above the protein-binding adjusted EC_{50} (55 ng/mL for wild-type virus, ie, for treatment-naïve HIV-1 infected patients and treatment-experienced HIV-1 infected patients with no DRV RAMs for which a boosted DRV once daily regimen is indicated).[21,22]

3.5.1.3. FTC

Two short term monotherapy studies (NDA021752/Mod5.3.3.2/FTC-101 and FTC-102 CSRs) identified FTC at a dose of 200 mg once-daily to provide maximal antiviral activity in HIV-1 infected subjects. This was confirmed through a pharmacological dose response E_{max} model showing that the antiviral effect of FTC reaches a plateau as dose increases, with little difference in the activity between the 200 and 400 mg doses.[33]

3.5.1.4. TAF

The following antiviral activity data and evaluation of PK/PD relationships for TAF efficacy contributed to dose selection for TAF with boosted DRV:

- The antiviral activity and TAF PK at doses of 8, 25 and 40 mg once daily, in the TAF proof-of-concept study GS-US-120-0104. From this, a TAF 25 mg once daily dose administered alone provided near maximal antiviral activity, and was chosen for further development. The TAF exposure with D/C/F/TAF 800/150/200/10 mg (mean AUC ~130 ng.h/mL) is similar to that of TAF 25 mg in study GS-US-120-0104 (mean AUC ~115 ng.h/mL, Section 2.2.3.2).
- The absence of a PK/PD relationship across a wide range of TAF exposures (AUC_{tau} range: 47.2 to 1,869.3 ng.h/mL) in the Phase 3 studies in the E/C/F/TAF development program (pooled data GS-US-292-0104 and GS-US-292-0111, Section 2.2.3.3).
- The absence of a PK/PD relationship in the Phase 3 study GS-US-311-1089 (AUC_{tau} range: 30.3 to 466.7 ng.h/mL) evaluating F/TAF in combination with a variety of third agents, including DRV/rtv (Section 2.2.3.4).
- The TAF exposure with D/C/F/TAF 800/150/200/10 mg (TAF AUC_{tau} range TMC114FD2HTX3001: 70.9 to 400 ng.h/mL) is comprised within the range of TAF exposures for which there was no PK/PD relationship, in the above studies.
- No PK/PD relationship was observed across the range of TAF exposures in the D/C/F/TAF Phase 3 study TMC114FD2HTX3001 (TAF AUC_{tau} range: 70.9 to 400 ng.h/mL) or the Phase 2 study GS-US-299-0102 (AUC_{tau} range: 38.3 to 295.6 ng.h/mL); virologic response at Week 48 was similar in all TAF AUC quartiles and there was no trend for a relationship between TAF exposure and virologic failure at Week 48.
- The intracellular TFV-DP exposure with D/C/F/TAF is 6.5-fold higher compared to DRV+COBI+F/TDF, which is consistent with the E/C/F/TAF studies.

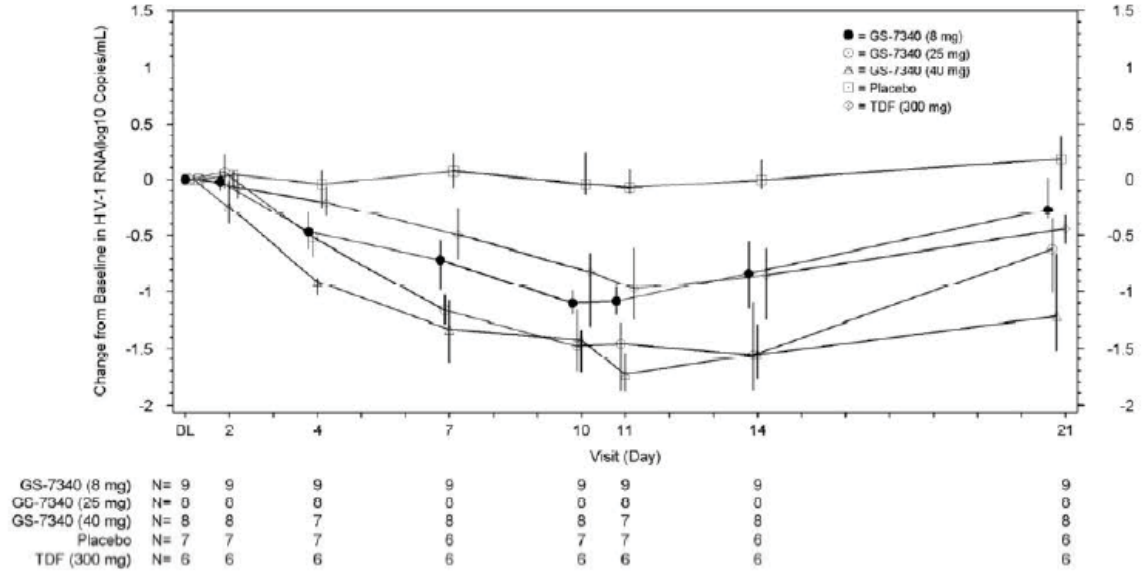
The following subsections provide more details on each of these aspects, including a discussion on the TFV exposure, where applicable.

3.5.1.4.1. TAF Proof-of-Concept Study, GS-US-120-0104

In the proof-of-concept study GS-US-120-0104 (Section 2.2.3.2) following once daily administration of single agent TAF 8, 25, 40 mg, or TDF 300 mg, the median (Q1, Q3) $DAVG_{11}$ values (the primary efficacy endpoint) were −0.76 (−0.86, −0.57), −0.94 (−1.12, −0.76), −1.08 (−1.35, −0.97), and −0.48 (−0.57, −0.34) log10 copies/mL, respectively. The median $DAVG_{11}$ (log_{10} copies/mL) in the TAF 25 mg and 40 mg once daily treatment groups showed significantly greater decreases compared with the TDF 300 mg once daily treatment group (−0.94 and −1.08 versus −0.48, p=0.017 and p=0.006, respectively) with a statistically significant difference also observed between the TAF 8 mg and 40 mg once daily treatment groups (−0.76 versus −1.08, p=0.003). Median (Q1, Q3) change from baseline to Day 11 in HIV-1 RNA values were −1.08 (−1.20, −0.96), −1.46 (−1.88, −1.28), −1.73 (−1.88, −1.55) and −0.97 (−1.24, −0.62) log_{10} copies/mL for TAF 8, 25, 40 mg, and TDF 300 mg once daily, respectively (Figure 24). The decreases in median viral load for both TAF 25 mg and TAF 40 mg once daily were statistically

significantly greater than that observed for TAF 8 mg once daily (p=0.030 and 0.002, respectively).

Figure 24: Median (Q1, Q3) Change from Baseline in HIV-1 RNA (log_{10} copies/mL) by Visit (Full Analysis Set) (Study GS-US-120-0104)



Baseline HIV-1 RNA was defined to be the geometric mean of the last 2 available nonmissing HIV-1 RNA values before the first dose.

The PK/PD relationship between TAF plasma exposure and antiviral activity was explored using a maximum (PD) effect (E_{max}) model, where Effect = (E_{max} × log_{10} PK parameter)/(log_{10} PK parameter 50 + log PK parameter). Day 10 TAF C_{max}, AUC, and change from baseline in HIV-1 RNA were fit to E_{max} models that investigated both fixed (hill=1) and variable hill slopes. Models were evaluated using goodness of fit to select the most appropriate model. Results showed that TAF AUC fits well with an E_{max} model, resulting in an E_{max} of ~1.7 to 1.8 log_{10} copies/mL decline from baseline and a concentration of drug inhibiting virus replication by 50% (EC_{50}) value of approximately 32 ng.h/mL. A similar fit and E_{max} estimate was obtained using TAF C_{max}, which was somewhat expected given the relatively brief plasma circulation time of TAF (driven by a short half-life) and the resulting contribution of C_{max} to the overall AUC. Compared with the antiviral activity of TAF 40 mg, TAF 25 mg is expected to provide near-maximum activity (~1.7 to 1.8 log_{10} copies/mL).

In addition, the PK/PD relationship between TFV plasma exposures and antiviral activity was explored using an E_{max} model, where Effect = (E_{max} × log_{10} PK parameter)/(log_{10} PK parameter 50 + log PK parameter). Plasma TFV exposure, which was substantially lower with TAF versus TDF, did not correlate with antiviral activity.

The TAF and TFV PK parameters are summarized in Table 30 and Table 31, respectively; and the intracellular TFV-DP (PBMCs) PK is presented in Section 3.5.1.4.2.

The TAF exposure observed with D/C/F/TAF 800/150/200/10 mg in HIV-1 infected subjects in the Phase 2b study GS-US-299-0102 (mean AUC_{last} 130.5 ng.h/mL, mean C_{max} 163.0 ng/mL; see Section 2.2.2.1.3.1) and the Phase 3 study TMC114FD2HTX3001 (mean AUC_{tau} 132 ng.h/mL see Section 2.2.3.3) is similar to that of TAF 25 mg in study GS-US-120-0104 (mean AUC_{last} 115.2 ng.h/mL, mean C_{max} 177.2 ng/mL) (Table 30).

Table 30: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF (TAF PK Analysis Set) (Study GS-US-120-0104)

TAF PK Parameter	TAF Multiple-Dose PK Day 10 Mean (%CV) and Median (Range); t_{max} and $t_{1/2}$: Median (Range)		
	TAF 8 mg (N=9)	TAF 25 mg (N=8)	TAF 40 mg (N=8)
AUC_{last} (n.gh/mL)	54.7 (92.6)	115.2 (33.4)	308.9 (33.6)
	27.5 (20.3-103.3)	109.1 (101.4-132.9)	344.2 (213.4-383.4)
C_{max}, ng/mL	85.8 (116.3)	223.6 (58.8)	629.5 (57.0)
	41.5 (24.9-80.2)	177.2 (131.0- 18.3)	606.4 (299.6-948.4)
t_{max} (h)	0.50 (0.50-0.50)	0.50 (0.50-0.75)	0.50 (0.38-0.50)
$t_{1/2}$ (h)	0.38 (0.26-0.50)[a]	0.39 (0.34-0.54)	0.42 (0.32-0.49)

[a] N=8

AUC_{last} is presented for multiple-dose PK because TAF concentrations are BLQ by approximately 5 hours postdose and utilizing AUC_{last} instead of AUC_{∞} or AUC_{tau}, respectively, provides a more appropriate measure of exposure assessment. To account for the variability in the data, the mean and median AUC_{last} and C_{max} are presented.
AUC_{last}=area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration; C_{max}=maximum plasma concentration; t_{max}=time to C_{max}; $t_{1/2}$=terminal elimination half-life

Table 31: Summary of Single- and Multiple-Dose PK Parameter Estimates for TFV Following Once-Daily Dosing of TAF (TAF PK Analysis Set) (Study GS-US-120-0104)

	Mean (%CV); t_{max}/ $t_{1/2}$: Median (Range)							
	TFV Single-Dose PK[a]; Day 1				TFV Multiple-Dose PK; Day 10			
TAF PK	TAF 8 mg (N=9)	TAF 25 mg (N=8)	TAF 40 mg (N=8)	TDF 300 mg (N=6)	TAF 8 mg (N=9)	TAF 25 mg (N=8)	TAF 40 mg (N=8)	TDF 300 mg (N=6)
AUC^{a}, ng.h/mL	49.4 (30.3)	195.9 (27.2)	287.3 (33.7)	1719.2 (57.9)	65.5 (23.5)	267.7 (26.7)	405.8 (12.7)	1918.0 (39.4)
C_{max}, ng/mL	2.0 (31.1)	6.5 (40.1)	14.0 (20.3)	181.2 (50.5)	4.2 (24.7)	15.7 (22.1)	28.3 (8.7)	252.1 (36.6)
C_{tau}, ng/mL	0.7 (19.8)	2.4 (23.5)	4.0 (27.2)	23.9 (57.5)	2.1 (33.8)	9.21 (26.1)	13.3 (16.0)[b]	38.7 (44.7)
$t_{max,}$ h	1.00 (1.00-2.00)	1.50 (1.03-1.75)	1.00 (0.75-1.00)	1.25 (0.53-1.50)	1.50 (1.00-1.98)	1.50 (1.25-1.75)	1.29 (1.04-1.50)	1.25 (0.58-2.00)
$t_{1/2,}$ h	23.9 (18.3-37.2)[b]	29.8 (26.9-44.0)[b]	24.6 (20.3-28.5)	15.6 (14.2-17.1)	30.8 (26.9-55.6)[c]	40.2 (29.0-44.8)	36.0 (26.4-42.9)[b]	14.9 (12.2-16.8)

[a] AUC_{∞} and C_{24h} are presented for single-dose PK; AUC_{tau} is presented for multiple-dose PK
[b] N=7
[c] N=8

AUC=area under the plasma concentration-time curve; C_{max}=maximum plasma concentration; t_{max}=time to C_{max}; $t_{1/2}$=terminal elimination half-life; TAF: tenofovir disoproxil fumarate; TFV=tenofovir.

3.5.1.4.2. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111

A further evaluation of the PK/PD relationship of TAF (analysis performed by GSI) was based on data from the pivotal E/C/F/TAF Phase 3 studies, GS-US-292-0104 and GS-US-292-0111, in HIV-1 infected subjects.

Summary descriptive statistics of the TAF and TFV PK in these Phase 3 studies are presented in Section 2.2.3.3.

The pooled PK/PD analysis sets for TAF and TFV included all subjects who (1) were randomized and received at least 1 dose of E/C/F/TAF in study GS-US-292-0104 or GS-US-292-0111, and (2) had at least 1 non-missing TAF or TFV PK parameter, respectively, (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. The primary efficacy endpoint for the PK/PD analysis was the proportion of subjects with HIV 1 RNA <50 copies/mL at Week 48 as defined by the FDA snapshot algorithm.

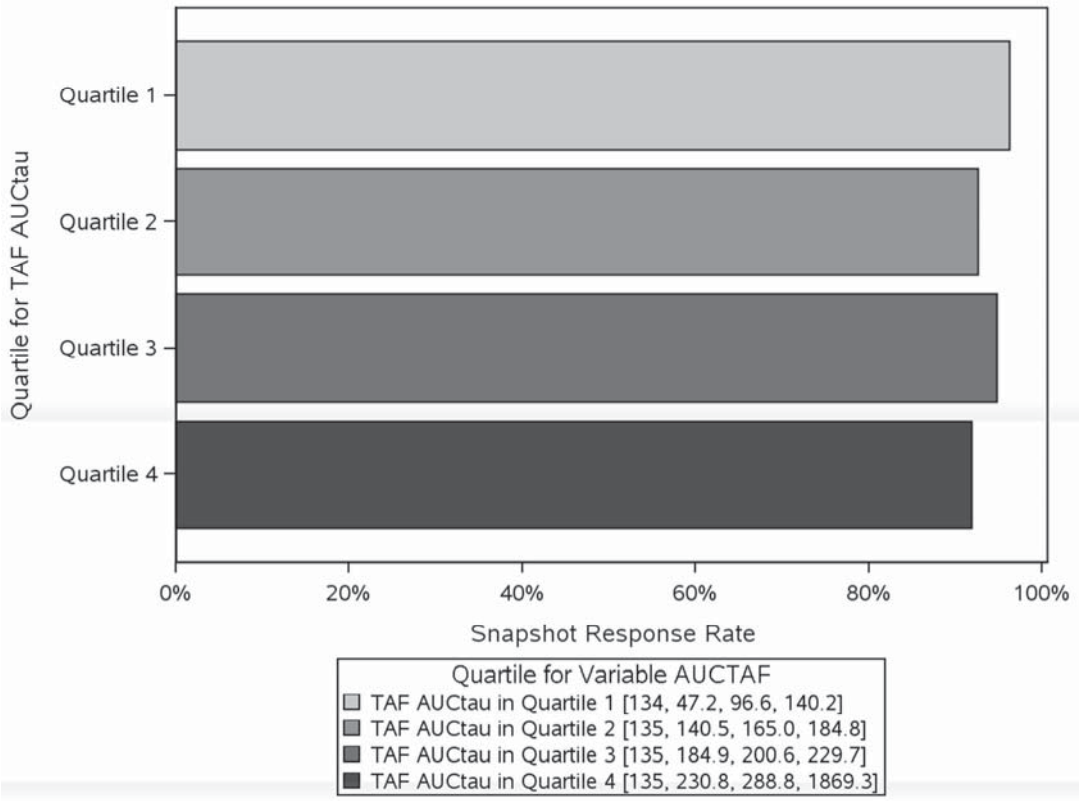
The results of the PK/PD analysis, using quartiles of TAF exposure, are presented in Table 32 and Figure 25. Virologic success was uniformly high across the categories of TAF AUC_{tau}, with no trends in exposure-response relationship across the wide range of TAF exposures observed. These results are also in accordance with the combined findings from the TAF population PK analyses that identified no statistically significant or clinically relevant covariates on TAF exposure (Section 3.2.1.2.1) and the comparable and high rates of efficacy observed across demographic characteristics.

The TAF exposure observed with the D/C/F/TAF 800/150/200/10 mg FDC in HIV-1 infected subjects in the Phase 2b study GS-US-299-0102 (mean AUC_{last} 130.5 ng.h/mL) and the Phase 3 study TMC114FD2HTX3001 (mean AUC_{tau} 132 ng.h/mL) also falls within this range of TAF exposures for which no PK/PD relationship is observed (see also Section 3.5.1.4.4).

Table 32: Percentage of Virologic Success at Week 48 Across Quartiles of TAF Exposure (TAF PK/PD Analysis Set) (Pooled Studies GS-US-292-0104 and GS-US-292-0111)

Quartile	N	TAF AUC_{tau}, ng.h/mL	Percentage of Virologic Success at Week 48 (HIV-1 RNA <50 copies/mL, Snapshot Analysis) (%)
Q1	134	47.2 to 140.2	96.3
Q2	135	140.5 to 184.8	92.6
Q3	135	184.9 to 229.7	94.8
Q4	135	230.8 to 1869.3	91.9

Figure 25: Percentage of Virologic Success at Week 48 (HIV-1 RNA <50 copies/mL, FDA Snapshot Algorithm) by TAF AUC_{tau}, ng.h/mL Quartile Subgroup (TAF PK/PD Analysis Set) (Pooled Studies GS-US-292-0104 and GS-US-292-0111)



The TAF PK/PD analysis set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.

Pooled Phase 3 data from the PK substudies in the pivotal E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 also allowed for a direct comparison of intracellular TFV-DP concentrations (pharmacologically active component) following administration with E/C/F/TAF versus E/C/F/TDF in HIV-1 infected subjects. The distinct metabolism of TAF, described in Section 3.1.3, provides stable and >4-fold higher intracellular levels of TFV-DP relative to TDF (Table 33 and Figure 26).

In a pooled analysis that included PK data from the Phase 2 study GS-US-292-0102 in addition to those from the 2 pivotal Phase 3 studies (GS-US-292-0104 and GS-US-292-0111), all of which evaluated E/C/F/TAF versus E/C/F/TDF in HIV-1 infected subjects, results were consistent with those in Table 33 (intracellular TFV-DP AUC_{tau} LS mean ratio [TAF vsTDF] of 437.25%; 90% CI: 285.57%, 669.49%).

This difference between TAF and TDF is even more pronounced (intracellular TFV-DP 6.5-fold higher) with D/C/F/TAF versus DRV+COBI+F/TDF (GS-US-299-0102, see Section 3.5.1.4.4). Also, the TFV-DP exposure in PBMCs observed with D/C/F/TAF 800/150/200/10 mg in HIV-1

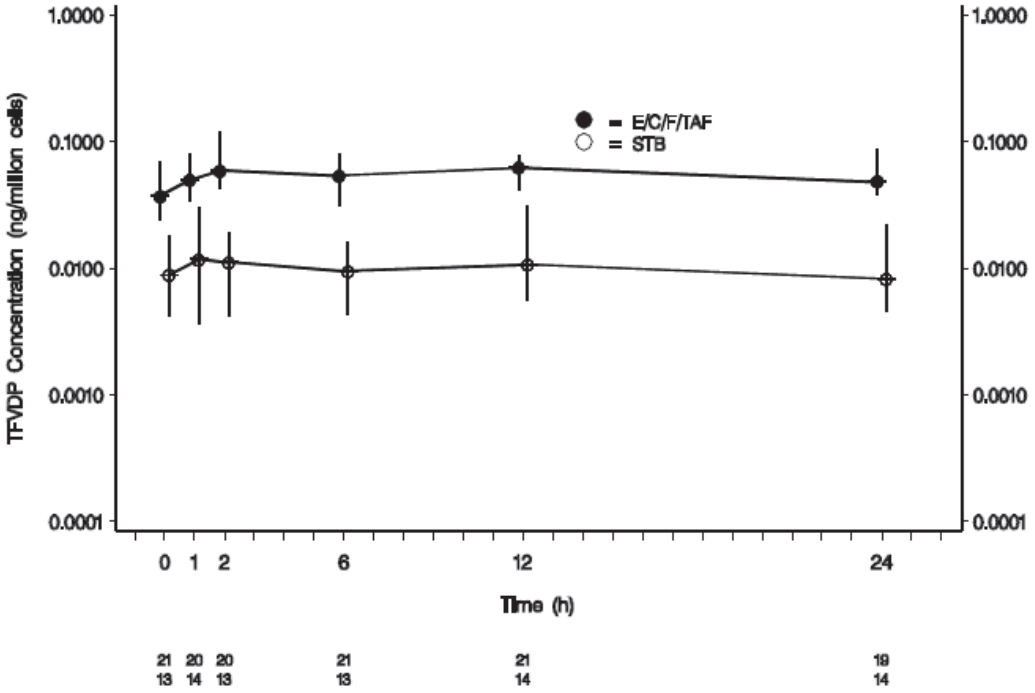
infected subjects in the Phase 2b study GS-US-299-0102 was higher compared to that for the pooled analysis of GS-US-292-0104 and GS-US-292-0111.

Table 33: Statistical Comparisons of Intracellular TFV DP PK Parameter Estimate Between Test (E/C/F/TAF) and Reference (E/C/F/TDF) Treatments, PK Substudy Analysis Set (Pooled Studies GS-US-292-0104 and GS-US-292-0111)

Parameter	LS Mean by Treatment		LS Mean Ratio (CI)
	E/C/F/TAF (N=21)	E/C/F/TDF (N=14)	
AUC_{tau}, µM.h/L	12.56	3.06	410.59 (233.64, 721.55)

AUC_{tau}: area under the plasma concentration-time curve over dosing interval; LS: least square

Figure 26: Median (Q1, Q3) Intracellular PBMC TFV-DP Concentrations: Intracellular TFV-DP profile After Administration of E/C/F/TAF or E/C/F/TDF (PK Substudy Analysis Set) (Pooled [2]Studies GS-US-292-0104 and GS-US-292-0111)

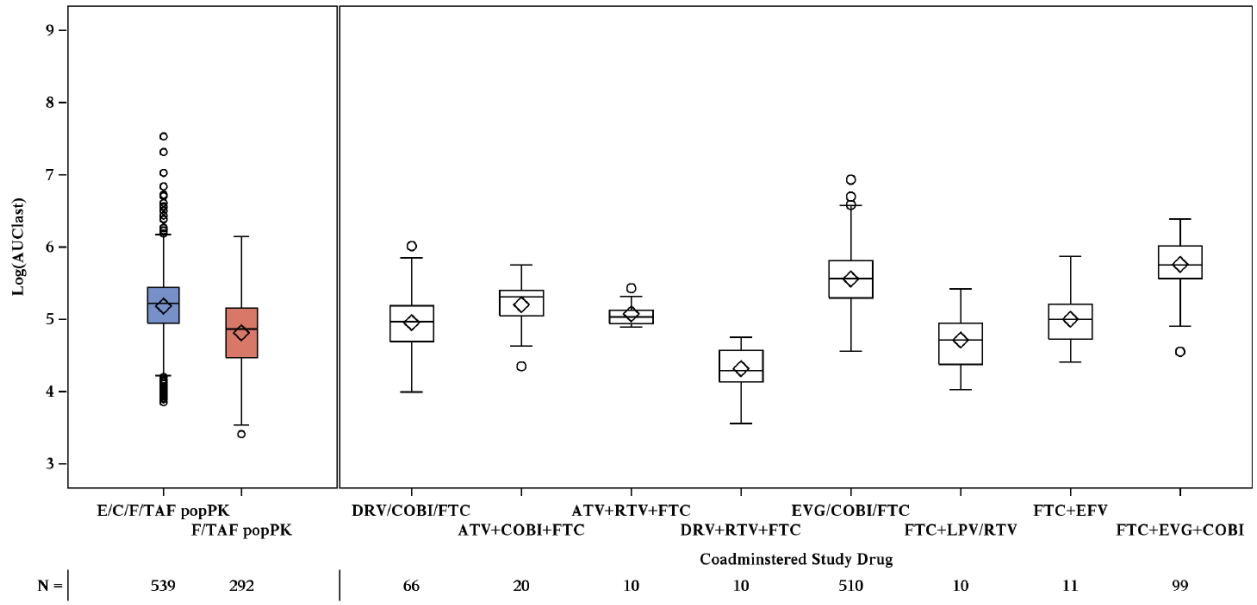


3.5.1.4.3. Study GS-US-311-1089: F/TAF With Different Third Agents

An additional evaluation of the PK/PD relationship of TAF was based on data from the Phase 3 study GS-US-311-1089 in virologically suppressed subjects switching from a regimen with F/TDF to F/TAF, in which F/TAF was administered in combination with a variety of third agents.

Table 20 (Section 2.2.3.4) and Figure 27 show that the TAF exposures obtained across the different subgroups in this study are consistent with the range of TAF exposures observed with E/C/F/TAF, and also the TAF exposures with the D/C/F/TAF FDC are within this range.

Figure 27: Comparison of TAF Exposures When Administered with Third Agents of Interest



Study drugs presented on the right panel were coadministered with TAF 10 mg except for FTC+EFV, which was coadministered with TAF 40 mg and dose normalized to TAF 25 mg (unboosted) based on dose proportionality results from Study GS-US-120-0104. Studies presented: GS-US-120-0118, GS-US-292-0102, GS-US-292-0103, GS-US-292-0108, GS-US-292-0110, GS-US-292-1316, GS-US-299-0101, GS-US-299-0102, and dose normalized to TAF 25 mg (unboosted) based on dose proportionality results from Study GS-US-120-0104. Boxplot whiskers include data within 1.5 times the interquartile range above and below the box. Circle=outlier; line inside box=median.

The results of the PK/PD analysis for GS-US-311-1089, using quartiles of PK exposure, are presented in Table 34. In line with observations in the E/C/F/TAF studies (Section 3.5.1.4.2), virologic success was uniformly high across the categories of TAF AUC_{last}, with no trends in exposure-response relationship across the range of TAF exposures observed. Across a wide range of TAF exposures (range: 30 to 467 ng.h/mL), which correspond to 78% to 98% of E_{max} of the TAF exposure-response model, the rates of virologic success were 93.2 to 97.3%. There were no apparent trends with virologic failure and TAF exposure (only 1 subject had virologic failure at Week 48, and the TAF exposure was in Quartile 4; this subject developed M184V with reduced susceptibility to FTC at virologic failure [Week 36]). The TAF exposure observed with D/C/F/TAF 800/150/200/10 mg in HIV-1 infected subjects in the Phase 2b study GS-US-299-0102 and the Phase 3 study TMC114FD2HTX3001 also is within this range of TAF exposures for which no PK/PD relationship is observed.

Virologic success and virologic failure rates in study GS-US-311-1089 by third agents is presented in Table 21.

Table 34: Percentage of Virologic Success and Virologic Failure at Week 48 Across Quartiles of TAF Exposure (TAF PK/PD Analysis Set) (Study GS-US-311-1089)

Quartile	TAF AUC_{tau} Quartile Range, ng.h/mL	N	Percentage of Virologic Success at Week 48 (HIV-1 RNA <50 copies/mL, Snapshot Analysis)	Percentage of Virologic Failure at Week 48 (HIV-1 RNA ≥50 copies/mL, Snapshot Analysis)
1	30.3 to 87.6	73	93.2	0
2	87.6 to 129.5	73	95.9	0
3	129.8 to 173.1	73	97.3	0
4	173.8 to 466.7	73	95.9	1.4[a]

[a] N=1 virologic failure at Week 48.
AUC=area under the plasma concentration-time curve; HIV=human immunodeficiency virus

3.5.1.4.4. D/C/F/TAF Studies GS-US-299-0102 and TMC114FD2HTX3001

An additional evaluation of the PK/PD relationship of TAF was based on data from the Phase 2 study GS-US-299-0102 and the Phase 3 study TMC114FD2HTX3001 in ART-naïve HIV-1 infected subjects treated with D/C/F/TAF or a combination of DRV+COBI+F/TDF. Details on the design and efficacy and safety results for these studies are presented in the Summary of Clinical Efficacy (Mod2.7.3/Sec3.1) and in the Summary of Clinical Safety (Mod2.7.4/Sec3.1.1).

TAF AUCs from Studies GS-US-299-0102 and TMC114FD2HTX3001 were estimated from a TAF population PK model; TAF exposures were estimable for 52 subjects in Study GS-US-299-0102 (see also Section 2.2.2.1) and 355 subjects in TMC114FD2HTX3001 (see also Section 2.2.2.2). As summarized in Table 35 and Figure 28, virologic success rates were similar across the quartiles of TAF AUCs in both D/C/F/TAF studies, with no trends in exposure-response relationship. Similarly, no apparent trend was observed with virologic failure.

The D/C/F/TAF Phase 2b study GS-US-299-0102 also allowed for a direct comparison of intracellular TFV-DP concentrations (pharmacologically active component) following administration with D/C/F/TAF versus DRV+COBI+F/TDF in HIV-infected subjects. The distinct metabolism of TAF, described in Section 3.1.3, provides stable and 6.5-fold higher intracellular levels of TFV-DP relative to TDF (Table 36). The TFV-DP intracellular concentrations were also higher than in the E/C/F/TAF Phase 3 studies.

Table 35: Percentage of Virologic Success and Virologic Failure at Week 48 Across Quartiles of TAF Exposure (TAF PK/PD Analysis Set) (Study GS-US-299-0102)

Quartile	N	TAF AUC_{tau}, ng.h/mL[a]	Percentage of Virologic Success at Week 48 (HIV-1 RNA <50 copies/mL, Snapshot Analysis)	Percentage of Virologic Failure at Week 48[b] (HIV-1 RNA≥50 Copies/mL, Snapshot Analysis)
Q1	13	38.3 to 65.7	76.9	15.4
Q2	13	67.0 to 83.3	84.6	7.7
Q3	13	89.9 to 120.6	76.9	15.4
Q4	13	122.6 to 295.6	76.9	7.7

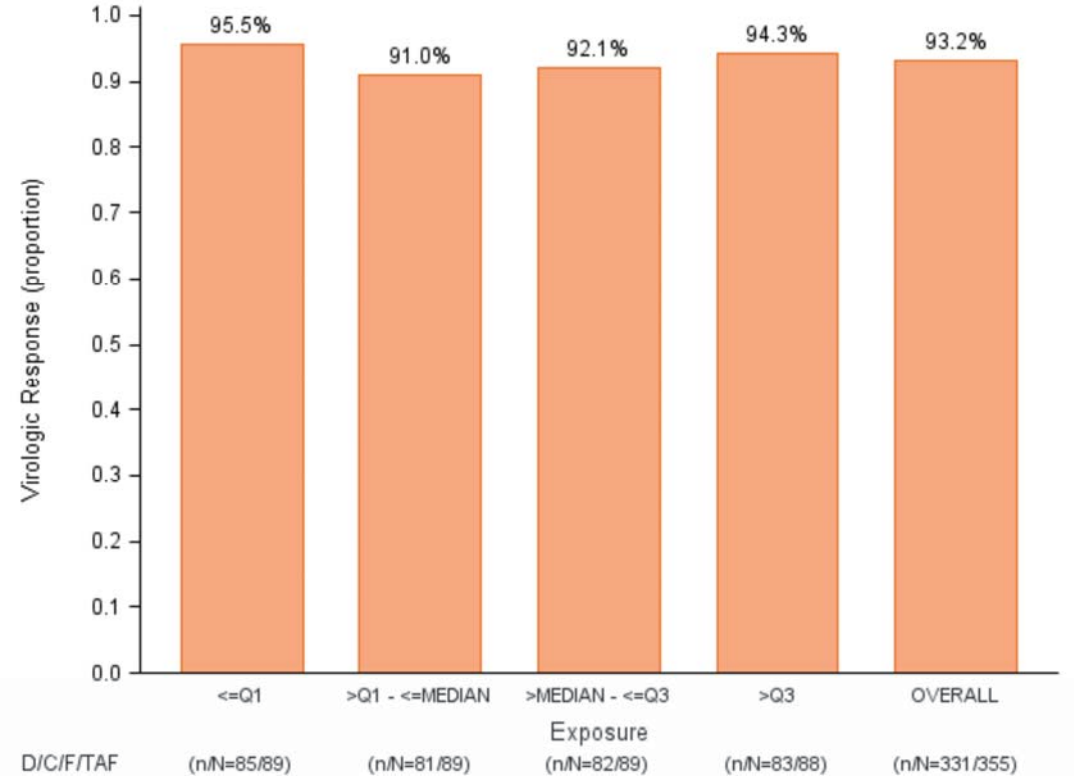
[a] TAF AUC_{tau} estimated by population PK model, evaluable for n=52 subjects
[b] PK data were available for 6 of the 7 virologic failure subjects. Percentages represent distribution of the 6 subjects
Source: Mod5.3.5.1/GS-US-299-0102/Sec16.2

Table 36: Statistical Comparisons of AUC_{tau} Between Test and Reference Treatments All Substudy PK Analysis Set (Study 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)

AUC: area under the plasma concentration-time curve; LS: least squares
Source: Mod5.3.5.1/GS-US-299-0102_CSR/Sec15.1/Tab56.

Figure 28: Proportion of Virologic Response (<50 Copies/mL) According to FDA Snapshot Approach through Week 48 by TAF PK quartiles (Study TMC114FD2HTX3001)



TAF AUC_{tau} (h*ng/mL): Q1=103.02; median=123.85; Q3=148.52
Source: Mod5.3.5.1/TMC114FD2HTX3001_CSR/Fig20

3.5.2. Pharmacokinetic/Pharmacodynamic Relationship - Safety

3.5.2.1. D/C/F/TAF

The safety of the D/C/F/TAF FDC was investigated in the 2 pivotal Phase 3 studies (TMC114FD2HTX3001 and TMC114IFD3013, Section 2.2.2.2 and 2.2.2.3) and Phase 2 study GS-US-299-0102 (Section 2.2.2.1). Safety data from these studies are detailed in Mod 2.7.4/Sec3.1.1. PK/PD analyses for safety parameters were performed on data from the Phase 3 studies (DRV and TAF for TMC114FD2HTX3001, DRV only for TMC114IFD3013).

In studies TMC114FD2HTX3001 and TMC114IFD3013, no apparent clinically relevant PK/PD relationships were observed between DRV AUC_{24h} and the occurrence of adverse events of interest (bone, convulsions, coronary artery, hyperglycemia, lipid-related, liver, ocular, pancreas, rash or severe skin AE, renal), or between DRV AUC_{24h} and treatment-emergent laboratory abnormalities (ALP, ALT, AST, total amylase, total bilirubin, glucose, total cholesterol, LDL, triglycerides, creatinine, urine albumin to creatinine ratio, urine protein to creatinine ratio).

In study TMC114FD2HTX3001, no apparent clinically relevant PK/PD relationships were observed between TAF AUC_{tau} and the occurrence of adverse events of interest (bone, convulsions, coronary artery, hyperglycemia, lipid-related, liver, ocular, pancreas, rash or severe skin AE, renal), or between TAF AUC_{tau} and treatment-emergent laboratory abnormalities (ALP, ALT, AST, total amylase, total bilirubin, glucose, total cholesterol, LDL, triglycerides, creatinine, urine albumin to creatinine ratio, urine protein to creatinine ratio).

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 the Phase 3 or 2 studies in HIV-1 infected subjects, there were no clinically relevant ECG findings that would suggest a potential effect of D/C/F/TAF on the QT interval (Mod2.7.4/Sec3.1.1).

The PK/PD relationships for safety for the different components of the D/C/F/TAF FDC have also been evaluated throughout their respective development programs. A summary of the relevant data is provided in Section 3.5.2.2 for DRV/COBI, Section 3.5.2.3 for FTC and Sections 3.5.2.4 and 3.5.2.5 for TAF and TFV, and complemented the overall evaluation of the safety and PK/PD profile for the D/C/F/TAF FDC.

3.5.2.2. DRV/COBI

In study GS-US-216-0130 (NDA205395), no apparent PK/PD relationships were observed between DRV AUC_{24h} or C_{0h} and the occurrence of rash, diarrhea, nausea, or vomiting, or between DRV AUC_{24h} and the worst toxicity grade in ALP, ALT, AST, amylase, lipase, glucose, total cholesterol, LDL, HDL, or triglycerides. This lack of an exposure-response relationship for safety after administration of DRV/COBI is consistent with the lack of exposure-response relationships observed previously after administration of DRV/rtv 800/100 mg once daily in ART-naïve and ART-experienced HIV-1 infected subjects (NDA021976). In study TMC114-

C211 in ART-naïve subjects, no apparent relationship was observed between the PK parameters for DRV and the occurrence of rash-, cardiac-, GI-, liver-, lipid-, and glucose-related AEs, or AEs in the nervous system disorders or psychiatric disorders system organ classes (SOCs). Similarly, in study TMC114-C229 in ART-experienced subjects, no apparent relationships were observed between the PK parameters for DRV and the occurrence of AEs leading to permanent discontinuation of study drug, or rash-, cardiac-, GI-, liver-, lipid-, and glucose-related AEs, or AEs of the nervous system disorders or psychiatric disorders SOCs, or laboratory lipid abnormalities.

3.5.2.2.1. QT/QTc Interval

A thorough QT/QTc study has been conducted in healthy subjects to evaluate the effect of DRV/rtv at doses of 1,600/100 mg once daily and 800/100 mg twice daily on ECG parameters (TMC114-C153, Section 2.2.1.1). Based on the overall population, the results of this study can be considered as a negative thorough QT/QTc study according to the ICH E14 Guidelines. The DRV treatments at the doses evaluated in this study were associated with small prolongations in QTc interval when compared to QTc changes observed in the placebo group. The 2-sided 90% CIs of the time-matched mean changes versus placebo showed that the upper bounds of both DRV/rtv groups for the overall population did not exceed 10 ms at any time point following single or multiple doses of DRV/rtv. A linear mixed model was developed to estimate the relationship between QTcF and DRV plasma concentration. The slope of this relationship was estimated to be 0.000659 ms.mL/ng, with a 90% 2-sided CIs of 0.000184 to 0.001135 ms.mL/ng. This observation suggests that the relationship between concentration and QTcF is “shallow” in that for every 1,000 ng/mL increase in DRV concentration, a very small additional shift in QTcF of 0.66 ms is predicted.

In a thorough QT/QTc study with COBI administered as a single agent, single doses of COBI 250 and 400 mg did not prolong the QTc interval (GS-US-216-0107, Section 2.2.1.1). The upper bounds of the 2-sided 90% CIs for baseline-adjusted mean differences in QTcF did not exceed 10 ms at any time point after dosing. Therefore, this study also met the ICH E14 definition of a negative thorough QT/QTc study.

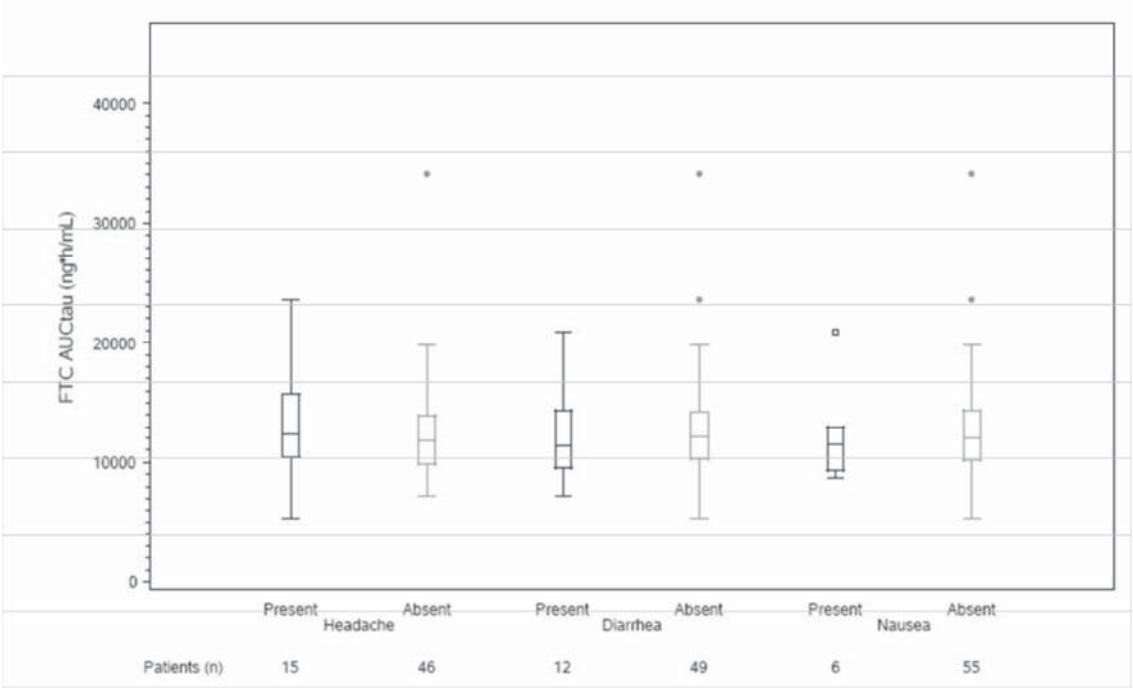
3.5.2.3. FTC

The PK and PK/safety relationships for FTC have not been evaluated in the D/C/F/TAF Phase 3 studies. The absence of clinically relevant PK/PD relationships for FTC safety is however derived from a wealth of evidence throughout the development of FTC as part of different ARV regimens. The PK/PD analyses, performed by GSI, indicated that there was no relevant relationship between the PK parameters of FTC and safety parameters of interest (eg, headache, nausea, diarrhea, changes in renal laboratory parameters such as creatinine), as further detailed below. Moreover, FTC has been used very widely for a substantial amount of time, in combination with boosted DRV-based HIV treatment regimens.

Pharmacokinetic/PD analyses of the FTC exposure-safety relationship were performed by GSI in ART-naïve HIV-1 infected subjects in E/C/F/TDF (Stribild) Phase 2/3 studies using FTC

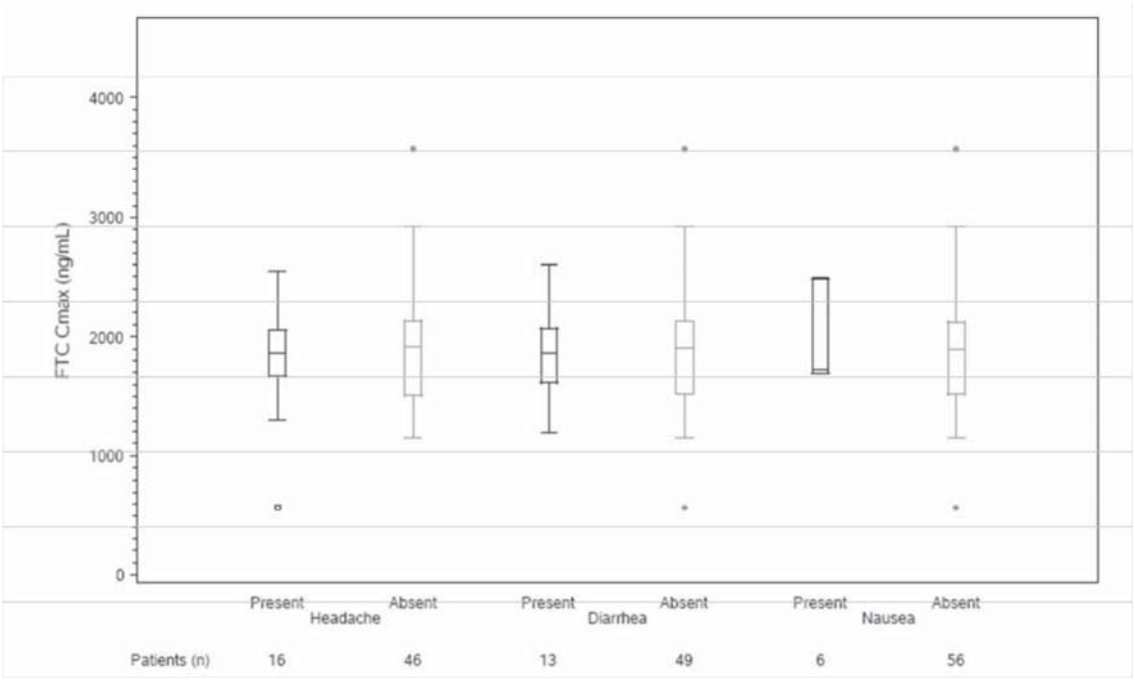
exposures derived from intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea. The relationships between FTC exposure and incidence of AEs (present/absent) are shown in Figure 29 for AUC_{tau} and in Figure 30 for C_{max}. FTC exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no FTC exposure-AE trends were observed.

Figure 29: Box Plot of FTC AUC_{tau} (ng.h/mL) Versus Incidence of Selected Adverse Events



Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.

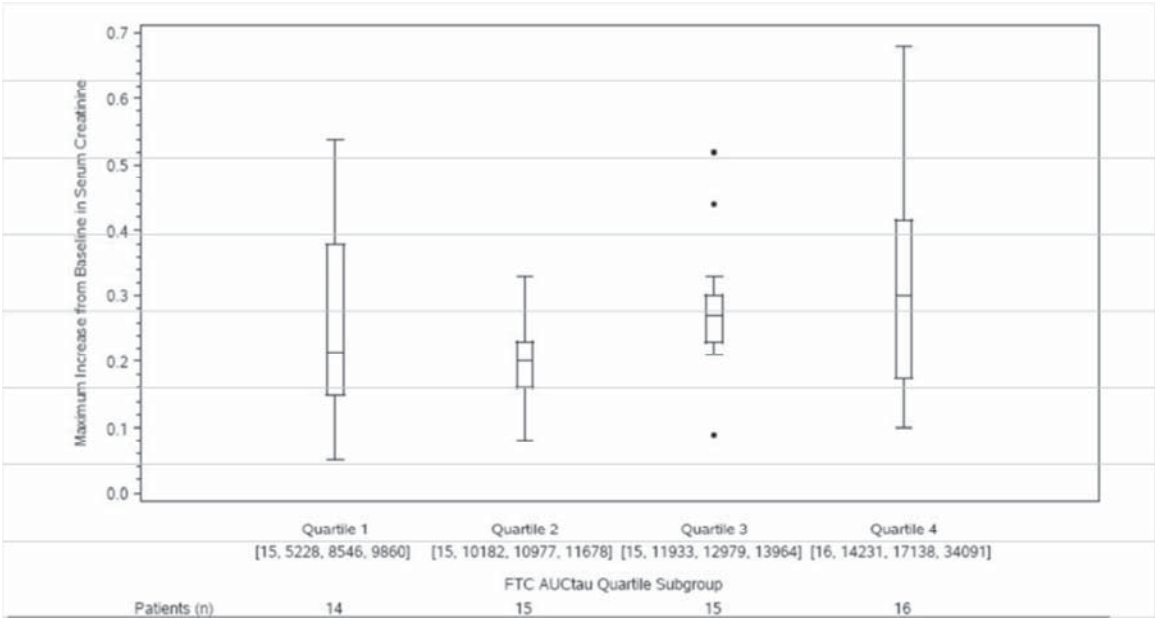
Figure 30: Box Plot of C_{max} (ng/mL) Versus Incidence of Selected Adverse Events



Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.

The relationship between FTC exposure quartiles and changes in renal laboratory parameters was also evaluated; FTC exposure versus serum creatinine change is shown in Figure 31. Across all FTC AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable, and no trends in exposure-changes in laboratory parameters were noted. Importantly, the range of FTC exposures explored in these PK/PD analyses covered the individual FTC exposures observed in the renally-impaired, HIV-1 infected subjects with $eGFR_{CG}$ <50 mL/min receiving E/C/F/TAF in Phase 3 Study GS-US-292-0112. Moreover, as demonstrated in Study GS-US-292-0112, subjects with $eGFR_{CG}$ <50 mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG}$ ≥50 mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

Figure 31: Box Plot of Maximum Increase From Baseline in Serum Creatinine (mg/dL) by FTC AUC_{tau} (ng.h/mL) Quartile Subgroup



Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5×IQR, and circles denote outliers >1.5 × IQR. Subject [redacted] with a maximum increase from baseline in serum creatinine of 2.95 mg/dL in the Quartile 4 subgroup was excluded from the figure for better visualization purposes. Numbers presented in the square brackets were the sample size, minimum, median, and maximum of FTC AUC_{tau} for subjects included in that subgroup. Sample size reported at the bottom of the figure was the number of subjects with nonmissing values for both the selected PK parameter and the selected safety endpoint.

3.5.2.4. TAF

The PK/PD analyses for TAF in non-D/C/F/TAF studies, performed by GSI, used the exposure parameters (ie, AUC_{tau} and C_{max}) for TAF (estimated from population PK modeling for TAF). The PK/PD analyses of the TAF exposure-safety relationship were performed in ART-naive HIV-1 infected subjects from E/C/F/TAF studies GS-US-292-0104 and GS-US-292-0111.

The safety endpoints for the TAF PK/PD analyses based on population PK estimates were:

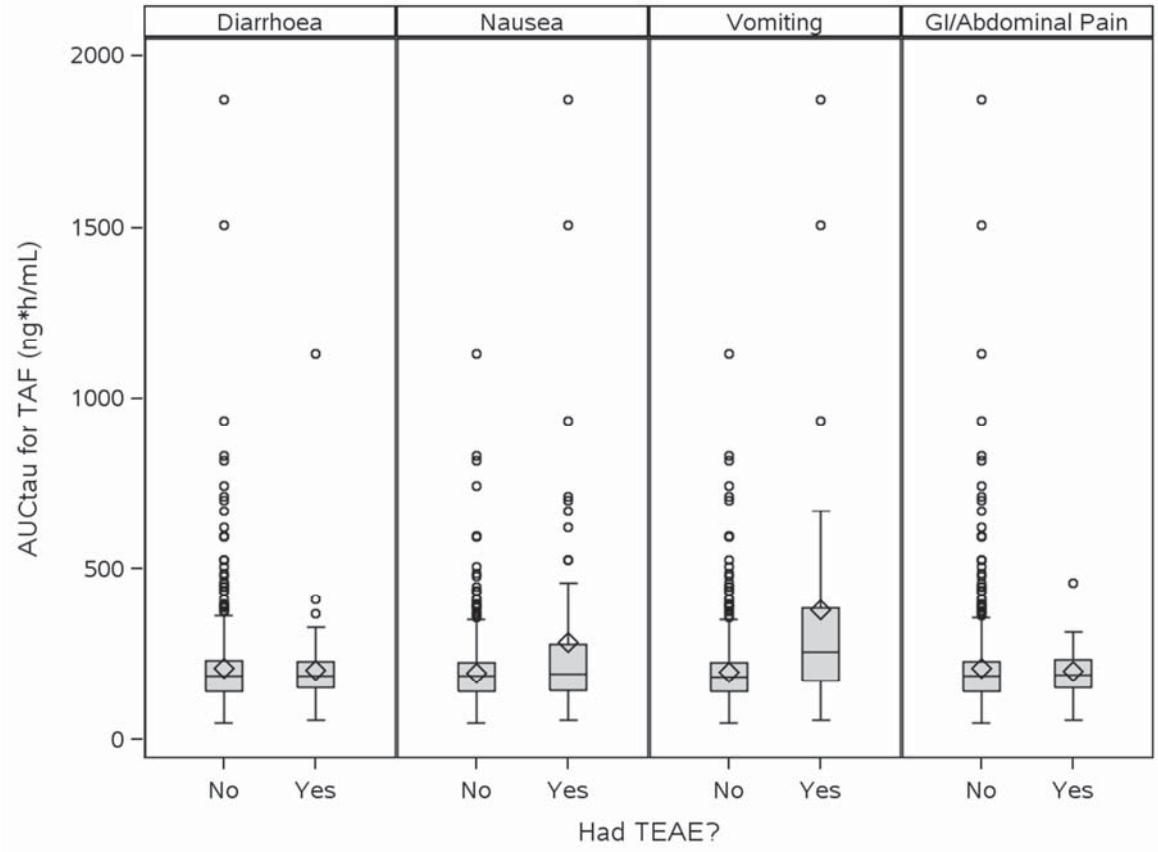
- Presence or absence of diarrhea, nausea (very common ≥10%), vomiting, and GI and abdominal pains (common ≥1% and <10%) [excluding oral and throat], which included: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, and GI pain).
- Percent change from baseline at Week 48 in hip and spine BMD.
- Maximum increase from baseline through Week 48 in serum creatinine.
- Change from baseline at Week 48 for select fasted lipids (total cholesterol, LDL, and HDL).

The relationships between TAF exposure and incidence of AEs (present=yes; absent=no) are shown in Figure 32 for AUC_{tau} and in Figure 33 for C_{max}.

For diarrhea and GI/abdominal pain, TAF exposure was comparable regardless of the presence or absence of either of those symptoms and no exposure-AE trends were observed with these AEs.

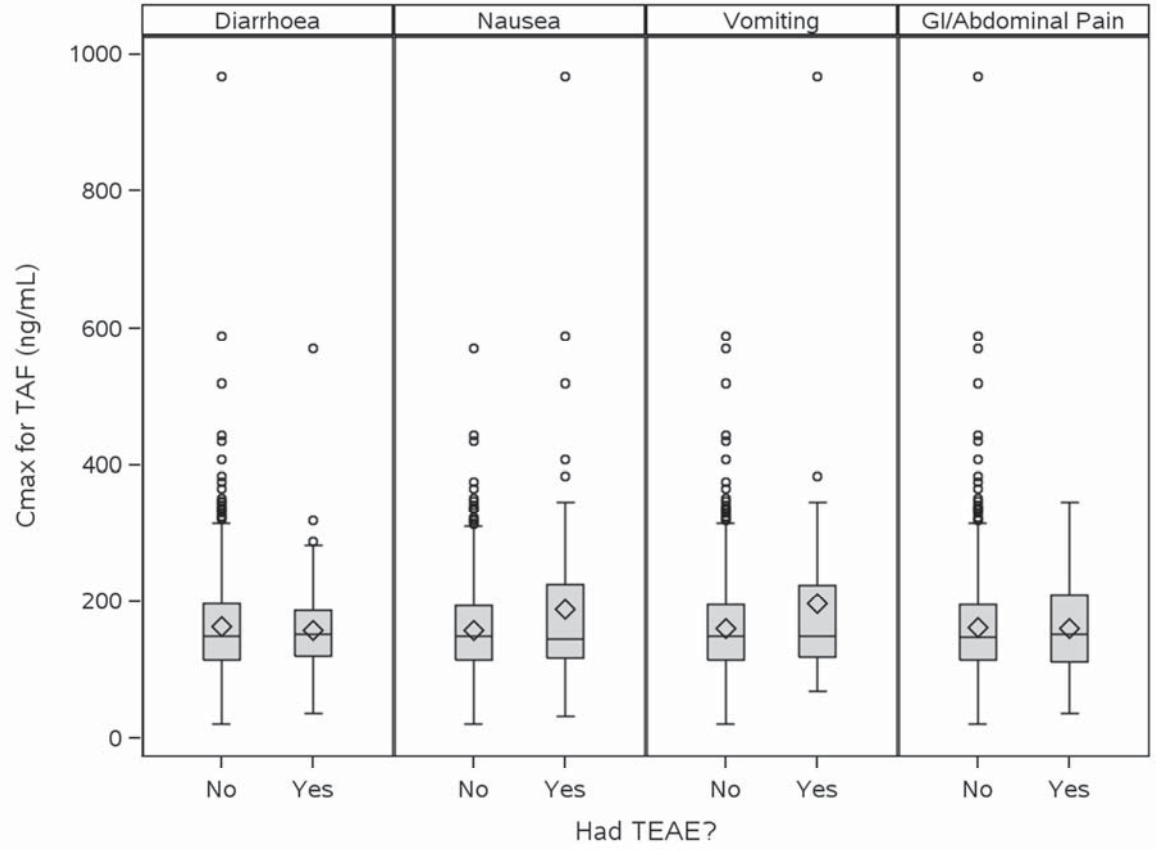
TAF exposure was generally comparable in the presence or absence of nausea and vomiting, but logistic regression analysis showed a trend between the highest TAF exposure and the presence of these AEs (nausea correlated with the highest 4% of TAF exposure; vomiting correlated with the highest 19% of TAF exposure). No trend was observed between exposure and severity. The overall incidence of nausea and vomiting was similar between treatment groups in studies GS-US-292-0104 and GS-US-292-0111.

Figure 32: Box Plot of TAF AUC_{tau} ng.h/mL by Selected Adverse Events TAF PK/PD Analysis Set (Studies GS-US-292-0104 and GS-US-292-0111)



Diarrhea: No (n=454), Yes (n=85); Nausea: No (n=463), Yes (n=76); Vomiting: No (n=508), Yes (n=31); GI/Abdominal Pains: No (n=512), Yes (n=27)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR. The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. AEs were coded using MedDRA Version 17.0. Diarrhea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat). AE=adverse event; AUC_{tau}=area under the plasma concentration-time curve over dosing interval; C_{max}=maximum plasma concentration; TEAE=treatment-emergent adverse event.

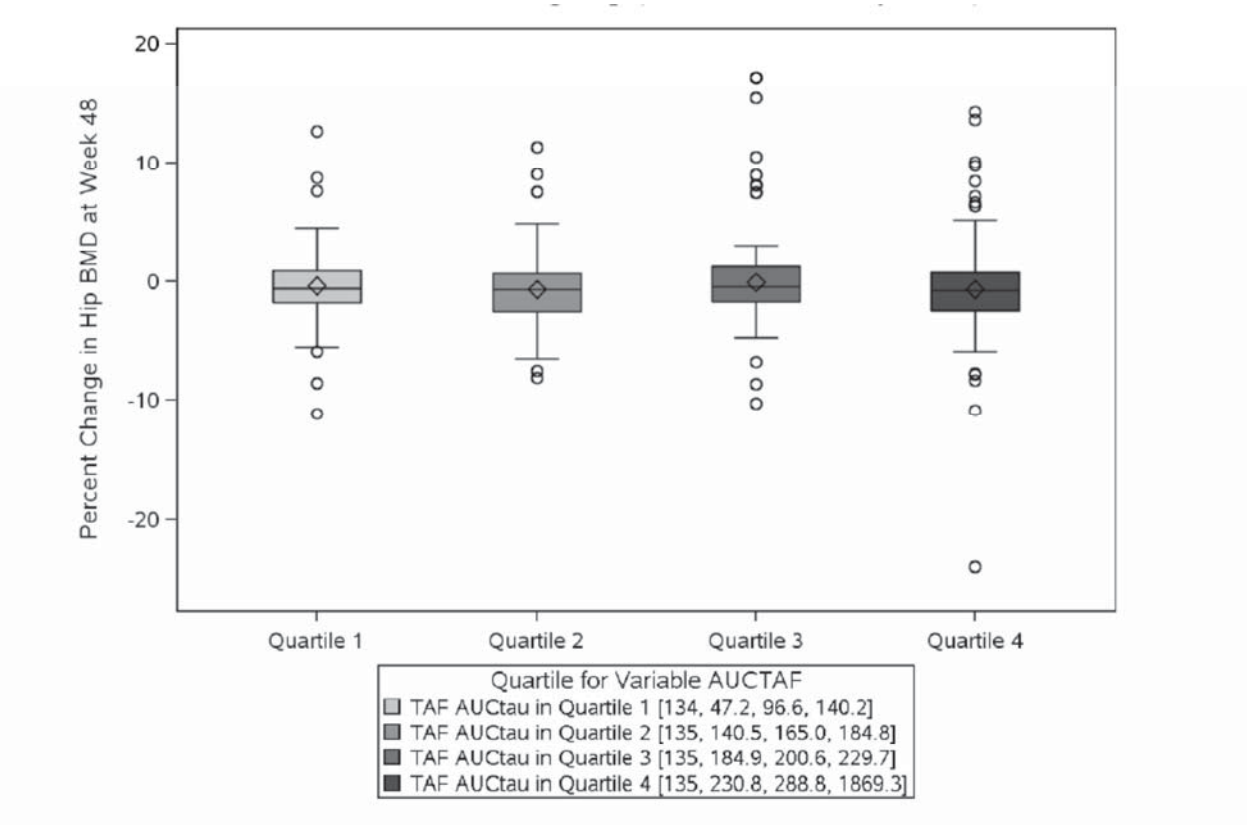
Figure 33: Box Plot of TAF C_{max} ng/mL by Selected Adverse Events TAF PK/PD Analysis Set (Studies GS-US-292-0104 and GS-US-292-0111)



Diarrhea: No (n=454), Yes (n=85); Nausea: No (n=463), Yes (n=76); Vomiting: No (n=508), Yes (n=31); GI/Abdominal Pains: No (n=512), Yes (n=27)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. AEs were coded using MedDRA Version 17.0. Diarrhea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).
AE=adverse event; AUC_{tau}=area under the plasma concentration-time curve over dosing interval; C_{max}=maximum plasma concentration; TEAE=treatment-emergent adverse event.

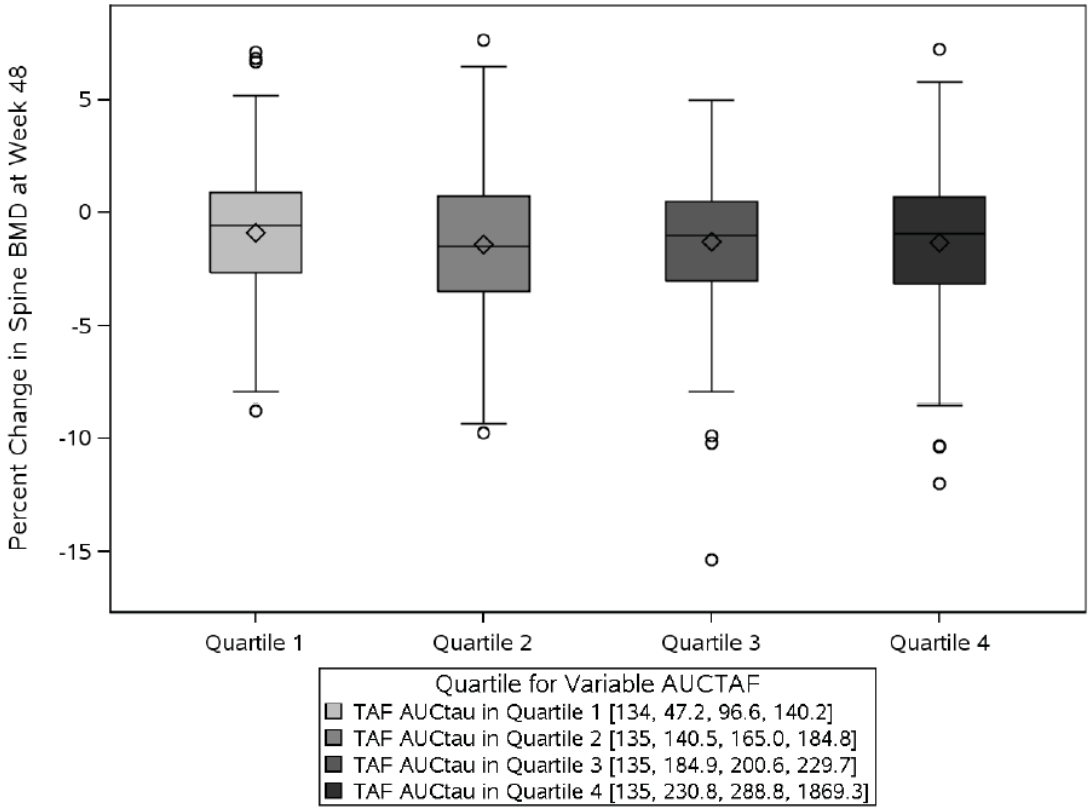
The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were also key safety endpoints in studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TAF exposure quartiles and changes in BMD at the hip and spine were evaluated and results of the analysis are shown in Figure 34 for hip BMD and in Figure 35 for spine BMD. The percentage change from baseline at Week 48 was comparable across TAF AUC_{tau} quartiles for both hip and spine BMD; no exposure changes in BMD trends were noted.

Figure 34: Box Plot of Percentage Change From Baseline at Week 48 in Hip BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUCtau for subjects included in the corresponding quartile.
AUC_{tau}=area under the plasma concentration-time curve over dosing interval; BMD=bone mineral density; C_{max}=maximum plasma concentration

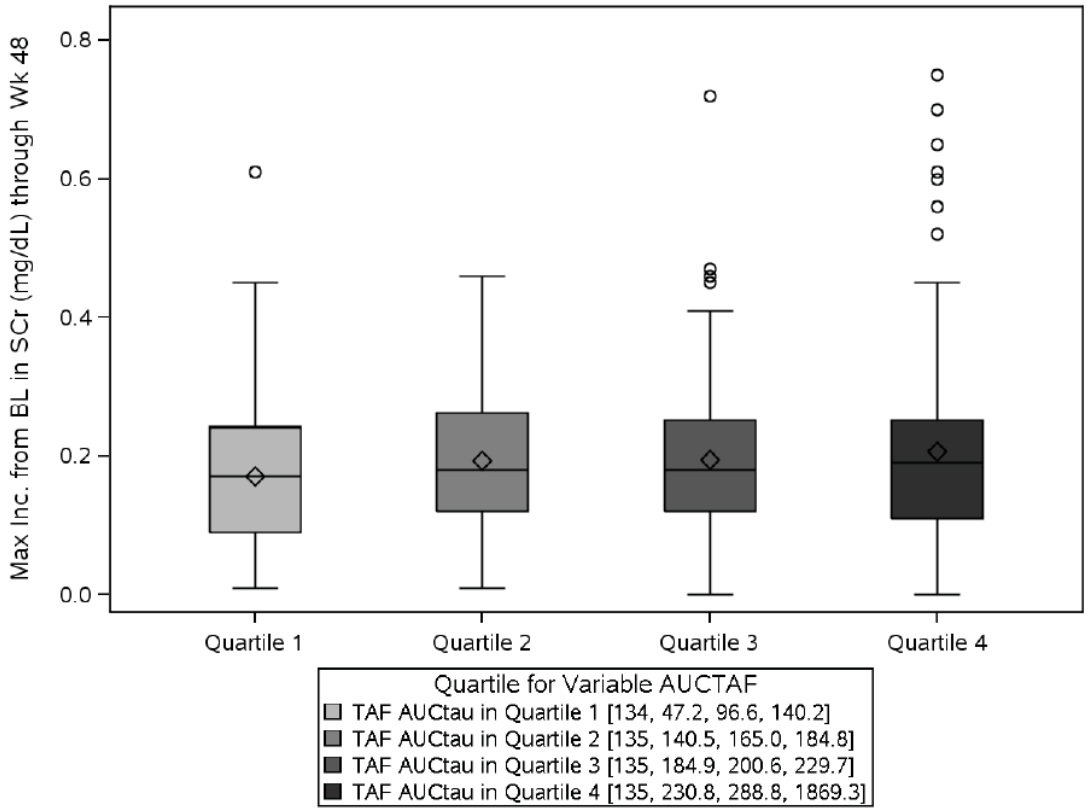
Figure 35: Box Plot of Percentage Change From Baseline at Week 48 in Spine BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.
AUC_{tau}=area under the plasma concentration-time curve over dosing interval; BMD=bone mineral density; C_{max}=maximum plasma concentration

Change from baseline in serum creatinine at Week 48 was a key safety endpoint of studies GS-US-292-0104 and GS-US-292-0111. The relationship between TAF exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated and results of the analysis are shown in Figure 36. Maximum increase from baseline in serum creatinine was comparable across TAF AUC_{tau} quartiles; no exposure changes in serum creatinine trends were noted.

Figure 36: Box Plot of Maximum Increase From Baseline in Serum Creatinine (mg/dL) by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR. The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.
AUC=area under the plasma concentration-time curve; C_{max}=maximum plasma concentration

3.5.2.4.1. QT/QTc Interval

The relationships between plasma TAF concentrations and changes in QTcF were evaluated in a thorough QT/QTc study with the TAF single agent (GS-US-120-0107, Section 2.2.1.1). A linear mixed-effect model was used to quantify the relationship between plasma concentrations of TAF and ΔΔQTcF with gender as a fixed effect and subject as a random effect. The statistical analyses of the relationship between TAF plasma concentrations and ΔΔQTcF are summarized in Table 37, the relationship between TAF plasma concentrations and ΔΔQTcF is depicted graphically in Figure 37, and the relationship between TAF plasma concentrations and ΔΔQTcF at t_{max} is depicted graphically in Figure 38. The results suggest that there is no statistically significant or pharmacologically meaningful association between TAF plasma concentration and ΔΔQTcF interval. At the observed TAF C_{max} (174.3 ng/mL) following administration of TAF 25 mg, mean ΔΔQTcF is predicted to be –0.373 msec (the upper 95% 1-sided CI=0.686). At the observed TAF C_{max} (859.0 ng/mL) following administration of TAF 125 mg, mean ΔΔQTcF is

predicted to be 0.389 msec (the upper 95% 1-sided CI=1.930). Both upper limits of the 1-sided 95% CIs were far below the ICH E14 recommended threshold of 10 msec. Similar analyses were performed to evaluate the relationship between TAF plasma concentrations and ΔQTcF, and the relationship between TAF plasma concentrations and raw QTcF. The results suggest that there is a statistically significant, small, negative association between TAF plasma concentrations and ΔQTcF and raw QTcF interval. This very weak association was maintained upon adjustment for gender.

Table 37: Statistical Analysis of the Relationship Between TAF Plasma Concentrations and Time-matched, Baseline-adjusted, Placebo-corrected QTcF (Study GS-US-120-0107)

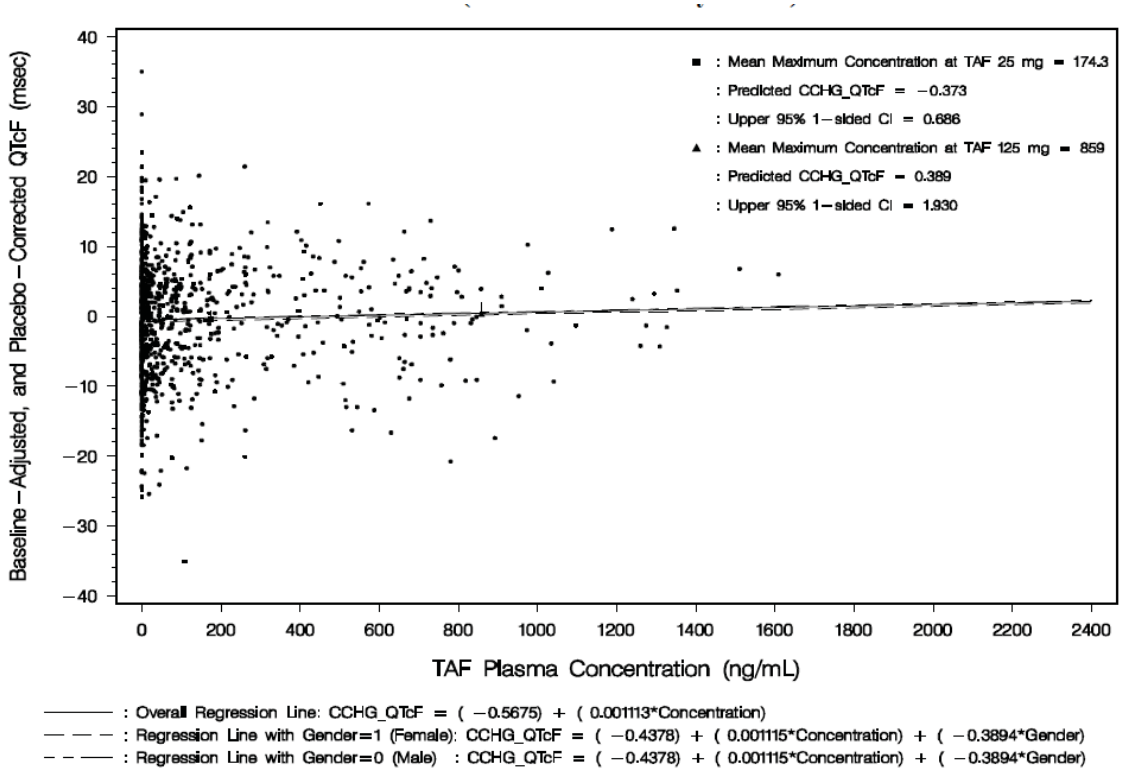
QTcF	Estimate	Standard Error	CI		P value
			Lower	Upper	
Time Matched Baseline Adjusted and Placebo Corrected QTcF					
Overall Regression Equation: ΔΔQTcF=a + (b × Concentration)					
Intercept (a)	-0.5675	0.6509	-1.8769	0.7420	0.39
Concentration (b)	0.001113	0.000921	-0.00069	0.002920	0.23
Regression Equation with Gender as a Fixed Effect: ΔΔQTcF=a + (b × Concentration) + (c × Gender[a])					
Intercept (a)	-0.4378	0.8006	-2.0494	1.1737	0.59
Concentration (b)	0.001115	0.000921	-0.00069	0.002922	0.23
Gender (c)	-0.3894	1.3746	-3.1563	2.3775	0.78

[a] For the regression equation with gender as a fixed effect, "Gender" was defined as 0 for male subjects and 1 for female subjects.

Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect. PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.

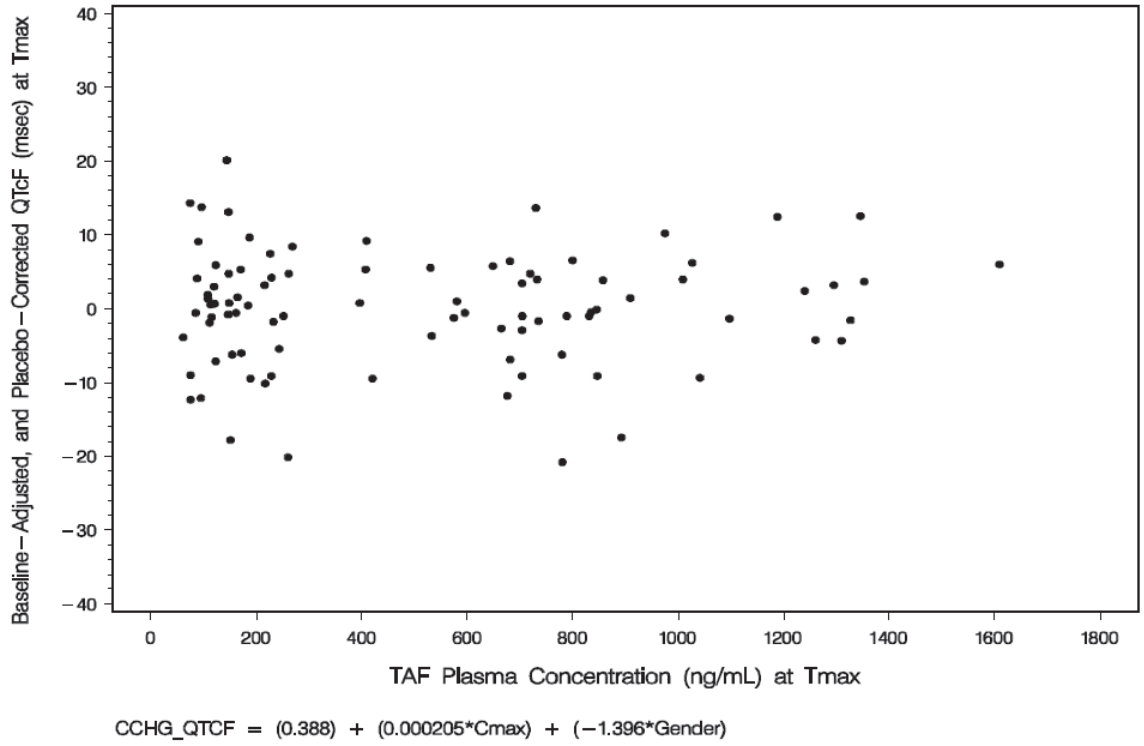
QTcF=QT interval corrected by Fridericia's formula

Figure 37: Scatter Plot of Time-matched, Baseline-adjusted, Placebo-corrected QTcF Versus TAF Plasma Concentration TAF PK/PD Analysis Set) (Study GS-US-120-0107)



Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect.; PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.
Upper 95% 1-sided CI was calculated based on overall PK/PD regression model.
QTcF=QT interval corrected by Fridericia's formula

Figure 38: Scatter Plot of Time-matched, Baseline-adjusted, Placebo-corrected QTcF at t_{max} Versus TAF Plasma Concentration TAF PK/PD Analysis Set) (Study GS-US-120-0107)



PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.
QTcF=QT interval corrected by Fridericia's formula; t_{max}=time to reach maximum plasma concentration

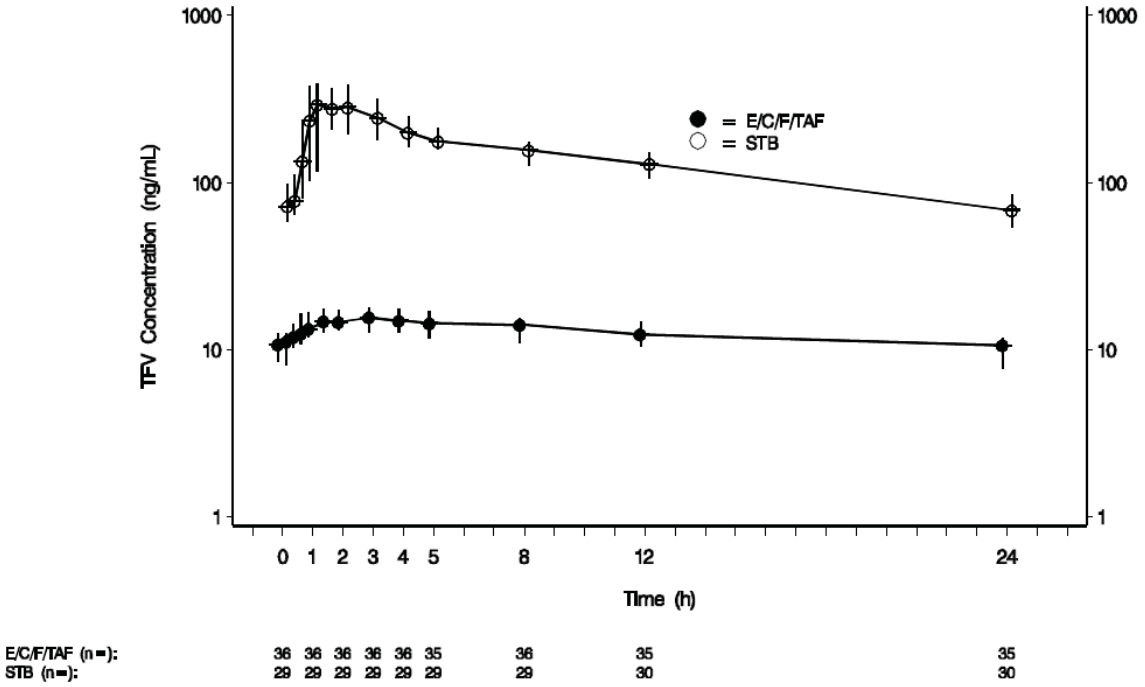
3.5.2.5. TFV

The PK and PK/safety relationships for FTC have not been evaluated in the D/C/F/TAF Phase 3 studies. The PK/PD analyses for TFV in non-D/C/F/TAF studies, performed by GSI, used the exposure parameters (ie, AUC_{tau} and C_{max}) for TFV (estimated from population PK modeling for TFV).

TAF has a distinct metabolism designed to maximize both antiviral potency and clinical safety. TAF is more stable in plasma than TDF and provides a large relative reduction in circulating levels of TFV of approximately 90% (Figure 39 and Table 38). Pooled Phase 3 data from the PK substudies in the E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 allowed for a direct comparison of plasma TFV concentrations following administration of E/C/F/TAF versus E/C/F/TDF in HIV-1 infected subjects.

In a pooled analysis that included PK data from the Phase 2 study GS-US-292-0102 in addition to those from the two Phase 3 studies (GS-US-292-0104 and GS-US-292-0111), all of which evaluated E/C/F/TAF versus E/C/F/TDF in HIV-1 infected subjects, results were consistent with those in Table 38 (plasma TFV AUC_{tau} LS mean ratio of 8.90% [90% CI: 8.20%, 9.65%]). This was also confirmed in the PK substudy of D/C/F/TAF Phase 2b study GS-US-299-0102 (plasma TFV AUC_{tau} LS mean ratio of 8.64% [90% CI: 6.99%, 10.68%]).

Figure 39: Median (Q1, Q3) Plasma TFV Concentrations; TFV PK Profile After E/C/F/TAF or E/C/F/TDF Administration (Semilogarithmic Scale, PK Substudy Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



STB=Stribild=E/C/F/TDF

Table 38: Statistical Comparisons of TFV PK Parameter Estimates Between Test (E/C/F/TAF) and Reference (E/C/F/TDF) Treatments (PK Substudy Analysis Set) (Studies GS-US-292-0104 and GS US 292 0111)

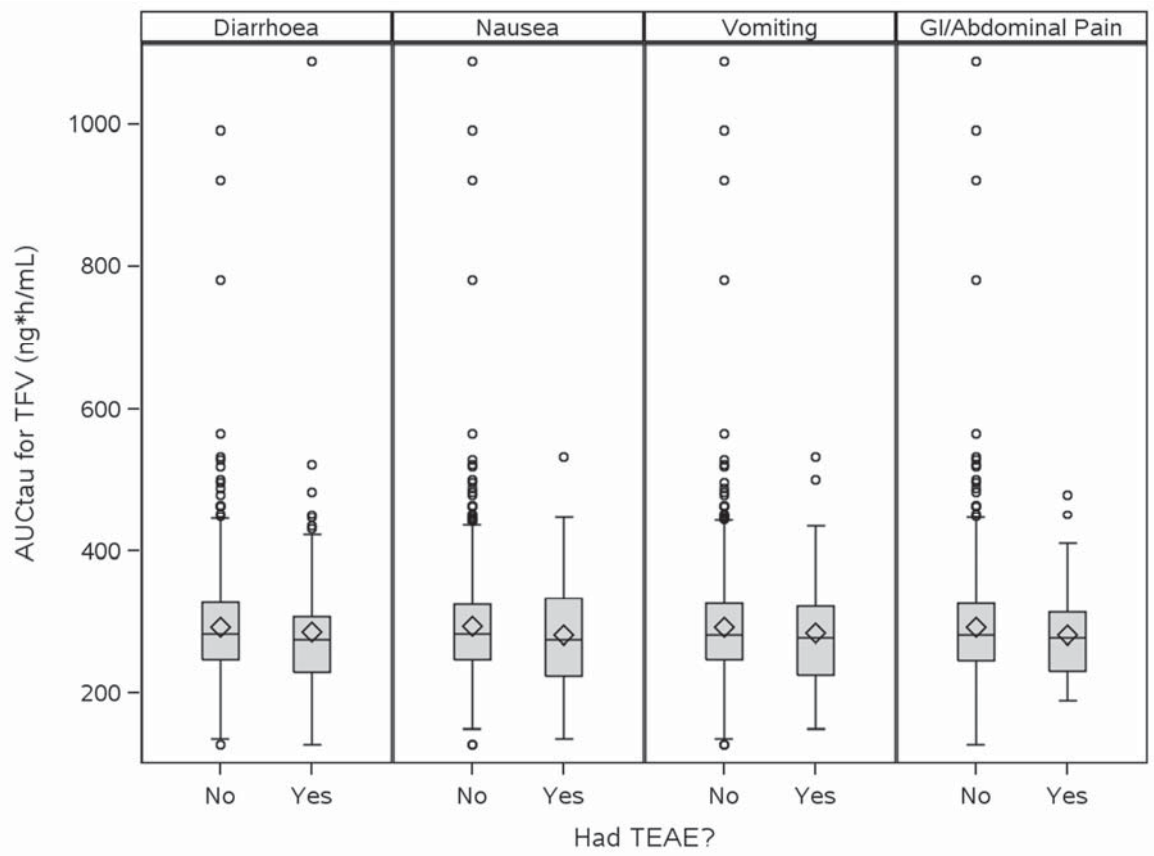
TFV PK Parameter	LS Mean by Treatment		LS Mean Ratio (%CI)
	E/C/F/TAF Test (N=36)	E/C/F/TDF Reference (N=30)	
AUC_{tau} (ng•h/mL)	290.25	3308.04[a]	8.77 (7.94, 9.69)
C_{max}, ng/mL	16.52	399.12[a]	4.14 (3.69, 4.64)
C_{tau}, ng/mL	9.70[b]	65.61	14.79 (13.08, 16.73)

[a] N=29
[b] N=35

AUC_{tau}=area under the plasma concentration-time curve over dosing interval; C_{max}=maximum plasma concentration; QTcF=QT interval corrected by Fridericia's formula

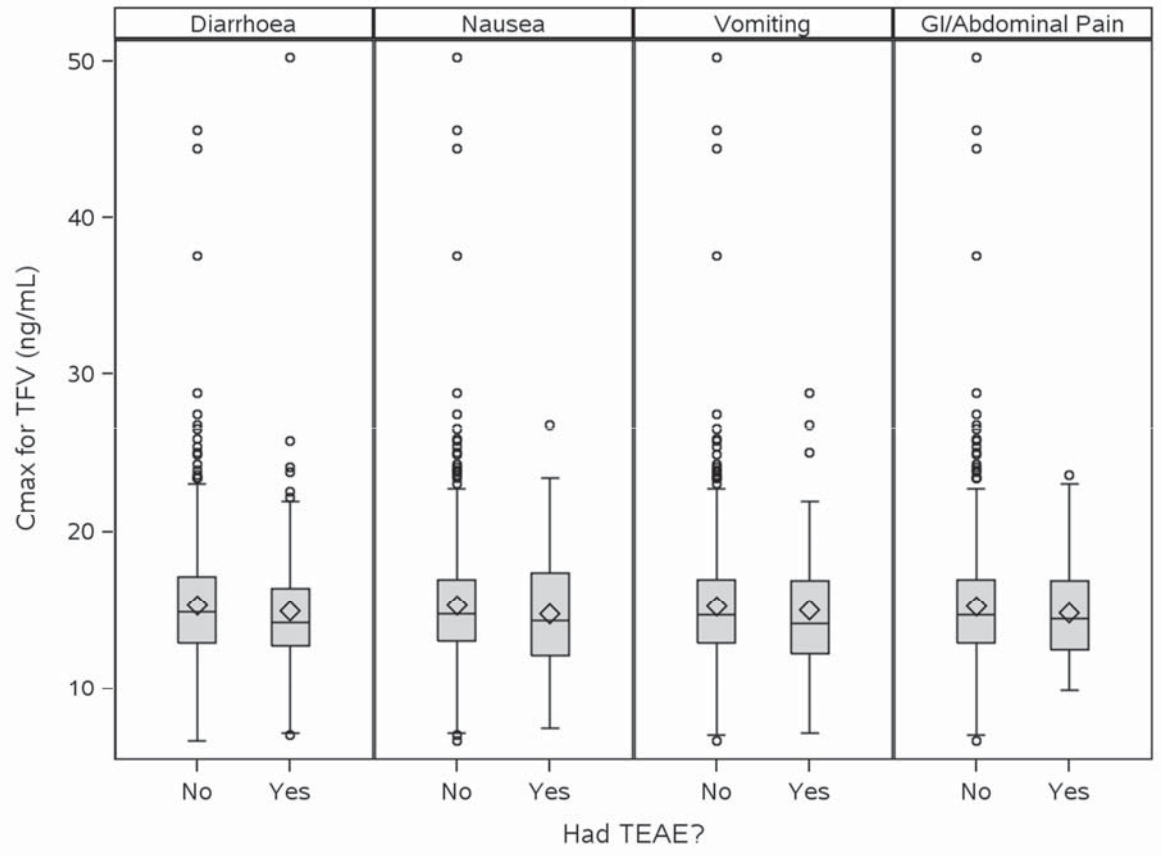
The PK/PD analyses of the TFV exposure-safety relationship were performed on data from ART-naïve HIV-1 infected subjects in E/C/F/TAF Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 using TFV exposures derived from population PK modeling versus safety parameters that included commonly observed AEs, namely diarrhea and nausea (very common ≥10%), and vomiting and GI/abdominal pain (common ≥1% and <10%). The relationships between TFV exposure and incidence of AEs (present=yes; absent=no) are shown in Figure 40 for AUC_{tau} and in Figure 41 for C_{max}.

Figure 40: Box Plot of TFV AUC_{tau}, ng.h/mL by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



Diarrhea: No (n=696), Yes (n=145); Nausea: No (n=715), Yes (n=126); Vomiting: No (n=781), Yes (n=60); GI/Abdominal Pains: No (n=788), Yes (n=53)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR. The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. AEs were coded using MedDRA Version 17.0.
Diarrhea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).

Figure 41: Box Plot of TFV C_{max}, ng/mL by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)

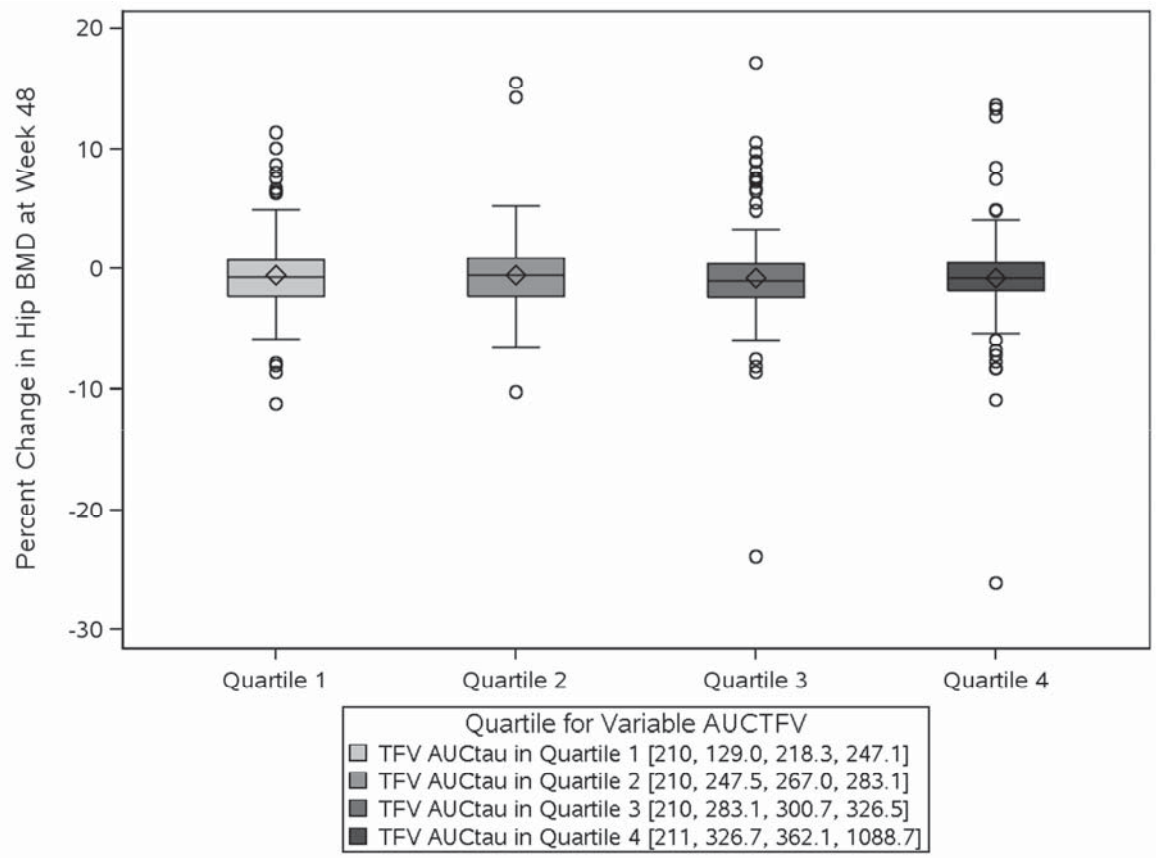


Diarrhea: No (n=696), Yes (n=145); Nausea: No (n=715), Yes (n=126); Vomiting: No (n=781), Yes (n=60); GI/Abdominal Pains: No (n=788), Yes (n=53)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR. The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. AEs were coded using MedDRA Version 17.0.
Diarrhea, nausea, and vomiting refer to MedDRA preferred terms, GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).

For diarrhea, GI/abdominal pain, nausea, and vomiting, TFV exposure was comparable regardless of the presence or absence of those symptoms and no exposure-AE trends were observed with these AEs.

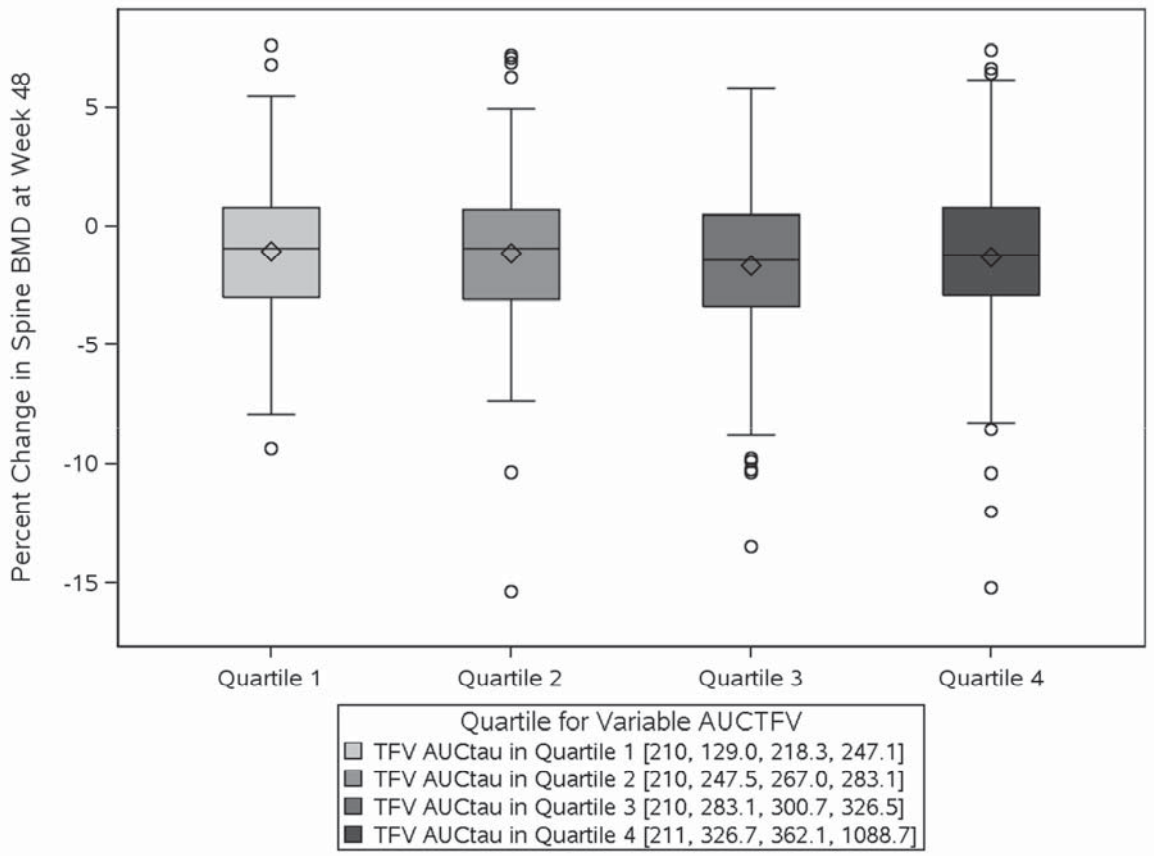
The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were also key safety endpoints in studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TFV exposure quartiles and changes in BMD at the hip and spine were evaluated and results of the analysis are shown in Figure 42 for hip BMD and in Figure 43 for spine BMD. The percentage change from baseline at Week 48 was comparable across all TFV AUC_{tau} quartiles for both hip and spine BMD; no exposure changes in BMD trends were noted.

Figure 42: Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TFV AUC_{tau} for subjects included in the corresponding quartile.

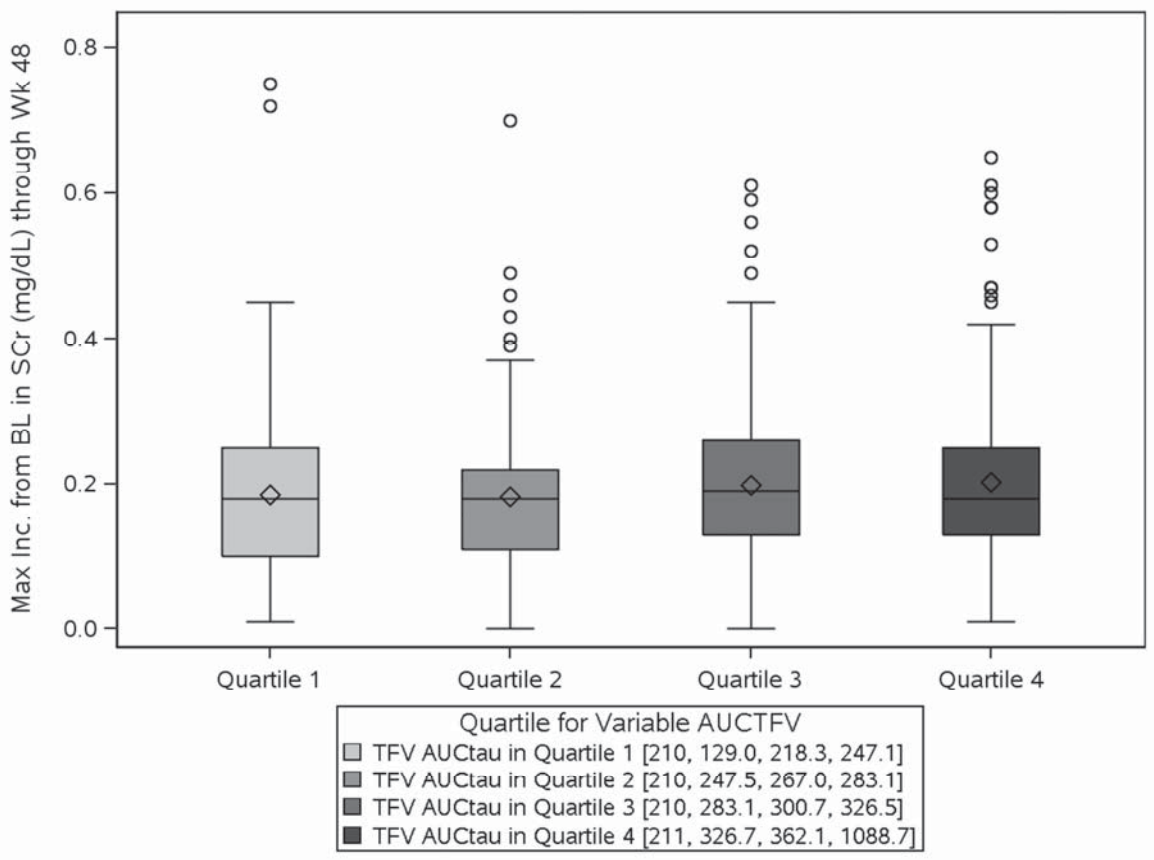
Figure 43: Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TFV AUC_{tau} for subjects included in the corresponding quartile.

Change from baseline in serum creatinine at Week 48 was a key safety endpoint of studies GS-US-292-0104 and GS-US-292-0111. The relationship between TFV exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated and results of the analysis are shown in Figure 44. Maximum increase from baseline in serum creatinine was comparable across TFV AUC_{tau} quartiles; no exposure changes in serum creatinine trends were noted.

Figure 44: Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set) (Studies GS-US-292-0104 and GS-US-292-0111)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers >1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis. Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TFV AUC_{tau} for subjects included in the corresponding quartile.

3.5.2.5.1. QT/QTc Interval

The relationships between TFV plasma concentrations and changes in QTcF were evaluated in a thorough QT/QTc study with the TAF single agent (GS-US-120-0107, Section 2.2.1.1).

A linear mixed-effect model was used to quantify the relationship between TFV plasma concentrations and ΔΔQTcF with gender as a fixed effect and subject as a random effect. The statistical analyses of the relationship between TFV plasma concentrations and ΔΔQTcF are summarized in Table 39, the relationship between TFV plasma concentrations and ΔΔQTcF is depicted graphically in Figure 45, and the relationship between TFV plasma concentrations and ΔΔQTcF at t_{max} is depicted graphically in Figure 46. The results suggest that there is a statistically significant, small, positive association between TFV plasma concentration and ΔΔQTcF interval. This small association was not considered clinically meaningful because the predicted population mean increases in ΔΔQTcF at the mean C_{max} with therapeutic and

supratherapeutic doses were far below the ICH E14 recommended threshold of 10 msec. This very weak association was maintained upon adjustment for gender.

At the observed TFV C_{max} (8.7 ng/mL) following administration of TAF 25 mg, mean ΔΔQTcF is predicted to be –0.570 msec (the upper 95% 1-sided CI=0.487). At the observed TFV C_{max} (50.8 ng/mL) following administration of TAF 125 mg, mean ΔΔQTcF is predicted to be 0.877 msec (the upper 95% 1-sided CI=2.259). Both upper limits of the 1-sided 95% CIs were far below the ICH E14 recommended threshold of 10 msec.

Similar analyses were performed to evaluate the relationship between TFV plasma concentrations and ΔQTcF, and the relationship between TFV plasma concentrations and raw QTcF. The results suggest that there is a statistically significant, small, negative association between TFV plasma concentrations and ΔQTcF and raw QTcF interval. This very weak association was maintained upon adjustment for gender.

Although there appears to be a statistically significant, positive association between plasma concentrations of TFV and ΔΔQTcF, the estimated slope is very small and the predicted population mean increase in ΔΔQTcF at the mean C_{max} under therapeutic and supratherapeutic doses are far below the ICH E14 recommended threshold of 10 msec. Taking into account the fact that TFV concentrations seem negatively associated with ΔQTcF and raw QTcF, we conclude that there is no pharmacologically meaningful association between plasma concentrations of TFV and ΔΔQTcF, ΔQTcF, or raw QTcF.

Table 39: Statistical Analysis of the Relationship between TFV Plasma Concentrations and Time-matched, Baseline-a, and Placebo-corrected QTcF (Study GS US--120-0107)

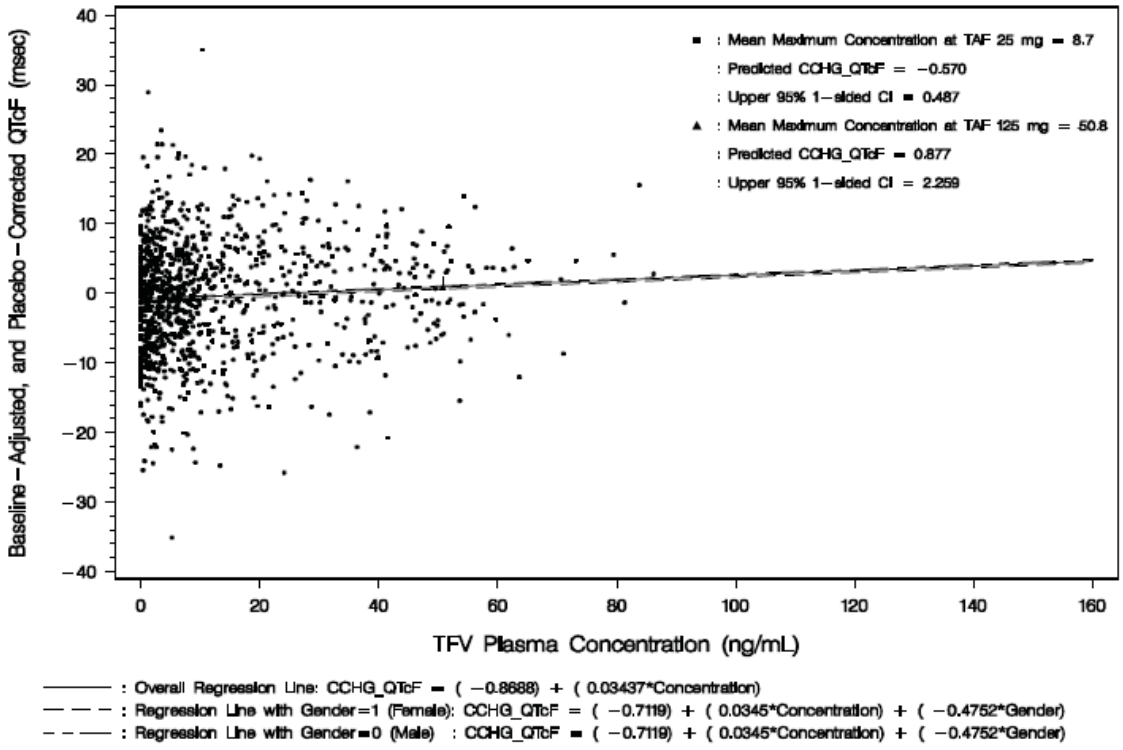
QTcF	Estimate	Standard Error	CI		P value
			Lower	Upper	
Time Matched Baseline Adjusted and Placebo Corrected QTcF					
Overall Regression Equation: ΔΔQTcF=a + (b × Concentration)					
Intercept (a)	-0.5675	0.6509	-1.8769	0.7420	0.39
Concentration (b)	0.001113	0.000921	-0.00069	0.002920	0.23
Regression Equation with Gender as a Fixed Effect: ΔΔQTcF=a + (b × Concentration) + (c × Gender[a])					
Intercept (a)	-0.4378	0.8006	-2.0494	1.1737	0.59
Concentration (b)	0.001115	0.000921	-0.00069	0.002922	0.23
Gender (c)	-0.3894	1.3746	-3.1563	2.3775	0.78

[a] For the regression equation with gender as a fixed effect, "Gender" was defined as 0 for male subjects and 1 for female subjects.

Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect. PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.

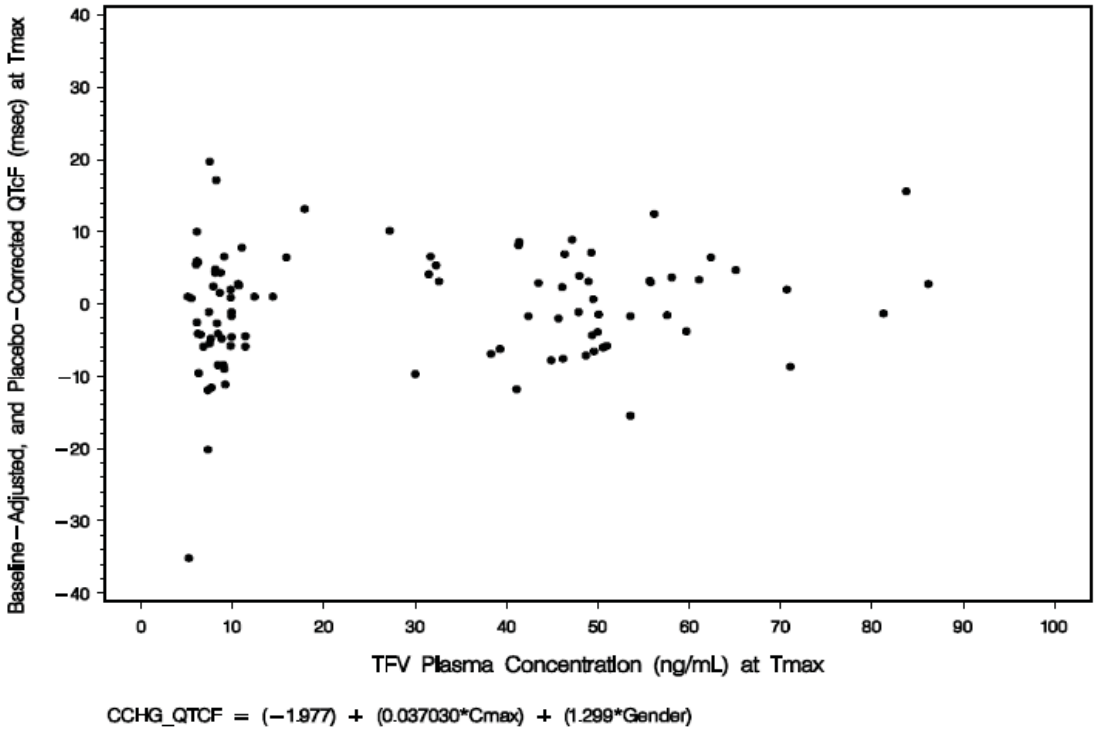
QTcF=QT interval corrected by Fridericia's formula

Figure 45: Scatter Plot of Time-matched, Baseline-adjusted, Placebo-corrected QTcF Versus TFV Plasma Concentration (TAF PK/PD Analysis Set; Study GS-US-120-0107)



Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect. PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect. Upper 95% 1-sided CI was calculated based on overall PK/PD regression model.
QTcF=QT interval corrected by Fridericia's formula

Figure 46: Scatter Plot of Time-matched, Baseline-adjusted, Placebo-corrected QTcF at t_{max} Versus TFV Plasma Concentration (TAF PK/PD Analysis Set; Study GS-US-120-0107)



PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.
QTcF=QT interval corrected by Fridericia's formula; t_{max}=time to reach maximum plasma concentration

3.6. Justification of Dose and Dosing Regimen

The D/C/F/TAF FDC is a single tablet regimen that includes the separate agents at doses of 800/150/200/10 mg. It is intended to be used in the same population for which DRV/COBI 800/150 mg once daily (PREZCOBIX/REZOLSTA) and F/TAF (Descovy) are registered and approved for coadministration as separate tablets; the intended population also includes adolescents, aged as of 12 years and weighing at least 40 kg.

The development of the D/C/F/TAF FDC tablet is based primarily on two pivotal Phase 3 studies with the D/C/F/TAF FDC in treatment-naïve and virologically suppressed HIV-1 infected subjects, respectively. The selection of doses for the components in the D/C/F/TAF FDC was based on the development programs of the single agents as well as the combination agents DRV/COBI and F/TAF.

PREZCOBIX/REZOLSTA (DRV 800 mg/COBI 150 mg as FDC) once-daily is indicated in combination with other ARV medicinal products for the treatment of HIV-1 infection in adults. This FDC formulation contains the same dose of DRV and COBI as the approved PREZISTA and Tybost medicines, respectively, for use as a once-daily regimen in the same indication. COBI has no antiviral effects and only acts as a PK booster. The efficacy and resistance profile for the DRV/COBI combination thus relies on DRV, and has been extensively established

throughout the DRV/rtv development program. Phase 1 studies (GS-US-216-0115 and TMC114IFD1001) formed the PK bridge by demonstrating comparable DRV PK with DRV/rtv (800/100 mg) and DRV/COBI (800/150 mg), as separate agents or as FDC. The results of these bridging PK studies allow extrapolation of the established safety, efficacy and resistance clinical data from DRV/rtv to the DRV/COBI combination. The phase 3 study GS-US-216-0130 further provided supportive clinical evidence for the DRV/COBI combination.

For FTC, the D/C/F/TAF FDC contains the same dose of FTC as the approved Emtriva and Truvada medicines for use with other ARV agents for the treatment of HIV-1 infection.

While currently, in the US, the approved dose of TAF for combination with boosted DRV is TAF 25 mg (as part of the F/TAF FDC, Descovy), a TAF 10 mg dose was selected for the D/C/F/TAF FDC development program. This choice was supported by the totality of TAF and TFV data from drug-drug interaction studies, the wide range of safe and efficacious TAF plasma exposure as established from the single-agent proof-of-concept study (GS-US-120-0104) and a number of Phase 2/3 F/TAF studies (either with E/C/F/TAF FDC or F/TAF FDC plus third agent), a Phase 2 study of D/C/F/TAF (study GS-US-299-0102), and intracellular TFV-DP (active) levels observed in combination with various third agents. The choice of the TAF 10 mg dose was based on ensuring that patients would have a TAF systemic exposure that is within the range of TAF exposures for which antiviral activity was shown and for which there was no PK/PD relationship, based on the extensive efficacy database from the above-mentioned studies. On the other hand, TFV systemic exposure was aimed to be as low as possible, to enhance the safety profile. An extensive discussion of the drug interactions and PK/PD evaluation leading to TAF dose selection is provided in Section 3.4.2 and Section 3.5, respectively. The efficacy of a TAF 10 mg qd dose in the presence of DRV/COBI 150/10 mg qd was confirmed in the two pivotal D/C/F/TAF Phase 3 studies.

For each of the components of the D/C/F/TAF FDC, the dose used in adults has shown to provide similar exposure in adolescent subjects aged ≥12 to <18 years compared to adults, and was shown to be safe and efficacious in the adolescent population. Also, the boosting effect of COBI was similar in adults and adolescents. Based on this, the D/C/F/TAF FDC combining DRV, COBI, FTC and TAF at doses of 800 mg, 150 mg, 200 mg and 10 mg given once daily is also considered appropriate for use in adolescents aged ≥12 years and weighing at least 40 kg.

Taken together, these considerations support the use of the D/C/F/TAF FDC for the treatment of HIV-1 infected adult and adolescent subjects. The D/C/F/TAF 800/150/200/10 mg FDC should be administered once daily, with food.

Conclusions based on the totality of data presented in this summary are provided at the beginning of this document, just prior to Section 1.

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The following reference list is also provided in Mod2.7.5, and linked from that location to Mod5.4, where applicable.

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APPENDICES

APPENDIX 1: CLINICAL PHARMACOLOGY STUDIES

Study ID	Objectives	Subjects	Dose/ Component Studied	Route	Section in Mod2.7.2 or Mod2.7.1	Location of Report or Prior NDA
Phase 1 – D/C/F/TAF						
TMC114FD2HTX1002	Bioavailability/ Food Effect	Healthy Subjects	800/150/200/10 mg (D/C/F/TAF) 800/150/200/10 mg (DRV + COBI + F/TAF) 150/150/200/10 mg (E/C/F/TAF)	oral	Mod2.7.1/Sec2.1.1.1	Mod5.3.1.1
GS-US-299-0101	Bioavailability	Healthy Subjects	800/150/200/25 mg (D/C/F/TAF) 800/150/200/25 mg (D/C/F/TAF) 800/150/200/10 mg (D/C/F/TAF) 800/150 mg (DRV/COBI) 200/25 mg (FTC + TAF)	oral	Mod2.7.1/Sec2.1.1.2	Mod5.3.1.1
TMC114FD2HTX1001	Bioequivalence	Healthy Subjects	800/150/200/10 mg (D/C/F/TAF) 800/150/200/10 mg DRV + COBI + F/TAF)	oral	Mod2.7.1/Sec2.2.1.1	Mod5.3.1.2
TMC114FD2HTX1004	Bioavailability	Healthy Subjects	800/150/200/10 mg (D/C/F/TAF)	oral	Mod2.7.1/Sec2.1.1.3	Mod5.3.1.1
Phase 2 – D/C/F/TAF						
GS-US-299-0102	Safety/Efficacy	HIV-1 patients	800/150/200/10 (D/C/F/TAF) 800 + 150 + 200 + 300 mg DRV + COBI + FDC F/TDF placebo	oral	2.2.2.1	Mod5.3.5.1

Study ID	Objectives	Subjects	Dose/ Component Studied	Route	Section in Mod2.7.2 or Mod2.7.1	Location of Report or Prior NDA
Pivotal Phase 3 – D/C/F/TAF						
TMC114FD2HTX3001	Efficacy/Safety	HIV-1 patients	800/150/200/10 (D/C/F/TAF) 800/150 + 200/300 mg DRV/COBI + FDC F/TDF placebo	oral	2.2.2.2	Mod5.3.5.1
TMC114IFD3013	Efficacy/Safety	HIV-1 patients	800/150/200/10 (D/C/F/TAF) boosted PI + F/TDF (200/300 mg)	oral	2.2.2.3	Mod5.3.5.1
Studies previously included in the approved marketing authorization for DRV, DRV/COBI						
Phase 1 - DRV/rtv:						
TMC114-C109	Mass-balance	Healthy	DRV 400 mg single dose rtv 100 mg bid	oral	2.1.1.2	NDA021976/Mod5.3.3.1
TMC114-C134	Hepatic impairment	Healthy and subjects with mild or moderate hepatic impairment	DRV/rtv 600/100 mg bid	oral	2.1.4.1	NDA021976/Mod5.3.3.3
TMC114-C123	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C124	Drug-drug interaction	Healthy	DRV/rtv 300/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C111	Drug-drug interaction	Healthy	DRV/rtv 300/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C119	Drug-drug interaction	HIV-1	DRV/rtv 300/100 mg bid; 400/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC125-C176	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC278-C112	Drug-drug interaction	Healthy	DRV/rtv 800/100 mg qd	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-A4001052	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	-[24]
TMC114-C122	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4

Study ID	Objectives	Subjects	Dose/ Component Studied	Route	Section in Mod2.7.2 or Mod2.7.1	Location of Report or Prior NDA
TMC114-C150	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C142	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C172	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C121	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C129	Drug-drug interaction	Healthy	Panel 1: DRV 400 mg bid Panel 2: DRV/rtv 400/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC125VIR1001	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C107	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C163	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C131	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
VX950-C124	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	-[41]
TMC114-C133	Drug-drug interaction	Healthy	DRV/rtv 300/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C120	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C171	Drug-drug interaction	Non-HIV subjects on stable buprenorphine/ naloxone maintenance therapy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C127	Drug-drug interaction	Non-HIV subjects on stable methadone therapy	DRV/rtv 600/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C128	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	2.1.5.2	NDA021976/Mod5.3.3.4
TMC114-C153	Thorough QT/QTc	Healthy	DRV/rtv 1600/100 mg qd; 800/100 mg bid	oral	2.2.1.1	NDA021976/Mod5.3.4.1
Phase 1 - COBI without DRV:						
GS-US-216-0111	Mass-balance	Healthy	150 mg qd	oral	2.1.1.2	NDA203094/Mod5.3.3.1

Study ID	Objectives	Subjects	Dose/ Component Studied	Route	Section in Mod2.7.2 or Mod2.7.1	Location of Report or Prior NDA
GS-US-216-0121	Renal impairment	Healthy and subjects with mild to moderate renal impairment	150 mg qd	oral	2.1.4.2	NDA203094/Mod5.3.3.3
GS-US-216-0124	Renal impairment	Healthy and subjects with severe renal impairment	150 mg qd	oral	2.1.4.2	NDA203094/Mod5.3.3.3
GS-US-183-0133	Hepatic impairment	Healthy and subjects with moderate hepatic impairment	150 mg qd	oral	2.1.4.1	NDA203094/Mod5.3.3.3
GS-US-216-0112	Drug-drug interaction	Healthy	150 mg qd	oral	2.1.5.2	NDA203094/Mod5.3.3.4
GS-US-201-0104	Drug-drug interaction	Healthy	150 mg qd	oral	2.1.5.2	NDA203094/Mod5.3.3.4
GS-US-216-0120	Drug-drug interaction	Healthy	150 mg qd	oral	2.1.5.2	NDA203094/Mod5.3.3.4
GS-US-216-0122	Drug-drug interaction	Healthy	150 mg qd	oral	2.1.5.2	NDA203094/Mod5.3.3.4
GS-US-216-0123	Drug-drug interaction	Healthy	150 mg qd	oral	2.1.5.2	NDA203094/Mod5.3.3.4
GS-US-236-0106	Drug-drug interaction	Healthy female	150 mg qd	oral	2.1.5.2	NDA203094/Mod5.3.3.4
Studies with TAF, FTC, F/TAF or E/C/F/TAF previously included in the approved marketing authorization for FTC/TAF						
Phase 1						
GS-US-120-0109	Mass-balance	Healthy Subjects	TAF	oral	2.1.1.3	NDA208215/Mod5.3.3.1
FTC-106	Mass-balance	Healthy Subjects	FTC	oral	2.1.1.3	NDA021752/Mod5.3.3.1
GS-US-120-0108	Renal impairment	Healthy subjects/ renally impaired subjcts	TAF	oral	2.1.4.2	NDA208215/Mod5.3.3.3
FTC-107	Renal impairment	Healthy subjects/ renally impaired subjects	TAF	oral	2.1.4.2	NDA021752/Mod5.3.3.3
GS-US-292-0112	Renal impairment	Healthy subjects/ renally impaired subjects	E/C/F/TAF FDC	oral	2.1.4.2	NDA207561/Mod5.3.5.2
GS-US-120-0114	Hepatic impairment	Mild or moderate hepatic impairment	TAF	oral	2.1.4.1	NDA208215/Mod5.3.3.3

Study ID	Objectives	Subjects	Dose/ Component Studied	Route	Section in Mod2.7.2 or Mod2.7.1	Location of Report or Prior NDA
GS-US-311-0101	Drug-drug interaction	Healthy Subjects	F/TAF 200/40 mg F/TAF 200/25 mg TAF 8 mg	oral	2.1.5.3	NDA208215/Mod5.3.3.4
GS-US-120-0117	Drug-drug interaction	Healthy Subjects	TAF (25 mg)	oral	2.1.5.3	NDA208215/Mod5.3.3.4
GS-US-120-1554	Drug-drug interaction	Healthy Subjects	TAF (25 mg)	oral	2.1.5.3	NDA208215/Mod5.3.3.4
GS-US-120-0118	Drug-drug interaction	Healthy Subjects	TAF (10 mg) FTC (200 mg)	oral	2.1.5.3	NDA208215/Mod5.3.3.4
GS-US-120-1538	Drug-drug interaction	Healthy Subjects	TAF (25 mg)	oral	2.1.5.3	NDA208215/Mod5.3.3.4
GS-US-292-1316	Drug-drug interaction	Healthy Subjects	150/150/200/10 mg (E/C/F/TAF)	oral	2.1.5.3	NDA207561/Mod5.3.3.4
GS-US-120-0107	Thorough QT	Healthy Subjects	TAF (25 mg) TAF (125 mg)	oral	2.2.1.1	NDA208215/Mod5.3.4.1
Phase 2/3						
GS-US-120-0104	Proof-of-concept	HIV-1 Infected Subjects	TAF (8 mg) TAF (25 mg) TAF (40 mg) TDF (300 mg)	oral	2.2.3.2	NDA208215/Mod5.3.4.2
GS-US-292-0104 GS-US-292-0111	Pooled data from these Phase 3 studies is discussed with respect to population PK and PD/PK analyses for this authorization – see Section 2.2.3.3					NDA207561/Mod5.3.5.1 NDA207561/Mod5.3.5.1
GS-US-311-1089	Switch Study	HIV-1 Infected Subjects	TAF TDF	oral	2.2.3.4	NDA208215/mod5.3.5.1
GS-US-292-0106	Pediatric Study	HIV-1 Infected Subjects	150/150/200/10 mg E/C/F/TAF	oral	2.2.3.1	Gaur et al, 2016[15]

APPENDIX 2: BIOAVAILABILITY PK PARAMETERS ACROSS CLINICAL STUDIES

Bioavailability PK Parameters of DRV, COBI, FTC and TAF After Single and Multiple Dose Administration of D/C/F/TAF FDC [Formulation: G001], (All Clinical Pharmacology and Biopharmaceutic Studies)

Dose (unit)	Formulation	n	t_{max} (h) Min - Max	t_{max} (h) Median	C_{max} (ng/mL) Mean	C_{max} (ng/mL) %CV	C_{max} (ng/mL) Median	AUC (ng.h/mL) Mean	AUC (ng.h/mL) %CV	AUC (ng.h/mL) Median	$t_{½}$ (h) Mean	$t_{½}$ (h) %CV	$t_{½}$ (h) Median	Study ID
Single Dose														
DRV		83	1.50 - 8.00	4.00	7042	21.0	7100	87200	31.4	83956	5.9	35.2	5.5	TMC114FD2HTX1001
DRV		23[a,c]	2.00 - 8.00	5.00	6670	22.8	6430	90809	48.7	76164	6.8	27.8	6.4	TMC114FD2HTX1002
DRV		23[a,d]	1.00 - 8.02	3.00	4089	45.1	4310	67504	52.8	56823	7.0	33.0	6.4	TMC114FD2HTX1002
DRV		24[a,e]	1.50 - 8.00	5.00	6629	23.3	6790	93541	42.5	89528	7.8	44.8	6.8	TMC114FD2HTX1002
DRV		30	1.00 - 8.00	4.00	8437	19.8	8475	116422	33.2	109598	5.5	41.4	5.0	TMC114FD2HTX1004[i]
COBI		93	1.50 - 6.00	4.00	894	28.5	866	6681	37.2	6507	3.7	18.7	3.6	TMC114FD2HTX1001
COBI		24[a,c]	1.50 - 6.00	4.00	801	19.8	799	6224	30.3	5769	3.6	19.9	3.4	TMC114FD2HTX1002
COBI		23[a,d]	1.00 - 6.00	3.00	704	52.3	619	5771	55.6	4910	4.1	22.5	4.2	TMC114FD2HTX1002
COBI		24[e]	2.00 - 6.10	5.00	711	23.1	699	6168	36.6	6420	3.9	14.6	3.9	TMC114FD2HTX1002
COBI		30	1.00 - 5.02	4.00	931	24.8	907	7883	44.4	7068	3.8	26.2	3.6	TMC114FD2HTX1004[i]
FTC		93	0.60 - 5.00	2.00	2041	23.5	1990	11722	16.7	11810	16.5	19.7	17.2	TMC114FD2HTX1001
FTC		24[a,b]	1.00 - 5.00	2.50	1691	24.5	1655	10595	16.8	10605	10.2	8.0	10.3	TMC114FD2HTX1002
FTC		24[a,c]	1.00 - 4.98	3.00	1677	24.5	1580	10365	16.9	10132	10.0	6.0	10.1	TMC114FD2HTX1002
FTC		24[a,d]	0.50 - 2.00	1.00	2247	25.5	2055	11593	22.2	10936	10.8	11.3	10.5	TMC114FD2HTX1002
FTC		24[a,e]	0.75 - 5.00	2.00	1785	27.2	1635	11499	17.9	11166	10.7	10.8	10.6	TMC114FD2HTX1002
FTC		30	0.75 - 4.02	2.00	1915	29.5	1805	11975	23.4	11547	16.7	23.4	17.3	TMC114FD2HTX1004[i]
TAF		94	0.25 - 3.50	1.50	110	49.0	97.2	123	34.2	117	0.3	37.3	0.3	TMC114FD2HTX1001
TAF		24[a,b]	0.50 - 5.00	1.50	102	60.7	87.6	114	49.1	98.9	0.5	34.9	0.5	TMC114FD2HTX1002
TAF		24[a,c]	0.50 - 3.00	1.28	105	90.3	66.8	123	55.3	93.1	0.4	28.3	0.4	TMC114FD2HTX1002
TAF		24[a,d]	0.25 - 0.75	0.50	180	50.3	144	106	42.2	100	0.3	59.0	0.3	TMC114FD2HTX1002
TAF		24[a,e]	0.25 - 5.00	0.88	107	61.0	105	117	44.1	107	0.5	29.1	0.5	TMC114FD2HTX1002
TAF		30	0.25 - 2.50	1.25	163	43.8	149	156	27.8	150	0.4	28.8	0.3	TMC114FD2HTX1004[i]
Multiple Dose														
DRV	1	10	2.00 - 4.00	3.00	9698.3	25.3	9809.6	112572.4	28.6	117361.4	7.89	39.1	8.85	GS-US-299-0101
DRV	2	10	1.00 - 4.00	3.49	9121.9	14.5	8977.8	102985.6	27.1	94182.0	10.82	47.6	9.10	GS-US-299-0101
DRV	3[f]	10	2.00 - 4.00	3.00	9743.2	14.3	9611.0	113654.8	23.8	113589.4	7.46	26.7	7.13	GS-US-299-0101
DRV	3[g]	19	1.50 - 4.00	3.00	9233.0	20.2	9165.3	106011.5	26.8	100843.0	7.44	31.5	6.84	GS-US-299-0101
DRV	3[h]	16	1.50 - 5.00	3.00	9534.9	18.3	9777.0	120107.9	38.9	102678.0	7.96	32.4	7.74	GS-US-299-0101
DRV		21	0.75 - 5.00	3.00	8826.2	33.3	8243.3	99301.8	45.3	93030.1	11.17	69.7	9.42	GS-US-299-0102
COBI	1	10	2.00 - 4.00	3.00	1227.3	24.0	1233.2	10001.5	36.9	9593.9	3.50	32.2	3.40	GS-US-299-0101
COBI	2	10	1.50 - 4.00	3.00	1366.0	23.9	1434.8	11316.0	31.5	10959.7	3.82	12.2	3.81	GS-US-299-0101
COBI	3[f]	10	1.50 - 4.00	3.00	1305.2	13.8	1314.1	10097.3	23.7	9675.2	3.09	12.6	2.90	GS-US-299-0101
COBI	3[g]	19	2.00 - 4.00	3.00	1237.3	15.4	1199.2	9229.9	18.9	9325.9	3.19	18.7	3.11	GS-US-299-0101

Dose (unit)	Formulation	n	t_{max} (unit) Min - Max	t_{max} (unit) Median	C_{max} (unit) Mean	C_{max} (unit) %CV	C_{max} (unit) Median	AUC (unit) Mean	AUC (unit) %CV	AUC (unit) Median	$t_{½}$ (unit) Mean	$t_{½}$ (unit) %CV	$t_{½}$ (unit) Median	Study ID
Multiple Dose (ctd)														
COBI	3[h]	16	1.50	5.00	3.00	1310.6	22.6	1443.4	10155.7	25.8	10407.7	3.77	26.6	3.48	GS-US-299-0101
COBI		21	1.52	5.02	3.03	1128.7	35.3	1036.0	8744.5	43.9	8097.5	3.36	26.0	3.16	GS-US-299-0102
FTC	1	10	1.00	3.00	1.50	2067.4	12.0	2121.5	12327.0	14.5	12927.1	5.57	20.7	4.99	GS-US-299-0101
FTC	2	10	1.00	4.00	1.75	2363.1	25.3	2206.8	13460.3	21.6	13694.5	6.36	27.3	6.26	GS-US-299-0101
FTC	3[f]	10	1.00	3.00	1.75	2198.9	20.7	2196.9	12602.1	16.4	12246.9	5.87	20.7	5.48	GS-US-299-0101
FTC	3[g]	19	1.00	3.00	1.50	2144.3	23.6	2084.3	12437.1	13.6	12290.1	12.55	50.1	9.36	GS-US-299-0101
FTC	3[h]	16	0.75	3.00	1.50	2362.8	17.4	2242.0	14886.6	27.0	14055.9	14.35	56.5	13.22	GS-US-299-0101
FTC		21	0.50	4.00	1.52	2056.4	25.3	1882.9	11918.0	35.9	10836.4	7.78	25.2	7.51	GS-US-299-0102
TAF	1	10	0.50	2.00	0.50	328.3	30.5	373.1	314.6	26.9	294.7	0.40	16.8	0.41	GS-US-299-0101
TAF	2	10	0.50	1.00	0.50	344.1	27.3	358.4	326.6	20.0	331.1	0.44	30.8	0.39	GS-US-299-0101
TAF	3[b]	10	0.50	1.00	0.50	130.7	39.2	110.5	116.4	26.0	109.9	0.51	73.2	0.41	GS-US-299-0101
TAF	3[g]	19	0.25	2.00	0.75	161.8	37.8	144.7	151.7	26.2	142.3	0.39	23.2	0.39	GS-US-299-0101
TAF	3[h]	16	0.50	2.00	0.75	184.0	35.8	199.7	166.7	30.0	152.3	0.41	40.4	0.37	GS-US-299-0101
TAF		21	0.25	2.02	0.53	163.0	51.9	135.0	130.5	34.1	122.9	0.52	48.1	0.45	GS-US-299-0102

[a] Maximum number of subjects analyzed.
[b] Treatment A: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet under fed conditions (standardized regular breakfast)
[c] Treatment C: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet under fed conditions (standardized regular breakfast)
[d] Treatment E: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet under fasted conditions
[e] Treatment F: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet under fed conditions (standardized high-fat breakfast)
[f] GS-US-299-0101: Part 1
[g] GS-US-299-0101: Part 3 – Cohort 1
[h] GS-US-299-0101: Part 3 – Cohort 2
[i] treatment tablet swallowed whole only

AUC: AUC_{∞} for single dose, AUC_{tau} for multiple dose
Source: Clinical Study Reports

Janssen Research & Development

Virology Summary

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults and Adolescents

D/C/F/TAF (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) (TMC114/JNJ-48763364/JNJ-35807551/JNJ-63625328)

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AF	assay failure
APV	amprenavir
ARV	antiretroviral
ART	antiretroviral treatment
ATV	atazanavir
AZT	zidovudine
BCO	biological cut-off
b.i.d.	twice daily
BL	baseline
bPI	Boosted protease inhibitor
CC_{50}	50% cytotoxic concentration
CCO	clinical cut-off
COBI	cobicistat
CRF ID	case report form identity
CRFs	Circulating Recombinant Forms
CSR	Clinical Study Report
CYP	Cytochrome P450
d4T	stavudine
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DC	discontinuation
ddI	didanosine
DLV	delavirdine
DNA	deoxyribonucleic acid
DRV	darunavir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
EC_{50}	50% effective concentration
EFV/FTC/TDF	efavirenz/emtricitabine/tenofovir disoproxil fumarate
EFV	efavirenz
ENF	enfuvirtide
ESTD	early study treatment discontinuation visit
ETR	etravirine
EVG	elvitegravir
F/TAF	emtricitabine/tenofovir alafenamide
F/TDF	emtricitabine/tenofovir disoproxil fumarate
FC	fold change in EC_{50} values
FDA	Food and Drug administration
FDC	fixed dose combination
FTC	emtricitabine
FTC-TP	emtricitabine 5′-triphosphate
HSA	human serum albumin
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HS	human serum
IDV	indinavir
IAS-USA	International Antiviral Society-USA
IN	integrase
INI	integrase inhibitor
INSTI	integrase strand transfer inhibitors

ITT	intent-to-treat
LPV	lopinavir
MOI	multiplicity of infection
n	number of observations/numerator in a (sub)group
N	number/denominator in a group
NDAs	New Drug Applications
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
NVP	nevirapine
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PDVF	protocol-defined virologic failure
PI	protease inhibitor
PK	pharmacokinetic(s)
PR	protease
qd	once daily
RAMs	resistance-associated mutations
RAP	resistance analysis population
RB	rebound
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
rtv	low-dose ritonavir
SDM	site-directed mutant
SQV	saquinavir
TAF	tenofovir alafenamide
TAMs	thymidine analog mutations
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TLOVR	time to loss of virologic response
TMC	Tibotec Medicinal Compound
TPV	tipranavir
USA	United States of America
VF	Virologic Failure
VL	viral load
WT	wild type

DEFINITION OF TERMS

Post-baseline resistance testing was performed on samples from subjects experiencing **Protocol-defined Virologic Failure:**

Protocol-defined Virologic Failure
= Virologic Nonresponse/Virologic Rebound/Viremic at Final Time Point
(Studies TMC114FD2HTX3001, GS-US-299-0102, GS-US-292-0106, and TMC114-C230)

Virologic Nonresponse TMC114FD2HTX3001, GS-US-299-0102, and GS-US-292-0106.	HIV-1 RNA <1 $\log_{10}$ reduction from baseline (and ≥50 copies/mL) at the Week 8 visit, confirmed at the following scheduled or unscheduled visit following Week 8.
TMC114-C230[a]	On-study at Week 12 and never achieved 2 consecutive VL <50 copies/mL.
Virologic Rebound TMC114FD2HTX3001	At any visit, after achieving confirmed consecutive HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥50 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit;
GS-US-299-0102	At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA to ≥ 400 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit
GS-US-292-0106	At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA ≥ 50 copies/mL, which was subsequently confirmed and ≥ 400 copies/mL at the following scheduled or unscheduled visit
	Or
TMC114FD2HTX3001 GS-US-299-0102 GS-US-292-0106	At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir which was subsequently confirmed at the following scheduled or unscheduled visit.
TMC114-C230[a]	On-study at Week 12 and achieved 2 consecutive VL <50 copies/mL, followed by 2 consecutive VL ≥50 copies/mL.
Viremic at Final Time Point TMC114FD2HTX3001, GS-US-299-0102, GS-US-292-0106, and TMC114-C230[a]	Any subject with on-treatment HIV-1 RNA ≥400 copies/mL (or HIV-1 RNA ≥50 copies/mL for Study TMC114-C230) at the study endpoint or study discontinuation after Week 8[b]

Protocol-defined Virologic Failure
= Virologic Rebound Cumulative Through Week 48
(Study TMC114IFD3013)

Virologic Rebound TMC114IFD3013	Confirmed HIV-1 RNA ≥50 copies/mL up to, and including the upper bound of the Week 48 window (ie, 54 weeks). Premature discontinuation (irrespective of reason) for which the last available (single) HIV-1 RNA ≥50 copies/mL. In addition, any subject with last available on-treatment HIV-1 RNA ≥50 copies/mL at the study cut-off (Week 48) was considered a virologic rebounder.

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed dose combination; HIV-1 = human immunodeficiency virus type 1; PDVF = Protocol-defined Virologic Failure.

a. TLOVR (non-virologic failure censored) algorithm.

b. GS-US-299-0102 and GS-US-292-0106: Viremic at Final Time Point only in case not meeting any of the other PDVF criteria.

1. INTRODUCTION

The information presented in this Summary of Virology establishes the clinical resistance profile of the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed dose combination (FDC) (800/150/200/10 mg) in adult and adolescent subjects infected with human immunodeficiency virus type 1 (HIV-1).

Extensive development programs including in-vitro virology studies and clinical studies were conducted to provide information on mechanism of drug action and in vitro antiviral activity/resistance, and clinical efficacy/resistance of the components of D/C/F/TAF.

Darunavir (DRV) is an HIV protease inhibitor (PI) with potent in vitro activity against wild type (WT) and multi-drug resistant HIV-1 strains and has demonstrated to have a high genetic barrier to the development of resistance.[5,9,14] It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Eleven HIV-1 protease mutations associated with DRV resistance (DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V) were previously identified based on an analysis of a pooled dataset of studies in highly treatment-experienced subjects (subjects had received treatment with DRV 600 mg and ritonavir (rtv) 100 mg twice daily); virologic efficacy has been shown to be compromised in the presence of 3 or more DRV resistance-associated mutations (RAMs) in the background of a high number (median of 14 or 15, respectively) of International Antiviral Society–USA (IAS-USA) PI RAMs.[7,6,22] Darunavir 800 mg once daily (qd) has been studied extensively across diverse populations (both treatment-naïve and treatment-experienced subjects) in clinical studies, demonstrating excellent efficacy and safety.[1,3,12,16,17,19,20] Across these studies of HIV-1–infected subjects taking a DRV 800 mg qd–based regimen, only 4 of 1,686 (0.2%) subjects developed post-baseline primary PI and/or DRV RAMs, and only 1 of 1,686 (<0.1%) subjects lost DRV phenotypic susceptibility, demonstrating DRV's high genetic barrier to the development of resistance.[15]

Cobicistat (COBI), a structural analogue of rtv, is a potent mechanism-based inhibitor of human hepatic microsomal cytochrome P450 (CYP)3A activity. COBI is devoid of anti-HIV activity and therefore does not select any HIV resistance mutations.

Emtricitabine (FTC) is a nucleoside analogue of 2'-deoxycytidine. Emtricitabine is efficiently phosphorylated to the corresponding 5′-triphosphate (FTC-TP). FTC-TP serves as an alternative substrate inhibitor of HIV-1 reverse transcriptase (RT) and is incorporated into nascent chain viral DNA. Incorporation results in the termination of DNA synthesis due to the lack of a hydroxyl group in the 3′-position of the sugar moiety of FTC, which in turn inhibits viral replication. HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir (TFV) is a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), the oral prodrug of TFV, is rapidly converted to TFV, which is then metabolized intracellularly to its active phosphorylated metabolite TFV diphosphate (TFV-DP),

and acts as a competitive inhibitor of HIV-1 RT to terminate the elongation of the viral DNA chain.

Tenofovir alafenamide (TAF) is a next generation oral prodrug of TFV. Tenofovir alafenamide is more stable in plasma than TDF, provides higher intracellular levels of TFV-DP, more effective suppression of residual viral replication, and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF. As both TAF and TDF are prodrugs of TFV, the in vitro HIV-1 resistance profile of TAF is comparable with the resistance profile of the parent nucleotide TFV.[4] TAF resistance selection experiments in vitro have demonstrated development of the K65R mutation in RT. Tenofovir alafenamide activity in vitro has been evaluated against a panel of nucleoside reverse transcriptase inhibitor (NRTI)-resistant HIV-1 clinical isolates. Viral breakthrough experiments in the presence of clinically relevant concentrations of TAF or TFV, as well as resistance analyses were conducted to assess TAF's resistance barrier compared with TFV. NRTI-resistant HIV-1 isolates with complex RT mutation patterns such as K65R, 3 to 5 thymidine analog mutations (TAMs), Q151M complex, or T69ins, with or without M184V, were profiled. In these experiments, several viruses harboring major NRTI-resistant mutations were fully inhibited by TAF, but were not inhibited by TFV at clinically relevant concentrations. In vitro resistance analyses demonstrated that TAF effectively suppressed viral isolates that contained multiple TAMs or K65R, isolates that are not effectively suppressed by TDF or TFV (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).

In a pooled analysis of the Gilead Studies GS-US-292-0104 and GS-US-292-0111 (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF] vs elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [E/C/F/TDF]) the development of resistance to FTC or TDF/TAF was rare. Up to Week 144, the development of one or more primary elvitegravir (EVG), FTC, or TAF RAMs was observed in HIV-1 isolates from 12 of 22 subjects with evaluable genotypic data from paired baseline and E/C/F/TAF treatment-failure isolates (12 of 866 subjects [1.4%]) compared with 12 of 20 treatment-failure isolates from subjects with evaluable genotypic data in the E/C/F/TDF treatment group (12 of 867 subjects [1.4%]). In the E/C/F/TAF group, the NRTI RAMs that emerged were M184V/I (n=11) and K65R/N (n=2). In the E/C/F/TDF group, the NRTI RAMs that emerged were M184V/I (n=9), K65R/N (n=4), and L210W (n=1). In phenotypic analyses of subjects in the final resistance analysis, HIV-1 isolates from 8 subjects had reduced susceptibility to FTC in the E/C/F/TAF group compared with HIV-1 isolates from 7 subjects in the E/C/F/TDF group. One subject in the E/C/F/TAF group and 2 subjects in the E/C/F/TDF group had reduced susceptibility to TFV.[11]

Fixed dose combinations of the D/C/F/TAF components (DRV/COBI and emtricitabine/tenofovir alafenamide [F/TAF]) are already approved, respectively as PREZCOBIX® and DESCOVY®, and can be used in combination.

1.1. Overall Structure of the Summary of Virology

No new in vitro virology studies have been conducted with the D/C/F/TAF FDC. The in vitro virology development program of D/C/F/TAF is entirely based on data from the individual

components. A high-level summary of in vitro virology data obtained from the individual virology research programs, that were designed to provide information on the mechanism of drug action, in vitro antiviral activity (in combination with current HIV-1 inhibitors), and in vitro drug resistance of DRV, COBI, FTC, and TAF, is presented in Section 3, with references to the New Drug Applications (NDAs) of the individual components, DRV/COBI and F/TAF.

In Section 4, clinical resistance data from individual studies are analyzed and summarized. Data supporting the resistance profile of the D/C/F/TAF FDC tablet in adults are available from 2 pivotal Phase 3 studies and 1 supportive Phase 2 study. Based on matching pharmacokinetic (PK) results for the individual components of the FDC tablet in adolescents and adults, the D/C/F/TAF (800/150/200/10 mg) FDC tablet can be used for the treatment of HIV-1 infection in both adults and adolescents.

An overview of the relevant clinical studies supporting the D/C/F/TAF clinical resistance profile by study drug and by study population, including their design, is presented in Section 2, Table 1.

Adult Population

Clinical resistance data with the D/C/F/TAF FDC tablet in adults are available from the following 3 clinical studies:

- 2 ongoing pivotal Phase 3 studies (Week 48 primary analyses available) in:
  - HIV-1 infected, antiretroviral treatment (ART)-naïve subjects (TMC114FD2HTX3001); and
  - HIV-1 infected, ART-experienced, virologically-suppressed subjects (TMC114IFD3013).
- 1 completed supportive Phase 2 study in HIV-1 infected, ART-naïve subjects (GS-US-299-0102; primary Week 24 and final Week 48 analyses).

Adolescent Population (Aged ≥12 to <18 Years)

No data are available with the D/C/F/TAF FDC tablet in the adolescent population. However, 2 studies with the individual components of the FDC tablet in adolescents showed exposures matching the adult exposures in clinical studies (Mod2.7.2/ClinPharm/Sec2.2.3, NDA021976/Mod2.7.2/ClinPharm/Sec3.14.2 (June 2012)), and provided resistance data in adolescents:

- 1 completed Phase 2 study in HIV-1 infected, ART-naïve subjects with DRV/rtv (TMC114-C230; primary Week 24 and final Week 48 analyses)
- 1 ongoing Phase 2/3 study in HIV-1 infected, ART-naïve subjects with the E/C/F/TAF FDC (GS-US-292-0106; Week 48 analyses).

2. TABULATION OF VIROLOGY STUDIES SUPPORTING THE RESISTANCE PROFILE OF D/C/F/TAF

- An overview of In Vitro Virology Studies of DRV and COBI can be found in PREZCOBIX Summary of Virology (NDA205395/Mod2.7.2/VirSum/Sec3 (11 Oct 2013)).

- An overview of In Vitro Virology Studies of TAF, TDF, FTC, and TFV/FTC can be found in the Descovy Summary of Clinical Pharmacology Studies (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).

- An overview of Clinical Studies supporting the clinical resistance profile of the D/C/F/TAF can be found in Table 1.

Table 1: Tabulated Overview of the Phase 3 and 2 Studies Supporting the Clinical Resistance Profile of the D/C/F/TAF FDC Tablet

Study (Phase, Status)	Study Design	Number of Subjects[a] by Treatment Regimen[b]	Primary Endpoint	Analysis Time Point	Source Reference	Included in
D/C/F/TAF						
HIV-1 Infected, ART-naïve, Adult Subjects						
TMC114FD2HTX3001 (Phase 3, ongoing)	Randomized, active-controlled, double-blind study to evaluate efficacy and safety of D/C/F/TAF FDC vs DRV/COBI+F/TDF	D/C/F/TAF FDC (N=362) or DRV/COBI+F/TDF (N=363)	Virologic response defined as HIV-1 RNA <50 copies/mL at Week 48 per FDA snapshot; noninferiority with maximum allowable difference of 10%	Week 48	TMC114FD2HTX3001 Week 48 CSR	Mod2.7.3
GS-US-299-0102 (Phase 2, completed)	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+F/TDF	D/C/F/TAF FDC (N=103) or DRV+COBI+F/TDF (N=50)	Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per FDA snapshot; noninferiority with maximum allowable difference of 12%	Week 48	GS-US-299-0102 Final CSR	Mod2.7.3
HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects						
TMC114IFD3013 (Phase 3, ongoing)	Randomized, active-controlled, open-label study to evaluate the efficacy, safety, and tolerability of switching to D/C/F/TAF FDC vs continuing the current bPI combined with F/TDF	Switch to D/C/F/TAF FDC (N=763) or Stay on bPI[c] combined with F/TDF (N=378)	Virologic rebound cumulative through Week 48 (confirmed HIV-1 RNA ≥50 copies/mL, or with a last single HIV-1 RNA ≥50 copies/mL in case of early discontinuation); noninferiority with maximum allowable difference of 4%	Week 48	TMC114IFD3013 Week 48 CSR	Mod2.7.3
DRV						
HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)						
TMC114-C230 (Phase 2, completed)	Open-label, single-arm study to evaluate the PK, safety, tolerability, and efficacy of DRV/rtv in combination with AZT/3TC or ABC/3TC	DRV/rtv + ARV background regimen[d] (N=12)	PK of DRV and rtv Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per TLOVR	Week 48	NDA 021976	Mod2.7.3
COBI and F/TAF (Extrapolated From E/C/F/TAF)						
HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)						
GS-US-292-0106 (Phase 2/3, ongoing)	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 substudy N=24)	Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per FDA snapshot (PK of EVG, TAF, COBI, FTC, and TFV)	Week 48	Abram et al. 2016[1] Gaur AH et al. 2016[10]	Mod2.7.3

Footnotes are on the next page

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ARV = antiretroviral; ATV= atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; CSR = Clinical Study Report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; FTC = emtricitabine; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); HIV-1 = human immunodeficiency virus type 1; LPV = lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetics; rtv = low-dose ritonavir; TFV = tenofovir; TLOVR = time to loss of virologic response.

[a] Subjects included in the Intent-to-treat population.

[b] Study drugs were dosed as indicated in the respective Prescribing Information: D/C/F/TAF 800/150/200/10 mg; DRV 400 mg x2; COBI 150 mg; DRV/COBI 800/150 mg; F/TDF 200/300 mg; DRV/rtv 800/100 mg; and E/C/F/TAF 150/150/200/10 mg.

[c] The current bPI consisted of DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv, dosed as indicated in the local Prescribing Information.

[d] The ARV background regimen consisted of AZT/3TC or ABC/3TC, dosed as indicated in the local Prescribing Information.

3. IN VITRO VIROLOGY DATA

3.1. Darunavir

3.1.1. Mechanism of Action

Darunavir is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 PR. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Darunavir tightly binds to the HIV-1 PR with a K_D of $4.5x10^{-12}$ M and shows resilience to the effects of HIV PI RAMs. Darunavir is not an inhibitor of any of 13 tested human cellular PRs (NDA205395/Mod2.7.2/VirSum (2 Oct 2013)).

3.1.2. Antiviral Activity in Vitro

Results of in vitro virology studies showed that DRV is a potent and selective inhibitor of WT and mutant HIV-1 PRs. Darunavir exhibited activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV type 2 (HIV-2) in acutely infected T-cell lines, human peripheral blood mononuclear cells (PBMCs) and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrated antiviral activity in vitro against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from <0.1 to 4.3 nM. These EC_{50} values were well below the 50% cellular toxicity concentration range of 87 μM to >100 μM. The EC_{50} value of DRV increased by a median factor of 5.4 in the presence of human serum.

Darunavir did not show antagonism when studied in combination with the PIs amprenavir (APV), ATV, indinavir (IDV), LPV, nelfinavir (NFV), RTV, saquinavir (SQV), or tipranavir (TPV), NRTIs abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), TFV, zalcitabine, or zidovudine (AZT), the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine (DLV), efavirenz (EFV), etravirine (ETR), nevirapine (NVP), or rilpivirine (RPV) and the fusion inhibitor enfuvirtide (ENF) (NDA205395/Mod2.7.2/VirSum).

3.1.3. Resistance in Vitro

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

In vitro selection of DRV-resistant virus from WT HIV-1 was lengthy (>3 years). The selected viruses were unable to grow in the presence of DRV concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to DRV (range: 23- to 50-fold) harbored 2 to 4 amino acid substitutions in the PR gene. The decreased susceptibility to DRV of the emerging viruses in the selection experiment could not be explained by the emergence of these PR mutations.

In vitro selection of DRV-resistant HIV-1 (range: 53- to 641-fold change in EC_{50} values [FC]) from 9 HIV-1 strains harboring multiple PI RAMs resulted in the overall emergence of

22 mutations in the PR, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V and I84V were present in more than 50% of the 9 DRV-resistant isolates. A minimum of 8 of these DRV in vitro selected mutations, from which at least 2 were already present in the PR prior to selection, were required in the HIV-1 PR to render a virus resistant (FC >10) to DRV.

In 1,113 clinical isolates resistant to APV, ATV, IDV, LPV, NFV, RTV, SQV and/or TPV and in 886 baseline isolates from the subjects enrolled in the ART-experienced POWER 1 (TMC114-C213) and POWER 2 (TMC114-C202) studies and in the POWER 3 (TMC114-C215) analysis, only the subgroups with >10 PI RAMs showed a median FC for DRV >10 (NDA205395/Mod2.7.2/VirSum (2 Oct 2013)).

3.1.4. Cross-Resistance

Cross-resistance has been observed among HIV PIs. Darunavir has a <10-fold decreased susceptibility against 90% of 3,309 clinical isolates resistant to APV, ATV, IDV, LPV, NFV, RTV, SQV and/or TPV showing that viruses resistant to most PIs remain susceptible to DRV.

Seven of the 9 DRV-resistant viruses selected from PI-resistant viruses had phenotypic data for TPV. Six of those showed a FC <3 for TPV, indicative of limited cross-resistance between these 2 PIs.

Cross-resistance between DRV and the NRTIs, the NNRTIs, the entry inhibitors or the integrase inhibitor, is unlikely because the viral targets for those inhibitors are different (NDA205395/Mod2.7.2/VirSum).

3.2. Cobicistat

3.2.1. Mechanism of Action

COBI is a mechanism-based inhibitor of CYP of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure of CYP3A substrates, such as DRV, where bioavailability is limited and half-life is shortened due to CYP3A-dependent metabolism.

3.2.2. Antiviral Activity in Vitro

The antiviral activity of COBI was tested in PBMCs against a panel of HIV-1 and HIV-2 primary isolates. Different groups of HIV-1 (M, N, and O), as well as the most prevalent group M subtypes (A, B, C, D, E, F, and G), were represented among the tested isolates. Cobicistat exhibited no antiviral activity against the viral isolates tested. Consistent with in vitro studies in immortalized T-cell lines, these findings further support the conclusion that COBI is devoid of selective antiviral activity. The in vitro antiviral activity of COBI was also evaluated in a HIV-1 cytopathic assay in MT-2 cells. There was no inhibition (100% activity remaining) of HIV replication in the presence of 30 μM COBI relative to the untreated control. These data indicate that COBI exhibits no in vitro anti-HIV activity, consistent with its lack of in vitro inhibition of HIV PR (COBI did not have any effect on the HIV-1 PR enzymatic activity at concentrations up to 30 μM). COBI does not antagonize the antiviral effect of DRV, FTC, or TFV (NDA205395/Mod2.7.2/VirSum).

3.3. Emtricitabine

3.3.1. Mechanism of Action

FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form FTC-TP. FTC-TP inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. FTC-TP is a weak inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

3.3.2. Antiviral Activity in Vitro

The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC50 values for FTC were in the range of 0.0013–0.64 μM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC50 values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC50 values ranged from 0.007–1.5 μM).[8]

In a study of FTC with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, integrase strand transfer inhibitors [INSTIs], and PIs) no antagonism was observed for these combinations (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

3.3.3. Resistance in Vitro

HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

3.3.4. Cross-Resistance

FTC-resistant viruses with the M184V or I substitution were cross-resistant to 3TC, but retained sensitivity to ddI, d4T, TFV, and AZT.

Viruses harboring substitutions conferring reduced susceptibility to d4T and AZT-thymidine analog substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or ddI (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

3.4. Tenofovir Alafenamide

3.4.1. Mechanism of Action

TAF is a phosphonoamidate prodrug of TFV (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to TFV through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite TFV-DP. Tenofovir diphosphate inhibits HIV-1

replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.[8]

Tenofovir has activity against HIV-1. Cell culture studies have shown that both TFV and FTC 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 cell culture (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

3.4.2. Antiviral Activity in Vitro

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC50 values for TAF ranged from 2.0 to 14.7 nM.[8]

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC50 values ranged from 0.91 to 2.63 nM).[8]

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs) no antagonism was observed for these combinations. Also no antagonism was observed in combination with COBI (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

3.4.3. Resistance in Vitro

HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

3.4.4. Cross-Resistance

Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to ABC, ddI, FTC, 3TC, and TFV.

HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture (NDA208215/Mod2.7.2/ClinPharm/Sec4.1).[8]

4. CLINICAL VIROLOGY DATA

4.1. Resistance Assessments

Samples for HIV-1 genotypic/phenotypic resistance testing were taken at the time points specified in the Time and Events Schedule of the respective protocols (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Protocol Amendment 2, Mod5.3.5.1/GS-US-299-0102-Final-CSR/Protocol, Mod5.3.5.1/TMC114IFD3013-W48-CSR/Protocol Amendment 4, and NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Protocol). For information on Study GS-US-292-0106, see Abram et al[1] and Gaur et al.[10]

Plasma samples were sequenced and phenotyped at [redacted] ([redacted], USA) using the [redacted] (HIV-1 PR/RT genotype), [redacted] (HIV-1 PR/RT phenotype), [redacted] (combined HIV-1 PR/RT genotype/phenotype), [redacted] (HIV-1 PR/RT/IN genotype), or [redacted] (combined HIV-1 PR/RT/IN genotype/phenotype) assay. Except for the Study TMC114-C230, in which plasma samples were genotyped and phenotyped at [redacted] ([redacted], Belgium) using the [redacted] (HIV-1 PR/RT genotype) and [redacted] (HIV-1 PR/RT phenotype) assays, respectively. For an overview of the used genotyping/phenotyping assays by study/visit, see Table 2.

Genotypic analyses of the PR and RT genes (and the integrase for Study GS-US-292-0106 only) were conducted at screening (and baseline for Study TMC114-C230), except for the switch Study TMC114IFD3013 that enrolled ART-experienced, virologically suppressed subjects (Table 2).

As defined in the respective protocols, subjects were to have full genotypic sensitivity to study drugs at study enrollment. In study TMC114IFD3013, previous virologic failure (VF) on DRV was not allowed and in case historical genotypes were available, subjects with DRV RAMs were excluded.

Table 2: Genotyping and Phenotyping by Study/Visit

Resistance Assay	TMC114 FD2HTX3001			GS-US-299-0102			TMC114 IFD3013			TMC114-C230			GS-US-292-0106		
	SCR [a]	BL	Post-BL	SCR [a]	BL	Post-BL	SCR [b]	BL	Post-BL	SCR [a]	BL	Post-BL	SCR [a]	BL	Post-BL
[redacted]										X	X	X			
[redacted]											X	X			
[redacted]	X			X					X						
[redacted]									(X)[c]						
[redacted]			X			X									
[redacted]													X		
[redacted]															X

SCR = screening; BL = baseline; Post-BL = Post-Baseline; preferably confirmed (or otherwise un-confirmed) Virologic Failure or at later time points, including HIV-1 RNA ≥400 copies/mL at the study endpoint or study discontinuation

a As defined in the respective protocols, subjects were to have full genotypic sensitivity to study drugs at study enrollment.

b Subjects were HIV-1 RNA suppressed (HIV-1 RNA< 50 copies/mL) at study enrollment.

c Phenotyping was only potentially foreseen in case of observed post-baseline genotypic resistance.

Post-baseline resistance testing was performed on samples from subjects experiencing Protocol-defined Virologic Failure (PDVF); see Table 3 for the definition of PDVF.

Table 3: Definition of Protocol-defined Virologic Failure in the Studies Supporting D/C/F/TAF FDC

Protocol-defined Virologic Failure = Virologic Nonresponse/Virologic Rebound/Viremic at Final Time Point (Studies TMC114FD2HTX3001, GS-US-299-0102, GS-US-292-0106, and TMC114-C230)	
Virologic Nonresponse TMC114FD2HTX3001, GS-US-299-0102, and GS-US-292-0106.	HIV-1 RNA <1 log10 reduction from baseline (and ≥50 copies/mL) at the Week 8 visit, confirmed at the following scheduled or unscheduled visit following Week 8.
TMC114-C230[a]	On-study at Week 12 and never achieved 2 consecutive VL <50 copies/mL.
Virologic Rebound TMC114FD2HTX3001	At any visit, after achieving confirmed consecutive HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥50 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit;
GS-US-299-0102	At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA to ≥ 400 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit
GS-US-292-0106	At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA ≥ 50 copies/mL, which was subsequently confirmed and ≥ 400 copies/mL at the following scheduled or unscheduled visit
	Or
TMC114FD2HTX3001 GS-US-299-0102 GS-US-292-0106	At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir which was subsequently confirmed at the following scheduled or unscheduled visit.
TMC114-C230[a]	On-study at Week 12 and achieved 2 consecutive VL <50 copies/mL, followed by 2 consecutive VL ≥50 copies/mL.
Viremic at Final Time Point TMC114FD2HTX3001, GS-US-299-0102, GS-US-292-0106, and TMC114-C230[a]	Any subject with on-treatment HIV-1 RNA ≥400 copies/mL (or HIV-1 RNA ≥50 copies/mL for Study TMC114-C230) at the study endpoint or study discontinuation after Week 8[b]
Protocol-defined Virologic Failure = Virologic Rebound Cumulative Through Week 48 (Study TMC114IFD3013)	
Virologic Rebound TMC114IFD3013	Confirmed HIV-1 RNA ≥50 copies/mL up to, and including the upper bound of the Week 48 window (ie, 54 weeks). Premature discontinuation (irrespective of reason) for which the last available (single) HIV-1 RNA ≥50 copies/mL. In addition, any subject with last available on-treatment HIV-1 RNA ≥50 copies/mL at the study cut-off (Week 48) was considered a virologic rebounder.

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed dose combination; HIV-1 = human immunodeficiency virus type 1; PDVF = Protocol-defined Virologic Failure.

[a] TLOVR (non-virologic failure censored) algorithm.

[b] GS-US-299-0102 and GS-US-292-0106: Viremic at Final Time Point only in case not meeting any of the other PDVF criteria.

Resistance testing was conducted when HIV-1 RNA was ≥400 copies/mL, which is close to the validated lower limits of detection of the Monogram Biosciences assays (500 copies/mL), except for Study TMC114-C230 where attempts were made if the viral load was >50 copies/mL with a resistance assay cut-off of 1,000 HIV-1 RNA copies/mL.

When feasible, depending on the viral load, resistance testing was performed at the time of (preferably confirmed, or at unconfirmed) VF or at later time points. Post-baseline VF plasma samples were genotyped and phenotyped (Table 2). For TMC114IFD3013, phenotyping was only planned to further investigate in case of observed post-baseline genotypic resistance.

Resistance testing at other time points could additionally be requested by the protocol virologist.

4.2. Analysis Methodologies

Resistance analyses were performed on the intent-to-treat (ITT) population: All subjects who were randomized and received at least 1 dose of treatment in the study. In the Janssen Studies TMC114FD2HTX3001, TMC114IFD3013, and TMC114-C230, ITT terminology was used and post-baseline resistance testing was performed on samples from subjects experiencing PDVF (see Section 4.1). Similarly, in the Gilead studies resistance analyses were performed on any subject meeting the criteria of the resistance analysis population (RAP terminology was used). The RAP included any subject who received at least 1 dose of study drug, maintained their study drug regimen (or within 72 hours after interruption or discontinuation of study drugs), and met one of the PDVF criteria (see Section 4.1).

4.2.1. Genotype

Evaluation of screening/baseline and treatment-emergent RAMs, or the presence of on-treatment (Study TMC114IFD3013) RAMs, was based on PI, nucleos(t)ide reverse transcriptase inhibitor (N(t)RTI), NNRTI, and integrase inhibitor (Study GS-US-292-0106) IAS-USA mutation lists defined for each study:

- IAS-USA 2015 list was used in Studies TMC114FD2HTX3001 and TMC114IFD3013[23]
- IAS-USA 2010 list was used in Study TMC114-C230[13]
- A modified IAS-USA list was used in GS-US-299-0102 (Mod5.3.5.1/GS-US-299-0102 Final CSR/Tab9-4) and GS-US-292-0106[1]

The most recent IAS-USA 2015 list of protease and reverse transcriptase (RT) mutations is presented in Table 4.

Table 4: IAS-USA 2015 List of Protease Inhibitor and Reverse Transcriptase Inhibitor Mutations

PR mutations

- IAS-USA Primary PI resistance-associated mutations:

  D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M

- IAS-USA Secondary PI resistance-associated mutations:

  L10C/F/I/R/V, V11I, G16E, K20I/M/R/T/V, L24I, L33I/F/V, E34Q, M36I/L/V, K43T, F53L/Y, I54A/S/T/V, D60E, I62V, L63P, I64L/M/V, H69K/R, A71I/L/T/V, G73A/C/S/T, V77I, V82I, I85V, N88D, L89I/M/V, I93L/M

- IAS-USA DRV resistance-associated mutations:

  V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V

RT mutations

- IAS-USA NRTI resistance-associated mutations:

  M41L, A62V, K65R/E/N, D67N, 69ins, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, K219E/Q

- IAS-USA Thymidine Analogue Mutations (TAMs):

  M41L, D67N, K70R, L210W, T215Y/F, K219Q/E

- IAS-USA NNRTI resistance-associated mutations:

  V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/S, H221Y, P225H, F227C, M230I/L

- IAS-USA TFV resistance-associated mutations:

  K65R/E/N, K70E

- IAS-USA FTC resistance-associated mutations:

  K65R/E/N, M184I/V

DRV = darunavir; FTC = emtricitabine; IAS = International Antiviral Society; PR = protease; RT = reverse transcriptase; TFV = tenofovir; USA = United States of America.

There are no relevant differences between the study specific IAS-USA lists used. Some noteworthy differences are:

- N83D is considered a Secondary PI RAM in GS-US-299-0102 and GS-US-292-0106 modified IAS-USA list iso a Primary PI RAM in IAS-USA 2010 and 2015
- L33F in GS-US-299-0102 and GS-US-292-0106 and I54V only in GS-US-299-0102 modified IAS-USA is considered a Primary PI RAM iso a Secondary in IAS-USA 2010 and 2015
- K65E/N is considered an NRTI RAM in IAS-USA 2015, but not in the other lists
- E44D, T69D/N, L74I, V118I, K219N/R were included as NRTI RAMs in GS-US-299-0102 and GS-US-292-0106 modified IAS-USA list, but not in in IAS-USA 2010 and 2015

At screening/baseline, frequency of the individual amino acid changes and the mean/median, and number of specific amino acid changes in HIV-1 PR (including IAS-USA secondary and primary

PI RAMs), and RT (including IAS-USA NRTI RAMs and NNRTI RAMs), as well as specific mutations associated with resistance to DRV, FTC, and TDF/TAF were tabulated.

RAMs were considered developing (emerging) if they were detected post-baseline but not at screening (or baseline).

For more details, refer to the individual Statistical Analysis Plans (SAPs) in the appendices of the Clinical Study Reports (CSRs) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Statistical Analysis Plan, Mod5.3.5.1/GS-US-299-0102-Final-CSR/ Statistical Analysis Plan, Mod5.3.5.1/TMC114IFD3013-W48-CSR/Statistical Analysis Plan, and NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Statistical Analysis Plan). For more details on study GS-US-292-0106, see Abram et al[1] and Gaur et al.[10]

4.2.2. Phenotype

Based on the genotype and applied algorithms ([redacted], [redacted], [redacted], or [redacted]), assessments of ARV drug susceptibility (sensitive, resistance possible, or resistant) were made and tabulated (= predicted phenotype).

When applicable (Table 2), true phenotypic resistance to ARVs was determined, based on the fold change (FC) in the 50% effective concentration in cell-based assays (EC_{50}). Each drug was categorized into sensitive/partially sensitive/resistant based on cut-off values on the [redacted], [redacted], or [redacted] report:

When one cut-off value is available, a drug is considered:

- Sensitive if the FC is below or equal to the clinical cut-off (CCO) when available or below or equal to the biological cut-off (BCO) otherwise;
- Resistant if the FC is above the CCO or BCO.

When two cut-off values are available, a drug is considered:

- Sensitive if the FC is below or equal to the lower cut-off;
- Partially sensitive if the FC is above the lower cut-off and below or equal to the higher cut-off;
- Resistant if the FC is above the higher cut-off.

BCOs and CCOs for the [redacted] phenotyping assay are provided in Table 5 (cut-offs of the older [redacted] report varied slightly).

Table 5: Biological Cut-offs and Clinical Cut-offs for the [redacted] Phenotyping Assay

Class	Drug	Generic name	Cut-off [redacted] (Plus Integrase) (V7045/V7145)
NRTI	AZT	Zidovudine	1.9
	3TC	Lamivudine	**3.5**
	ddI	Didanosine	**1.3 – 2.2**
	d4T	Stavudine	**1.7**
	ABC	Abacavir	**4.5 – 6.5**
	FTC	Emtricitabine	3.5
	TDF	Tenofovir	**1.4 – 4.0**
NNRTI	NVP	Nevirapine	4.5
	DLV	Delavirdine	6.2
	EFV	Efavirenz	3.0
	ETR	Etravirine	**2.9 – 10.0**
	RPV	Rilpivirine	2.0
PI	ATV	Atazanavir	**2.2**
	ATV/rtv	Boosted Atazanavir	**5.2**
	DRV/rtv	Boosted Darunavir	**10.0 – 90.0**
	APV/rtv or fAPV/rtv	Boosted Amprenavir or fosamprenavir	**4.0 – 11.0**
	IDV/rtv	Boosted Indinavir	**10.0**
	LPV/rtv	Boosted Lopinavir (Kaletra)	**9.0 – 55.0**
	NFV	Nelfinavir	3.6
	RTV	Ritonavir	2.5
	SQV/rtv	Boosted Saquinavir	**2.3 – 12.0**
	TPV/rtv	Boosted Tipranavir	**2.0 – 8.0**

Clinical cut-offs are shown in bold; cut-offs are based on the [redacted] algorithm

4.3. Resistance in HIV-1 Infected Adult Subjects

4.3.1. Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve Adult Subjects

4.3.1.1. Study Synopses

Study narrative is provided in Mod2.7.3/App1.

4.3.1.2. Antiviral Activity

At Week 48, the virologic response rate (HIV-1 RNA <50 copies/mL; FDA snapshot approach; primary endpoint) was similar in both treatment groups: 91.4% (331/362) in the D/C/F/TAF group vs 88.4% (321/363) in the control group. D/C/F/TAF was noninferior to the control (ie, lower limit of the stratified MH 95% CI >-10%): treatment difference (95% CI) in virologic response between D/C/F/TAF - control was 2.7 (-1.6; 7.1); corresponding one-sided noninferiority p-value <0.001. For more information, refer to Mod2.7.3/Sec3.1.1.

4.3.1.3. Resistance Data

An overview of the guidance for management of subjects in Study TMC114FD2HTX3001 meeting the criteria for VF and for resistance testing is provided in Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Protocol/Sec9.2.2.

4.3.1.3.1. Baseline Resistance

Genotypes (PR and RT) were generated for all subjects at screening.

The majority of subjects in both treatment groups were infected with HIV-1 subtype B (71.7% and 70.7%).

The prevalence of PI, NRTI, and NNRTI RAMs at screening was as expected in a treatment-naïve population and was balanced between treatment groups (Table 6). A low percentage of viruses harbored ≥1 DRV RAMs (6 with V11I and 1 with L33F) or primary PI RAMs (1.0% and 2.1%, respectively). Secondary PI RAMs were observed in almost all subjects (97.9%; with a median of 4 and a range from 0-8), reflecting the polymorphic nature of these mutations. For RT, NRTI and NNRTI RAMs were detected in 4.7% and 16.3% of the subjects respectively, with K103N being the most prevalent mutation (3.6%). No resistance mutations related to FTC or TDF/TAF were detected.

This mutation profile is reflected in the genotypic susceptibility assessments based on the [redacted] assay. As depicted by the protocol all subjects showed 100% susceptibility to DRV, FTC and TFV. In 10% of the patients NNRTI resistance was observed, mainly due to NVP and EFV resistance (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec 5.5.1).

Table 6: Prevalence of Mutations at Screening; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF	Control	Total
Analysis set: Intent-to-treat, N	362	363	725
Subjects with genotype at screening, N	361[b]	362[b]	723
Genotypic Susceptibility to, n(%):			
DRV/rtv	361 (100.0%)	362 (100.0%)	723 (100.0%)
FTC	361 (100.0%)	362 (100.0%)	723 (100.0%)
TFV	361 (100.0%)	362 (100.0%)	723 (100.0%)
All NNRTIs	327 (90.6%)	324 (89.5%)	651 (90.0%)
All NRTIs	353 (97.8%)	357 (98.6%)	710 (98.2%)
All PIs	335 (92.8%)	338 (93.4%)	673 (93.1%)
Subtype, n(%):			
A	14 (3.9%)	10 (2.8%)	24 (3.3%)
A1	20 (5.5%)	33 (9.1%)	53 (7.3%)
AE	5 (1.4%)	5 (1.4%)	10 (1.4%)
AG	19 (5.3%)	16 (4.4%)	35 (4.8%)
B	259 (71.7%)	256 (70.7%)	515 (71.2%)
C	5 (1.4%)	11 (3.0%)	16 (2.2%)
COMPLEX[c]	19 (5.3%)	22 (6.1%)	41 (5.7%)
Other[d]	20 (5.5%)	9 (2.5%)	29 (4.0%)
≥1 DRV RAMs[a], n(%):	3 (0.8%)	4 (1.1%)	7 (1.0%)
Mean	0.0	0.0	0.0
Median (Min; Max)	0.0 (0; 1)	0.0 (0; 1)	0.0 (0; 1)
V11I	2 (0.6%)	2 (0.6%)	4 (0.6%)
V11V/A/I/T	0	1 (0.3%)	1 (0.1%)
V11V/I	1 (0.3%)	0	1 (0.1%)
L33F	0	1 (0.3%)	1 (0.1%)

Table 6: Prevalence of Mutations at Screening; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF	Control	Total
DRV RAMs, n(%):			
0	358 (99.2%)	358 (98.9%)	716 (99.0%)
1	3 (0.8%)	4 (1.1%)	7 (1.0%)
≥1 Primary PI RAMs[a], n(%):	7 (1.9%)	8 (2.2%)	15 (2.1%)
Mean	0.0	0.0	0.0
Median (Min; Max)	0.0 (0; 1)	0.0 (0; 2)	0.0 (0; 2)
M46M/I	0	2 (0.6%)	2 (0.3%)
M46M/I/L	0	1 (0.3%)	1 (0.1%)
Q58E	2 (0.6%)	2 (0.6%)	4 (0.6%)
Q58Q/E	2 (0.6%)	2 (0.6%)	4 (0.6%)
V82L	1 (0.3%)	0	1 (0.1%)
L90M	2 (0.6%)	1 (0.3%)	3 (0.4%)
Primary PI RAMs, n(%):			
0	354 (98.1%)	354 (97.8%)	708 (97.9%)
1	7 (1.9%)	7 (1.9%)	14 (1.9%)
2	0	1 (0.3%)	1 (0.1%)
≥1 Secondary PI RAMs[a], n(%):	354 (98.1%)	354 (97.8%)	708 (97.9%)
Mean	3.6	3.8	3.7
Median (Min; Max)	4.0 (0; 8)	4.0 (0; 8)	4.0 (0; 8)
M36I	149 (41.3%)	155 (42.8%)	304 (42.0%)
I62V	98 (27.1%)	91 (25.1%)	189 (26.1%)
L63P	151 (41.8%)	140 (38.7%)	291 (40.2%)
H69K	87 (24.1%)	96 (26.5%)	183 (25.3%)
V77I	98 (27.1%)	109 (30.1%)	207 (28.6%)
L89M	82 (22.7%)	89 (24.6%)	171 (23.7%)
I93L	153 (42.4%)	150 (41.4%)	303 (41.9%)
Secondary PI RAMs, n(%):			
0	7 (1.9%)	8 (2.2%)	15 (2.1%)
1-2	81 (22.4%)	80 (22.1%)	161 (22.3%)
3-4	174 (48.2%)	142 (39.2%)	316 (43.7%)
5-8	99 (27.4%)	132 (36.5%)	231 (32.0%)
≥1 NRTI RAMs[a], n(%):	18 (5.0%)	16 (4.4%)	34 (4.7%)
Mean	0.1	0.0	0.1
Median (Min; Max)	0.0 (0; 2)	0.0 (0; 2)	0.0 (0; 2)
M41L	2 (0.6%)	2 (0.6%)	4 (0.6%)
M41M/L	1 (0.3%)	0	1 (0.1%)
A62A/V	0	1 (0.3%)	1 (0.1%)
A62V	10 (2.8%)	10 (2.8%)	20 (2.8%)
D67N	2 (0.6%)	1 (0.3%)	3 (0.4%)
K70K/R	0	1 (0.3%)	1 (0.1%)
V75I	1 (0.3%)	0	1 (0.1%)
L210W	2 (0.6%)	1 (0.3%)	3 (0.4%)
K219Q	2 (0.6%)	1 (0.3%)	3 (0.4%)
NRTI RAMs, n(%):			
0	343 (95.0%)	346 (95.6%)	689 (95.3%)
1	16 (4.4%)	15 (4.1%)	31 (4.3%)
2	2 (0.6%)	1 (0.3%)	3 (0.4%)

Table 6: Prevalence of Mutations at Screening; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF	Control	Total
≥1 NNRTI RAMs[a], n(%):	55 (15.2%)	63 (17.4%)	118 (16.3%)
Mean	0.2	0.2	0.2
Median (Min; Max)	0.0 (0; 4)	0.0 (0; 2)	0.0 (0; 4)
V90I	9 (2.5%)	9 (2.5%)	18 (2.5%)
K103N	12 (3.3%)	14 (3.9%)	26 (3.6%)
V106I	7 (1.9%)	11 (3.0%)	18 (2.5%)
E138A	11 (3.0%)	12 (3.3%)	23 (3.2%)
E138E/A	1 (0.3%)	4 (1.1%)	5 (0.7%)
V179D	4 (1.1%)	2 (0.6%)	6 (0.8%)
NNRTI RAMs, n(%):			
0	306 (84.8%)	299 (82.6%)	605 (83.7%)
1	48 (13.3%)	57 (15.7%)	105 (14.5%)
2	5 (1.4%)	6 (1.7%)	11 (1.5%)
≥ 3	2 (0.6%)	0	2 (0.3%)

The denominator is subjects with genotype at screening.
Genotypic Susceptibility assessment based on the [redacted] report.
[a] IAS-USA 2015 mutation list.[13]
[b] 1 subject in each treatment group had no screening genotypes, but were enrolled based on local genotypes.
[c] Subtype is assigned to Complex when the sequence contains 3 or more subtypes and/or Circulating Recombinant Forms (CRFs).
[d] Other subtypes include AB, BC, BF, D F, F1, F2, G
Secondary PI RAMs < 20% of the subjects are not shown. NNRTI RAMs < 1% of the subjects are not shown.
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab17

There were no differences in virologic response rate (<50 HIV-1 RNA copies/mL) at Week 48 between the treatment groups in any of the subgroups by HIV-1 subtype (B, non-B) and by baseline resistance factors (presence of primary PI and/or DRV RAMs, NRTI RAMs, NNRTI RAMs, M184V/I and number of primary and secondary PI RAMs) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.3). Out of the 7 subjects with a DRV RAM at screening, 6 had HIV RNA <50 copies/mL at week 48 and 1 discontinued due to other reason and the last available HIV RNA <50 copies/mL (according to the snapshot approach).

4.3.1.3.2. Development of Resistance

Post-baseline resistance testing was performed on samples from subjects experiencing PDVF (virologic nonresponse, virologic rebound, and/or viremic at final time point; see Section 4.1) and who had HIV-1 RNA ≥400 copies/mL at failure or at later time points. At Week 48, 8 subjects (2.2%) in the D/C/F/TAF group and 6 subjects (1.7%) in the control group showed PDVF, with virologic rebound criterion occurring the most. The categorical subdivision of PDVF is presented in Table 7 along with its outcome using the FDA snapshot approach.

Table 7: Cross-tabulation of Protocol-defined Virologic Failure versus Snapshot Algorithm (<50 Copies/mL) at Week 48; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF (N=362)				Control (N=363)			
	Snapshot Approach Week 48				Snapshot Approach Week 48			
	Virologic Success	Virologic Failure[a]	Missing Viral Load[b]	Total	Virologic Success	Virologic Failure[a]	Missing Viral Load[b]	Total
Protocol-defined virologic failure, n (%)	2 (0.6%)	6 (1.7%)	0	**8 (2.2%)**	2 (0.6%)	2 (0.6%)	2 (0.6%)	**6 (1.7%)**
- Virologic rebound, n (%)	2 (0.6%)	1 (0.3%)	0	**3 (0.8%)**	2 (0.6%)	1 (0.3%)	0	**3 (0.8%)**
- Virologic non-response, n (%)	0	0	0	**0**	0	0	0	**0**
- Viremic at final time point, n (%)	0	2 (0.6%)	0	**2 (0.6%)**	0	0	2 (0.6%)	**2 (0.6%)**
- Virologic rebound and Viremic at final time point, n (%)	0	1 (0.3%)	0	**1 (0.3%)**	0	1 (0.3%)	0	**1 (0.3%)**
- Virologic rebound, Virologic non-response and Viremic at final time point, n (%)	0	2 (0.6%)	0	**2 (0.6%)**	0	0	0	0

[a] Includes HIV RNA ≥50 copies/mL at Week 48, virologic failure leading to discontinuation and discontinued due to other reason and last available HIV RNA ≥50 copies/mL by snapshot approach.
[b] Includes discontinued due to AE/death, discontinued due to other reason and the last available HIV RNA <50 copies/mL (or missing), and missing data during window but on study by snapshot approach.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab18

Paired screening and post-baseline on-treatment genotypes were available for 7 subjects with PDVF in the D/C/F/TAF group and 2 in the control group. Individual viral load profiles of PDVF (with an 'x' marking the genotype/phenotype time point) are provided in Figure 1. None of these subjects developed DRV or primary PI RAMs. One subject in the D/C/F/TAF group developed a secondary PI RAM I62I/V. One subject (D/C/F/TAF group) developed an NRTI RAM at Week36 (Figure 1, subject [redacted]): ie, FTC RAM M184M/I/V, conferring phenotypic resistance to 3TC and FTC (Table 8 and Table 9). Observed DRV plasma concentrations for this subject were low and much lower than the anticipated DRV steady-state C0h for this subject (~692 ng/mL), which might indicate that the subject did not take the medication regularly as recommended. The subject was discontinued from the study due to noncompliance after the Week 48 database lock. Interestingly, this subject harbored a K103N mutation at screening, indicating transmitted NNRTI (EFV and NVP) resistance. All other subjects remained susceptible to all the drugs in the treatment regimen, based on the genotypic/phenotypic assessments of the [redacted] assay (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.5.2).

Three subjects in the D/C/F/TAF group and 2 subjects in the control group, who did not meet the definition of PDVF, had post-baseline off-treatment genotype data. One of the 3 subjects in the D/C/F/TAF group developed a secondary PI RAM I64I/L/M (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.5.2 and for the subject's viral load graphs see Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att2).

Table 8: Development of Mutations Post-baseline for Subjects with Protocol-defined Virologic Failure With On-treatment Genotypes; ITT (Study TMC114FD2HTX3001)

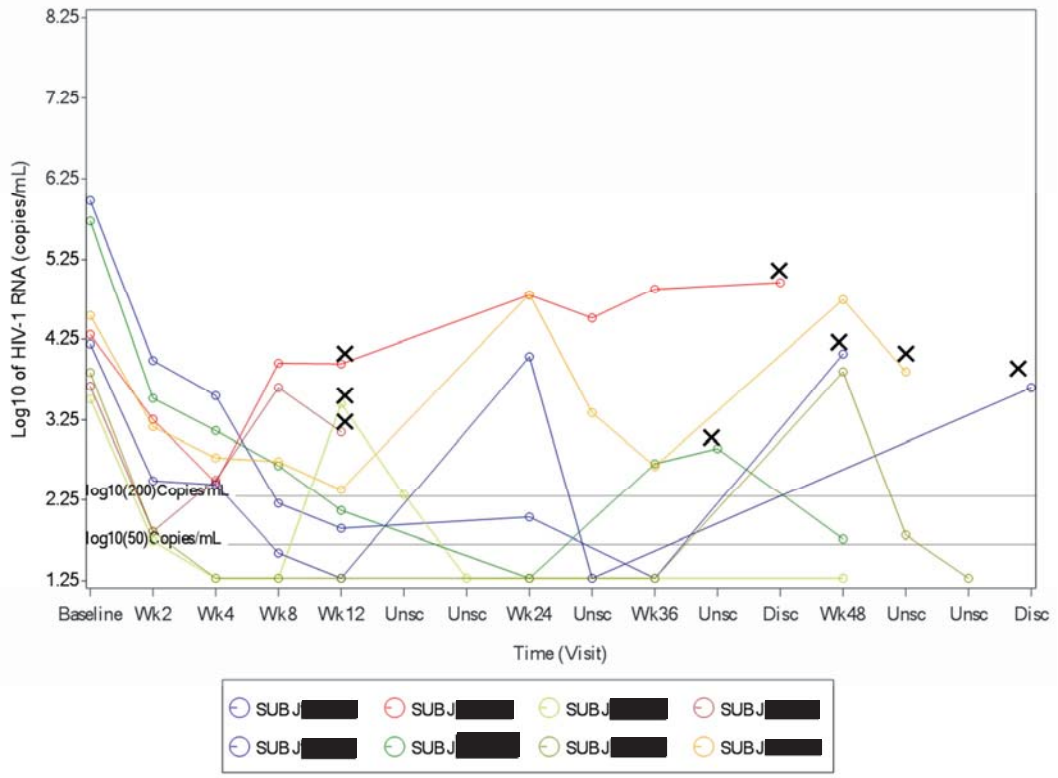
	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	362	363
Total number of virologic failures with screening and endpoint genotype, n	7	2
Subjects developing mutations[a] post-baseline[b], n		
DRV RAMs	0	0
Primary PI RAMs	0	0
Secondary PI RAMs	1	0
I62I/V	1	
NRTI RAMs	1	0
M184M/I/V	1	
NNRTI RAMs	0	0

[a] IAS-USA 2015 mutation list.[13]
[b] At unconfirmed or confirmed virologic failure or later time point(s).

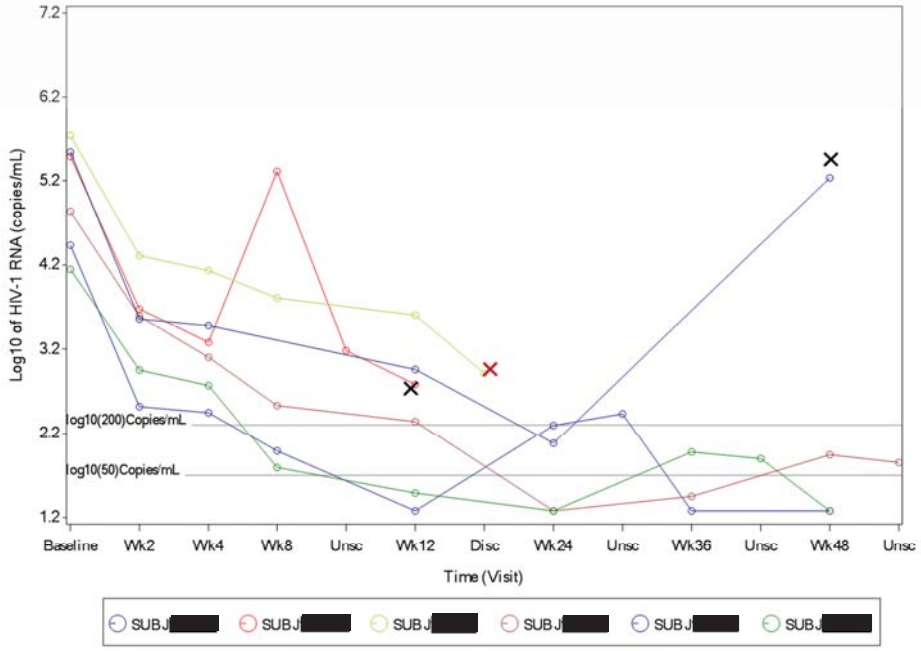
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab19

Figure 1: Individual Viral Load Profiles for Subjects with Protocol-defined Virologic Failure; ITT (Study TMC114FD2HTX3001)

D/C/F/TAF group



Control group



Note: X marks time point of genotype/phenotype; a red X indicates no genotype could be generated.

Source: Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Fig10

Table 9: Listing of Subjects with Protocol-defined Virologic Failure and Post-Baseline Genotype Data; ITT (Study TMC114FD2HTX3001)

Subject ID	Week 48 Snapshot Outcome	Virology Analysis Outcome [a]	Visit	HIV-1 RNA	HIV-1 Subtype	PI RAMs [b]	Emerging PI RAMs	NRTI/NNRTI RAMs [c]	Emerging NRTI/NNRTI RAMs
Treatment Group = D/C/F/TAF									
[redacted]	≥50 copies/mL	VIR	Screening	1090000	B	G16E[2] D60E[2] L63P[2] I93L[2]		-	
			Week 48	11700	B	G16E[2] D60E[2] L63P[2] I93L[2]	-	-	-
[redacted]	≥50 copies/mL	VIR / NR / RB	Screening	19900	B	K20M[2] L33V[2] M36L[2] I62V[2] I64V[2]		K103N[5]	
			Week 12	8810	B	K20M[2] L33V[2] M36L[2] I62V[2] I64V[2]	-	K103N[5]	-
			Week 36	75400	B	K20M[2] L33V[2] M36L[2] I62V[2] I64V[2]	-	K103N[5] M184M/I[4,8]/V[,4,8]	M184I[4,8]/V[,4,8]
[redacted]	<50 copies/mL	RB	Screening	6510	B	M36I[2]		-	
			Week 12	2840	B	M36I[2]	-	-	-
[redacted]	Virologic failure - discontinued due to other reason and last available HIV RNA ≥50 copies/mL	VIR / NR / RB	Screening	5620	B	M36M/I[2] I62V[2] V82I[2]		K103N[5]	
			Week 12	1260	B	M36M/I[2] I62V[2] V82I[2]	-	K103N[5]	-
[redacted]	≥50 copies/mL	VIR	Screening	9160	COMPLEX	M36I[2]		-	
			Week 48	4470	COMPLEX	M36I[2]	-	-	-
[redacted]	≥50 copies/mL	RB	Screening	1640000	B	G16G/E[2] M36I[2] I62V[2]		-	
			Week 36	787	B	G16E[2] M36I[2] I62V[2]	-	-	-
[redacted]	≥50 copies/mL	VIR / RB	Screening	92200	COMPLEX	K20K/R[2] M36I[2] Q58Q/E[1] H69K[2] L89M[2]		-	
			Week 24	2180	A1	K20R[2] M36I[2] Q58Q/E[1] I62I/V[2] H69K[2] L89M[2]	I62V[2]	-	-
			Week 48	7070	A1	K20K/R[2] M36I[2] Q58Q/E[1] H69K[2] L89M[2]	-	-	-
Treatment Group = Control									
[redacted]	Discontinued due to AE/death	VIR	Screening	365000	B	L10L/V[2] G16E[2] M36I[2]		E138A[5]	
			Week 12	606	B	L10L/V[2] G16E[2] M36I[2]	-	E138A[5]	-
[redacted]	≥50 copies/mL	VIR / RB	Screening	267000	COMPLEX	M36I[2] D60D/E[2] I64I/L[2]		-	
			Week 48	173000	BF	M36I[2] D60D/E[2] I64I/L[2]	-	-	-
[redacted]	Discontinued due to AE/death	VIR	Screening	1570000	COMPLEX	K20I[2] M36I[2] H69K[2] V82I[2] L89M[2]		-	
			Week 24	811	-	No sequence could be generated		No sequence could be generated	

Footnotes are on the next page

[a] RB= rebound, NR= non-response, VIR= viremic at final time point (any subject with on-treatment HIV-1 RNA ≥400 copies/mL at the study endpoint or study discontinuation after week 8 [and who did not meet any of the previous criteria]).
[b] PR Sequence (IAS-USA 2015): [1]Primary PI mutations; [2]Secondary PI mutations; [3]DRV resistance-associated mutations (not observed).
[c] RT Sequence IAS-USA 2015): [4]NRTI resistance-associated mutations; [5]NNRTI resistance-associated mutations; [6]Thymidine Analogue Mutations (TAMs) (not observed); [7]TFV resistance-associated mutations (not observed);[8]FTC resistance-associated mutations.
Subtype is assigned to Complex when the sequence contains 3 or more subtypes and/or Circulating Recombinant Forms (CRFs).

Source: Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab20

4.3.2. Phase 2 Study GS-US-299-0102 in HIV-1 Infected, ART-naïve Adult Subjects

4.3.2.1. Study Synopses

Study narrative is provided in Mod2.7.3/App1.

4.3.2.2. Antiviral Activity

D/C/F/TAF was determined to be noninferior to DRV+COBI (cobicistat) with F/TDF in terms of virologic response rate (HIV-1 RNA <50 copies/mL, FDA snapshot approach) at Week 24. Virologic response rates (HIV-1 RNA <50 copies/mL, FDA snapshot approach) at Week 24 were: 74.8% (77/103) in the D/C/F/TAF group vs 74.0% (37/50) in the DRV+COBI+F/TDF group. At week 48, the virologic response rate was 76.7% (79/103) in the D/C/F/TAF group vs 84.0% (42/50) in the DRV+COBI+F/TDF group (Mod5.3.5.2/GS-US-292-0102-W48-CSR/Tab9-1 and Tab9-2). For more information, refer to Mod2.7.3/Sec3.1.2.

4.3.2.3. Resistance Data

4.3.2.3.1. Baseline Resistance

A PR/RT genotyping report was obtained at screening for all subjects enrolled in the study to confirm genotypic sensitivity to DRV, TDF, and FTC. All subjects enrolled showed full genotypic sensitivity to DRV, FTC, and TDF, as stated in the protocol.

The prevalence of baseline PR and reverse RT resistance mutations was as expected in an ART-naïve population and balanced between treatment arms. Most subjects enrolled in the study (97.4%) had HIV-1 harboring secondary PI RAMs, reflecting the strong polymorphic nature of these mutations. Low level transmitted PI resistance was observed; 8 subjects had 1 or more primary PI RAM and 6 subjects had 1 DRV RAM at screening (4 L33F, I50L/V, and I54L/M), which did not adversely influence treatment response. Also, 9.8% of subjects were found to harbor HIV-1 with NRTI RAMs with the V118I being the most prevalent (6.5%). NNRTI RAMs were found in nearly 20% of subjects at screening, with the K103N/S mutation being the most prevalent (10.5%) (Table 10).

Overall 97% harbored HIV-1 subtype B.

Table 10: Prevalence of Mutations at Baseline; ITT (Study GS-US-299-0102)

	D/C/F/TAF	DRV+COBI+F/TDF	All
Analysis set: ITT, N	103	50	153
Subjects with genotype at screening, N	103	50	153
Subtype, n (%)			
B HIV-1	99 (96.1%)	49 (98%)	149 (97.4%)
Non-B HIV-1[a]	4 (3.9%)	0	4 (2.6%)
≥1 Primary PI-RAMs[b], n (%)	5 (4.9%)	3 (6%)	8 (5.2%)
Average Primary PI RAMs	1.2	1.0	1.1
L33F	1 (1%)	3 (6%)	4 (2.6%)
M46I/L	1 (1%)	0	1 (0.7%)
I50L/V	1 (1%)	0	1 (0.7%)
I54L/M/V	1 (1%)	0	1 (0.7%)
V82A/F/L/S/T	1 (1%)	0	1 (0.7%)
L90M	1 (1%)	0	1 (0.7%)
≥1 DRV RAMs, n (%):	3[c] (2.9%)	3[d] (6%)	6 (4.0%)
≥1 Secondary PI-RAMs[b], n (%)	101 (98.1%)	48 (96%)	149 (97.4%)
Average Secondary PI RAMs	3.5	3.2	3.4
M36I/L/V	37 (35.9%)	15 (30%)	52 (34%)
I62V	35 (34%)	18 (36%)	53 (34.6%)
L63P	59 (57.3%)	28 (56%)	87 (56.9%)
I64L/M/V	27 (26.2%)	21 (42%)	48 (31.4%)
V77I	41 (39.8%)	13 (26%)	54 (35.3%)
I93L/M	44 (42.7%)	12 (24%)	56 (36.6%)
≥1 NNRTI-RAMs[b], n (%):	20 (19.4%)	10 (20%)	30 (19.6%)
Average NNRTI RAMs	1.2	1.2	1.2
V90I	3 (2.9%)	0	3 (2%)
K103N/S	13 (12.6%)	3 (6%)	16 (10.5%)
V106A/I/M	1 (1%)	3 (6%)	4 (2.6%)
E138A/G/K/Q/R	2 (1.9%)	1 (2%)	3 (2%)
V179D/F/L/T	2 (1.9%)	1 (2%)	3 (2%)
≥1 NRTI RAMs[b], n (%):	14 (13.6%)	1 (2%)	15 (9.8%)
Average NRTI RAMs	1.0	1.0	1.0
T69D/N	2 (1.9%)	0	2 (1.3%)
V118I	9 (8.7%)	1 (2%)	10 (6.5%)
L210W	2 (1.9%)	0	2 (1.3%)
T215F/Y	1 (1%)	0	1 (0.7%)

[a] Non-B HIV-1 subtype distribution: AG, 1; C, 2; Complex, 1.
[b] Modified IAS-USA list (see 4.2.1)
[c] L33F, I50L/V, I54L/M
[d] 3 L33F
Source: Mod5.3.5.1/GS-US-299-0102 Final CSR/Tab9-4

4.3.2.3.2. Development of Resistance

Eight subjects were eligible for post-baseline resistance testing, including 7 who experienced confirmed virologic rebound and 1 with unconfirmed virologic rebound at the last study visit. Of these 8 subjects, 6 were in the D/C/F/TAF group (5.8%, 6 of 103 subjects), and 2 were in the DRV+COBI+F/TDF group (4.0%, 2 of 50 subjects).

The development of resistance to any of the components of the ARV regimens used in the study was rare. None of the 8 subjects developed primary PI or DRV RAMs through Week 48. One subject in the D/C/F/TAF arm had NRTI RAMs emerging (K65K/R and M184M/I) post Week 48 (Table 11). 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.

Out of the 7 remaining subjects with no resistance emerging, 2 subjects had HIV-1 RNA re-suppressed <50 copies/mL after resistance analysis, 2 subjects were discontinued for noncompliance, 2 subjects were lost to follow-up, and 1 subject with evidence of transmitted drug resistant HIV-1 at baseline (mutations I50L and V82M in PR, and K103N, L210W, and T215C in RT) completed the study with a viral load profile suggesting treatment noncompliance.

Table 11: Development of Mutations Post-baseline for Subjects with Protocol-defined Virologic Failure With On-treatment Genotypes; ITT (Study GS-US-299-0102)

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	103	50
Total number of virologic failures with screening and endpoint genotype, n	6	2
Subjects developing mutations[a] post-baseline, n		
DRV RAMs	0	0
Primary PI RAMs	0	0
NRTI RAMs	1	0
K65K/R	1	0
M184M/I	1	0
NNRTI RAMs	0	0

[a] Modified IAS-USA list (see 4.2.1)
Source: Mod5.3.5.1/GS-US-299-0102 Final CSR

4.3.3. Phase 3 Study TMC114IFD3013 in HIV-1 Infected, ART-experienced, Virologically Suppressed Adult Subjects

4.3.3.1. Study Synopses

Study narrative is provided in Mod2.7.3/App1.

4.3.3.2. Antiviral Activity

The protocol-defined virologic rebound (≥50 HIV-1 RNA copies/mL) rate cumulative through Week 48 in the ITT analysis set (primary efficacy endpoint) was low and similar in both

treatment groups: 2.5% (19/763) in the D/C/F/TAF group vs 2.1% (8/378) in the control group. D/C/F/TAF was noninferior to the control (ie, upper limit of the stratified MH 95% CI <4%): treatment difference (95% CI) D/C/F/TAF - control was 0.4 (-1.5;2.2); corresponding one-sided noninferiority p-value <0.001.

Using the HIV-1 RNA ≥200 copies/mL threshold, protocol-defined virologic rebound rate was 0.4% (ie, 3 subjects) in the D/C/F/TAF group; there were no virologic rebounders (HIV-1 RNA ≥200 copies/mL) through Week 48 in the control group

At Week 48, the virologic response rate (HIV-1 RNA <50 copies/mL) in the ITT analysis set per FDA snapshot approach in the D/C/F/TAF and the control group was high and similar (ie, approximately 94% in both treatment groups). The virologic failure rate was very low (<1.0%) in each treatment group with a difference (95% CI) in virologic failure rate at Week 48 between D/C/F/TAF and control of 0.3 (-0.7; 1.2).

In the D/C/F/TAF group, 12 out of the 19 rebounders (primary efficacy endpoint) were re-suppressed and considered responders at Week 48 (HIV-1 RNA <50 copies/mL) by the FDA snapshot approach. In the control group, 4 out of the 8 rebounders (primary endpoint) were re-suppressed and considered responders at Week 48 (HIV-1 RNA <50 copies/mL) by the FDA snapshot approach.

For more information, refer to Mod2.7.3/Sec3.1.3.

4.3.3.3. Resistance Data

4.3.3.3.1. Baseline Resistance

Study TMC114IFD3013 enrolled ART-experienced, virologically suppressed subjects (HIV-1 RNA copies/mL <50 at screening) and therefore no screening genotypes could be generated. Previous VF on DRV was not allowed and in case historical genotypes were available, subjects with DRV RAMs were excluded.

One subject with a V11I DRV RAM reported on a historical genotype was randomized and had HIV-1 RNA <50 copies/mL throughout the study until week 36, after which the subject was lost to follow-up.

4.3.3.3.2. Development of Resistance

An overview of the guidance for management of subjects in Study TMC114IFD3013 meeting the criteria for virologic rebound and for resistance testing is provided in Mod5.3.5.1/TMC114IFD3013-W48-CSR/Protocol/Sec9.3 and Attachment 1.

Due to the low proportion of rebounders of which the majority had relatively low viral load values, few samples were eligible for post-baseline genotyping (resistance testing performed when HIV-1 RNA ≥400 copies/mL). One rebounder in the D/C/F/TAF group and 3 rebounders in the control group had post-baseline genotypes. Viral load profiles for subjects with virologic rebound (HIV-1 RNA ≥50 copies/mL) are shown in Figure 2.

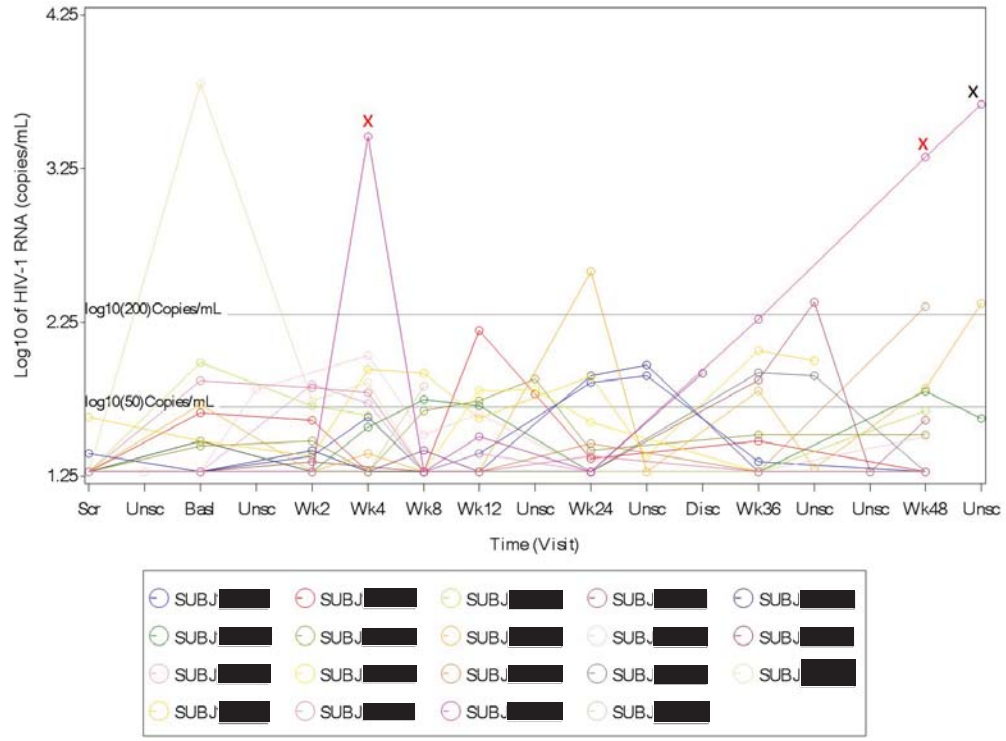
No DRV, primary PI, TFV, or FTC RAMs were observed (Table 12 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.6).

For these 4 post-baseline PR and RT sequences the predicted phenotypic assessment (based on the [redacted] assay) for all commercially available PIs, N(t)RTIs and NNRTIs is available in Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.6. All subjects had HIV-1 virus scored as susceptible to all the drugs in the treatment regimen. One subject had an NNRTI RAM E138E/G, conferring resistance to RPV (not related to any of the study drugs).

Two subjects in D/C/F/TAF group who did not show virologic rebound (according to the FDA snapshot approach these 2 subjects were marked as 'no viral load data in Week-48 window') had off-treatment genotypes at their Week 12 early study treatment discontinuation visit (ESTD) visit (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.6). One of these 2 subjects had a K103K/N NNRTI RAM conferring resistance to efavirenz (EFV) and NVP, which was related to previous use of Atripla (EFV/FTC/TDF).

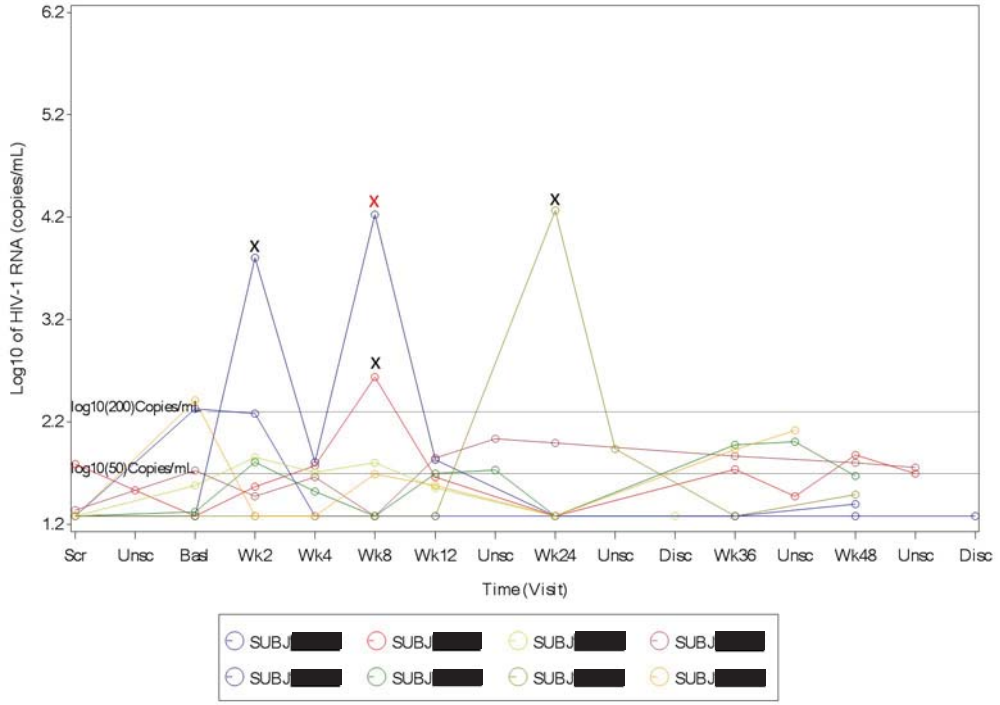
Figure 2: Individual Viral Load Profiles for Subjects with Virologic Rebound (≥50 Copies/mL); ITT (Study TMC114IFD3013)

D/C/F/TAF treatment group



Note: X marks time point of genotype; a red X indicates no genotype could be generated.

Control treatment group



Note: X marks time point of genotype; a red X indicates no genotype could be generated.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Fig7

Table 12: Listing of Rebounders with Post-Baseline Genotype Data; ITT (Study TMC114IFD3013)

Subject ID	HIV-1 Subtype	Week 48 Snapshot Outcome	Rebound Analysis Outcome [a]	Visit	HIV-1 RNA copies/ mL	PI RAMs [b]	NRTI/NNRTI RAMs [c]
Treatment Group = D/C/F/TAF#							
[redacted]		≥50 copies/mL	RB	Week 48	2110	No sequence could be generated	No sequence could be generated
	B	≥50 copies/mL	RB	Unscheduled Week 48	4650	M36I[2] D60E[2] I64V[2]	D67D/N[4,6]
Treatment Group = Control							
[redacted]	B	≥50 copies/mL	RB	Week 8	433	M36I[2] I62V[2] L63P[2] I64M[2]	-
[redacted]	A1	<50 copies/mL	RB	Week 2	6390	L10V[2] M36I[2] D60E[2] H69K[2] L89M[2]	E138E/G[5]
		<50 copies/mL	RB	Week 8	16700	No sequence could be generated	No sequence could be generated
[redacted]	B	<50 copies/mL	RB	Week 24	18400	I62V[2] I64L[2] A71V[2] V77I[2] I93L[2]	-

[a] Includes subjects with virologic rebound (RB), who discontinued from study with HIV-1 RNA ≥400 copies/mL at last visit discontinuation (DC) while receiving study drugs.
[b] PR Sequence (IAS-USA 2015): [1]Primary PI RAMs (none observed); [2]Secondary PI RAMs; [3]DRV RAMs (none observed).
[c] RT Sequence (IAS-USA 2015): [4]NRTI RAMs; [5]NNRTI RAMs; [6]Thymidine Analogue Mutations (TAMs).
[d] 'Resistance Possible' to TPV/rtv and ETR; resistance to RPV.
♯ 2 subjects (non-rebounders & 'no viral load data in Week-48 window' according to FDA snapshot approach) had off-treatment genotypes at the Week 12 ESTD visit):
- [redacted]: PI RAMs: M36I, D60E, I62V, L63P, A71A/T, I93L; NNRTI RAMs: K103K/N; Resistant to EFV and nevirapine; previous use of Atripla)
- [redacted]: PI RAMs: M36I, H69K, L89M, I93L (Sensitive to all ARVs)

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab28

4.4. Resistance in HIV-1 Infected Adolescent Subjects

4.4.1. Phase 2 Study TMC114-C230 in HIV-1 Infected, ART-naïve Adolescent Subjects

4.4.1.1. Study Synopses

Study narrative is provided in Mod2.7.3/App1.

4.4.1.2. Antiviral Activity

In the Phase 2 Study TMC114-C230 with DRV/rtv 800/100 mg once daily (in combination with AZT/3TC or ABC/3TC) in HIV-1 infected, ART-naïve adolescents, high virologic response rates were observed, demonstrating efficacy of DRV/rtv in this age group. Virologic response (HIV-1 RNA <50 copies/mL, FDA snapshot approach) was achieved in all 12 subjects at Week 24 and in 11 out of 12 subjects (91.7%) at Week 48. For more information, refer to Mod2.7.3/Sec3.2.1.

4.4.1.3. Resistance Data

4.4.1.3.1. Baseline Resistance

Genotype

The prevalence of primary PI RAMs, PI RAMs (here defined as primary and secondary PI RAMs), DRV RAMs, NRTI RAMs, and the HIV-1 subtype distribution at baseline are summarized in Table 13. None of the subjects had primary PI RAMs and 1 subject had 1 DRV RAM (V11I); this subject had a confirmed virologic response from Week 16 onwards until Week 48. None of the subjects harbored NRTI RAMs.

Table 13: Prevalence of Mutations at Baseline; ITT (Study TMC114-C230)

	DRV/rtv 800/100 mg qd
Analysis set: Intent-to-treat, N	12
Subjects with genotype at screening/baseline [b], N	12
Primary PI Mutations[a], Median (Range)	0 (0; 0)
Primary PI Mutations, n (%)	
0	12 (100)
PI RAMs[a,c], Median (Range)	4 (1; 6)
PI RAMs[c], n (%)	
0 - 2	2 (16.7)
3 - 4	5 (41.7)
5 - 6	5 (41.7)
DRV RAMs[a], Median (Range)	0 (0; 1)
DRV RAMs, n (%)	
0	11 (91.7)
1	1 (8.3)
NRTI RAMs[a], Median (Range)	0 (0; 0)
NRTI RAMs, n (%)	
0	12 (100)
HIV-1 Subtype, n (%)	
A1	2 (16.7)
B	4 (33.3)
C	1 (8.3)
CRF01_AE	2 (16.7)
CRF02_AG	3 (25.0)

[a] Based on the 2010 IAS-USA list of mutations[13]
[b] Baseline and pre-baseline data were combined to calculate resistance baseline values.
[c] PI RAMs include primary ánd secondary PI RAMs.
N = number of subjects; n = number of observations.
Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab9 and Tab10

Phenotype

The baseline phenotypic data for this study are based on the [redacted] assay.

All subjects were susceptible to all PIs and NRTIs, and therefore received a fully susceptible background regimen containing 2 NRTIs.

4.4.1.3.2. Development of Resistance

There was 1 (8.3%) virologic Nonresponder and 1 (8.3%) rebounder (TLOVR non-VF censored). Neither developed DRV RAMs or lost phenotypic susceptibility to any commercially available PI (including DRV) or any NRTI in the background regimen (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec6.2).

The nonresponder's viral load declined from baseline and the subject had an unconfirmed viral load <50 copies/mL at Week 24, and values >50 copies/mL thereafter. This subject had a treatment-emergent primary PI mutation (M46I). No emerging NRTI RAMs were observed. This subject was adherent based on the replies to the Study Adherence Questionnaire developed by PENTA until Week 16, but from Week 24 onwards the subject was nonadherent to intake of both DRV/rtv and ARVs in the background regimen. Based on pill count, this subject was nonadherent (both DRV/rtv and ARVs in the background regimen) throughout the study.

The rebounder's viral load returned to undetectable (<50 copies/mL) at Week 48, after rebound at Week 40. The subject had a treatment-emergent NRTI RAM (K219Q). Mutation K219Q is associated with resistance to AZT which was part of the subject's background regimen; phenotypic assessment showed that the HIV-1 virus was resistant to TDF but remained susceptible to all other NRTIs, including the ARVs in the subject's background regimen (ie, AZT and 3TC).

4.4.2. Phase 2/3 Study GS-US-292-0106 in HIV-1 Infected, ART-naïve Adolescent Subjects

4.4.2.1. Study Synopses

Study narrative is provided in Mod2.7.3/App1.

4.4.2.2. Antiviral Activity

In the Phase 2/3 Study GS-US-292-0106 with E/C/F/TAF FDC (150/150/200/10 mg) once daily in HIV-1 infected, ART-naïve adolescents, high virologic response rates were observed, demonstrating efficacy of E/C/F/TAF in this age group. Virologic response rate (HIV-1 RNA <50 copies/mL, FDA snapshot approach) was 90.0% (45/50) subjects at Week 24 and 92.0% (46/50) at Week 48. For more information, refer to Mod2.7.3/Sec3.2.2.

4.4.2.3. Resistance Data

4.4.2.3.1. Baseline Resistance

HIV-1 genotyping of the PR/RT and integrase genes was conducted at screening to assess for pre-existing resistance as part of the enrollment criteria for subjects who entered Study GS-US-292-0106. Subjects were to have genotypic sensitivity to EVG, FTC, and TFV (delivered as TAF). Consistent with enrollment criteria, no resistance-associated mutations were observed to EVG, FTC, or TFV at baseline. NRTI-associated resistance mutations were observed in 8% of subjects and NNRTI-associated resistance mutations were observed in 6% of subjects. Primary INSTI-associated resistance mutations and primary PI-associated resistance mutations were not observed in any subjects (0 of 50) at screening (Table 14).

The HIV-1 subtype was determined for each subject using the screening genotype. Overall, non-B subtype was predominant for this study.

Table 14: Prevalence of Mutations at Baseline; ITT (Study GS-US-292-0106)

	E/C/F/TAF
Analysis set: Intent-to-treat, N	50
Subjects with genotype at screening, N	50
≥1 NRTI RAMs[a], n (%)	4 (8.0%)
≥1 Primary INSTI RAMs[a], n (%)	0
≥1 NNRTI RAMs[a], n (%)	3 (6.0%)
≥1 Primary PI RAMs[a], n (%)	0
HIV-1 subtype, n (%)	
Subtype B	11 (22.0%)
Non-B Subtype	39 (78.0%)

E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAM = resistance-associated mutation; TAM = thymidine analogue mutation.
[a] Modified IAS-USA list (see 4.2.1)
Source: Abram et al. 2016[1]

4.4.2.3.2. Development of Resistance

Of the 50 subjects enrolled through Week 48 for Study GS-US-292-0106, 2 subjects (4%) were eligible for resistance testing. No emergent resistance to any of the study drugs was observed in either subject.[1,10]

5. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

In general, the prevalence of screening/baseline PR and RT resistance mutations was low and as expected in a treatment-naïve population. Overall there were 7 subjects with a DRV RAM pre-D/C/F/TAF treatment, in Studies TMC114FD2HTX3001 (3 V11I) , GS-US-299-0102 (L33F, I50V, I54L/M), and TMC114IFD3013 (V11I), who all had HIV-1 RNA<50 copies/mL at Week 48 (or at discontinuation) by FDA snapshot approach.

Overall in the Phase 2/3 studies included in this submission, the following was observed in subjects receiving D/C/F/TAF (see Table 15 for results from all Phase 2/3 studies):

- In 0 out of 1228 subjects receiving D/C/F/TAF DRV RAMs or primary PI RAMs were observed. No decreased susceptibility to DRV was observed.
- 2 out of 1228 (0.2%) subjects receiving D/C/F/TAF had emerging NRTI RAMs related to their F/TAF background regimen:
  - FTC RAM M184V/I was observed twice, conferring phenotypic resistance to FTC in one subject.
  - TDF/TAF RAM K65R was observed in one subject, however conferring no resistance to TFV (delivered as TAF).

These observations are in line with other studies investigating DRV 800 mg qd–based regimens (7 clinical phase 2 and 3 studies: TMC114-C211 [n=343], GS-US-299-0102 [n=153], GS-US-216-0130 [n=313], TMC114-C229 [n=294], TMC125HIV4007 [n=54], TMC114-HIV3006 [n=256], and TMC114IFD3003 [n=273]): Across a diverse population of HIV-1–infected subjects taking a DRV 800 mg qd–based regimen only 4 of 1,686 (0.2%) subjects developed post-baseline primary PI and/or DRV RAMs, and only 1 of 1,686 (<0.1%) subjects lost DRV phenotypic susceptibility.[15]

These observations are also in line with other studies investigating F/TAF vs F/TDF regimen. In a pooled analysis of phase 3 studies (GS-US-292-0104 and GS-US-292-0111) with E/C/F/TAF vs E/C/F/TDF, up to Week 144, the development of one or more primary FTC or TAF/TDF RAMs in the E/C/F/TAF and E/C/F/TDF group was as follows:

- M184V/I: 11 of 866 (1.3%) and 9 of 867 (1.0%), respectively (with 8 and 7 subjects showing reduced susceptibility to FTC)
- K65R/N: 2 of 866 (0.2%) and 4 of 867 (0.5%), respectively (with 1 and 2 subjects showing susceptibility to TFV).[11]

Table 15: Overview of Emerging Resistance in Phase 3 and 2 Clinical Studies Supporting DCFTAF FDC (Week 48 analyses of Studies TMC114FD2HTX3001, GS-US-299-0102, TMC114IFD3013, TMC114-C230, and GS-US-292-0106)

Study	ART	Subjects, n	Subjects with PDVF, n (%)	Subjects evaluated for resistance, n (%)	Subjects with ≥1 emergent RAM, n (%)	
					Protease	Reverse Transcriptase
					Primary PI/DRV	N(t)RTI
TMC114FD2HTX3001	**D/C/F/TAF**	**362**	**8 (2.2)**	**7 (1.9)**	**0**	**M184M/I/V [b] n = 1**
	DRV/COBI+F/TDF	363	6 (1.7)	2 (0.6)	0	0
GS-US-299-0102	**D/C/F/TAF**	**103**	**6 (5.8)**	**6 (5.8)**	**0**	**K65K/R + M184M/I [c] n=1**
	DRV+COBI+F/TDF	50	2 (4.0)	2 (4.0)	0	0
TMC114IFD3013	**D/C/F/TAF**	**763**	**19 (2.5)**	**1 (0.1)**	**0**	**0**
	bPI+F/TDF	378	8 (2.1)	3 (0.8)	0	0
TMC114-C230	DRV/rtv + AZT/3TC or ABC/3TC	12	2 (16.7)	2 (16.7)	M46I [a] n=1	K219Q [d] n=1
GS-US-292-0106	E/C/F/TAF[e]	50	2 (4.0)	2 (4.0)	-	0
Total	**D/C/F/TAF**	**1228**	**33 (2.7)**	**14 (1.1)**	**0**	**2 (0.2%)**

ART = antiretroviral Treatment; ABC/3TC = abacavir/lamivudine; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; F/TAF = emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; n= number of subjects; N(t)RTI = nucleos(t)ide reverse transcriptase inhibitor; PDVF = protocol-defined virologic failure; PI = protease inhibitor; RAM = resistance-associated mutation; rtv = low dose ritonavir.

a. M46I is a primary PI RAM, but not a DRV RAM; phenotypic assessment showed that the subject remained susceptible to all PIs, including DRV)
b. Conferring phenotypic resistance to FTC and 3TC.
c. Mutations K65R and M184I are associated with resistance to TAF/TDF and FTC, respectively. However, phenotypic susceptibilities to both FTC and TDF/TAF were in the sensitive range despite the presence of these mutations.
d. Mutation K219Q is associated with resistance to AZT which was part of the subject's background regimen; phenotypic assessment showed that the HIV-1 virus was resistant to TDF but remained susceptible to all other NRTIs, including the ARVs in the subject's background regimen (ie, AZT and 3TC).
e. No integrase inhibitor resistance observed.

6. CONCLUSION

Across the Phase 2/3 D/C/F/TAF studies, development of resistance to the study drugs was rare. None of the subjects with post-baseline resistance data developed DRV or primary PI RAMs and no subject had decreased susceptibility to DRV. Emerging FTC RAM M184V/I was observed twice, conferring phenotypic resistance to FTC in one subject. TDF/TAF RAM K65R emerged in 1 subject, however no phenotypic resistance to TFV (delivered as TAF) was observed.

The clinical efficacy and resistance data from the D/C/F/TAF Phase 3 and 2 studies demonstrate that the D/C/F/TAF FDC (800/150/200/10 mg) has a robust virological profile with a high genetic barrier to resistance, showing no emergence of DRV resistance and rare emergence of resistance to F/TAF in HIV-1 infected adult subjects.

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Janssen Research & Development

Summary of Clinical Efficacy

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults and Adolescents

D/C/F/TAF (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide, TMC114/JNJ-48763364/JNJ-35807551/JNJ-63625328)

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ABBREVIATIONS

abbreviations	description of abbreviated term
3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	acquired immune deficiency syndrome
ART	antiretroviral treatment
ARV	antiretroviral
ATV	atazanavir
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval tau
AUC_{24h}	area under the plasma concentration-time curve over the dosing interval of 24h
AZT	zidovudine
BMD	bone mineral density
BMI	body mass index
bPI	boosted protease inhibitor
C_{oh}	trough (predose) plasma concentration
CI	confidence interval
COBI (or C)	cobicistat
CSR	Clinical Study Report
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DMC	Data Monitoring Committee
DRV (or D)	darunavir
eGFR	estimated glomerular filtration rate
EVG (or E)	elvitegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ESTD	early study treatment discontinuation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC (or F)	emtricitabine
F/TDF	emtricitabine/tenofovir disoproxil fumarate (Truvada)
GSI	Gilead Sciences, Inc.
HIV-1	human immunodeficiency virus type 1
IAS	International Antiviral Society
INI	Integrase inhibitor
INSTI	integrase strand-transfer inhibitor
IQ	interquartile
ITT	intent-to-treat
LPV	lopinavir
MH	Mantel-Haenszel
NC=F	noncompleting is failure
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PD	pharmacodynamics(s)
PI	protease inhibitor
PK	pharmacokinetic(s)
PP	Per Protocol
PR	protease
RAM	resistance-associated mutation
RT	reverse transcriptase
rtv	(low-dose) ritonavir
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SE	standard error
SD	standard deviation
SSR	sample size re-estimations

TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TLOVR	time to loss of virologic response
VF	virologic failure
VL	viral load
WHO	World Health Organization

STUDY NAMING CONVENTIONS

Study numbers commencing with 'TMC114' in this dossier refer to studies conducted by the Sponsor, and study numbers commencing with 'GS' refer to studies conducted by Gilead Sciences, Inc (GSI).

1. INTRODUCTION

The information presented in this Summary of Clinical Efficacy establishes the efficacy and resistance profile of the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed dose combination (FDC) (800/150/200/10 mg) in adult and adolescent subjects infected with the human immunodeficiency virus type 1 (HIV-1).

In Section 2, an overview of the clinical studies supporting D/C/F/TAF efficacy is presented. Details on their design, including a reference to study narratives in Appendix 1 describing critical design features and critical results, extent of exposure, study population, and methods used are provided.

In Section 3, data from individual studies are analyzed and summarized:

- In Section 3.1, an efficacy and resistance summary is given of the Phase 3 and 2 studies with the D/C/F/TAF FDC in HIV-1 infected, antiretroviral treatment (ART)-naïve and -experienced adult subjects;
- In Section 3.2, a summary is given of efficacy and resistance data of darunavir (DRV) and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1 infected, ART-naïve adolescent subjects.

In Section 4, efficacy results in subgroups across studies and baseline resistance are summarized.

In Section 5, all the clinical information relevant to dosing is summarized.

In Section 6, information regarding persistence of efficacy is summarized.

In Section 7, the main conclusions of this summary are presented.

2. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

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

2.1. Overview of Clinical Studies Supporting D/C/F/TAF's Clinical Efficacy and Resistance Profile

Data supporting the efficacy and resistance profile of the D/C/F/TAF FDC tablet in adults are available from 2 ongoing pivotal Phase 3 studies and 1 completed supportive Phase 2 study. Based on matching PK results for the individual components of the FDC tablet in adolescents and adults, the Sponsor is of the opinion that the D/C/F/TAF (800/150/200/10 mg) FDC tablet can be used for the treatment of HIV-1 infection in both adults and adolescents.

An overview of the relevant clinical studies supporting the D/C/F/TAF efficacy and resistance by study drug and by study population, including their design and a reference to the study narratives in Appendix 1, is presented in Table 1:

Adult Population

Efficacy data with the D/C/F/TAF FDC tablet in adults are available from the following 3 clinical studies:

- 2 ongoing pivotal Phase 3 studies (Week-48 primary analyses available) in:
  - HIV-1 infected, ART-naïve subjects (TMC114FD2HTX3001); and
  - HIV-1 infected, ART-experienced, virologically suppressed subjects (TMC114IFD3013).
- 1 completed supportive Phase 2 study in HIV-1 infected, ART-naïve subjects (GS-US-299-0102; primary Week-24 and final Week-48 analyses).

Adolescent Population (Aged ≥12 to <18 Years)

No data are available with the D/C/F/TAF FDC tablet in the adolescent population. However, 2 studies with the individual components of the FDC tablet in adolescents showed exposures matching the adult exposures in clinical studies (Mod2.7.2/ClinPharm/Sec2.2.3, NDA021976/Mod2.7.2/ClinPharm/Sec3.14.2 [June 2012]), and provided efficacy data in adolescents:

- 1 completed Phase 2 study in HIV-1 infected, ART-naïve subjects with darunavir/(low-dose) ritonavir (DRV/rtv) (TMC114-C230; primary Week-24 and final Week-48 analyses).
- 1 ongoing Phase 2/3 study in HIV-1 infected, ART-naïve subjects with the E/C/F/TAF FDC (GS-US-292-0106; Week-48 data available).

A tabular summary for all studies referenced in the D/C/F/TAF FDC submission is available in Mod5.2.

Table 1: Tabulated Overview of the Phase 3 and 2 Studies Supporting the Clinical Efficacy and Safety Profile of the D/C/F/TAF FDC Tablet

Study (Phase, Status)	Study Design	Number of Subjects[a] by Treatment Regimen[b]	Primary Endpoint	Data Included in Application	Source Reference and Narrative Locations	Included in
D/C/F/TAF						
HIV-1 Infected, ART-naïve, Adult Subjects						
TMC114FD2HTX3001 (Phase 3, ongoing)	Randomized, active-controlled, double-blind study to evaluate efficacy and safety of D/C/F/TAF FDC vs DRV/COBI+F/TDF	Total: 725 - D/C/F/TAF FDC (N=362) or - DRV/COBI+F/TDF (N=363)	Virologic response defined as HIV-1 RNA <50 copies/mL at Week 48 per FDA snapshot; noninferiority with maximum allowable difference of 10%	Week 48 efficacy, resistance, PK, and safety	TMC114FD2HTX3001 Week 48 CSR Appendix 1: Study TMC114FD2HTX3001	Mod2.7.3 and Mod2.7.4
GS-US-299-0102 (Phase 2, completed)	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+F/TDF	Total: 153 - D/C/F/TAF FDC (N=103) or - DRV+COBI+F/TDF (N=50)	Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per FDA snapshot; noninferiority with maximum allowable difference of 12%	Week 48 efficacy, resistance, PK, and safety	GS-US-299-0102 Final CSR Appendix 1: Study GS-US-299-0102	Mod2.7.3 and Mod2.7.4
HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects						
TMC114IFD3013 (Phase 3, ongoing)	Randomized, active-controlled, open-label study to evaluate the efficacy, safety, and tolerability of switching to D/C/F/TAF FDC vs continuing the current bPI combined with F/TDF	Total: 1,141 - Switch to D/C/F/TAF FDC (N=763) or - Stay on bPI[c] combined with F/TDF (N=378)	Virologic rebound cumulative through Week 48 (confirmed HIV-1 RNA ≥50 copies/mL, or with a last single HIV-1 RNA ≥50 copies/mL in case of early discontinuation); noninferiority with maximum allowable difference of 4%	Week 48 efficacy, resistance, PK, and safety	TMC114IFD3013 Week 48 CSR Appendix 1: Study TMC114IFD3013	Mod2.7.3 and Mod2.7.4
DRV						
HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)[d]						
TMC114-C230 (Phase 2, completed)	Open-label, single-arm study to evaluate the PK, safety, tolerability, and efficacy of DRV/rtv in combination with AZT/3TC or ABC/3TC	DRV/rtv +ARV background regimen[e] (N=12)	PK of DRV and rtv Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per TLOVR	Week 48 PK, efficacy, resistance, and safety	Janssen NDA021976/ Mod5.3.5.2/ TMC114-C230-W48-CSR Appendix 1: Study TMC114-C230	Mod2.7.3 and Mod2.7.4

Study (Phase, Status)	Study Design	Number of Subjects[a] by Treatment Regimen[b]	Primary Endpoint	Data Included in Application	Source Reference and Narrative Locations	Included in
COBI and F/TAF (Extrapolated From E/C/F/TAF)						
HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)						
GS-US-292-0106[f] (Phase 2/3, ongoing)	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 substudy N=24)	PK of EVG, TAF, COBI, FTC, and TFV Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per FDA snapshot	Week 48 PK, efficacy, resistance, and safety	Abram et al. 2016[1] Clinical Trial.gov[3] Gaur et al. 2016 (poster)[4] Gaur et al. 2015[5] Gaur et al. 2016 (manuscript)[6] Appendix 1: Study GS-US-292-0106	Mod2.7.3 and Mod2.7.4

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ARV = antiretroviral; ATV= atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; CSR = Clinical Study Report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; FTC = emtricitabine; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); HIV-1 = human immunodeficiency virus type 1; LPV = lopinavir; N = number of subjects; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetics; rtv = low-dose ritonavir; TFV = tenofovir; TLOVR = time to loss of virologic response

[a] Subjects included in the Intent-to-treat population or Safety Analysis Set. For the definitions of analysis sets, refer to Section 2.2.

[b] Study drugs were dosed as follows: D/C/F/TAF 800/150/200/10 mg; DRV 400 mg x2; COBI 150 mg; DRV/COBI 800/150 mg; F/TDF 200/300 mg; DRV/rtv 800/100 mg; and E/C/F/TAF 150/150/200/10 mg.

[c] The current (screening) bPI consisted of DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv, dosed as indicated in the local Prescribing Information.

[d] In addition, recent results (Week 48 data) became available from a single-arm, open-label, Phase 2/3, switch Study GS-US-216-0128 in HIV-1 infected, virologically suppressed adolescents (aged ≥12 to <18 years). In this study, subjects received DRV plus COBI or ATV plus COBI (subjects switched from rtv to COBI in this study) in combination with 2 NRTIs.

[e] The ARV background regimen consisted of AZT/3TC or ABC/3TC, dosed as indicated in the local Prescribing Information.

[f] In this study, a patient population of virologically suppressed children (aged 6 to <12 years) was also included. However, these data are not described in this submission which focusses on adult and adolescent HIV-1 infected subjects.

2.2. Analysis Sets of the Phase 3 and 2 Studies

The analysis sets for the studies in HIV-1 infected, ART-naïve and -experienced, virologically suppressed adult subjects and in HIV-1 infected, ART-naïve adolescent subjects are presented in Table 2. Further clarification on the analysis sets used to describe efficacy results in the studies included in this Summary of Clinical Efficacy is provided below.

- The intent-to-treat (ITT) population = Full Analysis Set (FAS): All subjects who were randomized and received at least 1 dose of treatment in the study. In the Janssen Studies TMC114FD2HTX3001, TMC114IFD3013, and TMC114-C230, ITT terminology was used, and FAS was used in the Gilead Studies GS-US-299-102 and GS-US-292-0106. Note that randomization was not applicable in Studies TMC114-C230 or GS-US-292-0106 due to single arm open-label design.
- The per protocol (PP) population for the D/C/F/TAF Phase 3 and 2 studies in HIV-1 infected, ART-naïve and ART-experienced, virologically suppressed adults:

  All subjects

  – Who were randomized into the study,
  – Who received at least 1 dose of treatment in the study and had at least 1 assessment,
  – Without any major protocol deviation that was considered to potentially affect efficacy outcomes for Studies TMC114FD2HTX3001[a] and TMC114IFD3013[b], or who did not commit any major protocol violations, including violation of key entry criteria, in Study GS-US-299-0102 (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec4.5, Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec4.5, and Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec8.2).
- The Safety Analysis Set (SAS), used in Studies GS-US-299-0102 and GS-US-292-0106, included all subjects who were enrolled or randomized and received at least 1 dose of study drug, and had postbaseline safety assessments available.

[a] In addition, for Study TMC114FD2HTX3001, subjects with treatment adherence based on drug accountability derivation ii for the active ARVs <65% and subjects with no postbaseline viral load measurement (eg, discontinued within 2 weeks) were also excluded from the PP analysis set. For more details on the reasons for exclusion form the PP analysis set, refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec4.5.

[b] In addition, for Study TMC114IFD3013, subjects with a baseline HIV-1 RNA value ≥50 copies/mL and subjects with treatment adherence <65% per derivation ii were also excluded from the PP analysis set. For more details on the reasons for exclusion form the PP analysis set, refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec4.5.

Table 2: Analysis Populations - Studies TMC114FD2HTX3001, GS-US-299-0102, TMC114IFD3013, TMC114-C230, and GS-US-292-0106; All Subjects

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102		TMC114IFD3013		TMC114-C230	GS-US-292-0106
	D/C/F/TAF	DRV/COBI +F/TDF	D/C/F/TAF	DRV+COBI +F/TDF	D/C/F/TAF	current bPI[a] +F/TDF	DRV/rtv +AZT/3TC or ABC/3TC	E/C/F/TAF
Subjects randomized/enrolled	362	363	103	50	763	378	12	50
Subjects in ITT/FAS[b]	362	363	103	50	763	378	12	50
Subjects in SAS[b]	-	-	103	50	-	-	-	50
Subjects in the Week 48 PP Analysis Set[c]	348	344	85	46	721	358	-	-

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ATV = atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; CSR = clinical study report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FAS = Full Analysis Set; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat; LPV = lopinavir; N = number of subjects; PP = Per Protocol; rtv = ritonavir; SAS = Safety Analysis Set.

[a] DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv.

[b] For definitions of analysis populations, refer to Section 2.2.

[c] For reasons for exclusion from Week 48 PP Analysis Set, refer to the respective CSRs (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR, Mod5.3.5.1/GS-US-299-0102-Final-CSR, Mod5.3.5.1/TMC114IFD3013-W48-CSR, NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR).

[TABLE02.RTF] [/SAS/Z_TMC114/TMC114_DCF_TAF/FILES/RE/SCS_2017/PROGRAMS/TABLE2.SAS] 23JUN2017, 08:12
and Gaur et al. 2016 (manuscript)[6]

2.3. Study Populations in Phase 3 and 2 Studies

The main results in this submission characterizing the efficacy and resistance profile of the D/C/F/TAF FDC tablet in adults are available from the 2 ongoing pivotal Phase 3 studies. In addition, there was 1 completed exploratory Phase 2 study. For adolescents, the Sponsor relies on data from 1 completed Phase 2 and 1 ongoing Phase 2/3 study. For completeness, the Phase 2 and 2/3 data are succinctly presented in Section 3.1.2 and 3.2, and included in the tables of this section.

2.3.1. Extent of Exposure

Extent of exposure across Phase 3 and 2 studies in HIV-1 infected adult and adolescent subjects at the Week-48 cut-off is presented in Table 3.

The total number of HIV-1 infected subjects in the studies supporting this application is 2,081, of whom 1,290 subjects received test drug: 1,228 adult subjects received the D/C/F/TAF FDC (465 ART-naïve and 763 ART-experienced, virologically suppressed), 12 ART-naïve adolescent subjects received DRV, and 50 ART-naïve adolescent subjects received E/C/F/TAF.

In the Phase 3 Study TMC114FD2HTX3001 in adult, HIV-1 infected, ART-naïve subjects, the mean (standard deviation [SD]) duration of exposure was 46.8 (8.4) weeks to D/C/F/TAF and 46.0 (9.7) weeks to DRV/COBI+F/TDF. In the Phase 3 Study TMC114IFD3013 in adult, HIV-1 infected, ART-experienced, virologically suppressed subjects, the mean (SD) duration of exposure was 47.2 (6.6) weeks to D/C/F/TAF and 47.1 (7.6) weeks to bPI+F/TDF. In the supportive Phase 2 Study GS-US-299-0102 in adult, HIV-1 infected, ART-naïve subjects, the mean (SD) duration of exposure was 61.7 (20.3) weeks to D/C/F/TAF and 66.1 (14.8) weeks to DRV+COBI+F/TDF.

In the studies in adolescent, HIV-1 infected subjects, the mean (SD) duration of exposure was 49.3 (1.9) weeks to DRV/rtv (+zidovudine/lamivudine [AZT/3TC] or + abacavir/lamivudine [ABC/3TC]) in Study TMC114-C230 and the median (interquartile [IQ] range) was 60.1 (48.1; 84.1) weeks to E/C/F/TAF in Study GS-US-292-0106.

Table 3: Extent of Exposure Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
Subject-years of exposure	324	320	122	63	690	341	11	NA
Exposure (Weeks)								
Mean (SD)	46.75 (8.424)	45.95 (9.744)	61.65 (20.259)	66.09 (14.826)	47.21 (6.590)	47.05 (7.555)	49.30 (1.943)	NA
Median	48.14	48.14	68.00	69.07	48.14	48.14	48.14	60.1
IQ range	(47.86; 48.71)	(48.00; 48.57)	(65.43; 72.71)	(66.00; 73.57)	(48.00; 48.57)	(48.00; 48.86)	(47.93; 51.57)	(48.1; 84.1)
Range	(0.4; 60.3)	(1.1; 59.3)	(0.1; 80.4)	(8.4; 82.9)	(0.7; 54.1)	(0.6; 54.1)	(47.4; 52.1)	NA
Subjects with end of treatment phase reaching the analysis time point interval[c]								
Week 2	362 (100.0%)	363 (100.0%)	102 (99.0%)	50 (100.0%)	763 (100.0%)	378 (100.0%)	12 (100.0%)	50 (100.0%)
Week 4	355 (98.1%)	354 (97.5%)	100 (97.1%)	50 (100.0%)	761 (99.7%)	374 (98.9%)	12 (100.0%)	50 (100.0%)
Week 8	354 (97.8%)	352 (97.0%)	99 (96.1%)	50 (100.0%)	758 (99.3%)	372 (98.4%)	12 (100.0%)	50 (100.0%)
Week 12	353 (97.5%)	350 (96.4%)	99 (96.1%)	49 (98.0%)	753 (98.7%)	369 (97.6%)	12 (100.0%)	49 (98.0%)
Week 24	349 (96.4%)	347 (95.6%)	93 (90.3%)	48 (96.0%)	744 (97.5%)	367 (97.1%)	12 (100.0%)	48 (96.0%)
Week 36	347 (95.9%)	339 (93.4%)	91 (88.3%)	47 (94.0%)	739 (96.9%)	366 (96.8%)	12 (100.0%)	48 (96.0%)
Week 48	344 (95.0%)	335 (92.3%)	87 (84.5%)	46 (92.0%)	733 (96.1%)	363 (96.0%)	12 (100.0%)	48 (96.0%)

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ATV = atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; IQ = interquartile; ITT = intent-to-treat; LPV = lopinavir; N = number of subjects; NA = not available; rtv = ritonavir; SAS = Safety Analysis Set; SD = standard deviation.

[a] For studies GS-US-299-0102 and GS-US-292-0106, analyses were done on the SAS, which corresponds to the ITT population.

[b] DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv.

[c] Subject is counted if treatment duration in days is larger than or equal to the lower limit of the analysis time point interval.

[TABLE01.RTF] [/SAS/Z_TMC114/TMC114_DCF_TAF/FILES/RE/SCS_2017/PROGRAMS/TABLE1.SAS] 23JUN2017, 08:12
and Gaur et al. 2016 (manuscript)[6]

2.3.2. Subject Disposition

Subject disposition across Phase 3 and 2 studies in HIV-1 infected adult and adolescent subjects is presented in Table 4.

Across the Phase 3 and 2 studies in adults, substantially more subjects prematurely discontinued study treatment in the Phase 2 Study GS-US-299-0102 (18.4% in the D/C/F/TAF group and 16.0% in the control group; in this order throughout unless otherwise specified), compared to the Phase 3 Studies TMC114FD2HTX3001 (6.4% and 7.7%) and TMC114IFD3013 (4.5% and 5.3%). In the studies in adolescents, a total of 2 (4.0%) subjects prematurely discontinued study treatment (both in Study GS-US-292-0106).

- More subjects prematurely discontinued in the Phase 2 Study GS-US-299-0102 compared to the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013; primarily due to more subjects that were lost to follow-up in Study GS-US-299-0102 (9.7% and 8.0%, vs 1.4% and 1.4%, and 0.7% and 1.3%).
- In the adult, ART-naïve population, the incidence of subjects prematurely discontinuing study treatment due to adverse events (AEs) was lower in the D/C/F/TAF groups compared to the control groups (2.2% vs 4.1% for the double-blind Study TMC114FD2HTX3001 and 1.0% vs 4.0% for the double-blind Study GS-US-299-0102). In the adult, ART-experienced, virologically suppressed population, the discontinuation rate due to AEs was similar in both treatment groups (1.4% vs 1.1% for the open-label Study TMC114IFD3013). In the studies in adolescents, no subjects prematurely discontinued treatment due to AEs.
- Across studies, no subjects discontinued treatment due to efficacy-related reasons.

Table 4: Subject Disposition Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
Subjects prematurely discontinuing study treatment prior to the data cut-off date	23 (6.4%)	28 (7.7%)	19 (18.4%)	8 (16.0%)	34 (4.5%)	20 (5.3%)	0	2 (4.0%)
Reasons for prematurely discontinuing study treatment[c]								
Safety								
Adverse event	8 (2.2%)	15 (4.1%)	1 (1.0%)	2 (4.0%)	11 (1.4%)	4 (1.1%)	-	0
Death	0	1 (0.3%)	0	0	0	0	-	0
Pregnancy	0	0	0	0	0	0	-	0
Efficacy	0[d]	0	0	0	0	0	-	0
Other								
Lost to follow-up	5 (1.4%)	5 (1.4%)	10 (9.7%)	4 (8.0%)	5 (0.7%)	5 (1.3%)	-	1 (2.0%)
Non-compliance with study drug	1 (0.3%)	0	2 (1.9%)	0	2 (0.3%)	0	-	0
Other	2 (0.6%)	1 (0.3%)	0	0	6 (0.8%)	3 (0.8%)	-	0
Physician decision	3 (0.8%)[d]	0	2 (1.9%)	0	0	0	-	0
Study terminated by sponsor	0	0	0	0	0	0	-	0
Withdrawal by subject	4 (1.1%)	6 (1.7%)	4 (3.9%)	2 (4.0%)	10 (1.3%)	8 (2.1%)	-	1 (2.0%)

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ATV = atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; ESTD = early study treatment discontinuation; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat; LPV = lopinavir; N = number of subjects; rtv = ritonavir; SAS = Safety Analysis Set.

[a] For studies GS-US-299-0102 and GS-US-292-0106, analyses were done on the SAS, which corresponds to the ITT population.

[b] DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv.

[c] For Study TMC114FD2HTX3001, reasons for trial termination are shown.

[d] One subject reached a virologic endpoint per investigator's assessment. [redacted]

[TABLE03.RTF] [/SAS/Z_TMC114/TMC114_DCF_TAF/FILES/RE/SCS_2017/PROGRAMS/TABLE3.SAS] 23JUN2017, 08:13
and Gaur et al. 2016 (manuscript)[6]

2.3.3. Demographic Characteristics

Demographic characteristics are summarized in Table 5.

Demographic characteristics were generally similar between treatment groups in each study.

- In the Phase 3 study with ART-naïve subjects (TMC114FD2HTX3001), subjects were mostly white (83.2%), male (88.3%), with a mean (SD) age of 35.3 (10.08) years, and a mean (SD) body mass index (BMI) of 24.39 (3.85) kg/m^2. There was 1 (0.1%) subject aged more than 65 years, 11.7% females, 11.1% subjects were black or African American, and 13.2% subjects were of Hispanic ethnicity (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab2).
- In the Phase 2 study with ART-naïve subjects (GS-US-299-0102), subjects were mostly male (92.8%), most were either white (60.1%) or black (34.6%), with a mean (SD) age of 35 (11.2) years, and a mean (SD) BMI at baseline of 26.2 (4.81) kg/m^2. In total, 20.9% of subjects were of Hispanic ethnicity (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab8-4).
- In the Phase 3 study with ART-experienced, virologically suppressed subjects (TMC114IFD3013), subjects were mostly white (75.5%), male (82.0%), with a mean (SD) age of 45.1 (10.83) years and a mean (SD) BMI of 26.25 (5.19) kg/m^2. There were 2.9% subjects aged more than 65 years, 18.0% females, 20.9% of subjects were black or African American, and 15.0% subjects of Hispanic ethnicity (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab4).
- In Study TMC114-C230 with adolescents, the mean (SD) age was 14.7 (1.69) years. In Study GS-US-292-0106, the median (range) age was 15 (12; 17) years. These studies included 66.7% and 56.0% female subjects and 41.7% and 88.0% black subjects, respectively (Table 5).

Table 5: Demographic Characteristics Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
Age (Years)								
N	362	363	103	50	763	378	12	50
Mean (SD)	35.6 (10.17)	35.1 (9.99)	34.9 (11.35)	36.8 (10.85)	45.3 (10.86)	44.8 (10.77)	14.7 (1.69)	NA
Median	34.0	34.0	31.0	35.5	46.0	45.0	14.5	15
IQ range	(27.0; 42.0)	(27.0; 42.0)	(25.0; 42.0)	(28.0; 44.0)	(37.0; 53.0)	(37.0; 53.0)	(13.2; 16.4)	NA
Range	(19; 61)	(18; 71)	(20; 68)	(18; 57)	(19; 75)	(20; 78)	(13; 17)	(12; 17)
<18 years	0	0	0	0	0	0	12 (100.0%)	50 (100.0%)
≥18 to ≤50 years	326 (90.1%)	331 (91.2%)	91 (88.3%)	43 (86.0%)	507 (66.4%)	252 (66.7%)	0	0
>50 years	36 (9.9%)	32 (8.8%)	12 (11.7%)	7 (14.0%)	256 (33.6%)	126 (33.3%)	0	0
>50 to ≤65 years	36 (9.9%)	31 (8.5%)	11 (10.7%)	7 (14.0%)	231 (30.3%)	118 (31.2%)	0	-
>65 years	0	1 (0.3%)	1 (1.0%)	0	25 (3.3%)	8 (2.1%)	0	-
Sex								
N	362	363	103	50	763	378	12	50
Female	44 (12.2%)	41 (11.3%)	8 (7.8%)	3 (6.0%)	140 (18.3%)	65 (17.2%)	8 (66.7%)	28 (56.0%)
Male	318 (87.8%)	322 (88.7%)	95 (92.2%)	47 (94.0%)	623 (81.7%)	313 (82.8%)	4 (33.3%)	22 (44.0%)
Race								
Not Reported	1	1	-	-	5	0	-	-
Unknown	1	1	-	-	1	2	-	-
N	360	361	103	50	757	376	12	50
White	300 (83.3%)	300 (83.1%)	62 (60.2%)	30 (60.0%)	573 (75.7%)	282 (75.0%)	7 (58.3%)	0
Black	40 (11.1%)	40 (11.1%)	36 (35.0%)	17 (34.0%)	155 (20.5%)	82 (21.8%)	5 (41.7%)	44 (88.0%)
Asian	4 (1.1%)	7 (1.9%)	2 (1.9%)	1 (2.0%)	17 (2.2%)	9 (2.4%)	0	6 (12.0%)
Other	16 (4.4%)	14 (3.9%)	3 (2.9%)	2 (4.0%)	12 (1.6%)	3 (0.8%)	0	0
Ethnicity								
Not Reported	0	2	-	-	3	1	-	-
Unknown	2	0	-	-	0	1	-	-
N	360	361	103	50	760	376	12	-
Hispanic or Latino	50 (13.9%)	45 (12.5%)	23 (22.3%)	9 (18.0%)	111 (14.6%)	59 (15.7%)	1 (8.3%)	-
Not Hispanic or Latino	310 (86.1%)	316 (87.5%)	80 (77.7%)	41 (82.0%)	649 (85.4%)	317 (84.3%)	11 (91.7%)	-

Table 5: Demographic Characteristics Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
Region								
N	362	363	103	50	763	378	12	50
Non-United States	296 (81.8%)	296 (81.5%)	1 (1.0%)	2 (4.0%)	450 (59.0%)	197 (52.1%)	10 (83.3%)	39 (78.0%)
United States	66 (18.2%)	67 (18.5%)	102 (99.0%)	48 (96.0%)	313 (41.0%)	181 (47.9%)	2 (16.7%)	11 (22.0%)
Height (cm)								
N	362	363	103	50	762	378	12	50
Mean (SD)	176.0 (7.84)	175.5 (8.20)	174.3 (7.64)	176.0 (8.05)	174.1 (9.33)	174.3 (8.94)	158.4 (7.97)	NA
Median	176.0	176.0	175.3	175.6	175.0	175.0	158.8	157.8
IQ range	(171.0; 181.0)	(170.0; 181.0)	(170.2; 180.3)	(170.2; 182.0)	(168.0; 180.3)	(169.0; 180.3)	(152.0; 164.0)	NA
Range	(152; 206)	(152; 195)	(155; 192)	(152; 193)	(145; 201)	(147; 211)	(144; 172)	(122.5; 182.0)
Baseline Body Mass Index (kg/m^2)								
N	362	363	103	50	762	378	12	-
Mean (SD)	24.8 (4.11)	24.0 (3.54)	26.3 (4.97)	26.1 (4.53)	26.4 (5.32)	26.0 (4.92)	20.1 (2.33)	-
Median	24.1	23.6	25.1	24.7	25.4	24.8	20.3	-
IQ range	(22.0; 26.6)	(21.2; 26.1)	(22.4; 29.6)	(22.7; 29.0)	(22.7; 29.1)	(22.6; 28.6)	(18.6; 21.5)	-
Range	(17; 47)	(15; 37)	(18; 43)	(18; 38)	(16; 65)	(16; 45)	(16; 23)	-

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ATV = atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; IQ = interquartile; ITT = intent-to-treat; LPV = lopinavir; N = number of subjects; NA = not available; rtv = ritonavir; SAS = Safety Analysis Set; SD = standard deviation.

[a] For studies GS-US-299-0102 and GS-US-292-0106, analyses were done on the SAS, which corresponds to the ITT population.

[b] DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv.

[TABLE04.RTF] [/SAS/Z_TMC114/TMC114_DCF_TAF/FILES/RE/SCS_2017/PROGRAMS/TABLE4.SAS] 23JUN2017, 08:14
and Gaur et al. 2016 (manuscript)[6]

2.3.4. Baseline HIV Disease Characteristics

Baseline HIV disease characteristics are summarized in Table 6.

The HIV disease characteristics were generally similar between treatment groups within each study, taking into account the HIV-1 infected population studied.

- In the Phase 3 study with ART-naïve subjects (TMC114FD2HTX3001), the mean (SD) baseline HIV-1 RNA value was 4.48 (0.61) $\log_{10}$ copies/mL. At baseline, 17.9% of subjects had HIV-1 RNA ≥100,000 copies/mL. The mean (SD) baseline CD4+ cell count was 486.0 (230.74) cells/mm^3. About 40% of subjects had a CD4+ cell count >500 cells/mm^3 and 7.0% of subjects had a count <200 cells/mm^3. The mean time since HIV-1 diagnosis was 19.5 (33.5) months. The most common mode of HIV-1 infection was homosexual sex (70.9%). The majority of subjects had asymptomatic HIV-1 disease (84.4%). Few subjects had advanced (2.2%) or severe (0.1%) symptomatic HIV-1 infection (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab3).
- In the Phase 2 study with ART-naïve subjects (GS-US-299-0102), baseline HIV disease characteristics were similar to those in the Phase 3 study (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab8-5).
- In the Phase 3 study with ART-experienced, virologically suppressed subjects switching from a boosted protease inhibitor (bPI)+F/TDF-based regimen (TMC114IFD3013), subjects had to be suppressed for at least 2 months with 1 allowed blip (a single viral load elevation of ≥50 copies/mL and <200 HIV-1 RNA copies/mL, provided a subsequent viral load measurement is <50 HIV-1 RNA copies/mL prior to screening) during the year prior to screening. Previous virologic failure (VF) on DRV treatment was not allowed. In case historical data were available, subjects with genotypes showing DRV RAMs were excluded. Previous VF on other drugs than DRV was allowed. All subjects were virologically suppressed at screening (or at screening retest; n=5), and a minority (2.0%) had a baseline viral load ≥50 copies/mL (not stably suppressed). The mean (SD) baseline CD4+ cell count was 649.5 (252.99) cells/mm^3. About 70% of subjects had a CD4+ cell count >500 cells/mm^3 and 1.5% of subjects had a count <200 cells/mm^3. The mean time since HIV-1 diagnosis was 11.6 (8.4) years. The most common mode of HIV-1 infection was homosexual sex (64.4%). The majority of subjects had asymptomatic HIV disease (68.1%). A small proportion of subjects had advanced (8.9%) or severe (10.1%) symptomatic HIV-1 infection (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab5).
- In Study GS-US-292-0106 in adolescent subjects, baseline HIV disease characteristics were similar to those of the ART-naïve adult subjects. In Study TMC114-C230, a higher percentage of subjects (41.7%) had HIV-1 RNA ≥100,000 copies/mL, a lower percentage of subjects (8.3%) had a CD4+ cell count >500 cells/mm^3, and a lower percentage of subjects was asymptomatic (41.7%). In both studies, vertical transmission was the most common HIV risk factor (64.0% and 41.7%) (Table 6).

Table 6: Baseline HIV Disease Characteristics Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
HIV-1 RNA (log_{10} copies/mL)								
N	362	363	103	50	763	378	12	50
Mean (SD)	4.4 (0.64)	4.5 (0.58)	4.7 (0.52)	4.6 (0.51)	1.3 (0.17)	1.3 (0.20)	4.7 (0.60)	4.62 (0.59)
Median	4.4	4.6	4.7	4.6	1.3	1.3	4.9	4.7
IQ range	(4.0; 4.8)	(4.1; 4.9)	(4.4; 4.9)	(4.3; 4.9)	(1.3; 1.3)	(1.3; 1.3)	(4.5; 5.1)	NA
Range	(1; 7)	(3; 7)	(3; 6)	(4; 6)	(1; 4)	(1; 4)	(4; 6)	(3.3; 6.5)
HIV-1 RNA categories (copies/mL)								
≥100,000	60 (16.6%)	70 (19.3%)	23 (22.3%)	7 (14.0%)	0	0	5 (41.7%)	11 (22.0%)[d]
<100,000	302 (83.4%)	293 (80.7%)	80 (77.7%)	43 (86.0%)	763 (100.0%)	378 (100.0%)	7 (58.3%)	39 (78.0%)[d]
≥1,000 to <100,000	293 (80.9%)	292 (80.4%)	80 (77.7%)	43 (86.0%)	2 (0.3%)	1 (0.3%)	7 (58.3%)	NA
≥50 to <1,000	8 (2.2%)	1 (0.3%)	0	0	14 (1.8%)	6 (1.6%)	0	NA
<50	1 (0.3%)	0	0	0	747 (97.9%)	371 (98.1%)	0	NA
CD4+ cell count (cells/mm^3)								
N	362	363	103	50	763	378	12	50
Mean (SD)	497.3 (236.60)	474.7 (224.51)	394.7 (169.25)	463.5 (261.55)	653.3 (251.78)	641.7 (255.59)	316.9 (101.60)	471 (212.2)
Median	461.5	440.0	368.0	432.5	630.0	624.0	282.0	456
IQ range	(342.0; 617.0)	(325.0; 594.0)	(270.0; 515.0)	(320.0; 606.0)	(468.0; 806.0)	(466.0; 795.0)	(238.0; 393.0)	(332; 574)
Range	(46; 1454)	(38; 1456)	(7; 909)	(49; 1463)	(111; 1921)	(131; 1764)	(204; 515)	(95; 1,110)
CD4+ cell count categories (cells/mm^3)								
<50	1 (0.3%)	1 (0.3%)	1 (1.0%)	1 (2.0%)	0	0	0	
≥50 to <200	21 (5.8%)	28 (7.7%)	10 (9.7%)	9 (18.0%)	9 (1.2%)	8 (2.1%)	0	4 (8.0%)[c]
≥200 to <350	73 (20.2%)	79 (21.8%)	37 (35.9%)	8 (16.0%)	61 (8.0%)	38 (10.1%)	8 (66.7%)	NA
≥350 to ≤500	114 (31.5%)	121 (33.3%)	27 (26.2%)	12 (24.0%)	157 (20.6%)	72 (19.0%)	3 (25.0%)	NA
>500	153 (42.3%)	134 (36.9%)	28 (27.2%)	20 (40.0%)	536 (70.2%)	260 (68.8%)	1 (8.3%)	NA
Mode of infection (HIV risk factors)[e]								
Heterosexual sex	103 (28.5%)	103 (28.4%)	19 (18.4%)	8 (16.0%)	254 (33.3%)	114 (30.2%)	3 (25.0%)	12 (24.0%)
Homosexual sex	257 (71.0%)	257 (70.8%)	86 (83.5%)	43 (86.0%)	484 (63.4%)	251 (66.4%)	0	8 (16.0%)
IV drug use	3 (0.8%)	9 (2.5%)	0	2 (4.0%)	40 (5.2%)	17 (4.5%)	0	1 (2.0%)
Transfusion	1 (0.3%)	3 (0.8%)	0	0	9 (1.2%)	6 (1.6%)	1 (8.3%)	0

Table 6: Baseline HIV Disease Characteristics Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
Vertical transmission	0	0	0	0	3 (0.4%)	0	5 (41.7%)	32 (64.0%)
Occupational exposure	1 (0.3%)	2 (0.6%)	NA	NA	2 (0.3%)	1 (0.3%)	NA	0
Hemophilia-associated injections	0	0	NA	NA	2 (0.3%)	0	NA	0
Unknown	NA	NA	3 (2.9%)	0	NA	NA	0	0
Other	10 (2.8%)	12 (3.3%)	2 (1.9%)	2 (4.0%)	25 (3.3%)	13 (3.4%)	3 (25.0%)	0
Time since diagnosis HIV infection (years)								
N	362	363	0	0	763	378	12	50
Mean (SD)	1.6 (2.50)	1.6 (3.06)	-	-	11.8 (8.44)	11.3 (8.18)	3.8 (4.68)	NA
Median	0.5	0.4	-	-	9.3	8.9	1.7	1.0
IQ range	(0.2; 2.1)	(0.2; 1.5)	-	-	(4.2; 18.6)	(4.3; 17.5)	(0.2; 7.1)	NA
Range	(0; 16)	(0; 26)	-	-	(1; 35)	(1; 33)	(0; 13)	(0.0; 14.0)
Prior ARV use								
at least 1 PI prior to screening regimen	NA	NA	NA	NA	318 (41.7%)	154 (40.7%)	NA	NA
at least 1 NRTI prior to screening regimen	NA	NA	NA	NA	328 (43.0%)	146 (38.6%)	NA	NA
at least 1 prior NNRTI	NA	NA	NA	NA	225 (29.5%)	115 (30.4%)	NA	NA
WHO or CDC HIV disease status[f]								
WHO								
Clinical stage 1 (asymptomatic)	314 (86.7%)	298 (82.1%)	NA	NA	522 (68.4%)	255 (67.5%)	5 (41.7%)	NA
Clinical stage 2 (mild symptoms)	42 (11.6%)	54 (14.9%)	NA	NA	96 (12.6%)	51 (13.5%)	6 (50.0%)	NA
Clinical stage 3 (advanced symptoms)	6 (1.7%)	10 (2.8%)	NA	NA	66 (8.7%)	36 (9.5%)	1 (8.3%)	NA
Clinical stage 4 (severe symptoms)	0	1 (0.3%)	NA	NA	79 (10.4%)	36 (9.5%)	0	NA
CDC								
Asymptomatic	NA	NA	93 (90.3%)	44 (88.0%)	NA	NA	NA	NA
Symptomatic HIV Infection	NA	NA	8 (7.8%)	3 (6.0%)	NA	NA	NA	NA
AIDS	NA	NA	2 (1.9%)	3 (6.0%)	NA	NA	NA	NA

ABC/3TC = abacavir/lamivudine; AIDS = acquired immunodeficiency syndrome; ART = antiretroviral treatment; ATV = atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; CDC = Centers for Disease Control and Prevention; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; IQ = interquartile; ITT = intent-to-treat; IV = intravenous; LPV = lopinavir; N = number of subjects; NA = not available; rtv = ritonavir; SAS = Safety Analysis Set; SD = standard deviation; WHO = World Health Organization.

[a] For studies GS-US-299-0102 and GS-US-292-0106, analyses were done on the SAS, which corresponds to the ITT population.

[b] DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv.

[c] CD4+ cell count <200 cells/mL

[d] For Study GS-US-292-0106, the HIV-1 RNA categories were >100,000 copies/mL and ≤100,000 copies/mL.

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

[f] Subjects in Studies TMC114FD2HTX3001, TMC114IFD3013, and TMC114-C230 were classified according to the WHO and in Study GS-US-299-0102 according to the CDC classification.

[TABLE06.RTF] [/SAS/Z_TMC114/TMC114_DCF_TAF/FILES/RE/SCS_2017/PROGRAMS/TABLE6.SAS] 10JUL2017, 10:35

and Gaur et al. 2016 (poster)[4], Gaur et al. 2015[5], Gaur et al. 2016 (manuscript)[6]

2.4. Efficacy and Resistance Assessments and Statistical Methods of the Phase 3 and 2 Studies

Efficacy Assessments

- The primary efficacy endpoints of the studies supporting this Summary of Clinical Efficacy were:
  - In ART-naïve subjects:
    - The proportion of subjects who achieved HIV-1 RNA <50 copies/mL as defined by the Food and Drug Administration (FDA) snapshot approach
      - at Week 48 in Study TMC114FD2HTX3001,
      - at Week 24 in Study GS-US-299-0102, and
      - at Week 24 and 48 in Study GS-US-292-0106 (Note that efficacy was a secondary objective in this PK study).
    - The proportion of subjects who achieved confirmed plasma viral load HIV-1 RNA <50 copies/mL at Week 24 per time to loss of virologic response (TLOVR) in Study TMC114-C230.
  - In ART-experienced, virologically suppressed subjects (Study TMC114IFD3013):
    - The proportion of subjects with virologic rebound (confirmed HIV-1 RNA ≥50 copies/mL up to, and including the upper bound of the Week 48 window (ie, 54 weeks), or having discontinued prematurely (irrespective of reason) with the last available (single) HIV-1 RNA value on treatment being ≥50 copies/mL). In addition, any subject with last available on-treatment HIV-1 RNA ≥50 copies/mL at the study cut-off (Week 48) was considered a virologic rebounder. This proportion is used as the primary objective to demonstrate noninferiority of D/C/F/TAF FDC compared to control treatment (instead of virologic response rate at Week 48). With this cumulative approach, a subject will remain a rebounder if he/she experienced virologic rebound at any time point within the treatment period up to the Week 48 window (ie, up to 54 weeks) even if he/she has HIV-1 RNA <50 copies/mL at the Week 48 analysis time point, while with the snapshot approach this subject would be considered as a responder at Week 48.
    - A key secondary efficacy endpoint is the virologic response and failure rates at Week 48 (HIV-1 RNA <50 copies/mL, FDA snapshot approach).
- As the primary efficacy endpoints for the 2 pivotal Phase 3 studies in this submission, Studies TMC114FD2HTX3001 and TMC114IFD3013, are based on Week 48 data, Week 48 analyses are presented for all studies. Week 24 analyses are only presented for studies in which the primary efficacy endpoint is based on Week 24.
- No pooling or comparison of the Week 48 data of the above studies is considered appropriate. The Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 are conducted in different HIV-1 infected subject populations (ART-naïve subjects and ART-experienced, virologically suppressed, respectively), and also differ in design (double-blind and open-label, respectively). The Phase 3 Study TMC114FD2HTX3001 and Phase 2 Study GS-US-299-0102 are similar in study design and population, but the Phase 2

study was an exploratory study, with a limited sample size. A pooling of these studies would not result in a substantial increase in the number of subjects treated with D/C/F/TAF, as compared to the Phase 3 study alone (ie, ~360 subjects in TMC114FD2HTX3001 and 103 subjects in GS-US-299-0102).

Statistical Analysis

In both pivotal Phase 3 studies, the primary objective was to demonstrate noninferiority in efficacy of a D/C/F/TAF tablet vs the control regimen. As secondary objectives, superiority was to be evaluated in the event noninferiority was established. The primary efficacy endpoints in the 2 Phase 3 trials were compared between treatment groups utilizing the stratum-adjusted Mantel-Haenszel (MH) risk difference (D/C/F/TAF group - control group, with associated 95% two-sided confidence interval [CI]) in proportions, where the stratification factors were HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and CD4+ cell count (<200 cells/µL or ≥200 cells/µL) for Study TMC114FD2HTX3001, and bPI use for Study TMC114IFD3013. One-sided noninferiority and superiority p-values based on the same stratum-adjusted MH statistics were also presented to aid interpretation. Homogeneity of treatment effect across stratification factors was also assessed using a one-sided p-value from weighted least squares chi-squared statistics.

- For Study TMC114FD2HTX3001, noninferiority was established if the lower bound of the 95% CI of the stratum-adjusted Mantel-Haenszel difference between treatment groups (D/C/F/TAF group - control group) was >-10%. If noninferiority was achieved, superiority was evaluated and was established if the lower bound of the 95% CI was >0.
- For Study TMC114IFD3013, noninferiority was established if the upper bound of the 95% CI of the stratum-adjusted Mantel-Haenszel difference between treatment groups (D/C/F/TAF group - control group) was <4%. If noninferiority was achieved, superiority was evaluated and was established if the upper bound of the 95% CI was <0.
- For both studies, all efficacy and resistance analyses were conducted on the ITT analysis set. Key efficacy analyses were also conducted on the PP analysis set.

In addition, the following sensitivity analyses for virologic response rates were performed next to the FDA snapshot approach: TLOVR and Observed Case in Study TMC114FD2HTX3001 and TLOVR in Study TMC114IFD3013.

Blinded sample size re-estimations (SSR) were done for both pivotal Phase 3 Studies, TMC114FD2HTX3001 and TMC114IFD3013. The external, independent Data Monitoring Committee (DMC) performed these analyses as follows:

- For Study TMC114FD2HTX3001, the blinded SSR occurred when 445 out of the planned total of 670 subjects were enrolled, of which at least 30% had reached Week 12 and 1% Week 24.
- For Study TMC114IFD3013, the blinded SSR occurred when 985 out of the planned total of 1100 subjects were enrolled, of which at least 75% had reached Week 12 and 43% Week 24.

The blinded SSRs did not warrant an adjustment in the studies sample size. For more details on the methods for the blinded SSR, please refer to the DMC charter, Appendix A and B (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Data Monitoring Committee Charter and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Data Monitoring Committee Charter).

For more details, please refer to the individual Statistical Analysis Plans (SAPs) in the appendices of the CSRs (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Statistical Analysis Plan, Mod5.3.5.1/GS-US-299-0102-Final-CSR/Statistical Analysis Plan, Mod5.3.5.1/TMC114IFD3013-W48-CSR/Statistical Analysis Plan, and NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Statistical Analysis Plan). For more details on Study GS-US-292-0106, see Gaur et al. (2016).[6]

Resistance Assessments

Resistance analyses for all these efficacy studies were performed and are summarized in Section 3 (Mod2.7.2/VirSum/Sec4).

- Genotypic analyses were conducted at screening (plus baseline genotypic/phenotypic analyses for Study TMC114-C230), except for the switch Study TMC114IFD3013 that enrolled ART-experienced, virologically suppressed subjects.

- Postbaseline resistance testing was performed on samples from subjects experiencing

Protocol-defined Virologic Failure
= Virologic Nonresponse/Virologic Rebound/Viremic at Final Time Point
(Studies TMC114FD2HTX3001, GS-US-299-0102, GS-US-292-0106, and TMC114-C230)

Virologic Nonresponse	
TMC114FD2HTX3001/ GS-US-299-0102/ GS-US-292-0106	HIV-1 RNA <1 $\log_{10}$ reduction from baseline (and ≥50 copies/mL) at the Week 8 visit, confirmed at the following scheduled or unscheduled visit following Week 8.
TMC114-C230[a]	On-study at Week 12 and never achieved 2 consecutive viral loads (VLs) <50 copies/mL.
Virologic Rebound	
TMC114FD2HTX3001	At any visit, after achieving confirmed consecutive HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥50 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit.
GS-US-299-0102	At any visit, after achieving HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥400 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit.
GS-US-292-0106	At any visit, after achieving HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA ≥50 copies/mL, which was subsequently confirmed and ≥400 copies/mL at the following scheduled or unscheduled visit.
Or	
TMC114FD2HTX3001/ GS-US-299-0102/ GS-US-292-0106	At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir which was subsequently confirmed at the following scheduled or unscheduled visit.
TMC114-C230[a]	On-study at Week 12 and achieved 2 consecutive VL <50 copies/mL, followed by 2 consecutive VL ≥50 copies/mL.
Viremic at Final Time Point	
TMC114FD2HTX3001/ GS-US-299-0102/ GS-US-292-0106/ TMC114-C230[a]	Any subject with on-treatment HIV-1 RNA ≥400 copies/mL (or HIV-1 RNA ≥50 copies/mL for Study TMC114-C230) at the study endpoint or study discontinuation after Week 8[b].

Protocol-defined Virologic Failure
= Virologic Rebound Cumulative Through Week 48
(Study TMC114IFD3013)

Virologic Rebound	
TMC114IFD3013	Confirmed HIV-1 RNA ≥50 copies/mL up to, and including the upper bound of the Week 48 window (ie, 54 weeks). Premature discontinuation (irrespective of reason) for which the last available (single) HIV-1 RNA ≥50 copies/mL. In addition, any subject with last available on-treatment HIV-1 RNA ≥50 copies/mL at the study cut-off (Week 48) was considered a virologic rebounder.

a. TLOVR (non-virologic failure censored) algorithm.
b. GS-US-299-0102 and GS-US-292-0106: who did not meet any of the other PDVF criteria.

Resistance testing was conducted when HIV-1 RNA was ≥400 copies/mL, which is close to the validated lower limit of detection of the used resistance assays. For Study TMC114-C230, attempts were made if the viral load was >50 copies/mL with a

resistance assay cut-off of 1,000 HIV-1 RNA copies/mL. When feasible, resistance testing was performed at the time of (preferably confirmed, or otherwise at unconfirmed) virologic failure or at later time points. Post-screening virologic failure plasma samples were sequenced (population sequencing) and phenotyped. For Study TMC114IFD3013, phenotyping was only planned to further investigate in case of observed postbaseline genotypic resistance.

Evaluation of treatment-emergent resistance-associated mutations (RAMs) or the presence of on-treatment (Study TMC114IFD3013) RAMs was based on PI, nucleos(t)ide reverse transcriptase inhibitor (N(t)RTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and integrase inhibitor (INI) (Study GS-US-292-0106) mutation lists (International Antiviral Society [IAS]-USA) defined for each study (see Mod2.7.2/VirSum and the SAPs of each study, available in the appendices of the Clinical Study Reports [CSRs] in Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR, Mod5.3.5.1/GS-US-299-0102-Final-CSR, Mod5.3.5.1/TMC114IFD3013-W48-CSR, and NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR).[1,6] RAMs were considered treatment-emergent if they were detected postbaseline but not at screening (or baseline). Antiretroviral (ARV) drug susceptibility (based on genotype and phenotype) was tabulated and assessed.

3. SUMMARIES OF RESULTS OF THE INDIVIDUAL STUDIES

The data from the Phase 3 and 2 studies establish the efficacy and resistance profile of the D/C/F/TAF FDC (800/150/200/10 mg) in HIV-1 infected adult and adolescent subjects.

3.1. Efficacy and Resistance in HIV-1 Infected Adult Subjects

Data from the Phase 3 and 2 studies show robust efficacy and almost no resistance development in both HIV-1 infected, ART-naïve and ART-experienced, virologically suppressed adult subjects:

- The Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 establish that D/C/F/TAF is noninferior to a reference treatment used as control, in HIV-1 infected adult subjects.
- The immunologic response was in accordance with the virologic response in both ART-naïve and ART-experienced subjects.
- Development of resistance to any of the components of the ARV regimens used: no DRV resistance observed and a very low % for FTC and TDF/TAF (0.2%).

3.1.1. Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve Adult Subjects

The Week 48 results of this randomized, active-controlled, double-blind study in HIV-1 infected, ART-naïve adult subjects provide robust proof of efficacy. Noninferiority in efficacy compared to the control treatment, as determined by the proportion of virologic responders, was demonstrated for the D/C/F/TAF FDC in the ITT and supported by the sensitivity analyses. Treatment outcomes were similar across subgroups. The immunologic response was consistent with the virologic response. No developing DRV, Primary PI or TAF/TDF RAMs were observed and only 1 D/C/F/TAF subject developed an FTC RAM (M184V/I).

3.1.1.1. Efficacy Results

3.1.1.1.1. Primary Efficacy Endpoint

The virologic response rate at Week 48 was similar in both treatment groups in the ITT analysis set: 91.4% (331/362) in the D/C/F/TAF group vs 88.4% (321/363) in the control group (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Fig4 and Table 7). D/C/F/TAF was noninferior to the control (ie, lower limit of the stratified MH 95% CI >-10%): treatment difference (95% CI) in virologic response between D/C/F/TAF - control was 2.7 (-1.6; 7.1); corresponding one-sided noninferiority p-value <0.001. The virologic failure rate was low in each treatment group: 4.4% (16/362) vs 3.3% (12/363).

D/C/F/TAF was not superior to the control as the lower bound of the 95% CI around the difference in virologic response between D/C/F/TAF and control was not >0, with a corresponding one-sided superiority p-value of 0.111.

The results in the PP analysis set confirm the noninferiority of D/C/F/TAF vs control. The virologic response rate (HIV-1 RNA <50 copies/mL, FDA snapshot approach) in the PP analysis

set was similar as the response rate in the ITT analysis set, ie, 94.0% (327/348) in the D/C/F/TAF group vs 92.2% (317/344) in the control group with a difference (95% CI) between D/C/F/TAF and control of 1.5 (-2.3; 5.2), as was the virologic failure rate, ie, 4.0% (14/348) vs 2.3% (8/344) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab12 and Section 3.1.1.1.3.1).

Individual viral load profiles for subjects with virologic failure (HIV-1 RNA ≥50 copies/mL) can be found in Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.4.1.2 (FDA snapshot approach, ITT, Week 48).

Table 7: Proportion of Virologic Response (<50 Copies/mL) According to FDA Snapshot Approach at Week 48; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF		Control		D/C/F/TAF vs. Control		
						P-values	
	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	Difference in Proportions (95% CI)[b]	Non-inferiority/ Superiority	Homo-geneity
Analysis Set: Intent-to-treat, N	362		363				
<50 Copies/mL	362		363				
Virologic success:							
HIV RNA <50 copies/mL at Week 48							0.157[d]
						<.001[c]	0.201[e]
	331 (91.4%)	(88.1 ; 94.1)	321 (88.4%)	(84.7 ; 91.5)	2.7 (-1.6; 7.1)	0.111[g]	0.142[f]
Virologic failure:	16 (4.4%)	(2.5 ; 7.1)	12 (3.3%)	(1.7 ; 5.7)			
HIV RNA ≥50 copies/mL at Week 48	9 (2.5%)		9 (2.5%)				
Virologic failure - leading to discontinuation	1 (0.3%)[h]		0				
Virologic failure - discontinued due to other reason and last available HIV RNA ≥50 copies/mL[i]	6 (1.7%)		3 (0.8%)				
No viral load data in 48 Week window	15 (4.1%)	(2.3 ; 6.7)	30 (8.3%)	(5.6 ; 11.6)			
Discontinued due to AE/death	8 (2.2%)		16 (4.4%)				
Discontinued due to other reason and the last available HIV RNA <50 copies/mL (or missing)[j]	4 (1.1%)		9 (2.5%)				
Missing data during window but on study	3 (0.8%)		5 (1.4%)				

AE = adverse event; CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ESTD = early study treatment discontinuation; FDA = Food and Drug Administration; HIV = human immunodeficiency virus; ITT = Intent-to-treat; N = number of subjects in ITT analysis set; n = subject with observation.

[a] Two-sided Exact Clopper-Pearson 95% CI.

[b] Based on stratum adjusted MH test where stratification factors are HIV-1 RNA level (≤100,000 or > 100,000 copies/mL) and CD4+ cell count (< 200 or ≥200 cells/µL).

[c] One-sided p-value for non-inferiority of D/C/F/TAF vs Control (margin = 10%).

[d] One-sided p-value from weighted least squares chi-squared statistic for homogeneity of treatment effect across the combination of stratification factors.

[e] One-sided p-value from weighted least squares chi-squared statistic for homogeneity of treatment effect across the HIV-1 RNA factor.

[f] One-sided p-value from weighted least squares chi-squared statistic for homogeneity of treatment effect across the CD4+ cell count factor.

[g] One-sided p-value for the superiority of D/C/F/TAF vs Control.

[h] The subject reached a virologic endpoint per investigator's assessment. [redacted].

[i] Reasons for discontinuation included lost to follow-up (4 vs 2 subjects), withdrawal by subject (1 vs 1 subject), and other (1 vs 0 subjects).

[j] Reasons for discontinuation included lost to follow-up (0 vs 3 subjects), physician decision (2 vs 0 subjects), withdrawal by subject (1 vs 5 subjects), and other (1 vs 1 subject).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab11

3.1.1.1.2. Virologic Response Rate: Subgroup Analyses

Subgroups included baseline disease characteristics (viral load stratification factor, CD4+ cell count and combinations, WHO class), demographic characteristics (gender, age, race, ethnicity, region), adherence, HIV-1 subtype, presence of one or more primary and/or DRV RAMs, NRTI RAMs, NNRTI RAMs or M184V/I at screening and number of primary and secondary PI RAMs at screening (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.3).

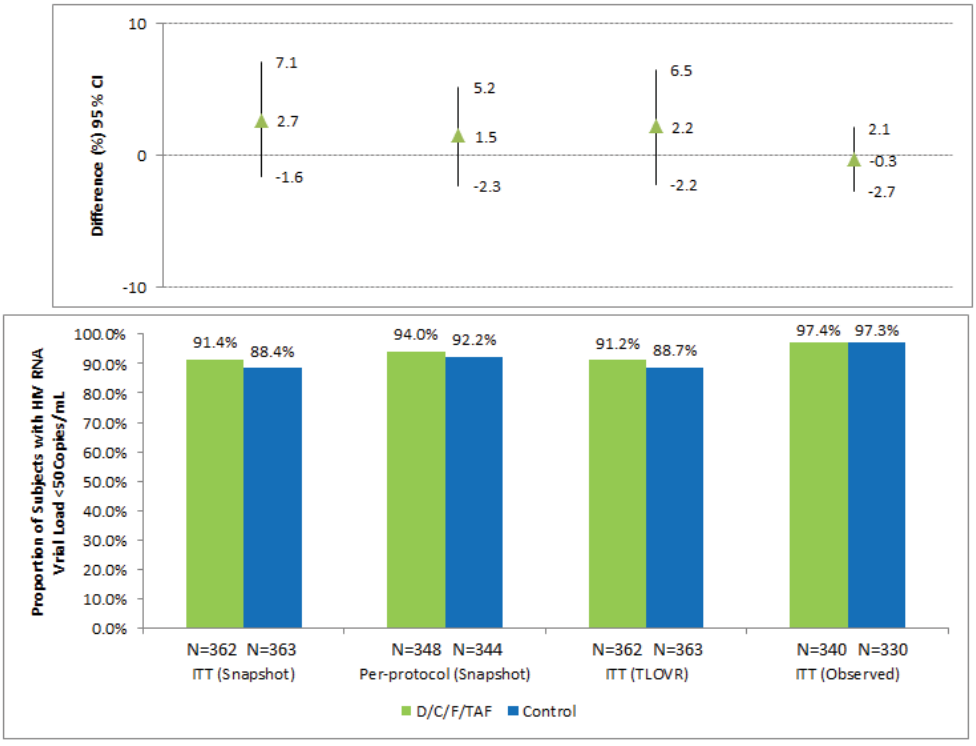
Results were consistent across strata as shown by the nonsignificant p-value for homogeneity test of treatment differences: HIV-1 RNA (p=0.14), CD4+ strata (p=0.20), and the combination thereof (p=0.16) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.3).

3.1.1.1.3. Major Secondary Endpoints

3.1.1.1.3.1. Endpoints Using the 50 HIV-1 RNA Copies/mL Threshold

The results for virologic response rate (HIV-1 RNA <50 copies/mL) were consistent across the different sensitivity analyses (ITT TLOVR, ITT observed) (Figure 1) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.4.1.3).

Figure 1: Bar Chart of Virologic Response (<50 Copies/mL) According to Different Sensitivity Analyses at Week 48; ITT (TMC114FD2HTX3001)



CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV = human immunodeficiency virus; ITT = Intent-to-treat; N = number of subjects in analysis set; PP = per protocol; TLOVR = time to loss of virologic response.
Treatment difference is D/C/F/TAF minus Control: Treatment difference (95% CI) based on stratum adjusted MH test where stratification factors are a combination of HIV-1 RNA level (<=100,000 or >100,000 copies/mL) and CD4+ cell count (<200 or >=200 cells/µL).
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Fig7

3.1.1.1.3.2. Endpoints Using the 200 HIV-1 RNA Copies/mL Threshold

The virologic response rate (HIV-1 RNA <200 copies/mL; FDA snapshot approach) at Week 48 was similar in both treatment groups: 92.8% (336/362) in the D/C/F/TAF group vs 90.6% (329/363) in the control group and a treatment difference (95% CI) of D/C/F/TAF - control of 2.2% (-1.8; 6.2) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Fig8 and Table 8).

The virologic failure rate was low in each treatment group: 2.8% (10/362) vs 1.1% (4/363). In addition, 4.4% (16/362) vs 8.3% (30/363) subjects had no viral load data in the Week 48 window.

Table 8: Proportion of Virologic Response (<200 Copies/mL) According to FDA Snapshot Approach at Week 48; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF		Control		D/C/F/TAF vs. Control
	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	Difference in Proportions (95% CI)[b]
Analysis Set: Intent-to-treat, N	362		363		
<200 Copies/mL	362		363		
Virologic success: HIV RNA <200 copies/mL at Week 48	336 (92.8%)	(89.7 ; 95.3)	329 (90.6%)	(87.2 ; 93.4)	2.2 (-1.8; 6.2)
Virologic failure	10 (2.8%)	(1.3 ; 5.0)	4 (1.1%)	(0.3 ; 2.8)	
No viral load data in 48 Week window	16 (4.4%)	(2.5 ; 7.1)	30 (8.3%)	(5.6 ; 11.6)	

CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDA = Food and Drug Administration; HIV = human immunodeficiency virus; ITT = Intent-to-treat; N = number of subjects in ITT analysis set; n = subject with observation.
[a] Two-sided Exact Clopper-Pearson 95% CI.
[b] Based on stratum adjusted MH test where stratification factors are HIV-1 RNA level (≤100,000 or >100,000 copies/mL) and CD4+ cell count (< 200 or ≥200 cells/µL).
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab13

3.1.1.1.3.3. Immunology Results

The mean (standard error [SE]) baseline CD4+ count values were 497.3 (12.44) cells/mm^3 in the D/C/F/TAF group and 474.7 (11.78) cells/mm^3 in the control group. When adjusted for baseline CD4+ count, LS mean estimates (SE) for changes (increases) from baseline in CD4+ cell count at Week 48 were 190.49 (10.472) cells/mm^3 in the D/C/F/TAF group and 172.01 (10.458) cells/mm^3 in the control group (Table 9). There was no statistically significant difference between treatment groups at Week 48 (p=0.213) Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.4.5).

Table 9: Change from Baseline in CD4+ Cell Count (Cells/mm^3) at Weeks 24 and 48 (ANCOVA); ITT (Study TMC114FD2HTX3001)

	LS Means	SE	95% CI	P-Value
Week 24				
D/C/F/TAF	153.74	8.879	(136.305; 171.169)	<.001
Control	125.29	8.867	(107.884; 142.701)	<.001
D/C/F/TAF - Control	28.44	12.556	(3.794; 53.095)	0.024
Week 48				
D/C/F/TAF	190.49	10.472	(169.927; 211.045)	<.001
Control	172.01	10.458	(151.478; 192.540)	<.001
D/C/F/TAF - Control	18.48	14.808	(-10.595; 47.550)	0.213

ANCOVA = analysis of covariance; CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = Intent-to-treat; LOCF = last observation carried forward; LS = least squares; NC=F = not completed is failure; SE = standard error.
ANCOVA model on the change from baseline, including the baseline value and treatment as covariates.
Based on NC= F analysis with values after discontinuation imputed with the baseline value. Other (intermittent) missing values are imputed using LOCF.
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab15

3.1.1.2. Resistance Determinations

No DRV or TAF/TDF resistance development was observed. Only 1 subject developed an FTC RAM, M184V/I.

3.1.1.2.1. Baseline Resistance

Genotypes (protease [PR] and reverse transcriptase [RT]) were generated for all subjects at screening.

The majority of subjects in both treatment groups were infected with HIV-1 subtype B (71.7% and 70.7%).

The prevalence of PI, NRTI, and NNRTI RAMs at screening was as expected in a treatment-naïve population and was balanced between treatment groups (Table 10). A low percentage of viruses harbored ≥1 DRV RAMs (6 V11I and 1 L33F) or primary PI RAMs (1.0% and 2.1%, respectively). Secondary PI RAMs were observed in almost all subjects (97.9%; with a median [range] of 4 [0-8] secondary PI RAMs), reflecting the polymorphic nature of these mutations. For RT, NRTI and NNRTI RAMs were detected in 4.7% and 16.3% of the subjects respectively. No resistance mutations related to FTC or TDF/TAF were detected.

As depicted by the protocol all subjects showed 100% susceptibility to DRV, FTC and TFV (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.5.1).

Table 10: Prevalence of Mutations[a] at Screening; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF	Control	Total
Analysis set: Intent-to-treat, N	362	363	725
Subjects with genotype at screening, N	361[b]	362[b]	723
Subtype B[c], n (%)	259 (71.7%)	256 (70.7%)	515 (71.2%)
≥ 1 RAM, n (%)			
DRV RAMs[d]	3 (0.8%)	4 (1.1%)	7 (1.0%)
Primary PI RAMs	7 (1.9%)	8 (2.2%)	15 (2.1%)
Secondary PI RAMs	354 (98.1%)	354 (97.8%)	708 (97.9%)
NRTI RAMs	18 (5.0%)	16 (4.4%)	34 (4.7%)
NNRTI RAMs	55 (15.2%)	63 (17.4%)	118 (16.3%)
Genotypic Susceptibility to, n(%):			
DRV/rtv	361 (100.0%)	362 (100.0%)	723 (100.0%)
FTC	361 (100.0%)	362 (100.0%)	723 (100.0%)
TFV	361 (100.0%)	362 (100.0%)	723 (100.0%)
All NNRTIs	327 (90.6%)	324 (89.5%)	651 (90.0%)
All NRTIs	353 (97.8%)	357 (98.6%)	710 (98.2%)
All PIs	335 (92.8%)	338 (93.4%)	673 (93.1%)

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV/rtv = darunavir/ritonavir; FTC = emtricitabine; IAS-USA = International Antiviral Society-United States of America; ITT = intent-to-treat; N = number of subjects in ITT analysis set; n = subject with observation; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAM = resistance-associated mutation; TFV = tenofovir.
Note: The denominator is subjects with genotype at screening.
Genotypic Susceptibility assessment based on the Monogram GenoSure® MG report.
a. Based on the IAU-USA 2015 mutation list.[9]
b. One subject in each treatment group had failed screening genotypes, but was enrolled based on local genotypes.
c. Non-B subtypes include: A, A1, AE, AG, C, COMPLEX, AB, BC, BF, D, F, F1, F2, G. Subtype is assigned to Complex when the sequence contains 3 or more subtypes and/or Circulating Recombinant Forms (CRFs).
d. IAS-USA DRV resistance-associated mutations: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V.[9]
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab17

Out of the 7 subjects with a DRV RAM at screening, 6 had virologic success at Week 48 and 1 discontinued due to other reason and the last available HIV-1 RNA <50 copies/mL according to the snapshot approach.

Virologic response rates (<50 HIV-1 RNA copies/mL) at Week 48 were consistent between the treatment groups in any of the subgroups by HIV-1 subtype (B, non-B) and baseline resistance factors (presence of primary PI and/or DRV RAMs, NRTI RAMs, NNRTI RAMs, M184V/I and by primary and secondary PI RAMs) (Section 3.1.1.1.2).

3.1.1.2.2. Development of Resistance

Post-screening resistance testing was performed on samples from subjects experiencing protocol-defined virologic failure (virologic nonresponse, virologic rebound, and/or viremic at final time point; see Section 2.4) and who had HIV-1 RNA ≥400 copies/mL at failure or at later time points. At Week 48, 8 subjects in the D/C/F/TAF group and 6 subjects in the control group showed protocol-defined virologic failure (for details on the protocol-defined virologic failures, see Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.5.2 and Mod2.7.2/VirSum/Sec4.3.1.3.2).

Paired screening and postbaseline on-treatment genotypes were available for 7 subjects with protocol-defined virologic failure in the D/C/F/TAF group and 2 in the control group. None of these subjects developed DRV or primary PI RAMs. One subject in the D/C/F/TAF group developed an FTC RAM M184I/V, conferring phenotypic resistance to 3TC and FTC (Table 11 and Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab20 and Mod2.7.2/VirSum/Sec4.3.1.3.2). The subject was discontinued from the study due to noncompliance (data post Week 48 database lock) (for more details see Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec5.5.2).

Table 11: Development of Mutations[a] Postbaseline for Subjects with Protocol-defined Virologic Failure With On-treatment Genotypes; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	362	363
Total number of virologic failures with screening and endpoint genotype	7	2
Subjects developing mutations post-baseline, n		
DRV RAMs	0	0
Primary PI RAMs	0	0
NRTI RAMs	1	0
M184M/I/V	1	
NNRTI RAMs	0	0

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; ITT = intent-to-treat; N = number of subjects in ITT analysis set; n = subject with observation; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAM = resistance-associated mutation.
[a] Based on the IAU-USA 2015 mutation list.[9]
Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab19

3.1.1.3. PK/PD Relationship

There were no apparent relationships (graphically, and via logistic regression) between the pharmacokinetics of DRV or TAF and efficacy (both overall, and when excluding subjects that discontinued prematurely for non-efficacy reasons) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec7).

Exposure to DRV

Virologic response rates were similar across the area under the plasma concentration-time curve over the dosing interval of 24h (AUC_{24h}) quartiles for DRV (93.3%, 95.5%, 92.1% and 92.0% in Q1 through Q4), with no trends in exposure-response relationship across the range of DRV exposures observed (ranging from 40,697 to 188,760 ng.h/mL).

Virologic response rates were similar across the trough (predose) plasma concentration (C_{0h}) quartiles for DRV (92.1%, 96.6%, 93.3% and 90.9% in Q1 through Q4), with no trends in exposure-response relationship across the range of DRV exposures observed (ranging from 418 to 5,895 ng.h/mL).

Exposure to TAF

Virologic response rates were similar across the area under the plasma concentration-time curve over the dosing interval tau (AUC_{tau}) quartiles for TAF (95.5%, 91.0%, 92.1% and 94.3% in Q1 through Q4), with no trends in exposure-response relationship across the range of TAF exposures observed (ranging from 71 to 400 ng.h/mL).

3.1.2. Phase 2 Study GS-US-299-0102 in HIV-1 Infected, ART-naïve Adult Subjects

This was an exploratory study to estimate relative efficacy without objective to demonstrate noninferiority at Week 48 and is thus only supportive for this submission.

D/C/F/TAF was determined to be noninferior to DRV+COBI (cobicistat) with F/TDF in terms of virologic response rate (HIV-1 RNA <50 copies/mL, FDA snapshot approach) at Week 24. The immunologic response was consistent with the virologic response. No developing DRV or primary PI RAMs were observed. One subject in the D/C/F/TAF arm had developing NRTI RAMs (K65K/R and M184M/I).

3.1.2.1. Efficacy Results

3.1.2.1.1. Primary Efficacy Endpoint

Virologic outcomes were similar between the 2 treatment groups D/C/F/TAF and DRV+COBI+F/TDF for the primary endpoint analysis (HIV-1 RNA <50 copies/mL, FDA snapshot approach, FAS, Week 24) with a difference (95% CI) in virologic response rate of 3.3% (-11.4% to 18.1%). D/C/F/TAF was determined to be noninferior to DRV+COBI+F/TDF (ie, lower bound of 95% CI was greater than -12%) (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab9-1).

3.1.2.1.2. Major Secondary Endpoints

Virologic Response at Week 48 (HIV-1 RNA <50 Copies/mL)

The virologic response rate (HIV-1 RNA <50 copies/mL, FDA snapshot approach, FAS) at Week 48 was 76.7% (95% CI, 67.3 to 84.5) in the D/C/F/TAF group and 84.0% (95% CI, 70.9 to 92.8) in the DRV+COBI+F/TDF group with a difference (95% CI) in virologic response between treatment groups of -6.2% (-19.9 to 7.4). The difference in virologic response rates was primarily due to a difference in the numbers of subjects who discontinued the study drugs for reasons unrelated to study drug (ie, other than virologic failure or AEs) (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab9-2).

Immunology Results

Following initiation of study drug, CD4+ cell counts for the FAS (observed data, ie, Missing=Excluded [M=E]) increased for each treatment group (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Fig9-3). The mean (SD) increases were similar for each treatment group through Week 48: D/C/F/TAF 231 (141.9) cells/µL; DRV+COBI+F/TDF 212 (151.5) cells/µL; difference (95% CI) in least square (LS) means: 18 cells/µL (-35 to 72 cells/µL) (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab19.1).

The change from baseline in CD4+ cell counts using the last observation carried forward (LOCF) imputation method (FAS) showed similar trends compared with the observed data (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab19.2 and Sec9.2.5).

3.1.2.2. Resistance Determinations

No developing DRV or primary PI RAMs were observed. One subject in the D/C/F/TAF arm had developing NRTI RAMs (K65K/R and M184M/I).

3.1.2.2.1. Baseline Resistance

A PR/RT genotyping report was obtained at screening for all subjects enrolled in the study in order to confirm genotypic sensitivity to DRV, TDF, and FTC. All subjects enrolled showed full genotypic sensitivity to DRV, emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF), as stated in the protocol.

The prevalence of baseline PR and RT resistance mutations was as expected in an ART-naïve population and balanced between treatment arms (Summary of Virology in Mod2.7.2/VirSum and Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab9-4).

Most subjects enrolled in the study (97.4%) had HIV-1 harboring secondary PI RAMs, reflecting the strong polymorphic nature of these mutations. Low level transmitted PI resistance was observed; 8 subjects had 1 or more primary PI RAM and 6 subjects had 1 DRV RAM at screening, which did not adversely influence treatment response. Also, 9.8% of subjects were found to harbor HIV‑1 with NRTI RAMs. NNRTI RAMs were found in nearly 20% of subjects at screening (for more details refer to Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec9.4 and Summary of Virology in Mod2.7.2/VirSum).

3.1.2.2.2. Development of Resistance

Eight subjects were eligible for postbaseline resistance testing. Of these 8 subjects, 6 were in the D/C/F/TAF group (5.8%, 6 of 103 subjects), and 2 were in the DRV+COBI+F/TDF group (4.0%, 2 of 50 subjects).

None of the 8 subjects developed primary PI RAMs through the initial Week 48 time point. One subject in the D/C/F/TAF arm had NRTI RAMs emerging (K65K/R and M184M/I) post Week 48. 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.

For more details refer to the Summary of Virology in Mod2.7.2/VirSum and the CSR in Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec9.4.

3.1.2.3. PK/PD Relationship

There was no PK/PD relationship between TAF exposure and virologic response rates.

Virologic response rates were similar across the AUC_{tau} quartiles (76.9%, 84.6%, 76.9% and 76.9% in Q1 through Q4), with no trends in exposure-response relationship across the range of TAF exposures observed (ranging from 38.3 to 295.6 ng.h/mL) (see the Summary of Clinical Pharmacology Studies in Mod2.7.2/ClinPharm/Sec3.5.1).

3.1.3. Phase 3 Study TMC114IFD3013 in HIV-1 Infected, ART-experienced, Virologically Suppressed Adult Subjects

The Week-48 results of this randomized, active-controlled, open-label study provide robust proof of efficacy in HIV-1 infected subjects, ART-experienced and virologically suppressed (HIV-1 RNA <50 copies/mL for at least 2 months). In these subjects, previous ART virologic failure was allowed, a history of failure on DRV treatment and DRV RAMs (if historical genotype was available) was not allowed. Subjects had to be suppressed for a minimum of only 2 months prior to screening, and had within 12 months prior to screening at most one viral load elevation between ≥50 copies/mL and <200 HIV-1 RNA copies/mL, after previously reaching viral suppression.

Noninferiority in efficacy, determined as the protocol-defined rebound rate cumulative through Week 48, was demonstrated of D/C/F/TAF FDC compared to control treatment. Low protocol-defined rebound rates cumulative through Week 48 and high response rates at Week 48 were observed with D/C/F/TAF FDC. Virologic rebound appeared to be driven by transient low-level viremia. The immunologic response was consistent with the virologic response. No resistance to study drugs was observed in either treatment group.

3.1.3.1. Efficacy Results

3.1.3.1.1. Primary Efficacy Endpoint

The protocol-defined virologic rebound rate cumulative through Week 48 in the ITT analysis set was low and similar in both treatment groups: 2.5% (19/763) in the D/C/F/TAF group vs 2.1% (8/378) in the control group (Table 12 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Fig4). D/C/F/TAF was noninferior to the control (ie, upper limit of the stratified MH 95% CI <4%): treatment difference (95% CI) D/C/F/TAF - control was 0.4 (-1.5; 2.2); corresponding one-sided noninferiority p-value <0.001.

Results were consistent across bPI strata as shown by the nonsignificant p-value for homogeneity test of treatment differences, ie, 0.73 (Table 12).

The results in the PP analysis set confirm the noninferiority of D/C/F/TAF vs control. The protocol-defined virologic rebound rate cumulative through Week 48 was low in both treatment groups for the PP analysis set: 1.9% (14/721) in the D/C/F/TAF group vs 0.8% (3/358) in the control group with a difference (95% CI) between D/C/F/TAF and control of 1.1 (-0.3; 2.5) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab18).

Individual viral load profiles for rebounders can be found in Mod5.3.5.1/TMC114IFD3013-W48-CSR/Fig7 (FDA snapshot approach, ITT, Week 48).

Table 12: Proportion of Protocol-defined Virologic Rebound (HIV-1 RNA ≥50 Copies/mL) Cumulative Through Week 48; ITT (Study TMC114IFD3013)

			Virologic Rebound Rate		D/C/F/TAF vs. Control		
						P-values	
Threshold	Treatment	N	n (%)	(95% CI)[b]	Difference in Proportions (95% CI)[a]	Non-inferiority/ Superiority	Homo-geneity
>=50 copies/mL	D/C/F/TAF	763	19 (**2.5%**)	(1.5 ; 3.9)	0.4 (-1.5; 2.2)	<.001[c] 0.654[d]	0.727[e]
	Control	378	8 (**2.1%**)	(0.9 ; 4.1)			

ATV = atazanavir; bPI = boosted protease inhibitor; CI = confidence interval; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; HIV = human immunodeficiency virus; ITT = Intent-to-treat; LPV = lopinavir; MH = mantel-Haensel; N = number of subjects in ITT analysis set; n = subject with observation; rtv = ritonavir.

[a] Based on MH test adjusting for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv).

[b] Two-sided Exact Clopper-Pearson 95% CI.

[c] One-sided p-value for non-inferiority of D/C/F/TAF vs Control (margin = 4%).

[d] One-sided p-value for the superiority of D/C/F/TAF vs Control.

[e] One-sided p-value from weighted least squares chi-squared statistic for homogeneity of treatment effect across the strata (bPI)

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab17

3.1.3.1.2. Major Secondary Endpoints

3.1.3.1.2.1. Endpoints Using the 50 HIV-1 RNA Copies/mL Threshold

Virologic Response and Failure Rate According to the FDA Snapshot Approach

At Week 48, the virologic response rate (HIV-1 RNA <50 copies/mL) in the ITT analysis set per FDA snapshot approach in the D/C/F/TAF and the control group was high and similar (ie, approximately 94% in both treatment groups) (Table 13). The virologic failure rate was very low (<1.0%) in each treatment group with a difference (95% CI) in virologic failure rate at Week 48 between D/C/F/TAF and control of 0.3 (-0.7; 1.2) (Table 14). In addition, 4.3% vs 5.8% of subjects had no viral load data in the Week-48 window.

Table 13: Virologic Response and Failure Categories According to Snapshot Approach (HIV-1 RNA <50 Copies/mL) at Week 48; ITT (Study TMC114IFD3013)

n(%)	D/C/F/TAF	Control
Analysis Set: Intent-to-treat, N	763	378
<50 copies/mL		
Virologic response:		
HIV RNA <50 copies/mL at Week 48	724 (94.9%)	354 (93.7%)
Virologic failure:	6 (0.8%)	2 (0.5%)
HIV RNA ≥50 copies/mL at Week 48	4 (0.5%)	2 (0.5%)
Virologic failure - leading to discontinuation	0	0
Virologic failure - discontinued due to other reason and last available HIV RNA ≥50 copies/mL[a]	2 (0.3%)	0
No viral load data in 48 Week window	33 (4.3%)	22 (5.8%)
Discontinued due to AE/death	11 (1.4%)	4 (1.1%)
Discontinued due to other reason and the last available HIV RNA <50 copies/mL (or missing)[b]	19 (2.5%)	16 (4.2%)
Missing data during window but on study	3 (0.4%)	2 (0.5%)

AE = adverse event; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV = human immunodeficiency virus; ITT = Intent-to-treat; N = number of subjects in ITT analysis set; n = subject with observation.
[a] Reasons for discontinuation included lost to follow-up (1 vs 0 subjects) and withdrawal by subject (1 vs 0 subjects).
[b] Reasons for discontinuation included lost to follow-up (4 vs 5 subjects), non-compliance with study drug (2 vs 0 subjects), withdrawal by subject (8 vs 8 subjects), and other (5 vs 3 subjects).
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab19

Table 14: Proportion of Virologic Failure (HIV-1 RNA ≥50 Copies/mL) According to Snapshot Approach at Week 48; ITT (Study TMC114IFD3013)

			Virologic Failure		D/C/F/TAF vs. Control
Threshold	Treatment	N	n (%)	(95% CI)[b]	Difference in Proportions (95% CI)[a]
≥50 copies/mL	D/C/F/TAF	763	6 (**0.8%**)	(0.3 ; 1.7)	0.3 (-0.7; 1.2)
	Control	378	2 (**0.5%**)	(0.1 ; 1.9)	

ATV = atazanavir; bPI = boosted protease inhibitor; CI = confidence interval; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; HIV = human immunodeficiency virus; ITT = Intent-to-treat; LPV = lopinavir; MH = mantel-Haensel; N = number of subjects in ITT analysis set; n = subject with observation; rtv = ritonavir.
[a] Based on MH test adjusting for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv).
[b] Two-sided Exact Clopper-Pearson 95% CI.
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab20

Protocol-defined Virologic Rebound Rate Versus FDA Snapshot Outcome

In the D/C/F/TAF group, 12 out of the 19 rebounders (primary endpoint) were re-suppressed and considered responders at Week 48 (HIV-1 RNA <50 copies/mL) by the FDA snapshot approach. Six rebounders were virologic failures at Week 48, and the remaining rebounder had missing viral load data in the Week 48 window (discontinued due to other reason and the last available HIV RNA <50 copies/mL).

In the control group, 4 out of the 8 rebounders (primary endpoint) were re-suppressed and considered responders at Week 48 (HIV-1 RNA <50 copies/mL) by the FDA snapshot approach. Two rebounders were virologic failures at Week 48, and the remaining 2 rebounders had missing viral load data in the Week-48 window (1 subject discontinued due to AE/death and 1 subject had missing data during window but was on study)
(Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab22).

3.1.3.1.2.2. Endpoints Using the 200 HIV-1 RNA Copies/mL Threshold

Protocol-defined Virologic Rebound Rate

The protocol-defined virologic rebound rate (HIV-1 RNA ≥200 copies/mL) cumulative through Week 48 in the D/C/F/TAF group was 0.4% (ie, 3 subjects). There were no virologic rebounders (HIV-1 RNA ≥200 copies/mL) through Week 48 in the control group (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.3.2.1).

Virologic Response and Failure Rate According to the FDA Snapshot Approach

Response rates at Week 48 by the FDA snapshot approach using the 200 HIV-1 RNA copies/mL threshold were similar between the treatment groups: 95.0% vs 94.2%. The virologic failure rate was low in the D/C/F/TAF group (3 subjects [0.4%]; all of the 3 D/C/F/TAF rebounders were virologic failures based on the FDA snapshot approach using the 200 copies/mL threshold). In the control group, there were no virologic failures. In addition, 4.6% vs 5.8% of subjects had no viral load data in the Week-48 window (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.3.2.1 and Sec5.3.2.2).

3.1.3.1.2.3. Subgroup Analyses

Subgroups included bPI (and booster) at screening, baseline disease characteristics (screening/baseline viral load, baseline CD4+ cell count and World Health Organization [WHO] Clinical Staging of HIV/acquired immune deficiency syndrome [AIDS]), demographic characteristics (gender, age [≤50, >50 years], race, ethnicity, region), adherence, number of prior ARVs/PIs/N(t)RTIs/NNRTIs used, prior ARV/PI/N(t)RTI/NNRTI virologic failure (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.4).

In general, differences in protocol-defined virologic rebound rate (≥50 HIV-1 RNA copies/mL) cumulative through Week 48 and virologic response rate (HIV-1 RNA <50 copies/mL) at Week 48 between the treatment groups were consistent across the various subgroups (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.4).

3.1.3.2. Immunology Results

The mean (SE) baseline CD4+ count values were 653.3 (9.12) cells/mm^3 in the D/C/F/TAF group and 641.7 (13.15) cells/mm^3 in the control group. When adjusting for baseline CD4+ cell counts, LS mean estimates (SE) for changes (increases) from baseline in CD4+ cell count at Week 48 were 18.69 (7.219) cells/mm^3 in the D/C/F/TAF group and 4.91 (9.073) cells/mm^3 in the control group (Table 15). There was no statistically significant difference between treatment groups at Week 48 (p=0.148) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.5).

Table 15: Change from Baseline in CD4+ Cell Counts (Cells/mm3) at Week 24 and 48 (ANCOVA); ITT (Study TMC114IFD3013)

	LS Means	SE	95% CI	P-Value
Week 24				
D/C/F/TAF	16.60	7.193	(2.491; 30.717)	0.021
Control	8.41	9.040	(-9.327; 26.147)	0.352
D/C/F/TAF - Control	8.19	9.483	(-10.412; 26.799)	0.388
Week 48				
D/C/F/TAF	18.69	7.219	(4.529; 32.857)	0.010
Control	4.91	9.073	(-12.889; 22.713)	0.588
D/C/F/TAF - Control	13.78	9.517	(-4.892; 32.454)	0.148

ANCOVA = analysis of covariance; CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = Intent-to-treat; LOCF = last observation carried forward; LS = least squares; NC=F = not completed is failure; SE = standard error.
ANCOVA model on the changes from baseline in CD4 cell count, including bPI at screening, baseline value and treatment as covariates.
Based on NC=F analysis with values after discontinuation imputed with the baseline value. Other (intermittent) missing values are imputed using LOCF.
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab26

3.1.3.3. Resistance Determinations

No DRV, primary PI, TDF/TAF, or FTC RAMs were observed in any rebounder.

3.1.3.3.1. Baseline Resistance

Study TMC114IFD3013 enrolled ART-experienced, virologically suppressed subjects (HIV-1 RNA copies/mL <50 at screening) and therefore no screening genotypes could be generated. Previous virologic failure on DRV was not allowed and in case historical genotypes were available, subjects with DRV RAMs were excluded. One subject with V11I mutation on its historical genotype was randomized and had HIV-1 RNA <50 copies/mL throughout the study until week 36, when the subject was lost to follow-up.

3.1.3.3.2. Development of Resistance

Due to the low proportion of rebounders of which the majority had low viral load values, few samples were eligible for postbaseline genotyping (resistance testing performed when HIV-1 RNA ≥400 copies/mL). One rebounder in the D/C/F/TAF group and 3 rebounders in the control group had postbaseline genotypes. No DRV, primary PI, TDF/TAF, or FTC RAMs were observed (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab28). For more details, refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec5.6 and Mod2.7.2/VirSum).

3.1.3.4. PK/PD Relationship

There were no apparent relationships (graphically, and via logistic regression) between the pharmacokinetics of DRV and virologic rebound or virologic failure (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7).

For DRV exposure expressed as AUC_{24h}, the proportion of protocol-defined virologic rebound through Week 48 and virologic failure at Week 48 per FDA snapshot approach were similar

across the AUC_{24h} quartiles for DRV (1.6%, 2.7%, 2.7% and 3.2%; and 1.1%, 0.5%, 0.5% and 1.1% in Q1 through Q4, respectively), with no trends in exposure-proportion relationship across the range of DRV exposures observed (ranging from 41,920 to 209,490 ng.h/mL) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7, Att-GPK02_EXT, and Att-TPK03_EXT).

For DRV exposure expressed as C_{0h}, the proportion of protocol-defined virologic rebound through Week 48 and virologic failure at Week 48 per FDA snapshot approach were similar across the $C0_h$ quartiles for DRV (1.1%, 3.7%, 2.1% and 3.2%; and 1.1%, 0.5%, 0.5% and 1.1% in Q1 through Q4, respectively), with no trends in exposure-proportion relationship across the range of DRV exposures observed (ranging from 231 to 6,757 ng.h/mL) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7, Att-GPK02_EXT, and Att-TPK03_EXT).

3.2. Efficacy and Resistance in HIV-1 Infected Adolescent Subjects

D/C/F/TAF is expected to show the same high level of efficacy as seen with DRV in combination with rtv and E/C/F/TAF in the adolescent population, based on PK data of DRV and the other individual components of D/C/F/TAF FDC.

3.2.1. Phase 2 Study TMC114-C230 in HIV-1 Infected, ART-naïve Adolescent Subjects

In the Phase 2 Study TMC114-C230 with DRV/ritonavir (rtv) 800/100 mg once daily (in combination with zidovudine/lamivudine (AZT/3TC) or abacavir (ABC)/lamivudine (3TC) in HIV-1 infected, ART-naïve adolescents, high virologic response rates were observed, demonstrating efficacy of DRV/rtv in this age group. The immunologic response was consistent with the virologic response. Development of resistance to the ARV regimen used in this study was rare.

3.2.1.1. Efficacy Results

3.2.1.1.1. Primary Efficacy Endpoint

At Week 24, 11 of 12 (91.7%) subjects had a confirmed virologic response, defined as the percentage of subjects with confirmed plasma viral load <50 copies/mL (TLOVR, ITT, primary efficacy parameter). At Week 48, 10 (83.3%) subjects had a confirmed virologic response (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab15 and Fig1).

The results for this virologic response parameter were consistent as confirmed by several sensitivity analyses (Observed Case, not completed is failure [NC=F], and TLOVR non-VF censored analyses) (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab16).

According to the FDA snapshot approach, virologic response (HIV-1 RNA <50 copies/mL) was achieved in all 12 subjects at Week 24 and in 11 out of 12 subjects (91.7%) at Week 48 (1 subject had HIV-1 RNA >50 copies/mL at Week 48) (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab17).

3.2.1.1.2. Major Secondary Endpoints

Virologic outcome using the HIV-1 RNA <400 copies/mL threshold at Week 48 (91.7%) was comparable with the <50 copies/mL threshold via TLOVR, and other sensitivity analyses (Observed Case, NC=F, and TLOVR non-VF censored analyses) (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab18 and Tab19).

The CD4+ cell count increased during the study. The mean (SE) change in CD4+ absolute cell count at Week 48 from baseline (NC=F, ITT) was 221 (22.4) x 10^6/L and the median (range) change was 221 (64-370) x 10^6/L (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab22).

3.2.1.2. Resistance Determinations

3.2.1.2.1. Baseline Resistance

All subjects were susceptible to all PIs, including DRV, and NRTIs, and therefore received a fully susceptible background regimen containing 2 NRTIs (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab11). No primary PI or NRTI RAMs were detected at baseline. One subject harbored 1 DRV RAM (V11I) (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab10) and this subject had a confirmed virologic response from Week 16 onwards until Week 48.

3.2.1.2.2. Development of Resistance

There was 1 (8.3%) never-suppressed subject and 1 (8.3%) rebounder (TLOVR non-VF censored). Neither developed DRV RAMs or lost phenotypic susceptibility to any commercially available PI (including DRV) or any NRTI in the background regimen (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec6.2). The never-suppressed subject's viral load declined from baseline and the subject had an unconfirmed viral load <50 copies/mL at Week 24, and values >50 copies/mL thereafter. This subject had a treatment-emergent primary PI mutation (M46I). The rebounder's viral load returned to undetectable (<50 copies/mL) at Week 48, after rebound at Week 40. The subject had a treatment-emergent NRTI RAM (K219Q).

3.2.1.3. PK/PD Relationship

No apparent relevant relationships were observed between DRV AUC_{24h} or predose plasma concentration (C_{0h}) and virologic response, defined as plasma viral load HIV-1 RNA <50 copies/mL at Week 48 (NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Fig8).

3.2.2. Phase 2/3 Study GS-US-292-0106 in HIV-1 Infected, ART-naïve Adolescent Subjects

In HIV-1 infected, ART-naïve adolescents, the E/C/F/TAF FDC (150/150/200/10 mg) showed a robust virological and immunological response. No emergent resistance to any of the study drugs was observed.

3.2.2.1. Efficacy Results

3.2.2.1.1. Primary Efficacy Endpoint

At Week 24, the virologic response rate was 90.0% (45 of 50 subjects) in the FAS (FDA snapshot approach, HIV-1 RNA <50 copies/mL).[5]

At Week 48, the virologic response rate was 92.0% (46 of 50 subjects) in the FAS (FDA snapshot approach, HIV-1 RNA <50 copies/mL) (Table 16).

Table 16: Virologic Outcomes at Week 48 for HIV-1 RNA Cut-off at 50 Copies/mL (FDA Snapshot Approach); FAS (GS-US-292-0106)

	E/C/F/TAF (N=50)
Virologic Success at Week 48	
HIV-1 RNA <50 copies/mL	46 (92.0%)
Virologic Failure at Week 48	3 (6.0%)
HIV-1 RNA ≥50 copies/mL	2 (4.0%)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 copies/mL[a]	1 (2.0%)
No Virologic Data in Week-48 Window	1 (2.0%)
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[a]	1 (2.0%)

AE = adverse event; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDA = Food and Drug Administration; FAS = Full Analysis Set; HIV-1 = human immunodeficiency virus type 1.

a. Discontinuation due to other reasons includes 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.

Source: adapted from Gaur et al. 2016 (manuscript)[6]

3.2.2.1.2. Major Secondary Endpoints

The mean (SD) CD4+ cell count was 471 (212.2) cells/µL at baseline, 659 (288.4) cells/µL at Week 24 and 685 (245.4) cells/µL at Week 48.[6]

3.2.2.2. Resistance Determinations

No subjects developed resistance to study drugs.[6]

3.2.2.2.1. Baseline Resistance

Consistent with enrollment criteria, all enrolled subjects demonstrated full sensitivity to EVG, FTC, and tenofovir.

NRTI-associated resistance mutations were observed in 8% of subjects and NNRTI-associated resistance mutations were observed in 6% of subjects. Primary INSTI-associated resistance mutations and primary PI-associated resistance mutations were not observed in any subjects (0 of 50) at screening.

The HIV-1 subtype was determined for each subject using the screening genotype. The majority of subjects had non-B HIV-1 subtype (78% overall, 39 of 50 subjects) (Mod2.7.2/VirSum/Tab14).[1]

3.2.2.2.2. Development of Resistance

Two subjects were eligible for resistance testing. No emergent resistance to any of the study drugs was observed in either subject (Summary of Virology in Mod2.7.2/VirSum).[6]

3.2.2.3. PK/PD Relationship

No PK/PD analysis was done for this study. The PK data for this study are summarized in the Summary of Clinical Pharmacology in Module 2.7.2/ClinPharm/Sec2.2.3.1.

4. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

As discussed in Section 2.4, no pooling or comparison of the studies described in this summary supporting D/C/F/TAF efficacy is considered appropriate. Therefore, this section is limited to subgroup analyses across relevant studies and baseline resistance, and concludes with presenting key efficacy results across studies/populations.

Treatment outcomes were similar across subgroups in Study TMC114FD2HTX3001 and TMC114IFD3013. For more details, refer to Sections 3.1.1.1.2 and 3.1.3.1.2.3.

Overall there were 7 subjects with a DRV RAM pre-D/C/F/TAF treatment, in Studies TMC114FD2HTX3001 (3 V11I), GS-US-299-0102 (L33F, I50V, I54L/M), and TMC114IFD3013 (V11I), who all had HIV-1 RNA<50 copies/mL at Week 48 (or at discontinuation) by FDA snapshot approach (Mod2.7.2/VirSum/Sec4.3.1.3.1, 4.3.2.3.1, 4.3.3.3.1, and 4.4.1.3.1).

Across the Phase 3 and 2 D/C/F/TAF studies, development of resistance to the study drugs was rare. None of the subjects with post-baseline resistance data developed DRV or primary PI RAMs and no subject developed phenotypic DRV resistance. Emerging FTC RAM M184V/I was observed twice, conferring phenotypic resistance to FTC in one subject. TDF/TAF RAM K65R emerged in 1 subject, however no phenotypic resistance to TFV (delivered as TAF) was observed. An overview of emerging resistance in the Phase 3 and 2 clinical studies supporting D/C/F/TAF is provided in Mod2.7.2/VirSum/Sec5.

The main efficacy results from the Phase 3, Phase 2/3, and Phase 2 studies included in this submission are summarized and presented side by side in Table 17. Results of the individual studies are provided in Section 3.

Table 17: Main Efficacy Endpoints of the Phase 3 and 2 Studies Supporting the Clinical Efficacy and Safety Profile of the D/C/F/TAF FDC Tablet

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102		TMC114IFD3013		TMC114-C230	GS-US-292-0106
Efficacy Endpoint (Analysis Set)	D/C/F/TAF N=362	DRV/COBI+ F/TDF N=363	D/C/F/TAF N=103	DRV+COBI+ F/TDF N=50	D/C/F/TAF (N=763)	current bPI +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF N=50
Virologic Outcome - Snapshot								
(ITT/FAS) N	362	363	103	50	763	378	12	50
Virologic Success at Week 48								
HIV-1 RNA <50 copies/mL	331 (91.4%)	321 (88.4%)	79 (76.7%)	42 (84.0%)	724 (94.9%)	354 (93.7%)	11 (91.7%)	46 (92.0%)
adjusted % difference (95% CI)	2.7 (-1.6; 7.1)		-6.2% (-19.9%; 7.4%)		1.2 (-1.7; 4.1)		-	-
Virologic Failure at Week 48	16 (4.4%)	12 (3.3%)	16 (15.5%)	6 (12.0%)	6 (0.8%)	2 (0.5%)	1 (8.3%)	3 (6.0%)
HIV-1 RNA ≥50 copies/mL	9 (2.5%)	9 (2.5%)	7 (6.8%)	4 (8.0%)	4 (0.5%)	2 (0.5%)	-	2 (4.0%)
Discontinued Study Drug Due to Lack of Efficacy	1 (0.3%)[a]	0	0	0	0	0	-	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 copies/mL	6 (1.7%)	3 (0.8%)	9 (8.7%)	2 (4.0%)	2 (0.3%)	0	-	1 (2.0%)
No Virologic Data in Week-48 Window	15 (4.1%)	30 (8.3%)	8 (7.8%)	2 (4.0%)	33 (4.3%)	22 (5.8%)	0	1 (2.0%)
Discontinued Study Drug Due to AE/Death	8 (2.2%)	16 (4.4%)	1 (1.0%)	1 (2.0%)	11 (1.4%)	4 (1.1%)	-	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL (or missing)	4 (1.1%)	9 (2.5%)	7 (6.8%)	1 (2.0%)	19 (2.5%)	16 (4.2%)	-	1 (2.0%)
Virologic Success at Week 48 (PP, N)	348	344	85	46	721	358	-	-
HIV-1 RNA <50 copies/mL	327 (94.0%)	317 (92.2%)	79 (92.9%)	42 (91.3%)	694 (96.3%)	342 (95.5%)	-	-
adjusted % difference (95% CI)	1.5 (-2.3; 5.2)		2.4% (-8.8%; 13.7%)		0.7 (-1.8; 3.3)		-	-
Virologic Rebound Through Week 48 (≥50 copies/mL), N	-	-	-	-	763	378	-	-
Virologic rebound (ITT)	-	-	-	-	19 (2.5%)	8 (2.1%)	-	-
adjusted % difference (95% CI)					0.4 (-1.5; 2.2)			
N					721	358		
Virologic rebound (PP)	-	-	-	-	14 (1.9%)	3 (0.8%)	-	-
adjusted % difference (95% CI)					1.1 (-0.3; 2.5)			

ABC/3TC = abacavir/lamivudine; AE = adverse event; ART = antiretroviral treatment; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; CI = confindence interval; COBI = cobicistat; CSR = Clinical Study Report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FAS = Full Analysis Set; FDC = fixed-dose combination; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); HIV-1 = human immunodeficiency virus type 1; ITT = Intent-to-treat; N = number of subjects; PP = Per Protocol; rtv = low-dose ritonavir

[a] This subject reached a virologic endpoint per investigator's assessment. [redacted]

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR, Mod5.3.5.1/GS-US-299-0102-Final-CSR, Mod5.3.5.1/TMC114IFD3013-W48-CSR, and NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR, and Gaur et al. 2016 (manuscript)[6]

5. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The considerations below support the use of the D/C/F/TAF (800/150/200/10 mg) FDC for the treatment of HIV-1 infection in adult and adolescent subjects.

In adults, the efficacy of the D/C/F/TAF (800/150/200/10 mg) FDC tablet is demonstrated by the results of the 2 pivotal Phase 3 studies. These studies showed a robust efficacy in both ART-naïve and ART-experienced, virologically suppressed, adult subjects.

In adolescents, the proposed use of the D/C/F/TAF (800/150/200/10 mg) FDC tablet for the treatment of HIV-1 infection is based on the approval of the separate components DRV, COBI, FTC, and TAF in adolescents. Studies supporting this indication are Study TMC114-C230 and GS-US-292-0106; recent data from Study GS-US-216-0128[10] in adolescents provide further supportive evidence. The exposures of the individual components of the D/C/F/TAF FDC have been shown to be similar in adults and in adolescents using the same doses. Boosted DRV and F/TAF have shown potent efficacy and consistent immunological response in HIV-1 infected ART-naïve adolescents, similar to results from studies in HIV-1 infected, ART-naïve adults. Furthermore, the exposure to COBI as well as its capacity as a PK enhancer, have been shown to be similar in adults and adolescents.

For more details on the PK results of the above studies, refer to the Summary of Clinical Pharmacology Studies in Mod2.7.2/ClinPharm/Sec2.2.3.1 and NDA021976/Mod2.7.2/ClinPharm/Sec3.14.2 (June 2012).

6. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

The Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 are still ongoing. Long-term efficacy and resistance data of D/C/F/TAF treatment up to Week 96 and beyond are expected at a later stage.

Long-term efficacy of the single agents has already been established as described below.

Long-term efficacy of DRV treatment has been studied up to Week 192 in combination with rtv and F/TDF 200/300 mg in the Phase 3 Study TMC114-C211. In this randomized, controlled, open-label study, ART-naïve subjects received 192 weeks of treatment with an optional extension phase. After 96 weeks of treatment, virologic response rates (TLOVR - ITT) were 79.0% in the DRV/rtv group and 70.8% in the comparator group with lopinavir (LPV)/rtv. The difference in percentage (95% CI) was 8.2% (1.7; 14.7) (NDA021976/Mod5.3.5.1/TMC114-C211-W96-CRR/Tab12 and Tab13). After 192 weeks of treatment, virologic response rates (FDA snapshot approach) were 70% and 61% for DRV/rtv and LPV/rtv, respectively, with a difference (95% CI) of 9% (1.9; 16.1).[1]

Long-term efficacy of F/TAF treatment used at a dose of 200/10 mg as E/C/F/TAF has been studied in Studies GS-US-292-0104 and GS-US-292-0111. In these randomized, double-blind studies in ART-naïve subjects, subjects received treatment with E/C/F/TAF or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) for 144 weeks. After 96 weeks of treatment, rates of virologic response were 87% and 85% in the E/C/F/TAF and the E/C/F/TDF groups, respectively, with a difference (95% CI) of 1.5% (-1.8; 4.8).[1] After 144 weeks of treatment, virologic response was 84% and 80%, with a difference (95% CI) of 4.2% (0.6%; 7.8%).[7] Long-term efficacy data of F/TAF treatment (administered at a dose of 200/10 mg or 200/25mg, according to the third agent) has been established up to Week 96 in ART-experienced virologically suppressed subjects switching from an F/TDF based regimen (Study GS-US-311-1089).[12]

Emergence of RAMs and phenotypic resistance against DRV and F/TAF regimens were rare in all studies up to 144 and 192 weeks:

- Study TMC114-C211 (DRV/rtv): Through 192 weeks, no subjects developed primary PI RAMs and just one subject developed a DRV RAM (secondary PI RAM V11I, without phenotypic resistance to DRV or any other PI). Four (out of 343) subjects developed NRTI RAMs (M184I/V [n=1], M184V [n=2], and M184V+K70E [n=1]) accompanied with a loss of FTC susceptibility (NDA021976/Mod5.3.5.1/TMC114-C211-Week192-CRR/Tab29 and Tab 30).
- In a pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF vs E/C/F/TDF): Up to Week 144, the development of one or more primary EVG, FTC, or TAF RAM was observed in HIV-1 isolates from 12 of 22 subjects with evaluable genotypic data from paired baseline and E/C/F/TAF treatment-failure isolates (12 of 866 subjects [1.4%]) compared with 12 of 20 treatment-failure isolates from subjects with evaluable genotypic data in the E/C/F/TDF treatment group (12 of 867 subjects [1.4%]). In the E/C/F/TAF group, the NRTI RAMs that emerged were M184V/I (n=11) and K65R/N (n=2). In the

E/C/F/TDF group, the NRTI RAMs that emerged were M184V/I (n=9), K65R/N (n=4), and L210W (n=1). In phenotypic analyses of subjects in the final resistance analysis, HIV-1 isolates from 8 subjects had reduced susceptibility to FTC in the E/C/F/TAF group compared with HIV-1 isolates from 7 subjects in the E/C/F/TDF group. One subject in the E/C/F/TAF group and 2 subjects in the E/C/F/TDF group had reduced susceptibility to TFV.[7]

7. SUMMARY AND CONCLUSIONS

7.1. Summary of Efficacy and Resistance Data in Adults

The Week 48 results of the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 established that D/C/F/TAF is noninferior to a reference treatment used as control, in HIV-1 infected adult subjects.

In HIV-1 infected, ART-naïve adults (Study TMC114FD2HTX3001) who were treated with either the D/C/F/TAF FDC or reference treatment DRV/COBI+F/TDF:

- Virologic response (FDA snapshot approach, HIV-1 RNA <50 copies/mL, ITT) at Week 48 was 91.4% vs 88.4% in the D/C/F/TAF and control group, respectively. The stratum-adjusted difference (95% CI) in virologic response between the D/C/F/TAF FDC and the reference treatment was 2.7% (-1.6 to 7.1); the lower bound was higher than -10%, allowing to conclude noninferiority.
- Results were consistent across the sensitivity analyses, and across the various subgroups (eg, by baseline disease and demographic characteristics).

In HIV-1 infected, ART-experienced, virologically suppressed adults (Study TMC114IFD3013) who switched from a boosted PI+F/TDF-containing regimen to the D/C/F/TAF FDC or remained on their baseline regimen through Week 48:

- Virologic rebound (ITT) is defined as having confirmed HIV-1 RNA ≥50 copies/mL up to, and including the upper bound of the Week 48 window (ie, 54 weeks), or having discontinued prematurely (irrespective of reason) with the last available (single) HIV-1 RNA value on treatment being ≥50 copies/mL. In addition, any subject with last available on-treatment HIV-1 RNA ≥50 copies/mL at the study cut-off (Week 48) was considered a virologic rebounder. In both treatment groups, comparable low protocol-defined rebound rates cumulative through 48 weeks were observed (2.5% vs 2.1%). The stratum-adjusted difference (95% CI) in protocol-defined virologic rebound cumulative through Week 48 between D/C/F/TAF and the reference treatment was -0.4% (-1.5 to 2.2); the upper bound was lower than 4%, allowing to conclude noninferiority.
- Results were consistent in the various subgroups, such as bPI, adherence, and demographic characteristics.
- Protocol-defined virologic rebound rate cumulative through Week 48 appeared to be driven by transient low-level viremia:
  - Many rebounders (12/19 vs 4/8 in the D/C/F/TAF and control group, respectively) were re-suppressed and considered responders at Week 48 (<50 copies/mL, FDA snapshot response).
  - Rebounders had viral loads mainly between ≥50 and <200 copies/mL.
  - The rebound rate using the HIV-1 RNA 200 copies/mL threshold was 0.4% vs 0%.
  - Virologic failure (FDA snapshot approach HIV-1 RNA ≥50 copies/mL) at Week 48 was <1% in both treatment groups (ie, 0.8% vs 0.5%) with a stratum-adjusted difference (95% CI) between D/C/F/TAF and control of 0.3 (-0.7; 1.2).

  - Virologic response (FDA snapshot approach, HIV-1 RNA <50 copies/mL) was 94.9% vs 93.7% in the D/C/F/TAF and control group, respectively, at Week 48.

- The level of ART experience did not appear to influence the rebound and response rate: In this treatment-experienced population, prior ARV/PI/NRTI/NNRTI use (prior to the bPI+2NRTIs screening regimen) or previous ARV/PI/NRTI/NNRTI failure had no effect on the virologic rebound and response rate in either treatment group.

In Studies TMC114FD2HTX3001 and TMC114IFD3013, immunologic response was consistent with the virologic response with mean increase from baseline in CD4+ cell count at Week 48 of:

- 190.49 cells per mm^3 in the D/C/F/TAF group and 172.01 cells per mm^3 in the control groups in ART-naïve subjects.
- 18.69 cells per mm^3 in the D/C/F/TAF group and 4.91 cells per mm^3 in the control groups in ART-experienced, virologically suppressed subjects. As expected in this suppressed population, the mean CD4+ count at baseline was already high.

Through 48 weeks in the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013:

- No resistance associated with DRV or TAF was observed postbaseline.
- Only one treatment-naïve subject in the D/C/F/TAF group developed an M184I/V mutation conferring FTC resistance.

Overall, no apparent PK/PD relationships were observed between DRV and TAF exposures obtained after once-daily administration of the D/C/F/TAF FDC tablet and the evaluated efficacy parameters.

7.2. Summary of Efficacy and Resistance Data in Adolescents

No PK/PD relationship data are available with the D/C/F/TAF FDC tablet in the adolescent population (aged ≥12 to <18 years and weighing at least 40 kg). However, the Sponsor proposes the use of the D/C/F/TAF FDC tablet for the treatment of HIV-1 infection in adolescents, based on the results of Studies TMC114-C230, GS-US-292-0106, and GS-US-216-0128[10]. In these 3 studies, the D/C/F/TAF components studied showed similar exposures in adolescents and in adults; boosted DRV and F/TAF showed similar efficacy and immunological results in adults and in adolescents. Furthermore, the boosting effect of COBI was shown to be the same in adolescents and adults.

In HIV-1 infected, ART-naïve adolescents who were on DRV/rtv 800/100 mg once daily (Study TMC114-C230):

- Virologic response (FDA snapshot approach, HIV-1 RNA <50 copies/mL, ITT) was 91.7% at Week 48.
- The mean change in CD4+ absolute cell count from baseline at Week 48 was 221 x 10^6/L.
- No development of resistance to DRV or NRTI background regimen was observed.

In HIV-1 infected ART-naïve adolescents who were on the E/C/F/TAF FDC (150/150/200/10 mg) (Study GS-US-292-0106):

- The virologic response rate (FDA snapshot approach, HIV-1 RNA <50 copies/mL, ITT) was 92.0% at Week 48.
- The immunologic response was consistent with the virologic response with an increase in mean (SD) CD4+ from 471 (212.2) cells/µL at baseline to 685 (245.4) cells/µL at Week 48.
- No development of resistance to F/TAF was observed.

7.3. Conclusions

The clinical data from the D/C/F/TAF Phase 3 studies in HIV-1 infected, ART-naïve and -experienced adult subjects demonstrate that once-daily use of the D/C/F/TAF FDC (800/150/200/10 mg) has a robust and sustained virological and immunological profile, similar to that of established boosted PI triple-drug ART, with no emergence of DRV resistance and rare emergence of resistance to F/TAF in HIV-1 infected adults.

Evidence for the long-term efficacy of the D/C/F/TAF combination is provided by the historical data of the approved individual combinations, ie, DRV/COBI (800/150 mg) and F/TAF (used in the E/C/F/TAF 150/150/200/10 mg FDC).

The efficacy of the D/C/F/TAF FDC in adolescents can be assumed to be the same as in adults, based on the PK data from the historical DRV/rtv and E/C/F/TAF studies and from the currently ongoing DRV+COBI study[10], which showed similar exposures compared to adults in adolescent subjects.

Therefore, the Sponsor proposes the use of the D/C/F/TAF FDC tablet for the treatment of HIV-1 infection in adults and adolescents.

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Appendix

Appendix 1: Study Narratives of Studies Contributing Significantly to Efficacy and Safety

Study TMC114FD2HTX3001

Location:	Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR
Title:	A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen vs a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects.
Primary Objective:	The primary objective was to demonstrate noninferiority in efficacy of a D/C/F/TAF FDC tablet vs DRV/COBI FDC coadministered with F/TDF FDC in HIV-1 infected, ART-naïve adult subjects, as determined by the proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 48 (FDA snapshot approach), with a maximum allowable difference of 10%.
Safety Data Collection:	Safety assessment was based on reported AEs, clinical laboratory tests, vital sign measurements, physical examinations, follow-up on specific toxicities, and a bone investigation substudy. The bone investigation substudy was performed at selected study sites, to assess bone biomarkers and dual energy x-ray absorptiometry (DXA) scans, in 212 subjects (113 in the D/C/F/TAF treatment group vs 99 in the control group) who provided informed consent for the substudy.

Study Design and Subject Population:

This is an ongoing, 96-week, multicenter, Phase 3 study consisting of a 48-week randomized, double-blind active-controlled treatment period, to evaluate safety and efficacy of a D/C/F/TAF FDC vs DRV/COBI FDC coadministered with F/TDF FDC in ARV ART-naïve HIV-1 infected adult subjects, followed by an open-label single-arm D/C/F/TAF treatment period for all subjects up to Week 96 to assess long-term efficacy, resistance, and safety.

Subjects were considered ART-naïve if they had never been treated with an ARV including post-exposure prophylaxis and pre-exposure prophylaxis. A screening HIV-1 genotype report had to show full sensitivity to DRV, TFV and FTC.

Prior to or at the baseline visit (Day 1), subjects who met all eligibility criteria were randomized in a 1:1 ratio to 1 of the 2 treatment groups:

- D/C/F/TAF group: Regimen of a single tablet containing DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg (D/C/F/TAF FDC) once daily, and DRV/COBI FDC-matching and F/TDF FDC-matching placebo tablets once daily;
- Control group: Regimen of DRV 800 mg/COBI 150 mg FDC coadministered with FTC 200 mg/TDF 300 mg FDC once daily, and D/C/F/TAF FDC-matching placebo tablet once daily.

Randomization was stratified by HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and by CD4+ cell count (<200 cells/mm^3 or ≥200 cells/mm^3) at screening.

After Week 48, subjects continued to take their blinded study drug and attended visits every 12 weeks until all subjects had reached Week 48, and treatment assignments were unblinded. Provided the results from the primary analysis do not preclude (further) exposure of subjects to D/C/F/TAF, all subjects were to return for an unblinding visit and were to receive the D/C/F/TAF FDC tablet treatment in an open-label single-group treatment phase up to Week 96.

After Week 96, subjects were/will be given the opportunity to continue D/C/F/TAF treatment during an extension phase in order to collect long-term safety and efficacy data on D/C/F/TAF and until the D/C/F/TAF FDC tablet became commercially available and was reimbursed, or could be accessed through another source in the country where he/she is living, or until the sponsor terminated clinical development.

Extent of Exposure:

A total of 725 subjects was enrolled and treated in this study: 362 on D/C/F/TAF and 363 on DRV/COBI+F/TDF.

The mean (SD) duration of D/C/F/TAF intake during the study was 46.8 (8.4) weeks. The total subject-years of D/C/F/TAF exposure was 324.3.

Summary of Results and Conclusions:

In HIV-1 infected, treatment-naïve adults, treatment with once daily D/C/F/TAF resulted in similar high virologic response rates at Week 48 vs DRV/COBI+F/TDF (91.4% vs 88.4%) in the ITT analysis set and was found to be noninferior to the control group (95% CI: -1.6; 7.1) in the Week-48 analysis.

Results were consistent across the sensitivity analyses, and across the various subgroup analysis (eg, by baseline disease and demographic characteristics).

The mean (SE) baseline CD4+ count values were 497.3 (12.44) cells/mm^3 in the D/C/F/TAF group and 474.7 (11.78) cells/mm^3 in the control group. When adjusted for baseline CD4+ count, LS mean estimates for changes from baseline in CD4+ cell count and CD4+/lymphocytes (%) at Week 48 were 190.49 cells/mm^3 and 7.56% in the D/C/F/TAF group and 172.01 cells/mm^3 and 7.78% in the control group. There were no statistically significant differences between treatment groups (p=0.213 and p=0.596, respectively).

No resistance associated with DRV or TAF was observed postbaseline. Only one subject in the D/C/F/TAF group developed an M184I/V mutation conferring FTC resistance.

Based on AEs and other safety assessments, no safety concerns were identified.

There was one fatal event in the control group (not related to the study drug): sepsis occurring in the context of a sclerosing cholangitis. The incidence of SAEs and AEs leading to discontinuation was low (ie, at most 4.7% in the D/C/F/TAF group).

Rash occurred in a similar proportion of subjects in each treatment group and led to early discontinuation of treatment in, respectively, 1.7% and 1.4% of subjects. No severe skin reactions occurred in the D/C/F/TAF group; in the control group, 0.8% of subjects experienced a severe skin reaction that led to treatment discontinuation. The subjects recovered 12 to 22 days later.

Due to the absence of lipid-protective effect of a TDF-based regimen compared to a TAF-based regimen, lipids increased at Week 48 vs baseline in the D/C/F/TAF group, but these were not reflected in clinically relevant differences between the treatment groups in median changes from baseline in the TC/HDL ratio. Lipid-lowering treatment was initiated by 1.7% vs 0.6% subjects during the treatment phase.

At Week 48, the subjects showed a better renal and bone safety profile when using a TAF-based regimen compared to a TDF-based regimen. In the D/C/F/TAF group versus control, there were:

- Greater increases in $eGFR_{cyst}$, a lower incidence of proteinuria, and a lower incidence of increases in markers of potential proximal renal tubulopathy.
- Stable hip and spine bone mineral density compared to decreases in the control group.

Pharmacokinetics of COBI-boosted DRV and TAF were in line with historical studies. There were no apparent clinically relevant relationships between DRV or TAF exposure and efficacy or safety parameters of interest.

Study GS-US-299-0102

Location:	Mod5.3.5.1/GS-US-299-0102 Final CSR
Title:	A Phase 2, randomized, double-blinded study of the safety and efficacy of D/C/F/TAF FDC tablet vs COBI-boosted DRV plus F/TDF FDC in HIV-1 infected, ART-naïve adults
Primary Objective:	The primary objective was to evaluate the efficacy of a regimen containing D/C/F/TAF vs DRV+COBI+F/TDF in HIV-1 infected, ART-naïve adult subjects, as determined by the achievement of HIV-1 RNA <50 copies/mL at Week 24.
Safety Data Collection:	Adverse events (AEs) and clinical laboratory tests, including bone mineral density (BMD) using dual energy x-ray absorptiometry (DXA), bone biomarkers, serum creatinine, estimated glomerular filtration rate (eGFR), and renal biomarkers, were performed to evaluate the safety and tolerability of the treatment regimens.
Study Design and Subject Population:	This was a randomized, double-blinded, multicenter, active-controlled study. Subjects were considered ART-naïve if there was no prior use of any approved or experimental anti-HIV drug for any length of time. A screening genotype report had to show full sensitivity to DRV, TDF and FTC. One hundred and fifty-three subjects were randomized and received 1 of the following treatments: • FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg + placebos-to-match DRV 800 mg (400-mg tablet x 2) and COBI 150-mg tablet and FDC tablet of FTC 200 mg/TDF 300 mg once daily (103 subjects) • DRV 800 mg (400-mg tablet x 2) + COBI 150-mg tablet + FDC tablet of FTC 200 mg/TDF 300 mg + placebo-to-match D/C/F/TAF once daily (50 subjects)
Extent of Exposure	In total, 153 subjects received at least 1 dose of study drug (D/C/F/TAF: 103 subjects; DRV+COBI+F/TDF: 50 subjects). The median (Q1; Q3) duration of exposure to study drug was 68.0 (65.4; 72.7) weeks in the D/C/F/TAF group and 69.1 (66.0, 73.6) weeks in the DRV+COBI+F/TDF group. The majority of subjects in each treatment group (>75% in each group) received study drug for ≥60 weeks.

Summary of Results and Conclusions:

D/C/F/TAF once daily was non-inferior to DRV+COBI+F/TDF once daily when administered for 24 weeks to HIV-1 infected, ART-naïve subjects as assessed using the FDA-defined snapshot approach with HIV-1 RNA cut-off at 50 copies/mL, in accordance with the primary objective of this study. Virologic success rates at Week 24 were as follows: D/C/F/TAF 74.8%, DRV+COBI+F/TDF 74.0%; difference in percentages (95% CI): 3.3% (-11.4% to 18.1%). Virologic success rates for the Week 24 PP Analysis Set were supportive of those for the FAS, and were as follows: D/C/F/TAF 84.6%, 77 of 91 subjects; DRV+COBI+F/TDF 78.7%, 37 of 47 subjects; difference in percentages (95% CI): 8.3% (-5.3% to 22.0%).

The rates of virologic success through Week 48 when assessed using the FDA-defined snapshot approach (HIV-1 RNA <50 copies/mL) were as follows: D/C/F/TAF 76.7%, DRV+COBI+F/TDF 84.0%; difference (95% CI) in percentages: -6.2% (-19.9 to 7.4). Virologic success rates for the Week 48 PP Analysis Set were similar between the 2 treatment groups, and were as follows: D/C/F/TAF 92.9%, 79 of 85 subjects, DRV+COBI+F/TDF 91.3%, 42 of 46 subjects; difference in percentages (95% CI): 2.4% (-8.8% to 13.7%).

Both groups had increases from baseline in mean CD4+ cell counts (Week 24: D/C/F/TAF 186 cells/µL, DRV+COBI+F/TDF 139 cells/µL; Week 48: D/C/F/TAF 231 cells/µL, DRV+COBI+F/TDF 212 cells/µL).

Development of resistance to any of the components of the ARV regimens used in the study was rare. No phenotypic resistance was observed.

Subjects who received D/C/F/TAF had intracellular tenofovir diphosphate (TFV-DP) concentrations 6.5-fold higher than subjects who received DRV+COBI+F/TDF. Conversely, subjects who received D/C/F/TAF had plasma TFV levels 91% lower than those who received DRV+COBI+F/TDF.

Both D/C/F/TAF and DRV+COBI+F/TDF were well tolerated, with comparably low rates of SAEs and AE-related drug discontinuation in both treatment groups. D/C/F/TAF showed a preferential renal and bone safety profile compared with those who received DRV+COBI+F/TDF, as evidenced by significantly less of each of the following:

- Reduction in eGFR
- Tubular proteinuria
- Decline in hip and spine BMD
- Changes in markers of bone turnover

Increases from baseline in fasting total cholesterol, fasting LDL cholesterol, fasting HDL cholesterol, and fasting triglycerides were noted in the D/C/F/TAF group.

Study TMC114IFD3013

Location:	Mod5.3.5.1/TMC114IFD3013-W48-CSR
Title:	A Phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen vs continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects.
Primary Objective:	The primary objective was to demonstrate noninferiority in efficacy of a D/C/F/TAF once-daily single-tablet regimen relative to continuing the current bPI combined with F/TDC in virologically suppressed (HIV 1 RNA <50 copies/mL) HIV-1 infected subjects, in regard to the proportion of virologic rebounders through Week 48, with a maximum allowable difference of 4%.
Safety Data Collection:	Safety assessment was based on reported AEs, clinical laboratory tests, vital sign measurements, physical examinations, follow-up on specific toxicities, and a bone investigation substudy. A bone investigation substudy was performed at selected study sites, to assess bone biomarkers and dual energy x-ray absorptiometry (DXA) scans, in 317 subjects (209 in the D/C/F/TAF treatment group vs 108 in the control group) who provided informed consent for the substudy.

Study Design and Subject Population:

This is an ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 study to evaluate the efficacy, safety and tolerability of switching to a D/C/F/TAF once-daily single-tablet regimen in virologically suppressed (HIV 1 RNA <50 copies/mL), HIV-1 infected adult subjects over a 48-week treatment period vs continuing the current regimen of a bPI in combination with F/TDF.

Subjects were considered ART-experienced and virologically suppressed if there was documented evidence of having been virologically suppressed while on a stable ARV regimen prior to screening: at least 1 plasma HIV-1 RNA measurement <50 copies/mL (or HIV-1 RNA undetectable by a local HIV-1 RNA test) occurring between 12 and 2 months prior to the screening visit while on the stable ARV regimen and HIV-1 RNA <50 copies/mL at the screening visit. A single viral load elevation of ≥50 copies/mL and <200 HIV-1 RNA copies/mL after previously reaching viral suppression ('blip') within 12 months prior to screening was allowed, provided a subsequent viral load measurement was <50 HIV-1 RNA copies/mL (or HIV-1 RNA undetectable by a local HIV-1 RNA test) prior to screening. A history of failure on DRV treatment and DRV resistance-associated mutations (RAMs) (including V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V), if documented historical genotypes were available, were not allowed.

Eligible subjects were being treated with a stable ARV regimen consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) combined with F/TDF only, for at least 6 consecutive months preceding the screening visit, and with a suppressed viral load prior to and at screening. Subjects treated with the combination DRV+COBI+F/TDF and having completed the required visits in the Gilead Sciences Inc (GSI) sponsored Study GS-US-216-0130, and who were fulfilling the present protocol criteria, were also given the option to participate. Prior to or at the baseline visit (Day 1), subjects who met all eligibility criteria were randomized in a 2:1 ratio to 1 of the 2 treatment groups:

- D/C/F/TAF group: Switch to regimen of an FDC tablet containing DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg (further referred to as D/C/F/TAF tablet) once daily;
- Control group: Continue current regimen consisting of a bPI (limited to DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) combined with F/TDF only.

Randomization was stratified by bPI used at screening.

Once they had completed their Week-48 visit, subjects from the D/C/F/TAF group were to enter the extension phase. In addition, subjects in the control group were to receive the D/C/F/TAF tablet in the extension phase if, according to the investigator they were to benefit from it and if all conditions were fulfilled (which included adequate viral load results). Subjects from the control group were required to attend a switch visit at Week 52 to receive D/C/F/TAF. All subjects in the extension phase were to attend visits every 12 weeks until Week 96. As from Week 96, all subjects were/are to be offered the possibility to continue D/C/F/TAF treatment, if they wished and if they continued to benefit from it, until D/C/F/TAF became commercially available and was reimbursed, or could be accessed through another source in the country where he/she was living, or until the sponsor terminated clinical development. After Week 96, subjects were to attend visits every 6 months.

Extent of Exposure:

A total of 1,141 subjects were enrolled and treated in this study: 763 switched to the D/C/F/TAF FDC, and 378 remained on their bPI regimen in combination with F/TDF.

The mean (SD) duration of D/C/F/TAF intake during the study was 47.2 (6.6) weeks. The total subject-years of D/C/F/TAF exposure was 690.3.

Summary of Results and Conclusions:

In HIV-1 infected, treatment-experienced, virologically suppressed adults, switching to once-daily D/C/F/TAF resulted in similar low protocol-defined virologic rebound rate cumulative through Week 48 vs continuing TDF-based bPI regimen (2.5% vs 2.1%) in the ITT analysis set inferring noninferiority (95% CI: -1.5; 2.2), and a high virologic suppression rate (94.9% vs 93.7%) in the Week 48 analysis.

Results were consistent in the PP population and across various subgroups, such as bPI, adherence, and demographic characteristics.

The mean (standard error) baseline CD4+ count values were 653.3 (9.12) cells/mm^3 in the D/C/F/TAF group and 641.7 (13.15) cells/mm^3 in the control group. When adjusting for baseline CD4+ cell count, LS mean estimates for change from baseline in CD4+ cell count were 18.69 cells/mm^3 in the D/C/F/TAF and 4.91 cells/mm^3 in the control group. There were no statistically significant differences between treatment groups (p=0.148).

One rebounder in the D/C/F/TAF group and 3 rebounders in the control group had postbaseline genotypes. No resistance associated with any of the study drugs was observed postbaseline.

D/C/F/TAF treatment adherence appeared to be 5% to 6% better than for the control treatment.

Based on AEs and other safety assessments, no safety concerns were identified.

In the D/C/F/TAF group, there was a higher incidence of AEs at least possibly related and of AEOIs. These findings were expected as, similar to what has been observed in other 'switch' studies, subjects in the switch group have a higher risk of developing an ADR as they are exposed to a new drug, compared to the control group who continues an existing treatment. The higher incidence of AEOIs in the D/C/F/TAF group was mainly driven by a higher frequency of rash AEOIs and lipid-related AEOIs, which are known ADRs to DRV/COBI. The fact that this was an open label study may have affected the causality assessment of these events.

The higher incidence of rash AEOIs in the D/C/F/TAF group compared to the control group was mainly due to the high incidence of rash in subjects who switch from another PI to DRV or who switch from rtv to COBI as booster at baseline. None of the rash AEOIs were of clinical concern as all rash AEOIs were transient and nonserious and all drug related rash AEOIs were grade 1.

Due to the loss of lipid-protective effect of a TDF-based regimen after a switch to a TAF-based regimen, lipids increased at Week 48 vs baseline, but these were not reflected in clinically relevant differences between the treatment groups in median changes from baseline in the TC/HDL ratio. Lipid-lowering treatment was initiated by 2.5% vs 1.9% subjects during the treatment phase.

At Week 48, the subjects showed a better renal and bone safety profile when switching from a TDF-based regimen to a TAF-based regimen. In the D/C/F/TAF group vs the control group, there was:

- A preservation of the GFR (as assessed by $eGFR_{cyst}$).
- A lower incidence of tubular proteinuria and a trend towards a lower incidence of increases in markers of potential proximal renal tubulopathy.
- Increases in hip and spine BMD compared to decreases in the control group.

Pharmacokinetics of COBI-boosted DRV were in line with historical studies. There were no apparent clinically relevant relationships between DRV exposure and efficacy or safety parameters of interest.

Study TMC114-C230

Location:	NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR
Title:	A phase II, open-label trial, to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV/rtv once daily in ART-naïve HIV-1 infected adolescents aged between 12 and <18 years.
Primary Objective:	The primary objective of this study was to evaluate the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low-dose ritonavir (DRV/rtv) administered at 800/100 mg once daily in combination with an investigator-selected background regimen, consisting of either zidovudine (AZT)/lamivudine (3TC) or abacavir (ABC)/3TC, over a 24-week treatment period in antiretroviral (ARV) ART-naïve HIV 1 infected adolescents aged between 12 and < 18 years and weighing ≥ 40 kg.
Safety Data Collection:	At each visit, the subject and caregiver were asked about any untoward medical occurrences, which were recorded as AEs/HIV-related events. The occurrence of WHO Clinical Stage 4 events was also recorded. For subjects experiencing specific AEs, toxicity management was to be done. Other safety assessments included clinical laboratory tests, ECG, vital signs, physical examination, and Tanner stage assessments.
Study Design and Subject Population:	TMC114-C230 is a 48-week, open-label, single-arm, Phase II study to evaluate the pharmacokinetics, safety, tolerability, and efficacy of DRV/rtv administered once daily, in combination with 2 NRTIs, in ART-naïve HIV-1 infected subjects aged between 12 and <18 years and weighing ≥40 kg. A total of 12 ARV ART-naïve subjects were included in the study. Subjects were considered ART-naïve if they had never received treatment with an ARV drug, including investigational ARVs. Subjects received the recommended dose of DRV/rtv for ART-naïve HIV-1 infected adults, ie, 800/100 mg once daily, in combination with an investigator-selected background regimen for 48 weeks. The investigator-selected background regimen was either AZT/3TC or ABC/3TC, whichever was approved and marketed or considered local standard of care for subjects aged between 12 and <18 years in a particular country. Selection was also based on results from the screening resistance data. Statistical analyses were performed at Week 24 (primary analysis) and at Week 48 (final analysis).
Extent of Exposure:	A total of 12 ARV ART-naïve subjects were enrolled and treated in the study. The mean duration of DRV/rtv intake during the study was 49.6 weeks. The total patient-years of DRV/rtv exposure was 11.4.

Summary of Results and Conclusions:

The 48-weeks efficacy results from study TMC114-C230 in ART-naïve HIV-1 infected adolescents between 12 and <18 years of age and weighing ≥40 kg demonstrate that DRV/rtv 800/100 mg once daily, in combination with an investigator-selected background consisting of AZT/3TC or ABC/3TC, is efficacious in the studied population. At Week 24, 11 out of 12 subjects (91.7%) had a confirmed plasma viral load <50 copies/mL; and at Week 48, 10 subjects (83.3%) had a confirmed virologic response (<50 copies/mL).

There was 1 (8.3%) never-suppressed subject and 1 (8.3%) rebounder. None developed DRV RAMs or lost phenotypic susceptibility to any commercially available PI (including DRV) or any NRTI in the background regimen.

The safety data from study TMC114-C230 up to Week 48 demonstrated that DRV/rtv, administrated at 800/100 mg once daily, in combination with AZT/3TC or ABC/3TC, was generally safe in the studied population. There were no new clinically relevant safety findings compared with the known DRV/rtv safety profile in HIV-1 infected adults and in ART-experienced HIV-1 infected subjects between 6 and < 18 years.

The noncompartmental and population pharmacokinetic analyses showed that the DRV pharmacokinetics following administration of DRV/rtv 800/100 mg once daily in pediatric subjects aged between 12 and <18 years are comparable to those obtained in adults at the same dose. The geometric mean DRV AUC_{24h} following DRV/rtv 800/100 mg once-daily administration was 80.7 µg.h/mL, which represents 90.0% of the target adult exposure (geometric mean of 89.7 µg.h/mL in study TMC114-C211).

No apparent relationships were observed between the DRV pharmacokinetics and efficacy or safety parameters at Week 48.

There were no new clinically relevant findings compared with the known DRV/rtv safety profile in HIV-1 infected adults and in ART-experienced HIV-1 infected subjects between 12 and <18 years. There were no deaths, and no AEs led to treatment discontinuation. The incidence of grade 3 or 4 AEs, AEs considered at least possibly related to DRV, serious adverse events (SAEs), and AEs of interest was generally consistent with rates observed in adults and ART-experienced subjects between 6 and <18 years. By preferred term, the most frequent AEs were vomiting (4 subjects, 33.3%), and anemia and nausea (both in 3 subjects, 25.0%). Diarrhea, pyrexia, furuncle, sinusitis, and cough occurred each in 2 subjects (16.7%). All other AEs occurred in 1 subject.

The results of the Week 48 analysis of study TMC114-C230 support the use of DRV/rtv 800/100 mg once daily, in combination with other ARVs, in ART-naïve HIV-1 infected adolescents aged between 12 and <18 years, and weighing ≥40 kg.

Study GS-US-292-0106

Location:	Supportive references (Abram et al. 2016[1], Clinical Trial.gov[3], Gaur et al. 2015[5], Gaur et al. 2016 [manuscript][6], Gaur et al. 2016 [poster][4]) are included in Mod2.7.5.
Title:	A Phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the E/C/F/TAF FDC tablet in HIV-1 infected ART-naïve adolescents and virologically suppressed children Of note, the data on the patient population of virologically suppressed children are not included in this submission.
Primary Objective:	The primary objectives of this study were to determine steady-state PK of EVG, TAF components of E/C/F/TAF, to confirm the dose of E/C/F/TAF FDC, and to evaluate safety and tolerability through 24 weeks of treatment.
Safety Data Collection:	Baseline and postbaseline safety assessments included AEs, clinical laboratory tests, physical examinations, and vital signs. Urine was collected for analysis of renal laboratory parameters. The eGFR was calculated using the Schwartz formula. DXA scans of the spine and TBLH were conducted to assess BMD.
Study Design and Subject Population:	This is an ongoing, Phase 2/3, open-label study to confirm the dose of the E/C/F/TAF FDC in HIV-1 infected, ART-naïve adolescents (HIV-1 RNA ≥1,000 copies/mL) and to evaluate the PK, safety, tolerability, and antiviral activity of the E/C/F/TAF FDC in HIV-1 infected, ARV treatment naïve adolescents (HIV-1 RNA ≥1,000 copies/mL) with a screening genotype report showing sensitivity to EVG, FTC, and TFV (Cohort 1) and virologically suppressed HIV-1 infected children (Cohort 2). Subjects had to have eGFR (Schwartz formula) ≥90 mL/min/1.73 m^2. The outcomes included the PK parameters AUC_{tau} (defined as concentration of drug over a dosing interval for EVG) and AUC_{last} (defined as the concentration of drug from time zero to the last observable concentration) for EVG and TAF, and the safety through Week 24 and Week 48. Subjects aged 12 to <18 years and subjects aged 6 to <12 years and weighing ≥25 kg received the E/C/F/TAF 150/150/200/10-mg FDC once daily with food.
Extent of Exposure:	In total, 50 HIV-infected ART-naïve adolescent subjects were enrolled and received at least 1 dose of E/C/F/TAF. The median (Q1; Q3) duration of exposure to E/C/F/TAF was 60.1 (48.1; 84.1) weeks.

Summary of Results and Conclusions:

High virologic success was achieved (as assessed using the FDA-defined snapshot approach with HIV-1 RNA <50 copies/mL) in ART-naïve adolescents (90.0% and 92.0% virologic success at Weeks 24 and 48, respectively), demonstrating efficacy of the E/C/F/TAF FDC in this age group. These results are in accordance with PK data that confirmed the E/C/F/TAF 150/150/200/10-mg doses for each component.

There was evidence of a robust immunological response to E/C/F/TAF in ART-naïve adolescents, with an increase in mean (SD) CD4+ cell count from 471 (212.2) cells/μL at baseline to 685 (245.4) cells/μL at Week 48.

E/C/F/TAF was well tolerated, as evidenced by the low incidence of study drug-related SAEs and the absence of AEs leading to discontinuation of study drug.

The lack of notable changes from baseline in height-age spine and TBLH BMD Z-scores at Week 48 indicates that subjects mineralized bone at rates consistent with those of the reference population. Few subjects experienced a clinically relevant decrease from baseline in BMD.

Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration. There were decreases from baseline in proteinuria, as assessed by UPCR.

Janssen Research & Development

Summary of Clinical Safety

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults and Adolescents

D/C/F/TAF (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide, TMC114/JNJ-48763364/JNJ-35807551/JNJ-63625328)

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ABBREVIATIONS

abbreviation	description of abbreviated term
3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
AE	adverse event
AEOI	adverse event of interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral treatment
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC_{tau}	area under the plasma concentration-time curve across the dosing interval (Note: for D/C/F/TAF, where the dosing interval is 24 hours, AUC_{tau} and AUC_{24h} have the same meaning)
AUC_{24h}	area under the plasma concentration-time curve over the 24h dosing interval
AZT	zidovudine
BA	bioavailability
BE	bioequivalence
BIS	bone investigation substudy
BMD	bone mineral density
BMI	body mass index
bPI	boosted protease inhibitor
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{min}	minimum plasma concentration
COBI or C	cobicistat
CPK	creatine phosphokinase
CRF	case report form
CSR	clinical study report
CTX	collagen type 1 cross-linked C-telopeptide
DAIDS	division of AIDS
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DRV or D	darunavir
DXA	dual energy x-ray absorptiometry
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ECG	electrocardiogram
(e)GFR	(estimated) glomerular filtration rate
$eGFR_{CG}$	eGFR based on serum creatinine calculated using the Cockcroft-Gault method
$eGFR_{CKD-EPI}$	eGFR based on serum creatinine calculated using the CKD-EPI method
$eGFR_{cr}$	eGFR based on serum creatinine
$eGFR_{cyst}$	eGFR based on serum cystatin C calculated using the CKD-EPI method
EVG or E	elvitegravir
FDA	Food and Drug Administration
FDC	fixed-dose combination
FE_{PO4}	fractional excretion of phosphate
FEUA	fractional excretion of uric acid
FTC or F	emtricitabine
F/TAF	emtricitabine/tenofovir alafenamide

F/TDF	emtricitabine/tenofovir disoproxil fumarate
GGT	gamma-glutamyl transferase
GSI	Gilead Sciences Inc
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus type 1
HMG CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation
IQ	interquartile
ITT	intent-to-treat
IV	intravenous
LDL	low density lipoprotein
LPV	lopinavir
LS	least squares
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
NCEP	National Cholesterol Education Program
NDA	new drug application
NRTI	nucleoside reverse transcriptase inhibitor
P1NP	procollagen type 1 N-terminal propeptide
PANNA	study on Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women recruited from different HIV treatment centers in Europe
PI	protease inhibitor
PK	pharmacokinetic(s)
PRT	proximal renal tubulopathy
PT	preferred term
PTH	parathyroid hormone
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected according to Fridericia's formula
RBP	retinol-binding protein
RNA	ribonucleic acid
rtv	low-dose ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SCS	Summary of Clinical Safety
SD	standard deviation
SE	standard error
SMT	Safety Management Team
SOC	system organ class
TAF	tenofovir alafenamide
TBLH	total body less head
TC	total cholesterol
TC/HDL	total cholesterol to HDL cholesterol ratio
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio

STUDY NAMING CONVENTIONS

Study numbers commencing with 'TMC114' in this dossier refer to studies conducted by the Sponsor, and study numbers commencing with 'GS' refer to studies conducted by Gilead Sciences, Inc.

1. INTRODUCTION

The information presented in this Summary of Clinical Safety (SCS) establishes the safety profile of the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed-dose combination (FDC) (800/150/200/10 mg) in human immunodeficiency virus type 1 (HIV-1) infected adult and adolescent subjects.

In Section 2 of this SCS, an overview of the clinical studies supporting D/C/F/TAF safety is presented. A reference is provided to study narratives describing critical design features, critical results, extent of exposure, study population, and methods used for the main studies establishing the D/C/F/TAF safety profile.

In Section 3, data from individual studies are summarized:

- Section 3.1: Phase 3 and 2 studies with the D/C/F/TAF FDC in HIV-1 infected adult subjects, and Phase 1 (ie, bioequivalence [BE] and bioavailability [BA]) studies with the D/C/F/TAF FDC in HIV-1 negative subjects.
- Section 3.2: Phase 2 and Phase 2/3 studies with the individual components of the D/C/F/TAF FDC in HIV-1 infected adolescent subjects.
- Section 3.3: supportive studies with the individual components of the D/C/F/TAF FDC (ie, thorough QT studies and studies in subjects with renal impairment).
- Section 3.4: relationships between pharmacokinetic (PK) and safety parameters for the Phase 3 studies in HIV-1 infected adult subjects.

In Section 4, results of the adverse event (AE) analysis from the Phase 3 studies with the D/C/F/TAF FDC in HIV-1 infected adult subjects are summarized, including the D/C/F/TAF adverse drug reactions (ADRs) identified in these studies.

In Section 5, a summary is given of important safety data collected since Week 48 up to the data cut-off date of 1 June 2017 in the 2 ongoing Phase 3 studies with the D/C/F/TAF FDC in HIV-1 infected adult subjects. This summary will focus on deaths, discontinuations, serious AEs (SAEs), grade 3/4 AEs, and grade 3/4 laboratory abnormalities.

In Section 6, safety data in special groups and situations are presented. Intrinsic and extrinsic factors, drug interactions, pregnancy and lactation, overdose, drug abuse, withdrawal and rebound, ability to drive or operate machinery and impairment of mental ability are considered.

As mentioned in Section 7, postmarketing data are not yet available for the D/C/F/TAF FDC.

In Section 8, overall conclusions on the safety data in this SCS are presented.

2. OVERALL SAFETY EVALUATION PLAN, EXTENT OF EXPOSURE, AND STUDY POPULATIONS

2.1. Overview of Clinical Studies and Study Populations Supporting D/C/F/TAF Safety

A brief overview of the design of the studies supporting both clinical efficacy and safety, and the studies providing supportive clinical safety is provided in Table 1 and Table 2, respectively. These tables also contain a reference to the study narratives for the main studies establishing the D/C/F/TAF safety profile. An overview of the number of HIV-1 infected subjects treated with the D/C/F/TAF FDC in these clinical studies is presented in Table 3.

Note that study numbers commencing with 'TMC114' in this dossier refer to studies conducted by the Sponsor, and study numbers commencing with 'GS' refer to studies conducted by Gilead Sciences, Inc (GSI).

A tabular summary of all studies included in the D/C/F/TAF FDC submission is available in Mod5.2.

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

No pooling or comparison of the Week-48 data of the studies included in this submission is considered appropriate. The Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 are conducted in different HIV-1 infected subject populations (ART-naïve subjects and ART-experienced, virologically suppressed subjects, respectively), and also differ in design (double-blind and open-label, respectively). The Phase 3 Study TMC114FD2HTX3001 and Phase 2 Study GS-US-299-0102 are similar in study design and population, but the Phase 2 study was an exploratory study, with a limited sample size. A pooling of these studies would not result in a substantial increase in the number of subjects treated with D/C/F/TAF, as compared to the Phase 3 study alone (ie, ~360 subjects in TMC114FD2HTX3001 and 103 subjects in GS-US-299-0102).

Table 1: Tabulated Overview of the Phase 3 and 2 Studies Supporting the Clinical Efficacy and Safety Profile of the D/C/F/TAF FDC Tablet

Study (Phase, Status)	Study Design	Number of Subjects[a] by Treatment Regimen[b]	Primary Endpoint	Data Included in Application	Source Reference and Narrative Locations	Included in
D/C/F/TAF						
HIV-1 Infected, ART-naïve, Adult Subjects						
TMC114FD2HTX3001 (Phase 3, ongoing)	Randomized, active-controlled, double-blind study to evaluate efficacy and safety of D/C/F/TAF FDC vs DRV/COBI+F/TDF	Total: 725: D/C/F/TAF FDC (N=362) or DRV/COBI+F/TDF (N=363)	Virologic response defined as HIV-1 RNA <50 copies/mL at Week 48 per FDA snapshot; noninferiority with maximum allowable difference of 10%	Week 48 efficacy, resistance, PK, and safety	TMC114FD2HTX3001 Week 48 CSR Mod2.7.3/App1/TMC114FD2HTX3001	Mod2.7.3 and Mod2.7.4
GS-US-299-0102 (Phase 2, completed)	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+F/TDF	Total: 153: D/C/F/TAF FDC (N=103) or DRV+COBI+F/TDF (N=50)	Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per FDA snapshot; noninferiority with maximum allowable difference of 12%	Week 48 efficacy, resistance, PK, and safety	GS-US-299-0102 Final CSR Mod2.7.3/App1/GS-US-299-0102	Mod2.7.3 and Mod2.7.4
HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects						
TMC114IFD3013 (Phase 3, ongoing)	Randomized, active-controlled, open-label study to evaluate the efficacy, safety, and tolerability of switching to D/C/F/TAF FDC vs continuing the current bPI combined with F/TDF	Total: 1,141: Switch to D/C/F/TAF FDC (N=763) or Stay on bPI[c] combined with F/TDF (N=378)	Virologic rebound cumulative through Week 48 (confirmed HIV-1 RNA ≥50 copies/mL, or with a last single HIV-1 RNA ≥50 copies/mL in case of early discontinuation); noninferiority with maximum allowable difference of 4%	Week 48 efficacy, resistance, PK, and safety	TMC114IFD3013 Week 48 CSR Mod2.7.3/App1/TMC114IFD3013	Mod2.7.3 and Mod2.7.4
DRV						
HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)[d]						
TMC114-C230 (Phase 2, completed)	Open-label, single-arm study to evaluate the PK, safety, tolerability, and efficacy of DRV/rtv in combination with AZT/3TC or ABC/3TC	DRV/rtv +ARV background regimen[e] (N=12)	PK of DRV and rtv; Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per TLOVR	Week 48 PK, efficacy, resistance, and safety	Janssen NDA 021976 Mod2.7.3/App1/TMC114-C230	Mod2.7.3 and Mod2.7.4

Table 1: Tabulated Overview of the Phase 3 and 2 Studies Supporting the Clinical Efficacy and Safety Profile of the D/C/F/TAF FDC Tablet

Study (Phase, Status)	Study Design	Number of Subjects[a] by Treatment Regimen[b]	Primary Endpoint	Data Included in Application	Source Reference and Narrative Locations	Included in
COBI and F/TAF (Extrapolated From E/C/F/TAF)						
HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)						
GS-US-292-0106[f] (Phase 2/3, ongoing)	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 substudy N=24)	PK of EVG, TAF, COBI, FTC and TFV; Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per FDA snapshot	Week 48 PK, efficacy, resistance, and safety	Gaur et al. 2016 (poster)[7] Gaur et al. 2015[8] Gaur et al. 2016 (manuscript)[9] Mod2.7.3/App1/GS-US-292-0106	Mod2.7.3 and Mod2.7.4

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ARV = antiretroviral; ATV = atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; COBI = cobicistat; CSR = clinical study report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; FTC = emtricitabine; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada®); HIV-1 = human immunodeficiency virus type 1; LPV = lopinavir; N = number of subjects; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetics; rtv = low-dose ritonavir; TFV = tenofovir; TLOVR = time to loss of virologic response.

[a] Subjects included in the Intent-to-treat population or Safety Analysis Set. For the definitions of analysis sets, refer to Mod2.7.3/Sec2.2.

[b] Study drugs were dosed as follows: D/C/F/TAF 800/150/200/10 mg; DRV 400 mg x2; COBI 150 mg; DRV/COBI 800/150 mg; F/TDF 200/300 mg; DRV/rtv 800/100 mg; and E/C/F/TAF 150/150/200/10 mg.

[c] The current (screening) bPI consisted of DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv, dosed as indicated in the local Prescribing Information.

[d] In addition, recent results (Week-48 data) became available from the single-arm, open-label, Phase 2/3, switch Study GS-US-216-0128 in HIV-1 infected, virologically suppressed adolescents (aged ≥12 to <18 years). In this study, subjects received DRV plus COBI or ATV plus COBI (subjects switched from rtv to COBI in this study) in combination with 2 NRTIs.

[e] The ARV background regimen consisted of AZT/3TC or ABC/3TC, dosed as indicated in the local Prescribing Information.

[f] In this study, a subject population of virologically suppressed children (aged 6 to <12 years) was also included. However, these data are not described in this submission which focuses on adult and adolescent HIV-1 infected subjects.

Table 2: Tabulated Overview of Studies Providing Supportive Clinical Safety Data for the D/C/F/TAF FDC Tablet

Population	Study	Treatment[a]	Number of Subjects	Study Design	Source Reference and Narrative Locations	Included in
Healthy Volunteers						
D/C/F/TAF studies						
	TMC114FD2HTX1001 (BE)	• D/C/F/TAF FDC; DRV+COBI+F/TAF	96	Phase 1, single-center, open-label, randomized, 2-way crossover study to evaluate the single-dose PK of DRV 800 mg, FTC 200 mg, and TAF 10 mg in the presence of COBI 150 mg, and the pivotal BE of the D/C/F/TAF FDC	TMC114FD2HTX1001 Final CSR **Supportive study, no narrative provided.**	Mod2.7.4
	TMC114FD2HTX1002 (BA, food effect)	• D/C/F/TAF FDC; DRV+COBI+F/TAF • D/C/F/TAF FDC; E/C/F/TAF FDC • D/C/F/TAF FDC in fed and fasted state	72	Phase 1, 3-panel, open-label, randomized, 2-way crossover study to evaluate the impact of food (fasting or high-calorie/high-fat breakfast) on the single-dose PK of DRV, COBI, FTC and TAF when administered as D/C/F/TAF FDC and the relative BA of these ARVs in different formulations/combinations	TMC114FD2HTX1002 Final CSR **Supportive study, no narrative provided.**	Mod2.7.4
	TMC114FD2HTX1004 (BA)	• D/C/F/TAF FDC as a whole tablet; D/C/F/TAF FDC as a split tablet; D/C/F/TAF FDC as a crushed tablet	30	Phase 1, randomized, open-label, 3-period, 3-treatment crossover study to assess, under fed conditions, the PK and relative BA of a single dose of the D/C/F/TAF FDC tablet swallowed as a whole tablet relative to that of a split or crushed tablet, and to evaluate the short-term safety and tolerability in healthy adult subjects	TMC114FD2HTX1004 Final CSR **Supportive study, no narrative provided.**	Mod2.7.4
	GS-US-299-0101 (BA)	• Part 1: D/C/F/TAF FDC (3 formulations)[b] • Part 2: – DRV+COBI+F/TDF; DRV+COBI – DRV+COBI+F/TDF; F/TDF • Part 3: – D/C/F/TAF FDC; DRV+COBI – D/C/F/TAF FDC; FTC+TAF	102	Phase 1, adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple-cohort, single-center study to evaluate the relative BA of 3 formulations of D/C/F/TAF FDC	GS-US-299-0101 Final CSR **Supportive study, no narrative provided.**	Mod2.7.4

Table 2: Tabulated Overview of Studies Providing Supportive Clinical Safety Data for the D/C/F/TAF FDC Tablet

Population	Study	Treatment[a]	Number of Subjects	Study Design	Source Reference and Narrative Locations	Included in
Thorough QT studies with individual components						
	TMC114-C153	• DRV/rtv 1600/100 mg and 800/100 mg; moxifloxacin, PBO	40	Phase 1, open-label, randomized, placebo- and active-controlled, 4-way crossover study to evaluate ECG intervals in healthy adults receiving DRV/rtv	Investigator's Brochure (Mod5.4) and Prescribing Information[15] **Supportive study, no CSR or narrative provided.**	Mod2.7.4
	GS-US-216-0107	• COBI 250 mg and 400 mg; PBO; moxifloxacin	48	Phase 1, single-dose, randomized, partially-blinded, placebo- and positive-controlled, 4-period crossover study to evaluate the effects of COBI on the QT/QTc interval in healthy subjects	Investigator's Brochure (Mod5.4) and Prescribing Information[15,18] **Supportive study, no CSR or narrative provided.**	Mod2.7.4
	GS-US-120-0107	• TAF 25 mg and 125 mg; PBO; moxifloxacin	59	Phase 1, partially-blinded, randomized, placebo- and positive-controlled, 4-period, single-dose crossover study to evaluate the effect of TAF on the QT/QTc interval in healthy subjects	Investigator's Brochure (Mod5.4) and Prescribing Information[4,10,19] **Supportive study, no CSR or narrative provided.**	Mod2.7.4
Special Populations						
Studies in subjects with renal impairment						
	GS-US-236-0118	• E/C/F/TDF FDC; • ATV/COBI + 2 NRTIs or DRV/COBI + 2 NRTIs	106	Phase 3, open-label, multicenter, study to evaluate the safety of COBI-containing highly active ARV regimens in HIV-1 infected subjects with **mild to moderate renal impairment**	Janssen NDA 205395 SUR **Supportive study, no CSR or narrative provided.**	Mod2.7.4
	GS-US-292-0112	• E/C/F/TAF FDC	248	Phase 3, open-label, multicenter, multiple cohort study to evaluate the safety, efficacy, and tolerability of E/C/F/TAF FDC in HIV-1 positive subjects with **mild to moderate renal impairment**	Pozniak et al[14] **Supportive study, no CSR or narrative provided.**	Mod2.7.4

ARV = antiretroviral; ATV = atazanavir; BA = bioavailability; BE = bioequivalence; COBI = cobicistat; CSR = clinical study report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; ECG = electrocardiogram; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; FDC = fixed-dose combination; FTC = emtricitabine; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; NDA = new drug application; NRTI = nucleoside reverse transcriptase inhibitor; PBO = placebo; PK = pharmacokinetics; QTc = QT interval corrected for heart rate; rtv = ritonavir; SUR = Safety Update Report; TAF = tenofovir alafenamide.

[a] Unless otherwise specified, doses of study drugs are as follows: D/C/F/TAF 800/150/200/10 mg; DRV 800 mg or 400 mg x2; COBI 150 mg; FTC 200 mg; TAF 25 mg; F/TAF 200/10 mg; E/C/F/TAF 150/150/200/10 mg; F/TDF 200/300 mg; E/C/F/TDF 150/150/200/300 mg; moxifloxacin 400 mg; ATV/COBI 300/150 mg; and DRV/COBI 800/150 mg.

[b] Three formulations of the D/C/F/TAF FDC were investigated: 800/150/200/25-mg monolayer FDC; 800/150/200/25-mg bilayer FDC; and 800/150/200/10-mg monolayer FDC.

Table 3: Number of Subjects Enrolled or Randomized and Treated in the Studies With the D/C/F/TAF FDC Included in the Summary of Clinical Safety

	D/C/F/TAF group (N)	Control group (N)	Total (N)	Section
TOTAL	**1,491**	**1,007**	**2,319**	
D/C/F/TAF in HIV-1 Infected Adult Subjects	**1,228**	**791**	**2,019**	
ART-naïve				
Phase 3 (TMC114FD2HTX3001)	362	363[a]	725	3.1.1.1
Phase 2 (GS-US-299-0102)	103	50[b]	153	3.1.1.3
ART-experienced, Virologically Suppressed				
Phase 3 (TMC114IFD3013)	763	378[c]	1,141	3.1.1.2
D/C/F/TAF in HIV-1 Negative Adult Subjects[d]	**263**	**216**	**300**	
Phase 1 BE (TMC114FD2HTX1001)	96	96[e]	96	3.1.2
Phase 1 BA, food effect (TMC114FD2HTX1002)	72	48[f]	72	3.1.2
Phase 1 BA (TMC114FD2HTX1004)	30[g]	0	30	3.1.2
Phase 1 BA (GS-US-299-0101)	65[h]	72[i]	102	3.1.2

ART = antiretroviral treatment; ATV = atazanavir; BA = bioavailability; BE = bioequivalence; bPI = boosted protease inhibitor; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide; FTC = emtricitabine; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; LPV = lopinavir; N = number of subjects; rtv = low-dose ritonavir; TAF = tenofovir alafenamide.

[a] Control: DRV/COBI (800/150 mg) FDC + F/TDF (200/300 mg) FDC.

[b] Control: DRV (400 mg x2) + COBI (150 mg) + F/TDF (200/300 mg) FDC.

[c] Control: bPI (DRV with rtv or COBI, ATV with rtv or COBI, or LPV with rtv) + F/TDF (200/300 mg) FDC.

[d] Due to the crossover design of the Phase 1 studies, some subjects received multiple treatments per study (for more details, refer to Mod5.3.1.2/TMC114FD2HTX1001-Final-CSR, Mod5.3.1.1/TMC114FD2HTX1002-Final-CSR, Mod5.3.1.1/TMC114FD2HTX1004-Final-CSR, and Mod5.3.1.1/GS-US-299-0101-Final-CSR).

[e] Control: DRV (800 mg) + COBI (150 mg) + F/TAF (200/10 mg) FDC.

[f] Control: 24 subjects received DRV (800 mg) + COBI (150 mg) + F/TAF (200/10 mg) FDC; and 24 subjects received E/C/F/TAF (150/150/200/10 mg) FDC.

[g] Each subject sequentially received the D/C/F/TAF (800/150/200/10-mg) FDC as a whole tablet, as a split tablet, and as a crushed tablet in the order determined by randomization.

[h] Three different formulations of the D/C/F/TAF FDC were investigated in this study: 10 subjects received the 800/150/200/25-mg monolayer FDC; 10 subjects received the 800/150/200/25-mg bilayer FDC; and 45 subjects received the 800/150/200/10-mg monolayer FDC (which is the formulation used in the other studies with the D/C/F/TAF FDC).

[i] Control: 36 subjects received DRV (400 mg x2) + COBI (150 mg) + F/TDF (200/300 mg) FDC; 40 subjects received DRV (400 mg x2) + COBI (150 mg); 16 subjects received F/TDF (200/300 mg) FDC; and 16 subjects received FTC (200 mg) + TAF (25 mg).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR, Mod5.3.5.1/TMC114IFD3013-W48-CSR, Mod5.3.5.1/GS-US-299-0102-Final-CSR, Mod5.3.1.2/TMC114FD2HTX1001-Final-CSR, Mod5.3.1.1/TMC114FD2HTX1002-Final-CSR, Mod5.3.1.1/TMC114FD2HTX1004-Final-CSR, and Mod5.3.1.1/GS-US-299-0101-Final-CSR.

2.2. Safety Assessments and Statistical Methods of Phase 3 and 2 Studies

This section presents a high-level overview of the safety assessments and statistical methods for the Phase 3 and 2 studies included in this SCS, with the main focus on the pivotal Phase 3 studies. Further details on the safety assessments can be found in the study protocol and the clinical study report (CSR) of each study, and details on the statistical methods are described in the statistical analysis plan (SAP) of each study (available in the appendices of the CSRs).

2.2.1. Adverse Events

The data in scope for the analyses of the individual studies in Section 3 differ according to the study. For Studies TMC114FD2HTX3001 and TMC114IFD3013, the data up to each subject's Week-48 visit were in scope for the analyses. For the other studies, either the final analysis is presented or the Week-48 analysis (ie, cut-off at the time the last subject completed the Week-48 visit or prematurely discontinued).

In Section 5, safety data from the 2 ongoing studies (TMC114FD2HTX3001 and TMC114IFD3013) are discussed. For each study, the period in scope for this safety review starts after the Week-48 visit and ends at the data cut-off date of 1 June 2017. Outputs generated include all data after the Week-48 visit (ie, treatment phase and follow-up phase).

Unless specified otherwise, (1) the AEs presented in this SCS are treatment-emergent AEs (ie, either newly appearing after study treatment started, or worsening of a condition which was already present at baseline), (2) AEs are reported by preferred term (PT), (3) causality assessments for study drugs are always according to the investigator, and (4) AE tables are by System Organ Class (SOC) and by PT, both ordered by frequency. The original terms used by investigators to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 for Studies TMC114FD2HTX3001 and TMC114IFD3013, Version 17.0 for Study GS-US-299-0102, and Version 12.1 for Study TMC114-C230.

2.2.1.1. Adverse Events of Interest

In addition to standard safety assessments, the following AEs of interest (AEOIs) were analyzed in the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013:

- AEOIs reflecting safety concerns with TAF/TDF:
  - Renal events
  - Bone events
  - Ocular events
- AEOIs reflecting mainly safety concerns with DRV:
  - Severe skin events
  - Rash events
  - Liver events (including the safety concern of hepatitis B virus [HBV] flare after TAF/TDF discontinuation in co-infected subjects)
  - Hyperglycemia events
  - Lipid-related events
  - Immune reconstitution inflammatory events
  - Coronary artery events

- Other AEOIs:
  - Pancreas events
  - Lipodystrophy events
  - Cardiac conduction events
  - Convulsion
  - Lactic acidosis/severe hepatomegaly with steatosis
  - Hemophilia/bleeding events

The safety outputs were reviewed by a medical monitor for any events of HBV flare, lactic acidosis, or severe hepatomegaly with steatosis which have been associated with the use of emtricitabine/tenofovir disoproxil fumarate (F/TDF), and for hemophilia complications which have been associated with the use of some boosted protease inhibitors (bPIs). The other AEOI groups included a broad list of terms, defined a priori, to identify potential cases (refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Statistical Analysis Plan for a list of all PTs belonging to each AEOI group). Since many of these terms were clinically non-specific, only those cases that upon medical review were specifically suggestive of/compatible with the AEOIs are discussed.

Laboratory abnormalities of interest (see Section 2.2.2.1) are provided together with the AEOIs, under the appropriate sections.

2.2.1.2. Adverse Drug Reactions

The AEs reported during Studies TMC114FD2HTX3001, TMC114IFD3013, and GS-US-299-0102 were reviewed by medical experts for identification of ADRs associated with D/C/F/TAF, according to the principles described in Appendix 2.

The incidences of ADRs in Studies TMC114FD2HTX3001 and TMC114IFD3013 are derived from the statistical analysis of AEs. The exact numbers and percentages of the ADR incidences may differ from the AE incidences due to the grouping of PTs. An overview of the D/C/F/TAF ADRs and the grouping of PTs into medical concepts and their resulting SOCs are provided in Appendix 3.

2.2.1.3. Differences in Analysis of Adverse Events Across Studies

In the studies conducted by the Sponsor, the causality between an AE and the study drug was assessed by the investigator as not related, doubtfully, possibly, probably, or very likely related. In the statistical analysis, the latter 3 were grouped as ‘at least possibly related’.

In the studies conducted by GSI, the causality between an AE and the study drug was assessed by the investigator as either ‘not related’ or ‘related’ (for definitions refer to Mod5.3.5.1/GS-US-299-0102-Final-CSR/Protocol and Protocol Amendments). These 2 categories correspond to the 2 grouped categories of the Sponsor ‘not/doubtfully related’ and ‘at least possibly related’.

To distinguish between studies conducted by the Sponsor and studies conducted by GSI, refer to STUDY NAMING CONVENTIONS.

2.2.2. Clinical Laboratory Tests

2.2.2.1. Laboratory Tests of Interest

In addition to standard assessments (mainly hematology), the following laboratory tests of interest were analyzed in the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013:

- Pancreatic parameters: total amylase, lipase.
- Liver-related parameters:
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bilirubin (total, direct, indirect).

      An analysis was performed to identify all subjects meeting Hy's law criteria, ie, subjects showing 3-fold or greater elevations above the upper limit of normal (ULN) of ALT or AST and a concomitant elevation of serum total bilirubin to >2x ULN, without a concomitant elevated serum ALP (defined as serum ALP activity ≥2x ULN).
    - Urine/dipstick: bilirubin, urobilinogen.
- Lipid parameters: cholesterol, high density lipoprotein (HDL) cholesterol (all types), low density lipoprotein (LDL) cholesterol (all types), total cholesterol (TC)/HDL, triglycerides; these were analyzed both irrespective of fasting status, and separately from fasting samples.

  In addition, lipid parameters were analyzed according to the National Cholesterol Education Program (NCEP) categories:
    - Triglycerides abnormally high (≥150 mg/dL).
    - Total cholesterol abnormally high (≥200 mg/dL).
    - LDL abnormally high (≥100 mg/dL).
    - HDL abnormally low (<40 mg/dL).
- Glucose parameters were analyzed both irrespective of fasting status, and separately for fasting samples:
    - Blood: glucose.
    - Urine/dipstick: glucose, ketones.
- Renal parameters:
    - Blood: total protein, creatinine, blood urea nitrogen, uric acid, phosphorus, potassium, sodium, bicarbonate, chloride, albumin.

- Urine/chemistry: creatinine, sodium, phosphate, glucose, urine albumin, urine protein.
- Urine/dipstick: glucose, protein.

2.2.2.2. Creatinine and Glomerular Filtration

Serum Creatinine and Cystatin C

Estimated glomerular filtration rate based on serum creatinine ($eGFR_{cr}$) was calculated according to the Cockcroft-Gault formula[3] ($eGFR_{CG}$) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[11] ($eGFR_{CKD-EPI}$), and eGFR based on serum cystatin C was calculated according to the CKD-EPI formula ($eGFR_{cyst}$).

The difference between the 2 treatment groups in change from baseline in serum creatinine and various estimates of GFR were tested using analysis of covariance (ANCOVA) at Week 48, including corresponding baseline value and other clinically relevant factors in the model. The nominal p-values were used without any adjustments, interpreted at the 5% level.

Proximal Renal Tubular Function

Proteinuria was assessed quantitatively (through measurement of total urine protein, total urine albumin, urine protein to creatinine ratio [UPCR] and urine albumin to creatinine ratio [UACR]), and by urinalysis (dipstick).

Other renal biomarkers included retinol binding protein (RBP) and beta-2-microglobulin, RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio, and urine fractional excretion of phosphate (FE_{PO4}).

The following abnormalities were considered potential markers of treatment-emergent subclinical proximal renal tubulopathy (PRT):

1. Increase in serum creatinine ≥0.40 mg/dL from baseline.
2. Confirmed ≥2 grade level increase from baseline in graded proteinuria.
3. Confirmed ≥1 grade level increase from baseline in graded hypophosphatemia.
4. Confirmed ≥1 grade level increase from baseline in graded glycosuria concurrent with serum glucose ≤100 mg/dL (normoglycemic glycosuria).

A confirmed laboratory abnormality was defined as an abnormality observed at 2 consecutive postbaseline measurements or an abnormality observed at 1 measurement followed by study drug discontinuation.

A treatment-emergent subclinical PRT was defined as confirmed abnormalities in any 2 out of the 4 renal parameters (serum creatinine and 1 or more of the 3 other markers of tubular dysfunction).

The following abnormalities were considered potential markers of baseline subclinical PRT:

1. Grade ≥1 serum creatinine.
2. Grade ≥2 proteinuria.
3. Grade ≥1 hypophosphatemia.
4. Grade ≥1 glycosuria concurrent with serum glucose ≤100 mg/dL (normoglycemic glycosuria).

A baseline subclinical PRT was defined as abnormalities in any 2 out of the 4 renal parameters (serum creatinine and 1 or more of the 3 other markers of tubular dysfunction).

2.2.2.3. Differences in Laboratory Analyses Across Studies

In the studies conducted by the Sponsor and in the ADR analysis, abnormalities in clinical laboratory data were determined using the criteria defined by the division of acquired immunodeficiency syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.
(Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Protocol and Amendments)

In the studies conducted by GSI, laboratory abnormalities were graded using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Protocol and Protocol Amendments and Statistical Analysis Plan).

The main differences between these 2 scales relevant for the evaluation of the safety profile of the D/C/F/TAF FDC are listed in Table 4. For all other laboratory parameters, the differences between the DAIDS and GSI grading tables are limited to small numerical differences in the boundaries of the ranges for the different grades (see Appendix 1).

Table 4: Main differences Between the DAIDS and GSI Grading Scales for Severity of Adverse Events and Laboratory Abnormalities Relevant for D/C/F/TAF Safety Evaluation

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine				
DAIDS grading scale	1.1 to 1.3x ULN[a]	>1.3 to 1.8x ULN[a] OR Increase of >0.3 mg/dL above baseline	>1.8 to <3.5x ULN[a] OR Increase of 1.5 to <2.0x above baseline	≥3.5x ULN[a] OR Increase of ≥2.0x above baseline
GSI grading scale	>1.5 to 2.0 mg/dL	>2.0 to 3.0 mg/dL	>3.0 to 6.0 mg/dL	>6.0 mg/dL
Amylase				
DAIDS grading scale	1.1 to <1.5x ULN[b]	1.5 to <3.0x ULN[b]	3.0 to <5.0x ULN[b]	≥5.0x ULN[b]
GSI grading scale	>1.0 to 1.5x ULN[c]	>1.5 to 2.0x ULN[c]	>2.0 to 5.0x ULN[c]	>5.0x ULN[c]
Triglycerides (fasting)				
DAIDS grading scale	150 to 300 mg/dL 1.71 to 3.42 mmol/L	>300 to 500 mg/dL >3.42 to 5.7 mmol/L	>500 to <1,000 mg/dL >5.7 to 11.4 mmol/L	>1,000 mg/dL >11.4 mmol/L
GSI grading scale	NA	500 to 750 mg/dL 5.64 to 8.47 mmol/L	>750 to 1200 mg/dL >8.47 to 13.55 mmol/L	>1200 mg/dL >13.55 mmol/L

DAIDS = Division of acquired immunodeficiency syndrome (AIDS); GSI = Gilead Sciences, Inc; NA = not applicable; ULN = upper limit of normal.

[a] ULN = 1.1 mg/dL (female aged 18 to <70 years), 1.2 mg/dL (male aged 18 to <50 years; female aged 70 to <80 years), 1.3 mg/dL (male aged 50 to <70 years), or 1.5 mg/dL (male aged 70 to <80 years).

[b] ULN = 100 U/L (male/female aged 18 to <50 years), 120 U/L (male/female aged 50 to <60 years), 150 U/L (male/female aged 60 to <70 years, or 252 U/L (male/female aged 70 to <83 years).

[c] ULN = 100 U/L (male aged 18 to 49 years; female aged 29 to 46 years), 120 U/L (male aged 50 to 59 years; female aged 51 to 56 years), or 150 U/L (male aged 60 to 69 years; female aged 62 years).

Source:
Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Protocol and Amendments (DAIDS grading scale Version 2.0, November 2014), and Statistical Analysis Plan, Mod5.3.5.1/GS-US-299-0102-Final-CSR/Protocol and Protocol Amendments (GSI grading scale Version 21 September 2011), and Statistical Analysis Plan.

To distinguish between studies conducted by the Sponsor and studies conducted by GSI, refer to STUDY NAMING CONVENTIONS.

2.2.3. Bone Investigations

In the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013, the following bone markers were analyzed:

- Bone formation markers:
  - Serum total ALP
  - Serum type 1 procollagen N-terminal (P1NP)
- Bone resorption markers:
  - Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)
- Other:
  - Parathyroid hormone (PTH)
  - 25-hydroxy vitamin D (25-OH VitD)

A dual energy x-ray absorptiometry (DXA) scan was performed of spine and hip to analyze the following parameters:

- Bone mineral density (BMD) values

- BMD T-scores

The BMD status was derived based on T-scores using the following categories:

	Osteoporosis	Osteopenia	Normal
T-score	<-2.5	-2.5 to <-1	≥-1

The between-treatment difference of the percent change in BMD at Week 48 was estimated using ANCOVA model, including baseline BMD value, race, gender, baseline body mass index (BMI) and age at study entry, and current smoking status (Y/N). The nominal p-values were used without any adjustments, interpreted at the 5% level.

2.3. Extent of Exposure Across Phase 3 and 2 Studies

Extent of exposure across Phase 3 and 2 studies in HIV-1 infected adult and adolescent subjects at the Week-48 cut-off is presented in Mod2.7.3/Tab3.

The total number of HIV-1 infected subjects in the studies supporting this application is 2,081, of whom 1,290 subjects received test drug: 1,228 adult subjects received the D/C/F/TAF FDC (465 ART-naïve and 763 ART-experienced, virologically suppressed), 12 ART-naïve adolescent subjects received DRV, and 50 ART-naïve adolescent subjects received E/C/F/TAF.

In the Phase 3 Study TMC114FD2HTX3001 in adult, HIV-1 infected, ART-naïve subjects, the mean (standard deviation [SD]) duration of exposure was 46.8 (8.4) weeks to D/C/F/TAF and 46.0 (9.7) weeks to DRV/COBI+F/TDF. In the Phase 3 Study TMC114IFD3013 in adult, HIV-1 infected, ART-experienced, virologically suppressed subjects, the mean (SD) duration of exposure was 47.2 (6.6) weeks to D/C/F/TAF and 47.1 (7.6) weeks to bPI+F/TDF. In the supportive Phase 2 Study GS-US-299-0102 in adult, HIV-1 infected, ART-naïve subjects, the mean (SD) duration of exposure was 61.7 (20.3) weeks to D/C/F/TAF and 66.1 (14.8) weeks to DRV+COBI+F/TDF.

In the studies in adolescent, HIV-1 infected subjects, the mean (SD) duration of exposure was 49.3 (1.9) weeks to DRV/rtv (+zidovudine/lamivudine [AZT/3TC] or + abacavir/lamivudine [ABC/3TC]) in Study TMC114-C230 and the median (interquartile [IQ] range) duration of exposure was 60.1 (48.1; 84.1) weeks to E/C/F/TAF in Study GS-US-292-0106.

2.4. Analysis Sets of Phase 3 and 2 Studies

The analysis sets for the studies in HIV-1 infected, ART-naïve and -experienced, adult subjects and HIV-1 infected, ART-naïve, adolescent subjects are presented in Mod2.7.3/Tab2.

Safety analyses were performed on:

- The intent-to-treat (ITT) population for Studies TMC114FD2HTX3001, TMC114IFD3013, and TMC114-C230: All subjects who were randomized and received at least 1 dose of treatment in the study.
    - In addition, for Studies TMC114FD2HTX3001 and TMC114IFD3013, the bone investigation substudy (BIS) analysis set includes all subjects in the ITT set having at

least 1 postbaseline value either in bone biomarker or in BMD data. Subjects are grouped according to the treatment group (D/C/F/TAF or control) to which they were randomized.

- The Safety Analysis Set (SAS) for Studies GS-US-299-0102 and GS-US-292-0106: All subjects who were enrolled or randomized and received at least 1 dose of study drug, and had postbaseline safety assessments available.
    - The spine DXA analysis set includes all subjects in the SAS who had nonmissing spine BMD values for the baseline visit and at least 1 postbaseline visit.
    - The hip DXA analysis set includes all subjects in the SAS who had nonmissing hip BMD values for the baseline visit and at least 1 postbaseline visit.
    - The total body less head (TBLH) DXA analysis set includes all subjects in the SAS who had nonmissing baseline and at least 1 postbaseline TBLH BMD value.

2.5. Subject Disposition Across Phase 3 and 2 Studies

Subject disposition across Phase 3 and 2 studies in HIV-1 infected adult and adolescent subjects is presented in Mod2.7.3/Tab4.

Across the Phase 3 and 2 studies in adults, substantially more subjects prematurely discontinued study treatment in the Phase 2 Study GS-US-299-0102 (18.4% in the D/C/F/TAF group and 16.0% in the control group; in this order throughout unless otherwise specified), compared to the Phase 3 Studies TMC114FD2HTX3001 (6.4% and 7.7%) and TMC114IFD3013 (4.5% and 5.3%), primarily due to a higher number of subjects being lost to follow-up in Study GS-US-299-0102 (9.7% and 8.0%, vs 1.4% and 1.4%, and 0.7% and 1.3%).

In the studies in adolescents, a total of 2 (4.0%) subjects prematurely discontinued study treatment (both in Study GS-US-292-0106).

In the adult, ART-naïve population, the incidence of subjects prematurely discontinuing study treatment due to AEs was lower in the D/C/F/TAF groups compared to the control groups (2.2% vs 4.1% for the double-blind Study TMC114FD2HTX3001, and 1.0% vs 4.0% for the double-blind Study GS-US-299-0102). In the adult, ART-experienced, virologically suppressed population in the open-label Study TMC114IFD3013, the discontinuation rate due to AEs was similar in both treatment groups (1.4% vs 1.1%).

In the studies in adolescents, no subjects prematurely discontinued treatment due to AEs.

Across studies, no subjects discontinued treatment due to efficacy-related reasons.

2.6. Demographic and Other Characteristics of Study Populations in Phase 3 and 2 Studies

2.6.1. Demographic Characteristics

Demographic characteristics are summarized in Mod2.7.3/Tab5.

Demographic characteristics were generally similar between treatment groups in each study.

In the Phase 3 study with ART-naïve subjects (TMC114FD2HTX3001), subjects were mostly white (83.2%), male (88.3%), with a mean (SD) age of 35.3 (10.08) years and a mean (SD) BMI of 24.39 (3.85) kg/m^2. There was 1 (0.1%) subject aged more than 65 years, 11.7% females, 11.1% of subjects were black or African American, and 13.2% of subjects were of Hispanic ethnicity (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab2).

In the Phase 2 study with ART-naïve subjects (GS-US-299-0102), subjects were mostly male (92.8%), most were either white (60.1%) or black (34.6%), with a mean (SD) age of 35 (11.2) years, and a mean (SD) BMI at baseline of 26.2 (4.81) kg/m^2. In total, 20.9% of subjects were of Hispanic ethnicity (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab8-4).

In the Phase 3 study with ART-experienced, virologically suppressed subjects (TMC114IFD3013), subjects were mostly white (75.5%), male (82.0%), with a mean (SD) age of 45.1 (10.83) years and a mean (SD) BMI of 26.25 (5.19) kg/m^2. There were 2.9% of subjects aged more than 65 years, 18.0% females, 20.9% of subjects were black or African American, and 15.0% of subjects were of Hispanic ethnicity (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab4).

In Study TMC114-C230 with adolescents, the mean (SD) age was 14.7 (1.69) years. In Study GS-US-292-0106, the median (range) age was 15 (12; 17) years. These studies included 66.7% and 56.0% female subjects and 41.7% and 88.0% black subjects, respectively (Mod2.7.3/Tab5).

2.6.2. Baseline HIV Disease Characteristics

Baseline HIV disease characteristics are summarized in Mod2.7.3/Tab6.

The HIV disease characteristics were generally similar between treatment groups within each study and across studies, taking into account the HIV-1 infected population studied.

In the Phase 3 study with ART-naïve subjects (TMC114FD2HTX3001), the mean (SD) baseline HIV-1 RNA value was 4.48 (0.61) $\log_{10}$ copies/mL. At baseline, 17.9% of subjects had HIV-1 RNA ≥100,000 copies/mL. The mean (SD) baseline CD4+ cell count was 486.0 (230.74) cells/mm^3. About 40% of subjects had a CD4+ cell count >500 cells/mm^3 and 7.0% of subjects had a count <200 cells/mm^3. The mean time since HIV-1 diagnosis was about 19.5 (33.5) months. The most common mode of HIV-1 infection was homosexual sex (70.9%). The majority of subjects had asymptomatic HIV-1 disease (84.4%). Few subjects had advanced (2.2%) or severe (0.1%) symptomatic HIV-1 infection (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab3).

In the Phase 2 study with ART-naïve subjects (GS-US-299-0102), baseline HIV disease characteristics were similar to those in the Phase 3 study (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab8-5).

In the Phase 3 study with ART-experienced, virologically suppressed subjects switching from a bPI+F/TDF-based regimen (TMC114IFD3013), all subjects were virologically suppressed at screening (or at screening retest; n=5), and a minority (2.0%) had a baseline viral load

≥50 copies/mL (not stably suppressed). The mean (SD) baseline CD4+ cell count was 649.5 (252.99) cells/mm^3. About 70% of subjects had a CD4+ cell count >500 cells/mm^3 and 1.5% of subjects had a count <200 cells/mm^3. The mean (SD) time since HIV-1 diagnosis was 11.6 (8.4) years. The most common mode of HIV-1 infection was homosexual sex (64.4%). The majority of subjects had asymptomatic HIV disease (68.1%). A small proportion of subjects had advanced (8.9%) or severe (10.1%) symptomatic HIV-1 infection (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab5).

In Study GS-US-292-0106 in adolescent subjects, baseline HIV disease characteristics were similar to those of the ART-naïve adult subjects. In Study TMC114-C230, a higher percentage of subjects (41.7%) had HIV-1 RNA ≥100,000 copies/mL, a lower percentage of subjects (8.3%) had a CD4+ cell count >500 cells/mm^3, and a lower percentage of subjects was asymptomatic (41.7%). In both studies, vertical transmission was the most common HIV risk factor (64.0% and 41.7%) (Mod2.7.3/Tab6).

2.6.3. General Baseline Characteristics

General baseline characteristics are summarized in Table 5.

Except for Study TMC114-C230, co-infection with HBV or hepatitis C virus (HCV) was an exclusion criterion in the Phase 3 and 2 studies supporting this submission, hence none of the subjects in these studies presented a baseline status of co-infection with HBV or HCV. In Study TMC114-C230 in adolescents, 1 subject was reported with HBV co-infection at baseline.

Across studies, the subjects' general baseline characteristics differed mainly in terms of renal function:

- Screening $eGFR_{CG}$ ≥50 mL/min was allowed in Study TMC114IFD3013 with ART-experienced subjects while in Studies TMC114FD2HTX3001 and GS-US-299-0102 with ART-naïve subjects, screening $eGFR_{CG}$ had to be at least 70 mL/min. This is reflected in the baseline renal parameters:
  - In Study TMC114FD2HTX3001, the mean (SD) baseline $eGFR_{CG}$ was 122.5 (27.40) mL/min. At baseline, 0.3% of subjects had an $eGFR_{CG}$ <70 mL/min. The mean (SD) baseline $eGFR_{cyst}$ was 113.3 (17.63) mL/min/1.73 m^2. In this study, 10.3% of subjects had $eGFR_{cyst}$ Chronic Kidney Disease (CKD) stage 2 (between 60 and <90 mL/min/1.73 m^2), and 1.0% of subjects had $eGFR_{cyst}$ CKD stage 3 or 4 (between 15 and <60 mL/min/1.73 m^2) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab4).
  - In Study GS-US-299-0102, mean (SD) baseline $eGFR_{CG}$ (118.3 [28.40] mL/min) was comparable to that in the Phase 3 study in ART-naïve subjects. The mean (SD) $eGFR_{cyst}$ was 105.2 (17.79) mL/min/1.73 m^2. A higher percentage of subjects (17.5% on D/C/F/TAF and 20.0% on control) had $eGFR_{cyst}$ CKD stage 2 (between 60 and <90 mL/min) (Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab8-5 and Table 5).
  - In Study TMC114IFD3013, the mean (SD) baseline $eGFR_{CG}$ was 107.4 (30.46) mL/min. At baseline, 7.8% of subjects had a baseline $eGFR_{CG}$ <70 mL/min. The mean (SD) baseline $eGFR_{cyst}$ was 110.5 (17.22) mL/min/1.73 m^2. In this study, 11.7% of subjects

had $eGFR_{cyst}$ CKD stage 2 (between 60 and <90 mL/min/1.73 m^2), and 1.0% of subjects had $eGFR_{cyst}$ CKD stage 3 (between 30 and <60 mL/min/1.73 m^2) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab6).

- In Study GS-US-292-0106 in adolescents, where screening $eGFR_{cr}$ had to be at least 90 mL/min/1.73 m^2 (calculated using the Schwartz formula), the median (IQ range) baseline eGFR was 156.0 (129.0; 185.0) mL/min/1.73 m^2 (Table 5).

- In Study TMC114IFD3013, eligible subjects had to be on treatment with a TDF-based antiretroviral (ARV) regimen. In this study, 0.4% of subjects met the study-defined criteria for a baseline subclinical PRT. In Study TMC114FD2HTX3001 with ART-naïve subjects, 0.1% of subjects met the study-defined criteria for a baseline subclinical PRT (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab4 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab6).

No relevant differences in general baseline characteristics were observed between the treatment groups within each study, except for the following (Table 5):

- In the D/C/F/TAF group in Study TMC114FD2HTX3001, there was a slightly higher proportion of subjects with a medical history of diabetes or hyperglycemia (2.5% vs 1.7%), and a slightly lower proportion of subjects with a medical history of cardiovascular disease (1.1% vs 2.8%), or dyslipidemia (3.9% vs 5.8%).
- In the D/C/F/TAF group in Study TMC114IFD3013, there was a slightly higher proportion of subjects with a medical history of cardiovascular disease (4.5% vs 2.4%), chronic renal disorder (2.4% vs 1.1%), or diabetes or hyperglycemia (8.1% vs 5.3%).

Table 5: General Baseline Characteristics Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
Nicotine use								
N	362	363	103	50	763	378	12	-
No	NA	NA	NA	NA	NA	NA	11 (91.7%)	NA
No (but former user)	40 (11.0%)	35 (9.6%)	NA	NA	181 (23.7%)	73 (19.3%)	NA	NA
No (never used)	167 (46.1%)	142 (39.1%)	NA	NA	325 (42.6%)	175 (46.3%)	NA	NA
Yes	155 (42.8%)	186 (51.2%)	NA	NA	257 (33.7%)	130 (34.4%)	1 (8.3%)	NA
Alcohol consumption								
N	362	363	103	50	763	378	12	-
No	NA	NA	NA	NA	NA	NA	11 (91.7%)	NA
No (but former user)	20 (5.5%)	13 (3.6%)	NA	NA	93 (12.2%)	53 (14.0%)	NA	NA
No (never used)	89 (24.6%)	91 (25.1%)	NA	NA	172 (22.5%)	55 (14.6%)	NA	NA
Yes	253 (69.9%)	259 (71.3%)	NA	NA	498 (65.3%)	270 (71.4%)	1 (8.3%)	NA
Drug use								
N	362	363	103	50	763	378	12	-
No	NA	NA	NA	NA	NA	NA	11 (91.7%)	NA
No (but former user)	54 (14.9%)	66 (18.2%)	NA	NA	203 (26.6%)	105 (27.8%)	NA	NA
No (never used)	252 (69.6%)	230 (63.4%)	NA	NA	428 (56.1%)	207 (54.8%)	NA	NA
Yes	56 (15.5%)	67 (18.5%)	NA	NA	132 (17.3%)	66 (17.5%)	1 (8.3%)	NA
$eGFR_{CG}$ (mL/min)								
N	362	363	103	50	761	378	NC	50
Mean (SD)	123.5 (29.47)	121.5 (25.17)	119.6 (26.89)	115.7 (31.41)	107.5 (30.56)	107.0 (30.29)	NC	NA
Median	119.3	118.4	116.0	109.6	104.2	103.3	NC	156.0[c]
IQ range	(104.8; 135.2)	(103.2; 138.4)	(97.0; 137.6)	(92.5; 131.4)	(86.9; 122.5)	(86.3; 122.4)	NC	(129.0; 185.0)[c]
Range	(74; 257)	(57; 207)	(77; 223)	(74; 259)	(47; 315)	(36; 230)	NC	(101; 284)[c]
<70 mL/min	0	2 (0.6%)	0	0	58 (7.6%)	31 (8.2%)	NC	NA
$eGFR_{cyst}$ (mL/min/1.73 m^2)								
N	362	363	101	50	763	378	NC	-
Mean (SD)	113.6 (16.47)	113.0 (18.73)	105.4 (17.85)	104.8 (17.85)	110.1 (16.96)	111.2 (17.73)	NC	NA
Median	117.1	118.0	106.7	109.2	113.1	114.0	NC	NA
IQ range	(102.7; 124.9)	(104.6; 126.1)	(95.0; 119.0)	(95.8; 118.0)	(102.8; 120.9)	(100.4; 123.0)	NC	NA
Range	(51; 150)	(26; 151)	(63; 137)	(53; 132)	(44; 161)	(48; 155)	NC	NA
CKD Stage 2: Mild CKD: ≥60 and <90 mL/min/1.73 m^2	33 (9.1%)	42 (11.6%)	18 (17.5%)	10 (20.0%)	94 (12.3%)	39 (10.3%)	NC	NA

Table 5: General Baseline Characteristics Across Phase 3 and 2 Studies in HIV-1 Infected Subjects; ITT

	ADULTS						ADOLESCENTS	
	ART-naïve Subjects				ART-experienced, Virologically Suppressed Subjects		ART-naïve Subjects	
	TMC114FD2HTX3001		GS-US-299-0102[a]		TMC114IFD3013		TMC114-C230	GS-US-292-0106[a]
	D/C/F/TAF (N=362)	DRV/COBI +F/TDF (N=363)	D/C/F/TAF (N=103)	DRV+COBI +F/TDF (N=50)	D/C/F/TAF (N=763)	current bPI[b] +F/TDF (N=378)	DRV/rtv +AZT/3TC or ABC/3TC (N=12)	E/C/F/TAF (N=50)
CKD Stage ≥3: Moderate CKD: <60 mL/min/1.73 m^2	3 (0.8%)	4 (1.1%)	0	1 (2.0%)	7 (0.9%)	4 (1.1%)	NC	NA
Subclinical proximal renal tubulopathy[d]	0	1 (0.3%)	NA	NA	2 (0.3%)	2 (0.5%)	NA	NA
History of chronic renal disorder	1 (0.3%)	1 (0.3%)	NA	NA	18 (2.4%)	4 (1.1%)	NA	NA
History of Diabetes/hyperglycemia	9 (2.5%)	6 (1.7%)	NA	NA	62 (8.1%)	20 (5.3%)	NA	NA
History of Dyslipidemia	14 (3.9%)	21 (5.8%)	NA	NA	241 (31.6%)	116 (30.7%)	NA	NA
History of Lipodystrophy	0	1 (0.3%)	NA	NA	55 (7.2%)	23 (6.1%)	NA	NA
History of Overweight/Obesity	3 (0.8%)	1 (0.3%)	NA	NA	0	0	NA	NA
History of Cardiovascular disease	4 (1.1%)	10 (2.8%)	NA	NA	34 (4.5%)	9 (2.4%)	NA	NA
Hepatitis C positive (both serology and RNA)	0	0	0	0	0	0	0	-
Hepatitis B positive serology (HBsAg)	0	0	0	0	0	0	1 (12.5%)	-

ABC/3TC = abacavir/lamivudine; ART = antiretroviral treatment; ATV = atazanavir; AZT/3TC = zidovudine/lamivudine; bPI = boosted protease inhibitor; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; eGFR = estimated glomerular filtration rate; $eGFR_{CG}$ = eGFR based on serum creatinine calculated using the Cockcroft-Gault method; $eGFR_{cyst}$ = eGFR based on serum cystatin C calculated using the CKD-EPI method; F/TDF = emtricitabine/tenofovir disoproxil fumarate; HBsAg = hepatitis B surface antigen; HIV-1 = human immunodeficiency virus type 1; IQ = interquartile; ITT = intent-to-treat; LPV = lopinavir; N = number of subjects; NA = not available; NC = not calculated; rtv = ritonavir; SAS = Safety Analysis Set; SD = standard deviation.

[a] For studies GS-US-299-0102 and GS-US-292-0106, analyses were done on the SAS, which corresponds to the ITT population.

[b] DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv.

[c] $eGFR_{cr}$ by Schwartz formula (mL/min/1.73 m^2).

[d] Confirmed abnormalities in any 2 out of the 4 renal parameters (serum creatinine +1 or more of the 3 other markers of tubular dysfunction).

[TABLE05.RTF] [/SAS/Z_TMC114/TMC114_DCF_TAF/FILES/RE/SCS_2017/PROGRAMS/TABLE5.SAS] 23JUN2017, 08:15
and Gaur et al. 2016 (manuscript)[9]

3. RESULTS OF THE INDIVIDUAL STUDIES

3.1. Safety of the D/C/F/TAF FDC in Adult Subjects

3.1.1. Safety of the D/C/F/TAF FDC in HIV-1 Infected, Adult Subjects

3.1.1.1. Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve, Adult Subjects

Safety findings from Study TMC114FD2HTX3001 are consistent with the known safety profiles of the individual components of the D/C/F/TAF FDC:

- Rash occurred in a similar proportion (13.0% vs 10.7%) of subjects in each treatment group and led to early discontinuation of treatment in, respectively, 1.7% and 1.4% of subjects. No severe skin reactions occurred in the D/C/F/TAF group; in the control group, 0.8% of subjects experienced a severe skin reaction that led to treatment discontinuation. The subjects recovered 12 to 22 days later.
- Deaths, other SAEs, and AEs leading to discontinuation each occurred in <6% of subjects.
- Lipids increased at Week 48 vs baseline in the D/C/F/TAF group, but these were not reflected in clinically relevant differences between the treatment groups in median changes from baseline in the TC/HDL ratio. Lipid-lowering treatment was initiated for 1.7% vs 0.6% of subjects during the treatment phase.
- At Week 48, the subjects showed a better renal and bone safety profile when using a TAF-based regimen compared to a TDF-based regimen, with:
    - Greater increases in $eGFR_{cyst}$, a lower incidence of proteinuria, and a lower incidence of increases in markers of potential PRT.
    - Stable hip and spine BMD compared to decreases in the control group.

3.1.1.1.1. Extent of Exposure

Number of Subjects
- D/C/F/TAF (800/150/200/10 mg): 362 subjects.
- DRV/COBI (800/150 mg) + F/TDF (200/300 mg): 363 subjects.

Exposure
- D/C/F/TAF:
    - Mean (SD) exposure: 46.8 (8.4) weeks.
    - Subject-years of exposure[a]: 324.3.
- DRV/COBI+F/TDF:
    - Mean (SD) exposure: 46.0 (9.7) weeks.
    - Subject-years of exposure[a]: 319.7.
- For the n (%) of subjects by week of study, refer to Mod2.7.3/Tab3.
- For a Kaplan-Meier curve of the time to discontinuation of study, refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Fig3.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Fig2 (subject disposition) and Tab8 (extent of exposure).

[a] Subject-years of exposure calculated via the following formula:
mean of treatment duration (in weeks) x N x 7 / 365.25.

3.1.1.1.2. Adverse Events

(Number of subjects with events for D/C/F/TAF vs control [DRV/COBI+F/TDF])

Deaths

1 subject in the control group experienced a fatal grade 4 SAE of sepsis during the follow-up phase after study drug interruption for a grade 4 sclerosing cholangitis. The event was considered not related to the study drug.

AEs leading to discontinuation

1.9% vs 4.4% of subjects.

- No AEs leading to permanent discontinuation of the study drug occurred in >2 subjects per treatment group, except for rash, reported in 4 (1.1%) vs 5 (1.4%) subjects.

SAEs

4.7% vs 5.8% of subjects.

- No SAEs were reported in >2 subjects per treatment group.
- No SAEs were considered related to the study drug in the D/C/F/TAF group.
- 6 (1.7%) subjects were reported with related SAEs in the control group (ie, rash and toxic skin eruption in 2 subjects each, and bone marrow edema and Stevens-Johnson syndrome in 1 subject each).

AEs overall & most frequent

86.2% vs 84.6% of subjects had at least 1 AE.

- The majority of AEs were grade 1 or 2. Grade 3 or 4 AEs were reported in 5.2% vs 6.1% of subjects.
- The most frequently reported AE in both treatment groups was diarrhea (19.6% vs 18.2%).
- Other AEs reported in ≥10% of subjects in any of the treatment groups were: headache (13.0% vs 8.8%), nasopharyngitis (11.0% vs 8.5%), and nausea (7.7% vs 12.4%).

Causality of AEs

34.8% vs 41.6% of subjects had at least 1 related AE.

- The most frequently reported related AEs (in ≥5% of subjects in either treatment group) were diarrhea (8.6% vs 11.0%), rash (6.1% vs 3.9%), and nausea (5.5% vs 9.9%).

Narratives

Refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/W48-Subject-Narratives.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.2.1 (AEs overall), Sec6.2.2.1 (deaths), Sec6.2.2.2 (SAEs), and Sec6.2.2.3 (AEs leading to discontinuation).

3.1.1.1.3. Events of Interest

Renal events of interest

AEOIs

The incidence of renal AEOIs was 0.6% vs 2.2%.

- Renal AEOIs consisted for all but one event of laboratory-related events (0.3% vs 2.2%).
- 1 clinical renal AEOI was reported in a subject in the D/C/F/TAF group: grade 1, nonserious polyuria, doubtfully related to the study drug. The AE was not suggestive of a potential PRT.
- None of the renal AEOIs resulted in study drug discontinuation.
- No event of Fanconi syndrome was reported.

Creatinine

- In both treatment groups, there was an increase from baseline in mean serum creatinine.
- The mean increase from baseline at W48 in serum creatinine was larger in the control group (ie, least squares [LS] means estimates of +4.84 µmol vs +8.15 µmol); the difference between treatment groups was statistically significant ($p<0.001$, ANCOVA) (Table 6).
- 2 (0.6%) subjects in the control group (and none in the D/C/F/TAF group) were reported with a grade 1 AE of blood creatinine increased. None were serious or led to study drug discontinuation. Both subjects were also reported with the AE creatinine clearance decreased (grade 1 in one subject and grade 3 in the other subject).

$eGFR_{cr}$

- Results for $eGFR_{cr}$ ($eGFR_{CG}$ or $eGFR_{CKD\text{-}EPI}$) mirror the findings on serum creatinine.
- In both treatment groups, there was a decrease from baseline in mean $eGFR_{CG}$.
- The mean decrease from baseline at W48 in $eGFR_{CG}$ was larger in the control group (ie, LS means estimates of -5.16 mL/min vs -11.20 mL/min); the difference between treatment groups was statistically significant ($p<0.001$, ANCOVA). Similar findings were observed for $eGFR_{CKD\text{-}EPI}$ (Table 6).
- Changes from baseline to last on-treatment $eGFR_{CG}$ CKD stage tended to be more favorable in the D/C/F/TAF group: 3.6% vs 0.8% of subjects had an improved $eGFR_{CG}$ CKD stage, and 6.4% vs 15.9% had a worsened $eGFR_{CG}$ CKD stage. Findings were similar for $eGFR_{CG}$ percent changes from baseline and for $eGFR_{CKD\text{-}EPI}$.
- 3 (0.8%) vs 7 (1.9%) subjects were reported with an AE of creatinine clearance decreased. None were serious or led to study drug discontinuation. All but one event were grade 1 or 2.

$eGFR_{cyst}$

- In both treatment groups, $eGFR_{cyst}$ increased over time.
- The mean increase from baseline at W48 in eGFRcyst was larger in the D/C/F/TAF group (ie, LS means estimates of +5.32 mL/min/1.73 m^2 vs +2.92 mL/min/1.73 m^2); the difference between treatment groups was statistically significant ($p=0.001$, ANCOVA) (Table 6).
- There were no relevant differences between the treatment groups in improvements (ie, decreases in CKD stage) from baseline to last on-treatment $eGFR_{cyst}$ CKD stage: 8.2% vs 8.5% had an improved $eGFR_{cyst}$ CKD stage, and 0.8% vs 2.8% had a worsened $eGFR_{cyst}$ CKD stage.
- 1 subject in the control group was reported with the grade 2 AE cystatin C abnormal (nonserious, did not lead to study drug discontinuation, possibly related).

Table 6: Change from Baseline in Serum Creatinine and eGFRs at Week 48 (ANCOVA); ITT (Study TMC114FD2HTX3001)

	LS Means Estimate	SE	95% CI	p-Value
Serum Creatinine (µmol/L):				
D/C/F/TAF	4.84	0.502	(3.85; 5.82)	<.001
Control	8.15	0.510	(7.15; 9.15)	<.001
D/C/F/TAF – Control	-3.32	0.716	(-4.72; -1.91)	<.001
Estimated glomerular filtration rate based on serum creatinine (CKD-EPI formula) (mL/min/1.73 m^2):				
D/C/F/TAF	-6.04	0.551	(-7.12; -4.96)	<.001
Control	-9.16	0.559	(-10.25; -8.06)	<.001
D/C/F/TAF – Control	3.12	0.786	(1.57; 4.66)	<.001
Estimated glomerular filtration rate based on serum creatinine (Cockcroft-Gault formula) (mL/min):				
D/C/F/TAF	-5.16	0.790	(-6.71; -3.61)	<.001
Control	-11.20	0.802	(-12.78; -9.63)	<.001
D/C/F/TAF – Control	6.04	1.126	(3.83; 8.25)	<.001
Estimated glomerular filtration rate based on serum cystatin C (CKD-EPI formula) (mL/min/1.73 m^2):				
D/C/F/TAF	5.32	0.525	(4.29; 6.35)	<.001
Control	2.92	0.532	(1.88; 3.97)	<.001
D/C/F/TAF – Control	2.40	0.747	(0.93; 3.87)	0.001

ANCOVA model on the change from baseline in various renal parameters, including treatment as a factor and baseline renal values as covariate.

ANCOVA = analysis of covariance; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; LS = least squares; SE = standard error.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab29, Tab30, and Tab31.

Study-defined potential subclinical PRT

- None of the subjects in the D/C/F/TAF group met the study-defined criteria for a treatment-emergent potential subclinical PRT compared to 2 (0.6%) subjects in the control group. None of these 2 control subjects had AEs consistent with PRT reported. No relevant concomitant AEs were reported.

Renal biomarkers

In the D/C/F/TAF group, there was an improvement of the proteinuria at W48 vs baseline, compared to the control group:

- Median UACR decreased at W48 in both treatment groups; the decreases were greater in the D/C/F/TAF group: ie, -0.58 vs -0.15 mg/g. The difference in median change from baseline in UACR between the treatment groups was statistically significant at W48.
- 3.8% vs 5.5% of subjects had clinically significant albuminuria (UACR ≥30 mg/g) at W48; 2.5% vs 4.2% of subjects with an UACR <30 mg/g (albuminuria within normal range) at baseline had a worsening to an UACR ≥30 mg/g (clinically significant albuminuria) at W48.
- Findings were similar for UPCR.

By subgroup There was no apparent effect of the baseline eGFR CKD stage on the occurrence of renal AEOIs nor on the occurrence of significant AEs (ie, deaths, SAEs, AEs leading to discontinuation, and AEOIs) in the D/C/F/TAF group.
The subgroup analyses do not suggest a safety concern for subjects with a decreased renal function ($eGFR_{CG}$ between 70 and <90 mL/min) and treated with D/C/F/TAF.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.1.2 (AEOIs), Sec6.3.1.3.1 (serum creatinine), Sec6.3.1.3.2 ($eGFR_{cr}$), Sec6.3.1.3.3 ($eGFR_{cyst}$), Sec6.3.1.3.4 (PRT), Sec6.3.1.3.5 (renal biomarkers), and Sec6.3.1.4 (by subgroup).

Bone events of interest

AEOIs The incidence of bone AEOIs was 7.7% vs 10.7%.
- None of the AEOIs resulted in study drug discontinuation.
- Fractures were reported in 1.1% vs 0.6% of subjects (p=0.451).
- Upon medical review, all fractures were traumatic, none were suspected to be osteoporotic.

BMD In the D/C/F/TAF group, the BMD evolution at the hip and spine region from baseline to W48 was more favorable compared to the control group.
- At W48, there were no relevant percent changes in BMD at the hip and spine region in the D/C/F/TAF group (ie, LS means estimates of 0.17% and -0.68%, respectively). There were negative percent changes in BMD at the hip and spine region in the control group (ie, LS means estimates of -2.69% and -2.38%, respectively). The difference between treatment groups was statistically significant at each region (Table 7).
- 12.5% vs 2.4% (hip) and 12.5% vs 4.7% (spine) of subjects had a ≥3% increase from baseline BMD at W48 (Table 8).
- 12.5% vs 44.7% (hip) and 27.1% vs 41.2% (spine) of subjects had a ≥3% decrease from baseline BMD at W48 (Table 8).
- 5.2% vs 1.2% (hip) and 3.1% vs 1.2% (spine) of subjects had improvement of the BMD clinical status from baseline at W48 (ie, T-score of osteoporosis to osteopenia, osteoporosis to normal, or osteopenia to normal).
- 3.1% vs 14.1% (hip) and 8.3% vs 15.3% (spine) of subjects had worsening of the BMD clinical status from baseline at W48 (ie, T-score of normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis).

Table 7: Percent Change From Baseline in BMD at Week 48 (ANCOVA); BIS (Study TMC114FD2HTX3001)

	LS Means	SE	95% CI	p-Value
Hip region bone mineral density (g/cm^2)				
D/C/F/TAF	0.17	0.322	(-0.461; 0.808)	0.589
Control	-2.69	0.342	(-3.363; -2.014)	<.001
D/C/F/TAF – Control	2.86	0.470	(1.934; 3.791)	<.001
Spine region bone mineral density (g/cm^2)				
D/C/F/TAF	-0.68	0.402	(-1.473; 0.115)	0.093
Control	-2.38	0.428	(-3.221; -1.533)	<.001
D/C/F/TAF – Control	1.70	0.588	(0.539; 2.858)	0.004
Femoral neck region bone mineral density (g/cm^2)				
D/C/F/TAF	-0.27	0.414	(-1.085; 0.549)	0.518
Control	-2.96	0.440	(-3.830; -2.094)	<.001
D/C/F/TAF – Control	2.69	0.605	(1.500; 3.887)	<.001

ANCOVA = analysis of covariance; BIS = bone investigation substudy; CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; LS = least squares; SE = standard error.

ANCOVA model on the percent changes from baseline per time point, including baseline BMD value as covariate.

Note: Only subjects who participated in the bone investigation substudy were included.
Note: A DXA scan up to 28 days post-baseline was used as a baseline scan.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab43.

Table 8: Proportion of Subjects With at Least 3/5/7% Change From Baseline in BMD at Week 48; BIS (Study TMC114FD2HTX3001)

	D/C/F/TAF	Control
Analysis Set: Bone Investigation Substudy, N	113	99
Hip region bone mineral density (g/cm^2)		
N	96	85
No Change	5 (5.2%)	0
<3% increase	32 (33.3%)	18 (21.2%)
≥3% increase	12 (12.5%)	2 (2.4%)
≥5% increase	5 (5.2%)	0
≥7% increase	2 (2.1%)	0
<3% decrease	35 (36.5%)	27 (31.8%)
≥3% decrease	12 (12.5%)	38 (44.7%)
≥5% decrease	2 (2.1%)	22 (25.9%)
≥7% decrease	1 (1.0%)	6 (7.1%)
Spine region bone mineral density (g/cm^2)		
N	96	85
No Change	1 (1.0%)	0
<3% increase	30 (31.3%)	15 (17.6%)
≥3% increase	12 (12.5%)	4 (4.7%)
≥5% increase	8 (8.3%)	3 (3.5%)
≥7% increase	7 (7.3%)	2 (2.4%)
<3% decrease	27 (28.1%)	31 (36.5%)
≥3% decrease	26 (27.1%)	35 (41.2%)
≥5% decrease	15 (15.6%)	19 (22.4%)
≥7% decrease	4 (4.2%)	7 (8.2%)
Femoral neck region bone mineral density (g/cm^2)		
N	96	85
No Change	0	0
<3% increase	22 (22.9%)	14 (16.5%)
≥3% increase	14 (14.6%)	6 (7.1%)
≥5% increase	9 (9.4%)	2 (2.4%)
≥7% increase	5 (5.2%)	1 (1.2%)
<3% decrease	39 (40.6%)	20 (23.5%)
≥3% decrease	21 (21.9%)	45 (52.9%)
≥5% decrease	9 (9.4%)	22 (25.9%)
≥7% decrease	2 (2.1%)	13 (15.3%)

BIS = bone investigation substudy; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DXA = dual energy x-ray absorptiometry; N = number of subjects with data.

Note: Only subjects who participated in the bone investigation substudy were included.
Note: A DXA scan up to 28 days post-baseline was used as a baseline scan.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab44.

Bone biomarkers Bone biomarkers suggested less bone turnover in the D/C/F/TAF group than in control, with stable values for all markers in the D/C/F/TAF group and an increase in all markers in the control group.

Use of anti-osteoporosis medication 2.5% vs 4.4% of subjects not taking antiosteoporotic drugs (including bisphosphonates, calcium, or vitamin D) during the screening phase, started a new antiosteoporotic treatment during the treatment phase (ie, total number of subjects using antiosteoporotic drugs during the study minus number of subjects using antiosteoporotic drugs during the screening phase and continued this treatment during the treatment phase).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.2.2 (AEOIs), Sec6.3.2.3.1 (BMD), Sec6.3.2.3.2 (biomarkers), and Sec6.3.2.1 (medical history and baseline conditions).

Ocular events of interest

AEOIs Ocular AEOIs were reported in 0.3% vs 0.8% of subjects.

- There were no serious or grade 3 or 4 ocular AEOIs, none led to discontinuation of study drug, and none were considered related to the study drug.
- Upon medical review, none of the events were consistent with posterior uveitis.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.10.

Lipid-related events of interest

AEOIs The incidence of lipid-related AEOIs was 6.6% vs 3.3%.

- None of the AEOIs resulted in study drug discontinuation.
- These events were considered to be related to study drug for 4.1% vs 1.7% of subjects.

Laboratory parameters

- In both treatment groups, the levels of all lipid parameters significantly increased by W24 (except for TC/HDL in the control group), with larger changes being observed in the D/C/F/TAF group. These levels remained stable afterwards, through W48.
- Median changes from baseline (ie, increases) in fasting lipid parameters at W48 were statistically significantly larger in the D/C/F/TAF group than in the control group (Table 9).
- These increases were not reflected in clinically relevant differences between the treatment groups in median changes from baseline in the TC/HDL ratio.
- Similar findings were observed for changes from baseline (either as worst case graded abnormality or category change):
  - Graded abnormalities were observed for:
    - Increases in total cholesterol: 45.5% vs 20.7% of subjects.
    - Decreases in HDL cholesterol: 3.2% vs 4.7% of subjects.
    - Increases in LDL cholesterol: 35.4% vs 17.5% of subjects.
    - Increases in triglycerides: 35.7% vs 23.4% of subjects.
  - Grade 3 or 4 increases in fasting lipid parameters were observed in:
    - Total cholesterol: 1.7% vs 0.6% of subjects.
    - LDL cholesterol: 4.9% vs 1.2% of subjects.
    - Triglycerides: 1.2% vs 1.2% of subjects.

- Worsened NCEP categories at W48 vs baseline were observed for:
  - Total cholesterol: 37.5% vs 13.8% of subjects.
  - HDL cholesterol: 5.8% vs 16.2% of subjects.
  - LDL cholesterol: 45.5% vs 23.9% of subjects.
  - Triglycerides: 28.2% vs 16.5% of subjects.
- Improved NCEP categories at W48 vs baseline were observed for:
  - Total cholesterol: 1.6% vs 4.0% of subjects.
  - HDL cholesterol: 32.0% vs 18.9% of subjects.
  - LDL cholesterol: 6.8% vs 15.5% of subjects.
  - Triglycerides: 8.1% vs 7.4% of subjects.

Use of lipid-modifying agents

1.7% and 0.6% of subjects not taking lipid-lowering drugs (including fibrates, 3-hydroxy-3-methyl-glutaryl-coenzyme A [HMG CoA] reductase inhibitors [-statins], nicotinic acid and derivatives, and other lipid modifying agents) during the screening phase, started a new lipid-lowering treatment during the treatment phase (ie, total number of subjects using lipid-lowering drugs during the study minus number of subjects using lipid-lowering drugs during the screening phase and continued this treatment during the treatment phase).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.3.2 (AEOIs), Sec6.3.3.3 (laboratory parameters), and Sec6.3.3.1 (medical history and baseline conditions).

Table 9: Change from Baseline at Week 48 for Fasting Lipid Parameters; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF (N=362)				Control (N=363)				D/C/F/TAF vs Control
	N	Median	Min; Max	p-value[a]	N	Median	Min; Max	p-value[a]	p-value[b]
Total Cholesterol (mg/dL), Fasting Samples Only									
Baseline	343	163.0	(89; 402)		333	162.4	(77; 294)		0.510
Change at Week 48	309	28.6	(-131; 109)	<.001	297	10.4	(-73; 172)	<.001	<.001
HDL Cholesterol (mg/dL), Fasting Samples Only									
Baseline	343	41.8	(16; 117)		333	42.2	(16; 98)		0.889
Change at Week 48	309	4.3	(-46; 49)	<.001	297	1.5	(-37; 53)	0.001	<.001
LDL Cholesterol (mg/dL), Fasting Samples Only									
Baseline	343	96.3	(42; 327)		333	97.0	(21; 206)		0.911
Change at Week 48	308	17.4	(-116; 99)	<.001	297	5.0	(-69; 88)	<.001	<.001
Total Cholesterol/HDL Cholesterol, Fasting Samples Only									
Baseline	343	3.82	(1.9; 13.3)		333	3.75	(1.6; 9.3)		0.683
Change at Week 48	309	0.20	(-4.4; 7.5)	<.001	297	0.08	(-3.0; 5.1)	0.150	0.036
Triglycerides (mg/dL), Fasting Samples Only									
Baseline	343	96.5	(38; 495)		333	94.8	(39; 464)		0.802
Change at Week 48	309	23.9	(-356; 723)	<.001	297	14.2	(-150; 1059)	<.001	0.001

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HDL = high density lipoprotein; ITT = intent-to-treat; LDL = low density lipoprotein.

[a] Within treatment comparison assessed by Wilcoxon signed-rank test.
[b] Between treatment comparison assessed by Wilcoxon rank sum test.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab49.

Severe skin events of interest

AEOIs Severe skin AEOIs were reported in 1.7% vs 3.9%.

- No serious severe skin AEOIs occurred in the D/C/F/TAF group; in the control group, 3 (0.8%) subjects experienced serious severe skin AEOIs (upon medical review consistent with severe skin reactions: 1 event of Stevens-Johnson syndrome, 2 events of toxic skin eruption [verbatim: toxicodermia]) All 3 subjects discontinued study drug and recovered after 12 to 22 days. None had a prior history of sulfonamide allergy but 2 of them had a history of allergy to other drugs.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.6.

Rash events of interest

AEOIs Rash AEOIs were reported in 13.0% vs 10.7%.

- 2 subjects in the control group experienced a serious rash AEOI (both related to the study drug); the event was grade 3 and led to permanent study drug discontinuation in 1 subject.
- Rash AEOIs led to permanent discontinuation of the study drug in 6 (1.7%) vs 5 (1.4%) subjects. In addition, 1 subject in the control group had a grade 2 nonserious, study drug-related rash morbilliform that led to discontinuation.
- Rash AEOIs were considered study drug-related in 27 (7.5%) vs 22 (6.1%) subjects. In addition, 1 subject in the control group had a grade 2 nonserious, study drug-related rash morbilliform. All but 1 study drug-related rash AEOIs had a worst severity of grade 1 or 2.

By subgroup DRV is a sulfonamide derivative. Subjects who previously experienced a sulfonamide allergy were allowed to enter the study; 6 (1.7%) vs 4 (1.1%) subjects had a history of sulfonamide allergy.

The majority of rash events occurred in subjects without a history of sulfonamide allergy (Table 10). Only 1 (0.3%) subject in the control group who experienced 2 rash events had a history of sulfonamide allergy; the rash was due to a suspected Bactrim® allergy.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.7.

Table 10: Incidence (%) of Rash Events by Preferred Term, AE Attributes and History of Sulfonamide Allergy; ITT (Study TMC114FD2HTX3001)

	Any AEOI	Related	At Least Grade 3	At Least Grade 4	Serious AEOI	Permanent Stop
Sulfonamide Allergy = Yes						
D/C/F/TAF (N=6)						
Any Rash AEOI	0	0	0	0	0	0
Control (N=4)						
Any Rash AEOI	1 (25.0%)	0	0	0	0	0
Drug eruption	1 (25.0%)	0	0	0	0	0
Rash macular	1 (25.0%)	0	0	0	0	0
Sulfonamide Allergy = No						
D/C/F/TAF (N=356)						
Any Rash AEOI	47 (13.2%)	27 (7.6%)	0	0	0	6 (1.7%)
Rash	32 (9.0%)	22 (6.2%)	0	0	0	4 (1.1%)
Rash maculo-papular	3 (0.8%)	2 (0.6%)	0	0	0	1 (0.3%)
Rash papular	3 (0.8%)	0	0	0	0	0
Dermatitis allergic	2 (0.6%)	0	0	0	0	0
Rash macular	2 (0.6%)	0	0	0	0	0
Rash pruritic	2 (0.6%)	2 (0.6%)	0	0	0	0
Dermatitis	1 (0.3%)	0	0	0	0	0
Dermatitis acneiform	1 (0.3%)	0	0	0	0	0
Rash erythematous	1 (0.3%)	0	0	0	0	0
Rash generalised	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)
Control (N=359)						
Any Rash AEOI	38 (10.6%)	22 (6.1%)	1 (0.3%)	0	2 (0.6%)	5 (1.4%)
Rash	25 (7.0%)	14 (3.9%)	1 (0.3%)	0	2 (0.6%)	5 (1.4%)
Rash maculo-papular	2 (0.6%)	2 (0.6%)	0	0	0	0
Rash papular	2 (0.6%)	0	0	0	0	0
Dermatitis allergic	1 (0.3%)	1 (0.3%)	0	0	0	0
Rash macular	3 (0.8%)	1 (0.3%)	0	0	0	0
Rash pruritic	1 (0.3%)	1 (0.3%)	0	0	0	0
Dermatitis	2 (0.6%)	1 (0.3%)	0	0	0	0
Dermatitis acneiform	1 (0.3%)	0	0	0	0	0
Rash generalised	2 (0.6%)	2 (0.6%)	0	0	0	0

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att-TSFAE25c_EXT.

Liver events of interest

AEOIs

The incidence of liver AEOIs was 0.6% vs 1.4%.

- None of the AEOIs resulted in permanent discontinuation of the study drug.
- Grade 3 liver AEOIs were reported in 2 (0.6%) subjects in the D/C/F/TAF group, of which 1 was considered study drug-related and was reported as a 'liver injury' consisting of transient unexplained increases of ALT, AST and ALP between W4 and W12, without associated symptoms. The subject recovered while study drug was continued.

Laboratory parameters

- 2.5% vs 3.9% of subjects had ALT or AST ≥3xULN; none met Hy's law criteria.
- Elevated liver enzymes were observed during the treatment phase for 5.6% vs 7.3% (ALT), 9.5% vs 10.1% (AST), 0.6% vs 2.8% (ALP), and 3.1% vs 6.7% (gamma-glutamyl transferase) (Table 11).
- Grade 3 or 4 increases in liver enzymes were observed in 1.4% vs 0.8% of subjects for ALT, 1.1% vs 1.7% of subjects for AST, and 0% vs 0% of subjects for ALP.
- Grade 3 increases in direct bilirubin were observed in 2 subjects in the D/C/F/TAF group: for 1 subject, a grade 3 elevation in direct bilirubin at W48 was associated with acute hepatitis A (reported as SAE of 'hepatitis A', considered not related) and had normalized at the time of the next visit; the other subject had a transient grade 3 elevation in direct bilirubin at W4 (concurrently with elevations in ALT/AST) which had normalized at retest 3 days later (ALT/AST levels normalized by W8) without study drug interruption (reported as AE of 'symptoms of liver damage in laboratory tests', considered possibly related, no clinical symptoms of hepatitis reported).

Co-infection with HBV or HCV

No relevant subgroup analyses could be performed due to the absence of co-infected subjects at baseline.

During the study, 3 (0.8%) subjects in the D/C/F/TAF group and 3 (0.8%) in the control group developed hepatitis (hepatitis A in 1 subject in each treatment group and hepatitis C in the 4 other subjects). The medical review does not suggest a different clinical or laboratory safety profile in the 4 subjects who developed a hepatitis C co-infection during the study.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.4.1 (AEOIs), Sec6.3.4.2 (laboratory abnormalities), Sec6.3.4.3 (co-infection), Att-LSFAE01_EXT (individual subject data for AEs), and Att-LSFLAB03e_EXT (individual subject data for hepatic parameters).

Table 11: Treatment-emergent Worst On-treatment Toxicity Grades During the Treatment Period for Selected Liver Parameters; ITT (Study TMC114FD2HTX3001)

	D/C/F/TAF (N=362)	Control (N=363)
Worst treatment toxicity		
ALT, high		
N	358	358
Any Treatment emergent grade	20 (5.6%)	26 (7.3%)
Treatment emergent grade 1	14 (3.9%)	17 (4.7%)
Treatment emergent grade 2	1 (0.3%)	6 (1.7%)
Treatment emergent grade 3	4 (1.1%)	2 (0.6%)
Treatment emergent grade 4	1 (0.3%)	1 (0.3%)
AST, high		
N	358	358
Any Treatment emergent grade	34 (9.5%)	36 (10.1%)
Treatment emergent grade 1	27 (7.5%)	26 (7.3%)
Treatment emergent grade 2	3 (0.8%)	4 (1.1%)
Treatment emergent grade 3	4 (1.1%)	4 (1.1%)
Treatment emergent grade 4	0	2 (0.6%)
Alkaline phosphatase, high		
N	357	358
Any Treatment emergent grade	2 (0.6%)	10 (2.8%)
Treatment emergent grade 1	2 (0.6%)	7 (2.0%)
Treatment emergent grade 2	0	3 (0.8%)
Treatment emergent grade 3	0	0
Treatment emergent grade 4	0	0
Total bilirubin, high		
N	358	358
Any Treatment emergent grade	10 (2.8%)	7 (2.0%)
Treatment emergent grade 1	10 (2.8%)	5 (1.4%)
Treatment emergent grade 2	0	2 (0.6%)
Treatment emergent grade 3	0	0
Treatment emergent grade 4	0	0
Direct bilirubin, high		
N	358	358
Any Treatment emergent grade	2 (0.6%)	0
Treatment emergent grade 1	0	0
Treatment emergent grade 2	0	0
Treatment emergent grade 3	2 (0.6%)[a]	0
Treatment emergent grade 4	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects with post-baseline data.

[a] In 1 subject this was associated with acute hepatitis A at W48 (reported as SAE of 'hepatitis A', considered not related), value normal again at next visit; in the 2nd subject this was a transient elevation at W4, normalized at retest 3 days later (concurrent elevated ALT/AST levels normalized by W8) without study drug interruption (reported as AE of 'symptoms of liver damage in laboratory tests', considered possibly related, no clinical symptoms of hepatitis reported).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab54, Att-LSFAE01_EXT, and Att-LSFLAB03e_EXT.

Hyperglycemia events of interest

AEOIs The incidence of hyperglycemia AEOIs was 1.1% vs 1.4%.
- None of the AEOIs resulted in study drug discontinuation.

Laboratory parameters
- During the study, 13.7% vs 15.4% of subjects experienced fasting hyperglycemia and 1.1% vs 3.7% experienced fasting glycosuria.
- No grade 4 fasting hyperglycemia was reported. Grade 3 fasting hyperglycemia was observed in 0.3% vs 0% of subjects.

Use of anti-diabetic medication 1 (0.3%) subject in the D/C/F/TAF group not taking an antidiabetic treatment during the screening phase, started a new antidiabetic treatment during the treatment phase (ie, total number of subjects using antidiabetic drugs during the study minus number of subjects using antidiabetic drugs during the screening phase and continued this treatment during the treatment phase).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.5.2 (AEOIs), Sec6.3.5.3 (laboratory parameters), and Sec6.3.5.1 (medical history and baseline conditions).

Immune reconstitution inflammatory events of interest

AEOIs 1 (0.3%) subject in the D/C/F/TAF group was reported with a nonserious grade 1 AE immune reconstitution inflammatory syndrome (did not lead to discontinuation, considered probably related).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.8.

Coronary artery events of interest

AEOIs Coronary artery AEOIs were reported in 0.6% vs 1.4% of subjects.
- There were no serious or grade 4 coronary artery AEOIs, none led to discontinuation of study drug, and none were considered related to the study drug.
- 1 (0.3%) subject in each treatment group was reported with nonserious angina pectoris (grade 1 in the D/C/F/TAF group and grade 2 in the control group; both not related).
- The other reported AEOIs were events of blood creatine phosphokinase (CPK) increase (0.3% vs 1.1% of subjects), none related to coronary artery disease.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.9.

For the **other events of interest** (pancreas events, lipodystrophy events, cardiac conduction events, convulsion, lactic acidosis/severe hepatomegaly with steatosis, and hemophilia/bleeding events [see Section 2.2.1.1 for a full list of events of interest]), refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.11. There were no noteworthy findings.

3.1.1.2. Phase 3 Study TMC114IFD3013 in HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects

Safety findings from Study TMC114IFD3013 are consistent with the known safety profiles of the individual components of the D/C/F/TAF FDC, and with the fact that all subjects had prior exposure to a regimen containing a bPI + F/TDF:

- No deaths occurred during the study, and other SAEs and AEs leading to discontinuation each occurred in <5% of subjects.

- At Week 48, the subjects showed a better renal and bone safety profile when switching from a TDF-based regimen to a TAF-based regimen, with:
  - A preservation of the GFR (as assessed by $eGFR_{cyst}$).
  - A lower incidence of tubular proteinuria and a trend towards a lower incidence of increases in markers of potential PRT.
  - Increases in hip and spine BMD compared to decreases in the control group.
- There was a higher proportion of related AEs and AEOIs in the D/C/F/TAF group compared to the control group, which was expected for subjects being exposed to a new drug in a 'switch' study compared to subjects continuing their current treatment.
- The higher incidence of AEOIs in the D/C/F/TAF group was mainly driven by a higher frequency of rash AEOIs and lipid-related AEOIs, which are known ADRs to DRV/COBI. The fact that this was an open-label study may have affected the causality assessment of these events.
  - There was a higher incidence of rash in subjects who switched from another PI to DRV or who switched from rtv to COBI as booster at baseline. All rash AEOIs were transient and nonserious, and all drug-related rash AEOIs were grade 1.
  - Increases in fasting lipids occurred for D/C/F/TAF vs the control group, but were not reflected in changes in the TC/HDL ratio.

3.1.1.2.1. Extent of Exposure

Number of Subjects
- D/C/F/TAF (800/150/200/10 mg): 763 subjects.
- bPI+F/TDF (200/300 mg): 378 subjects.

Exposure
- D/C/F/TAF:
  - Mean (SD) exposure: 47.2 (6.6) weeks.
  - Subject-years of exposure[a]: 690.3.
- bPI+F/TDF:
  - Mean (SD) exposure: 47.1 (7.6) weeks.
  - Subject-years of exposure[a]: 340.9.
- For the n (%) of subjects by week of study, refer to Mod2.7.3/Tab3.
- For a Kaplan-Meier curve of the time to discontinuation of study drug, refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Fig3.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Fig2 (subjects disposition) and Tab14 (extent of exposure).

3.1.1.2.2. Adverse Events

(Number of subjects with events for D/C/F/TAF vs control [stay on bPI+F/TDF])

Deaths 0 subjects.

[a] Subject-years of exposure calculated via the following formula:
mean of treatment duration (ïn weeks) x N x 7 / 365.25.

AEs leading to discontinuation

1.4% vs 1.3% of subjects.

- No AEs leading to permanent discontinuation of study drug occurred in >2 subjects per treatment group.

SAEs

4.6% vs 4.8% of subjects.

- The most frequent SAE in the D/C/F/TAF group was pneumonia, reported in 3 (0.4%) subjects.
- 1 subject was reported with a related SAE in the D/C/F/TAF group (ie, pancreatitis).

AEs overall & most frequent

81.9% vs 82.3% of subjects had at least 1 AE.

- The majority of AEs were grade 1 or 2. Grade 3 or 4 AEs were reported in 6.8% vs 8.2% of subjects.
- The most frequently reported AEs (reported in ≥5% of subjects in either treatment group; all in less than 11% of subjects) were nasopharyngitis, upper respiratory tract infection, diarrhea, headache, back pain, vitamin D deficiency, and osteopenia.

Causality of AEs

Related AEs were more frequently reported in the D/C/F/TAF group compared to the control group (18.1% vs 7.4%).

- The related AEs in the D/C/F/TAF group were mainly known ADRs to one or more of the individual components of D/C/F/TAF. The most frequently reported related AEs in the D/C/F/TAF group were diarrhea, abdominal pain, headache, and nausea (reported in 1.0% to 2.1% of subjects).

Narratives

Refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/W48-Subject-Narratives.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.2.1 (AEs overall), Sec6.2.2.1 (deaths), Sec6.2.2.2 (SAEs), and Sec6.2.2.3 (AEs leading to discontinuation).

3.1.1.2.3. Events of Interest

Renal events of interest

AEOIs

The incidence of renal AEOIs was 1.7% vs 1.3%.

- Renal AEOIs consisted mainly of laboratory-related events (1.4% vs 0.8%).
- Clinical renal AEOIs were reported in 0.3% vs 0.5% of subjects, and led to study drug discontinuation in 0.1% vs 0.5% of subjects.
- No event of Fanconi syndrome was reported. One renal tubular disorder was reported in the control group. None of the other 3 clinical renal AEOIs met the study-defined criteria for potential subclinical PRT, nor were they suggestive of a potential PRT upon medical review.

Creatinine

- In both treatment groups, there was a non-clinically significant increase from baseline in mean serum creatinine.
- There was no statistically significant difference between treatment groups at W48 (LS means estimates at W48 vs baseline: +1.27 µmol/L in the D/C/F/TAF group and +0.65 µmol/L in the control group, p=0.340, ANCOVA) (Table 12).
- 4 (0.5%) vs 2 (0.5%) subjects had an AE of blood creatinine increased. None were serious or led to study drug discontinuation.

$eGFR_{cr}$

- Results for $eGFR_{cr}$ ($eGFR_{CG}$ or $eGFR_{CKD-EPI}$) mirror the findings on serum creatinine.
- In both treatment groups, there was a non-clinically significant decrease from baseline in mean $eGFR_{CG}$.
- There was no statistically significant difference between treatment groups at W48 (LS means estimates at W48 vs baseline: -0.94 mL/min in the D/C/F/TAF group and -0.20 mL/min in the control group, p=0.392, ANCOVA). Similar findings were observed for $eGFR_{CKD-EPI}$ (Table 12).
- There were no relevant differences between the treatment groups in changes from baseline to last on-treatment $eGFR_{CG}$ CKD stage: 6.3% vs 5.9% of subjects had an improved $eGFR_{CG}$ CKD stage, and 8.6% vs 7.2% had a worsened $eGFR_{CG}$ CKD stage. Findings were similar for $eGFR_{CG}$ percent changes from baseline and for $eGFR_{CKD-EPI}$.
- 6 (0.8%) vs 2 (0.5%) subjects had an AE of creatinine clearance decreased. None were serious or led to study drug discontinuation.

$eGFR_{cyst}$

- $eGFR_{cyst}$ remained stable in the D/C/F/TAF group and decreased in the control group. The changes were minimal and not clinically significant.
- The difference between treatment groups was statistically significant at W48 (LS means estimates at W48 vs baseline: -0.42 mL/min/1.73 m^2 in the D/C/F/TAF group and -1.76 mL/min/1.73 m^2 in the control group, p=0.034, ANCOVA) (Table 12).
- Shifts in $eGFR_{cyst}$ CKD stage from baseline to last on-treatment value, were more favorable in the D/C/F/TAF group compared to the control group: 5.3% vs 3.7% had an improved $eGFR_{cyst}$ CKD stage, and 4.5% vs 7.2% had a worsened $eGFR_{cyst}$ CKD stage.
- 1 subject in the control group had the grade 1 AE cystatin C increased (nonserious, did not lead to study drug discontinuation, possibly related).

Table 12: Change From Baseline in Serum Creatinine and eGFRs at Week 48 (ANCOVA); ITT (Study TMC114IFD3013)

	LS Means Estimate	SE	95% CI	p-Value
Serum Creatinine (µmol/L):				
D/C/F/TAF	1.27	0.368	(0.55; 1.99)	<.001
Control	0.65	0.530	(-0.39; 1.69)	0.218
D/C/F/TAF - Control	0.62	0.646	(-0.65; 1.88)	0.340
Estimated glomerular filtration rate based on serum creatinine (CKD-EPI formula) (mL/min/1.73 m^2):				
D/C/F/TAF	-1.97	0.369	(-2.69; -1.24)	<.001
Control	-0.88	0.531	(-1.92; 0.16)	0.099
D/C/F/TAF - Control	-1.09	0.646	(-2.36; 0.18)	0.092
Estimated glomerular filtration rate based on serum creatinine (Cockcroft-Gault formula) (mL/min):				
D/C/F/TAF	-0.94	0.492	(-1.91; 0.02)	0.056
Control	-0.20	0.708	(-1.59; 1.18)	0.773
D/C/F/TAF - Control	-0.74	0.862	(-2.43; 0.95)	0.392
Estimated glomerular filtration rate based on serum cystatin C (CKD-EPI formula) (mL/min/1.73 m^2):				
D/C/F/TAF	-0.42	0.360	(-1.13; 0.28)	0.242
Control	-1.76	0.517	(-2.77; -0.74)	<.001
D/C/F/TAF - Control	1.34	0.630	(0.10; 2.57)	0.034

ANCOVA model on the change from baseline in various renal parameters, including treatment as a factor and baseline renal values as covariate.

ANCOVA = analysis of covariance; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; LS = least squares; SE = standard error.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab37, Tab38, and Tab39.

Study-defined potential subclinical PRT

- None of the subjects in the D/C/F/TAF group met the study-defined criteria for a treatment-emergent potential subclinical PRT compared to 2 (0.5%) subjects in the control group. None of these 2 control subjects had AEs consistent with PRT reported; 1 of these was diagnosed with bladder cancer and discontinued the study drug.

Renal biomarkers

In the D/C/F/TAF group, there was an improvement of the proteinuria at W48 vs baseline, compared to the control group:

- Median UACR decreased in the D/C/F/TAF group and increased in the control group with a median change from baseline of -0.76 vs 0.40 mg/g. The difference in median change from baseline in UACR between the treatment groups was statistically significant at W48.
- 6.2% vs 14.2% of subjects had clinically significant albuminuria (UACR ≥30 mg/g) at W48; 2.1% vs 6.2% of subjects with an UACR <30 mg/g (albuminuria within normal range) at baseline had a worsening to an UACR ≥30 mg/g (clinically significant albuminuria) at W48.
- Findings were similar for UPCR.

By subgroup

- In subjects switching from DRV/COBI+F/TDF (n=98 and n=64), up to W48, there was a more favorable evolution in serum creatinine (decrease vs increase), and in $eGFR_{CG}$ and $eGFR_{cyst}$ (increase vs decrease) in the D/C/F/TAF group compared to the control group, consistent with the established favorable renal effects of TAF compared to TDF.
- In subjects switching from DRV/rtv+F/TDF (n=439 and n=202), up to W48, there was a more pronounced increase in serum creatinine and decrease in $eGFR_{CG}$ in the D/C/F/TAF group compared to the control group, consistent with the established COBI inhibitory effects on the tubular secretion of creatinine. There was a less pronounced decrease in $eGFR_{cyst}$ in the D/C/F/TAF group vs control.
- The subgroup analyses by baseline $eGFR_{CG}$ (<70, ≥70 mL/min) and $eGFR_{cyst}$ (<70, ≥70 mL/min/1.73 m^2) and $eGFR_{CG}$ CKD stages do not suggest a safety concern in subjects with a decreased renal function ($eGFR_{CG}$ between 50 and <90 mL/min).

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.1.2 (AEOIs), Sec6.3.1.3.1 (serum creatinine), Sec6.3.1.3.2 ($eGFR_{cr}$), Sec6.3.1.3.3 ($eGFR_{cyst}$), Sec6.3.1.3.4 (PRT), Sec6.3.1.3.5 (renal biomarkers), and Sec6.3.1.4 (by subgroup).

Bone events of interest

AEOIs

The incidence of bone AEOIs was 7.7% vs 7.4%.

- None of the AEOIs resulted in study drug discontinuation.
- Fractures were reported in 1.2% vs 0.5% of subjects (p=0.355).
- Upon medical review, all fractures were traumatic, none were suspected to be osteoporotic.

BMD

In the D/C/F/TAF group, the BMD evolution at the hip and spine region from baseline to W48 was more favorable compared to the control group.

- At W48, there was a positive percent change in BMD in the D/C/F/TAF group (ie, LS means estimates of 1.62% [hip] and 2.06% [spine]). In the control group, there was no relevant percent change (ie, LS means estimates of -0.08% [hip] and 0.01% [spine]). The difference between treatment groups was statistically significant at each region (Table 13).
- 20.2% vs 4.1% (hip) and 31.8% vs 8.9% (spine) of subjects had a ≥3% increase from baseline BMD at W48 (Table 14).
- 2.1% vs 8.2% (hip) and 7.8% vs 19.8% (spine) of subjects had a ≥3% decrease from baseline BMD at W48 (Table 14).
- 3.2% vs 1.0% (hip) and 8.3% vs 4.0% (spine) of subjects had improvement of the BMD clinical status from baseline at W48 (ie, T-score of osteoporosis to osteopenia, osteoporosis to normal, or osteopenia to normal).
- 0% vs 2.1% (hip) and 3.6% vs 4.0% (spine) of subjects had worsening of the BMD clinical status from baseline at W48 (ie, T-score of normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis).

Table 13: Percent Change From Baseline in BMD at Week 48 (ANCOVA); BIS (Study TMC114IFD3013)

	LS Means	SE	95% CI	p-Value
Hip region bone mineral density (g/cm^2)				
D/C/F/TAF	1.62	0.244	(1.136; 2.096)	<.001
Control	-0.08	0.288	(-0.646; 0.487)	0.782
D/C/F/TAF - Control	1.70	0.280	(1.144; 2.248)	<.001
Spine region bone mineral density (g/cm^2)				
D/C/F/TAF	2.06	0.324	(1.419; 2.692)	<.001
Control	0.01	0.391	(-0.760; 0.780)	0.979
D/C/F/TAF - Control	2.05	0.390	(1.277; 2.814)	<.001
Femoral neck region bone mineral density (g/cm^2)				
D/C/F/TAF	0.78	0.355	(0.082; 1.480)	0.029
Control	-0.40	0.419	(-1.227; 0.424)	0.339
D/C/F/TAF - Control	1.18	0.408	(0.379; 1.986)	0.004

ANCOVA = analysis of covariance; BIS = bone investigation substudy; CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; LS = least squares; SE = standard error.

ANCOVA model on the percent changes from baseline per time point, including baseline BMD value and bPI at screening as covariates.

Note: Only subjects who participated in the bone investigation substudy were included.
Note: A DXA scan up to 28 days can be used as baseline.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab54.

Table 14: Proportion of Subjects With at Least 3/5/7% Change From Baseline in BMD at Week 48; BIS (Study TMC114IFD3013)

	D/C/F/TAF	Control
Analysis Set: Bone Investigation Substudy, N	209	108
Hip region bone mineral density (g/cm^2)		
N	188	97
No Change	3 (1.6%)	0
<3% increase	106 (56.4%)	42 (43.3%)
≥3% increase	38 (20.2%)	4 (4.1%)
≥5% increase	9 (4.8%)	1 (1.0%)
≥7% increase	4 (2.1%)	0
<3% decrease	37 (19.7%)	43 (44.3%)
≥3% decrease	4 (2.1%)	8 (8.2%)
≥5% decrease	0	2 (2.1%)
≥7% decrease	0	0
Spine region bone mineral density (g/cm^2)		
N	192	101
No Change	1 (0.5%)	1 (1.0%)
<3% increase	70 (36.5%)	33 (32.7%)
≥3% increase	61 (31.8%)	9 (8.9%)
≥5% increase	29 (15.1%)	1 (1.0%)
≥7% increase	6 (3.1%)	1 (1.0%)
<3% decrease	45 (23.4%)	38 (37.6%)
≥3% decrease	15 (7.8%)	20 (19.8%)
≥5% decrease	3 (1.6%)	9 (8.9%)
≥7% decrease	2 (1.0%)	3 (3.0%)
Femoral neck region bone mineral density (g/cm^2)		
N	188	97
No Change	0	4 (4.1%)
<3% increase	59 (31.4%)	29 (29.9%)
≥3% increase	43 (22.9%)	11 (11.3%)
≥5% increase	14 (7.4%)	4 (4.1%)
≥7% increase	6 (3.2%)	1 (1.0%)
<3% decrease	67 (35.6%)	35 (36.1%)
≥3% decrease	19 (10.1%)	18 (18.6%)
≥5% decrease	5 (2.7%)	8 (8.2%)
≥7% decrease	0	2 (2.1%)

BIS = bone investigation substudy; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DXA = dual energy x-ray absorptiometry; N = number of subjects with data.

Note: Only subjects who participated in the bone investigation substudy were included.
Note: A DXA scan up to 28 days can be used as baseline.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab55.

Bone biomarkers Bone biomarkers suggested less bone turnover in the D/C/F/TAF group than in control, with a decrease for all markers in the D/C/F/TAF group and stable values for all markers in the control group.

Use of anti-osteoporosis medication 2.4% vs 2.9% of subjects not taking antiosteoporotic drugs (including bisphosphonates, calcium, or vitamin D) during the screening phase, started a new antiosteoporotic treatment during the treatment phase (ie, total number of subjects using antiosteoporotic drugs during the study minus number of subjects using antiosteoporotic drugs during the screening phase and continued this treatment during the treatment phase).

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.2.2 (AEOIs), Sec6.3.2.3.1 (BMD), Sec6.3.2.3.2 (biomarkers), and Sec6.3.2.1 (medical history and baseline conditions).

Ocular events of interest

AEOIs Ocular AEOIs were reported in 0.8% vs 0.5% of subjects.

- There were no serious or grade 3 or 4 ocular AEOIs, and none led to discontinuation of study drug.
- Ocular AEOIs were considered study drug-related in 1 (0.1%) vs 1 (0.3%) subject. One grade 3 AE vision blurred in the control group was considered study-drug related and led to permanent discontinuation of study drug.
- Upon medical review, none of the events were consistent with posterior uveitis.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.10.

Lipid-related events of interest

AEOIs The incidence of lipid-related AEOIs was 5.5% vs 2.6%.

- None of the AEOIs resulted in study drug discontinuation.
- These events were considered to be related to study drug for 2.4% vs 1.1% of subjects.

Laboratory parameters

- In the D/C/F/TAF group, the levels of all lipid parameters significantly increased by W24 and remained stable through W48.
- Increases from baseline in median fasting lipid parameters at W48 were larger in the D/C/F/TAF group than in the control group (except for triglycerides) (Table 15).
- These changes were not reflected in clinically relevant changes in the TC/HDL ratio.
- Similar findings were observed for changes at W48 from baseline (either as graded abnormality or category change):
  - Graded abnormalities were observed for:
    - Increases in total cholesterol: 48.8% vs 27.3% of subjects.
    - Decreases in HDL cholesterol: 2.8% vs 4.1% of subjects.
    - Increases in LDL cholesterol: 43.5% vs 20.1% of subjects.
    - Increases in triglycerides: 26.6% vs 25.6% of subjects.
  - Grade 3 or 4 increases in fasting lipid parameters were observed in 3.8% vs 1.4% of subjects for total cholesterol, 6.5% vs 1.7% of subjects for LDL cholesterol, and 1.9% vs 2.2% of subjects for triglycerides.

- Worsened NCEP categories vs baseline were observed for:
  - Total cholesterol: 36.4% vs 15.9% of subjects.
  - HDL cholesterol: 7.6% vs 13.2% of subjects.
  - LDL cholesterol: 46.3% vs 25.5% of subjects.
  - Triglycerides: 16.9% vs 20.7% of subjects.
- Improved NCEP categories vs baseline were observed for:
  - Total cholesterol: 7.5% vs 11.4% of subjects.
  - HDL cholesterol: 21.9% vs 12.6% of subjects.
  - LDL cholesterol: 10.8% vs 16.8% of subjects.
  - Triglycerides: 13.2% vs 12.0% of subjects.

Use of lipid-modifying agents

2.6% and 1.9% of subjects not taking lipid-lowering drugs (including fibrates, HMG CoA reductase inhibitors [-statins], nicotinic acid and derivatives, and other lipid-modifying agents) during the screening phase, started a new lipid-lowering treatment during the treatment phase (ie, total number of subjects using lipid-lowering drugs during the study minus number of subjects using lipid-lowering drugs during the screening phase and continued this treatment during the treatment phase).

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.3.2 (AEOIs), Sec6.3.3.3 (laboratory parameters), and Sec6.3.3.1 (medical history and baseline conditions).

Table 15: Change from Baseline at Week 48 for Fasting Lipid Parameters; ITT (Study TMC114IFD3013)

	D/C/F/TAF (N=763)				Control (N=378)				D/C/F/TAF vs Control
	N	Median	Min; Max	p-value[a]	N	Median	Min; Max	p-value[a]	p-value[b]
Total Cholesterol (mg/dL), Fasting Samples Only									
Baseline	740	184.3	(66; 344)		363	181.4	(89; 314)		0.091
Change at Week 48	689	19.7	(-159; 167)	<.001	334	1.3	(-142; 140)	0.031	<.001
HDL Cholesterol (mg/dL), Fasting Samples Only									
Baseline	740	47.4	(9; 166)		363	48.0	(19; 131)		0.740
Change at Week 48	686	2.7	(-75; 51)	<.001	333	0.0	(-47; 37)	0.584	<.001
LDL Cholesterol (mg/dL), Fasting Samples Only									
Baseline	738	107.3	(4; 249)		363	103.0	(37; 222)		0.053
Change at Week 48	684	15.7	(-131; 161)	<.001	333	1.9	(-107; 142)	0.083	<.001
Total Cholesterol/HDL Cholesterol, Fasting Samples Only									
Baseline	740	3.80	(1.4; 19.1)		363	3.80	(1.6; 8.5)		0.278
Change at Week 48	686	0.20	(-14.9; 6.7)	<.001	333	0.10	(-3.3; 15.1)	0.036	0.010
Triglycerides (mg/dL), Fasting Samples Only									
Baseline	739	123.0	(41; 1195)		363	123.0	(42; 702)		0.786
Change at Week 48	687	5.3	(-856; 543)	<.001	334	4.9	(-464; 461)	0.012	0.957

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HDL = high density lipoprotein; ITT = intent-to-treat; LDL = low density lipoprotein.

[a] Within treatment comparison assessed by Wilcoxon signed-rank test.

[b] Between treatment comparison assessed by van Elteren test, controlling for boosted PI used at screening.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab60.

Severe skin events of interest

AEOIs Severe skin AEOIs were reported in 0.8% of subjects in both treatment groups.
- There were no serious or grade 3 or 4 severe skin AEOIs, none led to discontinuation of study drug and none were considered related to the study drug.
- Upon medical review, none of the reported events were consistent with a severe skin reaction.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.6.

Rash events of interest

AEOIs The incidence of rash AEOIs was higher in the D/C/F/TAF group compared to the control group (4.6% vs 2.1%). None of the rash AEOIs were of clinical concern as these were at most grade 2, transient and nonserious; none led to discontinuation of the study drug. All drug-related rash AEOIs were grade 1.

By subgroup In the D/C/F/TAF group, rash AEOIs were reported more frequently by subjects switching from a screening regimen not containing DRV as PI or not containing COBI as booster.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.7.

Liver events of interest

AEOIs The incidence of liver AEOIs was 1.6% vs 2.6%.
- 1 liver AEOI in the D/C/F/TAF group led to permanent discontinuation of the study drug.

Laboratory parameters
- 3.5% vs 4.8% of subjects had ALT or AST ≥3xULN; none met the criteria for Hy's law.
- At W48, elevated liver enzymes were observed for 13.4% vs 12.8% (ALT), 11.8% vs 13.6% (AST), 0.7% vs 0.5% (ALP), and 4.5% vs 10.7% (gamma-glutamyl transferase) (Table 16).
- Grade 3 or 4 increases in liver enzymes were observed in 1.1% vs 2.4% of subjects (ALT), 1.4% vs 2.7% of subjects (AST), and 0% vs 0% of subjects (ALP).

Co-infection with HBV or HCV No relevant subgroup analyses could be performed due to the absence of co-infected subjects at baseline.
During the study 5 (0.7%) subjects in the D/C/F/TAF group and 6 (1.6%) in the control group developed hepatitis (unspecified hepatitis in 1 subject in the control group and hepatitis C in the 10 other subjects). The medical review does not suggest a different clinical or laboratory safety profile in the subjects who developed a viral hepatitis co-infection during the study.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.4.1 (AEOIs), Sec6.3.4.2 (laboratory abnormalities), and Sec6.3.4.3 (co-infection).

Table 16: Treatment-emergent Worst On-treatment Toxicity Grades During the Treatment Period for Selected Liver Parameters; ITT (Study TMC114IFD3013)

	D/C/F/TAF (N=763)	Control (N=378)
Worst treatment toxicity		
ALT, high		
N	761	376
Any Treatment emergent grade	103 (13.5%)	49 (13.0%)
Treatment emergent grade 1	77 (10.1%)	35 (9.3%)
Treatment emergent grade 2	18 (2.4%)	5 (1.3%)
Treatment emergent grade 3	5 (0.7%)	4 (1.1%)
Treatment emergent grade 4	3 (0.4%)	5 (1.3%)
AST, high		
N	761	376
Any Treatment emergent grade	91 (12.0%)	52 (13.8%)
Treatment emergent grade 1	68 (8.9%)	36 (9.6%)
Treatment emergent grade 2	12 (1.6%)	6 (1.6%)
Treatment emergent grade 3	7 (0.9%)	6 (1.6%)
Treatment emergent grade 4	4 (0.5%)	4 (1.1%)
Alkaline phosphatase, high		
N	761	376
Any Treatment emergent grade	5 (0.7%)	2 (0.5%)
Treatment emergent grade 1	3 (0.4%)	2 (0.5%)
Treatment emergent grade 2	2 (0.3%)	0
Treatment emergent grade 3	0	0
Treatment emergent grade 4	0	0
Total bilirubin, high		
N	761	376
Any Treatment emergent grade	16 (2.1%)	68 (18.1%)
Treatment emergent grade 1	13 (1.7%)	15 (4.0%)
Treatment emergent grade 2	2 (0.3%)	31 (8.2%)
Treatment emergent grade 3	1 (0.1%)	21 (5.6%)
Treatment emergent grade 4	0	1 (0.3%)
Direct bilirubin, high		
N	761	376
Any Treatment emergent grade	5 (0.7%)	6 (1.6%)
Treatment emergent grade 1	0	0
Treatment emergent grade 2	0	0
Treatment emergent grade 3	5 (0.7%)	6 (1.6%)
Treatment emergent grade 4	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects with post-baseline data.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab66.

Hyperglycemia events of interest

AEOIs The incidence of hyperglycemia AEOIs was 2.1% vs 0.8%.

- None of the AEOIs resulted in study drug discontinuation.

Laboratory parameters	• At W48, 19.8% vs 14.9% of subjects experienced fasting hyperglycemia and 3.7% vs 5.3% experienced fasting glycosuria. • No grade 4 hyperglycemia was reported. Grade 3 hyperglycemia was observed in 1.1% vs 0.5% of subjects.
Use of anti-diabetic medication	• 9 (1.2%) vs 1 (0.3%) subject not taking an antidiabetic treatment during the screening phase, started a new antidiabetic treatment during the treatment phase (ie, total number of subjects using antidiabetic drugs during the study minus number of subjects using antidiabetic drugs during the screening phase and continued this treatment during the treatment phase).

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.5.2 (AEOIs), Sec6.3.5.3 (laboratory parameters), and Sec6.3.5.1 (medical history and baseline conditions).

Immune reconstitution inflammatory events of interest

AEOIs No immune reconstitution inflammatory AEOIs were reported.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.8.

Coronary artery events of interest

AEOIs Coronary artery AEOIs were reported in 1.3% vs 1.6% of subjects.

- 2 (0.3%) subjects in the D/C/F/TAF group and 1 (0.3%) subject in the control group were reported with a serious coronary artery AEOI (coronary artery disease and myocardial infarction; all grade 3 or 4, all drug-related).
- None of the coronary artery events led to discontinuation.

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.9.

For the **other events of interest** (pancreas events, lipodystrophy events, cardiac conduction events, convulsion, lactic acidosis/severe hepatomegaly with steatosis, and hemophilia/bleeding events [see Section 2.2.1.1 for a full list of events of interest]), refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.11. There were no noteworthy findings.

3.1.1.3. Phase 2 Study GS-US-299-0102 in HIV-1 Infected, ART-naïve, Adult Subjects

Safety findings from Study GS-US-299-0102 are consistent with the known safety profiles of the individual components of the D/C/F/TAF FDC:

- No subjects died during the study, and other SAEs or AEs leading to discontinuation occurred each in <5% of subjects.
- Rash occurred in 11.7% vs 8.0% of subjects in the D/C/F/TAF group vs the control group, and led to early discontinuation of treatment in 1.0% vs 0% of subjects.
- The renal and bone safety profile for D/C/F/TAF compared favorably with the control group.
- No AEs indicative of posterior uveitis were reported.
- Increases in fasting lipids occurred for D/C/F/TAF vs the control group, but there were no relevant changes in the TC/HDL ratio.

3.1.1.3.1. Extent of Exposure

Number of Subjects
- D/C/F/TAF (800/150/200/10 mg): 103 subjects.
- DRV (2x400 mg) + COBI (150 mg) + F/TDF (200/300 mg): 50 subjects.

Exposure
- D/C/F/TAF:
  - Median (Q1; Q3) exposure: 68.0 (65.4; 72.7) weeks.
  - Subject-years of exposure[a]: 121.8.
- DRV+COBI+F/TDF:
  - Median (Q1; Q3) exposure: 69.1 (66.0; 73.6) weeks.
  - Subject-years of exposure: 63.3.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab8-2 (subject disposition) and Tab11-1 (exposure).

3.1.1.3.2. Events of Interest

(Number of subjects with events for D/C/F/TAF vs control [DRV+COBI+F/TDF])

Renal events

AEs
- AEs in the Renal and Urinary Disorders SOC were reported for 3 subjects in each treatment group (2.9% vs 6.0%). AEs in the Renal Function Analyses SOC were reported for 2 (1.9%) vs 0 subjects.
- Upon medical review, those consistent with PRT (excluding the lab AEs) were reported as follows, per treatment group:
  - D/C/F/TAF: none.
  - Control: Renal tubular disorder was reported as a grade 2 SAE for 1 subject (and led to study drug discontinuation).

Creatinine Increases from baseline in median **serum creatinine** were observed at W2 for each treatment group, and remained stable through W48. Increases tended to be smaller for the D/C/F/TAF group than for the control group (Table 17).

$eGFR_{cr}$
- Decreases from baseline in median **$eGFR_{CG}$** were observed at W2 for each treatment group, and remained stable through W48. Decreases were smaller for the D/C/F/TAF group than for the control group (Table 17).
- Observations for changes from baseline in median **$eGFR_{CKD-EPI}$** support those seen for $eGFR_{CG}$ (Table 17).

$eGFR_{cyst}$
- Median **$eGFR_{cyst}$** increased for the D/C/F/TAF group and remained stable for the control group (Table 17).

Subclinical PRT Not assessed.

Renal biomarkers & other
- Levels of **UPCR** and **UACR** decreased from baseline at W48 in both treatment groups. No statistically significant differences were observed in median percent change from baseline in **UPCR** or **UACR** at W48 between the 2 treatment groups, but decreases from baseline tended to be higher for the D/C/F/TAF group (Table 18).

[a] Subject-years of exposure calculated via the following formula: (mean exposure [weeks]) x N x 7 / 365.25.

- In the D/C/F/TAF group, there were less abnormalities than in the control group of other markers of tubulopathy (**RBP to creatinine ratio**, **beta-2-microglobulin to creatinine ratio**, and **FE_{PO4}**).

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec11.2.4.2.1 (AEs), Tab46.1 (RBP to creatinine ratio), Tab46.2 (beta-2-microglobulin to creatinine ratio), Tab48.1 (FE_{PO4} unadjusted), and Tab48.2 (FE_{PO4} adjusted).

Table 17: Changes From Baseline in Serum Creatinine, Serum Cystatin C and eGFR at Week 24 and Week 48 – GS-US-299-0102

Median (Q1; Q3)	N	D/C/F/TAF	N	DRV+COBI+F/TDF
Analysis set: SAS	103		50	
Serum Creatinine (mg/dL)				
Baseline	103	0.98 (0.87; 1.05)	50	1.01 (0.88; 1.11)
Change at Week 2	97	0.10 (0.01; 0.13)	50	0.11 (0.03; 0.20)
Change at Week 24	91	0.06 (-0.01; 0.14)	48	0.12 (0.00; 0.21)
Change at Week 48	87	0.06 (-0.02; 0.11)	46	0.12 (0.01; 0.18)
Serum Cystatin C (mg/L)[a]				
Baseline	101	0.84 (0.76; 0.93)	50	0.82 (0.75; 0.93)
Change at Week 24	89	-0.03 (-0.11; 0.03)	48	0.02 (-0.04; 0.11)
Change at Week 48	74	-0.07 (-0.13; 0.01)	42	-0.01 (-0.08; 0.07)
$eGFR_{CG}$ (mL/min)				
Baseline	103	116.0 (97.0; 137.6)	50	109.6 (92.5; 131.4)
Change at Week 2	97	-8.7 (-15.5; -1.2)	50	-8.7 (-20.0; -3.0)
Change at Week 24	91	-4.3 (-12.5; 4.7)	48	-10.7 (-20.3; -0.3)
Change at Week 48	87	-2.9 (-11.8; 6.2)	46	-10.6 (-22.4; -0.5)
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)				
Baseline	103	104.3 (92.6; 117.8)	50	102.4 (84.0; 111.2)
Change at Week 2	97	-8.6 (-14.3; -1.2)	50	-8.6 (-16.7; -2.8)
Change at Week 24	91	-5.0 (-15.2; 1.1)	48	-10.5 (-19.6; -0.4)
Change at Week 48	87	-5.9 (-12.7; 0.8)	46	-11.6 (-20.1; -1.8)
$eGFR_{cyst}$ (mL/min/1.73 m^2)[a]				
Baseline	101	106.7 (95.0; 119.0)	50	109.2 (95.8; 118.0)
Change at Week 24	89	3.2 (-4.1; 13.3)	48	-2.2 (-11.6; 3.5)
Change at Week 48	74	6.7 (-1.6; 14.9)	42	0.3 (-9.6; 12.0)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; $eGFR_{CG}$ = eGFR based on serum creatinine calculated using the Cockcroft-Gault method; $eGFR_{CKD\text{-}EPI}$ = eGFR based on serum creatinine calculated using the CKD-EPI method; $eGFR_{cyst}$ = eGFR based on serum cystatin C calculated using the CKD-EPI method; N = number of subjects with data; SAS = Safety Analysis Set.

[a] Changes at Week 2 were not assessed for serum cystatin C and $eGFR_{cyst}$.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab43.1 (creatinine), Tab43.2 (cystatin C), Tab44.1 ($eGFR_{CG}$), Tab44.2 ($eGFR_{CKD\text{-}EPI}$), and Tab44.3 ($eGFR_{cyst}$).

Table 18: Percent Changes From Baseline in Renal Biomarkers at Week 48 – GS-US-299-0102

Median (Q1; Q3)	N	D/C/F/TAF	N	DRV+COBI+F/TDF	p-value[a]
Analysis set: SAS	103		50		
% Change from BL at W48					
UPCR (mg/g)	84	-8.22 (-35.10; 21.31)	46	-27.52 (-48.28; 29.36)	0.19
UACR (mg/g)	84	-13.1 (-39.7; 28.2)	47	-22.6 (-58.8; 25.9)	0.17

BL = baseline; N = number of subjects with data; SAS = Safety Analysis Set; UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio.

[a] p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab46.3 (UPCR) and Tab46.4 (UACR).

Bone events

Fractures No **fracture events** were reported during the study in either treatment group.

BMD

- Decreases from baseline in mean **hip or spine BMD** were smaller for the D/C/F/TAF group than for the control group (Table 19).
- Fewer subjects in the D/C/F/TAF group compared with the control group had a **>3% decrease** from baseline in both hip (18.3% vs 61.7%) and spine BMD (32.6% vs 55.3%) at W48 (Table 20).

Table 19: Percent Changes From Baseline in Hip and Spine BMD at Week 24 and Week 48 - GS-US-299-0102

Mean (SD)	N	D/C/F/TAF	N	DRV+COBI+F/TDF	p-value[a]
Hip BMD (g/cm^2)[b]					
Baseline	85	1.02 (0.142)	48	1.09 (0.145)	0.011
Percent change at Week 24 (%)	85	-0.53 (2.410)	48	-2.09 (2.283)	<0.001
Percent change at Week 48 (%)	82	-0.84 (2.582)	47	-3.82 (2.651)	<0.001
Spine BMD (g/cm^2)[c]					
Baseline	86	1.12 (0.155)	48	1.18 (0.172)	0.059
Percent change at Week 24 (%)	86	-1.09 (2.972)	48	-3.82 (3.633)	<0.001
Percent change at Week 48 (%)	83	-1.57 (3.920)	47	-3.62 (3.128)	0.003

BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; N = number of subjects with data; SD = standard deviation.

[a] p-values were from the ANOVA model including treatment as a fixed effect.
[b] Only subjects with nonmissing hip BMD for the baseline visit were included in Hip DXA Analysis Set.
[c] Only subjects with nonmissing spine BMD for the baseline visit were included in Spine DXA Analysis Set.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab38.1 (hip) and Tab38.2 (spine).

Table 20: Categorical Distribution of Percent Changes in Hip and Spine BMD at Week 24 and Week 48 - GS-US-299-0102

n/N (%)	D/C/F/TAF	DRV+COBI+F/TDF
Analysis set: Hip DXA Analysis Set, N[a]	85	48
Changes in hip BMD		
Percent change at Week 24		
>5% Decrease	3/85 (3.5%)	7/48 (14.6%)
>3 to ≤5% Decrease	7/85 (8.2%)	12/48 (25.0%)
Percent change at Week 48		
>5% Decrease	5/82 (6.1%)	15/47 (31.9%)
>3 to ≤5% Decrease	10/82 (12.2%)	14/47 (29.8%)
Analysis set: Spine DXA Analysis Set, N[b]	86	48
Changes in spine BMD		
Percent change at Week 24		
>5% Decrease	6/86 (7.0%)	13/48 (27.1%)
>3 to ≤5% Decrease	14/86 (16.3%)	14/48 (29.2%)
Percent change at Week 48		
>5% Decrease	12/83 (14.5%)	10/47 (21.3%)
>3 to ≤5% Decrease	15/83 (18.1%)	16/47 (34.0%)

BMD = bone mineral density; DXA = dual energy x-ray absorptiometry; N = number of subjects with data; n = number of subjects with that observation.

[a] Only subjects with nonmissing hip BMD for the baseline visit were included in Hip DXA Analysis Set.
[b] Only subjects with nonmissing spine BMD for the baseline visit were included in Spine DXA Analysis Set.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab11-5 (hip) and Tab11-6 (spine).

Bone biomarkers

- Increases from baseline in median values for **CTX** and **P1NP** were smaller for the D/C/F/TAF group than for the control group (Table 21).
- Results for serum **bone-specific ALP** and **osteocalcin** were consistent with those for P1NP.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec11.2.4.1 (fractures), Tab41.3 (ALP), and Tab41.4 (osteocalcin).

Table 21: Percent Changes From Baseline in Bone Biomarkers at Week 24 and Week 48 - GS-US-299-0102

Median (Q1; Q3)	N	D/C/F/TAF	N	DRV+COBI+F/TDF	p-value[a]
CTX (ng/mL)					
Baseline	101	0.324 (0.205; 0.420)	50	0.342 (0.214; 0.420)	0.66
Percent change at Week 24 (%)	89	33.0 (0.3; 68.0)	48	79.2 (33.7; 149.8)	<0.001
Percent change at Week 48 (%)	86	23.2 (-12.2; 77.2)	47	74.4 (34.9; 154.7)	<0.001
P1NP (ng/mL)					
Baseline	101	43.01 (33.38; 55.74)	50	42.29 (30.53; 60.42)	0.93
Percent change at Week 24 (%)	89	10.95 (-14.93; 34.18)	48	49.19 (24.68; 75.06)	<0.001
Percent change at Week 48 (%)	86	4.73 (-18.68; 27.12)	47	52.47 (20.57; 92.04)	<0.001

CTX = collagen type 1 cross-linked C-telopeptide; N = number of subjects with data; P1NP = procollagen type 1 N-terminal propeptide.

[a] p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab41.1 (CTX) and Tab41.2 (P1NP).

Lipid-related events

Laboratory parameters

- Increases from baseline were observed in median **fasting lipids** at W24 and W48 in each treatment group, with the exception of a decrease in fasting triglycerides at W48 for the control group. The median increases from baseline were greater for the D/C/F/TAF group than for the control group at both W24 and W48 (Table 22).
- Changes in LDL and HDL cholesterol were not reflected in clinically relevant worsening of the median **TC/HDL ratio** (Table 22).
- **Graded abnormalities** were more commonly reported for the D/C/F/TAF group than for the control group:
  - Graded fasting hypercholesterolemia: 57.6% vs 36.7% (the majority were grade 1).
  - Graded fasting LDL: 53.5% vs 34.7% (the majority were grade 1). Grade 3 fasting LDL was reported for 5.1% vs 8.2% of subjects. No grade 4 fasting LDL abnormalities were reported in either group.

AEs

The incidence of **lipid-related AEs** was similar in both treatment groups (4.9% vs 4.0% had AEs of hyperlipidemia); these events were considered to be related to study drug for 1 subject in each treatment group (1.0% vs 2.0%).

Use of lipid-modifying agents

A similar percentage of subjects in each treatment group received concomitant **lipid-modifying agents** (14.6% vs 14.0%):

- D/C/F/TAF: 10/15 subjects were continuing treatment from baseline, while 5/15 initiated treatment during the study.
- Control: 3/7 subjects were continuing treatment from baseline, and 4/7 subjects initiated treatment during the study.

Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab22 (AEs), Tab26 (related AEs), Tab32 (laboratory abnormalities), Tab51 (concomitant non-ARV medication), and List12 (concomitant non-ARV medication).

Table 22: Changes From Baseline in Fasting Lipid Parameters at Week 24 and Week 48 - GS-US-299-0102

Median (Q1; Q3)	N	D/C/F/TAF	N	DRV+COBI+F/TDF	p-value[a]
Analysis set: SAS	103		50		
Fasting Total Cholesterol (mg/dL)					
Baseline	100	156 (137; 174)	49	158 (137; 190)	0.27
Change at Week 24	88	31 (10; 49)	47	14 (0; 32)	0.014
Change at Week 48	83	40 (13; 58)	45	5 (-9; 26)	<0.001
Fasting Direct LDL Cholesterol (mg/dL)					
Baseline	100	93 (81; 108)	49	101 (79; 136)	0.14
Change at Week 24	88	22 (9; 37)	47	7 (-5; 28)	0.004
Change at Week 48	83	26 (9; 44)	45	4 (-9; 17)	<0.001
Fasting HDL Cholesterol (mg/dL)					
Baseline	100	42 (33; 50)	49	42 (37; 53)	0.20
Change at Week 24	88	3 (-1; 10)	47	2 (-2; 10)	0.35
Change at Week 48	83	7 (1; 14)	45	3 (-3; 7)	0.009
Fasting Triglycerides (mg/dL)					
Baseline	100	99 (76; 156)	49	99 (69; 129)	0.54
Change at Week 24	88	24 (-4; 55)	47	10 (-17; 38)	0.13
Change at Week 48	83	29 (-6; 72)	45	-5 (-23; 29)	0.007
Fasting Total Cholesterol to HDL Ratio					
Baseline	100	3.8 (3.1; 4.7)	49	3.8 (3.1; 4.8)	0.87
Change at Week 24	88	0.3 (-0.1; 0.8)	47	0.2 (-0.3; 0.7)	0.47
Change at Week 48	83	0.0 (-0.2; 0.5)	45	-0.2 (-0.5; 0.4)	0.15

HDL = high density lipoprotein; LDL = low density lipoprotein; N = number of subjects with data.
[a] p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Tab11-10.

For more details on the safety results from Study GS-US-299-0102 refer to:

- AEs: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec11.2.1 (common AEs), Sec11.2.2 (severity of AEs), Sec11.2.3 (related AEs), Sec11.3 (deaths), Sec11.4 (SAEs), and Sec11.5 (discontinuations).
- Bone, renal and ocular safety: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec11.2.4.
- Clinical laboratory evaluations: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec11.6.
- Concomitant non-ARV medication: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec11.7.2.
- Other observations related to safety: Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec11.7, Sec11.8, and Sec11.9.

3.1.2. Safety of the D/C/F/TAF FDC in Healthy Adult Subjects (TMC114FD2HTX1001, TMC114FD2HTX1002, TMC114FD2HTX1004, and GS-US-299-0101)

In the Phase 1 BE, BA, and food effect studies, single or multiple doses of the D/C/F/TAF FDC tablet were safe and well tolerated in healthy adult subjects. No unexpected findings were observed, and the safety profile did not differ significantly between treatments in these studies.

BE Study TMC114FD2HTX1001

In this open-label, randomized, 2-way crossover BE study, 94 healthy adult subjects received a single oral dose of D/C/F/TAF 800/150/200/10 mg as the FDC tablet (Mod5.3.1.2/TMC114FD2HTX1001-Final-CSR).

BA/Food Effect Study TMC114FD2HTX1002	In this 3-panel, open-label, randomized, 2-way crossover study, 72 healthy adult subjects received a single oral dose of D/C/F/TAF 800/150/200/10 mg as the FDC tablet (Mod5.3.1.1/TMC114FD2HTX1002-Final-CSR).
BA Study TMC114FD2HTX1004	In this randomized, open-label, 3-period, 3-treatment crossover study, 30 healthy adult subjects sequentially received the D/C/F/TAF (800/150/200/10-mg) FDC as a whole tablet, as a split tablet, and as a crushed tablet in the order determined by randomization (Mod5.3.1.1/TMC114FD2HTX1004-Final-CSR).
BA Study GS-US-299-0101	In this adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple-cohort study, 65 healthy adult subjects received once-daily oral doses of the D/C/F/TAF 800/150/200/10-mg FDC tablet (or the 800/150/200/25-mg FDC tablet) for 12 or 21 consecutive days (Mod5.3.1.1/GS-US-299-0101-Final-CSR).

3.2. Safety of DRV, COBI and F/TAF in Adolescent Subjects

No clinical studies were performed with the D/C/F/TAF FDC tablet in HIV-1 infected pediatric or adolescent subjects. The safety of D/C/F/TAF in HIV-1 infected adolescents (aged 12 to <18 years), is supported by data from clinical studies with DRV (Study TMC114-C230), and with COBI and F/TAF as part of the E/C/F/TAF FDC (Study GS-US-292-0106).

3.2.1. Phase 2 Study TMC114-C230 in HIV-1 Infected, ART-naïve, Adolescent Subjects

There were no safety issues in Study TMC114-C230 performed in 12 adolescent subjects. All subjects tolerated the study drug very well:

- There were no deaths and no subjects had an AE leading to study drug discontinuation; SAEs were reported for 4 subjects.
- Rash was reported for 1 subject.
- Increases were reported in fasting lipids (total cholesterol in 66.7% of subjects, LDL cholesterol in 50.0% of subjects, and HDL cholesterol in 8.3% of subjects), but there were no relevant changes in the TC/HDL ratio.

3.2.1.1. Extent of Exposure

Number of Subjects	• DRV (2x400 mg) + rtv (100 mg): 12 subjects. • Background regimen: AZT/3TC (6 subjects) or ABC/3TC (6 subjects).
Exposure	• Median (Q1; Q3) exposure DRV/rtv: 48.5 (47.7; 52.4) weeks. • Subject-years of exposure: 11.4.

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab7 (subject disposition) and Tab14 (exposure).

3.2.1.2. Adverse Events

Deaths 0 subjects.

AEs leading to discontinuation 0 subjects.

SAEs
- 4 (33.3%) subjects.
- No SAEs were reported for >1 subject, except for anemia which occurred in 2 subjects.
- No SAEs were considered to be at least possibly related to DRV.

Grade 3/4 AEs
- 3 (25.0%) subjects experienced grade 3/4 AEs.
- No grade 3/4 AE was reported for >1 subject, except for the SAE anemia which occurred in 2 subjects.

AEs overall Overall, AEs were reported for 11 (91.7%) subjects.

Common AEs AEs reported for >1 (>10%) subject: vomiting, anemia, nausea, diarrhea, pyrexia, furuncle, sinusitis, and cough. All other AEs occurred in 1 subject.

Causality of AEs
- 2 (16.7%) subjects had AEs considered at least possibly related to DRV: nausea was reported for 2 subjects, abdominal pain, diarrhea, vomiting, and dizziness for 1 subject each.
- No subjects experienced grade 3/4 AEs considered at least possibly related to DRV.

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab25 (overall summary of AEs), Sec8.2.3.2 (SAEs), Sec8.2.2.1 (grade 3/4 AEs), Tab26 (common AEs), and Sec8.2.2.2 (related AEs).

3.2.1.3. Events of Interest

Rash events

AEOIs **Rash** was reported for 1 subject (grade 1 and considered doubtfully related to DRV).

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.2.3.4.1.

Lipid-related events

Laboratory parameters
- There was a trend for an increase from baseline in the median values of **fasting lipids over time** (Table 23).
- These increases were not reflected in changes in the median **TC/HDL ratio** (Table 23).
- No grade 3/4 **lipid abnormalities** were reported. Abnormalities were reported in 8 (66.7%) subjects for total cholesterol (any grade), 6 (50.0%) subjects for LDL cholesterol (any grade), 2 subjects for HDL cholesterol (1 [8.3%] subject above and 1 [8.3%] subject below normal), and 0 subjects for triglycerides (any grade).

AEOIs No **lipid-related AEOIs** were reported during the study.

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab35 (laboratory abnormalities) and Sec8.2.3.4.6 (AEOIs).

Table 23: Changes From Baseline in Fasting Lipid Parameters at Week 48 – TMC114-C230

	N	Median	Q1; Q3
Total Cholesterol (mg/dL)			
Baseline	10	145.78	126.06; 155.84
Change at Week 24	9	33.64	19.33; 43.31
Change at Week 48	9	23.59	3.09; 42.54
LDL Cholesterol (mg/dL)			
Baseline	10	85.07	62.65; 94.74
Change at Week 24	9	15.85	1.16; 21.27
Change at Week 48	9	15.08	5.41; 27.84
HDL Cholesterol (mg/dL)			
Baseline	10	46.79	38.28; 53.36
Change at Week 24	9	8.12	3.48; 9.67
Change at Week 48	9	9.28	6.19; 16.63
Total Cholesterol to HDL Cholesterol Ratio			
Baseline	10	3.19	2.78; 3.79
Change at Week 24	9	0.26	-0. 45; 0.37
Change at Week 48	9	-0.43	-0.49; 0.45
Triglycerides (mg/dL)			
Baseline	10	79.27	60.23; 108.95
Change at Week 24	9	28.34	11.51; 90.35
Change at Week 48	9	17.71	-6.2; 104.52

HDL = high density lipoprotein; LDL = low density lipoprotein; N = number of subjects with data.
Source: Derived from [ADHOC_TSFLAB01.RTF] [/SAS/2114/TMC114C230/FILES/RE/CSR_WEEK_48/MACROS/ADHOC_TSFLAB01.SAS*] 10FEB2017, 14:30.

Liver events

AEOIs No **liver-related AEOIs** were reported during the study.

Laboratory parameters There were no clinically relevant mean **changes from baseline** for any of the selected liver-related laboratory parameters (Table 24). The increase in **ALP** is considered to be physiologic and related to the bone growth in this population.

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.2.3.4.5 (AEOIs) and Sec8.3.1.1 (laboratory abnormalities).

Table 24: Changes From Baseline in Liver-related Parameters at Week 48 – TMC114-C230

	N	Mean (SE) Baseline Value	N	Mean (SE) Change from Baseline at Week 48
ALT (U/L)	12	28.2 (5.59)	12	-11.3 (5.95)
AST (U/L)	12	31.8 (4.45)	12	-7.8 (4.54)
ALP (U/L)	12	158.8 (26.40)	12	16.3 (14.64)
Total bilirubin (µmol/L)	12	8.1 (0.80)	12	-1.6 (1.13)
Direct bilirubin (µmol/L)	12	2.1 (0.23)	12	-0.5 (0.29)
Indirect bilirubin (µmol/L)	12	6.3 (0.64)	12	-1.3 (0.86)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of subjects with data; SE = standard error.
Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab32.

Hyperglycemia events

AEOIs No **glucose-related AEOIs** were reported during the study.

Laboratory parameters There was no clinically relevant **change from baseline in mean fasting glucose** (Table 25).

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.2.3.4.7 (AEOIs).

Table 25: Changes From Baseline in Fasting Glucose at Week 48 – TMC114-C230

	N	Mean (SE) Baseline Value	N	Mean (SE) Change from Baseline at Week 48
Glucose (mmol/L)	10	4.8 (0.14)	9	0.2 (0.11)

N = number of subjects with data; SE = standard error.
Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Tab34.

Pancreas events

AEOIs No **pancreatic AEOIs** were reported during the study.

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.2.3.4.4.

Cardiovascular safety

AEOIs No **cardiac AEOIs** were reported during the study.

Vital signs / ECG No clinically relevant changes from baseline were observed for mean **vital signs** or **ECG parameters**. There were no treatment-emergent vital signs or ECG abnormalities.

Source: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.2.3.4.2 (AEOIs) and Sec8.4 (vital signs/ECG).

For more details on the safety results from Study TMC114-C230 refer to:

- AEs: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.2.
  Clinical laboratory evaluations: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.3.
- Other observations related to safety: NDA021976/Mod5.3.5.2/TMC114-C230-W48-CSR/Sec8.5.

3.2.2. Phase 2/3 Study GS-US-292-0106 in HIV-1 Infected, ART-naïve, Adolescent Subjects

Results from Study GS-US-292-0106 show that COBI and F/TAF have a similar safety profile in adolescents compared to adults:

- There were no deaths and no subjects had an AE leading to study drug discontinuation; 6 (12.0%) subjects had SAEs.
- There were no notable changes from baseline in height-age adjusted spine and TBLH BMD Z-scores after 48 weeks of treatment. Of the 3 subjects who had a clinically relevant (≥4%) decrease from baseline in spine BMD at W24, 1 still had ≥4% decrease at Week 48. No subject had a ≥4% decrease from baseline in TBLH BMD.

- Changes from baseline in serum creatinine and $eGFR_{cr}$ (Schwartz formula) were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual GFR.
- One subject experienced intermediate uveitis considered related to study drug.

3.2.2.1. Extent of Exposure

Number of Subjects	• E/C/F/TAF (150/150/200/10 mg): 50 subjects.
Exposure	• Median (Q1; Q3) exposure E/C/F/TAF: 60.1 (48.1; 84.1) weeks.

Source: Gaur et al. 2016 (manuscript)[9]

3.2.2.2. Adverse Events

Deaths	0 subjects.
AEs leading to discontinuation	0 subjects.
SAEs	• 6 (12.0%) subjects. • The SAE intermediate uveitis was considered drug-related; it resolved while continuing study drug.
Grade 3/4 AEs	• 6 (12.0%) subjects experienced grade 3 or 4 AEs
AEs overall	Overall, AEs were reported for 42 (84.0%) subjects.
Causality of AEs	• 18 (36.0%) subjects had a related AE. • Related AEs reported in >2 (5.0%) subjects were: nausea, abdominal pain, vomiting, upper abdominal pain, diarrhea, and somnolence. • 1 (2.0%) subject had a related grade 3 or 4 AE.

Source: Gaur et al. 2016 (manuscript and poster)[7,9]

3.2.2.3. Events of Interest

Renal events

AEs	• No AEs consistent with PRT were reported. • Urinary retention was reported as a **renal SAE** (considered unrelated to the study drug).
Creatinine	• Increases from baseline in median **serum creatinine** were observed at W1 and remained stable over time with a median (IQ range) baseline value of 0.58 (0.50; 0.79) mg/dL and a median (IQ range) change from baseline of 0.07 [0.02; 0.15] mg/dL at W48.
eGFR	• Decreases from baseline in median **$eGFR_{cr}$ (Schwartz formula)** were observed at W1 and remained stable over time with a median (IQ range) baseline value of 156.0 (129.0; 185.0) mg/dL and a median (IQ range) change from baseline of -15.0 [-30.0; 0.0] mg/dL at W24 and -12.2 [-31.5; 1.0] mg/dL at W48.

Renal biomarkers & other	• Median (IQ range) percent change from baseline in **UPCR** was -27.0% (55.1; 19.5) at W48. • Median serum **phosphorus** values were within normal ranges throughout the study.

Source: Gaur et al. (manuscript and poster)[7,9]

Bone events

BMD	• Small change (<5%) was observed in **spine and TBLH BMD** with median (IQ range) change of 3.3% (0.8; 7.1) for spine and 0.9% (0.5; 2.6) for TBLH at W48. • Few subjects had a **≥4% decrease** from baseline in spine and TBLH BMD at W24 and/or W48: o Spine BMD: 3 (6.4%) subjects at W24; 1 (2.1%) subject at W48. o TBLH BMD: 0 subjects at W24 or W48. • There were no notable changes from baseline in **height-age adjusted spine and TBLH BMD Z-scores** with median (IQ range) changes from baseline of 0.03 (0.16; 0.20) and 0.09 (0.33; 0.07) at W48.

Source: Gaur et al. 2016 (manuscript and poster)[7,9], Gaur et al. 2015[8]

Ocular events

AEs	• 1 subject experienced the SAE intermediate uveitis considered related to the study drug (and resolved without study drug discontinuation).[9]

Hyperglycemia events

Laboratory parameters	• There were no graded abnormalities in urine glucose.[9]

3.3. Studies With Individual Components in Adult Subjects Supporting Cardiac (QT) and Renal Safety

No thorough QT studies were performed with the D/C/F/TAF FDC, nor any studies in subjects with creatinine clearance <50 mL/min. The Sponsor relies on the studies performed with the individual components of the D/C/F/TAF FDC to support the safety of the D/C/F/TAF FDC on the QT interval, and in subjects with renal impairment. The main findings of these relevant supportive clinical studies are briefly summarized.

3.3.1. Phase 1 Thorough QT Studies in Healthy, Adult Subjects, With Individual Components (TMC114-C153, GS-US-216-0107, and GS-US-120-0107)

Results from the Phase 1 thorough QT studies with DRV, COBI, and TAF in healthy adult subjects did not reveal any concerns with regards to cardiac safety.

Thorough QT Study TMC114-C153 in Healthy Subjects (DRV)

In this open-label, randomized, placebo- and active-controlled, 4-way crossover thorough QT study, 40 healthy subjects were administered supratherapeutic doses of DRV 1,600 mg and rtv 100 mg once daily and DRV 800 mg and rtv 100 mg twice daily (approximately 2 times the

recommended DRV dose) for 7 days. At the mean maximum DRV concentration of 6,599 ng/mL observed in this study, the mean increase in QT interval corrected according to Fridericia's formula (QTcF) was 2.2 ms with a 90% 2-sided confidence interval (CI) of -2.0 to 6.3 ms. When evaluating the 2-sided 90% CI on the time-matched mean changes in QTcF vs placebo control, the upper bounds of both DRV co-administered with rtv groups never exceeded the 1-ms boundary. In the setting of this study, DRV co-administered with rtv did not appear to prolong the QTc interval.[15]

Thorough QT Study GS-US-216-0107 in Healthy Subjects (COBI)

The effect of a single dose of COBI 250 mg and 400 mg (approximately 1.7 and 2.7 times the recommended dose, respectively) on QTc was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg), 4-period crossover thorough QT study in 48 healthy subjects. In this study, no significant QTc prolongation effect of COBI was detected. The dose of 400 mg COBI is expected to provide information on a high exposure clinical scenario. Prolongation of the PR interval was noted in subjects receiving COBI in the same study. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline correction was 9.5 (12.1) ms for COBI 250 mg and 20.2 (22.8) ms for COBI 400 mg.[15,18]

Thorough QT Study GS-US-120-0107 in Healthy Subjects (TAF)

In a thorough QT study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.[4,10,19]

3.3.2. Phase 3 Studies in Adult Subjects With Renal Impairment, With Individual Components (GS-US-236-0118, and GS-US-292-0112)

The Phase 3 D/C/F/TAF studies (TMC114IFD3013 and TMC114FD2HTX3001) in HIV-1 infected subjects included respectively 239 and 62 subjects with $eGFR_{CG}$ 70 to <90 mL/min, 84 and 2 subjects with $eGFR_{CG}$ 50 to <70 mL/min, and 5 and 0 subjects with $eGFR_{CG}$ <50 mL/min. The review of the safety data of these studies did not suggest any particular concern in these subjects compared to the subjects with normal renal function (see Section 3.1.1.2.3 and Section 3.1.1.1.3).

Historical Phase 1 and Phase 3 studies with COBI, FTC, or TAF in adult subjects with variable degrees of renal impairment did not raise any safety concerns and support the use of these ARTs in subjects with a creatinine clearance ≥30 mL/min without the need to adjust the ART dose.[5,10,15,18] Two of these studies are of more specific interest, as they concern DRV with COBI in subjects with an $eGFR_{CG}$ between 50 and <90 mL/min (Study GS-US-236-0118), and COBI, FTC, and TAF in subjects with an $eGFR_{CG}$ between 30 and <70 mL/min (Study GS-US-292-0112). The main findings of these 2 studies are further summarized below.

Phase 3 Study GS-US-236-0118 in HIV-1 Infected Subjects With Mild to Moderate Renal Impairment (COBI)

Study GS-US-236-0118 was an open-label, multicenter, multiple-cohort Phase 3 study in HIV-1 infected adult subjects with stable, mild to moderate renal function ($eGFR_{CG}$ 50 to <90 mL/min). Subjects were enrolled in 1 of the following 2 cohorts to receive 96 weeks of treatment with study drug:

- Cohort 1 (33 ART-naïve subjects with HIV-1 RNA ≥1000 copies/mL at screening): E/C/F/TDF 150/150/200/300 mg.
- Cohort 2 (73 ART-experienced, virologically suppressed subjects receiving a regimen of ATV/rtv 300/100 mg plus 2 NRTIs (52 subjects) or DRV/rtv 800/100 mg plus 2 NRTIs (21 subjects): these subjects switched their PK enhancer (rtv 100 mg) to COBI 150 mg at baseline, while continuing the other components of their ARV regimen.

The data from Cohort 2 demonstrated that COBI-boosted PI containing treatments do not alter renal function.
Source: NDA205395/SUR/Mod5.3.5.2/GS-US-236-0118-CSR.

Phase 3 Study GS-US-292-0112 in HIV-1 Infected Subjects With Mild to Moderate Renal Impairment (E/C/F/TAF)

Study GS-US-292-0112 was a single-arm, open-label Phase 3 study to assess the safety, tolerability, and efficacy of the E/C/F/TAF 150/150/200/10-mg FDC tablet in ART-naïve and ART-experienced HIV-1 positive, adult subjects with mild to moderate renal impairment. The primary objective of this study was to evaluate the effect of E/C/F/TAF on renal parameters at W24. Other objectives included change from baseline at W48 and W96 in eGFR estimations, measured GFR, and change from baseline in renal biomarkers.[14]

In total, 242 subjects with stable $eGFR_{CG}$ 30 to 69 mL/min (including 80 subjects with baseline $eGFR_{CG}$ <50 mL/min) were enrolled and switched to E/C/F/TAF.

Adverse Events

- Most AEs reported were mild or moderate in severity.
- AEs leading to study drug discontinuation were reported for 8 (3%) subjects, 2 of them discontinued due to decreased GFR:
  - 1 subject who had uncontrolled hypertension discontinued study drug after 3 months of therapy and was assessed by the investigator to have worsening renal insufficiency possibly related to the study drug.
  - 1 subject was considered to have progression of hypertension-related CKD unrelated to the study drug.
- None of the subjects in the study had laboratory evidence of **PRT (including Fanconi syndrome)**. Adverse events, grades, and frequencies were similar in subjects with baseline eGFR <50 or ≥50 mL/min.

Laboratory Parameters

- No clinically appreciable change from baseline in **estimated creatinine clearance** ($eGFR_{CG}$, $eGFR_{CKD-EPI}$, and $eGFR_{cyst}$) was observed through W48, with direction and magnitude varying by filtration marker and equation.
- Results were similar for subjects whether **baseline eGFR** was <50 or ≥50 mL/min or whether they switched from a TDF-based regimen.

Renal Biomarkers & Other

- Significant improvements in **total proteinuria (UPCR)**, **albuminuria (UACR)**, and **tubular proteinuria (urine RBP/creatinine ratio and beta-2-microglobulin/creatinine ratio)** were observed.
- Improvements in renal parameters were particularly marked in subjects switching to E/C/F/TAF from a TDF-containing regimen, whereas renal function in subjects switching from non-TDF regimens did not have significant changes.
- The prevalence of significant proteinuria (UPCR >200 mg/g) and albuminuria (UACR ≥30 mg/g) decreased from 42% to 11% and from 49% to 21%, respectively. These changes occurred at W1 and remained through W48.
- Significant improvements in other measures of renal tubular function, including **fractional excretion of uric acid (FEUA)** (median [Q1; Q3] change from baseline to W48: -1.5 [-3.6; 0.0]; p<0.001), were observed, whereas there was no significant change in **FE_{PO4}** (median [Q1; Q3] change from baseline to W48: 1.1 [-4.1; 6.1]; p=0.07] or serum **phosphorus** (median [Q1; Q3] change from baseline to W48: 0.0 [-0.4; 0.4]; p=0.50).

Baseline GFR <50 mL/min

The subjects with baseline GFR <50 mL/min, being slightly older and more often having hypertension, also had no significant change from baseline estimated creatinine clearance, and other measures of renal function improved significantly from baseline to W48.[14]

Although FTC, 1 of the components of E/C/F/TAF, is not recommended for daily use in individuals with creatinine clearance <50 mL/min (below 50 mL/min, every other day dosing is recommended[5]), no discrete toxicity associated with the administration of E/C/F/TAF (which also contains FTC 200 mg) to this population was identified. Based on the results from this study in 242 HIV-1 infected, virologically suppressed subjects with mild ($eGFR_{CG}$ of 50 to <70 mL/min, n=162) to moderate ($eGFR_{CG}$ of 30 to <50 mL/min, n=80) renal impairment, **no dose adjustment** is required for subjects with $eGFR_{CG}$ of ≥30 mL/min.[10,14]

3.4. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic data (population PK) is available for subjects enrolled in the D/C/F/TAF group of Study TMC114FD2HTX3001 for DRV and TAF, and of Study TMC114IFD3013 for DRV (see Mod2.7.2/ClinPharm/Sec2.2.2.2.3.1 and Sec 2.2.2.3.3.1).

The data from both Phase 3 studies show that the DRV PK parameters were in line with historical data for COBI-boosted DRV in HIV-1 infected subjects. There were no apparent clinically relevant relationships between the PK of DRV and safety parameters of interest in either study (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec7 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec7).

The data from Study TMC114FD2HTX3001 show that the TAF PK parameters were in line with historical data for TAF 10 mg in the presence of DRV/COBI in HIV-1 infected patients and for TAF 25 mg in the proof of concept study, respectively. There were no apparent clinically relevant relationships between the PK of TAF and safety parameters of interest (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec7).

Note that in Study TMC114FD2HTX3001, the median DRV area under the plasma concentration-time curve over the 24h dosing interval (AUC_{24h}) was higher in the small subgroup of subjects with a laboratory abnormality in UACR (≥30mg/g; n=28) or in UPCR (≥200mg/g; n=23) compared to the median AUC_{24h} in subjects without such laboratory abnormalities, but the AUC_{24h} ranges largely overlapped. For the TAF area under the plasma concentration-time curve across the dosing interval (AUC_{tau}), such a difference was less pronounced. In Study TMC114IFD3013, the DRV AUC_{24h} (median and range) was similar between subjects with or without laboratory abnormalities in UACR or in UPCR. Based on the combined data from both Phase 3 studies it can be concluded that the observations in Study TMC114FD2HTX3001 are not clinically relevant.

Pharmacokinetic data are available from a PK substudy of Study GS-US-299-0102 and TAF population PK analysis for a limited number of subjects; PK/PD analyses for safety parameters were not performed on data from this study (see Mod2.7.2/ClinPharm/Sec3.5.2).

4. ADVERSE DRUG REACTIONS THROUGH WEEK 48

The AEs reported during Studies TMC114FD2HTX3001, TMC114IFD3013, and GS-US-299-0102 were reviewed by internal medical experts for identification of ADRs associated with D/C/F/TAF (see Section 2.2.1.2 for more details on this analysis).

An overview of ADRs in the Week-48 analyses of Studies TMC114FD2HTX3001 and TMC114IFD3013 is presented in the sections below.

These results show that:

- The majority of the ADRs identified during treatment with the D/C/F/TAF FDC were mild (grade 1) in severity (37.3% in Study TMC114FD2HTX3001 and 21.0% in Study TMC114IFD3013).
- The only ADRs with a frequency of >2% and at least of moderate severity (≥grade 2) were rash and diarrhea in Study TMC114FD2HTX3001, and diarrhea and headache in Study TMC114IFD3013.
- There was only 1 (0.3%) subject with an ADR of grade 3 severity in Study TMC114FD2HTX3001, and 3 (0.4%) subjects with ADRs of grade 3 severity in Study TMC114IFD3013. No subjects in either of the studies experienced ADRs of grade 4 severity during treatment with the D/C/F/TAF FDC.
- The percentage of subjects who discontinued treatment with the D/C/F/TAF FDC due to ADRs was 1.9% in Study TMC114FD2HTX3001 and 0.5% in Study TMC114IFD3013.

4.1. Double-blind Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve, Adult Subjects

An overview of the D/C/F/TAF ADRs identified in the ART-naïve population of Study TMC114FD2HTX3001 is presented in Table 26. No new ADRs were identified in the study compared to the known safety profile of DRV/COBI and F/TAF. Overall, 182 (50.3%) subjects experienced at least 1 ADR during treatment with the D/C/F/TAF FDC. The most frequently occurring ADRs (in >5% of subjects) during treatment with the D/C/F/TAF FDC were diarrhea (19.6%), headache (13.0%), rash (12.2%), nausea (7.7%), and fatigue (5.2%) (Table 27).

For the ADR tables presenting the incidences of all ADRs by PT and all ADRs at least grade 2, refer to Appendix 4. For the incidences of all serious ADRs, all ADRs at least grade 3, and all ADRs leading to treatment discontinuation, refer respectively to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att-TSFAE40_EXT, Att-TSFAE42_EXT, and Att-TSFAE43_EXT.

The majority of the ADRs identified during treatment with D/C/F/TAF were mild (grade 1) in severity. The most frequent ADRs (in >2% of subjects) for D/C/F/TAF that were moderate (grade 2) were rash (4.4%) and diarrhea (3.9%). A severe (grade 3) ADR (headache) occurred in 1 (0.3%) subject during treatment with the D/C/F/TAF FDC. No grade 4 ADRs were identified

during treatment with the D/C/F/TAF FDC. The proportion of subjects who discontinued treatment with D/C/F/TAF due to ADRs, regardless of severity, was 1.9%.

An overview of the D/C/F/TAF ADRs and the grouping of PTs into medical concepts and their resulting SOCs are provided in Appendix 3.

Table 26: Summary Table of Adverse Drug Reactions for D/C/F/TAF; ITT (Study TMC114FD2HTX3001)

Phase = Treatment

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	362	363
with at least one ADR	182 (50.3%)	175 (48.2%)
with at least one Serious ADR	0	3 (0.8%)
with at least one death due to ADR	0	0
with at least one worst grade 1 ADR	135 (37.3%)	117 (32.2%)
with at least one worst grade 2 ADR	46 (12.7%)	53 (14.6%)
with at least one worst grade 3 ADR	1 (0.3%)	4 (1.1%)
with at least one worst grade 4 ADR	0	1 (0.3%)
with at least one worst grade 1 or 2 ADR	181 (50.0%)	170 (46.8%)
with at least one worst grade 3 or 4 ADR	1 (0.3%)	5 (1.4%)
with at least one worst grade 2, 3 or 4 ADR	47 (13.0%)	58 (16.0%)
with at least one ADR for which study medication was permanently stopped	7 (1.9%)	8 (2.2%)
with at least one ADR for which study medication was temporarily stopped	5 (1.4%)	3 (0.8%)

ADR = adverse drug reaction; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; N = number of subjects; ITT = intent-to-treat.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att-TSFAE38_EXT.

Table 27: Incidence (%) of Adverse Drug Reactions for D/C/F/TAF by System Organ Class and ADR Term; ITT (Study TMC114FD2HTX3001)

Phase = Treatment SOC[a] ADR[b]	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	362	363
Any adverse drug reaction	182 (50.3%)	175 (48.2%)
Gastrointestinal disorders	115 (31.8%)	117 (32.2%)
Diarrhoea	71 (19.6%)	66 (18.2%)
Nausea	28 (7.7%)	45 (12.4%)
Abdominal pain	15 (4.1%)	22 (6.1%)
Vomiting	15 (4.1%)	15 (4.1%)
Dyspepsia	12 (3.3%)	10 (2.8%)
Flatulence	7 (1.9%)	2 (0.6%)
Abdominal distension	6 (1.7%)	1 (0.3%)
Skin and subcutaneous tissue disorders	55 (15.2%)	44 (12.1%)
Rash	44 (12.2%)	37 (10.2%)
Pruritus	9 (2.5%)	6 (1.7%)
Urticaria	4 (1.1%)	3 (0.8%)
Angioedema	3 (0.8%)	0
Stevens-Johnson syndrome	0	1 (0.3%)
Nervous system disorders	47 (13.0%)	32 (8.8%)
Headache	47 (13.0%)	32 (8.8%)
General disorders and administration site conditions	33 (9.1%)	30 (8.3%)
Fatigue	19 (5.2%)	18 (5.0%)
Asthenia	14 (3.9%)	12 (3.3%)
Metabolism and nutrition disorders	5 (1.4%)	4 (1.1%)
Anorexia	4 (1.1%)	4 (1.1%)
Diabetes mellitus	1 (0.3%)	0
Immune system disorders	3 (0.8%)	1 (0.3%)
(Drug) hypersensitivity	2 (0.6%)	1 (0.3%)
Immune reconstitution syndrome	1 (0.3%)	0
Musculoskeletal and connective tissue disorders	3 (0.8%)	7 (1.9%)
Myalgia	3 (0.8%)	7 (1.9%)
Psychiatric disorders	2 (0.6%)	2 (0.6%)
Abnormal dreams	2 (0.6%)	2 (0.6%)

ADR = adverse drug reaction; AE = adverse event; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; PT = preferred term; SOC = system organ class.
All AEs were coded using MedDRA version 19.1.

[a] SOC: Highest level of hierarchy in MedDRA terminology; comprises groupings by etiology, manifestation site, or purpose.
[b] ADR term: The PTs grouped under each ADR are described in Appendix 3.

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att-TSFAE45_EXT.

Graded DAIDS abnormalities in selected laboratory parameters, considered ADRs, are presented in Table 28. In the D/C/F/TAF group, elevations in cholesterol, LDL cholesterol, triglycerides, lipase, glucose, creatinine, amylase, AST, and ALT were reported.

Table 28: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Reactions for D/C/F/TAF; ITT (Study TMC114FD2HTX3001)

Phase = Treatment

	D/C/F/TAF	Control	Limits
Analysis set: Intent-to-treat, N	362	363	
Hepatic Parameters			
ALT, high, N	358	358	
Any treatment emergent grade 2, 3 or 4	6 (1.7%)	9 (2.5%)	
Treatment emergent grade 2	1 (0.3%)	6 (1.7%)	2.5 to <5.0x ULN[a]
Treatment emergent grade 3	4 (1.1%)	2 (0.6%)	5.0 to <10.0x ULN[a]
Treatment emergent grade 4	1 (0.3%)	1 (0.3%)	≥10.0x ULN[a]
AST, high, N	358	358	
Any treatment emergent grade 2, 3 or 4	7 (2.0%)	10 (2.8%)	
Treatment emergent grade 2	3 (0.8%)	4 (1.1%)	2.5 to <5.0x ULN[b]
Treatment emergent grade 3	4 (1.1%)	4 (1.1%)	5.0 to <10.0x ULN[b]
Treatment emergent grade 4	0	2 (0.6%)	≥10.0x ULN[b]
Alkaline phosphatase, high, N	357	358	
Any treatment emergent grade 2, 3 or 4	0	3 (0.8%)	
Treatment emergent grade 2	0	3 (0.8%)	2.5 to <5.0x ULN[c]
Treatment emergent grade 3	0	0	5.0 to <10.0x ULN[c]
Treatment emergent grade 4	0	0	≥10.0x ULN[c]
Pancreatic Parameters			
Amylase (total), high, N	357	358	
Any treatment emergent grade 2, 3 or 4	8 (2.2%)	17 (4.7%)	
Treatment emergent grade 2	7 (2.0%)	17 (4.7%)	1.5 to < 3.0x ULN[d]
Treatment emergent grade 3	0	0	3.0 to <5.0x ULN[d]
Treatment emergent grade 4	1 (0.3%)	0	≥5.0x ULN[d]
Lipase, high, N[e]	13	22	
Any treatment emergent grade 2, 3 or 4	1 (7.7%)	6 (27.3%)	
Treatment emergent grade 2	1 (7.7%)	4 (18.2%)	1.5 to <3.0x ULN[f]
Treatment emergent grade 3	0	2 (9.1%)	3.0 to <5.0x ULN[f]
Treatment emergent grade 4	0	0	≥5.0x ULN[f]
Lipid Parameters			
Cholesterol, fasting limits, high, fasting samples only, N	345	338	
Any treatment emergent grade 2, 3 or 4	68 (19.7%)	18 (5.3%)	
Treatment emergent grade 2	62 (18.0%)	16 (4.7%)	240 to <300 mg/dL
Treatment emergent grade 3	6 (1.7%)	2 (0.6%)	≥300 mg/dL
Treatment emergent grade 4	0	0	NA
LDL, fasting limits, high, fasting samples only, N	345	338	
Any treatment emergent grade 2, 3 or 4	48 (13.9%)	17 (5.0%)	
Treatment emergent grade 2	31 (9.0%)	13 (3.8%)	160 to <190 mg/dL
Treatment emergent grade 3	17 (4.9%)	4 (1.2%)	≥190 mg/dL
Treatment emergent grade 4	0	0	NA

Table 28: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Reactions for D/C/F/TAF; ITT (Study TMC114FD2HTX3001)

Phase = Treatment	D/C/F/TAF	Control	Limits
Triglycerides, fasting limits, high, fasting samples only, N	345	338	
Any treatment emergent grade 2, 3 or 4	28 (8.1%)	17 (5.0%)	
Treatment emergent grade 2	24 (7.0%)	13 (3.8%)	>300 to 500 mg/dL
Treatment emergent grade 3	3 (0.9%)	3 (0.9%)	>500 to <1,000 mg/dL
Treatment emergent grade 4	1 (0.3%)	1 (0.3%)	>1,000 mg/dL
Glucose Parameters			
Glucose, serum, fasting limits, high, fasting samples only, N	357	356	
Any treatment emergent grade 2, 3 or 4	24 (6.7%)	20 (5.6%)	
Treatment emergent grade 2	23 (6.4%)	20 (5.6%)	>125 to 250 mg/dL
Treatment emergent grade 3	1 (0.3%)	0	>250 to 500 mg/dL
Treatment emergent grade 4	0	0	>500 mg/dL
Renal Parameters			
Creatinine, high, N	358	358	
Any treatment emergent grade 2, 3 or 4	16 (4.5%)	49 (13.7%)	
Treatment emergent grade 2	15 (4.2%)	49 (13.7%)	>1.3 to 1.8x ULN[g] OR Increase of >0.3 mg/dL above baseline
Treatment emergent grade 3	0	0	>1.8 to <3.5x ULN[g] OR Increase of 1.5 to <2.0x above baseline
Treatment emergent grade 4	1 (0.3%)	0	≥3.5x ULN[g] OR Increase of ≥2.0x above baseline

ALT = alanine aminotransferase; AST = aspartate aminotransferase; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; LDL = low density lipoprotein; N = number of subjects with data on treatment; ULN = upper limit of normal.

[a] ALT: ULN = 34 U/L (female aged 18 to <69 years), 32 U/L (female 69 to 150 years), 43 U/L (male aged 18 to <69 years), or 35 U/L (male aged 69 to 150 years).

[b] AST: ULN = 34 U/L (female aged 18 to <150 years), or 36 U/L (male aged 18 to <150 years).

[c] Alkaline phosphatase: ULN = 106 U/L (female aged 18 to <50 years), 123 U/L (female aged 50 to <80 years), 129 U/L (male aged 18 to <50 years), 131 U/L (male aged 50 to <60 years), 125 U/L (male aged 60 to <70 years), or 130 U/L (male aged 70 to <80 years).

[d] Amylase: ULN = 100 U/L (male/female aged 18 to <50 years), 120 U/L (male/female aged 50 to <60 years), 150 U/L (male/female aged 60 to <70 years), or 252 U/L (male/female aged 70 to <83 years).

[e] Only reflex lipase testing was performed when total amylase >1.5x ULN.

[f] Lipase: ULN = 100 U/L (male/female aged 18 to <60 years), 120 U/L (male/female aged 60 to <70 years), or 130 U/L (male/female aged 70 to <150 years).

[g] Creatinine: ULN = 1.1 mg/dL (female aged 18 to <70 years), 1.2 mg/dL (male aged 18 to <50 years; female aged 70 to <80 years), 1.3 mg/dL (male aged 50 to <70 years), or 1.5 mg/dL (male aged 70 to <80 years).

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att-TSFAE44_EXT.

4.2. Open-label Phase 3 Study TMC114IFD3013 in HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects

An overview of the D/C/F/TAF ADRs identified in the ART-experienced population of Study TMC114IFD3013 is presented in Table 29. No new ADRs were identified in the study compared to the known safety profile of DRV/COBI and F/TAF. Overall, 236 (30.9%) subjects experienced at least 1 ADR during treatment with the D/C/F/TAF FDC. The most frequently

occurring ADRs (in >5% of subjects) during treatment with the D/C/F/TAF FDC were diarrhea (7.9%), headache (7.6%), and abdominal pain (5.4%) (Table 30).

For the ADR tables presenting the incidences of all ADRs by PT and all ADRs at least grade 2, refer to Appendix 5. For the incidences of all serious ADRs, all ADRs at least grade 3, and all ADRs leading to treatment discontinuation, refer respectively to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE40_EXT, Att-TSFAE42_EXT, and Att-TSFAE43_EXT.

The majority of the ADRs identified during treatment with D/C/F/TAF were mild (grade 1) in severity. The most frequent ADRs (in >2% of subjects) for D/C/F/TAF that were moderate to severe (grade 2 to 3) were diarrhea (2.5%) and headache (2.4%). Adverse reactions that were severe (grade 3) were abdominal pain, diarrhea, and pancreatitis acute (all 0.1%). No grade 4 ADRs were identified during treatment with the D/C/F/TAF FDC. The proportion of subjects who discontinued treatment with D/C/F/TAF due to ADRs, regardless of severity, was 0.5%.

An overview of the D/C/F/TAF ADRs and the grouping of PTs into medical concepts and their resulting SOCs are provided in Appendix 3.

Table 29: Summary Table of Adverse Drug Reactions for D/C/F/TAF; ITT (Study TMC114IFD3013)

Phase = Treatment

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	763	378
with at least one ADR	236 (30.9%)	84 (22.2%)
with at least one Serious ADR	4 (0.5%)	2 (0.5%)
with at least one death due to ADR	0	0
with at least one worst grade 1 ADR	160 (21.0%)	58 (15.3%)
with at least one worst grade 2 ADR	73 (9.6%)	21 (5.6%)
with at least one worst grade 3 ADR	3 (0.4%)	4 (1.1%)
with at least one worst grade 4 ADR	0	1 (0.3%)
with at least one worst grade 1 or 2 ADR	233 (30.5%)	79 (20.9%)
with at least one worst grade 3 or 4 ADR	3 (0.4%)	5 (1.3%)
with at least one worst grade 2, 3 or 4 ADR	76 (10.0%)	26 (6.9%)
with at least one ADR for which study medication was permanently stopped	4 (0.5%)	1 (0.3%)
with at least one ADR for which study medication was temporarily stopped	3 (0.4%)	2 (0.5%)

ADR = adverse drug reaction; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; N = number of subjects; ITT = intent-to-treat.
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE38_EXT.

Table 30: Incidence (%) of Adverse Drug Reactions for D/C/F/TAF by System Organ Class and ADR Term; ITT (Study TMC114IFD3013)

Phase = Treatment SOC[a] ADR[b]	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	763	378
Any adverse drug reaction	236 (30.9%)	84 (22.2%)
Gastrointestinal disorders	134 (17.6%)	41 (10.8%)
Diarrhoea	60 (7.9%)	16 (4.2%)
Abdominal pain	41 (5.4%)	13 (3.4%)
Vomiting	22 (2.9%)	3 (0.8%)
Nausea	21 (2.8%)	7 (1.9%)
Dyspepsia	13 (1.7%)	4 (1.1%)
Abdominal distension	9 (1.2%)	0
Flatulence	8 (1.0%)	3 (0.8%)
Pancreatitis acute	1 (0.1%)	0
Nervous system disorders	58 (7.6%)	16 (4.2%)
Headache	58 (7.6%)	16 (4.2%)
Skin and subcutaneous tissue disorders	44 (5.8%)	13 (3.4%)
Rash	28 (3.7%)	7 (1.9%)
Pruritus	11 (1.4%)	3 (0.8%)
Angioedema	4 (0.5%)	4 (1.1%)
Urticaria	4 (0.5%)	0
General disorders and administration site conditions	43 (5.6%)	11 (2.9%)
Fatigue	34 (4.5%)	10 (2.6%)
Asthenia	9 (1.2%)	1 (0.3%)
Metabolism and nutrition disorders	14 (1.8%)	4 (1.1%)
Diabetes mellitus	9 (1.2%)	1 (0.3%)
Anorexia	4 (0.5%)	2 (0.5%)
Lipodystrophy	1 (0.1%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	13 (1.7%)	4 (1.1%)
Myalgia	12 (1.6%)	4 (1.1%)
Osteonecrosis	1 (0.1%)	0
Psychiatric disorders	9 (1.2%)	1 (0.3%)
Abnormal dreams	9 (1.2%)	1 (0.3%)
Immune system disorders	4 (0.5%)	2 (0.5%)
(Drug) hypersensitivity	4 (0.5%)	2 (0.5%)
Hepatobiliary disorders	0	1 (0.3%)
Acute hepatitis	0	1 (0.3%)

ADR = adverse drug reaction; AE = adverse event; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; PT = preferred term; SOC = system organ class.
All AEs were coded using MedDRA version 19.1.

[a] SOC: Highest level of hierarchy in MedDRA terminology; comprises groupings by etiology, manifestation site, or purpose.
[b] ADR term: The PTs grouped under each ADR are described in Appendix 3.
Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE45_EXT.

Graded DAIDS abnormalities in selected laboratory parameters, considered ADRs, are presented in Table 31. In the D/C/F/TAF group, elevations in cholesterol, LDL cholesterol, lipase, glucose, triglycerides, creatinine, amylase, ALT, AST, and alkaline phosphatase were reported.

Table 31: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Reactions for D/C/F/TAF; ITT (Study TMC114IFD3013)

Phase = Treatment

	D/C/F/TAF	Control	Limits
Analysis set: Intent-to-treat, N	763	378	
Hepatic Parameters			
ALT, high, N	761	376	
Any treatment emergent grade 2, 3 or 4	26 (3.4%)	14 (3.7%)	
Treatment emergent grade 2	18 (2.4%)	5 (1.3%)	2.5 to <5.0x ULN[a]
Treatment emergent grade 3	5 (0.7%)	4 (1.1%)	5.0 to <10.0x ULN[a]
Treatment emergent grade 4	3 (0.4%)	5 (1.3%)	≥10.0x ULN[a]
AST, high, N	761	376	
Any treatment emergent grade 2, 3 or 4	23 (3.0%)	16 (4.3%)	
Treatment emergent grade 2	12 (1.6%)	6 (1.6%)	2.5 to <5.0x ULN[b]
Treatment emergent grade 3	7 (0.9%)	6 (1.6%)	5.0 to <10.0x ULN[b]
Treatment emergent grade 4	4 (0.5%)	4 (1.1%)	≥10.0x ULN[b]
Alkaline phosphatase, high, N	761	376	
Any treatment emergent grade 2, 3 or 4	2 (0.3%)	0	
Treatment emergent grade 2	2 (0.3%)	0	2.5 to <5.0x ULN[c]
Treatment emergent grade 3	0	0	5.0 to <10.0x ULN[c]
Treatment emergent grade 4	0	0	≥10.0x ULN[c]
Pancreatic Parameters			
Amylase (total), high, N	761	376	
Any treatment emergent grade 2, 3 or 4	36 (4.7%)	28 (7.4%)	
Treatment emergent grade 2	32 (4.2%)	26 (6.9%)	1.5 to < 3.0x ULN[d]
Treatment emergent grade 3	3 (0.4%)	1 (0.3%)	3.0 to <5.0x ULN[d]
Treatment emergent grade 4	1 (0.1%)	1 (0.3%)	≥5.0x ULN[d]
Lipase, high, N[e]	43	33	
Any treatment emergent grade 2, 3 or 4	8 (18.6%)	6 (18.2%)	
Treatment emergent grade 2	3 (7.0%)	4 (12.1%)	1.5 to <3.0x ULN[f]
Treatment emergent grade 3	3 (7.0%)	0	3.0 to <5.0x ULN[f]
Treatment emergent grade 4	2 (4.7%)	2 (6.1%)	≥5.0x ULN[f]
Lipid Parameters			
Cholesterol, fasting limits, high, fasting samples only, N	738	363	
Any treatment emergent grade 2, 3 or 4	188 (25.5%)	32 (8.8%)	
Treatment emergent grade 2	160 (21.7%)	27 (7.4%)	240 to <300 mg/dL
Treatment emergent grade 3	28 (3.8%)	5 (1.4%)	≥300 mg/dL
Treatment emergent grade 4	0	0	NA
LDL, fasting limits, high, fasting samples only, N	738	363	
Any treatment emergent grade 2, 3 or 4	167 (22.6%)	23 (6.3%)	
Treatment emergent grade 2	119 (16.1%)	17 (4.7%)	160 to <190 mg/dL
Treatment emergent grade 3	48 (6.5%)	6 (1.7%)	≥190 mg/dL
Treatment emergent grade 4	0	0	NA

Table 31: Incidence (%) of Treatment-emergent Laboratory Abnormalities, Grade 2 to 4, Considered Adverse Reactions for D/C/F/TAF; ITT (Study TMC114IFD3013)

Phase = Treatment

	D/C/F/TAF	Control	Limits
Triglycerides, fasting limits, high, fasting samples only, N	738	363	
Any treatment emergent grade 2, 3 or 4	55 (7.5%)	31 (8.5%)	
Treatment emergent grade 2	41 (5.6%)	23 (6.3%)	>300 to 500 mg/dL
Treatment emergent grade 3	11 (1.5%)	8 (2.2%)	>500 to <1,000 mg/dL
Treatment emergent grade 4	3 (0.4%)	0	>1,000 mg/dL
Glucose Parameters			
Glucose, serum, fasting limits, high, fasting samples only, N	761	376	
Any treatment emergent grade 2, 3 or 4	61 (8.0%)	23 (6.1%)	
Treatment emergent grade 2	53 (7.0%)	21 (5.6%)	>125 to 250 mg/dL
Treatment emergent grade 3	8 (1.1%)	2 (0.5%)	>250 to 500 mg/dL
Treatment emergent grade 4	0	0	>500 mg/dL
Renal Parameters			
Creatinine, high, N	761	376	
Any treatment emergent grade 2, 3 or 4	43 (5.7%)	25 (6.6%)	
Treatment emergent grade 2	41 (5.4%)	24 (6.4%)	>1.3 to 1.8x ULN[g] OR Increase of >0.3 mg/dL above baseline
Treatment emergent grade 3	2 (0.3%)	1 (0.3%)	>1.8 to <3.5x ULN[g] OR Increase of 1.5 to <2.0x above baseline
Treatment emergent grade 4	0	0	≥3.5x ULN[g] OR Increase of ≥2.0x above baseline

ALT = alanine aminotransferase; AST = aspartate aminotransferase; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; LDL = low density lipoprotein; N = number of subjects with data on treatment; ULN = upper limit of normal.

[a] ALT: ULN = 34 U/L (female aged 18 to <69 years), 32 U/L (female 69 to <150 years), 43 U/L (male aged 18 to <69 years), or 35 U/L (male aged 69 to <150 years).

[b] AST: ULN = 34 U/L (female aged 18 to <150 years), or 36 U/L (male aged 18 to <150 years).

[c] Alkaline phosphatase: ULN = 106 U/L (female aged 18 to <50 years), 123 U/L (female aged 50 to <80 years), 129 U/L (male aged 18 to <50 years), 131 U/L (male aged 50 to <60 years), 125 U/L (male aged 60 to <70 years), or 130 U/L (male aged 70 to <80 years).

[d] Amylase: ULN = 100 U/L (male/female aged 18 to <50 years), 120 U/L (male/female aged 50 to <60 years), 150 U/L (male/female aged 60 to <70 years), or 252 U/L (male/female aged 70 to <83 years).

[e] Only reflex lipase testing was performed when total amylase >1.5x ULN.

[f] Lipase: ULN = 100 U/L (male/female aged 18 to <60 years), 120 U/L (male/female aged 60 to <70 years), or 130 U/L (male/female aged 70 to <150 years).

[g] Creatinine: ULN = 1.1 mg/dL (female aged 18 to <70 years), 1.2 mg/dL (male aged 18 to <50 years; female aged 70 to <80 years), 1.3 mg/dL (male aged 50 to <70 years), or 1.5 mg/dL (male aged 70 to <80 years).

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE44_EXT.

5. SAFETY IN ONGOING STUDIES

In this section, safety data from the 2 ongoing randomized, active-controlled Phase 3 studies (Studies TMC114FD2HTX3001 [AMBER] and TMC114IFD3013 [EMERALD]) are discussed. For each study, the period in scope for this safety review starts after the Week-48 visit and ends at the data cut-off date of 1 June 2017.

Summary tables are presented for significant AEs, ie, any deaths, SAEs, AEs leading to discontinuation, and AEOIs. Narratives (Council for International Organizations of Medical Sciences [CIOMS] I forms) are provided for all fatal cases and SAEs, and Case Report Forms are made available for each subject who died during the study or who discontinued the study due to an SAE. For follow-up information on SAEs that were reported in the Week-48 analysis of these studies, refer to the CIOMS I forms that are provided with the respective CSRs (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/W48-Subject-Narratives and Mod5.3.5.1/TMC114IFD3013-W48-CSR/W48-Subject-Narratives).

Note that this analysis was done on an uncleaned database, which led to some discrepancies between the cases listed in the analysis and the CIOMS I forms retrieved from the Global Medical Safety database from Janssen Research & Development LLC. Any discrepancies that occurred are explained in the following sections.

5.1. Double-blind Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve, Adult Subjects

After Week 48, subjects in Study TMC114FD2HTX3001 continued to take their blinded study drug until the unblinding visit, after which all subjects started open-label treatment with the D/C/F/TAF FDC tablet up to Week 96.

5.1.1. Extent of Exposure

At Week 48, 339 subjects in the D/C/F/TAF group and 335 subjects in the control group were ongoing. Of these, 5 subjects (3 vs 2, respectively) discontinued subsequently, and had no further visits beyond Week 48. The reasons for discontinuation were noncompliance with study drug (2 vs 0), lost to follow-up (1 vs 1), and physician decision (0 vs 1) (Mod5.3.5.1/TMC114FD2HTX3001/SCS-Statistical Output/Att-Discont).

The open-label treatment phase of the study included 336 subjects in the D/C/F/TAF group and 333 subjects in the control group. These constitute the safety data set presented in this section, which covers the period after the Week-48 visit until 1 June 2017.

In the D/C/F/TAF group, the mean (SD) exposure to D/C/F/TAF was 25.2 (8.2) weeks since the Week-48 visit (Table 32). In the control group, the majority of subjects (N=303) did not yet switch to D/C/F/TAF. For the 30 subjects in the control group who had switched to D/C/F/TAF by the time of the cut-off, the mean (SD) exposure to D/C/F/TAF was 0.8 (0.4) weeks. In the control group (N=333, including these 30 subjects prior to switching to D/C/F/TAF), the mean (SD) exposure to DRV/COBI+F/TDF was 25.3 (8.0) weeks since the Week-48 visit.

Table 32: Extent of Exposure - TMC114FD2HTX3001; ITT

	D/C/F/TAF	CONTROL	
	D/C/F/TAF group continued use from W48+1d (N=336)[a]	Control group not yet switched to D/C/F/TAF from W48+1d (N=333)[a,c]	Control group switched to D/C/F/TAF from unblinding visit (N=30)[a,c]
Subject-years of exposure	162.5	161.4	0.5
Exposure (Weeks)			
Mean (SD)	25.24 (8.208)	25.29 (8.007)	0.82 (0.422)
Median (Q1;Q3)	24.14 (18.07; 32.14)	24.43 (18.00; 32.14)	1 (0.43; 1.14)
(Min; Max)	(0.9; 47.0)	(4.4; 48.0)	(0.1; 1.6)

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects; SD = standard deviation.

Cut-off Date = 01 June 2017.
D/C/F/TAF group exposure = from Week 48 +1 day till cut-off or discontinuation; Control group not switched exposure = from Week 48 +1 day till cut-off, discontinuation or unblinding visit; Control group on D/C/F/TAF exposure = from unblinding visit +1 day till cut-off or discontinuation.

[a] 3/339 subjects in the D/C/F/TAF group discontinued the study in the open-label treatment phase and had no further visits beyond Week 48.

[b] 2/335 subjects in the control group discontinued the study in the open-label treatment phase and had no further visits beyond Week 48.

[c] 30/333 subjects in the control group who continued the study had switched to D/C/F/TAF by the time of the cut-off, and are included in both control columns (ie, prior to and after switching to D/C/F/TAF).

[TABLE26.RTF] [/SAS/3027/TMC114FD2HTX3001/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/TABLE26.SAS]
18JUL2017, 13:30

5.1.2. Adverse Events

No deaths were reported in the study since the Week-48 analysis, and no subjects discontinued study drugs due to AEs (Table 33). Newly emerging SAEs were reported for 3.6% of subjects in the D/C/F/TAF group (continued use) and for 5.1% of subjects in the control group (not yet switched to D/C/F/TAF) (considered related to study drugs for 0.3% vs 0%; Table 34). Newly emerging AEOIs were reported for 5.4% vs 4.5% of subjects (considered related to study drugs for 2.1% vs 1.2%).

No AEs were reported for the 30 switch subjects in the brief period between their switch and the cut-off date of 1 June 2017 (Mod5.3.5.1/TMC114FD2HTX3001/SCS-Statistical Output/Tab30).

Table 33: Summary of Main Safety Data - TMC114FD2HTX3001; ITT

	From W48 until 1 June 2017	
	D/C/F/TAF	CONTROL
	D/C/F/TAF group continued use from W48+1d (N=336)	Control group not yet switched to D/C/F/TAF from W48+1d (N=333)[a]
Subjects Experiencing		
Death	0	0
Any AE Leading to Premature Study Drug Discontinuation	0	0
Any SAE	12 (3.6%)	17 (5.1%)
Any Grade 3/4 AE	13 (3.9%)	12 (3.6%)
Any AEOI	18 (5.4%)	15 (4.5%)
Any AE	133 (39.6%)	145 (43.5%)

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects; SAE = serious adverse event.

[a] Note that for the 30 control subjects who switched to D/C/F/TAF, only data prior to the switch are presented in this table as no AEs were reported during the brief period following their switch.

[TABLE27.RTF] [/SAS/3027/TMC114FD2HTX3001/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/TABLE27.SAS]
18JUL2017, 13:30

Table 34: Summary of Adverse Events at Least Possibly Related to Study Drug - TMC114FD2HTX3001; ITT

	From W48 until 1 June 2017	
	D/C/F/TAF	CONTROL
	D/C/F/TAF group continued use from W48+1d (N=336)	Control group not yet switched to D/C/F/TAF from W48+1d (N=333)[a]
Subjects Experiencing		
Death	0	0
Any AE Leading to Premature Study Drug Discontinuation	0	0
Any SAE	1 (0.3%)	0
Any Grade 3/4 AE	2 (0.6%)	0
Any AEOI	7 (2.1%)	4 (1.2%)
Any AE	10 (3.0%)	9 (2.7%)

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects; SAE = serious adverse event.

[a] Note that for the 30 control subjects who switched to D/C/F/TAF, only data prior to the switch are presented in this table as no AEs were reported during the brief period following their switch.

[TABLE28.RTF] [/SAS/3027/TMC114FD2HTX3001/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/TABLE28.SAS]
18JUL2017, 13:30

For details on the individual cases, refer to Table 39 (D/C/F/TAF group continued use), and Table 40 (control group not yet on D/C/F/TAF) in Appendix 6.

Narratives (CIOMS I forms) for subjects experiencing newly emerging SAEs are provided in Mod5.3.5.1/TMC114FD2HTX3001-CIOMS I Report, and can be accessed individually through the subject numbers in Table 39 and Table 40, and in the text below.

In 8 subjects in the D/C/F/TAF group (continued use) and 4 subjects in the control group (not yet switched to D/C/F/TAF), the significant AEs (either serious, leading to discontinuation, or consisting of AEOIs) were assessed as at least possibly related to the study drug. The majority of these AEs in the D/C/F/TAF group and all in the control group were consistent with the known safety profile of the study treatment (ie, lipid increases, osteopenia, and proteinuria).

Adverse events that were considered related to the study drug, but that were not consistent with the known safety profile of the study drug were reported in 2 subjects in the D/C/F/TAF group:

- Subject [redacted] with no medical history was reported with grade 2 SAEs of back pain and hematuria. Both events were assessed by the investigator as possibly related to the formation of DRV crystals in the urine (no analyses available), and resolved within 8 days with intravenous (IV) hydration and symptomatic treatment. The study medication was not interrupted.
- Subject [redacted] with no medical history was reported with the nonserious grade 2 AE of cholestasis (verbatim: cholestasis secondary to acute viral hepatitis [hepatitis A virus: HAV]). The AE of cholestasis was assessed as possibly related to study drug and resolved within 6 days. The study drug was interrupted and the subject was discontinued from the study for the SAE of acute viral hepatitis (HAV), which was assessed as not related to study drug.

Between Week 48 and the cut-off date of 1 June 2017, 1 pregnancy and 2 pregnancies of partners were reported in this study:

- Subject [redacted] in the D/C/F/TAF group had a positive pregnancy test after the Week-48 visit. An AE of normal pregnancy has been noted for this subject. Abortion was induced a week after confirmation of the pregnancy and the subject is continuing in the study.
- Subject [redacted] in the D/C/F/TAF group was reported with a pregnancy of partner, with an expected delivery date of [redacted]. An ultrasound was performed on [redacted], showing that the clinical condition of the fetus was normal and the status of the pregnancy was continuing. All laboratory tests were normal.
- Subject [redacted] in the control group was reported with a pregnancy of partner, for which the outcome was unspecified.

For a listing of all AEs reported between Week 48 and the cut-off date of 1 June 2017, refer to Mod5.3.5.1/TMC114FD2HTX3001/SCS-Statistical Output/Tab29, Tab30, and Tab31.

5.2. Open-label Phase 3 Study TMC114IFD3013 in HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects

In Study TMC114IFD3013, subjects from the D/C/F/TAF group entered the extension phase once they had completed their Week-48 visit. In addition, subjects in the control group started taking the D/C/F/TAF tablet in the extension phase after attending a switch visit at Week 52.

5.2.1. Extent of Exposure

At Week 48, 729 subjects in the D/C/F/TAF group and 358 subjects in the control group were ongoing. Of these, 6 subjects in the control group discontinued the study before their switch visit: 4 subjects discontinued due to practical reasons and 2 subjects were lost to follow-up after the projected Week-48 visit (data on file and Mod5.3.5.1/TMC114IFD3013/SCS-Statistical Output/Att-Listing-Noswitch).

The extension phase of the study included 729 subjects in the D/C/F/TAF group and 352 subjects in the control group. These constitute the safety data set presented in this section, which covers the period after the Week-48 visit until 1 June 2017.

In the D/C/F/TAF group, the mean (SD) exposure to D/C/F/TAF was 39.2 (12.8) weeks since the Week-48 visit (Table 35). In the control group, the mean (SD) exposure to D/C/F/TAF was 35.4 (12.9) weeks.

Table 35: Extent of Exposure - TMC114IFD3013; ITT

	From W48 until 1 June 2017	
	D/C/F/TAF	
	D/C/F/TAF group continued use from W48+1d (N=729)	Control group switched to D/C/F/TAF from W52 (N=352)[a]
Subject-years of exposure	547.8	238.5
Exposure (Weeks)		
Mean (SD)	39.21 (12.777)	35.35 (12.940)
Median (Q1;Q3)	40.14 (28.43; 50.43)	36.36 (24.57; 46.57)
(Min; Max)	(12.0; 62.0)	(8.3; 57.4)

D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects; SD = standard deviation.

[a] 6/358 subjects in the control group discontinued the study before their switch visit.

[TABLE33.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/TABLE33.SAS] 07JUL2017, 15:11

5.2.2. Adverse Events

No deaths were reported in the study since the Week-48 analysis (Table 36 and Table 43). In the extension phase of the study, 0.3% of subjects in the D/C/F/TAF group (continued use) and 0.9% of subjects in the control group (switched to D/C/F/TAF) discontinued study drug due to AEs. Newly emerging SAEs were reported for 3.2% and 4.5% of subjects (considered related to D/C/F/TAF for 0% and 0.3%; Table 37). Newly emerging AEOIs were reported for 6.0% and 6.8% of subjects (considered related to D/C/F/TAF for 0.7% and 1.4%). Prior to switch, ie, when control subjects were still on treatment with bPI+F/TDF, AEOIs were reported for 2 subjects. None were assessed as related to study drug (Table 43).

Table 36: Summary of Main Safety Data - TMC114IFD3013; ITT

	From W48 until 1 June 2017	
	D/C/F/TAF	
	D/C/F/TAF group continued use from W48+1d (N=729)	Control group switched to D/C/F/TAF from W52 (N=352)[a]
Subjects Experiencing		
Death	0	0
Any AE Leading to Premature Study Drug Discontinuation	2 (0.3%)	3 (0.9%)
Any SAE	23 (3.2%)	16 (4.5%)
Any Grade 3/4 AE	36 (4.9%)	21 (6.0%)
Any AEOI	44 (6.0%)	24 (6.8%)
Any AE	411 (56.4%)	197 (56.0%)

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects; SAE = serious adverse event.

[a] For control group switched to D/C/F/TAF from W52, AEs that occurred before W52 are excluded. For significant AEs that were reported in these subjects before switching to D/C/F/TAF, refer to Table 43.

[TABLE34.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/TABLE34.SAS] 07JUL2017, 15:11

Table 37: Summary of Adverse Events at Least Possibly Related to Study Drug - TMC114IFD3013; ITT

	From W48 until 1 June 2017	
	D/C/F/TAF	
	D/C/F/TAF group continued use from W48+1d (N=729)	Control group switched to D/C/F/TAF from W52 (N=352)[a]
Subjects Experiencing		
Death	0	0
Any AE Leading to Premature Study Drug Discontinuation	1 (0.1%)	3 (0.9%)
Any SAE	0	1 (0.3%)
Any Grade 3/4 AE	2 (0.3%)	3 (0.9%)
Any AEOI	5 (0.7%)	5 (1.4%)
Any AE	18 (2.5%)	23 (6.5%)

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects; SAE = serious adverse event.

[a] For control group switched to D/C/F/TAF from W52, AEs that occurred before W52 are excluded. For significant AEs that were reported in these subjects before switching to D/C/F/TAF, refer to Table 43.

[TABLE35.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/TABLE35.SAS] 07JUL2017, 15:12

For details on the individual cases, refer to Table 41 (D/C/F/TAF group continued use), Table 42 (control group on D/C/F/TAF after switch visit), and Table 43 (control group on bPI+F/TDF prior to switch visit) in Appendix 7.

Narratives (CIOMS I forms) for subjects experiencing newly emerging SAEs are provided in Mod5.3.5.1/TMC114IFD3013-CIOMS I Report, and can be accessed individually through the subject numbers in Table 41 and Table 42, and in the text below.

In 6 subjects in the D/C/F/TAF group (continued use) and 8 subjects in the control group (switched to D/C/F/TAF), the significant AEs (either serious, leading to discontinuation, or consisting of AEOIs) were assessed as at least possibly related to the study drug. The majority of

these AEs were consistent with the known safety profile of the study treatment (ie, lipid increases, rash, diarrhea, vomiting, osteopenia, and proteinuria).

Adverse events that were not consistent with the known safety profile of the study drug, but that were considered related to the study drug or for which the study drug was discontinued, were reported in 4 subjects in the D/C/F/TAF group (continued use) and 2 subjects in the control group (switched to D/C/F/TAF):

D/C/F/TAF group (continued use):

- Subject [redacted] with no relevant renal medical history was reported with a grade 3 SAE of acute kidney injury. The subject had been diagnosed with Hodgkin lymphoma for which she was treated with chemotherapy. She was hospitalized for right lower lobe pneumonia and experienced acute kidney injury after IV contrast administration during a chest computed tomography (CT) scan. The subject was evaluated by a nephrologist and the event was considered to be secondary to IV contrast. The investigator decided to discontinue the subject from the study as evaluation of study drug was not possible due to side effects from the chemotherapy.
- Subject [redacted] with a medical history of hypertension, hematuria, impaired fasting glucose, and former use of [redacted] was reported with a grade 3 SAE of acute renal failure. The subject was hospitalized because of street drug overdose. Additional AEs included rhabdomyolysis and delirium. All AEs were assessed as not related to the study drug and resolved within 3 days. Study drug was temporarily interrupted and the subject resumed normal dose after 10 days.
- Subject [redacted] with no relevant medical history was reported with a nonserious grade 4 CPK increase. The CPK value returned to normal within 8 days. No concurrent ALT/AST increases were noted. Study drug was not interrupted. This report did not relate to coronary artery disease. The increase was possibly due to excessive physical exercise, but relatedness to D/C/F/TAF could not be excluded.
- Subject [redacted] with a medical history of hypertension and dyslipidemia was reported with a nonserious grade 1 AE of arteriosclerosis coronary artery (verbatim: slight coronary sclerosis). The event was assessed as possibly related to study drug and to HIV. Treatment with atorvastatin once daily was started. Study drug was not interrupted and the subject continued in the study.

Control group (switched to D/C/F/TAF):

- Subject [redacted] with a medical history of untreated hypertension was reported with a nonserious grade 2 AE of vertigo. The event was assessed as possibly related to study drug. Blood pressure at the time of reporting was 147/97 mmHg. The event resolved the next day. Study drug was withdrawn and subject was discontinued from the study because of the AE.
- Subject [redacted] with a medical history of hypertension and hypercholesterolemia was reported with a nonserious grade 1 AE of jaundice (verbatim: icterus). The event resolved within 2 days. No concurrent AEs were reported. All liver parameters (including

bilirubin) had been normal at all measurements during the study. Study drug was not interrupted and the subject continued in the study.

No pregnancies were reported between Week 48 and the cut-off date of 1 June 2017 in this study.

Note that an SAE of overdose was reported between Week 72 and Week 84 for Subject [redacted], but that this case was reassessed as nonserious by the investigator and therefore is not listed in Table 42 (control group on D/C/F/TAF after switch visit). For details on this case, refer to the CIOMS I form for Subject [redacted].

For a listing of all AEs reported between Week 48 and the cut-off date of 1 June 2017, refer to Mod5.3.5.1/TMC114IFD3013/SCS-Statistical Output/Tab36, Tab37a, and Tab37b.

6. SAFETY IN SPECIAL GROUPS AND SITUATIONS

6.1. Intrinsic Factors

6.1.1. Pediatric and Adolescent Subjects

No clinical studies were performed with the D/C/F/TAF FDC tablet in HIV-1 infected pediatric or adolescent subjects. Available data for the components of D/C/F/TAF indicate that the overall safety profile in **adolescent subjects aged 12 to <18 years** and weighing at least 40 kg was similar to that observed in the adult population.

The safety assessment of DRV once daily in adolescent subjects is based on the 48-week analysis of safety data from the Phase 2 Study TMC114-C230 in 12 HIV-1 infected, ART-naïve, adolescent subjects aged from 12 to <18 years and weighing at least 40 kg (Section 3.2.1).

The safety of COBI and F/TAF was evaluated through 48 weeks in a single-arm clinical study (Study GS-US-292-0106) in which HIV-1 infected, treatment-naïve, adolescent subjects aged 12 to <18 years received EVG, COBI, FTC and TAF as an FDC tablet (Section 3.2.2).

Furthermore, recent results from an ongoing Phase 2/3 switch study (GS-US-216-0128) in 22 HIV-1 infected, virologically suppressed adolescents (aged ≥12 to <18 years) who received DRV plus COBI (150 mg once daily; n=8) or ATV plus COBI (150 mg once daily; n=14) in combination with 2 NRTIs (TDF-based regimen: n=10) support the use of COBI 150 mg as a pharmaco-enhancer of DRV or ATV in adolescents. In this study in which subjects switched from rtv to COBI, COBI was well tolerated, with no discontinuations due to AEs and no study drug-related SAEs or grade 3/4 AEs. A small decline in $eGFR_{cr}$ (Schwartz formula) was observed as expected with the use of COBI, which inhibits tubular secretion of creatinine.[12]

Overall, the combined results from these studies suggest that there are no safety concerns for the use of D/C/F/TAF in HIV-1 infected adolescent subjects.

No clinical studies have been performed with the D/C/F/TAF FDC in **pediatric subjects aged 3 to <12 years** or weighing less than 40 kg.

6.1.2. Elderly Subjects

Limited information is available on the use of the D/C/F/TAF FDC, DRV or COBI in subjects aged above 65 years. Clinical studies with the D/C/F/TAF FDC included a total of 35 subjects >65 years of whom 26 subjects received the D/C/F/TAF FDC:

- 1 subject (on control) in Study TMC114FD2HTX3001.
- 33 subjects (25 on D/C/F/TAF and 8 on control) in Study TMC114IFD3013.
- 1 subject (on D/C/F/TAF) in Study GS-US-299-0102.

In the Phase 3 Study TMC114IFD3013, a subgroup analysis showed no clinically relevant differences in safety profiles between elderly subjects (aged >65 years) and those between

18 and 65 years of age (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE03a_EXT). Although no safety issues are expected with D/C/F/TAF in elderly subjects, the D/C/F/TAF FDC is to be used with caution in subjects >65 years of age, due to the greater frequency of decreased hepatic function (see Section 6.1.4), concomitant disease(s), or polypharmacy.

6.1.3. Subjects With Renal Impairment

Available data from the ongoing Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 provide information on 300 subjects with $eGFR_{CG}$ 70 to <90 mL/min (191 on D/C/F/TAF), 86 subjects with $eGFR_{CG}$ 50 to <70 mL/min (55 on D/C/F/TAF), and 5 subjects with $eGFR_{CG}$ <50 mL/min (3 on D/C/F/TAF). The data do not suggest any safety concerns in these subjects (see Section 3.1.1.1.3 and Section 3.1.1.2.3).

In addition, available data for the components of D/C/F/TAF indicate that the overall safety profile in subjects with mild to moderate renal impairment was similar to that observed in the adult population with normal renal function.

The safety of DRV/COBI has been evaluated in Phase 3 Study GS-US-236-0118 in HIV-1 infected subjects with baseline $eGFR_{CG}$ between 50 and <90 mL/min (see Section 3.3.2). In this study, 73 HIV-1 infected, ART-experienced subjects with mild to moderate renal impairment switched from ATV/rtv (300/100 mg) or DRV/rtv (800/100 mg) treatment with 2 NRTIs to ATV/COBI (300/150 mg) or DRV/COBI (800/150 mg) once-daily treatment. This study showed a renal safety profile of DRV in combination with COBI and the F/TDF FDC similar to the renal safety profile of the E/C/F/TDF FDC.

The safety of E/C/F/TAF has been assessed in 248 HIV-1 infected subjects with baseline $eGFR_{CG}$ 30 to <70 mL/min in Phase 3 Study GS-US-292-0112 (see Section 3.3.2). Results from this study showed that the use of the E/C/F/TAF FDC is safe in these subjects, regardless of their eGFR level at baseline (<50 mL/min or ≥50 mL/min) and regardless of their prior treatment regimen (ie, TDF-based or not). Moreover, the renal parameters improved in subjects who were on a prior TDF-based regimen before switching to E/C/F/TAF.

The combined results from these studies suggest that there are no safety concerns for the use of D/C/F/TAF in HIV-1 infected subjects with $eGFR_{CG}$ ≥30 mL/min.

6.1.4. Subjects With Hepatic Impairment

No clinical studies have been performed with the D/C/F/TAF FDC in subjects with hepatic impairment. Also, no subjects with clinically significant functional hepatic impairment (ie, Child-Pugh class A, B or C) have been included in the 2 Phase 3 studies with the D/C/F/TAF FDC, because this was a protocol exclusion criterion in both studies.

Limited data are available from Phase 1 studies with DRV, COBI, and TAF in HIV-1 negative adult subjects with **mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment**. No clinically significant safety findings were identified in these studies, and no dose adjustment is required in this patient population.[4,15,16,18] No studies have been performed

with the components of the D/C/F/TAF FDC in subjects with **severe hepatic impairment (Child-Pugh class C)**.

6.1.5. Subjects Co-infected With HIV-1 and Hepatitis B/C, and Risk of Hepatitis B Flare-up

Limited information is available on the use of the D/C/F/TAF FDC in subjects co-infected with HIV-1 and HBV and/or HCV as these subjects were excluded from the Phase 3 and 2 studies with the D/C/F/TAF FDC. However, new onset (or flared) acute viral hepatitis or drug-induced liver injury was monitored in these studies. The review of the data did not suggest an increased hepatotoxicity in subjects developing hepatitis B or C co-infection while on D/C/F/TAF treatment. See Section 3.1.1.1.3 and 3.1.1.2.3 for more details. The risk of hepatitis B flare-up following treatment discontinuation could not be assessed in these studies.

Hepatotoxicity in Subjects Co-infected With Hepatitis B or C

There is limited experience with DRV (boosted with rtv) in subjects co-infected with HIV-1 and HBV and/or HCV, showing that co-infected subjects were more likely to have baseline and treatment-emergent hepatic transaminase elevations than those without chronic viral hepatitis.[15,16]

Subjects co-infected with HIV and HBV and/or HCV were excluded from the Phase 3 and 2 studies, but 1 specific F/TAF study (Study GS-US-292-1249) investigated the efficacy and safety of E/C/F/TAF in 77 HIV-1/HBV co-infected adults.[6] The results of this study showed that the E/C/F/TAF FDC was well tolerated in HIV-1/HBV co-infected adults. No subjects had an on-treatment ALT flare, and assessments of other liver-related parameters did not reveal any concerns for increased hepatic risk.

One can reasonably assume that the safety profile will be similar for the D/C/F/TAF FDC.

Risk of Hepatitis B Flare-up After Discontinuation of F/TAF

Tenofovir alafenamide is a HBV nucleoside analog reverse transcriptase inhibitor and is indicated for the treatment of chronic HBV infection in adults with compensated liver disease.[19] Discontinuation of D/C/F/TAF therapy in subjects co-infected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC or TAF components of the D/C/F/TAF FDC.[4,19] Subjects co-infected with HIV-1 and HBV who discontinue the D/C/F/TAF FDC should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. The D/C/F/TAF FDC should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), lamivudine, or adefovir dipivoxil used for the treatment of HBV infection.

6.1.6. Lactic Acidosis/Severe Hepatomegaly With Steatosis

F/TAF

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC, a component of F/TAF, and TDF, another prodrug of TFV, alone or in combination with other ARVs. Treatment with F/TAF should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).[4]

D/C/F/TAF

There were no subjects reported with lactic acidosis or severe hepatomegaly with steatosis in the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 (refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.11.5 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.11.5.

6.1.7. Hemophilia/Bleeding Events

No events related to hemophilia were reported in the ongoing Phase 3 study TMC114FD2HTX3001 (refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.11.6). In the Phase 3 Study TMC114IFD3013, there were 2 subjects with hemophilia, both in the D/C/F/TAF group. Neither subject experienced a bleeding event (refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.3.11.6).

6.2. Extrinsic Factors

Subgroup analyses of the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 showed no clinically relevant differences in safety for the demographic factors ethnicity (Hispanic or Latino vs not Hispanic or Latino) and region (Europe vs North America) (Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE03a_EXT).

In Study TMC114IFD3013, analysis of the bPI used at screening showed an effect of this factor on the incidence of rash AEOIs (Section 3.1.1.2.3). In the D/C/F/TAF group, rash AEOIs were reported more frequently for subjects switching from a screening regimen not containing DRV as bPI (ie, in 5.3% of subjects who switched to DRV vs 4.3% of subjects already on DRV) or not containing COBI as booster (ie, in 4.9% of subjects who switched to COBI as booster vs 2.9% of subjects already on COBI). None of the rash events were of clinical concern as none led to study drug discontinuation, all were transient and nonserious, and all drug-related rash events were grade 1.

6.3. Drug 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.[4,15]

For an overview of the theoretic drug interactions and proposed contraindications with the D/C/F/TAF FDC, refer to the Summary of Clinical Pharmacology Studies in Mod2.7.2/ClinPharm/Sec3.4.2.

6.4. Pregnancy, Lactation and Fertility

6.4.1. Pregnancy

No adequate and well-controlled studies of the D/C/F/TAF FDC, or its components, have been conducted in pregnant women. Pregnancy has been listed as an exclusion criterion for all D/C/F/TAF FDC clinical studies conducted to date. Female subjects of childbearing potential were required to use effective contraceptive methods.

No pregnancies were reported in the Phase 1 Studies TMC114FD2HTX1001, TMC114FD2HTX1002, TMC114FD2HTX1004, or GS-US-299-0101, or in the Phase 2 Study GS-US-299-0102 with the D/C/F/TAF FDC.

In Study TMC114FD2HTX3001, 1 pregnancy in a study participant and 2 pregnancies of partners were reported after the Week-48 analysis cut-off date. The pregnancy in a study participant led to an induced abortion, and for the 2 pregnancies of partners, the outcome is unknown (for details, refer to Section 5.1.2).

In Study TMC114IFD3013, 1 subject in the control group had an ectopic pregnancy leading to a surgical intervention during the 48-week treatment phase (for details, refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.2.2.4).

Pregnancy data related to the D/C/F/TAF FDC are being submitted to the Antiretroviral Pregnancy Registry (APR), a voluntary prospective, exposure-registration, observational study.[1] Darunavir, COBI, FTC, and TAF use during pregnancy have been evaluated in a limited number of women as reported to the APR (Table 38).

Table 38: Summary of Antiretroviral Treatments by Trimester of Earliest Exposure - Prospective Registry Cases with Follow-up Data Closed Through 31 July 2016

	First Trimester	Second Trimester	Third Trimester	Overall
Pregnancies enrolled	9,210	6,797	2,331	18,341
DRV	428	146	80	659
COBI	90	23	8	122
FTC	2,571	782	297	3,654
TAF	1	1	1	3

Source: APR interim report 1 January 1989 through 31 July 2016.[1]

For DRV, sufficient numbers of first trimester exposures have been monitored to detect at least a 2-fold increase in risk of overall birth defects. No such increases have been detected to date. For FTC, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. At the time of the interim report there were insufficient data to make similar comparisons for other drugs or specific subgroups of defects.[1]

DRV

Based on prospective reports to the APR through July 2016 of 615 live births following exposure to DRV-containing regimens during pregnancy (including 385 exposed in the first trimester and 230 exposed in the second/third trimester), there was no difference in the rate of overall birth defects for DRV compared with the background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.6% (95% CI: 1.2% to 4.7%) with first trimester exposure to DRV containing-regimens and 1.7% (95% CI: 0.5% to 4.4%) with second/third trimester exposure to DRV-containing regimens.

In addition, data on the use of DRV/rtv in pregnant women are also available from the Phase 3b Study TMC114HIV3015. This multiple-arm, open-label study assessed the PK of DRV/rtv (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen in 34 HIV-1 infected pregnant women (n=17 in each cohort). Data from this study indicated that total DRV but not unbound DRV exposure was decreased during pregnancy. Furthermore, observed plasma concentrations of DRV were adequate to suppress HIV and to prevent mother-to-child transmission. There were no new clinically relevant safety findings compared with the known safety profile of DRV/rtv in HIV-1 infected adults.

COBI

Based on prospective reports to the APR through July 2016 of 116 exposures to COBI-containing regimens during pregnancy resulting in live births (including 83 exposed in the first trimester and 33 in the second/third trimester), there has been one report of a birth defect after first trimester exposure.

FTC

Based on prospective reports to the APR through July 2016 of 3,406 exposures to FTC-containing regimens during pregnancy (including 2,326 exposed in the first trimester and 1,080 exposed in the second/third trimester), there was no difference between FTC and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.3% (95% CI: 1.7% to 3.0%) with first trimester exposure to FTC-containing regimens and 2.0% (95% CI: 1.3% to 3.1%) with the second/third trimester exposure to FTC-containing regimens.

TAF

Based on prospective reports to the APR through July 2016 of 4 exposures to TAF-containing regimens during pregnancy resulting in live births (including 1 exposed in the first trimester and 3 in the second/third trimester), there have been no birth defects reported.

In addition, a non-company sponsored, investigator-initiated study on Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women recruited from different HIV treatment centers in Europe (PANNA) is currently ongoing. The primary objective of this study (non-randomized, open-label, parallel-group, multi-center) is to describe the PK of ARV agents during pregnancy for which no or only limited PK data during pregnancy are available. Pharmacokinetic data will be collected in the 3rd trimester of pregnant HIV-infected women and at 4 to 6 weeks postpartum. The secondary objective is to describe the safety of the ARV agents during pregnancy and the efficacy in terms of viral load response of the mother and prevention of mother-to-child transmission. The PANNA study will include pregnant HIV-infected women treated with DRV, COBI, and FTC.[17]

6.4.2. Lactation

Breast-feeding has been an exclusion criterion for all D/C/F/TAF FDC clinical trials conducted to date. It is not known whether DRV, COBI, or TAF are excreted in human milk. Emtricitabine is excreted in human milk (see further details below). Moreover, there is insufficient information on the effects of COBI, FTC, and TFV in newborns/infants, and DRV should not be used in children <3 years.

F/TAF

Samples of breast milk obtained from 5 HIV-infected mothers given F/TDF show that TFV is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the TFV 50% inhibitory concentration [IC_{50}]).[2] The same samples show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC_{50} but 3 to 12 times lower than the minimum plasma concentration (C_{min}) achieved from oral administration of FTC. Breastfed infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown. Tenofovir-associated risks, including the risk of viral resistance to TFV, in infants breastfed by mothers being treated with TAF are unknown.

6.4.3. Fertility

No human data on the effect of DRV, COBI, FTC or TAF on fertility are available.

6.5. Overdose

Increases in exposure when administering the D/C/F/TAF FDC with rtv or COBI are anticipated to be minimal as the inhibition of cytochrome P450 3A is already near maximal for the D/C/F/TAF FDC (Mod2.7.2/ClinPharm/Sec3.4.2.2).

There is no specific antidote for overdose with the D/C/F/TAF FDC. Treatment of overdose with the D/C/F/TAF FDC consists of general supportive measures.

Limited clinical experience is available with the components of the D/C/F/TAF FDC at doses higher than the therapeutic doses:

DRV/COBI

Human experience of acute overdose with DRV is limited. Single doses up to 3,200 mg of the oral solution of DRV alone and up to 1,600 mg of the tablet formulation of DRV in combination with rtv have been administered to healthy volunteers without untoward symptomatic effects (see NDA021976/Mod5.3.3.1/TMC114-C101-CSR/Sec4 and Section 3.3.1).

No particular safety issues have been identified following administration of supratherapeutic doses up to 400 mg single dose of COBI (see Section 3.3.1).

Since DRV and COBI are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.[15]

F/TAF

Limited clinical experience is available at doses higher than the recommended dose of FTC in F/TAF. In 1 clinical pharmacology study, single doses of FTC 1,200 mg (6 times the FTC dose in F/TAF) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.[4]

Limited clinical experience is available at doses higher than the recommended dose of TAF. In a thorough QT study in 48 healthy subjects, TAF administered at a supratherapeutic dose approximately 5 times the recommended therapeutic dose was well tolerated, did not affect the QT/QTc interval and did not prolong the PR interval (see Section 3.3.1).

Up to 30% of the FTC dose may be removed by hemodialysis. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether FTC or TFV may be removed by peritoneal dialysis.[4]

D/C/F/TAF

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.

In Study TMC114FD2HTX3001, none of the subjects experienced a (possible) overdose with the study drug (see Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.2.2.5).

In Study TMC114IFD3013, a D/C/F/TAF overdose was reported for 3 subjects:

- One subject in the D/C/F/TAF group presented symptoms of nausea and vomiting. No information is available on the dose taken for this subject.

- No symptoms were reported for 1 subject in the D/C/F/TAF group who took 2 tablets per day for 2 weeks (refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec6.2.2.5).
- No symptoms were reported for 1 subject in the control group who switched to D/C/F/TAF, but no information is available on the dose taken (refer to Section 5.2.2).

6.6. Drug Abuse

No systematic examination of the abuse potential of the D/C/F/TAF FDC was performed in the preclinical and clinical studies included in this submission. However, the potential for illegal use is unlikely given that the intracellular target of the D/C/F/TAF FDC is virus-specific.

6.7. Withdrawal and Rebound

D/C/F/TAF

Clinical studies or systematic analyses to evaluate the potential withdrawal and rebound effects of the D/C/F/TAF FDC have not been conducted. Examination of the safety parameters during washout periods and during follow-up periods after last intake of study drug showed that the overall safety/tolerability profile of the D/C/F/TAF FDC (or of combined treatment with the individual components) was not negatively impacted by interruption or discontinuation of treatment.

F/TAF

For the risk of hepatitis B flare-up after discontinuation of F/TAF, see Section 6.1.5.

6.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been performed on the effects of the D/C/F/TAF FDC on the ability to drive or use machines.

7. POSTMARKETING DATA

There is no postauthorization experience with the D/C/F/TAF FDC, as this FDC is not marketed yet in any country.

8. SUMMARY AND CONCLUSIONS

8.1. Summary of Safety Data in Adults

The safety profile of D/C/F/TAF has been characterized in 2 pivotal Phase 3 studies: Study TMC114FD2HTX3001 in ART-naïve subjects (N=362 on D/C/F/TAF, N=363 in control group on DRV/COBI+F/TDF) and Study TMC114IFD3013 in ART-experienced, virologically suppressed subjects (N=763 on D/C/F/TAF, N=378 in control group on bPI+F/TDF). Study TMC114FD2HTX3001 provides the clearest safety profile characterization of D/C/F/TAF because of the double-blind design, the assessment in an ART-naïve population, and the substitution of TDF by TAF as the only difference between the treatment groups. Study TMC114IFD3013 included subjects treated for at least 6 months with a bPI+F/TDF-based regimen prior to randomization, thus selecting a subject population tolerating this regimen. The switch design of this study allowed assessment of potential improvement of renal and bone toxicity in subjects switching from their prior regimen to the D/C/F/TAF FDC.

The Week-48 analyses of these Phase 3 studies did not indicate a safety concern. The AE and ADR profiles after once-daily treatment with the D/C/F/TAF 800/150/200/10-mg FDC were consistent with those expected in the subject population and the known safety profiles of the individual components of the D/C/F/TAF FDC, and established the favorable renal and bone profile of D/C/F/TAF compared to an F/TDF-based regimen.

Skin Reactions

In Study TMC114FD2HTX3001, at Week 48 with D/C/F/TAF (Section 3.1.1.1.3)

- Rash AEOIs were reported in 13.0% of subjects on D/C/F/TAF and led to discontinuation of treatment in 1.7% of subjects.
  - Control group: 10.7% of subjects had a rash AEOI, and 1.4% discontinued treatment.
- There were no reports of severe skin reactions with D/C/F/TAF.
  - Control group: 3 (0.8%) subjects with severe skin reactions (Stevens-Johnson syndrome [n=1], toxicodermia [n=2]); all led to treatment discontinuation.

In Study TMC114IFD3013, at Week 48 with D/C/F/TAF (Section 3.1.1.2.3)

- Rash AEOIs were reported more frequently in the D/C/F/TAF group compared to the control group (4.6% vs 2.1%).
  - This was mainly due to the high incidence of rash in subjects who switched from another PI to DRV or from rtv to COBI at baseline.
  - None of the rash events were of clinical concern as none led to study drug discontinuation, all were transient and nonserious, and all drug-related rash events were grade 1.
- There were no reports of severe skin reactions in this study.

Effect of TAF vs TDF on Lipid Parameters

Tenofovir has known lipid-lowering effects. Administration of TAF as compared to TDF results in a lower plasma concentration of TFV. Consistent herewith, subjects on a TAF-based regimen, compared to a TDF-based regimen, exhibited more substantial increases in lipid parameters. For the D/C/F/TAF group (see Section 3.1.1.1.3 and Section 3.1.1.2.3):

- Larger increases in median fasting lipid parameters.
- Higher percentages of subjects with a worsening in NCEP category vs baseline. These changes had limited clinical impact:
  - Abnormalities were not reflected in clinically relevant differences between treatment groups in mean changes in the TC/HDL ratio vs baseline.
  - A limited number of subjects (6 [1.7%] in Study TMC114FD2HTX3001 and 19 [2.5%] in Study TMC114IFD3013) were newly started on a lipid-lowering treatment.
    - In the control group this occurred respectively in 2 (0.6%) and 7 (1.9%) subjects.

Effect of TAF vs TDF on Renal Parameters

Tenofovir disoproxil fumarate is known to be associated with nephrotoxicity, including elevated risks of reduced kidney function, proteinuria, and proximal tubular dysfunction in some subjects. Tenofovir alafenamide results in lower circulating levels of TFV relative to TDF. Subjects on a TAF-based regimen, compared to a TDF-based regimen, are expected to show a better renal safety profile, for instance in markers of the glomerular function and the renal proximal tubular function. The positive effects on eGFR, when based on serum creatinine, can be masked by the inhibitory effects of COBI on the renal tubular secretion of creatinine. Estimated GFR based on serum cystatin C is therefore a better parameter to assess the 'actual' glomerular function. In the Phase 3 studies, favorable effects of TAF on the renal safety were observed as follows:

In Study TMC114FD2HTX3001, at Week 48 with D/C/F/TAF (Section 3.1.1.1.3)

- Serum creatinine increased and $eGFR_{cr}$ decreased (ie, COBI effect), but less so compared to the control group (TAF vs TDF effect).
- $eGFR_{cyst}$ increased by a greater degree than in the control group (TAF vs TDF effect).
- No cases of clinical PRT (including Fanconi syndrome) or study-defined potential subclinical PRT were observed.
  - Control group: 2 cases of study-defined potential subclinical PRT were observed.
- Proteinuria improved significantly (urine protein to creatinine ratio, urine albumin to creatinine ratio, retinol-binding protein, and beta-2-microglobulin).
- No renal AEs led to treatment discontinuations.
  - Control group: 1 subject discontinued due to an increased beta-2 microglobulinuria.

In Study TMC114IFD3013, at Week 48 with D/C/F/TAF (Section 3.1.1.2.3)

- Although the differences between treatement groups were not statistically significant, larger increases in serum creatinine and larger decreases in $eGFR_{cr}$ were observed in subjects switching to D/C/F/TAF.
  - These minor but consistent COBI effects on serum creatinine were more apparent in the subgroup of subjects switching from a DRV/rtv+F/TDF-based regimen to D/C/F/TAF.
- GFR_{cyst} was stable in the D/C/F/TAF group compared to the control group where a modest decrease was observed.
  - These minor but consistently favorable (ie, absence of negative) effects on the $eGFR_{cyst}$ were more apparent in the subgroup of subjects switching from a DRV/COBI+F/TDF-based regimen to D/C/F/TAF.
- No cases of clinical PRT (including Fanconi syndrome) or study-defined potential subclinical PRT were reported.
  - Control group: 1 case of renal tubular disorder and 2 cases of study-defined potential subclinical PRT were reported.
- Proteinuria improved significantly (urine protein to creatinine ratio, urine albumin to creatinine ratio, retinol-binding protein, and beta-2-microglobulin).
- In the D/C/F/TAF group, a renal AE led to study drug discontinuation in 0.1% of subjects (chronic kidney disease).
  - Control group: 0.5% of subjects discontinued due to a renal AE (renal tubular disorder and toxic nephropathy).

Effect of TAF vs TDF on BMD

Tenofovir disoproxil fumarate is known to be associated with reduced BMD. Subjects on a TAF-based regimen, compared to a TDF-based regimen, were expected to show less spine and hip BMD loss. This effect was shown in the D/C/F/TAF group compared to the control group in the Phase 3 studies, when comparing Week 48 vs baseline:

In Study TMC114FD2HTX3001, at Week 48 with D/C/F/TAF (Section 3.1.1.1.3)

- BMD was stable at the hip and spine region.
  - Control group: decreases in BMD were observed.
- Improvement of BMD clinical status was more frequent.
  - Control group: worsening of BMD clinical status was more frequent.
- Bone biomarkers suggested less bone turnover, with stable values for all markers.
  - Control group: all bone biomarkers increased.

In Study TMC114IFD3013, at Week 48 with D/C/F/TAF (Section 3.1.1.2.3)

- BMD increased at the hip and spine region.
  - Control group: BMD decreased.

- Improvement of BMD clinical status was more frequent.
  - Control group: worsening of BMD clinical status was more frequent
- Bone biomarkers suggested less bone turnover, with a decrease for all markers.
  - Control group: stable values for all bone biomarkers.

Eye Disorders

No cases consistent with posterior uveitis were reported in the Phase 3 studies (see Section 3.1.1.1.3 and Section 3.1.1.2.3).

8.2. Summary of Safety Data in Adolescents

The following data support the safety of D/C/F/TAF in HIV-1 infected adolescents (aged 12 to <18 years):

- Results from Study TMC114-C230 with DRV/rtv (N=12), which showed a similar safety profile in adolescents compared to adults, with:
  - Rash reported for 1 subject.
  - Increases in fasting lipids (total cholesterol in 66.7% of subjects, LDL cholesterol in 50.0% of subjects, and HDL cholesterol in 8.3% of subjects), but without relevant changes in the TC/HDL ratio.
- Preliminary results from the switch Study GS-US-216-0128 (N=22), which showed no new safety concerns for the combined use of DRV+COBI in this subject population, with, as expected:
  - A small decline in $eGFR_{cr}$ (Schwartz formula), associated with the use of COBI,
- Results from Study GS-US-292-0106 with the E/C/F/TAF FDC (N=50), which showed that COBI and F/TAF as part of the E/C/F/TAF FDC were well tolerated in HIV-1 infected adolescents:
  - Bone turnover rates consistent with those of the reference population, as shown by the limited changes in BMD Z-scores at Week 48. Of the 3 subjects who had a clinically relevant (≥4%) decrease from baseline in spine BMD at W24, 1 still had ≥4% decrease at Week 48. No subject had a ≥4% decrease from baseline in TBLH BMD.
  - Changes from baseline in serum creatinine and $eGFR_{cr}$ (Schwartz formula) consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and not considered reflective of changes in actual GFR.
  - No cases of posterior uveitis. One subject experienced intermediate uveitis considered related to study drug that resolved without without study drug discontinuation.

The use of the D/C/F/TAF FDC in adolescents is supported by the clinical and PK data from the historical DRV/rtv and E/C/F/TAF studies and from the currently ongoing study with DRV+COBI in adolescent subjects.

8.3. Summary of Safety Data in Subjects With Renal Impairment

The safety of the D/C/F/TAF FDC in HIV-1 infected subjects with renal impairment is supported by the following data:

- $eGFR_{CG}$ 50 to <90 mL/min (Study GS-US-236-0118):
  - The overall safety profile of DRV in combination with COBI and F/TDF in subjects with $eGFR_{CG}$ 50 to <90 mL/min was similar to that observed in the adult population with normal renal function.
- $eGFR_{CG}$ 30 to <70 mL/min (Study GS-US-292-0112):
  - The overall safety profile of COBI and F/TAF in subjects $eGFR_{CG}$ 30 to <70 mL/min was similar to that observed in the adult population with normal renal function.
  - Subjects with $eGFR_{CG}$ <50 mL/min at baseline did not have a different safety profile compared to subjects with $eGFR_{CG}$ ≥50 mL/min.
  - Renal parameters improved in subjects who were on a prior TDF-based regimen before switching to E/C/F/TAF.
- In addition, the subgroup analyses in the Phase 3 studies did not suggest a safety concern in subjects with a decreased renal function ($eGFR_{CG}$ 50 to <90 mL/min).

8.4. Conclusions

Clinical data from the D/C/F/TAF Phase 3 and 2 studies demonstrate that the D/C/F/TAF FDC (800/150/200/10 mg) has a favorable safety profile, and that treatment with D/C/F/TAF FDC has an improved renal and bone safety profile compared to a regimen with a TDF-containing backbone.

These data together with the historical data from other studies with the D/C/F/TAF components support the safe use of the D/C/F/TAF FDC for the proposed population of adults and adolescents.

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APPENDICES

Appendix 1: Further Differences Between the DAIDS and GSI Grading Scales for Severity of Adverse Events and Laboratory Abnormalities Relevant for D/C/F/TAF Safety Evaluation in Addition to Those Listed in Table 4.

	Grade 1	Grade 2	Grade 3	Grade 4
Lipase				
DAIDS grading scale	1.1 to <1.5x ULN	1.5 to <3.0x ULN	3.0 to <5.0x ULN	≥5.0x ULN
GSI grading scale	>1.0 to 1.5x ULN	>1.5 to 3.0x ULN	>3.0 to 5.0x ULN	>5.0x ULN
ALT				
DAIDS grading scale	1.25 to <2.5x ULN	2.5 to <5.0x ULN	5.0 to <10.0x ULN	≥10.0x ULN
GSI grading scale	1.25 to 2.5x ULN	>2.5 to 5.0x ULN	>5.0 to 10.0x ULN	>10.0x ULN
AST				
DAIDS grading scale	1.25 to <2.5x ULN	2.5 to <5.0x ULN	5.0 to <10.0x ULN	≥10.0x ULN
GSI grading scale	1.25 to 2.5x ULN	>2.5 to 5.0x ULN	>5.0 to 10.0x ULN	>10.0x ULN
ALP				
DAIDS grading scale	1.25 to <2.5x ULN	2.5 to <5.0x ULN	5.0 to <10.0x ULN	≥10.0x ULN
GSI grading scale	1.25 to 2.5x ULN	>2.5 to 5.0x ULN	>5.0 to 10.0x ULN	>10.0x ULN
Hyperbilirubinemia (total)				
DAIDS grading scale				
>28 days of age	1.1 to <1.6x ULN	1.6 to <2.6x ULN	2.6 to <5.0x ULN	≥5.0x ULN
GSI grading scale				
>14 days of age	>1.0 to 1.5x ULN	>1.5 to 2.5x ULN	>2.5 to 5.0x ULN	>5.0x ULN
Total cholesterol (fasting)				
DAIDS grading scale				
≥18 years of age	200 to <240 mg/dL 5.18 to <6.19 mmol/L	240 to <300 mg/dL 6.19 to <7.77 mmol/L	≥300 mg/dL ≥7.77 mmol/L	NA
<18 years of age	170 to <200 mg/dL 4.40 to <5.15 mmol/L	200 to <300 mg/dL 5.15 to <7.77 mmol/L	≥300 mg/dL ≥7.77 mmol/L	NA
GSI grading scale				
≥18 years of age	200 to 239 mg/dL 5.16 to 6.19 mmol/L	>239 to 300 mg/dL >6.19 to 7.77 mmol/L	>300 mg/dL >7.77 mmol/L	NA
<18 years of age	170 to 199 mg/dL 4.39 to 5.15 mmol/L	>199 to 300 mg/dL >5.15 to 7.77 mmol/L	>300 mg/dL >7.77 mmol/L	NA
LDL cholesterol (fasting)				
DAIDS grading scale				
≥18 years of age	130 to <160 mg/dL 3.37 to <4.12 mmol/L	160 to <190 mg/dL 4.12 to <4.90 mmol/L	≥190 mg/dL ≥4.90 mmol/L	NA
>2 to <18 years of age	110 to <130 mg/dL 2.85 to <3.34 mmol/L	130 to <190 mg/dL 3.34 to <4.90 mmol/L	≥190 mg/dL ≥4.90 mmol/L	NA
GSI grading scale				
≥18 years of age	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	>190 mg/dL >4.92 mmol/L	NA
>2 to <18 years of age	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	>190 mg/dL >4.92 mmol/L	NA
Hypoglycemia (fasting)				
DAIDS grading scale	55 to 64 mg/dL 3.05 to 3.55 mmol/L	40 to <55 mg/dL 2.22 to <3.05 mmol/L	30 to <40 mg/dL 1.67 to <2.22 mmol/L	<30 mg/dL <1.67 mmol/L
GSI grading scale	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to <55 mg/dL 2.20 to <3.03 mmol/L	30 to <40 mg/dL 1.64 to <2.20 mmol/L	<30 mg/dL <1.64 mmol/L

	Grade 1	Grade 2	Grade 3	Grade 4
Hyperglycemia (fasting)				
DAIDS grading scale	110 to 125 mg/dL	>125 to 250 mg/dL	>250 to 500 mg/dL	>500 mg/dL
	6.11 to <6.95 mmol/L	6.95 to <13.89 mmol/L	13.89 to <27.75 mmol/L	≥27.75 mmol/L
GSI grading scale	110 to 125 mg/dL	>125 to 250 mg/dL	>250 to 500 mg/dL	>500 mg/dL
	6.08 to 6.96 mmol/L	>6.96 to 13.90 mmol/L	>13.90 to 27.79 mmol/L	>27.79 mmol/L
Hypophosphatemia				
DAIDS grading scale				
>14 years of age	2.0 mg/dL to < LLN	1.4 to <2.0 mg/dL	1.0 to <1.4 mg/dL	<1.0 mg/dL
	0.81 mmol/L to < LLN	0.65 to <0.81 mmol/L	0.32 to <0.65 mmol/L	<0.32 mmol/L
≥1 to ≤14 years of age	3.0 to <3.5 mg/dL	2.5 to <3.0 mg/dL	1.5 to <2.5 mg/dL	<1.5 mg/dL
	0.97 to <1.13 mmol/L	0.81 to <0.97 mmol/L	0.48 to <0.81 mmol/L	<0.48 mmol/L
<1 years of age	3.5 to <4.5 mg/dL	2.5 to <3.5 mg/dL	1.5 to <2.5 mg/dL	<1.5 mg/dL
	1.13 to <1.45 mmol/L	0.81 to <1.13 mmol/L	0.48 to <0.81 mmol/L	<0.48 mmol/L
GSI grading scale				
>14 years of age	2.0 to < LLN mg/dL	1.5 to <2.0 mg/dL	1.0 to <1.5 mg/dL	<1.0 mg/dL
	0.63 to <0.70 mmol/L	0.47 to <0.63 mmol/L	0.31 to <0.47 mmol/L	<0.31 mmol/L
≥1 to ≤14 years of age	3.0 to 3.5 mg/dL	2.5 to <3.0 mg/dL	1.5 to <2.5 mg/dL	<1.5 mg/dL
	0.96 to 1.12 mmol/L	0.80 to <0.96 mmol/L	0.47 to <0.80 mmol/L	<0.47 mmol/L
<1 years of age	3.5 to 4.5 mg/dL	2.5 to <3.5 mg/dL	1.5 to <2.5 mg/dL	<1.5 mg/dL
	1.12 to 1.46 mmol/L	0.80 to <1.12 mmol/L	0.47 to <0.80 mmol/L	<0.47 mmol/L
Hypokalemia				
DAIDS grading scale	3.0 to <3.4 mEq/L	2.5 to <3.0 mEq/L	2.0 to <2.5 mEq/L	<2.0 mEq/L
	3.0 to <3.4 mmol/L	2.5 to <3.0 mmol/L	2.0 to <2.5 mmol/L	<2.0 mmol/L
GSI grading scale	3.0 to 3.4 mEq/L	2.5 to <3.0 mEq/L	2.0 to <2.5 mEq/L	<2.0 mEq/L
	3.0 to 3.4 mmol/L	2.5 to <3.0 mmol/L	2.0 to <2.5 mmol/L	<2.0 mmol/L
Hyperkalemia				
DAIDS grading scale	5.6 to <6.0 mEq/L	6.0 to <6.5 mEq/L	6.5 to <7.0 mEq/L	≥7.0 mEq/L
	5.6 to <6.0 mmol/L	6.0 to <6.5 mmol/L	6.5 to <7.0 mmol/L	≥7.0 mmol/L
GSI grading scale	5.6 to ≤6.0 mEq/L	>6.0 to ≤6.5 mEq/L	6.5 to ≤7.0 mEq/L	>7.0 mEq/L
	5.6 to ≤6.0 mmol/L	>6.0 to ≤6.5 mmol/L	6.5 to ≤7.0 mmol/L	>7.0 mmol/L

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DAIDS = Division of acquired immunodeficiency syndrome (AIDS); GSI = Gilead Sciences Inc; LDL = low density lipoprotein; LLN = lower limit of normal; NA = not applicable; ULN = upper limit of normal.

For the ULNs/LLNs of the individual parameters, refer to:

- Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Statistical Analysis Plan (for the limits used in the DAIDS grading scale).
- Mod5.3.5.1/GS-US-299-0102-Final-CSR/Statistical Analysis Plan (for the limits used in the GSI grading scale).

Source:
Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Protocol and Amendments (DAIDS grading scale Version 2.0, November 2014), Mod5.3.5.1/GS-US-299-0102-Final-CSR/Protocol and Protocol Amendments (GSI grading scale Version 21 September 2011), and Statistical Analysis Plan (GSI grading scale update in the SAP).

Appendix 2: Adverse Drug Reactions Algorithm

ALGORITHM FOR IDENTIFYING ADVERSE DRUG REACTIONS FOR THE GENERATION OF THE ADR SECTION 4.8 OF THE DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (D/C/F/TAF) COMPANY CORE DATA SHEET

Step 1: Creation of Tables and Listings of AEs

1.1 All AEs

A frequency tabulation of all reported treatment-emergent AE preferred terms, and the corresponding numbers (counts) will be created from the to be reviewed dataset. Preferred terms will be presented per SOC.

1.2 Grouping AEs/Preferred Terms

Upon medical review, preferred terms will be grouped under the same medical concept where clinically relevant. After grouping, a new frequency tabulation will be generated including the grouping per medical concept.

1.3 Excluding AEs/Preferred Terms unlikely to represent potential ADRs – Category 'C'

From the new Frequency Tabulation, the following preferred terms/medical concepts will be excluded from the review process, as considered unlikely these represented a potential ADR:

1. any preferred terms/medical concepts relating to infections (viral, fungal, bacterial, etc.) or AIDS defining illnesses (CDC Category B and C class), as these relate to conditions associated to the underlying HIV infection itself;
2. any preferred terms/medical concepts relating to malignancies, as such conditions are unlikely to develop as ADRs within the relative short duration of exposure of the subjects in the to be reviewed dataset;
3. any preferred terms/medical concepts relating to Surgical and Medical Procedures, as the procedure as such cannot be an ADR, instead it is the underlying condition leading to the procedure that needs to be reviewed as appropriate for the potential of being an ADR.

All these preferred terms/medical concepts will be documented in the Frequency Tabulations as **Review Category 'C'** (ie, not to be reviewed).

1.4 Excluding AEs already identified as ADRs – Category 'D'

All preferred terms/medical concepts already earlier identified as ADRs to either DRV/rtv, DRV/COBI or F/TAF will be documented in the Frequency Tabulations as Review Category 'D' (ie considered as ADRs to D/C/F/TAF).

1.5 In the remaining set of AEs, selecting the most relevant preferred terms/medical concepts for review – Category 'A'

Preferred terms/medical concepts will be selected for review if they fulfilled at least one of the following criteria:

- led – at least in one instance – to permanent study drug discontinuation;
- were – at least in one instance – considered as at least possibly related to D/C/F/TAF by the investigator;
- were reported – at least in one instance – as a SAE (irrespective of causality);
- corresponded to events of special interest, as listed in the SAP for the phase III trials;
- reached an absolute incidence of 1.0% or higher.

Preferred terms/medical concepts fulfilling these criteria will be documented as Review Category 'A' (ie, to be reviewed).

1.6 Those not fulfilling the above criteria will be documented as Review Category 'B' (ie, not to be reviewed) in the Frequency Tabulation.

1.7 Selecting Tools (tabulation and list) for helping the review

A frequency tabulation containing the preferred terms/medical concepts of all review categories (A to D) will form the basis of the individual case review. This frequency tabulation will provide:

- the number of subjects per preferred term/medical concept,
- the number of serious cases,
- the number of cases at least possibly related per investigator,
- the number of cases leading to permanent drug discontinuation,
- the review category, as defined above.

For the preferred terms/medical concepts selected for review (Review Category A) an additional list will be created, presenting per preferred term/medical concept:

- the CRF IDs,
- the causality assessment by investigator,
- seriousness,
- if the event led to permanent discontinuation or not,
- the time to onset (ie, time to onset of the 1st event if the subject presented more than 1 identical event).

Pre-filled forms will be generated that contain pre-printed the subject's main details as well as the different assessment criteria upon which the case assessment will be based (see Part 2).

Step 2: The Medical Review Process

2.1 Review of the preferred terms/medical concepts from Review Category A

A medical review will be performed on the preferred terms/medical concepts from Review Category A. These preferred terms/medical concepts will be reviewed until either:

- there is a case where the preferred term/medical concept is considered probably related to D/C/F/TAF per company's assessment;
- there are 3 well documented cases where the preferred term/medical concept is considered possibly related to D/C/F/TAF per company's assessment.

When all cases for this preferred term/medical concept are reviewed and the above mentioned stop criteria are not met, this preferred term/medical concept will not be an ADR.

2.2 Documentation of the review

The ADR determination has to follow a documented, structured approach and the reasons for determining the preferred term/medical concept as probably or possibly related to D/C/F/TAF (or not) will be clearly documented (see Part 2 Criteria For Case Assessment).

Step 3: The Adjudication Process

The assessments provided by the medical review team will be reviewed at individual case and/or at multiple case level, and adjudicated by the Safety Management Team (SMT), including representation from Janssen R&D, Infectious Diseases & Vaccines Medical Department, and Global Medical Safety (eg, Medical Safety Officer, Pharmacovigilance Physician). The ADR designation could include, apart from clinical judgment, multiple case review assessment criteria, as described in table "Multiple Case-review" of Part 2 Criteria For Case Assessment (see below). The medical assessment will also include the accumulated body of evidence with regards to the safety profile of F/TAF as provided by Gilead. The preferred term/medical concept retained by the Adjudication Panel as potential ADRs will form the Draft list of potential ADRs.

Step 4: Creation of the Final ADR List

The draft list of potential ADRs will be reviewed and discussed in the SMT medical and safety group. After further review and approval by Gilead, the resulting list will be considered the final ADR list for D/C/F/TAF, and will form the basis for the generation of the ADR section 4.8 of the Company Core Data Sheet.

- The ADRs (preferred terms/medical concepts) will be presented per SOC.
- The ADRs can be grouped to medical concepts or renamed to other Medical Dictionary for Regulatory Activities (MedDRA) preferred terms that cover the same medical concept.
- Preferred terms coding to the SOC Investigations can be relocated to the SOC that cover the medical concept (eg, aspartate aminotransferase increased to be presented under SOC Hepatobiliary disorders).

PART 2: Criteria for Case Assessment

The medical review to determine an ADR as mentioned above has to use a structured approach and inclusion and exclusion codes (adapted from the CIOMS III and V Working Group) to determine events identified as ADRs and events excluded as ADRs, respectively. The criteria used for the individual case and the multiple case reviews are presented in the table below. The reasons for determining the preferred term as probably or possibly related or downgrading a causality assessment of the investigator are to be clearly documented on the pre-filled form.

Individual Case Review	
Exclusion Codes	**Inclusion Codes**
A. Likely related to the underlying condition (medical history, concomitant medications, concurrent conditions, identified risk factors, etc.)	**Definitive evidence** **D1.** Positive re-challenge
B. Temporal relationship does not support causality – Event occurs prior to study drug administration – Event begins >30 days after last dose of study drug	**D2.** Recognized consequence of overdose
C. After review of the individual event, it appears not to be plausible	**D3.** Event is commonly drug-related (eg, neutropenia, Stevens-Johnson syndrome)
D. Negative re-challenge: time on re-exposure, to the same dose or higher, is longer than the time to onset of the original event	**D4.** Known mechanism
E. Poorly documented event (eg, from compassionate use)	**D5.** Similar findings in animal or *in vitro* models
F. Event does not meet any of the inclusion criteria 1-10	**Supportive evidence** **S1.** Time to onset plausible
	S2. Positive de-challenge, ie, the AE disappears after stopping the drug without a specific treatment being applied known to be effective for the AE
	S3. Lack of confounding risk factors/lack of alternative explanation
	S4. Amount and duration of exposure consistent/plausible with cause and effect
	S5. Co-medication unlikely to play a role
	S6. Investigator's causality assessment
	S7. Recognized class effect
	S8. Rarity of event in comparable untreated population
	S9. Pharmacokinetic evidence (eg, interaction)
	S10. Closeness of drug characteristics to those of other drugs known to cause the AE

Multiple Case Review – Criteria supporting an association	
1.	Positive outcome in targeted safety study
2.	Consistently higher incidence versus active comparator (whether statistically significant or not)
3.	Positive dose response relationship (from Phase 1 or 2 studies)
4.	Higher incidence versus comparator(s) of event specific discontinuations
5.	Earlier onset and/or greater severity versus active comparator
6.	Consistency in pattern of clinical presentation
7.	Consistency of time to onset
8.	Consistent trend across studies
9.	Consistent pattern of clinical presentation & latency
10.	Class effects

Appendix 3: Grouping of Preferred Terms in Medical Concepts and Resulting System Organ Classes for Identified Adverse Drug Reactions

Adverse Drug Reaction System Organ Class	Adverse Drug Reaction	Adverse Event Preferred Term
Gastrointestinal disorders	Abdominal distension	Abdominal distension
	Abdominal pain	Abdominal pain
		Abdominal pain lower
		Abdominal pain upper
	Diarrhoea	Diarrhoea
		Frequent bowel movements
	Dyspepsia	Dyspepsia
	Flatulence	Flatulence
	Nausea	Nausea
	Pancreatitis acute	Pancreatitis
		Pancreatitis acute
	Vomiting	Vomiting
General disorders and administration site conditions	Asthenia	Asthenia
	Fatigue	Fatigue
Hepatobiliary disorders	Acute hepatitis	Hepatitis
		Hepatitis acute
		Hepatotoxicity
Immune system disorders	(Drug) hypersensitivity	Drug hypersensitivity
		Hypersensitivity
	Immune reconstitution syndrome	Immune reconstitution inflammatory syndrome
		Immune reconstitution syndrome
Metabolism and nutrition disorders	Anorexia	Decreased appetite
	Diabetes mellitus	Diabetes mellitus
		Diabetes mellitus inadequate control
		Type 2 diabetes mellitus
		Glucose tolerance impaired
	Lipodystrophy	Facial wasting
		Fat redistribution
		Fat tissue increased
		Lipoatrophy
		Lipodystrophy acquired
		Lipohypertrophy
		Partial lipodystrophy
Musculoskeletal and connective tissue disorders	Myalgia	Myalgia

	Osteonecrosis	Osteonecrosis
Nervous system disorders	Headache	Headache
Psychiatric disorders	Abnormal dreams	Abnormal dreams
Reproductive system and breast disorders	Gynaecomastia	Gynaecomastia
		Hypertrophy breast
Skin and subcutaneous tissue disorders	Angioedema	Allergic oedema
		Angioedema
		Circumoral oedema
		Conjunctival oedema
		Corneal oedema
		Epiglottic oedema
		Eye oedema
		Eye swelling
		Eyelid oedema
		Face oedema
		Gingival oedema
		Gingival swelling
		Gleich's syndrome
		Hereditary angioedema
		Laryngeal oedema
		Laryngotracheal oedema
		Lip oedema
		Lip swelling
		Oculorespiratory syndrome
		Oedema mouth
		Oropharyngeal swelling
		Palatal oedema
		Periorbital oedema
		Pharyngeal oedema
		Scleral oedema
		Small bowel angioedema
		Swelling face
		Swollen tongue
		Tongue oedema
		Tracheal oedema
	Pruritus	Prurigo
		Pruritus
		Pruritus generalised
	Rash	Generalised erythema
		Rash
		Rash erythematous

		Rash generalised
		Rash macular
		Rash maculo-papular
		Rash morbilliform
		Rash papular
		Rash pruritic
	Stevens-Johnson syndrome	Stevens-Johnson syndrome
	Toxic epidermal necrolysis	Toxic epidermal necrolysis
	Urticaria	Urticaria
		Urticaria chronic
		Urticaria papular
		Urticaria cholinergic
		Idiopathic urticaria
	Acute generalized exanthematous pustulosis	Acute generalized exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms	Drug reaction with eosinophilia and systemic symptoms

Appendix 4: Treatment-emergent Adverse Drug Reactions in Study TMC114FD2HTX3001

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114FD2HTX3001)
Phase = Treatment

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	362	363
Any adverse drug reaction	182 (50.3%)	175 (48.2%)
Gastrointestinal disorders	115 (31.8%)	117 (32.2%)
Diarrhoea	71 (19.6%)	66 (18.2%)
Diarrhoea	71 (19.6%)	66 (18.2%)
Nausea	28 (7.7%)	45 (12.4%)
Nausea	28 (7.7%)	45 (12.4%)
Abdominal pain	15 (4.1%)	22 (6.1%)
Abdominal pain	11 (3.0%)	13 (3.6%)
Abdominal pain upper	5 (1.4%)	8 (2.2%)
Abdominal pain lower	0	1 (0.3%)
Vomiting	15 (4.1%)	15 (4.1%)
Vomiting	15 (4.1%)	15 (4.1%)
Dyspepsia	12 (3.3%)	10 (2.8%)
Dyspepsia	12 (3.3%)	10 (2.8%)
Flatulence	7 (1.9%)	2 (0.6%)
Flatulence	7 (1.9%)	2 (0.6%)
Abdominal distension	6 (1.7%)	1 (0.3%)
Abdominal distension	6 (1.7%)	1 (0.3%)
Skin and subcutaneous tissue disorders	55 (15.2%)	44 (12.1%)
Rash	44 (12.2%)	37 (10.2%)
Rash	32 (8.8%)	25 (6.9%)
Rash maculo-papular	3 (0.8%)	2 (0.6%)
Rash papular	3 (0.8%)	2 (0.6%)
Rash macular	2 (0.6%)	4 (1.1%)
Rash pruritic	2 (0.6%)	1 (0.3%)
Rash erythematous	1 (0.3%)	0
Rash generalised	1 (0.3%)	2 (0.6%)
Rash morbilliform	0	1 (0.3%)
Pruritus	9 (2.5%)	6 (1.7%)
Pruritus	9 (2.5%)	4 (1.1%)
Prurigo	0	1 (0.3%)
Pruritus generalised	0	1 (0.3%)
Urticaria	4 (1.1%)	3 (0.8%)
Urticaria	4 (1.1%)	3 (0.8%)
Angioedema	3 (0.8%)	0
Eyelid oedema	2 (0.6%)	0
Periorbital oedema	1 (0.3%)	0
Stevens-Johnson syndrome	0	1 (0.3%)
Stevens-Johnson syndrome	0	1 (0.3%)
Nervous system disorders	47 (13.0%)	32 (8.8%)
Headache	47 (13.0%)	32 (8.8%)
Headache	47 (13.0%)	32 (8.8%)
General disorders and administration site conditions	33 (9.1%)	30 (8.3%)
Fatigue	19 (5.2%)	18 (5.0%)
Fatigue	19 (5.2%)	18 (5.0%)
Asthenia	14 (3.9%)	12 (3.3%)

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114FD2HTX3001)
Phase = Treatment

	D/C/F/TAF	Control
Asthenia	14 (3.9%)	12 (3.3%)
Metabolism and nutrition disorders	5 (1.4%)	4 (1.1%)
Anorexia	4 (1.1%)	4 (1.1%)
Decreased appetite	4 (1.1%)	4 (1.1%)
Diabetes mellitus	1 (0.3%)	0
Diabetes mellitus	1 (0.3%)	0
Immune system disorders	3 (0.8%)	1 (0.3%)
(Drug) hypersensitivity	2 (0.6%)	1 (0.3%)
Hypersensitivity	2 (0.6%)	1 (0.3%)
Immune reconstitution syndrome	1 (0.3%)	0
Immune reconstitution inflammatory syndrome	1 (0.3%)	0
Musculoskeletal and connective tissue disorders	3 (0.8%)	7 (1.9%)
Myalgia	3 (0.8%)	7 (1.9%)
Myalgia	3 (0.8%)	7 (1.9%)
Psychiatric disorders	2 (0.6%)	2 (0.6%)
Abnormal dreams	2 (0.6%)	2 (0.6%)
Abnormal dreams	2 (0.6%)	2 (0.6%)

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att-TSFAE45_EXT.

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF of at Least Grade 2 by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114FD2HTX3001)
Phase = Treatment

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	362	363
Any ADR of grade 2, 3 or 4	47 (13.0%)	58 (16.0%)
Gastrointestinal disorders	22 (6.1%)	32 (8.8%)
Diarrhoea	14 (3.9%)	18 (5.0%)
Diarrhoea	14 (3.9%)	18 (5.0%)
Dyspepsia	4 (1.1%)	3 (0.8%)
Dyspepsia	4 (1.1%)	3 (0.8%)
Nausea	3 (0.8%)	13 (3.6%)
Nausea	3 (0.8%)	13 (3.6%)
Vomiting	3 (0.8%)	6 (1.7%)
Vomiting	3 (0.8%)	6 (1.7%)
Abdominal pain	2 (0.6%)	3 (0.8%)
Abdominal pain	2 (0.6%)	1 (0.3%)
Abdominal pain upper	0	2 (0.6%)
Flatulence	1 (0.3%)	0
Flatulence	1 (0.3%)	0
Skin and subcutaneous tissue disorders	17 (4.7%)	18 (5.0%)
Rash	16 (4.4%)	16 (4.4%)
Rash	9 (2.5%)	10 (2.8%)
Rash maculo-papular	2 (0.6%)	1 (0.3%)
Rash papular	2 (0.6%)	1 (0.3%)
Rash generalised	1 (0.3%)	1 (0.3%)
Rash macular	1 (0.3%)	2 (0.6%)
Rash pruritic	1 (0.3%)	0
Rash morbilliform	0	1 (0.3%)
Pruritus	2 (0.6%)	2 (0.6%)
Pruritus	2 (0.6%)	2 (0.6%)
Angioedema	1 (0.3%)	0
Eyelid oedema	1 (0.3%)	0
Stevens-Johnson syndrome	0	1 (0.3%)
Stevens-Johnson syndrome	0	1 (0.3%)
Nervous system disorders	7 (1.9%)	11 (3.0%)
Headache	7 (1.9%)	11 (3.0%)
Headache	7 (1.9%)	11 (3.0%)
General disorders and administration site conditions	5 (1.4%)	7 (1.9%)
Fatigue	5 (1.4%)	6 (1.7%)
Fatigue	5 (1.4%)	6 (1.7%)
Asthenia	0	1 (0.3%)
Asthenia	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	2 (0.6%)	2 (0.6%)
Myalgia	2 (0.6%)	2 (0.6%)
Myalgia	2 (0.6%)	2 (0.6%)
Metabolism and nutrition disorders	0	2 (0.6%)
Anorexia	0	2 (0.6%)
Decreased appetite	0	2 (0.6%)
Psychiatric disorders	0	2 (0.6%)

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF of at Least Grade 2 by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114FD2HTX3001)
Phase = Treatment

	D/C/F/TAF	Control
Abnormal dreams	0	2 (0.6%)
Abnormal dreams	0	2 (0.6%)

Source: Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att-TSFAE47_EXT.

Appendix 5: Treatment-emergent Adverse Drug Reactions in Study TMC114IFD3013

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114IFD3013)
Phase = Treatment

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	763	378
Any adverse drug reaction	236 (30.9%)	84 (22.2%)
Gastrointestinal disorders	134 (17.6%)	41 (10.8%)
Diarrhoea	60 (7.9%)	16 (4.2%)
Diarrhoea	60 (7.9%)	16 (4.2%)
Abdominal pain	41 (5.4%)	13 (3.4%)
Abdominal pain	29 (3.8%)	7 (1.9%)
Abdominal pain upper	12 (1.6%)	5 (1.3%)
Abdominal pain lower	1 (0.1%)	1 (0.3%)
Vomiting	22 (2.9%)	3 (0.8%)
Vomiting	22 (2.9%)	3 (0.8%)
Nausea	21 (2.8%)	7 (1.9%)
Nausea	21 (2.8%)	7 (1.9%)
Dyspepsia	13 (1.7%)	4 (1.1%)
Dyspepsia	13 (1.7%)	4 (1.1%)
Abdominal distension	9 (1.2%)	0
Abdominal distension	9 (1.2%)	0
Flatulence	8 (1.0%)	3 (0.8%)
Flatulence	8 (1.0%)	3 (0.8%)
Pancreatitis acute	1 (0.1%)	0
Pancreatitis	1 (0.1%)	0
Nervous system disorders	58 (7.6%)	16 (4.2%)
Headache	58 (7.6%)	16 (4.2%)
Headache	58 (7.6%)	16 (4.2%)
Skin and subcutaneous tissue disorders	44 (5.8%)	13 (3.4%)
Rash	28 (3.7%)	7 (1.9%)
Rash	23 (3.0%)	4 (1.1%)
Rash erythematous	2 (0.3%)	0
Rash pruritic	2 (0.3%)	1 (0.3%)
Rash macular	1 (0.1%)	0
Rash papular	1 (0.1%)	0
Rash generalised	0	1 (0.3%)
Rash maculo-papular	0	1 (0.3%)
Pruritus	11 (1.4%)	3 (0.8%)
Pruritus	11 (1.4%)	2 (0.5%)
Pruritus generalised	0	1 (0.3%)
Angioedema	4 (0.5%)	4 (1.1%)
Angioedema	1 (0.1%)	0
Face oedema	1 (0.1%)	0
Gingival swelling	1 (0.1%)	0
Swelling face	1 (0.1%)	1 (0.3%)
Eye swelling	0	3 (0.8%)
Tongue oedema	0	1 (0.3%)
Urticaria	4 (0.5%)	0
Urticaria	3 (0.4%)	0
Idiopathic urticaria	1 (0.1%)	0

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114IFD3013)
Phase = Treatment

	D/C/F/TAF	Control
General disorders and administration site conditions	43 (5.6%)	11 (2.9%)
Fatigue	34 (4.5%)	10 (2.6%)
Fatigue	34 (4.5%)	10 (2.6%)
Asthenia	9 (1.2%)	1 (0.3%)
Asthenia	9 (1.2%)	1 (0.3%)
Metabolism and nutrition disorders	14 (1.8%)	4 (1.1%)
Diabetes mellitus	9 (1.2%)	1 (0.3%)
Diabetes mellitus	6 (0.8%)	0
Type 2 diabetes mellitus	2 (0.3%)	0
Diabetes mellitus inadequate control	1 (0.1%)	0
Glucose tolerance impaired	0	1 (0.3%)
Anorexia	4 (0.5%)	2 (0.5%)
Decreased appetite	4 (0.5%)	2 (0.5%)
Lipodystrophy	1 (0.1%)	1 (0.3%)
Lipodystrophy acquired	1 (0.1%)	0
Facial wasting	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	13 (1.7%)	4 (1.1%)
Myalgia	12 (1.6%)	4 (1.1%)
Myalgia	12 (1.6%)	4 (1.1%)
Osteonecrosis	1 (0.1%)	0
Osteonecrosis	1 (0.1%)	0
Psychiatric disorders	9 (1.2%)	1 (0.3%)
Abnormal dreams	9 (1.2%)	1 (0.3%)
Abnormal dreams	9 (1.2%)	1 (0.3%)
Immune system disorders	4 (0.5%)	2 (0.5%)
(Drug) hypersensitivity	4 (0.5%)	2 (0.5%)
Hypersensitivity	3 (0.4%)	2 (0.5%)
Drug hypersensitivity	1 (0.1%)	0
Hepatobiliary disorders	0	1 (0.3%)
Acute hepatitis	0	1 (0.3%)
Hepatitis acute	0	1 (0.3%)

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE45_EXT.

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF of at Least Grade 2 by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114IFD3013)
Phase = Treatment

	D/C/F/TAF	Control
Analysis set: Intent-to-treat, N	763	378
Any ADR of grade 2, 3 or 4	76 (10.0%)	26 (6.9%)
Gastrointestinal disorders	40 (5.2%)	15 (4.0%)
Diarrhoea	19 (2.5%)	8 (2.1%)
Diarrhoea	19 (2.5%)	8 (2.1%)
Abdominal pain	15 (2.0%)	4 (1.1%)
Abdominal pain	12 (1.6%)	2 (0.5%)
Abdominal pain upper	4 (0.5%)	2 (0.5%)
Nausea	4 (0.5%)	3 (0.8%)
Nausea	4 (0.5%)	3 (0.8%)
Dyspepsia	3 (0.4%)	1 (0.3%)
Dyspepsia	3 (0.4%)	1 (0.3%)
Vomiting	3 (0.4%)	2 (0.5%)
Vomiting	3 (0.4%)	2 (0.5%)
Abdominal distension	2 (0.3%)	0
Abdominal distension	2 (0.3%)	0
Pancreatitis acute	1 (0.1%)	0
Pancreatitis	1 (0.1%)	0
Nervous system disorders	18 (2.4%)	1 (0.3%)
Headache	18 (2.4%)	1 (0.3%)
Headache	18 (2.4%)	1 (0.3%)
Skin and subcutaneous tissue disorders	9 (1.2%)	3 (0.8%)
Angioedema	4 (0.5%)	2 (0.5%)
Angioedema	1 (0.1%)	0
Face oedema	1 (0.1%)	0
Gingival swelling	1 (0.1%)	0
Swelling face	1 (0.1%)	0
Eye swelling	0	2 (0.5%)
Pruritus	2 (0.3%)	0
Pruritus	2 (0.3%)	0
Rash	2 (0.3%)	1 (0.3%)
Rash	1 (0.1%)	1 (0.3%)
Rash papular	1 (0.1%)	0
Urticaria	2 (0.3%)	0
Idiopathic urticaria	1 (0.1%)	0
Urticaria	1 (0.1%)	0
General disorders and administration site conditions	7 (0.9%)	5 (1.3%)
Fatigue	7 (0.9%)	4 (1.1%)
Fatigue	7 (0.9%)	4 (1.1%)
Asthenia	0	1 (0.3%)
Asthenia	0	1 (0.3%)
Metabolism and nutrition disorders	7 (0.9%)	2 (0.5%)
Diabetes mellitus	6 (0.8%)	0
Diabetes mellitus	5 (0.7%)	0
Type 2 diabetes mellitus	1 (0.1%)	0
Lipodystrophy	1 (0.1%)	1 (0.3%)
Lipodystrophy acquired	1 (0.1%)	0
Facial wasting	0	1 (0.3%)

Incidence (%) of Adverse Drug Reactions for D/C/F/TAF of at Least Grade 2 by System Organ Class, ADR Term and Preferred Term; ITT (Study TMC114IFD3013)
Phase = Treatment

	D/C/F/TAF	Control
Anorexia	0	1 (0.3%)
Decreased appetite	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	5 (0.7%)	2 (0.5%)
Myalgia	4 (0.5%)	2 (0.5%)
Myalgia	4 (0.5%)	2 (0.5%)
Osteonecrosis	1 (0.1%)	0
Osteonecrosis	1 (0.1%)	0
Psychiatric disorders	3 (0.4%)	0
Abnormal dreams	3 (0.4%)	0
Abnormal dreams	3 (0.4%)	0
Immune system disorders	1 (0.1%)	1 (0.3%)
(Drug) hypersensitivity	1 (0.1%)	1 (0.3%)
Drug hypersensitivity	1 (0.1%)	0
Hypersensitivity	0	1 (0.3%)
Hepatobiliary disorders	0	1 (0.3%)
Acute hepatitis	0	1 (0.3%)
Hepatitis acute	0	1 (0.3%)

Source: Mod5.3.5.1/TMC114IFD3013-W48-CSR/Att-TSFAE47_EXT.

Appendix 6: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114FD2HTX3001

Table 39: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114FD2HTX3001 (Cut-off Date: 1 June 2017) – D/C/F/TAF Group Continued Use From W48+1d

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Deaths								
0								
SAEs								
Transient ischaemic attack	[redacted]	Male, 4[redacted]	Grade 3	568	NOT	NON	Yes	RC
Viral infection		Male, 3[redacted]	Grade 3	509	NOT	NON	No	RC
Syphilis		Male, 3[redacted]	Grade 2	549	NOT	NON	Yes	RC
Depression		Male, 3[redacted]	Grade 1	416	NOT	NON	Yes	RC
Basal cell carcinoma		Male, 2[redacted]	Grade 3	428	NOT	NON	No	UK
Appendicitis		Male, 4[redacted]	Grade 2	391	NOT	TMP	Yes	RC
Fistula	[redacted][d]	Male, 2[redacted]	Grade 3	497	NOT	NON	Yes	RC
Haemorrhoids			Grade 3	497	NOT	NON	Yes	RC
Meningitis	[redacted][e]	Male, 4[redacted]	Grade 3	457	NOT	NON	Yes	RCo
Osteoarthritis	[redacted]	Female, 2[redacted]	Grade 3	337	NOT	NON	Yes	RC
Hepatitis viral	[redacted][e]	Male, 3[redacted]	Grade 2	364	NOT	TMP	Yes	SQ
Anal abscess	[redacted]	Male, 3[redacted]	Grade 3	435	NOT	NON	Yes	RC
Back pain	[redacted]	Male, 2[redacted]	Grade 2	343	POS	NON	Yes	RC
Haematuria			Grade 2	343	POS	NON	Yes	RC
AEs Leading to Premature Study Drug Discontinuation								
0								
AEOIs								
Amylase increased	[redacted]	Female, 5[redacted]	Grade 4	420	NOT	NON	No	UK
Blood cholesterol increased		Female, 5[redacted]	Grade 2	421	POS	NON	No	UK
Low density lipoprotein increased			Grade 2	421	POS	NON	No	RC
Low density lipoprotein increased			Grade 1	505	POS	NON	No	UK
Conjunctivitis	[redacted]	Male, 3[redacted]	Grade 1	499	NOT	NON	Yes	RCo
Rash generalised			Grade 1	389	NOT	NON	Yes	RC
Rash generalised			Grade 1	397	NOT	NON	Yes	RC
Dyslipidaemia	[redacted]	Male, 5[redacted]	Grade 1	512	NOT	NON	No	RCo
Blood creatine phosphokinase increased		Male, 3[redacted]	Grade 1	504	NOT	NON	No	NR
Low density lipoprotein increased		Female, 4[redacted]	Grade 3	421	POS	NON	No	SQ
Low density lipoprotein increased			Grade 2	505	POS	NON	No	UK
Epilepsy	[redacted]	Male, 2[redacted]	Grade 1	364[f]	NOT	NON	Yes	RC
Rash	[redacted][e]	Male, 4[redacted]	Grade 3	471	NOT	NON	No	UK
Type 2 diabetes mellitus			Grade 1	478	NOT	NON	Yes	UK
Rash generalised	[redacted]	Male, 5[redacted]	Grade 2	354	NOT	NON	Yes	RC
Rash		Male, 3[redacted]	Grade 2	342	NOT	NON	Yes	UK
Osteopenia		Male, 3[redacted]	Grade 1	351	POS	NON	Yes	RCo
Blood cholesterol increased		Male, 5[redacted]	Grade 1	332	POS	NON	Yes	UK

Table 39: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114FD2HTX3001 (Cut-off Date: 1 June 2017) – D/C/F/TAF Group Continued Use From W48+1d

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Blood cholesterol increased	[redacted]	Male, 2[redacted]	Grade 2	421	POS	NON	No	UK
Cholestasis	[redacted][e]	Male, 3[redacted]	Grade 2	376	POS	TMP	Yes	RC
Hypertriglyceridaemia	[redacted]	Male, 4[redacted]	Grade 3	343	NOT	NON	No	UK
Dyslipidaemia	[redacted]	Female, 5[redacted]	Grade 3	421	POS	NON	No	UK
Radius fracture	[redacted]	[redacted]	Grade 2	361	NOT	NON	Yes	RC
Hyperlipidaemia	[redacted]	Male, 5[redacted]	Grade 1	421	NOT	NON	No	UK
Skin exfoliation	[redacted]	Male, 3[redacted]	Grade 1	399	NOT	NON	No	UK

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; PT = preferred term; SAE = serious adverse event.

[a] Drug relationship as assessed by the investigator and summarized into: at least possibly related (POS; including the categories possibly, probably, and very likely related) or not related (NOT; including the categories not related and doubtfully related).

[b] Action taken towards study drug: NON = dose not changed; PER = drug permanently withdrawn; TMP = drug temporarily withdrawn; RED = dose reduced; INC = dose increased; UNK = unknown; NAP = not applicable.

[c] Outcome: RC = recovered/resolved; RCo = recovering/resolving; NR = not recovered/not resolved; SQ = recovered/resolved with sequelae; FT = fatal; UK = unknown.

[d] No CIOMS I forms were available for these SAEs, because the cases were still in workflow at the time of the cut-off.

[e] Subject listed in multiple risk categories in this table.

[f] Imputed due to partial AE onset date (the first day of the month was used).

[TABLE29.RTF] [/SAS/3027/TMC114FD2HTX3001/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/LISTING29.SAS] 18JUL2017, 13:29

Table 40: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114FD2HTX3001 (Cut-off Date: 1 June 2017) – Control Group Not Yet on D/C/F/TAF From W48+1d

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to onset	Causality[a]	Action taken with Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Deaths								
0								
SAEs								
Latent syphilis		Male, 2	Grade 2	464	NOT	NON	Yes	RC
Vascular stent restenosis	[d]	Male, 4	Grade 2	356	NOT	NON	No	RC
Syphilis		Male, 2	Grade 2	341	NOT	NON	Yes	RC
Road traffic accident		Female, 3	Grade 2	500	NOT	NON	No	RC
Hepatitis A		Male, 3	Grade 2	542	NOT	NON	Yes	RCo
Clostridium difficile colitis		Male, 2	Grade 3	339	NOT	NON	Yes	RC
Myocarditis infectious			Grade 3	552	NOT	NON	Yes	RCo
Humerus fracture		Male, 2	Grade 3	362	NOT	NON	Yes	RC
Intervertebral disc protrusion		Male, 3	Grade 2	443	NOT	NON	Yes	RC
Mumps		Female, 3	Grade 4	514	NOT	NON	Yes	RC
Osteoporosis	[d]	Male, 3	Grade 2	395	NOT	NON	Yes	RC
Hepatitis A		Male, 3	Grade 4	429	NOT	NON	No	RCo
Anal abscess		Male, 2	Grade 2	400	NOT	NON	Yes	RC
Hepatitis A		Male, 3	Grade 3	451	NOT	NON	Yes	RC
Alcohol poisoning		Male, 3	Grade 3	417	NOT	NON	No	RC
Suicidal ideation			Grade 3	417	NOT	NON	No	RC
Arthralgia		Female, 5	Grade 3	345	NOT	NON	Yes	RCo
Suicide attempt		Male, 3	Grade 3	386	NOT	TMP	Yes	RC
Appendicitis		Male, 2	Grade 3	391	NOT	NON	Yes	RC
AEs Leading to Premature Study Drug Discontinuation								
0								
AEOIs								
Amylase increased		Male, 2	Grade 1	414	NOT	NON	No	NR
Conjunctivitis			Grade 1	373	NOT	NON	Yes	RC
Hyperglycaemia		Male, 4	Grade 1	462	NOT	NON	No	RC
Radius fracture		Male, 5	Grade 1	421	NOT	NON	Yes	RC
Dyslipidaemia		Male, 4	Grade 1	582	NOT	NON	No	RCo
Mouth ulceration	[d]	Male, 4	Grade 1	424	NOT	NON	No	RC
Alanine aminotransferase increased		Male, 2	Grade 1	414	NOT	NON	No	RC
Aspartate aminotransferase increased			Grade 1	414	NOT	NON	No	RC
Blood creatine phosphokinase increased			Grade 1	414	NOT	NON	No	RC
Fat redistribution		Male, 3	Grade 1	453[e]	NOT	NON	Yes	RCo
Osteopenia		Male, 3	Grade 1	344	POS	NON	Yes	UK
Lower limb fracture		Male, 2	Grade 2	456	NOT	NON	Yes	RCo
Osteoporosis	[d]	Male, 3	Grade 2	398	NOT	NON	No	UK
Proteinuria		Male, 4	Grade 1	416	POS	NON	No	UK
Hypertriglyceridaemia		Male, 3	Grade 2	405	POS	NON	No	UK

Table 40: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114FD2HTX3001 (Cut-off Date: 1 June 2017) – Control Group Not Yet on D/C/F/TAF From W48+1d

Osteopenia	[redacted]	Male, 3	Grade 1	336	POS	NON	No	RCo
Glycosuria		Male, 5	Grade 1	370	NOT	NON	No	RC

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; PT = preferred term; SAE = serious adverse event.

[a] Drug relationship as assessed by the investigator and summarized into: at least possibly related (POS; including the categories possibly, probably, and very likely related) or not related (NOT; including the categories not related and doubtfully related).

[b] Action taken towards study drug: NON = dose not changed; PER = drug permanently withdrawn; TMP = drug temporarily withdrawn; RED = dose reduced; INC = dose increased; UNK = unknown; NAP = not applicable.

[c] Outcome: RC = recovered/resolved; RCo = recovering/resolving; NR = not recovered/not resolved; SQ = recovered/resolved with sequelae; FT = fatal; UK = unknown.

[d] Subject listed in multiple risk categories in this table.

[e] Imputed due to partial AE onset date (the first day of the month was used).

[TABLE31.RTF] [/SAS/3027/TMC114FD2HTX3001/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/LISTING31.SAS] 18JUL2017, 13:30

Appendix 7: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114IFD3013

Table 41: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114IFD3013 (Cut-off Date: 1 June 2017) – D/C/F/TAF Group Continued Use From W48 +1d

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Deaths								
0								
SAEs								
Acute kidney injury	[redacted]	Female, 5[redacted]	Grade 3	368	NOT	PER	Yes	RC
Pneumonia			Grade 3	365	NOT	PER	No	RC
Oesophageal rupture	[redacted]	Male, 2[redacted]	Grade 3	557	NOT	NON	No	RC
Pneumonia			Grade 3	557	NOT	NON	No	RC
Essential tremor	[redacted]	Male, 6[redacted]	Grade 3	385	NOT	NON	No	RCo
Acute kidney injury		Male, 4[redacted]	Grade 3	462	NOT	TMP	Yes	RC
Delirium			Grade 3	462	NOT	TMP	Yes	RC
Overdose			Grade 3	462	NOT	TMP	Yes	RC
Rhabdomyolysis			Grade 3	462	NOT	TMP	Yes	RC
Polyarthritis	[redacted]	Male, 3[redacted]	Grade 2	617	NOT	NON	Yes	RC
Prostate cancer		Male, 7[redacted]	Grade 3	339	NOT	NON	Yes	SQ
Peptic ulcer		Male, 6[redacted]	Grade 3	585	NOT	NON	No	RC
Anal abscess		Male, 7[redacted]	Grade 3	344	NOT	NON	Yes	RC
Anal squamous cell carcinoma			Grade 4	371	NOT	NON	Yes	RC
Deep vein thrombosis	[redacted]	Male, 4[redacted]	Grade 2	442	NOT	NON	No	RC
Pulmonary embolism			Grade 4	442	NOT	NON	Yes	RC
Pneumonia	[redacted]	Male, 5[redacted]	Grade 2	381	NOT	NON	Yes	RC
Foreign body	[redacted][d]	Female, 4[redacted]	Grade 3	442	NOT	NON	Yes	RC
Peripheral artery stenosis	[redacted]	Male, 5[redacted]	Grade 2	526	NOT	NON	Yes	RC
Peripheral artery stenosis			Grade 3	600	NOT	NON	No	RC
Atrial fibrillation	[redacted]	Male, 5[redacted]	Grade 3	411	NOT	NON	Yes	RC
Chills			Grade 3	411	NOT	NON	Yes	RC
Pyrexia			Grade 3	411	NOT	NON	Yes	RC
Urosepsis			Grade 3	411	NOT	NON	Yes	RC
Multiple fractures	[redacted]	Male, 4[redacted]	Grade 3	578	NOT	NON	Yes	NR
Prostatitis		Male, 5[redacted]	Grade 2	346	NOT	NON	Yes	RC
Septic shock			Grade 3	455	NOT	NON	Yes	RC
Non-cardiac chest pain	[redacted]	Female, 4[redacted]	Grade 2	357	NOT	NON	Yes	RC
Pneumothorax		Male, 5[redacted]	Grade 3	537	NOT	NON	No	RC
Chest pain		Female, 4[redacted]	Grade 3	552	NOT	NON	No	RC
Dizziness			Grade 3	552	NOT	NON	No	RC
Gastritis			Grade 3	552	NOT	NON	No	RC
Skull fracture	[redacted]	Male, 5[redacted]	Grade 2	471	NOT	NON	Yes	RC
Subdural haematoma			Grade 2	471	NOT	NON	Yes	RC
Lymphocele	[redacted]	Male, 6[redacted]	Grade 3	376	NOT	NON	Yes	RC
Hepatitis A		Male, 4[redacted]	Grade 4	552	NOT	NON	Yes	RCo
Urosepsis		Female, 5[redacted]	Grade 3	383	NOT	NON	Yes	RC

Table 41: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114IFD3013 (Cut-off Date: 1 June 2017) – D/C/F/TAF Group Continued Use From W48 +1d

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Lumbar vertebral fracture	[redacted]	Male, 6[redacted]	Grade 2	418	NOT	NON	Yes	NR
AEs Leading to Premature Study Drug Discontinuation								
Blood corticotrophin decreased	[redacted]	Female, 4[redacted]	Grade 2	486	POS	PER	Yes	NR
Cortisol decreased			Grade 2	486	POS	PER	Yes	NR
Flushing			Grade 2	486	POS	PER	No	NR
AEOIs								
Diabetes mellitus inadequate control	[redacted]	Male, 4[redacted]	Grade 3	421	NOT	NON	No	NR
Hyperlipidaemia		Male, 5[redacted]	Grade 1	656	NOT	NON	Yes	NR
Drug eruption		Male, 3[redacted]	Grade 1	459	NOT	NON	No	RCo
Conjunctivitis		Male, 3[redacted]	Grade 2	407	NOT	NON	No	RC
Gamma-glutamyltransferase increased		Male, 3[redacted]	Grade 2	510	NOT	NON	No	UK
Rash pruritic		Male, 2[redacted]	Grade 1	577	NOT	NON	No	RC
Dermatitis		Male, 5[redacted]	Grade 2	569	NOT	NON	Yes	NR
Blood cholesterol increased		Male, 3[redacted]	Grade 3	482	NOT	NON	No	UK
Low density lipoprotein increased			Grade 3	484	NOT	NON	No	UK
Conjunctivitis	[redacted]	Male, 3[redacted]	Grade 2	389	NOT	NON	Yes	RC
Foot fracture			Grade 2	480	NOT	NON	Yes	RC
Blister	[redacted]	Male, 3[redacted]	Grade 1	570	NOT	NON	No	RC
Conjunctivitis			Grade 2	500	NOT	NON	Yes	RC
Osteopenia	[redacted]	Male, 3[redacted]	Grade 1	435	NOT	NON	No	NR
Rash		Male, 4[redacted]	Grade 1	589	NOT	NON	No	UK
Rash	[redacted][d]	Female, 4[redacted]	Grade 1	462	NOT	NON	Yes	RC
Conjunctivitis		Male, 2[redacted]	Grade 1	397	NOT	NON	Yes	RC
Vitreous floaters		Male, 4[redacted]	Grade 1	415[e]	NOT	NON	No	RCo
Hypercholesterolaemia		Male, 5[redacted]	Grade 2	427	NOT	NON	Yes	NR
Proteinuria		Male, 5[redacted]	Grade 2	430	NOT	NON	No	NR
Angina pectoris		Male, 4[redacted]	Grade 1	575	NOT	NON	No	RC
Proteinuria		Female, 4[redacted]	Grade 1	438	NOT	NON	Yes	NR
Dyslipidaemia		Female, 5[redacted]	Grade 2	420	NOT	NON	Yes	NR
Proteinuria		Male, 5[redacted]	Grade 1	421	POS	NON	Yes	UK
Drug withdrawal convulsions		Female, 3[redacted]	Grade 2	529	NOT	NON	Yes	UK
Type V hyperlipidaemia		Male, 5[redacted]	Grade 3	421	POS	NON	No	NR
Diabetes mellitus		Male, 5[redacted]	Grade 2	593	NOT	NON	No	NR
Hepatic steatosis		Male, 5[redacted]	Grade 1	348	NOT	NON	No	UK
Humerus fracture		Male, 5[redacted]	Grade 2	387	NOT	NON	Yes	RC
Conjunctivitis		Male, 5[redacted]	Grade 1	561	NOT	NON	Yes	RC
Fibula fracture		Male, 5[redacted]	Grade 1	414	NOT	NON	No	UK
Osteopenia		Male, 5[redacted]	Grade 2	401	NOT	NON	No	NR
Conjunctivitis		Female, 3[redacted]	Grade 1	592	NOT	NON	Yes	RCo
Dermatitis allergic		Male, 4[redacted]	Grade 2	586	NOT	NON	Yes	UK
Rash			Grade 2	345	NOT	NON	Yes	RC

Table 41: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis in the Ongoing Study TMC114IFD3013 (Cut-off Date: 1 June 2017) – D/C/F/TAF Group Continued Use From W48 +1d

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Arteriosclerosis coronary artery	[redacted]	Male, 6	Grade 1	365	POS	NON	Yes	UK
Genital ulceration		Male, 3	Grade 1	522	NOT	NON	No	RC
Hypercholesterolaemia		Male, 5	Grade 3	414	NOT	NON	Yes	UK
Rash		Male, 3	Grade 1	365	NOT	NON	Yes	RC
Dermatitis		Male, 3	Grade 2	468	NOT	NON	Yes	RC
Amylase increased		Male, 4	Grade 4	419	NOT	TMP	No	NR
Blood creatine phosphokinase increased		Male, 2	Grade 4	345	POS	NON	No	RC
Conjunctivitis		Male, 5	Grade 1	434	NOT	NON	Yes	RC
Rash		Male, 5	Grade 2	372	NOT	NON	Yes	NR
Hyperlipidaemia		Male, 4	Grade 2	422	POS	NON	Yes	NR

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; PT = preferred term; SAE = serious adverse event.

[a] Drug relationship as assessed by the investigator and summarized into: at least possibly related (POS; including the categories possibly, probably, and very likely related) or not related (NOT; including the categories not related and doubtfully related).

[b] Action taken towards study drug: NON = dose not changed; PER = drug permanently withdrawn; TMP = drug temporarily withdrawn; RED = dose reduced; INC = dose increased; UNK = unknown; NAP = not applicable.

[c] Outcome: RC = recovered/resolved; RCo = recovering/resolving; NR = not recovered/not resolved; SQ = recovered/resolved with sequelae; FT = fatal; UK = unknown.

[d] Subject listed in multiple risk categories in this table.

[e] Imputed due to partial AE onset date (the first day of the month was used).

[TABLE36.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/LISTING36.SAS] 07JUL2017, 15:12

Table 42: Significant Adverse Events per Risk Category Reported At/After Week 52 in the Ongoing Study TMC114IFD3013 (Cut-off Date: 1 June 2017) - Control Group Switched to D/C/F/TAF From Week 52

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Time to Onset	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Deaths									
0									
SAEs									
Cholelithiasis	[redacted]	Male, 4	Grade 2	121	483	NOT	NON	Yes	RC
Colitis	[redacted]	Male, 4	Grade 4	281	647	NOT	NON	Yes	RC
Diarrhoea			Grade 2	281	647	NOT	NON	Yes	UK
Pyrexia			Grade 3	281	647	NOT	NON	Yes	UK
Inflammatory bowel disease	[redacted][d]	Male, 3	Grade 3	305	667	NOT	NON	Yes	RC
Depression	[redacted]	Male, 5	Grade 3	288	644	NOT	TMP	No	UK
Adjustment disorder	[redacted]	Male, 2	Grade 2	55	413	NOT	NON	Yes	RC
Pneumonia	[redacted][d]	Male, 5	Grade 3	194	562	NOT	TMP	Yes	RC
Acute kidney injury	[redacted]	Male, 5	Grade 4	260	629	POS	PER	No	RCo
Malaria			Grade 2	255	624	NOT	PER	No	RCo
Perineal abscess	[redacted]	Male, 3	Grade 2	112	468	NOT	NON	Yes	RC
Dyspnoea	[redacted][d]	Male, 4	Grade 2	129	492	NOT	NON	Yes	RC
Suicidal ideation	[redacted]	Male, 4	Grade 2	11	387	NOT	NON	No	UK
Necrotising fasciitis	[redacted]	Male, 5	Grade 4	182	545	NOT	NON	Yes	RC
Pneumonia	[redacted]	Male, 6	Grade 3	194	555	NOT	NON	No	RC
Depression	[redacted]	Male, 5	Grade 3	4[e]	368[e]	NOT	TMP	Yes	RC
Suicidal ideation			Grade 3	4[e]	368[e]	NOT	TMP	No	RC
Cellulitis	[redacted]	Male, 6	Grade 3	96	460	NOT	NON	Yes	RC
Enchondromatosis	[redacted]	Male, 4	Grade 3	147	503	NOT	NON	No	UK
Tendon rupture[f]			Grade 3	216	572	NOT	NON	No	UK
Myocardial infarction	[redacted]	Male, 6	Grade 4	130	495	NOT	NON	No	RC
AEs Leading to Premature Study Drug Discontinuation									
Vertigo	[redacted][d]	Male, 5	Grade 2	83	450	POS	PER	No	RC
Diarrhoea	[redacted]	Female, 5	Grade 2	2	364	POS	PER	No	RC
Nausea			Grade 2	2	364	POS	PER	No	RC
Vomiting			Grade 2	2	364	POS	PER	No	RC
AEOIs									
Hyperlipidaemia	[redacted]	Male, 5	Grade 2	309	674	NOT	NON	No	NR
Type 2 diabetes mellitus			Grade 3	309	674	NOT	NON	Yes	NR
Hypokalaemia	[redacted][d]	Male, 3	Grade 1	305	667	NOT	NON	Yes	RC
Hand fracture	[redacted]	Male, 3	Grade 2	249	608	NOT	NON	Yes	UK
Wrist fracture	[redacted]	Female, 5	Grade 1	186	547	NOT	NON	No	RC
Hypercholesterolaemia	[redacted]	Female, 6	Grade 1	156	518	NOT	NON	Yes	RCo
Hypercholesterolaemia	[redacted]	Female, 4	Grade 1	64	413	POS	NON	Yes	NR
Hepatic steatosis	[redacted][d]	Male, 5	Grade 2	0	368	NOT	NON	No	NR
Hepatic steatosis	[redacted][d]	Male, 5	Grade 1	193	561	NOT	NON	No	UK

Table 42: Significant Adverse Events per Risk Category Reported At/After Week 52 in the Ongoing Study TMC114IFD3013 (Cut-off Date: 1 June 2017) - Control Group Switched to D/C/F/TAF From Week 52

Risk category/PT	Subject ID & Location of Narrative	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Time to Onset	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Osteoporosis	[redacted]	Male, 4[redacted]	Grade 2	89	448	NOT	NON	No	NR
Tibia fracture	[redacted][d]	Male, 4[redacted]	Grade 1	223	586	NOT	NON	Yes	NR
Type 2 diabetes mellitus	[redacted]	Female, 7[redacted]	Grade 2	124	491	NOT	NON	Yes	RCo
Visual impairment	[redacted]	Male, 5[redacted]	Grade 3	123	486	NOT	NON	No	NR
Conjunctivitis	[redacted]	Male, 3[redacted]	Grade 2	246	608	NOT	NON	Yes	UK
Proteinuria	[redacted]	Male, 5[redacted]	Grade 2	60	423	POS	NON	No	RC
Polyuria	[redacted]	Male, 5[redacted]	Grade 2	0	364	NOT	NON	No	RCo
Jaundice	[redacted]	Male, 5[redacted]	Grade 1	15	371	POS	NON	No	RC
Rash	[redacted]	Male, 5[redacted]	Grade 1	12	368	NOT	NON	No	RC
Alanine aminotransferase increased	[redacted]	Male, 3[redacted]	Grade 2	59	421	NOT	NON	No	UK
Aspartate aminotransferase increased			Grade 1	59	421	NOT	NON	No	UK
Blood creatine phosphokinase increased			Grade 1	59	421	NOT	NON	No	UK
Angina pectoris	[redacted]	Male, 6[redacted]	Grade 3	33	396	NOT	NON	Yes	RC
Diabetes mellitus			Grade 2	57	420	NOT	NON	No	UK
Hypercholesterolaemia	[redacted]	Male, 4[redacted]	Grade 2	142	507	POS	NON	Yes	UK
Blood creatine phosphokinase increased	[redacted]	Male, 5[redacted]	Grade 3	116	479	NOT	NAP	No	RC
Blood creatine phosphokinase increased	[redacted]	Male, 2[redacted]	Grade 3	58	421	NOT	NON	No	RC
Rash	[redacted]	Female, 4[redacted]	Grade 2	27	385	POS	NON	Yes	RC
Rash	[redacted]		Grade 3	36	394	POS	TMP	Yes	RC

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; PT = preferred term; SAE = serious adverse event.

[a] Drug relationship as assessed by the investigator and summarized into: at least possibly related (POS; including the categories possibly, probably, and very likely related) or not related (NOT; including the categories not related and doubtfully related).

[b] Action taken towards study drug: NON = dose not changed; PER = drug permanently withdrawn; TMP = drug temporarily withdrawn; RED = dose reduced; INC = dose increased; UNK = unknown; NAP = not applicable.

[c] Outcome: RC = recovered/resolved; RCo = recovering/resolving; NR = not recovered/not resolved; SQ = recovered/resolved with sequelae; FT = fatal; UK = unknown.

[d] Subject listed in multiple risk categories in this table.

[e] Imputed due to partial AE onset date (the first day of the month was used).

[f] No CIOMS form was available for this SAE , because this case was still in workflow at the time of the cut-off.

[TABLE37B.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/LISTING37.SAS] 07JUL2017, 15:13

Table 43: Significant Adverse Events per Risk Category Reported Since the Week-48 Analysis Before First D/C/F/TAF Intake in the Ongoing Study TMC114IFD3013 (Cut-off Date: 1 June 2017) – Control Group Switched to D/C/F/TAF

Risk category/PT	Subject ID	Sex, Age	Grade	Time to First D/C/F/TAF Intake	Time to Onset	Causality[a]	Action Taken With Study Drug[b]	Concomitant Treatment Started for AE	Outcome[c]
Deaths									
0									
SAEs									
0									
AEs Leading to Premature Study Drug Discontinuation									
0									
AEOIs									
Proteinuria	[redacted]	Male, 4	Grade 1	-22	342	NOT	NAP	No	RC
Dyslipidaemia		Male, 4	Grade 1	-30	338	NOT	NAP	No	RCo

AE = adverse event; AEOI = adverse event of interest; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; PT = preferred term; SAE = serious adverse event.

[a] Drug relationship as assessed by the investigator and summarized into: at least possibly related (POS; including the categories possibly, probably, and very likely related) or not related (NOT; including the categories not related and doubtfully related).

[b] Action taken towards study drug: NON = dose not changed; PER = drug permanently withdrawn; TMP = drug temporarily withdrawn; RED = dose reduced; INC = dose increased; UNK = unknown; NAP = not applicable.

[c] Outcome: RC = recovered/resolved; RCo = recovering/resolving; NR = not recovered/not resolved; SQ = recovered/resolved with sequelae; FT = fatal; UK = unknown.

[TABLE37A.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/SCS_ONGOING_TRIAL_01JUN2017/PROGRAMS/LISTING37.SAS] 07JUL2017, 15:13

Janssen Research & Development

Summary of Clinical Safety- Safety of Ongoing Studies Addendum

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults and Adolescents

D/C/F/TAF (Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide, TMC114/JNJ-48763364/JNJ-35807551/JNJ-63625328)

Status:	Approved
Date:	14 September 2017
Prepared by:	Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number:	Report Body: EDMS-ERI-148818673, Version 1.0

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ABBREVIATIONS

abbreviation	description of abbreviated term
AE	adverse event
CIOMS	Council for International Organizations of Medical Sciences
CSR	Clinical Study Report
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
FDC	fixed dose combination
NDA	new drug application
SAE	serious adverse event
SCS	Summary of Clinical Safety

1. INTRODUCTION

In this Summary of Clinical Safety (SCS) Safety of Ongoing Studies Addendum, additional safety information from 1 June up to 30 June 2017 of the 2 ongoing randomized, active-controlled Phase 3 studies (Studies TMC114FD2HTX3001 [AMBER] and TMC114IFD3013 [EMERALD]) is presented.

For each study, the period covered in the darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) fixed-dose combination (FDC) SCS Safety of Ongoing Studies started after the Week-48 visit and ended at the data cut-off date of 1 June 2017 (Mod2.7.4/SCS/Sec5). Due to a delayed submission, the cut-off date of 1 June 2017 is no longer in agreement with the proposed safety reporting period up to a maximum of 90 days prior to the US new drug application (NDA) submission date.

This addendum describes additional safety data from 1 June up to 30 June 2017 based on CIOMS I and II forms retrieved from the Global Medical Safety database from Janssen Research & Development LLC.

2. OVERALL SAFETY EVALUATION PLAN, EXTENT OF EXPOSURE, AND STUDY POPULATIONS

No update is required for this section.

3. RESULTS OF THE INDIVIDUAL STUDIES

No update is required for this section.

4. ADVERSE DRUG REACTIONS THROUGH WEEK 48

No update is required for this section.

5. SAFETY IN ONGOING STUDIES

5.1. Double-blind Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve, Adult Subjects

After Week 48, subjects in Study TMC114FD2HTX3001 continued to take their blinded study drug until the unblinding visit, after which all subjects started open-label treatment with the D/C/F/TAF FDC tablet up to Week 96.

5.1.1. Discontinuations

During the reporting period of 1 June up to 30 June 2017, no additional subjects discontinued (Table 1).

5.1.2. Adverse Events

No deaths were reported in the study since the Week-48 analysis.

Newly emerging serious adverse events (SAEs) were reported for 2 subjects in the D/C/F/TAF group (continued use) and for no subjects in the control group. None of these events were considered related to the study drug.

Narratives (Council for International Organizations of Medical Sciences [CIOMS] I forms) for subjects experiencing newly emerging SAEs are provided in Appendix 2.1.

Follow-up information for adverse events (AEs) reported in the Clinical Study Reports (CSRs) and original SCS is available for 6 subjects.

Narratives (CIOMS I forms) for subjects with new follow-up information are provided in Appendix 2.2.

Between 1 June 2017 and 30 June 2017, 1 pregnancy was reported in this study:

- Subject [redacted] in the D/C/F/TAF group was reported with a pregnancy, with an expected delivery date of [redacted]. For more details, refer to the narrative (CIOMS I form) in Appendix 2.1.

5.2. Open-label Phase 3 Study TMC114IFD3013 in HIV-1 Infected, ART-experienced, Virologically Suppressed, Adult Subjects

In Study TMC114IFD3013, subjects from the D/C/F/TAF group entered the extension phase once they had completed their Week-48 visit. In addition, subjects in the control group started taking the D/C/F/TAF tablet in the extension phase after attending a switch visit at Week 52.

5.2.1. Discontinuations

During the reporting period of 1 June up to 30 June 2017, no additional subjects discontinued (Table 2).

5.2.2. Adverse Events

No deaths were reported in the study since the Week-48 analysis.

Newly emerging SAEs were reported for 4 subjects in the D/C/F/TAF group (continued use) and for 1 subject in the control group (switched to D/C/F/TAF). None of these events were considered related to the study drug.

Narratives (CIOMS I forms) for subjects experiencing newly emerging SAEs are provided in Appendix 2.3.

Follow-up information for AEs reported in the CSRs and original SCS is available for 7 subjects.

Narratives (CIOMS I forms) for subjects with new follow-up information are provided in Appendix 2.4.

Between 1 June 2017 and 30 June 2017, 1 pregnancy of partner was reported in this study:

- Subject [redacted] in the D/C/F/TAF group was reported with a pregnancy of partner, with the date of the last menstrual period on [redacted]. Ultrasounds were performed on [redacted] and [redacted], showing that the clinical condition of the fetus was normal and the status of the pregnancy was continuing. For more details, refer to the narrative (CIOMS I form) in Appendix 2.3.

6. SAFETY IN SPECIAL GROUPS AND SITUATIONS

No update is required for this section.

7. POSTMARKETING DATA

No update is required for this section.

8. SUMMARY AND CONCLUSIONS

No update is required for this section.

REFERENCES

No update is required for this section.

APPENDICES

Appendix 1: Discontinuations After Week-48 Analysis up to 30 June 2017

Table 1: Subjects Discontinued or With Missing Information After Week-48 Analysis (Study TMC114FD2HTX3001)

Planned Arm Code	Unique Subject Identifier	Week 48 Visit Date	Unblinded Visit Date	Discontinuation Date	Discontinuation Reason
CONTROL ARM	[redacted]	.	.	[redacted]	LOST TO FOLLOW-UP
		.	.		PHYSICIAN DECISION
D/C/F/TAF ARM		.	.		NON-COMPLIANCE WITH STUDY DRUG
	[redacted]	.	.	[redacted]	LOST TO FOLLOW-UP
		.	.		NON-COMPLIANCE WITH STUDY DRUG

[DISCONT.RTF] [/SAS/3027/TMC114FD2HTX3001/FILES/RE/SCS_ONGOING_TRIAL_30JUN2017/PROGRAMS/CREATEADSL.SAS]
12SEP2017, 15:56

Table 2: Subjects Discontinued or With Missing Information After Week-48 Analysis (Study TMC114IFD3013)

Description of Planned Arm	Unique Subject Identifier	Discontinuation Date	Discontinuation Reason
CONTROL ARM	[redacted]	[redacted]	WITHDRAWAL BY SUBJECT
			OTHER
			LOST TO FOLLOW-UP
			WITHDRAWAL BY SUBJECT
			OTHER
			LOST TO FOLLOW-UP

[DISCONT.RTF] [/SAS/3027/TMC114IFD3013/FILES/RE/SCS_ONGOING_TRIAL_30JUN2017/PROGRAMS/UNTITLED.SAS*]
13SEP2017, 07:49

Appendix 2: CIOMS I and II Forms (2 June up to 30 June)

Appendix 2.1: **TMC114FD2HTX3001 – CIOMS I and II for New Cases**
Appendix 2.2: **TMC114FD2HTX3001 – CIOMS I and II for Updated Cases**
Appendix 2.3: **TMC114IFD3013 – CIOMS I and II for New Cases**
Appendix 2.4: **TMC114IFD3013 – CIOMS I and II for Updated Cases**

CIOMS Report for SDE00256388 Study TMC114FD2HTX3001 Initial

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Results:	3 cases selected from 3 matching the following criteria
Start Date :	[redacted]
End Date :	
Date Type :	Version Initially Received
Version :	Highest In Date Range
Invalid Cases :	Excluded
Workflow Cases :	Excluded
Deleted Cases :	Excluded
Protocol Number(s) :	TMC114FD2HTX3001
First Case Version Date Range :	Between [redacted]

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	3[redacted] Year	F	??	???	????

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

EXPOSURE DURING PREGNANCY(10073513)

This pregnancy report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerns a 3[redacted] year old female (subject [redacted] from [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☐ NA UNK

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION: Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☐ NA UNK

17. INDICATIONS FOR USE: HIV INFECTION

18. THERAPY DATES (from/to): [redacted] - ??-??-????

19. THERAPY DURATION: UNK

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Pregnant Expected Date of Delivery: [redacted] LMP Date: [redacted]

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no :
Patient no : [redacted]

24b. MFR. CONTROL NO. [redacted](0)

24c. DATE RECEIVED BY MFR. [redacted]

24d. REPORT SOURCE

- [X] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

- [ ] INITIAL
- [ ] FOLLOWUP
- [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

The subject's weight was [redacted] kilograms and height was unspecified The subject's concurrent condition included HIV. It was unspecified if the subject had been pregnant before.

The subject was enrolled in the study and received treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) initiated on [redacted] for HIV. Concomitant medications were not reported.

On an unspecified date, the subject experienced drug exposure during pregnancy. The subject's last menstrual period was on [redacted], with an expected delivery date of [redacted].

Action taken with darunavir/cobicistat/emtricitabine/tenofovir alafenamide was unspecified.

The subject outcome was unspecified for drug exposure during pregnancy.

The investigator considered the causality between drug exposure during pregnancy and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is not serious.

No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. EXPOSURE DURING PREGNANCY [10073513]

Change in dose	Unknown
Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: HIV INFECTION ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	3[redacted] Year	M	[redacted]	[redacted]	[redacted]

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PNEUMOTHORAX(10035759)

This report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerned a 3[redacted]-year-old male (subject [redacted] site [redacted] from [redacted]

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: HIV INFECTION ??-??-???? - Ongoing

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

The subject weighed [redacted] kilograms and height was [redacted] centimeters. The subject's concurrent condition included HIV and medical history was not provided.

The subject was randomized and received treatment with blinded darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) 1 dose (800/150/200/10 mg) a day along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral) 1 dose (800/150 mg) a day coadministered with emtricitabine/tenofovir disoproxil (tablet, oral) 1 dose (200/300 mg) a day along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV. Concomitant medications were not reported.

On [redacted], the subject experienced cough, fever and thoracic pain. On [redacted], the subject went to the emergency room for clinical examination, laboratory analysis, and chest radiography (results unspecified). The differential diagnosis was pneumopathie or (illegible) pulmonary. The diagnosis was acute infectious pneumopathy. Treatment included Amoxicillin one gram three times/day, seven days oral (per OS).

On [redacted], the subject had his follow-up visit and had remained on the same treatment. Clinical examination showed cough reduction, pain basi thoracic reduction. On auscultation, the subject had decreased vesicular breathing and no signs of severity. The subject had experienced a pneumothorax and was hospitalized.

Diagnostic data included a thoracic radiography that showed right completed pneumothorax without retraction of mediastinum. Pleural effusion moderated and (illegible) lingual opacities of infectious origin. Pleural effusion was homolateral to pneumothorax and contralateral to pneumopathie.

Treatment included installation of drain. On [redacted], the drain was removed.

The subject was clinically stable at the time of this report.

Action taken with study drugs was dose not changed.

The subject outcome was not provided.

The investigator assessed the pneumothorax as severe in severity and not related to trial procedure.

The investigator considered the causality between pneumothorax and study drugs as not related.

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil) using the Summary of Product Characteristics dated [redacted].

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

The blind has not been broken for this case.

This report is serious (hospitalization).Additional information was received from the investigator, on [redacted].

The subject had recovered from the serious event of pneumothorax on [redacted], previously not provided.
Senders Comments/Medical Assessment: V1:

Follow-up information does not alter the prior causality assessment (remains as not related).

This report received from clinical trial TMC114FD2HTX3001 concerned a 3[redacted]-year-old male subject who experienced Pneumothorax about 14 months after initiation of blinded study treatment for HIV infection. Pneumothorax was determined to be of infectious origin and is confounded by underlying HIV infection. In the presence of above risk factor and with no pharmacological plausibility, the event is considered not related to study treatment.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
CHEST X-RAY	[redacted]	unspecified		
		see Other Diagnostics		
LABORATORY TEST		unspecified		
PHYSICAL EXAMINATION		unspecified		
PULMONARY PHYSICAL EXAMINATION		see Other Diagnostics		

Pulmonary physical exam ([redacted]): Clinical examination showed cough reduction, pain basi thoracic reduction. On auscultation, the subject had decreased vesicular breathing and no signs of severity. Chest x-ray ([redacted]): showed right completed pneumothorax without retraction of mediastinum. Pleural effusion moderated, (illegible) lingual opacities of infectious origin. Pleural effusion was homolateral to pneumothorax and contralateral to pneumopathie.

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. PNEUMOTHORAX [10035759]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No. 2
Drug DARUNAVIR/COBICISTAT (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

COMPARATOR) Tablet

Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing

Causality

1. PNEUMOTHORAX [10035759]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	3
Drug	EMTRICITABINE W/TENOFOVIR DISOPROXIL (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet
Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing

Causality

1. PNEUMOTHORAX [10035759]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	4
Drug	PLACEBO (PLACEBO) Tablet
Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing

Causality

1. PNEUMOTHORAX [10035759]

Change in dose	Dose Not changed
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	2[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

HEPATITIS A(10019719)

This report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerns a 2[redacted]-year-old male (subject [redacted] site [redacted] from [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - [redacted]

19. THERAPY DURATION

581 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: RADIUS FRACTURE ??-???-[redacted] - ??-??-????

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO. [redacted]

24c. DATE RECEIVED BY MFR. [redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

[redacted]

The subject's weight was [redacted] kilograms and height was [redacted] centimeters. The subject's medical history and concurrent conditions included: HIV infection, acute sinusitis beginning [redacted] paraproctitis beginning [redacted] chronic prostatitis beginning [redacted] fracture of the right radius beginning [redacted] infectious mononucleosis (in childhood), cytomegalovirus infection beginning [redacted] allergic reaction (strawberry and cosmetics), and decreased creatinine clearance beginning [redacted] (toxicity grade 2).

The subject was randomized and treated with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral, batch 4373400) 1 dose daily along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral, batch 4373614) 1 dose daily coadministered with emtricitabine/tenofovir disoproxil (tablet, oral, batch 4373432) 1 dose daily along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV infection. Concomitant medications were not reported.

On [redacted], the subject experienced acute hepatitis A. The symptom included fever of 39.7 degrees Celsius. On [redacted], nausea and diarrhea occurred and lasted for 3 days. On [redacted], the subject's stool was of normal consistency but had a white color. On [redacted], the subject detected scleral icterus and yellowness of the skin. The subject called the ambulance and was hospitalized on [redacted]. The subject was treated with paracetamol, enterofuril, and intravenous glucose and sodium chloride. On [redacted], the subject notified the investigator of admission and indicated the ALT level was 1163 [illegible]/L and hepatitis A IgM was positive. The subject reported he was diagnosed with acute hepatitis A.

Treatment with study drug was withdrawn on [redacted].

The subject's outcome was not provided.

The investigator assessed the events as grade 2 or moderate in severity, not related to HIV, and not related to study procedures.

The investigator considered the causality between acute hepatitis A and study drug as not related.

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil fumarate) using the Summary of Product Characteristics dated [redacted].

The blind has not been broken for this case.

This report is serious (hospitalization).Additional information was received from the investigator on [redacted].

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

The subject reported by phone to the site the lab results of [redacted]: alanine aminotransferase 425 IE/L and bilirubin total 27 mkmol/l. The subject had clinical improvement but it was not enough to be discharged from the hospital. The hospitalization will be continued at least till [redacted].
Senders Comments/Medical Assessment: V1:

The follow-up information does not alter the prior causality assessment.

This 2[redacted]-year-old male subject experienced hepatitis A infection approximately 1 year and 6 months following blinded study therapy initiation for HIV infection. Hepatitis A is usually transmitted via fecal-oral route, via contaminated food and water and predisposed also by HIV infection. Thus causality is considered not related to blinded study drug.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ALANINE AMINOTRANSFERASE	??[redacted]	1163 /L		
	[redacted]	425 IE/L		
BILIRUBIN TOTAL		27 mkmol/l		
BODY TEMPERATURE		39.7 Celsius		
HEPATITIS A IGM	??-[redacted]	positive		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. HEPATITIS A [10019719]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No. 2
Drug DARUNAVIR/COBICISTAT (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet

Daily Dose 1) 1 Dose(s), 1 in 1 Day
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 1) [redacted] - Stopped

Causality

1. HEPATITIS A [10019719]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No. 3
Drug EMTRICITABINE W/TENOFOVIR DISOPROXIL

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

(DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet

Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Stopped

Causality

1. HEPATITIS A [10019719]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	4
Drug	PLACEBO (PLACEBO) Tablet
Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Stopped

Causality

1. HEPATITIS A [10019719]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Other relevant history (Cont...)

Medical History: PROSTATITIS ??-???-[redacted] - Ongoing
Medical History: ACUTE SINUSITIS ??-???-[redacted] - ??-??-????
Medical History: CYTOMEGALOVIRUS INFECTION ??-???-[redacted] - Ongoing
Medical History: PROCTITIS ??-???-[redacted] - ??-??-????
Medical History: CREATININE RENAL CLEARANCE DECREASED [redacted] - Ongoing : Comments: toxicity grade 2
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: HYPERSENSITIVITY ??-??-???? - Ongoing : Comments: strawberry and cosmetics
Medical History: INFECTIOUS MONONUCLEOSIS ??-??-???? - ??-??-???? : Comments: in childhood

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 Study TMC114FD2HTX3001 Initial

Results: 3 cases selected from 3 matching the following criteria

Start Date : [redacted]

End Date : [redacted]

Date Type : Version Initially Received

Version : Highest In Date Range

Invalid Cases : Excluded

Workflow Cases : Excluded

Deleted Cases : Excluded

Protocol Number(s) : TMC114FD2HTX3001

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 Study TMC114FD2HTX3001 Initial

First Case Version Date Range : Between [redacted]

CIOMS II Report

SDE00256388 Study TMC114FD2HTX3001 Initial

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	3[redacted] Year	F	, in Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
EXPOSURE DURING PREGNANCY	Unknown	No	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	3[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
PNEUMOTHORAX	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION
Suspect Drugs: DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR (1Dose(s))

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR (1Dose(s))

PLACEBO (1Dose(s))

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	2[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

MedDRA 20.0

CIOMS II Report

SDE00256388 Study TMC114FD2HTX3001 Initial

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]						

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
HEPATITIS A	Unknown	Yes	Not Related	UNLABELED	UNLABELED

Comments:

Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION

Disease Type: RADIUS FRACTURE, PROSTATITIS, ACUTE SINUSITIS, PROCTITIS, CYTOMEGALOVIRUS INFECTION, CREATININE RENAL CLEARANCE DECREASED, HIV INFECTION, INFECTIOUS MONONUCLEOSIS, HYPERSENSITIVITY

Suspect Drugs: DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR (1Dose(s)-581Day)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR (1Dose(s)-581Day)

PLACEBO (1Dose(s)-581Day)

MedDRA 20.0

CIOMS Report for SDE00256388 Study TMC114FD2HTX3001 Follow-up

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Results:	7 cases selected from 7 matching the following criteria
Start Date :	[redacted]
End Date :	
Date Type :	Version Initially Received
Version :	Highest In Date Range
Invalid Cases :	Excluded
Workflow Cases :	Excluded
Deleted Cases :	Excluded
Protocol Number(s) :	TMC114FD2HTX3001
First Case Version Date Range :	Between [redacted]

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	4[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

MENINGITIS(10027199)

This report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerned a 4[redacted]-year-old male (subject [redacted] site [redacted] from [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: SINUSITIS ??-[redacted] - Ongoing : Comments: severity grade 2; treated with multiple courses of antibiotics, 3 month

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (7)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

[redacted].

The subject weighed [redacted] kilograms and height was [redacted] centimeters. The subject's concurrent condition included HIV and medical history was not provided.

The subject was randomized and received treatment with blinded darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) 1 dose(s) a day along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral) 1 dose(s) a day coadministered with emtricitabine/tenofovir disoproxil (tablet, oral) 1 dose(s) a day along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV. Concomitant medications were not provided.

On [redacted] the subject experienced an ear infection, and on [redacted] the ear drum perforated.

On [redacted], the subject experienced meningitis and was admitted to the hospital the same day.

The dose of study drug was not changed.

The subject has not recovered from meningitis.

The investigator causality between meningitis and study drug was reported as not related.

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil) using the Summary of Product Characteristics dated [redacted].

The blind has not been broken for this case.

This report is serious (hospitalization).Additional information was received from the investigator on [redacted].

The event severity was moderate and not related to trial procedure.Additional information was received from the investigator, inclusive of discharge hospital records, on [redacted].

Additional concurrent conditions included allergies to aspirin (acetylsalicylic acid) and penicillin (both unknown reaction), sinusitis (treated with multiple courses of antibiotics), and celiac disease.

Ear nose and throat reviewed and discharged the subject home from the emergency department with discharge medications clindamycin and ciprofloxacin.

On [redacted], after taking only one to two doses of the antibiotics, the subject

complained of worsening facial and left ear pain, blurry vision difficulty with word finding and confusion. The subject's system's review was otherwise unremarkable.

Presenting symptoms in the emergency department included worsening left earache and purulent discharge.

Additional diagnostic and laboratory studies included computerized tomogram of the head that was consistent with left otomastoiditis and osteomyelitis. A magnetic resonance imaging study of the head showed cortical hyper intensity and gyral swelling involving left temporoparietal lobe and diffusion restriction along cortex of base of left temoral lobe associated with leptomeningitis. No abscess formation or fluid collection as yet. Evidence of left otomastoiditis without subperiosteal collection/ abscess. A swab (captured as culture) of left ear discharge showed S.pyrogens, cererbral spinal fluid and blood cultures showed no growth to date.

Treatment included intravenous vancomycin, ceftriaxone and dexamethasone. On an unspecified date a tympanostomy (also reported as myringotomy tube) was placed and ciprofloxacin drops were initiated.

Over the course of hospitalization, the subject showed interval improvement in overall well-being, but experienced continued difficulty with hearing (left ear) and only minor improvement in word-finding. The subject remained afebrile throughout the hospitalization. The subject experienced hyponatremia (non-serious) treated with free water restriction and hyperglycemia (non-serious) (likely 2/2 dexamethasone) was treated with sliding scale insulin.

The subject was discharged on [redacted] with discharge diagnoses of meningitis and otomastoiditis. The specific cause of infection had not been isolated. Discharge medications included ciprofloxacin/dexamethasone, salinex spray/saline washes, Nasonex (mometasone furoate), Cipradex drops, vancomycin, and ceftriaxone. The subject was to have a nurse visit to administer the intravenous antibiotics, to be completed on [redacted]. The subject was to have an magnetic resonance imaging study prior to completion of antibiotics and then a follow-up visit with infectious disease scheduled for [redacted].Additional information was received from the investigator on [redacted] and processed with information, inclusive of medical records, received on [redacted].

Additional concurrent history included recurrent sinusitis for three months, ear drum perforation, ear infection, and osteomastoiditis (captured as otomastoiditis).

It was confirmed the subject started with an ear infection on [redacted]. The subject was seen in the emergency room on [redacted] with pain in his left ear and purulent discharge and diagnosed with worsening of ear infection (toxicity grade 1); worsening to osteomastoiditis (ongoing; toxicity grade 3) and discharged on antibiotics clindamycin and ciprofloxacin.

Additional laboratory results included CD4 249 at time of current illness and above 500 prior to current illness. Left ear drainage was positive for group A Streptococcus.

Over the course of the hospitalization (hospital admit date [redacted]) he underwent lumbar puncture which showed 74 white blood cells with 91% neutrophils, glucose of 4.4 and protein 0.49. His condition improved and his confusion resolved. On [redacted], his vancomycin was 22.6 (too high). Vancomycin was adjusted to one gram IV every eight hours and repeat level on [redacted] was 17.7, considered therapeutic.

Post discharge visit with infectious disease ([redacted]), the subject had no further confusion; hearing on the left side had improved, previously he had no hearing; he no longer had any pain in the mastoid region bilaterally. He had experienced breakdown of the skin in the corners of his mouth as well as in the genital and perianal area. His family physician told him that he had evidence of candidiasis and was prescribed clotrimazole cream topically as well as nystatin swish and swallow. His symptoms were reported as much better. At the time of his visit he reported a new rash on his chest, back, and predominantly on his abdomen and his upper legs, reported to be pruritic. He had not experienced a rash like this in the past and was tolerating antibiotics with no concerns. A repeat nuclear magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) were performed that showed almost complete resolution of the left temporoparietal cortical signal abnormality, but persistent otomastoiditis. He continued to have persistent opacification and enhancement of left mastoid air cells. Laboratory data included creatinine, stable, at 66. The newly developed rash was suspected to be secondary to vancomycin and ceftriaxone. The subject is to complete a complete blood count, creatinine and liver enzymes to assess the rash. The plan was to stop the vancomycin if the lab values were normal. If the rash was to continue the ceftriaxone, and alternate therapy was planned. Intravenous ceftriaxone was decreased to 2 g every 24 hours. A red blood cell sedimentation rate (ESR) and C-reactive protein were performed for baseline osteomyelitis (results not provided).

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

At the next visit with infectious disease ([redacted]), his physical exam showed some skin breakdown in the corners of his lips bilaterally with some exudate present. His ears and tympanic membrane appeared normal and there was no mastoid tenderness. The view of the left side was limited, but there did seem to be a perforation superiorly. He had a maculopapular rash over his chest, back, abdomen and upper thighs, both anteriorly and posteriorly. His genital area had some erythema of the glans penis and perianal region. He also has some palmar erythema. Laboratory data included alkaline phosphatase, bilirubin and liver transaminases were normal, hemoglobin 120, white blood cell count 8.7, platelet count 260, creatinine 73, ESR 41 and C-reactive protein 22. The rash, lesions on lips, and discomfort in the genital area were thought to be a hypersensitivity reaction to the antibiotics with associated mucosal candidiasis with the possibility of a serious drug reaction, therefore both the vancomycin and ceftriaxone were stopped on [redacted]. Oral levofloxacin was initiated to treat organisms involved in mastoiditis, including Streptococcus pneumoniae, Haemophilus influenza and group A Streptococcus. The subject was referred to an allergist based on his childhood history penicillin allergy (reaction unknown). An ECG was ordered to follow the subject's QT interval while on levofloxacin.

Final diagnosis was meningitis and otomastoiditis, likely secondary to a bacterial infection that began as sinusitis and progressed to otitis media. Information was received for the interim unblinding on [redacted] and processed with additional information received from the investigator on [redacted]. The interim analysis treatment assignment of study TMC114FD2HTX3001 occurred on [redacted].

Additional information received from the investigator on [redacted] contained no new information.Additional information was received, inclusive of follow-up visit record, from the investigator on [redacted] and processed with additional information received via a query response from the investigator, on [redacted].

Concurrent condition sinus infection started [redacted]. CSF cultures were confirmed as "ultimately negative", but the cultures were performed after antibiotics had been administered. Therefore, antibiotics were continued.

The subject was seen on [redacted] in the infectious disease clinic for his bacterial meningitis secondary to otomastoiditis with associated osteomyelitis on the left side. The subject had continued his levofloxacin and had tolerated it well. The subject has had no fever, chills or sweats. He had some discomfort on the left side of his neck thought to be related to the way he was sleeping. The subject's left ear felt a little more blocked than it did previously, but continued treatment with Ciprodex (ciprofloxacin hydrochloride) drops.

The subject's skin had become more red and itchy since the last visit which prompted an emergency room visit the weekend before this follow-up visit. The subject's lab work remained good and came back negative for hepatitis or other concerning features; he was sent home. Lesions on his lips and gluteal cleft region have improved on clotrimazole cream. Treatment continues with nystatin for oral thrush. A herpes simplex virus (HSV) swab was taken [redacted] since the lesion in his lip may be consistent with that.

Vital signs included blood pressure 155/92, heart rate 116, oxygen saturation 98% on room air, and temperature 36.7 Celsius. On exam, view of his left ear was blocked by a crystal-like substance. This may have been wax, other debris or perhaps crystallized medication. The lesion on his left upper lip was predominantly crusted over. The gluteal cleft region was examined and he had some mucosal breakdown in the cleft, but it looks overall less erythematous and better than it had in the past. His penis remained erythematous as it was last week, but there were no mucosal lesions and no breakdown. He continued with some palmar erythema as well.

Laboratory and diagnostics included an electrocardiogram (ECG) to assess any QT prolongation with levofloxacin; corrected QT interval was 435; occasional premature atrial complexes seen, but otherwise showed sinus rhythm. ESR was down to 3 from previous of 41 and a CRP was 5.3 from previous of 21.9. Complete blood count (CBC) revealed a white blood cell count of 8. 8 (normal), eosinophil 0.992 (elevated), hemoglobin 131 and platelets 300. His electrolytes were normal and creatinine 80; hemoglobin A1C 7.4% and a fasting glucose of 6.7.

The subject had bacterial meningitis, otomastoiditis, and osteomyelitis. The meningitis was now treated and the subject was switched to levofloxacin to treat the remaining osteomyelitis due to his allergic reaction. Levofloxacin will be continued for a total of four weeks. Total antibiotic treatment for osteomyelitis will have been six weeks. The subject was presumed to have candidiasis of the oropharynx and gluteal cleft region; topical therapy has improved the condition. There may have been a component of herpes simplex virus (HSV) as well, although at the time it was resolving. The subject was to return for follow-up on [redacted] where he will have a repeat ESR and C-reactive protein.Additional information was received from the investigator, on [redacted] inclusive of follow-up visit record, and via a query response on [redacted].

The investigator confirmed that the conditions of candidiasis and allergic reaction were not considered serious adverse events.

On [redacted], the subject was seen in the infectious disease clinic. He reported feeling well and had completed seven weeks of antibiotic therapy. The initial starting dose of levofloxacin was 750 mg daily, but was decreased to 500 mg daily because the subject had complained of musculoskeletal symptoms. The symptoms started two and one-half

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

weeks ago at the time of the visit while he was lifting some pillows. Symptoms had been migratory, but seem to have been localized around the right shoulder joint. The symptoms were improving, but were persistent. The subject had also complained of stiffness in his hands and thighs, not associated with pain, but had worsened since beginning levofloxacin. He has no other swollen joints and no pain in his Achilles tendons. The subject had loose stools and at least three stools per day, which was not his normal pattern. There was no associated abdominal pain or cramping. The subject continued to have some hearing issues on the affected side as well as some mild discomfort and fullness in that ear. His tympanostomy tube was unlocked by ear, nose and throat surgeons two weeks ago. Fluid had still been accumulating behind the area, and ciprofloxacin hydrochloride ear drops were continued. The subject had noticed some serous drainage, but the ear was not persistently draining throughout the day. The candida infection involving his oropharynx and gluteal cleft has resolved. His constitutional symptoms had resolved.

On examination, he appeared well. His right tympanic membrane appeared normal and on the left side, his tympanostomy tube was visible with no surrounding cellulitis or active drainage. He had some very mild discomfort on palpation over the left mastoid process, but there was no erythema or bogginess over that site currently. His oropharyngeal exam was unremarkable. His right shoulder, he had full range of motion without pain and his rotator cuff testing was unremarkable. There was some slight fullness to the area compared to the left side with tenderness to palpation anteriorly. Bicipital tendonitis testing was negative. Based on this exam, it was suspected this was more likely a mild subdeltoid or subacromial bursitis than bicipital tendinopathy.

Laboratory data included inflammatory markers (unspecified, captured as laboratory test), results not available. He had a previous eosinophilia after his drug rash, which had resolved. His biochemical markers (unspecified, captured as laboratory test) were near normal (results not provided).

The subject was to continue levofloxacin based on his understanding of the ear, nose and throat team, that he was to continue the treatment until full resolution of accumulating inflammatory fluid. He was counseled on potential side effects including tendinopathy and Clostrium difficile infection and advised to contact the clinic if either his diarrhea or shoulder pain worsened. Clostridium difficile is to be sent at next visit in three weeks to ensure he had not developed colitis.Revision to the information received on [redacted].

Upon review the following correction was made: the date information was received from the investigator, inclusive of follow-up medical record via a query response was amended from [redacted] to [redacted], in the narrative.
Senders Comments/Medical Assessment: V6:

On follow up, event symptoms and tretment details were reported. This information does not change our previous causality assessment.

This is a follow-up report to a 4[redacted]-year-old male with concurrent history included recurrent sinusitis for three months, ear drum perforation, ear infection, and osteomastoiditis who experienced meningitis about 3 months after being on the blinded study drug for HIV infection. Infections can occur with the background indication of HIV, so concurrent recurrent sinusitis, ear drum perforation, ear infection, and osteomastoiditis may provide explanation for the event, hence causality was considered as not related to the study medication.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ALKALINE PHOSPHATASE	[redacted]	normal		
BILIRUBIN		normal		
BLOOD CULTURE	??-[redacted]	no growth to date		
BLOOD ELECTROLYTES	[redacted]	normal		
BLOOD PRESSURE		155/92		
BODY TEMPERATURE	??[redacted]	remained afebrile throughout the hospitalization Celsius		
	[redacted]	36.7 Celsius		
C-REACTIVE PROTEIN		22		
		5.3		
CD4 LYMPHOCYTES	??-???-????	500 prior to current illnes		
	??-[redacted]	249		
COMPUTERISED TOMOGRAM HEAD	??-[redacted]	see Other Diagnostics		
CREATININE	[redacted]	66		
		73		
		80		
CSF CULTURE	??-[redacted]	negative		

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
CSF GLUCOSE	??-???-????	4.4		
CSF NEUTROPHIL COUNT	??-???-????	91 %		
CSF PROTEIN	??-???-????	0.49		
CSF WHITE BLOOD CELL COUNT	??-???-????	74		
CULTURE	??-[redacted]	group A Streptococcus		
		swab: left ear discharge showed S.pyrogens		
DRUG LEVEL	[redacted]	vancomycin 22.6 too high		
		17.7 considered therapeutic		
ECG		see Other Diagnostics		
EOSINOPHIL COUNT		0.992 elevated		
FASTING BLOOD GLUCOSE		6.7		
HEART RATE		116		
HEMOGLOBIN		120		
		131		
HEMOGLOBIN A1C		7.4 %		
HERPES SIMPLEX TEST		results not provided		
LABORATORY TEST		biochemical markers; near normal		
	[redacted]	inflammatory markers results not available		
MAGNETIC RESONANCE IMAGING	??-[redacted]	MRI and MRV post discharge see Other Diagnostics		
		see Other Diagnostics		
OXYGEN SATURATION		98 %		
PHYSICAL EXAMINATION		post discharge see Other Diagnostics		
		see Other Diagnostics		
PLATELETS		260		
		300		
RED BLOOD CELL SEDIMENTATION RATE		41		
		3		
TRANSAMINASES		normal		
WHITE BLOOD CELL COUNT		8.7		
		8.8 normal		

CT head ([redacted]): that was consistent with left otomastoiditis and osteomyelitis; magnetic resonance imaging study of the head ([redacted]): showed cortical hyper intensity and gyral swelling involving left temporoparietal lobe and diffusion restriction along cortex of base of left temoral lobe associated with leptomeningitis. No abscess formation or fluid collection as yet. Evidence of left otomastoiditis without subperiosteal collection/ abscess.

Physical examination post discharge ([redacted]) showed new rash on his chest, back and predominantly on his abdomen and his upper legs, reported to be pruritic. He had not experienced a rash like this in the past and was tolerating antibiotics with no concerns.

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

At the next visit, his physical exam showed some skin breakdown in the corners of his lips bilaterally with some exudate present. His ears and tympanic membrane appeared normal and there was no mastoid tenderness. The view of the left side was limited, but there did seem to be a perforation superiorly. He had a macularpapular rash over his chest, back, abdomen and upper thighs, both anteriorly and posteriorly. His genital area had some erythema of the glans penis and perianal region. He also has some palmar erythema. MRI and MRV [redacted] post discharge): showed almost complete resolution of the left termporoparietal cortical signal abnormality, but persistent otomastoiditis. He continued to have persistent opacification and enhancement of left mastoid air cells. [redacted] ECG: corrected QT interval was 435; occasional premature atrial complexes seen, but otherwise showed sinus rhythm. Physical exam ([redacted]): his tympanostomy tube was visible with no surrounding cellulitis, active drainage. He had some very mild discomfort on palpation over left mastoid process. His right shoulder, had full range of motion without pain. Based on this exam, it was suspected this was more likely a mild subdeltoid or subacromial bursitis than bicipital tendinopathy.

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. MENINGITIS [10027199]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: EAR INFECTION [redacted] - ??-??-???? : Comments: worsened [redacted] to toxicity grade 1
Medical History: MASTOIDITIS [redacted] - Ongoing : Comments: toxicity grade 3
Medical History: TYMPANIC MEMBRANE PERFORATION [redacted] - Ongoing
Drug History: ASPIRIN ??-??-??????-??-???? Indication: Reaction: UNEVALUABLE EVENT
Drug History: PENICILLIN NOS ??-??-??????-??-???? Indication: Reaction: UNEVALUABLE EVENT
Medical History: COELIAC DISEASE ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	3[redacted] Year	M	??	???	????

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PREGNANCY OF PARTNER([redacted])

This pregnancy report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerns a 3[redacted]- year-old male (subject [redacted] site [redacted] from [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☒ NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
800/150/200/10MG	Oral

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)	19. THERAPY DURATION
[redacted] - Ongoing	Ongoing

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Other History: No alcohol use or recreational drug use.

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO. [redacted] (3)

24c. DATE RECEIVED BY MFR. [redacted]

24d. REPORT SOURCE

☒ STUDY ☐ LITERATURE

☒ HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP ☐ FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

The subject's weight and height were not reported. The subject's concurrent conditions included HIV infection.

The subject was randomized and received treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) daily along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral) daily coadministered with emtricitabine/tenofovir disoproxil (tablet, oral) daily along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV infection. Concomitant medications were not reported.

On an unspecified date, the subject's partner became pregnant (coded as pregnancy of partner).

The dose of study drugs was not changed.

The subject outcome was unspecified for pregnancy of partner.

The investigator considered the causality between pregnancy of partner and study drugs as not related.

The blind has not been broken for this case.

This report is not serious.

This case, from the same reporter is linked to [redacted].Additional information was received from the investigator on [redacted].

The subject's concurrent conditions included non smoker. Other medical history included no alcohol use or recreational drug use.

The expected delivery date was [redacted]. The clinical condition of the fetus was [redacted] The status of the pregnancy was continuing. The first prenatal exam was on [redacted]. The pregnancy outcome was [redacted]

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil fumarate) using the Summary of Product Characteristics dated [redacted].Additional information was received on [redacted].

The interim analysis treatment assignment of study TMC114FD2HTX3001 occurred on [redacted].Additional information was received from the investigator on [redacted].

The subject's partner did not experience any medical problems over the course of the pregnancy. The outcome of the pregnancy was not interrupted. Treatment administered on

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

[redacted], to the subject's partner included intravaginal "misolar" for pregnancy and epidural ropivacaine and fentanyl for birth. On [redacted], the subject's partner delivered a [redacted] baby by [redacted] [redacted] gestational age was [redacted]. Apgar score not provided. Additional treatment on [redacted] included, intravenous analgesia (unspecified), for ongoing pain.

The [redacted] baby's appearance was mature and the clinical condition appeared normal. The baby did not receive any medical therapy different from normal newborn care and the hospitalization was not prolonged. The subject's partner was not breast feeding the baby. The relationship between the pregnancy outcome and use of the study drug was reported as no abnormalities.

No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. PREGNANCY OF PARTNER [10050192]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: NON-TOBACCO USER ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	2[redacted] Year	F	??	???	????

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [ ] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

EXPOSURE VIA FATHER([redacted])

This pregnancy report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerns a female of unspecified age (partner subject number [redacted] site

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

partner's dosing dose:800/150/200/10mg

16. ROUTE OF ADMINISTRATION

Unknown

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Other History: No alcohol use or recreational drug use.

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO. [redacted] (4)

24c. DATE RECEIVED BY MFR. [redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

number [redacted]), from [redacted]

The female partner's weight and height were not reported. Her concurrent conditions were not reported.

The male subject received treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) daily along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral) daily coadministered with emtricitabine/tenofovir disoproxil (tablet, oral) daily along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV infection. Concomitant medications were not reported.

On an unspecified date, the female partner became pregnant characterizing paternal drug exposure during pregnancy. It was unspecified if she had been pregnant before.

The female partner outcome was unspecified for paternal drug exposure during pregnancy. The status of the pregnancy and condition of the fetus were unspecified.

Action taken with dose of study drugs was dose not changed.

The investigator considered the causality between paternal drug exposure during pregnancy and study drugs as not related.

The blind has not been broken for this case.

This report is not serious.

This case, from the same reporter is linked to [redacted].Additional information was received from the investigator on [redacted].

The local reference number was added to the case: [redacted]

This report concerns a 2[redacted] year old female. Subject demographics were updated (date of birth). The subject's weight was [redacted] kilograms and height was [redacted] centimeters. The subject's medical history included non-smoker. The subject had not been pregnant before.

The subject's last menstrual period was on [redacted], with an expected delivery date of [redacted]. The subject's pregnancy was confirmed on [redacted]. The first prenatal exam was on [redacted]. The pregnancy outcome was unspecified. An ultrasound was performed on [redacted]. The clinical condition of the fetus was normal. The status of the pregnancy was continuing. The subject was on natifar and had a tetanius vaccine.

Laboratory data also included: blood test [redacted] normal , [redacted] normal , [redacted] [redacted] normal , [redacted] normal glucose [redacted] normal. Other diagnostics

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

included urocultive on [redacted], [redacted], [redacted], [redacted] were normal.Additional information received from the investigator on [redacted] contained no new information (duplicate of the information received initially on [redacted]). No changes were made to this report.Additional information was received on [redacted].

The interim analysis treatment assignment of study TMC114FD2HTX3001 occurred on [redacted]. Additional information was received from the investigator on [redacted].

The female partner did not experience any medical problems over the course of her pregnancy. The outcome of the pregnancy was not interrupted. Treatment administered on [redacted], to the female partner included intravaginal "misolar" for pregnancy and epidural ropivacaine and fentanyl for birth. On [redacted], the female partner delivered a [redacted]; gestational age was [redacted]. Apgar score not provided. Additional treatment on [redacted] included, intravenous analgesia (unspecified), for ongoing pain.

The [redacted] baby's appearance was mature and the clinical condition appeared normal. The baby did not receive any medical therapy different from normal newborn care and the hospitalization was not prolonged. The female partner was not breast feeding the baby. The relationship between the pregnancy outcome and study medication was reported as no abnormalities.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
BLOOD TEST	[redacted]	normal		
		normal		
		normal		
		normal		
GLUCOSE		normal		

urocultive [redacted], [redacted] normal

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. EXPOSURE VIA FATHER [10071403]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Pregnant Expected Date of Delivery: [redacted] LMP Date: [redacted]
Medical History: NON-TOBACCO USER ??-??-???? - ??-??-????

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
PRIVATE	[redacted]	[redacted]	[redacted]	[redacted]	3[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

HEPATITIS A(10019719)

This report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerns a 3[redacted]-year-old male (subject [redacted]-[redacted] site [redacted] from [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT (DARUNAVIR/COBICISTAT) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
1 Dose(s), 1 in 1 Day	Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)	19. THERAPY DURATION
[redacted] - Ongoing	Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

PYRIDOXINE (PYRIDOXINE) Oral Oral [redacted] - Ongoing5 mg,1 in 1 Day

23. OTHER RELEVANT HISTORY

Medical History: HIV INFECTION [redacted] - Ongoing

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO. [redacted] (3)

24c. DATE RECEIVED BY MFR. [redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

The subject's weight was [redacted] kilograms and height [redacted] centimeters. The subject's concurrent conditions included HIV and nephrolithiasis; medical history included skin allergy.

The subject was randomized and received treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) one table once a day, along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral) one table once a day, coadministered with emtricitabine/tenofovir disoproxil (tablet, oral) one tablet once a day, along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV. Concomitant medications included magnesium for prophylaxis, pyridoxine for prophylaxis B6 deficiency, 25 OH vitamin D reduced level (ergocalciferol) for vitamin D level reduction, and calcium for osteopenia.

On [redacted], the subject presented to the emergency room and experienced acute viral hepatitis A. The subject had been febrile since [redacted] with nausea and minor vomiting. Fever persisted in spite of anitpyretics. He was hospitalized for diagnostics. Laboratory data included ([redacted]) aspartate aminotransferase (AST) 2953 u/l (NR: 10-59 u/l), alanine aminotransferase (ALT) 3039 u/l (NR: 10-70 u/l), serum bilirubin 53.7 micromol/L (NR: 3-22 micromol/L); Hepatitis A virus IGM antibodies positive; Hepatitis B surface antigen, hepatitis C virus antibodies, Epstein Barr virus IGM antibodies, cytomegalovirus IgM antibodies were negative. Blood morphology showed slight leucopenia 3.2 x10E3/mm3 and quick index (captured as quick's test) was 70%.

Treatment included intravenous hydration.

Action taken with study drugs was not changed.

The subject had not recovered from acute viral hepatitis A.

The investigator assessed the event as not related to trial procedure.

The investigator considered the causality between acute viral hepatitis A and study drugs as not related.

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil) using the Summary of Product Characteristics dated [redacted].

The blind has not been broken for this case.

This report is serious (hospitalization).Additional information was received on [redacted]

The interim analysis treatment assignment of study TMC114FD2HTX3001 occurred on [redacted]

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

[redacted].Additional information was received via a query response from the investigator on [redacted].

Additional concurrent conditions included osteopenia.

Additional symptoms on admission included high fever (unspecified) and general malaise.

Additional laboratory data included elevated liver enzymes (captured as transaminases) with slightly elevated bilirubin and leucopenia. A urine test confirmed urinary tract infection (organism not specified).

Additional treatment included diet (unspecified) and medication against vomiting, Torecan (thiethylperazine maleate). Urinary tract infection was treated with intravenous (IV) ciprofloxacine 2 x 400 mg for six days. The hospital course was uncomplicated, and the subject had been improving at the time of this report.

The investigator assessed the event as grade 2 or moderate and not related to HIV.

The subject was recovering from the serious event of acute viral hepatitis A (updated from not recovered). The subject was discharged on [redacted]. Laboratory data on [redacted] included ALT 633 IU (elevated) and AST 212 IU (elevated). Further control in outpatient clinic and liver enzyme tests were planned.Additional information was received from the investigator on [redacted].

Laboratory data also included: On [redacted], alanine aminotransferase was 61 IU, aspartate aminotransferase 26 IU, and liver enzymes were within normal range, subject fully recovered.

The subject had recovered from acute viral hepatitis A on [redacted] (previously recovering).

Senders Comments/Medical Assessment: V3:

Follow-up information provided with regard to event outcome. This does not alter the previous causality assessment (remains as not related).

This report concerns a 3[redacted]-year-old male subject who developed acute viral hepatitis A approximately 18 months after initiation of study therapy for HIV-1 infection. The underlying HIV infection is a known predisposing factor hepatitis a infection, therefore causality was considered as not related to study therapy.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ALANINE AMINOTRANSFERASE	[redacted]	3039 U/L	10	70
		633 elevated U/L		
		61 IU U/L		
ASPARTATE AMINOTRANSFERASE		2953 U/L	10	59
		212 elevated U/L		
		26 IU U/L		
CMV IGG ANTIBODY		negative		
EPSTEIN-BARR VIRUS IGM ANTIBODY		negative		
HEPATITIS A IGM		positive		
HEPATITIS B SURFACE ANTIGEN		negative		
HEPATITIS C ANTIBODY		positive		
LEUCOCYTE COUNT		leucopenia 10E3/mm3		
		3.2 10E3/mm3		
LIVER ENZYMES		within normal range, subject fully recovered		
QUICK'S TEST		70 %		
SERUM BILIRUBIN		slightly elevated mcmol/L	3	22
		53.7 mcmol/L		

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
TRANSAMINASES	[redacted]	elevated		
URINE CULTURE		confirmed urinary tract infection		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT (DARUNAVIR/COBICISTAT) Tablet

Causality

1. HEPATITIS A [10019719]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No. 2
Drug EMTRICITABINE W/TENOFOVIR DISOPROXIL (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet

Daily Dose 1) 1 Dose(s), 1 in 1 Day
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 1) [redacted] - Ongoing

Causality

1. HEPATITIS A [10019719]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: DERMATITIS ALLERGIC ??-??-???? - ??-??-????
Medical History: NEPHROLITHIASIS ??-??-???? - Ongoing
Medical History: OSTEOPENIA ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	4[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

TRANSIENT ISCHAEMIC ATTACK([redacted])

This report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerns a 4[redacted]-year-old male (subject [redacted] site [redacted] from [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
1 Dose(s), 1 in 1 Day	Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)	19. THERAPY DURATION
[redacted] - Ongoing	Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE) Oral Oral ??-[redacted] - Ongoing12.5 mg,2 in 1 Day

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: TRANSIENT ISCHAEMIC ATTACK ??-???-[redacted] - ??-??-???? : Comments: or stroke (resolved)

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001 Center no : [redacted] Patient no : [redacted]	24b. MFR. CONTROL NO. [redacted] (2)
24c. DATE RECEIVED BY MFR. [redacted]	24d. REPORT SOURCE [X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE [ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

[redacted]

Information was received for the interim unblinding on [redacted] and was processed with initial information received from the investigator on [redacted].

The subject's weight was [redacted] pounds and height [redacted] inches. The subject's concurrent conditions included HIV, hypertension, seasonal allergies, anxiety, depression, insomnia and herpes. Medical history included transient ischemic attack (TIA) or stroke [redacted] that resolved.

The subject was randomized and received treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) once a day, along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral) once a day, coadministered with emtricitabine/tenofovir disoproxil (tablet, oral) once a day, along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV. Concomitant medications included vitamin C, fish oil and calcium carbonate for general nutrition (captured as vitamin supplementation), lisinopril and hydrochlorothiazide for hypertension, dozol for insomnia, valaciclovir hydrochloride for herpes, acetylsalicylic acid for cardiac health (captured as cardiac prophylaxis), montelukast sodium for seasonal allergies, alprazolam for anxiety, and bupropion hydrochloride for depression.

On [redacted], the subject experienced a transient ischemic attack and was hospitalized. Symptoms included dizziness and left-sided body numbness. Differential diagnosis included transient ischemic attack.

On [redacted], treatment included oral Plavix (clopidogrel bisulfate).

Action taken with study drugs was dose not changed.

The subject had recovered and was discharged on [redacted]. Clopidogrel bisulfate was ongoing at the time of discharge.

The investigator assessed the event as grade 3 or severe in severity, not related to trial procedure, and not related to HIV.

The investigator considered the causality between transient ischemic attack and study drugs as not related.

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil) using the Summary of Product Characteristics dated [redacted].

The blind has not been broken for this case.

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

This report is serious (hospitalization).

The interim analysis treatment assignment of study TMC114FD2HTX3001 occurred on [redacted].Additional information was received from the investigator, inclusive of medical records, on [redacted].

Additional concurrent conditions included obesity (BMI [redacted]), Dyslipidemia, social drinker, ex-smoker ([redacted] stopped [redacted]), no use of recreational drugs, and drug allergy to Percocet (oxycet) causing nausea and vomiting. Historical drugs include fenofibrate for dyslipidemia (stopped recently by primary physician).

Study drugs continued unchanged during the hospitalization.

On [redacted], the subject developed dizziness five hours prior to admission. He was unable to describe the dizziness, but it was very similar to when he had a stroke in the past, He did not identify any alleviating or aggravating factors, and the dizziness was constant. He had some relief after he had arrived at the emergency room. The dizziness was associated with left-sided body numbness and tingling. He denied headache, blurry vision, loss of consciousness. He was placed on stoke alert, no tissue plasminogen activator was recommended. Vital signs included 98.3, blood pressure was elevated on arrival and then 155/103, respiratory rate 12, heart rate 73, oxygen saturation 98% on room air. Physical exam included head atraumatic, pupils reactive, subject was alert, awake and oriented times three; cranial nerves II through XII were intact; muscle strength 5/5 muscle group; reflexes symmetrical and normal, and sensitivity to light touch was normal. Admitting diagnoses were dizziness/left-sided body numbness, rule out TIA versus stoke and accelerated hypertension.

Laboratory and diagnostic data included comprehensive metabolic panel (CMP) was unremarkable, potassium 4.2, troponin at 17:35 <0.03 and at 22:56 <0.03, white blood cell count (WBC) 8.7, hemoglobin 13.8, hematocrit 39.7, platelet count 275, international normalized ratio 1, hemoglobin A1C 5.3, liver function tests were normal, triglycerides 106, total cholesterol 216, HDL 82, LDL 113; chest x-ray showed no acute abnormality, electrocardiogram (ECG) showed ST elevation in lateral leads, most likely repolarization abnormality. ECG was reviewed with cardiology and repeat ECG was normal (subject had denied chest pain). Computerized tomogram of the head showed no evidence of intracranial abnormality. On [redacted], troponin <0.03, magnesium 1.8 (low); his ECG showed QTc prolongation; nuclear magnetic resonance imaging of brain and magnetic resonance angiogram of brain and carotids were negative; echocardiogram was reported as being suboptimal and study quality was limited by the subject's body habitus, the study showed ejection fraction 65-69%; NIVL carotid duplex (captured as carotid artery ultrasound)showed less than 50% bilateral carotid artery stenosis by velocity criteria and antegrade bilateral vertebral artery flow; seen by physical, occupational and speech therapy and it was determined that the therapies were not needed at the time. On [redacted], magnesium was 2.0.

Additional treatment included switching from acetylsalicylic acid to oral Plavix (clopidogrel), oral atorvastatin, increased lisinopril from 10 mg to 20 mg once a day (previously reported subject was taking 20 mg/day), oral temazepam and oral alprazolam for anxiety, injection Lovenox (enoxaparin sodium) for deep venous thrombosis prophylaxis, injection ondansetron, oral magnesium oxide, intravenous magnesium sulfate and potassium chloride replacement protocol, continue montelukast, and intravenous fluid. Neurology and physical therapy evaluations were requested and weight loss was recommended; subject was on a regular cardiac diet in the hospital.

Over the course of the hospitalization, the subject's blood pressure was well controlled. Blood pressure over 24 hours ([redacted] to [redacted]) 119-155 mmHg systolic and 75-103 mmHg diastolic. On [redacted], cardiology was consulted and assessed the subject as having prolonged QT interval 670 ms; ST abnormality most likely due to QT prolongation on first ECG. On IV magnesium, the QT interval was 436 ms (also reported as 407 ms) with improvement in the ST abnormality on the second ECG. Possibilities included Wellbutrin (bupropion hydrochloride) as well as antiviral medications for HIV. The QT prolongation improved after IV magnesium. The plan of treatment was to continue oral magnesium, 2D echocardiogram and consult pharmacy to evaluate medications. Blood pressure over 24 hours ([redacted] to [redacted]) 119-153 mmHg systolic and 78-93 mmHg diastolic. On [redacted], bupropion hydrochloride was stopped.

The final diagnosis was TIA; stroke was ruled out. The subject had recovered and was discharged on [redacted], updated from [redacted]. The subject was to have an ECG done in one to two weeks after discharge by his primary physician. If the subject was to restart antidepressants he would need to have his ECGs monitored. Discharge medications included oral temazepam, oral alprazolam, oral atorvastatin, oral clopidogrel, oral Lisinopril, oral magnesium oxide, and oral montelukast.Additional information was received from the investigator, inclusive of medical records, via a query response, on [redacted].

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Allergy to oxycet causing nausea and vomiting was updated to subject preference that he does not like to take oxycet, therefore he explained he was allergic. Treatment with clopidogrel was started on [redacted], updated from [redacted]. The investigator confirmed that QT prolongation was not considered a serious adverse event.
Senders Comments/Medical Assessment: V2:

Follow up reports event treatment details, also investigator confirmed that QT prolongation was considered as non-serious adverse event.This information does not change our previous causality assessment.

This is a follow up report to a 4[redacted]-year-old male subject with medical histories of obesity, dyslipidemia, tobacco use, hypertension, and transient ischemic attack (TIA) who experienced TIA approximately 1.5 years following study therapy initiation for HIV. The event is alternatively explained by pre-existing histories of obesity, dyslipidemia, tobacco use, hypertension and TIA, therefore causality is considered not related to study therapy. Follow up information included update on concurrent conditions, additional diagnostics, treatment/discharge medications, and clinical course which does not alter the prior causality assessment for TIA (remains as not related). ECG revealed QTc prolongation which subsequently improved following magnesium treatment (IV) and with ongoing study therapy use. Of note, concurrent diuretic therapy (hydrochlorothiazide) is known to be associated with hypomagnesemia. Event is not anticipated per protocol.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
BLOOD PRESSURE	[redacted]	elevated on admission to ER		
		155/103		
BLOOD PRESSURE DIASTOLIC	[redacted]	over 24 hours [redacted]: 75-103 mmHg		
	[redacted]	over 24 hours [redacted]:78-93 mmHg		
BLOOD PRESSURE SYSTOLIC	[redacted]	over 24 hours [redacted]:119-155		
		over 24 hours [redacted]:119-153		
CAROTID ARTERY ULTRASOUND		see Other Diangositcs		
CHEST X-RAY		no acute abnormality		
CHOLESTEROL TOTAL		216		
COMPREHENSIVE METABOLIC PANEL		unremarkable		
COMPUTERIZED TOMOGRAM HEAD		no evidence of intracranial abnormality		
ECG		see Other Diagnostics		
		see Other Diagnostics		
ECHOCARDIOGRAM	[redacted]	see Other Diagnostics		
HDL	[redacted]	82		
HEART RATE		73		
HEMATOCRIT		39.7		
HEMOGLOBIN		13.8		
HEMOGLOBIN A1C		5.3		
INTERNATIONAL NORMALIZED RATIO		1		
LDL	[redacted]	113		
LIVER FUNCTION TEST		normal		
MAGNESIUM		1.8 low		
		2.0		
MRI ANGIOGRAPHY		negative of brain and carotids		
MRI BRAIN	[redacted]	negative		
OXYGEN SATURATION		98% on room air %		

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
PHYSICAL EXAMINATION	[redacted]	see Other Diagnostics		
PLATELET COUNT	[redacted]	275		
POTASSIUM		4.2		
RESPIRATORY RATE		12		
TRIGLYCERIDES		106		
TROPONIN		at 17:35 <0.03		
		at 22:56 <0.03		
	[redacted]	<0.03		
WHITE BLOOD CELL COUNT		8.7		

Physical examination ([redacted]): included head atraumatic, pupils reactive, subject was alert, awake and oriented times three; cranial nerves II through XII were intact; muscle strength 5/5 muscle group; reflexes symmetrical and normal and sensitivity to light touch was normal. ECG [redacted]: QTc prolongation 670 ms, showed ST elevation in lateral leads, most likely repolarization abnormality. ECG was reviewed with cardiology. ECG repeat [redacted]: repeat was normal; QTc prolongation 436 ms (also reported as 407 MS) after IV magnesium. Carotid artery ultrasound (NIVL carotid duplex) [redacted]: showed less than 50% bilateral carotid artery stenosis by velocity criteria and antegrade bilateral vertebral artery flow. Echocardiogram [redacted]: was reported as being suboptimal and study quality was limited by the subject's body habitus, the study showed ejection fraction 65-69%.

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. TRANSIENT ISCHAEMIC ATTACK [10044390]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No. 2
Drug ASPIRIN (ACETYLSALICYLIC ACID)

Daily Dose 1) 81 mg, 1 in 1 Day
Indication 1) CARDIOVASCULAR EVENT PROPHYLAXIS
Route of Admin. 1) Oral
Therapy Dates/Duration 1) ??-???-[redacted] - Stopped

Seq. No. 3
Drug MONTELUKAST SODIUM (MONTELUKAST SODIUM)

Daily Dose 1) 10 mg, 1 in 1 Day
Indication 1) SEASONAL ALLERGY
Route of Admin. 1) Oral

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Therapy Dates/Duration	1) ??-[redacted] - Ongoing
Seq. No.	4
Drug	ALPRAZOLAM (ALPRAZOLAM)
Daily Dose	1) 0.5 mg, 1 in 1 As Necessary
Indication	1) ANXIETY
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-[redacted] - Ongoing
Seq. No.	5
Drug	WELLBUTRIN (BUPROPION HYDROCHLORIDE)
Daily Dose	1) 150 mg, 1 in 1 Day
Indication	1) DEPRESSION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-[redacted] - Stopped
Seq. No.	6
Drug	LISINOPRIL (LISINOPRIL)
Daily Dose	1) 10 mg, 1 in 1 Day
Daily Dose	2) 20 mg, 1 in 1 Day
Indication	1) HYPERTENSION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-??-???? - Stopped
Therapy Dates/Duration	2) ??-[redacted] - Ongoing
Seq. No.	7
Drug	CALTRATE (CALCIUM CARBONATE)
Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) VITAMIN SUPPLEMENTATION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-???-[redacted] - Ongoing
Seq. No.	8
Drug	TYLENOL PM (DOZOL)
Daily Dose	1) 1 Dose(s), 1 in 1 As Necessary
Indication	1) INSOMNIA
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-???-[redacted] - Ongoing
Seq. No.	9
Drug	VALACYCLOVIR (VALACICLOVIR HYDROCHLORIDE)
Daily Dose	1) 500 mg, 1 in 1 As Necessary
Indication	1) HERPES VIRUS INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-[redacted] - Ongoing

Other relevant history (Cont...)

Medical History: OBESITY ??-???-[redacted] - Ongoing : Comments: BMI [redacted]
Drug History: FENOFIBRATE ??-??-??????-??-???? Indication: DYSLIPIDAEMIA Reaction:
Drug History: PERCOCET ??-??-??????-??-???? Indication: Reaction: NAUSEA
Drug History: PERCOCET ??-??-??????-??-???? Indication: Reaction: VOMITING
Medical History: ABSTAINS FROM RECREATIONAL DRUGS ??-??-???? - Ongoing

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Medical History: ANXIETY ??-??-???? - Ongoing
Medical History: DEPRESSION ??-??-???? - Ongoing
Medical History: DYSLIPIDAEMIA ??-??-???? - Ongoing
Medical History: EX-TOBACCO USER ??-??-???? - Ongoing : Comments: smoked for more than 20 years; stopped [redacted]
Medical History: HERPES VIRUS INFECTION ??-??-???? - Ongoing
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: HYPERTENSION ??-??-???? - Ongoing
Medical History: INSOMNIA ??-??-???? - Ongoing
Medical History: SEASONAL ALLERGY ??-??-???? - Ongoing
Medical History: SOCIAL ALCOHOL DRINKER ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
PRIVATE	[redacted]	[redacted]	[redacted]	[redacted]	2[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

MYOCARDITIS INFECTIOUS([redacted])

This report was received from clinical trial TMC114FD2HTX3001: A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects. EudraCT #: 2015-000754-38, and concerns a 2[redacted]-year-old [redacted] male (subject [redacted], site [redacted] from

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - [redacted]

19. THERAPY DURATION

474 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

VANCOMYCIN (VANCOMYCIN) Oral Oral [redacted] - Ongoing250 mg,3 in 1 Week

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: OSTEOPOROSIS [redacted] - Ongoing : Comments: Toxicity grade 2

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

[redacted]

The subject's weight was [redacted] kilograms and height was [redacted] centimeters. The subject's concurrent conditions included HIV, recurrent upper respiratory tract infections, Hashimoto's thyroiditis, and osteoporosis; medical history included albinism, gonorrhea, nausea, pharyngitis, diarrhea, acute hepatitis type C, beta 2 microglobinuria (captured as beta 2 microglobulin increased), angina tonsillaris, alanine aminotransferase (ALT) elevation, aspartate aminotransferase (AST) elevation, faintness (vertigo), enterocolitis of most probably clostridium difficile etiology (captured as enterocolitis), loose stools, suspicion of giardiasis, and proctitis.

The subject was randomized and received treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral, batch 4373400) one tablet daily, along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral, batch 4373614) one tablet daily, coadministered with emtricitabine/tenofovir disoproxil (tablet, oral, batch 4373432) one tablet daily, along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, all initiated on [redacted] for HIV. The subject received treatment from [redacted] to [redacted]. The subject missed dosing from [redacted] to [redacted]. The subject resumed treatment on [redacted] to [redacted]. The subject missed dosing on [redacted]. The subject resumed treatment on [redacted]. Concomitant medications included symbiotic for diarrhea, vancomycin for enterocolitis of most probably clostridium difficile etiology, doxycycline for pharyngitis, lactobacillus acidophilus and lactobacillus rhamnosus for prophylaxis diarrhea, and loperamide hydrochloride for diarrhea.

On [redacted], the subject experienced infectious myocarditis and was hospitalized. Symptoms included chest pain for three hours radiating to the left arm. On physical examination, there was no signs of overt heart failure, blood pressure 95/55 and heart rate 75/min.

Diagnostic date included electrocardiogram (ECG) that showed normal sinus rhythm, right bundle branch block and ST elevation antero-lateral myocardial infarction. Coronarography (captured as computerized tomogram coronary artery) did not reveal any pathology of coronary arteries. Echocardiography showed no signs of abnormal heart contractility and no signs of right ventricular overload. Laboratory data showed elevated CTNI (captured as troponin) 11,254 ng/ml (NR: 00-0.10) on [redacted], and 15,931 ng/ml (NR: 00-0.10) on the next day. PCT (captured as procalcitonin) was negative. Repeated echocardiography showed EF 60%, trace of pericardial effusion (locally up to 8 mm, on the borderline of right and left ventricle), without segmental abnormalities of contractility. Cardiac magnetic resonance imaging (MRI) and viral serology for myocarditis results were pending.

Treatment included oral acetylsalicylic acid, oral clopidogrel one time, intravenous (IV) unfractioned heparin, IV pantoprazole and oral trimetazidine.

During the hospitalization course, there were no recurrence of complaints, arrhythmia. No clinical symptoms of infection were observed.

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Action taken with study drugs was dose not changed.

The subject was recovering from the serious event of infectious myocarditis. After observation, the patient was discharged in good clinical status to further ambulatory follow up of primary care physician and cardiologist.

The investigator assessed the event as grade 3 or severe in severity, not related to trial procedure, and not related to HIV.

The investigator considered the causality between infectious myocarditis and study drugs as doubtful. Company causality was assessed as not related.

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil) using the Summary of Product Characteristics dated [redacted].

The blind has not been broken for this case

This report is serious (hospitalization).Additional information was received from the investigator on [redacted] and [redacted].

On [redacted], a cardiac magnetic resonance imaging with contrast showed delayed enhancement in periapical segment and neighboring part of right ventricle, of about 10 mm of length, what may have corresponded to inflammatory changes. The other parts of the myocardium were homogenous. There were no signs of myocardial edema, pericardiaI fluid layer over left and right ventricle, maximally 5 mm. Normal pericardiaI laminae. No signs of segmental contractility abnormalities had been noted. Cardiac valves were without abnormalities. Normal aortic bulb and ascending aorta right ventricular outlet tract (RVOT) and left ventricular outlet tract (LVOT) were of normal width. Left ventricle: left ventricular end diastolic diameter (LVEDd) 4.4cm (NR: 3.5-4.7 cm), left ventricular end systolic diameter (LVESd) 3.4 cm (NR: 2.2-3.8 cm), PWd 0.8cm (NR: 0.6-1.1 cm), PWs 1.3 cm (NR: l.0-1.5 cm). lntraventricular septum diastolic thickness: 0.9 cm (NR: 0.9-1.2 cm); Right ventricle: PVEDd 2.6 cm (NR: 2.6-4.3 cm).

The subject was discharged on [redacted].

On [redacted], serology results included Influenza type A lgG antibodies positive, Influenza type A lgM antibodies negative, Influenza type B lgG antibodies positive, Influenza type B lgM antibodies negative, Epstein-Barr virus (EBV) lgG antibodies 70.5 U/ml (positive >20 U/ml), EBV lgM antibodies 48.4 U/L (positive >40 U/ml), Parvovirus B19 lgG 2.34 U/ml (negative <4 U/ml), Parvovirus B19 lgM 0.80 U/ml (borderline result 0.8-1.1 U/ml).

On [redacted], the subject had a follow-up visit.
Senders Comments/Medical Assessment: V1:

Additional information was received with regard to the diagnostic results. This does not change our prior assessment of the case.

This 2[redacted]-year-old male subject experienced with medical histories of pharyngitis, acute hepatitis C, angina tonsillaris, enterocolitis, proctitis and recurrent upper respiratory tract infections experienced infectious myocarditis approximately 1.5 years following blinded study therapy initiation for HIV infection. The predisposing histories of multiple infections including ongoing recurrent upper respiratory tract infections provides an alternative explanation for infectious myocarditis, therefore causality is considered not related to blinded study therapy.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
BLOOD PRESSURE	[redacted]	99/55		
CARDIAC MRI		see Other Diagnostics		
COMPUTERIZED TOMOGRAM CORONARY ARTERY		no pathology of coronary arteries		
EBV IGG		70.5 U/mL		positive >20
EBV IGM		48.4 U/L		positive >40
ECG		see Other Diagnostics		
ECHOCARDIOGRAPHY		repeated test see Other Diagnostics		
		see Other Diagnostics		
HEART RATE		75 /min		
INFLUENZA A VIRUS IGG		positive		
INFLUENZA A VIRUS IGM		negative		
INFLUENZA B VIRUS IGG		positive		
INFLUENZA B VIRUS IGM		negative		

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
PARVOVIRUS B19 SEROLOGY	[redacted]	IgM 0.80 U/ml (borderline result 0.8-1.1 U/ml) U/mL		
		lgG 2.34 (negative <4 U/ml) U/mL		
PHYSICAL EXAMINATION	[redacted]	no signs of overt heart failure		
PROCALCITONIN		negative		
TROPONIN		11,254 ng/mL	0.0	0.10
		15,931 ng/mL		

ECG ([redacted]): normal sinus rhythm, right bundle branch block and ST elevation antero-lateral myocardial infarction. Echocardiography ([redacted]) showed no signs of abnormal heart contractility and no signs of right ventricular overload. Echocardiography (repeated [redacted]): EF 60%, trace of pericardial effusion (locally up to 8 mm, on the borderline of right and left ventricle), without segmental abnormalities of contractility. Cardiac MRI ([redacted]): with contrast showed delayed enhancement in periapical segment and neighboring part of right ventricle, of about 10 mm of length, what may have corresponded to inflammatory changes. The other parts of myocardium were homogenous. There were no signs of myocardial edema, pericardia I fluid layer over left and right ventricle-maximally 5 mm. Normal pericardia I laminae. No signs of segmental contractility abnormalities had been noted. Cardiac valves were without abnormalities. Normal aortic bulb and ascending aorta right ventricular outlet tract (RVOT) and left ventricular outlet tract (LVOT) were of normal width. Left ventricle: left ventricular end diastolic diameter (LVEDd) 4.4cm (NR: 3.5-4.7 cm), left ventricular end systolic diameter (LVESd) 3.4 cm (NR: 2.2-3.8 cm), PWd 0.8cm (NR: 0.6-1.1 cm), PWs 1.3 cm (NR: l.0-1.5 cm). lntraventricular septum diastolic thickness: 0.9 cm (NR: 0.9-1.2 cm); Right ventricle: PVEDd 2.6 cm (NR: 2.6-4.3cm).

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet
Daily Dose	2) 1 Dose(s), 1 in 1 Day 3) 1 Dose(s), 1 in 1 Day
Therapy Dates/Duration	2) [redacted] - Stopped 3) [redacted] - Ongoing

Causality

1. MYOCARDITIS INFECTIOUS [10066857]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Doubtful
Causality as per Mfr.	Not Related

Seq. No.	2
Drug	DARUNAVIR/COBICISTAT (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Daily Dose	2) 1 Dose(s), 1 in 1 Day
	3) 1 Dose(s), 1 in 1 Day
	1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	3) [redacted] - Ongoing
	1) [redacted] - Stopped
	2) [redacted] - Stopped

Causality

1. MYOCARDITIS INFECTIOUS [10066857]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Doubtful
Causality as per Mfr.	Not Related

Seq. No.	3
Drug	EMTRICITABINE W/TENOFOVIR DISOPROXIL (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet
Daily Dose	1) 1 Dose(s), 1 in 1 Day
	2) 1 Dose(s), 1 in 1 Day
	3) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	2) [redacted] - Stopped
	3) [redacted] - Ongoing
	1) [redacted] - Stopped

Causality

1. MYOCARDITIS INFECTIOUS [10066857]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Doubtful
Causality as per Mfr.	Not Related

Seq. No.	4
Drug	PLACEBO (PLACEBO) Tablet
Daily Dose	2) 1 Dose(s), 1 in 1 Day
	3) 1 Dose(s), 1 in 1 Day
	1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	3) [redacted] - Ongoing
	1) [redacted] - Stopped
	2) [redacted] - Stopped

Causality

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Causality

1. MYOCARDITIS INFECTIOUS [10066857]

Change in dose	Dose Not changed
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Concomitant Drugs (Cont...)

Seq. No.	2
Drug	DOXYCYCLINE (DOXYCYCLINE)
Daily Dose	1) 100 mg, 2 in 1 Day
Indication	1) PHARYNGITIS
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing
Seq. No.	3
Drug	LACTOBACILLUS ACIDOPHILUS (LACTOBACILLUS ACIDOPHILUS) Tablet
Daily Dose	1) 1 Dose(s), 2 in 1 Day
Indication	1) ANTIDIARRHOEAL SUPPORTIVE CARE
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing
Seq. No.	4
Drug	LACTOBACILLUS RHAMNOSUS (LACTOBACILLUS RHAMNOSUS) Tablet
Daily Dose	1) 1 Dose(s), 2 in 1 Day
Indication	1) ANTIDIARRHOEAL SUPPORTIVE CARE
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing
Seq. No.	5
Drug	LOPERAMID (LOPERAMIDE HYDROCHLORIDE) Tablet
Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) DIARRHOEA
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing

Other relevant history (Cont...)

Medical History: NAUSEA [redacted] : Comments: Toxicity grade 2
Medical History: PHARYNGITIS [redacted] : Comments: Toxicity grade 2
Medical History: DIARRHOEA [redacted] : Comments: Toxicity grade 2
Medical History: ACUTE HEPATITIS C [redacted] : Comments: Toxicity grade 2
Medical History: BETA 2 MICROGLOBULIN INCREASED [redacted] : Comments: Toxicity grade 2
Medical History: TONSILLITIS [redacted] : Comments: Toxicity grade 2
Medical History: ALANINE AMINOTRANSFERASE INCREASED [redacted] : Comments: Toxicity grade 4
Medical History: ASPARTATE AMINOTRANSFERASE INCREASED [redacted] : Comments: Toxicity grade 2

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Medical History: ENTEROCOLITIS [redacted] : Comments: most probably clostridium difficile etiology; Toxicity grade 3
Medical History: SYNCOPE [redacted] : Comments: vertigo, Toxicity grade 3
Medical History: DIARRHOEA [redacted] : Comments: Toxicity grade 1
Medical History: GIARDIASIS [redacted] : Comments: suspicion of giardiasis; Toxicity grade 2
Medical History: PROCTITIS [redacted] : Comments: Toxicity grade 2
Other History: ethnicity=[redacted]
Medical History: ALBINISM ??-??-???? - ??-??-????
Medical History: AUTOIMMUNE THYROIDITIS ??-??-???? - Ongoing
Medical History: GONORRHOEA ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: RESPIRATORY TRACT INFECTION ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	2[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

HAEMORRHOIDS ([redacted])

FISTULA ([redacted])

This report was received from clinical trial TMC114FD2HTX3001:A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination coadministered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination in antiretroviral treatment-naïve human immunodeficiency virus type 1 infected subjects, EudraCT #: 2015-000754-38, and concerns a 2[redacted] year

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

??-??-???? - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Other History: Race is [redacted].No use of amphetamines, benzodiazepines, cocaine, cannabinoids or opioids.

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114FD2HTX3001
Center no : [redacted]
Patient no :

24b. MFR. CONTROL NO. [redacted] (1)

24c. DATE RECEIVED BY MFR. [redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

old [redacted] male (subject [redacted] site [redacted] from [redacted] Local case identification number: [redacted]

The subject's weight and height were not reported. His concurrent conditions included HIV.

The subject was randomized and treated with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) along with darunavir/cobicistat-matching and emtricitabine/tenofovir disoproxil-matching placebo tablets versus darunavir/cobicistat (tablet, oral) coadministered with emtricitabine/tenofovir disoproxil (tablet, oral) along with darunavir/cobicistat/emtricitabine/tenofovir alafenamide-matching placebo tablet, doses and frequency unspecified, initiated on an unspecified date for HIV. Concomitant medications were not reported.

On [redacted], the subject experienced fistula and hemorrhoids, and he was hospitalized for surgery. He received treatment with Toradol (ketorolac tromethamine). The dose of study drugs was not changed.

On [redacted], the subject recovered from hemorrhoids and fistula, and was discharged from the hospital.

The investigator assessed the events as grade 3 or severe in severity, not related to HIV, and not related to study procedures.

The investigator considered the causality between hemorrhoids and study drugs as not related, and between fistula and study drugs as not related.

Labeling was assessed for Truvada (emtricitabine/tenofovir disoproxil fumarate) using the Summary of Product Characteristics dated [redacted].

The blind has not been broken for this case.

This report is serious (hospitalization).Additional information was received from the investigator on [redacted].

The subject's medical history included condyloma. Other medical history included: No use of amphetamines, benzodiazepines, cocaine, cannabinoids or opioids.
Senders Comments/Medical Assessment: VO;

This 2[redacted] year old white male subject experienced fistula and hemorrhoids while on blinded study therapy for HIV. Based on information provided and lack of biological plausibility the causality was considered as not related to blinded study therapy.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE-Blinded (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. HAEMORRHOIDS [10019022]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. FISTULA [10016717]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	2
Drug	DARUNAVIR/COBICISTAT (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet
Daily Dose	1)
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-??-???? - Ongoing

Causality

1. HAEMORRHOIDS [10019022]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. FISTULA [10016717]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	3
Drug	EMTRICITABINE W/TENOFOVIR DISOPROXIL (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR) Tablet
Daily Dose	1)
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-??-???? - Ongoing

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Causality

1. HAEMORRHOIDS [10019022]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. FISTULA [10016717]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	4
Drug	PLACEBO (PLACEBO) Tablet
Daily Dose	1)
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) ??-??-???? - Ongoing

Causality

1. HAEMORRHOIDS [10019022]

Change in dose	Dose Not changed
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

2. FISTULA [10016717]

Change in dose	Dose Not changed
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Other relevant history (Cont...)

Medical History: ANOGENITAL WARTS ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 Study TMC114FD2HTX3001 Follow-up

Results: 7 cases selected from 7 matching the following criteria

Start Date : [redacted]

End Date : [redacted]

Date Type : Version Initially Received

Version : Highest In Date Range

Invalid Cases : Excluded

Workflow Cases : Excluded

Deleted Cases : Excluded

Protocol Number(s) : TMC114FD2HTX3001

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 Study TMC114FD2HTX3001 Follow-up

First Case Version Date Range : Between [redacted]

CIOMS II Report

SDE00256388 Study TMC114FD2HTX3001 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	4[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
MENINGITIS	Not Recovered/Not Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION
Disease Type: SINUSITIS, EAR INFECTION, TYMPANIC MEMBRANE PERFORATION, MASTOIDITIS, COELIAC DISEASE, HIV INFECTION

[redacted]	[redacted]	Study	3[redacted] Year	M	, in Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
PREGNANCY OF PARTNER	Unknown	No	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, NON-TOBACCO USER

[redacted]	[redacted]	Study	2[redacted] Year	F	, in Tablet Unknown	UNK

MedDRA 20.0

CIOMS II Report

SDE00256388 Study TMC114FD2HTX3001 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
EXPOSURE VIA FATHER	Recovered/Resolved	No	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION
Disease Type: NON-TOBACCO USER

		Study	2 Year	M	, in	Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
HAEMORRHOIDS	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED
FISTULA	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION
Disease Type: ANOGENITAL WARTS, HIV INFECTION
Suspect Drugs: DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR

PLACEBO

		Study	3 Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

MedDRA 20.0

CIOMS II Report

SDE00256388 Study TMC114FD2HTX3001 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
HEPATITIS A	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Investigator #: [redacted], Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, NEPHROLITHIASIS, OSTEOPENIA, DERMATITIS ALLERGIC
Suspect Drugs: DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR (1Dose(s))
Concomitant Drugs: PYRIDOXINE (5mg)

[redacted]	[redacted]	Study	2[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
MYOCARDITIS INFECTIOUS	Recovering/Resolving	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION
Disease Type: OSTEOPOROSIS, NAUSEA, PHARYNGITIS, DIARRHOEA, ACUTE HEPATITIS C, BETA 2 MICROGLOBULIN INCREASED, TONSILLITIS, ASPARTATE AMINOTRANSFERASE INCREASED, ALANINE AMINOTRANSFERASE INCREASED, ENTEROCOLITIS, SYNCOPE, DIARRHOEA, GIARDIASIS, PROCTITIS, ALBINISM, GONORRHOEA, RESPIRATORY TRACT INFECTION, HIV INFECTION, AUTOIMMUNE THYROIDITIS
Suspect Drugs: DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR (1Dose(s)-474Day,1Dose(s)-19Day,1Dose(s))
DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE COMPARATOR (1Dose(s)-474Day,1Dose(s)-19Day,1Dose(s))
PLACEBO (1Dose(s)-474Day,1Dose(s)-2576Day,1Dose(s))
Concomitant Drugs: VANCOMYCIN (250mg)

MedDRA 20.0

CIOMS II Report

SDE00256388 Study TMC114FD2HTX3001 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
		DOXYCYCLINE (100mg) LACTOBACILLUS ACIDOPHILUS (1Dose(s)) LACTOBACILLUS RHAMNOSUS (1Dose(s)) LOPERAMIDE HYDROCHLORIDE (1Dose(s))				
[redacted]	[redacted]	Study	4[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
TRANSIENT ISCHAEMIC ATTACK	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments:

Protocol #: TMC114FD2HTX3001, Indication for use: HIV INFECTION

Disease Type: TRANSIENT ISCHAEMIC ATTACK, OBESITY, EX-TOBACCO USER, SOCIAL ALCOHOL DRINKER, HYPERTENSION, HIV INFECTION, INSOMNIA, HERPES VIRUS INFECTION, ANXIETY, SEASONAL ALLERGY, DYSLIPIDAEMIA, ABSTAINS FROM RECREATIONAL DRUGS, DEPRESSION

Concomitant Drugs: HYDROCHLOROTHIAZIDE (12.5mg)

ACETYLSALICYLIC ACID (81mg)

MONTELUKAST SODIUM (10mg)

ALPRAZOLAM (.5mg)

BUPROPION HYDROCHLORIDE (150mg)

LISINOPRIL (10mg)

CALCIUM CARBONATE (1Dose(s))

CIOMS II Report

SDE00256388 Study TMC114FD2HTX3001 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
	DOZOL (1Dose(s))					
	VALACICLOVIR HYDROCHLORIDE (500mg)					

MedDRA 20.0

CIOMS Report for SDE00256388 study TMC114IFD3013 Initial cases

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Results: 7 cases selected from 7 matching the following criteria

Start Date : [redacted]

End Date :

Date Type : Version Initially Received

Version : Highest In Date Range

Invalid Cases : Excluded

Workflow Cases : Excluded

Deleted Cases : Excluded

Protocol Number(s) : TMC114IFD3013

First Case Version Date Range : Between [redacted]

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	3[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

ANOGENITAL WARTS ([redacted]

HAEMORRHOIDS ([redacted]

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

CETIRIZINE (CETIRIZINE) Tablet Oral Oral [redacted] - Ongoing1 Dose(s),1 in 1 Day

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: PHARYNGITIS [redacted] : Comments: grade 2 or moderate

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no :
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

concerns a 3[redacted]-year-old male (subject [redacted] site [redacted] from [redacted]

Initial information received on [redacted], was processed with additional information received on [redacted] and [redacted].

The subject's weight was [redacted] kilograms and height was [redacted] centimeters. His concurrent conditions included HIV. Medical history included pharyngitis, rhinopharyngitis, depression worsening, and esophagitis.

The subject was treated with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) one dose, once a day, initiated on [redacted], for HIV. Concomitant medications were not reported.

On [redacted], the subject experienced anal condyloma. On [redacted], the subject experienced hemorrhoid and was hospitalized. The subject underwent surgery for the anal condyloma and had a hemorrhoidectomy.

Action taken with darunavir/cobicistat/emtricitabine/tenofovir alafenamide was dose not changed.

The subject had recovered from anal condyloma and hemorrhoid on [redacted] and was discharged from the hospital.

The investigator assessed the serious events of anal condyloma and hemorrhoid as grade 2 or moderate in severity and not related to trial procedure.

The investigator considered the causality between hemorrhoid and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related, and between anal condyloma and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization).Additional information was received from the investigator on [redacted].

Additional concurrent conditions included pollen allergy, allergy to cats, and dust allergy.

Concomitant medications included cetirizine and mometasone for pollen allergy, allergy to cats, and dust allergy, pantoprazole for esophagitis, lamotrigine and levomepromazine for depression.

On [redacted], additional treatment included absorbable hemostatic gelatin sponge; stopped on an unknown date in [redacted].
Senders Comments/Medical Assessment: V1:

The follow-up information does not alter the prior causality assessment.

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

This report concerns a 3[redacted]-year-old male subject with underlying HIV infection who was diagnosed with anal condyloma about 7 months following the initiation of the study therapy. He was subsequently diagnosed with hemorrhoid about a month later .

In the absence of pharmacological plausibility, the reported events are considered as not related to study therapy.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. ANOGENITAL WARTS [10059313]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. HAEMORRHOIDS [10019022]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No.	1
Drug	CETIRIZINE (CETIRIZINE) Tablet
Indication	2) ALLERGY TO ANIMAL
Indication	3) DUST ALLERGY
Seq. No.	2
Drug	PANTOPRAZOLE (PANTOPRAZOLE)
Daily Dose	1) 20 mg, in 1 As Necessary
Indication	1) OESOPHAGITIS
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Stopped
Seq. No.	3
Drug	LEVOMEPROMAZINE (LEVOMEPROMAZINE)
Daily Dose	1) 50 mg, 1 in 1 Day
Indication	1) DEPRESSION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing
Seq. No.	4

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Drug	MOMETASONE (MOMETASONE) Spray
Daily Dose	1) 1 Dose(s), 1 in 1 Day
Indication	1) SEASONAL ALLERGY
Indication	2) ALLERGY TO ANIMAL
Indication	3) DUST ALLERGY
Route of Admin.	1) Nasal
Therapy Dates/Duration	1) [redacted] - Ongoing
Seq. No.	5
Drug	LAMOTRIGINE (LAMOTRIGINE)
Daily Dose	1) 200 mg, 1 in 1 Day
Indication	1) DEPRESSION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing

Other relevant history (Cont...)

Medical History: NASOPHARYNGITIS [redacted] : Comments: grade 2 or moderate
Medical History: DUST ALLERGY [redacted] - Ongoing
Medical History: SEASONAL ALLERGY [redacted] - Ongoing
Medical History: DEPRESSION [redacted] : Comments: grade 2 or moderate
Medical History: OESOPHAGITIS [redacted] : Comments: grade 2 or moderate
Medical History: ALLERGY TO ANIMAL [redacted] - Ongoing
Medical History: HIV INFECTION ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	5[redacted] Year	F	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

POST PROCEDURAL COMPLICATION([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-3 and concerns a 5[redacted] year old female (subject [redacted], site [redacted])

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: KNEE ARTHROPLASTY ??-[redacted] - ??-??-????

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no :

24b. MFR. CONTROL NO.

[redacted](0)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

from [redacted].

The subject's weight was [redacted] kilograms and height was [redacted] centimeters. The subject's concurrent conditions included HIV and medical history included knee replacement (prosthesis) and meniscectomy in [redacted].

The subject was randomized and received treatment with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral, batch 4374063) 1 dose(s) a day, initiated on [redacted] for HIV. Concomitant medications were not reported.

On [redacted], the subject experienced loosened knee prosthesis, surgical revision (captured as complications of surgery). The subject's symptoms were left knee pain after falling. Following the fall, the subject was hospitalized on the same day. The subject had an x-ray for investigation. On [redacted], the subject was operated on with revision of the prosthesis. The risk factors were meniscectomy and knee replacement (prosthesis) in [redacted]. The subject recovered without any other event and was discharged on [redacted]. No action was taken with study medication.

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject had recovered from loosened knee prosthesis on [redacted].

The event was severe in severity and not related to trial procedure.

The investigator considered the causality between loosened knee prosthesis and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization).
Senders Comments/Medical Assessment: V0:

This is a case of a 5[redacted] year-old female, enrolled in open-label study involving darunavir/cobicistat/emtricitabine/tenofovir alafenamide, who experienced loosened knee prosthesis approximately 2 years after initiation of study therapy. Patient had a fall 7 years ago injuring her left knee, subsequently had meniscectomy and knee replacement (prosthesis). The event is a possible complication of the meniscestomy and knee replacement; hence considered not related to the study therapy.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Causality

1. POST PROCEDURAL COMPLICATION [10058046]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: MENISCUS REMOVAL ??-[redacted] - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	2[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

NON-CARDIAC CHEST PAIN([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and concerns a 2[redacted] year old male (subject [redacted], site [redacted]) from

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

ALBUTEROL (SALBUTAMOL) Inhalation Inhalation ??-??-???? - ??-??-????90 ug, in 1 As Necessary

23. OTHER RELEVANT HISTORY

Drug History: DARUNAVIR [redacted] - [redacted] Indication: HIV INFECTION Reaction:

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

the [redacted].

The subject's weight was [redacted] kilograms, and height was [redacted] inches. His concurrent conditions included HIV, [redacted], [redacted], alcohol use, no smoking, and no known allergies.

The subject participated in the control arm of the study from [redacted] to [redacted], receiving darunavir (tablets, oral) 800 mg daily, ritonavir (tablet, oral) 100 mg daily, and emtricitabine w/tenofovir disoproxil fumarate (tablet, oral) 1 dose daily for HIV.

The subject was then switched to treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral, batch 4373389) 1 dose once a day, initiated on [redacted] for HIV. Concomitant medications included salbutamol for wheezing and shortness of breath.

On [redacted], the subject presented to the emergency department approximately 2-4 hours after consuming [redacted] with complaints of progressive left-sided acute chest pain. He stated he used [redacted] earlier that morning, and concomitant [redacted] within 3 hours of taking the [redacted]. He had a gradual onset of left-sided chest pain that was non-radiating, 8/10 in intensity, associated with shortness of breath, lightheadedness, diaphoresis, which was constant until it reached its peak with gradual resolution on his way to the emergency room. He described the pain as more bothersome than pain, and felt as though someone was "squeezing my heart". Upon arrival to the emergency department, the subject was tachycardic, but "HD" stable. The episode lasted around 40 minutes and occurred at rest. He had experienced previous episodes of chest pain like this when he used [redacted], and stated that this time he was "worried" and therefore came to the emergency room for further evaluation. Nothing made the pain better other than time, and [redacted] made the pain worse. He denied fever, chills, nausea, vomiting. He endorsed palpitations.

The subject stated his [redacted] use had increased the last year to 2-3 times per week. He also stated that he drank 2-3 times per week, but each time he [redacted]. He had never been diagnosed with a mental health disorder, but felt like he might suffer from depression that was attributing to his drug and alcohol use.

The subject was admitted for further observation and 24 hour Troponin levels. Laboratory data on [redacted] was provided as follows:

absolute neutrophil count (NR: 1.8 - 7.0 10e3/mcl) 7.50 10e3/mcl as elevated (suspect demargination), blood alcohol <10 mg/dl, glucose (NR: 70 - 100 mg/dl) 107 mg/dl, liver function tests within normal limits, lymphocyte count (NR: 24 - 44 %) 19% (decreased), renal function test normal, sodium (NR: 137 - 147 mmol/l) 136 mmol/l, troponin (NR: 0.0 - 0.05 ng/ml) <0.01 ng/ml as a rule out for acute cardiopulmonary processes, urine drug screen positive for [redacted] and [redacted], chest x-ray: no clear acute cardiopulmonary processes, large left-sided colonic air with no evidence of obstruction. ECG revealed

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

sinus rhythm, normal rate, no ischemic ST changes or ischemic T wave changes which ruled out acute cardiopulmonary processes.

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject received 1 aspirin 325 mg, Ativan (lorazepam) as necessary, and Lovenox (enoxaparin). He started oral thiamine and folate replacement for alcohol abuse.

The subject recovered from acute chest pain on [redacted], and he was discharged to home on [redacted]. The chest pain subsided without the use of nitroglycerin. Site staff spoke with the subject on [redacted] after discharge. The subject reported doing well and chest pain resolved.

Risk factors included recent [redacted] use. Suspected causes included [redacted] use.

The investigator assessed the event as not related to trial procedure.

The investigator considered the causality between acute chest pain and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization).Additional information was received from the investigator on [redacted].

The event term was revised from acute chest pain to acute chest pain - non cardiac (coded in database as chest pain non cardiac).

Senders Comments/Medical Assessment: V1:

This is a report of a 2[redacted]- year-old male subject, enrolled on an open label study (TMC114IFD3013) who experienced non-cardiac chest pain approximately 9 months from therapy initiation of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) for HIV infection. The event is confounded by [redacted] use (known to the associated with chest pain) several hours prior to event onset and it was also reported that [redacted] made the pain worse. Of note, the event recovered with continued study therapy use. Hence, causality for non-cardiac chest pain is considered not related to D/C/F/TAF. Follow-up information reported that the event of acute chest pain was non-cardiac.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ABSOLUTE NEUTROPHIL COUNT	[redacted]	7.50; elevated (suspect demargination) 10E3/mcL	1.8	7.0
BLOOD ALCOHOL		< 10 mg/dL		
CHEST X-RAY		see other diagnostics		
ECG		see other diagnostics		
GLUCOSE		107 mg/dL	70	100
LIVER FUNCTION TESTS		within normal limits		
LYMPHOCYTE COUNT		19 (decreased) %	24	44
RENAL FUNCTION TEST		normal		
SODIUM		136 mmol/L	137	147
TROPONIN		<0.01; r/o acute cardiopulmonary processes ng/mL	0.0	0.05
URINE DRUG SCREEN	[redacted]	positive for [redacted] and [redacted]		

Chest x-ray [redacted]: no clear acute cardiopulmonary processes. Large left-sided colonic air with no evidence of obstruction.

ECG [redacted]: sinus rhythm, normal rate, no ischemic ST changes or ischemic T wave changes; r/o acute cardiopulmonary processes.

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Tablet

Causality

1. NON-CARDIAC CHEST PAIN [10062501]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No.	1
Drug	ALBUTEROL (SALBUTAMOL)
Indication	2) DYSPNOEA

Other relevant history (Cont...)

Drug History: EMTRICITABINE W/TENOFOVIR DISOPROXIL FUMARATE [redacted] - [redacted]
Indication: HIV INFECTION Reaction:
Drug History: RITONAVIR [redacted] - [redacted] Indication: HIV INFECTION Reaction:
Other History: no known allergies
Medical History: ALCOHOL USE ??-??-???? - Ongoing
Medical History: DRUG USE DISORDER ??-??-???? - Ongoing
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: NON-TOBACCO USER ??-??-???? - Ongoing
Medical History: SUBSTANCE USE ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	4[redacted] Year	M	??	???	????

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PREGNANCY OF PARTNER(10050192)

This pregnancy report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and concerns a 4[redacted]-year-old male (subject [redacted], site [redacted])

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☒ NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☒ NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Other History: The date of the partners last menstrual period was [redacted]. The partner did not have any maternal risk factors in the

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no :

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

☒ STUDY ☐ LITERATURE

☒ HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP ☐ FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

from [redacted].

The male subject's weight and height was not reported. The male subject's current conditions included HIV, no use of alcohol, tobacco or recreational drugs. The partner's concurrent conditions included HIV, no use of alcohol, tobacco or recreational drugs. The subject's partner had no familial history or congenital anomalies, significant obstetrical outcomes or hereditary disorders.

The male subject received treatment with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) dosing regimen not specified, initiated on [redacted], for HIV. Concomitant medications were not reported.

On an unspecified date, the female partner became pregnant, coded as pregnancy of partner, characterizing paternal drug exposure during pregnancy. The date of the partner's last menstrual period was [redacted]; pregnancy was confirmed on [redacted] by a urine test, and the date for the first prenatal exam was [redacted]. The partner did not have any maternal risk factors in the home, work or environment, including chemical exposure, x-rays, history or miscarriages. It was also reported that that the partner's subject experienced a previous early spontaneous abortion (date unspecified). The partner had not experienced any medical disorders or problems during this current pregnancy. The partner underwent ultrasounds on [redacted] and [redacted]; results were not provided. An additional diagnostic was performed (illegible; date and results not provided).

The status of the partner's pregnancy was continuing and condition of the fetus was normal.

The subject outcome was unspecified for pregnancy of partner.

Action taken with dose of study drugs was dose not changed.

The investigator considered the causality between pregnancy of partner and study drugs as not related.

This report is not serious.

This case, from the same reporter is linked to [redacted].Additional information was received from the investigator on [redacted].

The current HIV status of the female partner was HIV positive with an undetectable viral load.

The female subject's concomitant medications included Truvada (emtricitabine and tenofovir disoproxil fumarate) one tablet once daily and Kaletra (lopinavir and

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

ritonavir) two tablets twice daily.

No additional diagnostic studies were performed for the female partner.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
GYNAECOLOGICAL EXAMINATION	[redacted]	first prenatal exam		
PREGNANCY TEST URINE		positive for pregnancy of partner		
ULTRASOUND ANTENATAL SCREEN		results not provided		
		results not provided		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. PREGNANCY OF PARTNER [10050192]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: ABORTION SPONTANEOUS ??-??-???? - ??-??-???? : Comments: partner had spontaneous abortion
Medical History: ABSTAINS FROM ALCOHOL ??-??-???? - Ongoing : Comments: subject and partner
Medical History: ABSTAINS FROM RECREATIONAL DRUGS ??-??-???? - Ongoing : Comments: subject and partner
Medical History: HIV INFECTION ??-??-???? - Ongoing : Comments: partner and subject; female partner was HIV positive with an undetectable viral load
Medical History: NON-TOBACCO USER ??-??-???? - Ongoing : Comments: subject and partner

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	3[redacted] Year	F	??	???	????

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

EXPOSURE VIA FATHER(10071403)

This pregnancy report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects. EudraCT #: 2014-003052-31, and concerns a 3[redacted]-year-old [redacted] female (subject [redacted],

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☒ NA

15. DAILY DOSE

male partner is receiving open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☒ NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - ??-??-????

19. THERAPY DURATION

UNK

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

KALETRA (KALETRA) Capsule Oral [redacted] - Ongoing2 Dose(s),2 in 1 Day

(Cont.)

23. OTHER RELEVANT HISTORY

Other History: Ethnicity= [redacted]
The date of the partners last menstrual period was [redacted]. The subject did not have any

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no :

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP ☐ FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

site [redacted]) from [redacted].

The female subject's weight was [redacted] kilograms and height was [redacted] centimeters. Her concurrent conditions included HIV, no use of alcohol, tobacco or recreational drugs. She had no familial history or congenital anomalies, significant obstetrical outcomes or hereditary disorders. The subject's partner's current conditions included HIV, no use of alcohol, tobacco or recreational drugs.

The subject's partner received treatment with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) dosing regimen not specified, initiated on [redacted], for HIV. The female subject's concomitant medications included truvada and kaletra for HIV (dosing regimen illegible).

On an unspecified date, the subject became pregnant characterizing paternal drug exposure during pregnancy. The date of the subject's last menstrual period was [redacted]; pregnancy was confirmed [redacted] by a urine test, and the date for the first prenatal exam was [redacted]. The subject did not have any maternal risk factors in the home, work or environment, including chemical exposure, x-rays, history or miscarriages. It was also reported that that the subject experienced a previous early spontaneous abortion (date unspecified). The subject had not experienced any medical disorders or problems during this current pregnancy. Ultrasounds were performed on [redacted] and [redacted]; results were not provided. An additional diagnostic was performed (illegible; date and results not provided).

The subject outcome was unspecified for paternal drug exposure during pregnancy. The status of the pregnancy was continuing and condition of the fetus was normal.

Action taken with dose of study drugs was not applicable.

The investigator considered the causality between paternal drug exposure during pregnancy and study drugs as not related.

This report is not serious.

This case, from the same reporter is linked to [redacted].Additional information was received from the investigator on [redacted].

The current HIV status of the female partner was HIV positive with an undetectable viral load.

The female subject's concomitant medications included Truvada (emtricitabine and tenofovir disoproxil fumarate) one tablet once daily and Kaletra (lopinavir and ritonavir) two tablets twice daily.

No additional diagnostic studies were performed for the female partner.

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
GYNAECOLOGICAL EXAMINATION	[redacted]	first prenatal exam		
PREGNANCY TEST URINE		positive for pregnancy		
ULTRASOUND ANTENATAL SCREEN		results not provided		
		results not provided		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. EXPOSURE VIA FATHER [10071403]

Change in dose	Not Applicable
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No. 2
Drug TRUVADA (TRUVADA) Capsule

Daily Dose 1) 1 Dose(s), 1 in 1 Day
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 1) [redacted] - Ongoing

Other relevant history (Cont...)

Medical History: ABORTION SPONTANEOUS ??-??-???? - ??-??-???? : Comments: early
Medical History: ABSTAINS FROM ALCOHOL ??-??-???? - Ongoing : Comments: subject and parnter
Medical History: ABSTAINS FROM RECREATIONAL DRUGS ??-??-???? - Ongoing : Comments: subject and partner
Medical History: HIV INFECTION ??-??-???? - Ongoing : Comments: HIV positive with undetectable viral load
Medical History: NON-TOBACCO USER ??-??-???? - Ongoing : Comments: subject and partner

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
PRIVATE	[redacted]	[redacted]	[redacted]	[redacted]	3[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [ ] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

LOSS OF CONSCIOUSNESS([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and concerns a 3[redacted] year old [redacted] male (subject [redacted]-[redacted], site

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

CHOLECALCIFEROLUM (COLECALCIFEROL) Oral Oral [redacted] - ??-??-????2000 IU,1 in 1 Day

23. OTHER RELEVANT HISTORY

Medical History: VITAMIN D DEFICIENCY [redacted] - Ongoing

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted](0)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

[redacted] from [redacted].

Initial information was processed with additional information received on [redacted].

The subject's weight was [redacted] kilograms, and height was [redacted] centimeters. His concurrent conditions included HIV, right inguinal hernia, vitamin D deficiency, and seborrheic dermatitis; medical history included lues, hepatitis A, hepatitis B, proctitis, and sore throat.

The subject was treated with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral, batch 4373389) 1 dose once a day, initiated on [redacted] for HIV. Concomitant medications included colecalciferol for vitamin D deficiency.

On [redacted], the subject experienced temporary loss of consciousness, preceded by intensive diarrhea. The diarrhea was accompanied by moderate nausea and abdominal discomfort without fever. The subject was consulted on [redacted] in the emergency room. An ECG did not show any specific abnormalities and he was referred to primary care. At the visit on [redacted], the subject still complained of diarrhea without vomiting or fever. He was in good clinical state with blood pressure 106/67, heart rate 90/min, and physical examination showed no abnormalities. Results of a blood test were pending.

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject recovered from temporary loss of consciousness on [redacted].

The investigator assessed the event as severe (grade 3) in severity, not related to HIV, and not related to trial procedure.

The investigator considered the causality between temporary loss of consciousness and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (medically significant).
Senders Comments/Medical Assessment: V0:

This 3[redacted] year old [redacted] male subject experienced temporary loss of consciousness after almost 17 months of study therapy (emtricitabine/tenofovir disoproxil fumarate) for HIV. The loss of consciousness receded by intensive diarrhea, which could trigger a dehydration with subsequent blood pressure decrease. The subject recovered on the same day and without study therapy interruption. Based on information provided, causality was considered as not related, pending follow up information.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
BLOOD PRESSURE	[redacted]	106/67		
ECG		no specific abnormalities		
HEART RATE		90 /min		
PHYSICAL EXAMINATION		no abnormalities		

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. LOSS OF CONSCIOUSNESS [10024855]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: OROPHARYNGEAL PAIN [redacted] - ??-??-????
Medical History: SEBORRHOEIC DERMATITIS [redacted] - Ongoing
Other History: Race is [redacted]
Medical History: HEPATITIS A ??-??-???? - ??-??-????
Medical History: HEPATITIS B ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: INGUINAL HERNIA ??-??-???? - Ongoing
Medical History: PROCTITIS ??-??-???? - ??-??-????
Medical History: SYPHILIS ??-??-???? - ??-??-????

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	5[redacted] Year	F	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

CYSTOCELE([redacted])

OVARIAN CYST([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: POSTMENOPAUSE ??-???-[redacted] - Ongoing : Comments: Date of last menses [redacted]

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

concerned a 5[redacted]-year-old [redacted] female (subject [redacted] site [redacted] from [redacted]

Initial information was received on [redacted] and processed with additional information received on [redacted].

The subject's weight and height were not reported. Her concurrent conditions included HIV, bloating feeling in arms (captured as swelling both arms), postmenopausal (date of last menses [redacted] and urinary incontinence. Medical history included abdominal swelling, depressive symptoms, catarrh, pain of the right should (supraspinatus tendonitis), respiratory tract infection, and vaginitis.

The subject was treated with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) initiated on [redacted] for HIV. Concomitant medications were not reported.

On [redacted], the subject experienced cystocele and ovarian cyst. The subject did not experience any signs or symptoms. On [redacted], the subject was hospitalized for a programmed intervention, salpingo-oophorectomy and anterior vaginal plasty.

Concomitant or additional therapy was administered for the serious events of cystocele and ovarian cyst.

Action taken with darunavir/cobicistat/emtricitabine/tenofovir alafenamide regarding cystocele and ovarian cyst was dose not changed.

The subject had recovered from cystocele and ovarian cyst on [redacted] and was discharged from the hospital.

The investigator assessed the serious events of cystocele and ovarian cyst as toxicity grade 2 or moderate and not related to HIV.

The investigator considered the causality between the serious events of cystocele and ovarian cyst and study drug darunavir/cobicistat/emtricitabine/tenofovir alafenamide, as not related.

This report is serious (hospitalization).Additional information was received on [redacted] and [redacted] via a query response from the investigator.

The seriousness of the events, cystocele and ovarian cyst, was confirmed as hospitalization.

Treatment for the ovarian cyst was confirmed as salpingo-oophorectomy and for cystocele it was confirmed as anterior vaginal plasty.
Senders Comments/Medical Assessment: V1:

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

The follow-up information provided does not alter the prior causality assessment (remains as not related).

This 5[redacted]-year-old [redacted] female subject experienced cystocele and ovarian cyst approximately 17 months after initiation on study therapy for HIV. Subject's postmenopausal age and medical history of vaginitis and HIV could contributed to the events, so causality was considered as not related to study therapy.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. CYSTOCELE [10011803]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. OVARIAN CYST [10033132]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: DEPRESSION [redacted] - ??-[redacted] : Comments: Toxicity grade 2 or moderate
Medical History: ABDOMINAL DISTENSION [redacted] - ??-[redacted] : Comments: Toxicity grade 2 or moderate
Medical History: CATARRH [redacted] - [redacted] : Comments: Toxicity grade 2 or moderate
Medical History: MUSCULOSKELETAL PAIN ??-[redacted] - ??-[redacted] : Comments: Toxicity grade 2 or moderate; supraspinatus tendonitis
Medical History: PERIPHERAL SWELLING [redacted] - ??-[redacted] : Comments: Toxicity grade 1 or mild; bloating feeling in arms
Medical History: RESPIRATORY TRACT INFECTION [redacted] : Comments: Toxicity grade 1 or mild
Medical History: URINARY INCONTINENCE [redacted] : Comments: Toxicity grade 2 or moderate
Medical History: VAGINAL INFECTION [redacted] : Comments: Toxicity grade 1 or mild
Other History: Race=[redacted]

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Medical History: HIV INFECTION ??-??-???? - Ongoing

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 study TMC114IFD3013 Initial cases

Results: 7 cases selected from 7 matching the following criteria

Start Date : [redacted]

End Date : [redacted]

Date Type : Version Initially Received

Version : Highest In Date Range

Invalid Cases : Excluded

Workflow Cases : Excluded

Deleted Cases : Excluded

Protocol Number(s) : TMC114IFD3013

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 study TMC114IFD3013 Initial cases

First Case Version Date Range : Between [redacted]

CIOMS II Report

SDE00256388 study TMC114IFD3013 Initial cases

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	3[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
ANOGENITAL WARTS	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED
HAEMORRHOIDS	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments:

Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: PHARYNGITIS, NASOPHARYNGITIS, DUST ALLERGY, SEASONAL ALLERGY, DEPRESSION, OESOPHAGITIS, ALLERGY TO ANIMAL, HIV INFECTION
Concomitant Drugs: CETIRIZINE (1Dose(s))

PANTOPRAZOLE (20mg)

LEVOMEPROMAZINE (50mg)

MOMETASONE (1Dose(s))

LAMOTRIGINE (200mg)

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	5[redacted] Year	F	1 Dose(s), in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
POST PROCEDURAL COMPLICATION	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

MedDRA 20.0

CIOMS II Report

SDE00256388 study TMC114IFD3013 Initial cases

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	4 Year	M	, in Tablet Oral	UNK

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: KNEE ARTHROPLASTY, MENISCUS REMOVAL, HIV INFECTION

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
PREGNANCY OF PARTNER	Unknown	No	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: ABORTION SPONTANEOUS, ABSTAINS FROM ALCOHOL, ABSTAINS FROM RECREATIONAL DRUGS, NON-TOBACCO USER, HIV INFECTION

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	3 Year	F	, in Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
EXPOSURE VIA FATHER	Unknown	No	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, ABORTION SPONTANEOUS, NON-TOBACCO USER, ABSTAINS FROM ALCOHOL, ABSTAINS FROM RECREATIONAL DRUGS
Concomitant Drugs: KALETRA (2Dose(s))

MedDRA 20.0

CIOMS II Report

SDE00256388 study TMC114IFD3013 Initial cases

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
	TRUVADA (1Dose(s))					
[redacted]	[redacted]	Study	5[redacted] Year	F	, in Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
CYSTOCELE	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED
OVARIAN CYST	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: POSTMENOPAUSE, DEPRESSION, ABDOMINAL DISTENSION, CATARRH, MUSCULOSKELETAL PAIN, PERIPHERAL SWELLING, RESPIRATORY TRACT INFECTION, URINARY INCONTINENCE, VAGINAL INFECTION, HIV INFECTION

[redacted]	[redacted]	Study	3[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
LOSS OF CONSCIOUSNESS	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: VITAMIN D DEFICIENCY, OROPHARYNGEAL PAIN, SEBORRHOEIC DERMATITIS, HEPATITIS B, PROCTITIS, SYPHILIS, HIV INFECTION, INGUINAL HERNIA, HEPATITIS A

MedDRA 20.0

CIOMS II Report

SDE00256388 study TMC114IFD3013 Initial cases

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset

Concomitant Drugs: COLECALCIFEROL (2000IU)

[redacted]	[redacted]	Study	2[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
NON-CARDIAC CHEST PAIN	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments:

Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: SUBSTANCE USE, DRUG USE DISORDER, HIV INFECTION, NON-TOBACCO USER, ALCOHOL USE
Concomitant Drugs: SALBUTAMOL (90ug)

MedDRA 20.0

CIOMS Report for SDE00256388 study TMC114IFD3013 Follow-up

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Results:	7 cases selected from 7 matching the following criteria
Start Date :	[redacted]
End Date :	[redacted]
Date Type :	Version Initially Received
Version :	Highest In Date Range
Invalid Cases :	Excluded
Workflow Cases :	Excluded
Deleted Cases :	Excluded
Protocol Number(s) :	TMC114IFD3013
First Case Version Date Range :	Between [redacted]

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	5[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE(10009033)

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31 and concerned a 5[redacted] year old male (subject [redacted] site [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
1 Dose(s), 1 in 1 Day	Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)	19. THERAPY DURATION
[redacted] - Ongoing	Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

SPIRIVA (TIOTROPIUM BROMIDE) ??-??-???? - ??-??-????

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: CHRONIC OBSTRUCTIVE PULMONARY DISEASE ??-??-???? - Ongoing

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no :

24b. MFR. CONTROL NO. [redacted] (11)

24c. DATE RECEIVED BY MFR. [redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

from [redacted]

Initial information was processed with additional information received on [redacted].

The subject's weight was [redacted] kilograms and height was [redacted] centimeters. His concurrent conditions included HIV.

The subject was randomized and treated with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) 1 dose once a day, initiated on an unspecified date (date provided as a future date of [redacted]) and ongoing for HIV. Concomitant medications were not reported.

On [redacted], the subject experienced asthenia and dyspnea and was hospitalized the same day.

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

On [redacted], the subject recovered from asthenia and dyspnea. The subject was discharged from the hospital the next day on [redacted].

The investigator assessed the risk factor as a suspected cancerous lesion. The subject was to receive radiotherapy. Additional investigation and supporting diagnostics were related to chronic obstructive pulmonary disease (COPD).

The investigator considered the events not related to trial procedure.

The investigator considered the causality between asthenia and dyspnea and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization).Additional information was received from the investigator on [redacted].

The investigator clarified the subject experienced dyspnea during exercise. The subject was treated with terbutaline and ipratropium inhalation.

The investigator noted the suspected cause was COPD decompensation without a specific cause.Additional information was received from the investigator on [redacted] in response to a query.

The subject's concurrent conditions included COPD (known for years) and smoking.

The start date of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was [redacted]. Concomitant medications included tiotropium bromide and indacaterol maleate. The subject also underwent radiotherapy during [redacted].

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

No biopsy was realized for the suspected cancerous lesion, but suspected fixation lesion was seen on PET scan.Revision to the information received on [redacted].

Upon review the following corrections were made.

The previous version 2 dates for Version Initially Received, ICH Expedited Start, and Latest Information Received were corrected to [redacted] (previously reported as [redacted]).Additional information was received via a Data Update Request Form on [redacted].

On [redacted], the subject also experienced worsening COPD causing hospitalization.

The stop date of worsening COPD was [redacted]. The subject outcome was not provided.

The investigator assessed worsening COPD as grade 3 or severe.

The investigator causality assessment between worsening COPD and darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not provided. Company causality was assessed as not related.Additional information was received from the investigator on [redacted].

The SAE term of worsening COPD was removed. It was determined as not necessary to report as a new SAE since it was considered the same event as asthenia and dyspnea, which were already reported. The investigator clarified again that the suspected cause of the events was COPD decompensation without specific cause. Additional information was received on [redacted] via a Data Update Request Form (DURF). Report contained no new information and no changes were made to the case.Additional information was received from the investigator on [redacted].

The serious events of asthenia and dyspnea were removed from the case and the serious event of exacerbation of COPD (chronic obstructive pulmonary disease) was added to the case.

On [redacted], the subject experienced exacerbation of COPD.

The subject outcome was unspecified for exacerbation of COPD.

The investigator considered the causality between exacerbation of COPD and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.Additional information was received from the investigator on [redacted].

The subject had recovered (previously unspecified) from exacerbation of COPD on [redacted].Additional information was received from the investigator on [redacted] in response to a query.

It was confirmed the event was recovered.

This case, involving the same patient is linked to [redacted].Additional information was received via serious adverse event reconciliation (data update request form) on [redacted].

The month of subject's date of birth was updated.
Senders Comments/Medical Assessment: V9:

Follow up reports updated outcome for The subject had recovered (previously unspecified) from exacerbation of COPD o

The 5[redacted] year old male subject exerinced COPD exacerbation approximately 10 months after initiation of study therapy for HIV infection. Subject's history of smoking and COPD in view of underlying immunodeficiency may provide an explanation, so causality is considered not related to study therapy.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
PET/CT SCAN	??-???-????	suspected fixation, lesion		

Suspect Drug(s) (Cont...)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE [10009033]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No.	2
Drug	ONBREZ (INDACATEROL MALEATE)
Daily Dose	1)
Indication	1) PRODUCT USED FOR UNKNOWN INDICATION
Therapy Dates/Duration	1) ??-??-???? - ??-??-????

Other relevant history (Cont...)

Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: TOBACCO USER ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	5[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

ATRIAL FIBRILLATION([redacted])

UROSEPSIS([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
1 Dose(s), 1 in 1 Day	Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)	19. THERAPY DURATION
[redacted] - Ongoing	Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: HIV INFECTION ??-??-???? - Ongoing

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013 Center no : Patient no : [redacted]	24b. MFR. CONTROL NO. [redacted] (7)

24c. DATE RECEIVED BY MFR.	24d. REPORT SOURCE
[redacted]	[X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE [ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

concerns a 5[redacted] year old male (subject [redacted] site [redacted] from the [redacted]

The subject's weight was [redacted] pounds, and height was [redacted] inches. His concurrent conditions included HIV.

The subject was treated with darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) 1 dose once a day, initiated on [redacted] for HIV. Concomitant medications were not reported.

On an unspecified date, the subject experienced atrial fibrillation, chills, fever, and he was admitted to the hospital on [redacted]. Treatment included IV fluids, doxycycline, and Maxipime (cefepime).

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject had not recovered from atrial fibrillation, chills, and fever.

The investigator assessed the events as severe and not related to trial procedure.

The investigator considered the causality between atrial fibrillation, fever, chills, and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization).Additional information was received on [redacted] via a Data Update Request Form.

No new information was provided. No changes have been made to the report.Additional information was received on [redacted] via a Data Update Request Form.

The onset date for atrial fibrillation, fever, and chills was [redacted], and the stop date for the events was [redacted] (dates previously not reported).

The subject recovered from atrial fibrillation, fever, and chills on [redacted] (previously reported as not recovered).Additional information was received from the investigator on [redacted].

The subject's most recent weight was reported as [redacted] kilograms.

The subject was admitted to the hospital on [redacted] for a planned cryoablative procedure in relation to atrial fibrillation. He was kept overnight for observation.Additional information was received from the investigator via a query response on [redacted] and [redacted].

The subject underwent a planned cryoablation procedure. The procedure resolved the subject's atrial fibrillation.Additional information was received from the investigator on [redacted] and contained no new information. No new information was added to the

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

case.Additional information was received from the investigator on [redacted] and processed along with information received via data update request form (DURF) on [redacted].

The serious event of urosepsis was added to the case and the events of chills and fever were removed from the case.

On [redacted], the subject experienced urosepsis. The subject was discharged from the hospital on [redacted]. The subject had ablation procedure on [redacted] for atrial fibrillation. Hospitalization lasted less than 24 hours for this pre-planned procedure.

The subject had recovered from urosepsis on [redacted] and recovered from atrial fibrillation on [redacted] (previously [redacted]).

The investigator did not provide the causality between urosepsis and darunavir/cobicistat/emtricitabine/tenofovir alafenamide. Company causality was not related.Additional information was received via serious adverse event reconciliation (DURF) on [redacted].

The investigator considered the causality between urosepsis and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related, previously not provided.

Senders Comments/Medical Assessment: V7:

The follow-up information included update to investigator causality assessment for urosepsis (updated to not related) which does not alter the prior Company causality assessment (remains as not related).

This 5[redacted]-year-old male subject experienced atrial fibrillation and urosepsis approximately 1 year following study therapy initiation for HIV infection. The weight of the subject appears to reflect obesity (known to be a risk factor for atrial fibrillation) hence is a potential confounding factor. Of note, the events recovered with continued study drug use. Subjects underlying condition of immunodeficiency may provide an explanation for the event of urosepsis. Based upon the information provided, causality for all events are considered not related.

No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. ATRIAL FIBRILLATION [10003658]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. UROSEPSIS [10048709]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Causality

Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	5[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PERIPHERAL ARTERY STENOSIS([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and concerned a male of unspecified age (subject [redacted] site

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: ABDOMINAL FAT APRON ??-??-???? - Ongoing

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no :
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (2)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

[redacted] from [redacted]

The subject's weight was not reported and height was [redacted] centimeters.

Concurrent conditions included HIV and worsening of intermittent claudication, type 2 diabetes, hypertension, lipodystrophy, hyperlipidemia, recurrent gastric ulcer, buffalo neck (captured as buffalo hump), abdominal fat (captured as abdominal fat accumulation), gingivitis, gynecomastia, lombalgia (captured as low back pain).

Medical history included recurrent labial herpes, recurrent anal condyloma, seborrheic dermatitis, molluscum contagiosum, scrotal ulcer, peripheral polyneuropathy, intermittent claudication, lower limb polyneuritis, lower limb polyneuritis, diverticular hemorrhage (captured as diverticular bleed), and nephropathy microalbuminuria (captured as separate terms nephropathy and microalbuminuria).

The subject was treated with open-label darunavir (800 mg)/ cobicistat (150 mg)/ emtricitabine (200 mg)/ tenofovir alafenamide (10 mg) (tablet, oral, batch 4373389, medication kit number [redacted] initiated on [redacted] once daily for HIV. Concomitant medications were not reported.

The subject had a history of intermittent claudication with intermittent claudication worsening since [redacted], but only agreed to exams and investigations in [redacted]. On [redacted], the subject experienced left superficial femoral artery stenosis (captured as femoral artery stenosis). The subject was hospitalized on [redacted] for treatment.

Diagnostic data ([redacted]) included "ADLTA" and lower limbs angiography (captured as angiography) which showed left superficial femoral artery stenosis.

Treatment on [redacted] included balloon angioplasty.

Treatment with darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject had recovered from left superficial femoral artery stenosis on [redacted] and was discharged on [redacted].

The investigator assessed the left superficial femoral artery stenosis as not related to trial procedure.

The investigator considered the causality between left superficial femoral artery stenosis and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization).Additional information was received via serious adverse event data reconciliation on [redacted].

The report was updated with the subject's date of birth, age and age group. This report

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

concerns a 5[redacted] year old male. Additional information was received via serious adverse event reconciliation (data update request form) on [redacted].

The serious adverse term, captured as femoral artery stenosis, was updated to left superficial femoral artery stenosis.
Senders Comments/Medical Assessment: This male subject with histories of intermittent claudication, abdominal fat accumulation lower limb polyneuritis and hyperlipidemia experienced peripheral artery stenosis approximately 1-year and 5 months following study drug initiation for HIV infection. The event is confounded by histories of intermittent claudication, abdominal fat accumulation lower limb polyneuritis and hyperlipidemia. Based upon the information provided, causality is considered not related to study therapy.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ANGIOGRAPHY	[redacted]	see "Other Diagnostics"		

ADLTA and lower limbs angiography ([redacted]): left superficial femoral artery stenosis.

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. PERIPHERAL ARTERY STENOSIS [10072563]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Other relevant history (Cont...)

Medical History: ANOGENITAL WARTS ??-??-???? - ??-??-????
Medical History: BACK PAIN ??-??-???? - Ongoing
Medical History: DIVERTICULUM INTESTINAL HAEMORRHAGIC ??-??-???? - ??-??-????
Medical History: GASTRIC ULCER ??-??-???? - Ongoing
Medical History: GINGIVITIS ??-??-???? - Ongoing
Medical History: GYNAECOMASTIA ??-??-???? - Ongoing
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: HYPERLIPIDAEMIA ??-??-???? - Ongoing
Medical History: HYPERTENSION ??-??-???? - Ongoing
Medical History: INTERMITTENT CLAUDICATION ??-??-???? - Ongoing : Comments: worsening [redacted]
Medical History: LIPODYSTROPHY ACQUIRED ??-??-???? - Ongoing
Medical History: LIPOHYPERTROPHY ??-??-???? - Ongoing : Comments: buffalo neck
Medical History: MICROALBUMINURIA ??-??-???? - ??-??-????
Medical History: MOLLUSCUM CONTAGIOSUM ??-??-???? - ??-??-????
Medical History: NEPHROPATHY ??-??-???? - ??-??-????

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Medical History: ORAL HERPES ??-??-???? - ??-??-????
Medical History: POLYNEUROPATHY ??-??-???? - ??-??-????
Medical History: POLYNEUROPATHY ??-??-???? - ??-??-????
Medical History: SCROTAL ULCER ??-??-???? - ??-??-????
Medical History: SEBORRHOEIC DERMATITIS ??-??-???? - ??-??-????
Medical History: TYPE 2 DIABETES MELLITUS ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	4[redacted] Year	F	[redacted]	[redacted]	[redacted]

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

HYSTERECTOMY ([redacted])

LEIOMYOMA ([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

LEVOTHYROX (LEVOTHYROXINE SODIUM) Oral Oral [redacted] - Ongoing50 mg,1 in 1 Day

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: NECK PAIN [redacted] - ??-??-????

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no :
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (4)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

concerns a 4[redacted] year old female (subject [redacted] site [redacted] from [redacted]

The subject's weight was [redacted] kilograms, and height was [redacted] centimeters. Her concurrent conditions included HIV.

The subject was treated with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) 1 dose once a day, initiated on [redacted] for HIV. Concomitant medications were not reported.

On [redacted], a systematic uterus echography revealed endometrial enlargement (thickened endometrium). The subject was hospitalized on [redacted], and a hysterectomy was performed on [redacted]. Histopathology results showed a benign leiomyoma of 2 cm; no atypical endometrial cells.

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject recovered from thickened endometrium on [redacted]. On [redacted], the subject recovered from the hysterectomy and was discharged from the hospital. The investigator reported the outcome as uneventful.

The investigator assessed the events as grade 1 or mild, not related to HIV, and not related to trial procedure.

The investigator considered the causality between thickened endometrium, hysterectomy, and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization, medically significant).Additional information was received from the investigator on [redacted].

The subject's concurrent conditions included family history of asthma (in first degree family), insomnia, thyroid goitre, tubal ligation, "uterine dysplasia", and medical history included asthma, 3 cesarean sections, cushing's syndrome, epigastralgia, lipodystrophia, and neck pain.

Concomitant medications included levothyroxine sodium for thyroid goitre, hydroxyzine for insomnia, omeprazole for epigastralgia, and ferrous sulfate for deficiency prophylaxis.

The subject's final diagnosis was benign leiomyoma of the endometrium. Additional information was received from the investigator on [redacted].

The serious event of thickening of the endometrium was reassessed to benign leiomyoma of endometrium (captured as leiomyoma of endometrium).Additional information received via serious adverse event reconciliation on [redacted] contained no new information. No changes were made to this report.Additional information received via serious adverse event reconciliation on [redacted] contained no new information. No changes were made

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

to this report.
Senders Comments/Medical Assessment: V2:

Follow-up information received did not change the prior company causality assessment.

This 4[redacted]-year-old female underwent hysterectomy for thickened endometrium, which was later diagnosed to be benign leiomyoma of the endometrium, around 10 months after initiation of study therapy for HIV infection. The high frequency of smooth muscle overgrowth and tumors in HIV patients as well as the gender and the age (premenopausal) of the subject are possible risk factors for the event. Based on the information available, the causality was considered as not related to study therapy.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ECHOGRAPHY	[redacted]	endometrial enlargement of the uterus		
HISTOLOGY	??-???-????	see other diagnostics		

Histopathology: benign leiomyoma of 2 cm; no atypical endometrial cells.

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. HYSTERECTOMY [10021151]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. LEIOMYOMA [10024184]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No. 2
Drug ATARAX (HYDROXYZINE)

Daily Dose 1) 25 mg, 1 in 1 Day
Indication 1) INSOMNIA
Route of Admin. 1) Oral
Therapy Dates/Duration 1) [redacted] - Ongoing

Seq. No. 3
Drug OMEPRAZOLE (OMEPRAZOLE)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Daily Dose	1) 20 mg, 1 in 1 Day
Indication	1) ABDOMINAL PAIN UPPER
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing

Seq. No.	4
Drug	TARDYFERON (FERROUS SULFATE)
Daily Dose	1) 2 Dose(s), 1 in 1 Day
Indication	1) VITAMIN SUPPLEMENTATION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - Ongoing

Other relevant history (Cont...)

Medical History: ABDOMINAL PAIN UPPER [redacted] - ??-??-????
Other History: Concurrent conditions included "uterine dysplasia".
Medical History: ASTHMA ??-??-???? - ??-??-????
Medical History: ASTHMA ??-??-???? - Ongoing : Comments: in first degree family
Medical History: CAESAREAN SECTION ??-??-???? - ??-??-???? : Comments: 3
Medical History: CUSHING'S SYNDROME ??-??-???? - ??-??-????
Medical History: FEMALE STERILISATION ??-??-???? - Ongoing
Medical History: GOITRE ??-??-???? - Ongoing
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: INSOMNIA ??-??-???? - Ongoing
Medical History: LIPODYSTROPHY ACQUIRED ??-??-???? - ??-??-????

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	6[redacted] Year	M	[redacted]	[redacted]	[redacted]

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PNEUMONIA ([redacted])

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and concerns a 5[redacted] year old male (subject [redacted] site [redacted]

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: HIV INFECTION ??-??-???? - Ongoing

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no :

24b. MFR. CONTROL NO.

[redacted] (1)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

from the [redacted].

The subject's weight was [redacted] pounds and height was [redacted] inches. The subject's concurrent condition included HIV.

The subject was randomized and received treatment with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) 1 dose once a day, initiated on [redacted] for HIV. Concomitant medications were not reported.

On [redacted] the subject was admitted to the hospital with an episode of dyspnea. On [redacted], the subject was diagnosed with pneumonia and was being treated accordingly.

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject was recovering from pneumonia.

The event severity was severe and was not related to trial procedure.

The investigator considered the causality between pneumonia and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (hospitalization).Additional information was received from clinical via a serious adverse event data reconciliation form [redacted].

This report concerns a 6[redacted] year old male (previously 5[redacted] year old). Subject demographics were updated (date of birth).
Senders Comments/Medical Assessment: V1:

Additional information was received with regard to the subject's age. Below medical assessment comment updated accordingly. Our overall assessment of the reported event does not change as a result of this.

This 6[redacted]-year-old male subject experienced pneumonia approximately 1 year and 6 months following study therapy initiation for HIV infection. The event is confounded by predisposing HIV infection. Of note, the event is recovering and study therapy is being continued. Based upon the information provided, causality is considered not related to study therapy.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Causality

1. PNEUMONIA [10035664]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	[redacted]	[redacted]	[redacted]	[redacted]	5[redacted] Year	M	[redacted]	[redacted]	[redacted]

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

MALARIA([redacted]

ACUTE KIDNEY INJURY([redacted]

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - [redacted]

19. THERAPY DURATION

258 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

PARACETAMOL (PARACETAMOL) Unspecified Oral Oral [redacted] - ??-??-????1 g, in 1 As Necessary

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: PULMONARY TUBERCULOSIS ??-???-[redacted] - ??-??-????

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no : [redacted]

24b. MFR. CONTROL NO.

[redacted] (4)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

- [X] STUDY
- [ ] LITERATURE
- [X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

- [ ] INITIAL
- [ ] FOLLOWUP
- [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

concerns a 5[redacted]-year-old male (subject [redacted]-[redacted] site [redacted] from [redacted] report from [redacted]

The subject's weight was [redacted] kilograms and height was [redacted] centimeters.

The subject's concurrent conditions included HIV infection, hemorrhoids, no known allergies, and ex-smoker; medical history included pulmonary tuberculosis, pulmonary embolism with deep vein thrombosis, gastroesophageal reflux disease (GORD) without esophagitis, and scapular tendinitis.

The subject was randomized and treated with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (tablet, oral) 800 mg/150 mg/200 mg/10 mg (one dose) once a day, initiated on [redacted] for HIV infection. The most recent dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was received on [redacted]. Concomitant medications were not reported.

On [redacted], the subject experienced malaria with fever, nausea and anorexia. On [redacted], the subject experienced malaria and was hospitalized. Malaria was considered severe with sepsis and coagulase gram positive (CG) + clusters and chains (no identification available) (captured as culture).

Treatment included intravenous (IV) artemisinin (also reported as artesunate), Rocephin (ceftriaxone sodium), and gentamicin. The conclusion regarding control of malaria attack which occurred in Cameroon was treated on [redacted]; control monitoring was to be done in two days (day 7) and in 23 days (day 28).

The subject was discharged on [redacted] on artemeter lumefantrine and Oroken (cefixime). Artemeter lumefantrine was stopped on [redacted] (also reported as stopped on [redacted]).

On [redacted], the subject experienced acute renal failure and was hospitalized. Symptoms included abdominal pain, vomiting and constipation. Vital signs included 114/65, temperature 36 Celsius, oxygen saturation 98% and Glasgow 15.

On [redacted], the laboratory data included sodium 130 mmol/L (NR: 138-145 mmol/L), potassium 3.1 mmol/L (NR: 3.4-4.5 mmol/L); calcium total 2.04 mmol/L (NR: 2.15-2.50 mmol/L); urea 39.5 mmol/L (NR: 2.9-8.1 mmol/L); creatinine 1212 umol/L (also reported as 1200 umol/L) (NR: 62-105 umol/L); glucose 7.7 mmol/l (NR: 4.1-5.9 mmol/L); bilirubin total 9 umol/L (0-21 umol/L), aspartate aminotransferase (AST) 76.0 UI/L (NR: 0.0-51.0 UI/L); alanine aminotransferase (ALT) 47.6 UI/L (NR: 0.0-51.0 UI/L); Gamma GT 190 (NR: 0.0-71.0 UI/L); alkaline phosphatase 95.2 UI/L (NR: 55.0-129.0); lactate dehydrogenase (LDH) 572.4 UI/L (NR: 135.0-225.0 UI/L); haptoglobin 0.77 g/L (0.82-2.18 g/L); protein total 64 g/L (NR: 64-83 g/L); hemoglobin 11.2 g/dl with no signs of hemolysis (NR: 13.5-17.5 g/dl); blood gases showed no signs of acidosis, leukocytes 11.49 giga/L (NR:4.0-10.0 giga/L); and lymphocytes 3.58 giga/L (1.50-4.00 giga/L); search of

parasites/ search of hematozoa of malaria direct examination and thick drop (Giemsa) (captured as malaria antibody test and parasite blood test): negative, antigenemia was positive to Plasmodium falciparum and possibly another species. Diagnostics included a renal echography that was negative.

Treatment included rehydration; the nephrologist confirmed that there was no need for emergency dialysis; the decision regarding dialysis was ongoing. The subject's normal potassium favored tubulopathy.

On an unspecified date, the subject was parasitemia negative, consistent with recent malaria treatment. On [redacted], creatinine was 1361 umol/L. On an unspecified date during the hospitalization, blood smear negative; electrocardiogram showed heart rate 66 beats per minute, QRS fine, no Q-wave; chest x-ray showed no effusion, no cave or pathological shadow and urine hematuria plus no leukocyturia or nitrite.

No etiology for the renal failure at the time of this report. The subject had not anuria, no sign of overload, no acidosis, against a background of recent treatment for malaria and urinary tract infection treated with Oroken (cefixime).

On [redacted] Oroken (cefixime) was stopped.

Action taken with darunavir/cobicistat/emtricitabine/tenofovir alafenamide regarding malaria dose was not changed and for acute renal failure dose was interrupted by the subject.

The subject was recovering from the serious event of malaria and had not recovered from the serious event acute renal failure. The subject remained hospitalized for acute renal failure at the time of this report.

The investigator assessed malaria as grade 2 or moderate and acute renal failure as grade 4 or potentially life-threatening. Malaria and acute renal failure were not related to trial procedure and not related to HIV.

The investigator considered the causality between malaria and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related. The investigator considered the causality between acute renal failure and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as doubtful. Company causality for acute renal failure was assessed as not related.

This report is serious (hospitalization).Additional information was received from the investigator on [redacted], inclusive of a translation.

The subject's most recent weight was [redacted] kilograms.

Start date of study drug was [redacted] (previously reported as [redacted]).

Action taken with darunavir/cobicistat/emtricitabine/tenofovir alafenamide regarding malaria was drug withdrawn (previously reported as dose not changed) and action taken regarding acute renal failure was dose withdrawn (previously reported as drug interrupted).

The stop date of study drug was reported as [redacted]. Date of completion or discontinuation of study drug was also reported as [redacted]. The subject was discontinued early from the study due to the serious adverse event of acute renal failure.

Regarding the serious event of malaria, the second blood smear was negative on [redacted]. The last test would be performed in 2 weeks time. Regarding the serious event of acute renal failure, dialysis was performed on [redacted] and [redacted]. A renal biopsy would probably occur during the present week.

Additional information about the hospitalization in Cameroon included antibiotherapy linked to bacteremia with cocci gram positive (non-identified) on [redacted]. The subject received one injection of ceftriaxone and one of gentamicin.

Blood smear test on [redacted] was negative. Parasite blood test on [redacted] showed a search of parasites/ search of hematozoa of malaria direct examination and thick drop (Giemsa) was negative. Control at day 9 of malaria attack diagnosed in Cameroon.

Additional laboratory data included: calcium (NR: 2.15 - 2.50 mmol/l) [redacted] 2.07 mmol/l, [redacted] 2.15 mmol/l, [redacted] 2.21 mmol/l; c-reactive protein (NR: 0.0 - 5.0 mg/l) [redacted] 13.3 mg/l; creatinine (NR: 62 - 106 mcmol/l) [redacted] 969 mcmol/l, [redacted] 739 mcmol/l, [redacted] 436 mcmol/l; glucose (NR: 4.1 - 5.9 mmol/l) [redacted] 9.0 mmol/l; hemoglobin (NR: 13.5 - 17.5 g/dl) [redacted] 10.5 g/dl; leukocytes (NR: 4.0 - 10.0 10e9/l) [redacted] 14.05 10e9/l; potassium (NR: 3.4 - 4.5 mmol/l) [redacted] 4.8 mmol/l, [redacted] 5.4 mmol/l, [redacted] 4.9 mmol/l; protein (NR: 64 - 83 g/l) [redacted] 64 g/l; red blood cell count (NR: 4.50 - 5.90 10e12/l) [redacted] 3.59 10e12/l; sodium (NR: 136 - 145 mmol/l) [redacted] 139 mmol/l, [redacted] 142 mmol/l, [redacted] 139 mmol/l; urea (NR: 2.8 - 8.1 mmol/l) [redacted] 23.2 mmol/l, [redacted] 18.3 mmol/l, [redacted] 8.2 mmol/l; uric acid (NR: 200 - 415 mcmol/l) [redacted] 549 mcmol/l.

A new antiretroviral treatment was started on [redacted] with lopinavir, ritonavir, and

lamivudine.Additional medically important information was received from the investigator, inclusive of translated hospital medical records on [redacted], and from the clinical group on [redacted].

Baseline laboratory results included urine glucose, normal result for all measurements, urine protein negative until W48 ([redacted]) and "trace" at W60 [redacted] and W72 ([redacted]). There was no hypophosphatemia at all during the study. Urine B2MGB (also only measured until W48, [redacted]) was always < 0.300 mg/L. The subject had no hypophosphatemia at all during the study. At screening on [redacted], creatinine clearance, crockcroft and gault was 118 mL/min (NR: 85-125 mL/min), creatinine 0.9 mg/dL (NR: 0.5-1.3 mg/dL), and eGFR CKD Cystatin C (captured as eGFR status assay) 122 mL/min/1.73m^2; baseline day 1, [redacted], creatinine clearance, crockcroft and gault was 115 mL/min, creatinine 1.0 mg/dL, and eGFR CKD Cystatin C 125 mL/min/1.73m^2; [redacted], creatinine clearance, crockcroft and gault was 131 mL/min, creatinine 0.8 mg/dL, and eGFR CKD Cystatin C 122 mL/min/1.73m^2; [redacted], creatinine clearance, crockcroft and gault was 112 mL/min, creatinine 1.0 mg/dL, and eGFR CKD Cystatin C 118 mL/min/1.73m^2; [redacted], creatinine clearance, crockcroft and gault was 125 mL/min, creatinine 0.9 mg/dL, and eGFR CKD Cystatin C 120 mL/min/1.73m^2; [redacted], creatinine clearance, crockcroft and gault was 103 mL/min, creatinine 1.1 mg/dL, and eGFR CKD Cystatin C 116 mL/min/1.73m^2; [redacted], creatinine clearance, crockcroft and gault was 104 mL/min, creatinine 1.0 mg/dL, and eGFR CKD Cystatin C 117 mL/min/1.73m^2; [redacted], creatinine clearance, crockcroft and gault was 109 mL/min, creatinine 1.0 mg/dL, and eGFR CKD Cystatin C 117 mL/min/1.73m^2; [redacted], creatinine clearance, crockcroft and gault was 134 mL/min, creatinine 0.8 mg/dL, and eGFR CKD Cystatin C 114 mL/min/1.73m^2; [redacted] creatinine clearance, crockcroft and gault was 106 mL/min, creatinine 1.0 mg/dL; [redacted], creatinine clearance, crockcroft and gault was 116 mL/min, creatinine 0.9 mg/dL; [redacted], creatinine clearance, crockcroft and gault was 98 mL/min, creatinine 1.0 mg/dL.

The subject's most recent weight of [redacted] kilograms was reported, Additional concurrent conditions included dry skin and the medical history of pulmonary embolism as a result of deep vein thrombosis in [redacted] was updated to include the cause; prolonged air travel.

The subject had traveled to Cameroon from [redacted] to [redacted]; he had returned to France on [redacted]. The final dose of artemether/lumefantrine was on [redacted] (previously reported as both [redacted] and [redacted]).

The reason for the hospitalization admission on [redacted], was acute kidney failure post malaria and sepsis. Physical examination in the emergency room, cardio-pulmonary auscultation was clear, abdominal palpation was normal, skin: unremarkable. No sign of localization.

Additional laboratory and diagnostic data included LDH -4N [previously reported as 572.4 UI/L (NR: 135.0-225.0 UI/L)]; urine test strip (captured as urinalysis and previously reported as unspecified date, updated to [redacted]) showed proteinuria and hematuria reading at 1+ with remaining findings normal; no leukocyturia or nitrite; the ECG and chest x-ray were performed on [redacted] in the emergency room (previously reported as unspecified date) and were unremarkable; kidney ultrasound showed no dilatation of pelvicalyceal cavities.

Treatment on admission included Oroken (cefixime) 200 mg in the morning.

The subject was transferred to the nephrology department from the emergency room; vital signs blood pressure 125/66, "CF" 70/min, saturation 96%, and afebrile. Physical examination showed marked asthenia associated with anorexia. Mild thirst. Skinfold test minimal. Urinary tract and digestive system showed supple and pain-free abdomen, no palpated mass, no urinary functional manifestations. Constipation for 10 days. Conserved diuresis. The paraclinical examination included significant tenofovir overdose.

Laboratory results on [redacted], included tenofovir 120 ng/mL (also reported as 124 ng/mL) and emtricitabine 833 ng/mL (captured as antiviral drug level). On [redacted], drug level (unspecified) was 110 ng/ml. Emtricitabine 200 mg, one per day residual levels usually were 90+/ -70 ng/mL; tenofovir 300 mg, one per day residual levels usually were 44+/ -22 ng/mL. The residual plasma concentrations of emtricitabine and tenofovir measured, both seemed high for the respective administered doses four days after the study drug was stopped. The subject's tolerance and renal status were questioned. "CBEU" (captured as laboratory test) showed aseptic leukocyturia and no hematuria. The last blood smear for malaria was pending.

The hospital course included acute organic renal organ insufficiency as a result of probable acute tubular necrosis with tenofovir associated tubular toxicity, necessitating extrarenal purification (dialysis) during the first week. The subject experienced normocytic anemia on an unspecified date and was treated with Aranesp (darbepoetin alfa) 40 ug weekly, initiated on [redacted]. On [redacted], renal function began to recover with creatinine level of 298 umol/L; hemoglobin was 8.8 g/dL. The subject had no Multidrug-resistant bacteria or extensively drug-resistant bacteria; no blood transfusion, blood-derived medicines. An implantable device (unspecified) was placed.

The subject was recovering from the serious event acute renal failure updated from had not recovered.

The subject was discharged on [redacted]. Weekly biological follow-up was planned. Discharge medications included darbepoetin alfa, lamivudine, darunavir and ritoniavir.

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

The investigator considered the causality between acute renal failure and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as probable, updated from doubtful. Company causality for acute renal failure was assessed as possible.Additional information was received from the local safety officer on [redacted].

Laboratory test, "CBEU" is cytobacteriological examination of urine (captured as urine cytology), and "CF" is heart rate.Additional medically important information was received from the investigator on [redacted].

Start date of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was updated to [redacted] (previously reported as [redacted]).

Concomitant medications included paracetamol for scapular tendinitis and Dexeryl (glycerol/vaseline/liquid paraffin) for dry skin.

The subject's most recent blood smear was negative.

The subject recovered from malaria on [redacted] (also reported as recovering).

The subject had no history of renal pathology.

The subject received treatment with doxycycline [redacted] to [redacted], darbepoetin alpha [redacted] to [redacted], and cefixime [redacted] to [redacted].

On [redacted], the subject began new antiretroviral treatment with darunavir, ritonavir, and 3TC (lamivudine).

The subject was recovering (also reported as not recovered) from acute renal failure with MDRD=79 ml/min.

Hemoglobin had increased up to 12.5 g/dl. The subject was reportedly feeling better.

It was reported that renal function would be monitored closely by a nephrologist and the subject was informed that he had to avoid all drugs with potential nephrotoxicity.

The investigator considered the causality between acute renal failure and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as probable (also reported as doubtful).

Senders Comments/Medical Assessment: V4:

This is a follow up to a 5[redacted]-year-old male subject who experienced malarial infection approximately 8 months following study therapy initiation for HIV infection. Malaria is a vector borne infection predisposed by endemic regions, therefore causality for malaria is considered not related to study therapy (darunavir/cobicistat/emtricitabine/tenofovir alafenamide). About 3 days following last study therapy dose, subject also experienced acute renal failure which is confounded by concurrent cefixime use (known to be associated with acute renal failure) and severe falciparum malaria infection (acute renal failure is a known complication of severe falciparum malaria infection). Additionally, suspected causes for acute renal failure reported doxycycline and darbepoetin alpha therapies. However, despite these alternative factors, the contributory role of study therapy is considered possibly related considering the high emtricitabine and tenofovir plasma level findings. The follow-up information received which included study therapy dates, additional labs, and event outcome does not alter the prior Company causality assessment (remains as possibly related).

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ALANINE AMINOTRANSFERASE	[redacted]	47.6 IU/L	0.0	51.0
ALKALINE PHOSPHATASE	[redacted]	95.2 IU/L	55	129
ANTIVIRAL DRUG LEVEL	[redacted]	tenofovir 120 also reported as 124 ng/mL		
		emtricitabine 833 ng/mL		
	[redacted]	unknown antivrial 110 ng/mL		
ARTERIAL BLOOD GASES	[redacted]	showed no signs of acidosis		
ASPARTATE AMINOTRANSFERASE	[redacted]	76 IU/L	0.0	51.0
BILIRUBIN TOTAL	[redacted]	9 umol/L	0	21
BLOOD PRESSURE	[redacted]	nephrology unit 125/66		
	[redacted]	114/65		
BLOOD SMEAR TEST	??-???-????	negative		

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
BLOOD SMEAR TEST	??-[redacted]	negative		
		pending		
	[redacted]	negative		
BODY TEMPERATURE		afebrile in the nephrology unit		
		Celsius		
	[redacted]	36 Celsius		
C-REACTIVE PROTEIN		13.3 mg/L	0.0	5.0
CALCIUM		2.04 mmol/L	2.15	2.50
		2.07 mmol/L		
		2.15 mmol/L		
		2.21 mmol/L		
CHEST X-RAY		see Other diagnostics		
CREATININE		1200 mcmol/L	62	106
		1212 mcmol/L		
	[redacted]	1361 mcmol/L		
		969 mcmol/L		
		739 mcmol/L		
		436 mcmol/L		
		298 mcmol/L		
CREATININE		0.9 mg/dL	0.5	1.3
		1.0 mg/dL		
		0.8 mg/dL		
		1.0 mg/dL		
		0.9 mg/dL		
		1.1 mg/dL		
		1.0 mg/dL		
		1.0 mg/dL		
		0.8 mg/dL		
		1.0 mg/dL		
		0.9 mg/dL		
		1.0 mg/dL		
CREATININE CLEARANCE		109 mL/min	85	125
		118 mL/min		
		115 mL/min		
		131 mL/min		
		112 mL/min		
		125 mL/min		
		103 mL/min		
		104 mL/min		
		134 mL/min		
		106 mL/min		
		116 mL/min		
		98 mL/min		
CULTURE		see Other Diagnostics		
		see Other Diagnostics		
EGFR STATUS ASSAY		MDRD=79 ml/min		
		122 mL/min/1.73m^2		
		125 mL/min/1.73m^2		
		122 mL/min/1.73m		
		118 mL/min/1.73m^2		
		120 mL/min/1.73m^2		

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
EGFR STATUS ASSAY	[redacted]	116 mL/min/1.73m^2		
		117 mL/min/1.73m^2		
		117 mL/min/1.73m^2		
		114 mL/min/1.73m^2		
ELECTROCARDIOGRAM		see Other Diagnostics		
GAMMA GT		190 IU/L	0.0	71.0
GLASGOW COMA SCALE		15		
GLUCOSE		7.7 mmol/L	4.1	5.9
		9.0 mmol/L		
HAPTOGLOBIN		0.77 low g/L	0.82	2.18
HEART RATE		70 in nephrology unit /min		
HEMOGLOBIN		12.5 g/dL	13.5	17.5
		11.2 g/dL		
		10.5 g/dL		
		8.8 g/dL		
LACTATE DEHYDROGENASE		572.4 (-4N) IU/L	135.0	225.0
LEUKOCYTES		11.49 10E9/L	4.0	10.0
		14.05 10E9/L		
LYMPHOCYTES		3.58 giga/L	1.50	4.00
MALARIA ANTIBODY TEST		see Other Diagnostics		
OXYGEN SATURATION		96 in the nephrology unit %		
		98 %		
PARASITE BLOOD TEST		parasitemia negative		
		see Other Diagnostics		
		see Other Diagnostics		
PHYSICAL EXAMINATION		nephrology unit, see Other Diagnostics		
		see Other Diagnostics		
POTASSIUM		3.1 mmol/L	3.4	4.5
		4.8 mmol/L		
		5.4 mmol/L		
		4.9 mmol/L		
PROTEIN		64 g/L	64	83
		64 g/L		
PROTEIN URINE		negative week 48		
		trace week 60		
		trace week 72		
RED BLOOD CELL COUNT		3.59 10E12/L	4.50	5.90
RENAL SCAN		showed no dilatation of pelvicalyceal cavities		
SERUM PHOSPHATE		no hypophosphatemia at all during the study		
SODIUM		130 mmol/L	136	145
		139 mmol/L		
		142 mmol/L		
		139 mmol/L		
UREA		39.5 mmol/L	2.8	8.1
		23.2 mmol/L		

Continuation Sheet for CIOMS report **Mfr. Control No.: FR-JNJFOC-20170517888**

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
UREA	[redacted]	18.3 mmol/L	2.8	8.1
		8.2 mmol/L		
URIC ACID		549 mcmol/L	200	415
URINALYSIS		see Other Diagnostics (Urine strip)		
URINE CYTOLOGY		CBEU showed aseptic leukocyturia		
URINE GLUCOSE		normal result for all measurements for urine gluco		
WEIGHT		[redacted] kilograms		

Culture ([redacted]): coagulase gram positive (CG) + clusters and chains (no identification available). Malaria antibody test and parasite blood test ([redacted]): search of parasites/ search of hematozoa of malaria direct examination and thick drop (Giemsa): negative, antigenemia was positive to Plasmodium falciparum and possibly another species.

Culture ([redacted]): cocci gram positive (non-identified). Physical examination ([redacted]): cardio-pulmonary auscultation was clear, abdominal palpation was normal, skin: unremarkable. No sign of localization. Chest x-ray ([redacted]): no effusion, no cave or pathological shadow; unremarkable. ECG ([redacted]): heart rate 66 bpm, QRS fine, no Q-wave; unremarkable. Urine strip (Urinalaysis) ([redacted]): showed proteinuria and hematuria reading at 1+ with remaining findings normal; no leukocyturia or nitrite. Physical examination in the nephrology unit ([redacted]): showed marked asthenia associated with anorexia. Mild thirst. Skinfold test minimal. Urinary tract and digestive system showed supple and pain-free abdomen, no palpated mass, no urinary functional manifestations. Constipation for 10 days. Conserved diuresis.

Parasite blood test ([redacted]): search of parasites/ search of hematozoa of malaria direct examination and thick drop (Giemsa): negative. Control at Day 9 of malaria attack diagnosed in Cameroon.

Urine B2MGB (also only measured until W48, [redacted]) was always < 0.300 mg/L.

MDRD=79 ml/min

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

Causality

1. MALARIA [10025487]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Causality

Causality as per Mfr. Not Related

2. ACUTE KIDNEY INJURY [10069339]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Probable
Causality as per Mfr.	Possible

Concomitant Drugs (Cont...)

Seq. No.	2
Drug	DEXERYL (DEXERYL /01579901/)
Daily Dose	1) 1 Dose(s), 2 in 1 Day
Indication	1) DRY SKIN
Route of Admin.	1) Topical
Therapy Dates/Duration	1) [redacted] - ??-??-????

Other relevant history (Cont...)

Medical History: DEEP VEIN THROMBOSIS ??-???-[redacted] - ??-??-???? : Comments: pulmonary embolism with deep vein thrombosis; cause was prolonged air travel
Medical History: PULMONARY EMBOLISM ??-???-[redacted] - ??-??-???? : Comments: with deep vein thrombosis; cause was prolonged air travel
Medical History: GASTROOESOPHAGEAL REFLUX DISEASE ??-???-[redacted] - ??-??-???? : Comments: without esophagitis
Medical History: TENDONITIS ??-???-[redacted] - ??-??-????
Other History: No known allergies
No history of renal pathology.
Medical History: DRY SKIN ??-??-???? - Ongoing
Medical History: EX-TOBACCO USER ??-??-???? - Ongoing
Medical History: HAEMORRHOIDS ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	2. DATE OF BIRTH MO	2. DATE OF BIRTH YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	4.-6. REACTION ONSET MO	4.-6. REACTION ONSET YR
PRIVATE	[redacted]	[redacted]	[redacted]	[redacted]	4[redacted] Year	M	[redacted]	[redacted]	[redacted]

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

TENDON RUPTURE([redacted]

This report was received from clinical trial TMC114IFD3013: A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects, EudraCT #: 2014-003052-31, and concerns a 4[redacted] year old male (subject [redacted]-[redacted] site

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

1 Dose(s), 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

[redacted] - [redacted]

19. THERAPY DURATION

73 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

ROSUVASTATINUM (ROSUVASTATIN) Oral Oral [redacted] - ??-??-????20 mg, in 1 Day

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: VITAMIN D DECREASED [redacted] - ??-??-????

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : TMC114IFD3013
Center no : [redacted]
Patient no : [redacted]-[redacted]

24b. MFR. CONTROL NO.

[redacted] (2)

24c. DATE RECEIVED BY MFR.

[redacted]

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Describe Reaction(s) (include relevant test/lab data) (Cont...)

[redacted] from [redacted]

The subject's weight was [redacted] kilograms and height was [redacted] centimeters. The subject's concurrent conditions included HIV and medical history included contact dermatitis, seborrheic dermatitis, memory disturbances, hearing disturbance, total cholesterol increased, low vitamin D level, and athlete's foot.

The subject was treated with open-label darunavir/cobicistat/emtricitabine/tenofovir alafenamide (stable antiretroviral therapy) (tablet, oral) 1 dose once a day initiated on [redacted] to [redacted], 1 dose once a day initiated on [redacted] to [redacted], and 1 dose once a day initiated on [redacted] for HIV. Concomitant medications included rosuvastatin for total cholesterol elevation, colecalciferol for low vitamin D level, and hepatitis A vaccine.

On [redacted], the subject experienced right achilles tendon rupture and informed his treating physician the next day. Surgical intervention was planned to be performed in the next few days and would require hospitalization. According to the investigator, study medication was never stopped or modified due to the event.

The dose of darunavir/cobicistat/emtricitabine/tenofovir alafenamide was not changed.

The subject had not recovered from right achilles tendon rupture.

The event severity was grade 3 or severe, not related to HIV, and not related to trial procedure.

The investigator considered the causality between right achilles tendon rupture and darunavir/cobicistat/emtricitabine/tenofovir alafenamide as not related.

This report is serious (medically significant).

This case, involving the same patient is linked to [redacted].Additional information was received from the investigator on [redacted].

The seriousness criteria of hospitalization was added to the case.

The subject was admitted to the hospital on [redacted]. The subject underwent a surgical repair of the right achilles tendon rupture and was treated with enoxaparin, paracetamol, tramadol and cyclo 3 fort. The subject was discharged on [redacted]. There were no complications during postoperative course so far. The subject was on tract of convalescence.

The subject was recovering from right achilles tendon rupture (previously not recovered).

This report is serious (medically significant, hospitalization).Additional information

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

was received from the investigator on [redacted].

The serious criteria of medically important was removed from the case.

The investigator confirmed the subject did not report any specific trauma or fall proceeding his achilles tendon rupture.
Senders Comments/Medical Assessment: V2:

This a follow up report on a 4[redacted]-year-old male subject who experienced enchondroma and right Achilles tendon rupture approximately 5 and 7 months respectively following study therapy initiation for HIV. Enchondroma is a benign bone tumor involving overgrowth of cartilage whereas Achilles tendon rupture is an injury that affects the back of the lower leg especially when an individual with a sedentary lifestyle suddenly becomes active. Further, age and gender are predisposing factors. Events appear to be coincidental and given the lack of clear biologic plausibility, causality for these events are considered not related to study therapy. Follow up provided updates on queries and does not change the prior causality assessment.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE) Tablet
Daily Dose	2) 1 Dose(s), 1 in 1 Day 3) 1 Dose(s), 1 in 1 Day
Therapy Dates/Duration	2) [redacted] - Stopped 3) [redacted] - Ongoing

Causality

1. TENDON RUPTURE [10043248]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No.	2
Drug	CHOLECALCIFEROLUM (COLECALCIFEROL)
Daily Dose	1) 2000 IU, in 1 Day
Indication	1) VITAMIN D DECREASED
Route of Admin.	1) Oral
Therapy Dates/Duration	1) [redacted] - ??-??-????
Seq. No.	3
Drug	AVAXIM (HEPATITIS A VACCINE)
Daily Dose	1) 160 IU
Indication	1) HEPATITIS A IMMUNISATION
Route of Admin.	1) Intramuscular
Therapy Dates/Duration	1) [redacted] - Stopped

Continuation Sheet for CIOMS report **Mfr. Control No.:** [redacted]

Other relevant history (Cont...)

Medical History: BLOOD CHOLESTEROL INCREASED [redacted] - ??-??-????
Medical History: DERMATITIS CONTACT ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: HYPOACUSIS ??-??-???? - ??-??-????
Medical History: MEMORY IMPAIRMENT ??-??-???? - ??-??-????
Medical History: SEBORRHOEIC DERMATITIS ??-??-???? - ??-??-????
Medical History: TINEA PEDIS ??-??-???? - ??-??-????

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 study TMC114IFD3013 Follow-up

Results: 7 cases selected from 7 matching the following criteria

Start Date : [redacted]

End Date : [redacted]

Date Type : Version Initially Received

Version : Highest In Date Range

Invalid Cases : Excluded

Workflow Cases : Excluded

Deleted Cases : Excluded

Protocol Number(s) : TMC114IFD3013

CIOMS II Report

Run Information

User Name: [redacted]

Run Date: 12-Sep-2017

Parameters

Query Report Name: SDE00256388 study TMC114IFD3013 Follow-up

First Case Version Date Range : Between [redacted]

CIOMS II Report

SDE00256388 study TMC114IFD3013 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	5[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
PERIPHERAL ARTERY STENOSIS	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, MOLLUSCUM CONTAGIOSUM, HYPERTENSION, SEBORRHOEIC DERMATITIS, SCROTAL ULCER, LIPOHYPERTROPHY, LIPODYSTROPHY ACQUIRED, HYPERLIPIDAEMIA, GASTRIC ULCER, ORAL HERPES, INTERMITTENT CLAUDICATION, DIVERTICULUM INTESTINAL HAEMORRHAGIC, TYPE 2 DIABETES MELLITUS, POLYNEUROPATHY, NEPHROPATHY, GYNAECOMASTIA, GINGIVITIS, BACK PAIN, MICROALBUMINURIA, POLYNEUROPATHY, ANOGENITAL WARTS, ABDOMINAL FAT APRON

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	5[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: CHRONIC OBSTRUCTIVE PULMONARY DISEASE, HIV INFECTION, TOBACCO USER
Concomitant Drugs: TIOTROPIUM BROMIDE
INDACATEROL MALEATE

MedDRA 20.0

CIOMS II Report

SDE00256388 study TMC114IFD3013 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	4[redacted] Year	F	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
HYSTERECTOMY	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED
LEIOMYOMA	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments:

Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION

Disease Type: NECK PAIN, ABDOMINAL PAIN UPPER, CUSHING'S SYNDROME, INSOMNIA, ASTHMA, LIPODYSTROPHY ACQUIRED, FEMALE STERILISATION, GOITRE, CAESAREAN SECTION, HIV INFECTION, ASTHMA

Concomitant Drugs: LEVOTHYROXINE SODIUM (50mg)

HYDROXYZINE (25mg)

OMEPRAZOLE (20mg)

FERROUS SULFATE (2Dose(s))

[redacted]	[redacted]	Study	5[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
MALARIA	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED
ACUTE KIDNEY INJURY	Recovering/Resolving	Yes	Possible	UNLABELED	UNLABELED

MedDRA 20.0

CIOMS II Report

SDE00256388 study TMC114IFD3013 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	4[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: PULMONARY TUBERCULOSIS, PULMONARY EMBOLISM, DEEP VEIN THROMBOSIS, GASTROOESOPHAGEAL REFLUX DISEASE, TENDONITIS, HAEMORRHOIDS, EX-TOBACCO USER, DRY SKIN, HIV INFECTION
Concomitant Drugs: PARACETAMOL (1g)
DEXERYL /01579901/ (1Dose(s))

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
TENDON RUPTURE	Recovering/Resolving	Yes	Not Related	UNLABELED	UNLABELED

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	5[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: VITAMIN D DECREASED, BLOOD CHOLESTEROL INCREASED, DERMATITIS CONTACT, HYPOACUSIS, TINEA PEDIS, SEBORRHOEIC DERMATITIS, HIV INFECTION, MEMORY IMPAIRMENT
Concomitant Drugs: ROSUVASTATIN (20mg)
COLECALCIFEROL (2000IU)
HEPATITIS A VACCINE (160IU)

MedDRA 20.0

CIOMS II Report

SDE00256388 study TMC114IFD3013 Follow-up

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
ATRIAL FIBRILLATION	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED
UROSEPSIS	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
[redacted]	[redacted]	Study	6[redacted] Year	M	1 Dose(s),1 in 1 Day Tablet Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
PNEUMONIA	Recovering/Resolving	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: TMC114IFD3013, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION

MedDRA 20.0

Janssen Research & Development

Clinical Summary

Literature References

D/C/F/TAF (darunavir/cobicistat/emtricitabine/tenofovir alafenamide; TMC114/JNJ-48763364 /JNJ-35807551/JNJ-63625328)

Status:	Approved
Date:	11 September 2017
Prepared by:	Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number:	EDMS-ERI-145084537, 2.0

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REFERENCES

The references listed below are located in Module 5.4 unless marked by an asterisk to indicate that they are available on request. Within Module 5.4, references are arranged alphabetically by author or, if no author, by title.

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Janssen Research & Development

Tabular Listing of All Clinical Studies

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults and Adolescents

D/C/F/TAF (darunavir/cobicistat/emtricitabine/tenofovir alafenamide; TMC114/JNJ-48763364/JNJ-35807551/JNJ-63625328)

Status: Approved

Date: 8 September 2017

Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV

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5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-299-0101 (United States: 1)	Adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple-cohort, single-center study. To evaluate the bioavailability of 3 formulations of D/C/F/TAF FDC relative to the administration of individual components COBI-boosted DRV, FTC, TAF.	Healthy volunteers N=102; of whom 66 received D/C/F/TAF FDC	Part 1 (N=30), oral dose once daily for 21 days: Treatment A: D/C/F/TAF FDC Formulation 1 monolayer (DRV 800 mg/ COBI 150 mg/ FTC 200 mg/TAF 25 mg) Treatment B: D/C/F/TAF FDC Formulation 2 bilayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 25 mg) Treatment C: D/C/F/TAF FDC Formulation 3 monolayer (DRV 800 mg/ COBI 150 mg/ FTC 200 mg/TAF 10 mg) Part 2 (N=36), oral dose once daily for 20 days (10 days in each cohort): - Cohort 1 Treatment D: DRV 800 mg + COBI 150 mg + TVD (FTC 200 mg/ TDF 300 mg) Treatment E: DRV 800 mg + COBI 150 mg - Cohort 2 Treatment D: DRV 800 mg + COBI 150 mg + TVD (FTC 200 mg/ TDF 300 mg) Treatment F: TVD (FTC 200 mg/TDF 300 mg) Part 3 (N=36), oral dose once daily for 24 days (12 days in each cohort): - Cohort 1 Treatment C: D/C/F/TAF FDC Formulation 3 monolayer (DRV 800 mg/ COBI 150 mg/ FTC 200 mg/TAF 10 mg) Treatment E: DRV 800 mg + COBI 150 mg - Cohort 2 Treatment C: D/C/F/TAF FDC Formulation 3 monolayer (DRV 800 mg/ COBI 150 mg/ FTC 200 mg/TAF 10 mg) Treatment G: FTC 200 mg + TAF 25 mg	Completed Synopsis Full report 5.3.1.1

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114FD2HTX1002 (Belgium: 1)	Single-dose, open-label, randomized, crossover study. To assess the impact of food on the pharmacokinetics of darunavir, cobicistat, emtricitabine, and tenofovir alafenamide administered as a fixed-dose combination tablet, and the relative bioavailability of these antiretrovirals in different formulations/combinations.	Healthy volunteers N=72	Panel 1 (N=24): - Treatment A: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet under fed conditions (standardized regular breakfast) (test). - Treatment B: single oral dose of E/C/F/TAF 150/150/200/10 mg as 1x FDC tablet under fed conditions (standardized regular breakfast) (reference). Panel 2 (N=24): - Treatment C: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet under fed conditions (standardized regular breakfast) (test). - Treatment D: single oral dose of DRV as 1x 800-mg tablet, FTC/TAF as 1x 200/10-mg tablet and COBI as 1x 150-mg tablet under fed conditions (standardized regular breakfast) (reference). Panel 3 (N=24): - Treatment E: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet, under fasted conditions (test). - Treatment F: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet, with a standardized high-fat breakfast (reference). Subsequent treatment sessions were separated by a washout period of at least 7 days.	Completed Synopsis Full report 5.3.1.1

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114FD2HTX1004 (United States: 1)	Single-dose, open-label, randomized, 3-period, 3-treatment crossover study. To assess the relative bioavailability of the fixed-dose combination tablet darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) administered orally as a whole tablet, as a split tablet, and as crushed tablet in healthy subjects.	Healthy volunteers N=30	Treatment A: single oral dose of D/C/F/TAF 800/150/200/10 mg FDC tablet swallowed as an intact tablet with 240 mL of noncarbonated water under fed conditions (reference). Treatment B: single dose of D/C/F/TAF (800/150/200/10 mg) FDC tablet as a split tablet swallowed with 240 mL of noncarbonated water under fed conditions (test). Treatment C: single dose of D/C/F/TAF (800/150/200/10 mg) FDC tablet as a crushed tablet mixed in 4 ounces of applesauce under fed conditions (test). Subsequent treatment sessions were separated by a washout period of at least 7 days.	Completed Synopsis Full report 5.3.1.1

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114FD2HTX1001 (The Netherlands: 1)	Single-dose, open-label, randomized, crossover study. To assess the bioequivalence of darunavir 800 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg, in the presence of cobicistat 150 mg, administered as either a fixed-dose combination tablet or as separate agents.	Healthy volunteers N=96	Treatment A: single oral dose of D/C/F/TAF 800/150/200/10 mg as 1x FDC tablet under fed conditions (test). Treatment B: single oral dose of DRV as 1x 800-mg tablet, FTC/TAF as 1x 200/10-mg FDC tablet, and COBI as 1x 150-mg tablet under fed conditions (reference). Treatment sessions were separated by a washout period of at least 7 days.	Completed Synopsis Full report 5.3.1.2

5.3.1.3 In Vitro - In Vivo Correlation Study Reports and Related Information

Not applicable.

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Report Number	Report Title	Status Study Location in the FDC CTD
BA10833	Validation of a method for the determination of TMC114 and cobicistat in human EDTA plasma.	Completed Full report 5.3.1.4
BA10833 Amendment 3	Validation of an LC-MS/MS method for the determination of TMC114 and cobicistat in human EDTA plasma.	Completed Full report 5.3.1.4
BA10878, including Amendment 1 and 2	Partial validation of a method for the determination of emtricitabine in human EDTA plasma samples.	Completed Full report 5.3.1.4
QPS 60-1115	Validation of a Method for the Determination of GS-7340 in Human Plasma by LC-MS/MS.	Completed Full report 5.3.1.4
QPS 60-1115 Amendment 2	Validation of a Method for the Determination of GS-7340 in Human Plasma by LC-MS/MS.	Completed Full report 5.3.1.4
QPS 60-1115 Amendment 5	Validation of a Method for the Determination of GS-7340 in Human Plasma by LC-MS/MS.	Completed Full report 5.3.1.4
QPS 60-1115 Amendment 6	Validation of a Method for the Determination of GS-7340 in Human Plasma by LC-MS/MS.	Completed Full report 5.3.1.4

5.3.1 Reports of Biopharmaceutic Studies		
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies		
Report Number	**Report Title**	**Status** **Study Location in the FDC CTD**
QPS 60-1578	Validation of a Method for the Determination of GS-7340 in Human Plasma by LC-MS/MS	Completed Full report 5.3.1.4
QPS 60-1578 Amendment 1	Validation of a Method for the Determination of GS-7340 in Human Plasma by LC-MS/MS	Completed Full report 5.3.1.4
5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials		
5.3.2.1 Plasma Protein Binding Study Reports		
Not applicable.		
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies		
Not applicable.		
5.3.2.3 Reports of Studies Using Other Human Biomaterials		
Not applicable.		
5.3.3 Reports of Human Pharmacokinetic (PK) Studies		
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports		
Not applicable.		
5.3.3.2 Patient PK and Initial Tolerability Study Reports		
Not applicable.		
5.3.3.3 Intrinsic Factor PK Study Reports		
Not applicable.		
5.3.3.4 Extrinsic Factor PK Study Reports		
Not applicable.		

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	TMC114FD2HTX3001-TAF Pop PK-report (Not applicable)	TAF PK data from a randomized, active-controlled, double-blind study. Development of a population PK model for TAF & 48 week exposure metric estimation for TAF for subjects in the D/C/F/TAF arm of study TMC114FD2HTX3001	HIV-1 infected ART-naïve, adult subjects N=725; of whom 362 received D/C/F/TAF FDC Only data for subjects in the D/C/F/TAF arm were collected	See individual study: TMC114FD2HTX3001	Completed Full report 5.3.3.5
3	D/C/F/TAF Phase 3 – DRV Pop PK-report (Not applicable)	Pooled DRV PK data from a randomized, active-controlled, double-blind study and a randomized, active-controlled, open-label study. 48 week exposure metric estimation for DRV for subjects in the D/C/F/TAF arm of studies TMC114FD2HTX3001 and TMC114IFD3013	HIV-1 infected ART-naïve, adult subjects N=725; of whom 362 received D/C/F/TAF FDC and HIV-1 infected ART-experienced, virologically-suppressed, adult subjects N=1,141; of whom 763 received D/C/F/TAF FDC Only data for subjects in the D/C/F/TAF arms were collected	See individual studies: TMC114FD2HTX3001 and TMC114IFD3013	Completed Full report 5.3.3.5

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

Not applicable.

5.3.4.2 Patient PD and PK/PD Study Reports

Not applicable.

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	TMC114FD2HTX3001 (International, multicenter)	Randomized, active-controlled, double-blind study. To evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/ tenofovir alafenamide (D/C/F/TAF) once daily fixed dose combination regimen versus a regimen consisting of darunavir/cobicistat fixed dose combination co-administered with emtricitabine/tenofovir disoproxil fumarate fixed dose combination.	HIV-1 infected ART-naïve, adult subjects N=725; of whom 362 received D/C/F/TAF FDC	D/C/F/TAF group: D/C/F/TAF 800/150/200/10 mg FDC tablet; administered once daily, orally for 48 weeks (N=362). Control group: DRV/COBI 800/150 mg FDC co-administered with F/TDF 200/300 mg FDC; FDCs administered once daily, orally for 48 weeks (N=363)	Ongoing Data up to 13 March 2017 (Week 48) Synopsis Full report (Week 48) 5.3.5.1
	TMC114FD2HTX3001	CIOMS I reports, CIOMS II listings, and statistical outputs after Week 48 cut-off up to 1 June 2017	See above	See above	CIOMS I reports CIOMS II listings Statistical Outputs 5.3.5.1

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
2	GS-US-299-0102 (United States: 37 Puerto Rico: 1)	Randomized, double-blinded, multicenter, active-controlled study. To assess the safety and efficacy of a regimen containing darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF [D/C/F/TAF]) administered as a fixed-dose combination (FDC) tablet versus cobicistat-boosted darunavir (DRV+COBI) given with emtricitabine co-formulated with tenofovir disoproxil fumarate (Truvada, TVD).	HIV-1 infected ART-naïve, adult subjects N=153	Treatment Group 1: FDC tablet of DRV 800 mg/ COBI 150 mg/FTC 200 mg/TAF 10 mg + placebos-to-match DRV 800 mg (400-mg tablet x2) and COBI 150-mg tablet and FDC tablet of FTC 200 mg/TDF 300 mg once daily, orally for 48 weeks. Treatment Group 2: DRV 800 mg (400-mg tablet x2) + COBI 150-mg tablet + FDC tablet of FTC 200 mg/TDF 300 mg + placebo-to-match D/C/F/TAF once daily, orally for 48 weeks.	Completed Synopsis Full report 5.3.5.1
3	TMC114IFD3013 (International, multicenter)	Randomized, active-controlled, open-label study. To evaluate the efficacy, safety and tolerability of switching to a darunavir/ cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (F/TDF).	HIV-1 infected ART-experienced, virologically-suppressed, adult subjects N=1,141; of whom 763 received D/C/F/TAF FDC	D/C/F/TAF group: Switch at baseline to D/C/F/TAF 800/150/200/10 mg FDC tablet; administered once daily, orally for 48 weeks (N=763). Control group: Stay on bPI [a] combined with F/TDF 200/300 mg, administered orally for 48 weeks (N=378).	Ongoing Data up to 24 February 2017 (Week 48) Synopsis Full report (Week 48) 5.3.5.1
	TMC114IFD3013	CIOMS I reports, CIOMS II listings, and statistical outputs after Week 48 cut-off up to 1 June 2017	See above	See above	CIOMS I reports CIOMS II listings Statistical Outputs 5.3.5.1

[a.] The screening bPI consisted of either DRV once daily with rtv or COBI, ATV with rtv or COBI, or LPV with rtv; dosed as indicated in the local Prescribing Information.

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.2 Study Reports of Uncontrolled Clinical Studies (Pertinent to the Claimed Indication)

Not applicable.

5.3.5.3 Reports of Analyses of Data from More Than One Study

Not applicable.

5.3.5.4 Other Clinical Study Reports

Not applicable.

5.3.6 Reports of Postmarketing Experience

The D/C/F/TAF FDC tablet has not yet been marketed. Therefore, no reports of postmarketing experience are available.

5.3.7 Case Report Forms and Individual Patient Listings

Case Report Forms (CRFs) as well as individual patient listings for Deaths, other Serious Adverse Events (SAE) and withdrawals due to (S)AEs are submitted as part of the individual studies. Other random samples of CRFs can be made available upon request, within 5 to 10 working days. If the number of random samples of CRFs is substantial, timelines for delivery will be discussed and agreed upon.

Abbreviations: AE = adverse events; ART = antiretroviral treatment; bPI = boosted protease inhibitor; COBI = cobicistat; CRF = case report form; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EDTA = ethylenediaminetetraacetic acid; FDC = fixed-dose combination; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada®); FTC = emtricitabine; GS-7340 = tenofovir alafenamide; HIV-1 = human immunodeficiency virus type 1; LC-MS/MS = liquid chromatography tandem-mass spectrometry; PK = pharmacokinetics; N = number of subjects; OBR = optimized background regimen; SAE = serious adverse events; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TVD = Truvada (F/TDF).