Janssen Research & Development

Clinical Overview

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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LIST OF ABBREVIATIONS

Abbreviation	Description of Abbreviated Term
3TC	lamivudine
AAG	α1-acid glycoprotein
ABC	abacavir
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ART	antiretroviral treatment
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	Atripla®
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{24h}	area under the plasma concentration-time curve over 24 hours
AUC_{last}	area under the plasma concentration-time curve from 0 hours up to the time of the last measurable concentration after dosing
AUC_{tau}	area under the plasma concentration-time curve from time of administration up to the end of the dosing interval (AUC_{24h}=AUC_{tau} unless stated otherwise for this application)
AZT	zidovudine
BCRP	breast cancer resistance protein
BMD	bone mineral density
BMI	body mass index
bPI	boosted protease inhibitor
C_{0h}	predose plasma concentration
CatA	cathepsin A
CD4	clusters of differentiation 4
CG	Cockcroft-Gault
CI	confidence interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed analyte concentration
COBI or C	cobicistat
CSR	clinical study report
C_{tau}	plasma concentration at the end of the dosing interval
CTX	C-type collagen sequence
CV	cardiovascular
CYP	cytochrome P450
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DMC	Data Monitoring Committee
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
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CR}$	eGFR based on serum creatinine
$eGFR_{CG}$	eGFR based on serum creatinine by Cockcroft-Gault
eGFRCKD-EPI	eGFR based on serum creatinine by Chronic Kidney Disease Epidemiology Collaboration
$eGFR_{cyst}$	eGFR based on serum cystatin C (by Chronic Kidney Disease Epidemiology Collaboration)
EVG or E	elvitegravir

F/TAF	emtricitabine/tenofovir alafenamide
F/TDF	emtricitabine/tenofovir disoproxil fumarate
FDA	Food and Drug Administration
FDC	fixed-dose combination
$FEPO_4$	fractional excretion of phosphate
FTC or F	emtricitabine
GSI	Gilead Sciences, Inc.
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus type 1
ICH	International Conference on Harmonisation
ITT	intent-to-treat
LDL	low density lipoprotein
LOCF	last observation carried forward
LPV	lopinavir
LS	least square(s)
MATE1	multidrug and toxin extrusion protein 1
MDR1	multidrug resistance protein 1
NA	not applicable
NCEP	National Cholesterol Education Program
NDA	New Drug Application
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
OATP	organic anion transporter protein
P1NP	procollagen type 1 N terminal propeptide
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PDVF	protocol-defined virologic failure
P-gp	p-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PRT	proximal renal tubulopathy
PTH	parathyroid hormone
Q(1 or 3)	(first or third) quartile
RAM	resistance-associated mutation
RBP	retinol-binding protein
RNA	ribonucleic acid
RPV or R	rilpivirine
rtv	low-dose ritonavir
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ class
STB	Stribild®
$t_{1/2}$	apparent elimination half-life
t_{max}	time to reach maximum plasma concentration
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
TFV-DP	tenofovir diphosphate
TLOVR	time to loss of virologic response
TVD	Truvada® (F/TDF)
UACR	urine albumin to creatinine ratio
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
USPI	United States Package Insert
vs	versus

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. PRODUCT DEVELOPMENT RATIONALE

1.1. Rationale for D/C/F/TAF Development

Incomplete adherence to antiretroviral (ARV) regimens is a critical factor contributing to treatment failure of human immunodeficiency virus type 1 (HIV-1) infection and the development of drug resistance, and thus a primary barrier to successful long-term treatment.

Regimens including protease inhibitors (PIs) are generally considered by practicing HIV-1 clinicians to be the initial regimens of choice for patients with suboptimal or unknown adherence who are at higher risk for virologic failure, or when resistance testing results are unavailable. PIs have a high genetic barrier to resistance. Multiple primary and secondary protease mutations are generally required to reduce the activity of agents in this class. When virologic failure occurs, it rarely selects for PI resistance.[9] PI-based regimens may have a higher pill burden than other third-agent ARV drugs (typically 3 pills once daily). Therefore, there is a medical need for a simplified PI-based ARV regimen that combines potent and sustained efficacy, favorable tolerability, and minimal long-term toxicity, with practical, convenient dosing. There is currently no fixed-dose combination (FDC) available consisting of a complete boosted PI (bPI)-based regimen.

To address this need, the Sponsor and Gilead Sciences, Inc. (GSI) co-developed a 4-agent, once-daily FDC tablet containing the PI darunavir (DRV [800 mg]; developed by the Sponsor), the pharmacokinetic (PK) enhancer (booster) cobicistat (COBI [150 mg]; developed by GSI), the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC [200 mg]; developed by GSI), and the next-generation prodrug of the NRTI tenofovir (TFV), ie, tenofovir alafenamide (TAF [10 mg]; developed by GSI). This FDC tablet, hereafter referred to as the D/C/F/TAF FDC tablet, is the first complete single-tablet, once-daily, PI-based HIV-1 regimen. It offers the additional advantage of including a nucleos(t)ide reverse transcriptase inhibitor (N[t]RTI) backbone that has an improved renal and bone safety profile compared to a tenofovir disoproxil fumarate (TDF)-containing backbone. This FDC tablet, may promote better adherence to bPI-based regimens and represents a new, potent, safe, and convenient treatment of HIV-1 infected subjects.

GSI conducted the initial development of the D/C/F/TAF FDC tablet (up to and including the Phase 2 study). Janssen Research & Development conducted the Phase 3 studies and is responsible for regulatory approval, manufacturing, registration, distribution, and commercialization of the product worldwide.

The **proposed indication** of the D/C/F/TAF FDC tablet is for the treatment of HIV-1 infection in adult and adolescent patients aged 12 years and older.

1.2. Clinical Development Program

The clinical development program of the D/C/F/TAF FDC tablet was discussed with the United States (US) Food and Drug Administration (FDA) on several occasions, and the guidance and advice received on these occasions have been incorporated as appropriate (for details, refer to Mod1.6.3/meeting minutes 22-Oct-2014 and meeting comments 10-Feb-2017). All clinical studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the respective protocols.

An overview of the Phase 3 and 2 clinical studies in HIV-1 infected subjects providing efficacy and safety data for the D/C/F/TAF FDC tablet in adults and adolescents is presented in Table 1. More information about these Phase 3 and 2 studies, as well as information about formulation development studies of the D/C/F/TAF FDC tablet, is provided in Appendix 1. An overview of clinical studies with D/C/F/TAF FDC and the individual components in healthy subjects (Phase 1 studies) and special populations (Phase 1 or Phase 3) is presented in Mod2.7.4/Tab2.

Adult Population (Aged ≥18 Years)

Data with the D/C/F/TAF FDC tablet in adults are available from the following 7 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 Phase 2 study in HIV-1 infected, ART-naïve subjects (GS-US-299-0102; primary Week 24 and final Week-48 analyses).
- 4 completed Phase 1 studies in healthy subjects (TMC114FD2HTX1001; TMC114FD2HTX1002; TMC114FD2HTX1004; GS-US-299-0101).

Overall, the available results from the Phase 3 studies with the D/C/F/TAF FDC tablet and from the historical data (efficacy, safety, and PK) on the individual components of D/C/F/TAF, support the use of the D/C/F/TAF 800/150/200/10-mg FDC tablet in ART-naïve, HIV-1 infected patients and ART-experienced, HIV-1 infected patients, in line with the DRV once daily indication.[27,28]

Adolescent Population (Aged ≥12 to <18 Years)

No data are available with the D/C/F/TAF FDC tablet in the adolescent population. However, the Sponsor has carefully assessed the data and concludes that the D/C/F/TAF FDC tablet is appropriate to use for the treatment of HIV-1 infection in both adults and adolescents, aged ≥12 to <18 years and weighing at least 40 kg, based on the following (see Section 3.6):

- The metabolic factors that determine the pharmacokinetics have matured to adult values well

before adolescence.

- The individual components DRV, COBI, FTC, and TAF have been approved in adolescents at the same doses as used in adults.
- Studies with the individual components of the FDC tablet in adolescents (TMC114-C230 and GS-US-292-0106) showed exposures matching the adult exposures in clinical studies (refer to Mod2.7.2/ClinPharm/Sec2.2.3, NDA021976/Mod2.7.2/ClinPharm/Sec3.14.2 [June 2012]), and provided supportive efficacy and safety data in adolescents (see Sections 5.2 and 6.3).
  - Recent results from a Phase 2/3 switch study (GS-US-216-0128) in HIV-1 infected, virologically-suppressed adolescents support the use of COBI 150 mg as a pharmaco-enhancer of DRV (or atazanavir [ATV]) in adolescents; see Section 3.6).[5,20]
- The D/C/F/TAF FDC tablet is bioequivalent to co-administration of the individual components.

Special Populations

The proposed use of D/C/F/TAF in special populations, such as subjects with renal impairment, relies on data from relevant clinical studies with the individual components that have been previously submitted to the FDA.

Mode of administration

In order to facilitate intake for subjects that have difficulty swallowing larger tablets, a completed Phase 1 study (TMC114FD2HTX1004) assessed the relative bioavailability of the D/C/F/TAF FDC tablet when split or crushed (see Section 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 Mod2.7.3/App1/ TMC114FD2HTX3001	Mod2.7.3, 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, 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, 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 Mod2.7.3/App1/ TMC114-C230	Mod2.7.3, Mod2.7.4
COBI and F/TAF (Extrapolated From E/C/F/TAF)						
HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years) [d]						
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[15] Mod2.7.3/App1/ GS-US-292-0106	Mod2.7.3, Mod2.7.4

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; N = number of subjects; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetics; rtv = low-dose ritonavir; TFV = tenofovir; TLOVR = time to loss of virologic response; vs = versus.

a. Subjects included in the Intent-to-treat population or Safety Analysis Set. For the definitions of analysis sets, refer to Mod2.7.4/Sec2.4.

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. 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.[5,20]

e. The ARV background regimen consisted of AZT/3TC or ABC/3TC, dosed as indicated in the local Prescribing Information.

f. In this study, also a patient population of virologically suppressed children (aged 6 to <12 years) was included. However, these data are not described in this submission, which focuses on adult and adolescent HIV-1 infected subjects.

Source: Mod2.7.4/Tab1.

2. OVERVIEW OF BIOPHARMACEUTICS

The D/C/F/TAF FDC tablet contains 800 mg of DRV (as 867 mg of DRV ethanolate), 150 mg of COBI (as 288.5 mg of COBI on silicon dioxide), 200 mg of FTC, and 10 mg of TAF (as 11.2 mg of tenofovir alafenamide fumarate).

The development strategy for the D/C/F/TAF FDC tablet focused on the compatibility of the active ingredients with each other and with the other excipients of the formulation.

The final formulation is a yellow to yellowish-brown, capsule-shaped, immediate-release D/C/F/TAF FDC film-coated monolayer tablet manufactured via the co-dry granulation formulation concept. The D/C/F/TAF FDC tablet core contains silicon dioxide, croscarmellose sodium, microcrystalline cellulose and magnesium stearate as inactive ingredients. The tablets are film-coated with polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and yellow ferric oxide. The film coating is non-functional. A comprehensive overview of the formulation development process is provided in Mod3.2.P.2.2.1. There are no differences between the D/C/F/TAF FDC that was used in the Phase 3 clinical studies and the planned commercial formulation, except for the debossing (tablets without debossing in the double-blind phase of Study TMC114FD2HTX3001, while the planned commercial tablet, also used in Study TMC114IDF3013 and the open-label phase of Study TMC114FD2HTX3001, is debossed with "8121" on one side and "JG" on the other side).

Three completed clinical biopharmaceutical studies (GS-US-299-0101, TMC114FD2HTX1002, TMC114FD2HTX1001) evaluated the bioavailability and bioequivalence of DRV, COBI, FTC, and TAF as single agents or as the D/C/F/TAF 800/150/200/10-mg FDC, once-daily tablet formulation, in healthy subjects:

- Study GS-US-299-0101 (Mod2.7.1/Sec2.1.1.2) evaluated different prototype FDC formulations, from which the above monolayer tablet was chosen for further evaluation. The observed TAF exposures with the chosen FDC formulation are consistent with those observed after monotherapy with TAF 25 mg in HIV-1 infected subjects, are in the range where no PK/pharmacodynamic (PD) relationship for TAF efficacy was observed and the observed TFV plasma exposures are approximately 90% lower than those observed with the administration of TDF containing regimens (Mod2.7.2/ClinPharm/Sec3.5.1).
- Study TMC114FD2HTX1002 (Mod2.7.1/Sec2.1.1.1) was an initial evaluation of the relative bioavailability of DRV, COBI, FTC, and TAF when administered as the selected D/C/F/TAF FDC compared to the combination of DRV 800 mg + COBI 150 mg + emtricitabine/tenofovir alafenamide (F/TAF) FDC 200/10 mg; and also established the food effect for the D/C/F/TAF FDC.
- Study TMC114FD2HTX1001 (Mod2.7.1/Sec2.2.1.1) established bioequivalence of the D/C/F/TAF 800/150/200/10 mg FDC versus (vs) the combined administration of formulations of the separate agents (DRV 800 mg + COBI 150 mg + F/TAF 200/10 mg FDC).

In order to facilitate intake for subjects who have difficulty swallowing larger tablets, a completed clinical study (TMC114FD2HTX1004) assessed the relative bioavailability of the components in the D/C/F/TAF FDC tablet when split or crushed (and mixed with applesauce), compared to swallowed as a whole tablet. This study showed that splitting the FDC tablet immediately prior to use has no clinically relevant effects on the PK of DRV, COBI, FTC, and TAF (refer to Mod2.7.1/Sec3.1.3).

The D/C/F/TAF FDC needs to be taken with food, in line with other DRV-containing products, because of the improved bioavailability of DRV in the presence of food (Mod2.7.1/Sec3.2). Intake with food is also required in the 2 Phase 3 studies.

Information about the different components of the D/C/F/TAF FDC tablet, as well as commercially available different co-formulations of these compounds, is provided in Appendix 2.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

The PK properties of the individual components DRV, COBI, FTC, and TAF have been subject to comprehensive development programs to support their respective drug licenses, alone or in different combinations. This section provides a summary hereof. For additional information, refer to the Summary of Clinical Pharmacology Studies in Mod2.7.2/ClinPharm.

PK data with the D/C/F/TAF FDC tablet are available from:

- 4 completed Phase 1 studies in healthy adults (TMC114FD2HTX1001, TMC114FD2HTX1002, TMC114FD2HTX1004 and GS-US-299-0101);
- 1 completed Phase 2 study in HIV-1 infected, ART-naïve adults (GS-US-299-0102);
- 2 ongoing Phase 3 studies (Week 48 primary analyses of both studies are available) in:
  - HIV-1 infected, ART-naïve adults (TMC114FD2HTX3001; DRV, COBI, and TAF); and
  - HIV-1 infected, ART-experienced, virologically-suppressed adults (TMC114IFD3013; DRV and COBI).

The absorption, distribution, metabolism, and elimination characteristics of the components of the D/C/F/TAF FDC are characterized from the results of studies with the D/C/F/TAF FDC tablet, combined with applicable data from earlier clinical studies with the individual components.

The D/C/F/TAF 800/150/200/10-mg FDC tablet is bioequivalent to combined administration as separate formulations of DRV, COBI, and F/TAF (F/TAF administered as FDC tablet) in healthy subjects (TMC114FD2HTX1001).

3.1. Absorption

All components of the D/C/F/TAF FDC were rapidly absorbed following oral administration with food in healthy subjects. Median maximum plasma concentrations of DRV, COBI, FTC, and TAF were achieved 4.00, 4.00, 2.00, and 1.50 hours after dosing, respectively (refer to Mod2.7.1/Tab23). The PK data of the different components after administration of the D/C/F/TAF FDC tablet in the Phase 1, 2, and 3 studies were in line with historical data after administration of the separate formulations.

For details, refer to Mod2.7.2/ClinPharm/Sec2.2 and Sec3.1.1.

3.2. Distribution

Both DRV and COBI are largely (95% to 98%) bound to plasma proteins. For DRV, plasma protein binding is concentration-dependent (indicative for saturation of binding) and DRV binds primarily to plasma α1-acid glycoprotein (AAG). For COBI, plasma protein binding is concentration independent.

Plasma protein binding is low for FTC (estimated to be <4%) and moderate for TAF (mean percent unbound TAF values ranged from 14% to 23%).

For details, refer to Mod2.7.2/ClinPharm/Sec3.1.2.

3.3. Metabolism

DRV is extensively metabolized by the hepatic cytochrome P450 (CYP) system and primarily by CYP3A.

COBI is metabolized via CYP3A (major) and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. COBI increases the DRV exposure (via inhibition of CYP3A) such that DRV exposures (area under the plasma concentration-time curve over 24 hours [AUC_{24h}] and maximum observed analyte concentration [C_{max}]) comparable to DRV co-administered with ritonavir (rtv [low dose of 100 mg]) are achieved.

FTC undergoes only minor metabolism.

TAF has a distinct metabolism 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 metabolite tenofovir diphosphate (TFV-DP). Due to increased plasma stability and activation by Cathepsin A (CatA), as compared to TDF, TAF is more efficiently loaded into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages, which results in greater concentrations of TFV-DP in PBMCs (approximately 5- to 7-fold higher than with TDF) and lower exposure of TFV, its major metabolite, to the systemic circulation (approximately 90% lower than with TDF) and undesired tissues, including the kidney and bone.

For details, refer to Mod2.7.2/ClinPharm/Sec3.1.3.

3.4. Excretion

DRV is predominantly excreted in feces, with minimal renal excretion. The renal excretion of COBI is also low.

FTC is primarily eliminated from the plasma via renal excretion as unchanged drug.

TAF is extensively metabolized, and predominantly excreted as TFV. There is very minimal renal excretion for TAF.

For details, refer to Mod2.7.2/ClinPharm/Sec3.1.3.2.

3.5. Pharmacokinetics of D/C/F/TAF in HIV-1 Infected, Adult Subjects

3.5.1. Data from Phase 3 Studies With D/C/F/TAF FDC

PK data (population PK results) with the D/C/F/TAF FDC tablet in HIV-1 infected subjects in the Phase 3 studies TMC114FD2HTX3001 (ART-naïve subjects) and TMC114IFD3013 (ART-experienced, virologically-suppressed subjects) are summarized in Table 2. For more details, refer to Mod2.7.2/ClinPharm/Sec2.2.2.

Table 2: Population Pharmacokinetic Parameters of DRV and TAF After Administration of D/C/F/TAF 800/150/200/10 mg Once Daily in HIV-1 Infected Subjects (Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013)

	Mean (SD) and Median (Range)		
	DRV		TAF
Parameter	TMC114FD2HTX3001 (ART-naïve) N=355	TMC114IFD3013 (ART-experienced, Virologically-suppressed) N=750	TMC114FD2HTX3001 (ART-naïve) N=355
C_{0h}, ng/mL	1,899 (759) 1,783 (418 – 5,895)	1,813 (859) 1,679 (231 – 6,757)	NA
AUC_{24h}, ng.h/mL[a]	87,909 (20,232) 84,248 (40,697 – 188,760)	85,972 (22,413) 82,529 (41,920 – 209,490)	132 (41) 124 (71 - 400)

ART = antiretroviral treatment; AUC_{24h} = area under the plasma concentration-time curve over 24 hours; C_{0h} = predose plasma concentration; DRV = darunavir; N = number of subjects with data; NA = not applicable; SD = standard deviation; TAF = tenofovir alafenamide.

[a] Reported as AUC_{tau} (AUC from time of administration up to the end of the dosing interval) for TAF.

Source: Mod2.7.2/Sec2.2.2.

In both Phase 3 studies (TMC114FD2HTX3001 and TMC114IFD3013), there were no significant differences in DRV or TAF PK parameters between the different subgroups (eg, age category, estimated glomerular filtration rate [eGFR] category, or treatment adherence; refer to Mod2.7.2/ClinPharm/Sec2.2.2).

DRV PK

The PK estimates of DRV derived from the Phase 3 studies with D/C/F/TAF (Study TMC114FD2HTX3001 in ART-naïve, HIV-1 infected subjects and Study TMC114IFD3013 in ART-experienced, virologically-suppressed, HIV-1 infected subjects; see Table 2) were in line with those observed in the Phase 2 study with D/C/F/TAF (GS-US-299-0102 in ART-naïve, HIV-1 infected subjects; see Section 3.5.2) and with historical data with boosted DRV[28] (refer to Mod2.7.2/ClinPharm/Sec3.2.2.1):

- In HIV-1 infected subjects who received DRV/rtv 800/100 mg once daily in the DRV pivotal Phase 3 Study TMC114-C211 in ART-naïve subjects (mean [standard deviation, SD] AUC_{24h}: 93,026 [27,050] ng.h/mL; and C_{0h}: 2,281 [1,168] ng/mL);
- In HIV-1 infected subjects who received DRV/rtv 800/100 mg once daily in the DRV pivotal Phase 3 Study TMC114-C229 in ART-experienced, virologically-failing subjects with no DRV resistance-associated mutations (RAMs) (mean [SD] AUC_{24h}: 93,334 [28,626)] ng.h/mL; and C_{0h}: 2,160 [1,201] ng/mL);
- In HIV-1 infected subjects who received DRV/COBI 800/150 mg once daily in the DRV pivotal Phase 3 Study GS-US-216-0130 in ART-naïve subjects and ART-experienced, virologically-failing subjects with no DRV RAMs (mean [SD] AUC_{24h}: 100,152 [32,043] ng.h/mL; and C_{0h}: 2,043 [1,257] ng/mL).

TAF PK

The PK estimates of TAF from the Phase 3 study TMC114FD2HTX3001 (see Table 2) and PK data from the Phase 2 study GS-US-299-0102 (see Section 3.5.2 for more details), both in HIV-1 infected, ART-naïve subjects who received D/C/F/TAF (800/150/200/10 mg) FDC once daily, were in the range of historical TAF exposures in the proof-of-concept monotherapy study that showed potent antiviral activity of TAF (single-agent Study GS-US-120-0104; mean [SD] AUC_{tau}: 115 [33] ng.h/mL) and with TAF in other combinations in ART-naïve and ART-experienced, virologically-failing, HIV-1 infected subjects (refer to Mod2.7.2/ClinPharm/Sec3.2.2.3).

3.5.2. Data from Phase 2 Study With D/C/F/TAF FDC

More PK data with the D/C/F/TAF FDC tablet in HIV-1 infected subjects are available from a Phase 2 study (GS-US-299-0102). This study included a PK substudy in which 21 subjects received the D/C/F/TAF FDC tablet and 11 subjects received treatment with DRV+COBI+ emtricitabine/tenofovir disoproxil fumarate (F/TDF) (ie, reference treatment). The non-compartmental PK of DRV, COBI, FTC, TAF, and TFV following multiple-dose administration of the D/C/F/TAF FDC were assessed (see Mod5.3.5.1/GS-US-299-0102-Final-CSR/Sec10 and Mod2.7.2/ClinPharm/Sec2.2.2.1) and compared to those for DRV+COBI+F/TDF, where relevant.

Table 3: Pharmacokinetic Parameters of DRV, COBI, TAF, and FTC (GS-US-299-0102 PK Substudy, D/C/F/TAF Treatment Group)

	Mean (SD); t_{max}, $t_{1/2}$: Median (Range)			
Parameter	DRV N=21	COBI N=21	TAF N=21	FTC N=21
C_{max}, ng/mL	8,826.2 (33.3)	1,128.7 (35.3)	163.0 (51.9)	2,056.4 (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	99,301.8 (45.3)	8,744.5 (43.9)	-	11,918.0 (35.9)
C_{tau}, ng/mL	1,651.0 (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} = area under the plasma concentration-time curve from 0 hours up to the time of the last measurable concentration after dosing; AUC_{tau} = area under the plasma concentration-time curve 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; COBI = cobicistat; DRV = darunavir; FTC = emtricitabine; N = number of subjects; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = apparent elimination half-life; t_{max} = actual sampling time to reach the maximum observed analyte concentration; TAF = tenofovir alafenamide.

Source: Mod2.7.2/ClinPharm/Sec2.2.2.1.

The mean DRV, COBI, and FTC exposures were consistent with historical data for these agents.

No TAF was detectable 8 hours after administration and the mean AUC_{last} (130.5 ng.h/mL) in HIV-1 infected subjects was consistent with historical data for subjects receiving D/C/F/TAF (healthy subjects; mean [SD] AUC_{last} 116.4 [26.0] ng.h/mL) or TAF 25 mg single agent (proof-of-concept Study GS-US-120-0104; mean [% coefficient of variation] AUC_{last} 115.2 [33.4] ng.h/mL).

For the reference group (n=11 in the PK substudy), only plasma TFV and intracellular TFV-DP concentrations were determined.

The mean TFV exposure in plasma was substantially lower (approximately 90%) following administration of the D/C/F/TAF FDC compared to DRV+COBI+F/TDF, as was intended by the development of TAF as a new prodrug for TFV (mean [%CV] TFV AUC_{tau} 339.0 [37.1] ng.h/mL vs 3737.0 [26.8] ng.h/mL).

The intracellular TFV-DP AUC_{tau} was markedly higher (6.5-fold) in subjects who received D/C/F/TAF compared to subjects who received DRV+COBI+F/TDF (see Table 4). This was consistent with the previously observed approximately 5- to 7-fold increase in TFV-DP exposures following TAF 25 mg vs TDF 300 mg (GS-US-120-0104; see Section 3.3) and the >4-fold increase in TFV-DP concentrations in pooled Phase 3 studies with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) (GS-US-292-0104 and GS-US-292-0111; refer to Mod2.7.2/ClinPharm/Sec3.5.1.4.2).

Table 4: Statistical Comparisons of Intracellular TFV-DP AUC_{tau} Between Test and Reference Treatments; All Substudy PK Analysis Set (Study GS-US-299-0102)

Intracellular TFV-DP PK Parameter	LS Means by Treatment		LS Means 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, 1,585.00)

AUC_{tau} = area under the plasma concentration-time curve from time of administration up to the end of the dosing interval; CI = confidence interval; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada); LS = least squares; N = number of subjects; PK = pharmacokinetic; TFV-DP = tenofovir diphosphate.
Source: Mod2.7.2/ClinPharm/Sec2.2.2.1.

The pharmacokinetics of the different components of the D/C/F/TAF FDC tablet in HIV-1 infected subjects were comparable to that observed in healthy volunteers (refer to Mod2.7.2/ClinPharm/Sec3.2.3).

3.5.3. Pharmacokinetic Conclusions in HIV-1 Infected Adult Subjects

DRV exposures after administration of D/C/F/TAF FDC were consistent with historical data.

A dose of TAF 10 mg, when used with DRV/COBI 800/150 mg (as in D/C/F/TAF FDC) offers TAF exposures that are appropriate to have a drug regimen that is fully efficacious, which was also confirmed in the D/C/F/TAF Phase 3 studies. The TAF exposures were in the range of historical TAF exposures in the proof-of-concept monotherapy study that showed potent antiviral activity of TAF (TAF 25 mg monotherapy) and also overlapped with TAF exposures after administration of E/C/F/TAF (TAF 10 mg in the FDC) in studies that showed efficacy.

The Sponsor concludes that 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 appropriate for use in ART-naïve, HIV-1 infected patients and ART-experienced, HIV-1 infected patients, with no known or suspected resistance to DRV.

3.6. Pharmacokinetics of D/C/F/TAF in HIV-1 Infected, Adolescent Subjects

No data are available with the D/C/F/TAF (800/150/200/10 mg) FDC tablet in the adolescent population. In adolescents, the metabolic factors that determine the pharmacokinetics have matured to adult values well before adolescence and, generally, ARV doses are the same for adults and adolescents.[22] The application for the use of the D/C/F/TAF FDC tablet in HIV-1 infected adolescents, aged ≥12 to <18 years and weighing ≥40 kg, is based on the following facts (refer to Mod2.7.2/ClinPharm/Sec3.3.1.2):

DRV/rtv 800/100 mg once daily is indicated for adolescents aged ≥12 to <18 years and weighing at least 40 kg.[28]

DRV PK data in adolescents are available from the Phase 2 study TMC114-C230 with DRV/rtv 800/100 mg once daily in combination with zidovudine/lamivudine (AZT/3TC) or ABC/3TC for 48 weeks in 12 HIV-1 infected, ART-naïve adolescents. The results from this study showed that the DRV adult dose of 800 mg once daily is adequate for adolescents, because administration of DRV 800 mg once daily (in combination with rtv) in HIV-1 infected adolescents resulted in DRV exposure that was comparable to that achieved in adults. Furthermore, the safety profile of DRV in adolescent subjects (see Section 6.3) is similar to that observed in the adult population (see Section 6.2).

FTC 200 mg once daily is indicated for pediatric subjects weighing at least 33 kg.[12]

COBI 150 mg is approved as a pharmaco-enhancer for elvitegravir (EVG) as part of E/C/F/TAF (150/150/200/10 mg) FDC in adolescents aged ≥12 to <18 years weighing at least 35 kg.[16]

Recent results from an ongoing Phase 2/3 Study GS-US-216-0128 in HIV-1 infected, virologically-suppressed adolescents (aged ≥12 to <18 years) who received DRV plus COBI (150 mg once daily) in combination with 2 NRTIs showed that DRV exposure was within the safe and efficacious range as observed in adults.[5,20] The results from this study support the use of COBI 150 mg as a pharmaco-enhancer of DRV in adolescents.

TAF (adult tablet with either 10 or 25 mg) is approved as part of F/TAF FDC (Descovy®; including TAF 25 mg), E/C/F/TAF FDC (Genvoya®; including TAF 10 mg), and as part of rilpivirine (RPV)/F/TAF FDC (Odefsey; including TAF 25 mg) in adolescents aged ≥12 years.[10,16,23]

Use of the adult doses for **COBI**, **FTC,** and **TAF** for adolescents (≥12 to <18 years of age) is further derived from the clinical development of E/C/F/TAF FDC, containing the components COBI, FTC, and TAF at doses of 150 mg, 200 mg, and 10 mg, respectively. PK results from the Phase 2/3 Study GS-US-292-0106 with E/C/F/TAF FDC once daily for 48 weeks in 50 HIV-1 infected, ART-naïve, adolescent subjects showed that the COBI, FTC, and TAF exposures, co-administered at doses of 150 mg, 200 mg, and 10 mg, in adolescents were similar to exposures achieved in adults with the same dose. Additionally, the EVG exposure was similar in adults and adolescents, confirming that the boosting effect of COBI 150 mg once daily is similar in adolescents and adults.[15] The results from this study led to the approval of the E/C/F/TAF 150/150/200/10-mg FDC as well as the F/TAF 200/25-mg FDC and the RPV/F/TAF 25/200/25-mg FDC for use in adolescents aged ≥12 years of age.[10,16,23]

In summary, because adult doses for DRV, COBI, and F/TAF provide systemic exposures in adolescents aged ≥12 to <18 years within the safe and efficacious ranges as observed in adults, and the D/C/F/TAF FDC tablet is bioequivalent to co-administration of the individual components, the Sponsor concludes that 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 appropriate for use in adolescents aged ≥12 years and weighing at least 40 kg.

Further data supporting the use of the D/C/F/TAF FDC in adolescents aged ≥12 years to <18 years are described in Mod2.7.2/ClinPharm/Sec3.3.1.2 (PK data), Mod2.7.3/Sec3.2 (efficacy data) and Mod2.7.4/Sec3.2 (safety data).

3.7. Drug-drug Interactions

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 in comprehensive drug interaction programs performed with the separate agents. The following is a summary of the information most relevant to the D/C/F/TAF combination. Further details are provided in the Summary of Clinical Pharmacology Studies (Mod2.7.2/ClinPharm/Sec3.4.2).

The recommendations for use of the D/C/F/TAF FDC with other agents are based on a combination of recommendations in the currently approved United States Package Insert (USPI) for DRV/COBI and F/TAF, respectively.[10,27] The drug-drug interaction profile for the D/C/F/TAF FDC is mainly driven by the DRV/COBI components as the F/TAF components have only a low potential for drug-drug interactions.

DRV coadministered with COBI is an inhibitor of CYP3A and CYP2D6. COBI inhibits the following transporters: p-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein 1 (MATE1), organic anion transporter protein (OATP) 1B1, and OATP1B3. Based on in vitro data, COBI is not expected to induce CYP1A2 or CYP2B6, and based on in vivo data, COBI is not expected to induce multidrug resistance protein 1 (MDR1) or, in general, CYP3A to a clinically significant extent. The induction effect of COBI on CYP2C9, CYP2C19, or uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) is unknown, but is expected to be low based on CYP3A in vitro induction data.

Co-administration of D/C/F/TAF with medicinal products primarily metabolized by CYP3A and/or CYP2D6 or substrates of P-gp, BCRP, MATE1, OATP1B1, or OATP1B3 may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and can be associated with adverse events (AEs). For CYP3A substrates with a narrow therapeutic index, this may potentially lead to severe, life-threatening, or fatal events.

DRV is metabolized by CYP3A. COBI is metabolized by CYP3A, and to a minor extent, by CYP2D6. 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. Co-administration of D/C/F/TAF and other medicinal products that inhibit CYP3A may increase plasma concentrations of DRV and COBI.

TAF is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Medicinal products that strongly affect P-gp activity may lead to changes in TAF absorption. Medicinal products that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of efficacy of TAF and development of resistance. Co-administration of D/C/F/TAF with other medicinal products that inhibit P-gp are expected to increase the absorption and plasma concentrations of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A in vitro. TAF is not an inhibitor or inducer of CYP3A in vivo.

FTC is not an inhibitor of human CYP enzymes. In vitro and clinical drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low.

Since FTC and TFV are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, co-administration of D/C/F/TAF with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, TFV, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (eg, gentamicin), and high-dose or multiple non-steroidal anti-inflammatory drugs.

D/C/F/TAF should not be administered concomitantly with other ARVs that require PK enhancement since dosing recommendations for such combinations have not been established.

An overview of recommendations for expected interactions for D/C/F/TAF with potential concomitant drugs is provided in the proposed D/C/F/TAF Prescribing Information (refer to Mod1.14.1), which is based on studies conducted with the components of D/C/F/TAF - as individual agents or combined - or based on theoretical considerations for potential drug-drug interactions that may occur. For more details, refer to Mod2.7.2/ClinPharm/Sec3.4.2. Note that the recommendations and wording on DDIs in the proposed Prescribing Information (Mod1.14.1) have been further aligned with the current Prezcobix® and Descovy USPI recommendations.[10,27] Since D/C/F/TAF is intended as a complete regimen for the treatment of HIV-1 infection, and not expected to be coadministered with other HIV-1 ARVs, information regarding drug-drug interactions with other ARV products is not included in the proposed Prescribing Information for D/C/F/TAF.

3.8. Pharmacokinetics of D/C/F/TAF in Special Populations

The effect of intrinsic factors on the PK of DRV, COBI, FTC, and TAF when co-administered as the D/C/F/TAF FDC has been evaluated in the Phase 3 studies (covariate analyses population PK and subgroup analysis) and can further be derived from data with the individual components.

3.8.1. Age

Age (>12 years) is not considered to have a clinically relevant effect on the exposure to any of the individual components of the D/C/F/TAF FDC (refer to Mod2.7.2/ClinPharm/Sec3.3.1). There are limited data in **elderly** subjects. D/C/F/TAF FDC is to be used with caution in patients

above 65 years of age, due to the greater frequency of decreased hepatic function, concomitant disease(s) and/or polypharmacy (see also Section 6.7.2).

Data supporting the use of the D/C/F/TAF FDC in **adolescents** (≥12 years to <18 years) are described in Section 3.6.

Refer to Section 6.7.1 for recommendations in **children** <12 years.

3.8.2. Sex

Overall, sex is not considered to have a clinically relevant effect on the exposure of the D/C/F/TAF FDC components. Refer to the Summary of Clinical Pharmacology for more details (refer to Mod2.7.2/ClinPharm/Sec3.3.2).

3.8.3. Race/Ethnicity

Overall, there were no clinically relevant differences in the exposure of the D/C/F/TAF FDC components based on race/ethnicity. Refer to the Summary of Clinical Pharmacology for more details (refer to Mod2.7.2/ClinPharm/Sec3.3.6).

3.8.4. Renal Impairment

The effect of renal impairment on the PK of DRV, COBI, FTC, and TAF is summarized in Section 6.7.3. There is no clinically relevant effect of renal impairment on the PK of DRV, COBI, TAF, and TFV, while in patients with severe renal impairment, systemic FTC exposure was higher. Available data for the individual components of D/C/F/TAF FDC indicate that there are no safety concerns for the use of D/C/F/TAF in HIV-1 infected subjects with mild to moderate renal impairment. Refer to the Summary of Clinical Pharmacology for more details (refer to Mod2.7.2/ClinPharm/Sec3.3.5).

3.8.5. Hepatic Impairment

The effect of hepatic impairment on the PK of DRV, COBI, FTC, and TAF is summarized in Section 6.7.4. Based on all available data, no dose adjustment of D/C/F/TAF FDC is required in subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, while D/C/F/TAF FDC is not recommended for use in subjects with severe hepatic impairment. Refer to the Summary of Clinical Pharmacology for more details (refer to Mod2.7.2/ClinPharm/Sec3.3.4).

3.8.6. Co-infection With HIV-1 and Hepatitis B and/or Hepatitis C, and Risk of Hepatitis B Flare-up

The effect of co-infection with HIV-1 and hepatitis B (HBV) and/or hepatitis C (HCV) on the PK of DRV, COBI, FTC, and TAF is summarized in Section 6.7.5. Available results from clinical studies with the individual components of the D/C/F/TAF FDC did not show a clinically significant effect of hepatitis B and/or C infection on the PK of DRV and FTC. No safety issues are expected with the use of D/C/F/TAF FDC in co-infected subjects. Discontinuation of D/C/F/TAF in co-infected patients may be associated with severe acute exacerbations of

hepatitis B due to the FTC or TAF components (with activity against HBV) of the D/C/F/TAF FDC (refer to Mod2.7.4/Sec6.1.5).

Refer to the Summary of Clinical Pharmacology for more details (refer to Mod2.7.2/ClinPharm/Sec3.3.4).

3.9. Pharmacokinetic/Pharmacodynamic Relationships

Overall, no apparent clinically relevant PK/PD relationships (graphically and/or via logistic regression) have been observed between DRV and TAF exposures obtained after once-daily administration of the D/C/F/TAF FDC tablet in the Phase 3 studies (TMC114IFD3013 [DRV] and TMC114FD2HTX3001 [DRV and TAF]) and the evaluated efficacy (virologic rebound or virologic failure) and safety parameters. This is consistent with historical data of DRV studies, which showed no apparent PK/PD relationship for DRV (ie, no relationship between DRV exposure and efficacy and safety parameters), and with the available TAF data.

For further details, see Mod2.7.2/ClinPharm/Sec3.5.1 (efficacy) and Mod2.7.2/ClinPharm/Sec3.5.2 (safety).

3.10. Dose Selection of D/C/F/TAF FDC

DRV 800 mg boosted by COBI 150 mg, and FTC 200 mg in the D/C/F/TAF FDC tablet represent the marketed doses of these components. The dose of TAF 10 mg in the D/C/F/TAF FDC tablet that was selected for Phase 2 and Phase 3 clinical studies was expected (based on results from Phase 1 studies) to achieve:

- TAF plasma concentrations in a range for which potent antiviral activity with TAF as a stand-alone agent was demonstrated; and
- TFV plasma concentrations that are considerably lower than those obtained with TDF to improve the safety profile, in particular to have less renal toxicity and less bone mineral depletion.

The PK data from the Phase 1, 2, and 3 studies showed that the TAF plasma concentrations after administration of the D/C/F/TAF 800/150/200/10-mg FDC tablet are in the range of historical PK data after monotherapy with TAF 25 mg (ie, in the absence of a pharmaco-enhancer; see Section 3.5) and are also within the range of those obtained with E/C/F/TAF 150/150/200/10-mg FDC (refer to Mod2.7.2/ClinPharm/Sec3.2.2.3). In addition, administration of the D/C/F/TAF 10-mg FDC tablet resulted in ~90% lower steady-state TFV plasma exposure vs COBI-boosted DRV plus F/TDF (see Section 3.3).

The results from the Phase 3 studies with the D/C/F/TAF 800/150/200/10-mg FDC tablet once daily demonstrated efficacy in HIV-1 infected subjects (see Section 5) and a favorable safety profile (see Section 6) with less renal and bone toxicity compared to a regimen including TDF. These results lead to a positive benefit/risk assessment (Section 7). Therefore, the D/C/F/TAF FDC tablet at doses of 800/150/200/10 mg is the planned commercial formulation.

For details on the drug-drug interactions and PK/PD evaluation leading to the TAF 10-mg dose selection, refer to Mod2.7.2/ClinPharm/Sec3.4.2 and Sec3.6, respectively.

4. OVERVIEW OF CLINICAL STUDIES, STUDY POPULATION, AND EXTENT OF EXPOSURE SUPPORTING D/C/F/TAF EFFICACY, RESISTANCE, AND SAFETY PROFILE

An overview of the relevant clinical studies supporting the D/C/F/TAF FDC efficacy, resistance, and safety profile is provided in the sections below. A summary of the study design for all Phase 3, Phase 2, and Phase 1 clinical studies included in the D/C/F/TAF FDC submission is available in Mod5.2.

4.1. General Aspects of Phase 3 and 2 Clinical Studies With D/C/F/TAF FDC

4.1.1. Study Designs and Methods

Phase 3 and 2 Clinical Studies

An overview of the Phase 3 and 2 studies in HIV-1 infected subjects supporting the clinical efficacy, resistance, and safety profile of the D/C/F/TAF FDC tablet, including their designs and primary endpoints, is provided in Section 1.2 and Table 1; more information about these studies is given in Appendix 1.

Primary Efficacy Endpoints of Phase 3 and 2 Studies With D/C/F/TAF FDC

For the Phase 3 and 2 studies with the D/C/F/TAF FDC tablet, a summary of the primary and key secondary efficacy endpoints and their statistical methods is provided in Table 5. For more details and for the primary efficacy endpoints of the studies with the individual components of the FDC in adolescents, refer to Mod2.7.3/Sec2.4.

No efficacy pooling and no safety pooling have been performed of the Phase 3 and/or 2 studies, as agreed upon during the pre-NDA meeting (refer to Mod1.6.3/meeting comments 10-Feb-2017; also refer to Mod2.7.3/Sec2.4 and Mod2.7.4/Sec2.1 for details).

Resistance analyses were performed on samples from the Phase 3 and 2 studies. Samples for HIV-1 genotyping/phenotyping were taken throughout the studies and testing was performed on samples from subjects experiencing protocol-defined virologic failure with sufficient HIV-1 RNA copies/mL values (HIV-1 RNA >400 copies/mL). For details on the resistance testing/analysis performed in these studies and for the definition of protocol-defined virologic failure, refer to Mod2.7.3/Sec2.4, and to Mod2.7.2/VirSum/Sec4.1 and Sec4.2.

Table 5: Statistical Methods for Key Efficacy Endpoints of Phase 3 Studies With D/C/F/TAF FDC [a]

Phase 3 Study (Population)	Efficacy Endpoint	Statistical Method	Noninferiority Margin
TMC114FD2HTX3001 (ART-naïve)	Primary: HIV-1 RNA <50 copies/mL at Week 48	- According to the FDA snapshot approach [b]	- A maximum allowable difference of 10% [d]
	Key secondary: CD4+ cell count at Week 48	- Change from baseline (LS Means from ANCOVA adjusted for baseline value) [c]	- NA
TMC114IFD3013 (ART-experienced, virologically-suppressed)	Primary: Virologic rebound cumulative through Week 48	- Subjects with a confirmed HIV-1 RNA ≥50 copies/mL during treatment up to, and including the upper bound of the Week 48 window (ie, 54 weeks), or - Subjects who discontinued prematurely (irrespective of reason) with a last available (single) HIV-1 RNA ≥50 copies/mL - Subjects with last available on-treatment HIV-1 RNA ≥50 copies/mL at the study cut-off (Week 48)	- A maximum allowable difference of 4% [e]
	Key secondary:		
	- HIV-1 RNA <50 copies/mL at Week 48 and ≥50 copies/mL at Week 48	- According to the FDA snapshot approach [b]	- NA
	- CD4+ cell count at Week 48	- Change from baseline (LS Means estimates using ANCOVA model)	- NA

a. The key efficacy endpoint of the Phase 2 Study GS-US-299-0102 (ART-naïve HIV-1 infected adults) was the proportion of subjects who achieved HIV-1 RNA <50 copies/mL at Week 24 (primary) and at Week 48, according to the FDA snapshot approach. Noninferiority of D/C/F/TAF FDC vs control was to be concluded if the lower bound of the 2-sided 95% confidence interval of the stratum-adjusted Mantel-Haenszel difference between treatment groups (D/C/F/TAF FDC minus control) in the response rate was greater than -12% (ie, a margin of 12% is applied for noninferiority assessment).

b. Based on last HIV-1 RNA in Week 48 window (ie, Week 42-54).

c. Non-completer = Failure, ie, impute with baseline value (change=0) when discontinued prematurely, last observation carried forward (LOCF) otherwise.

d. Noninferiority of D/C/F/TAF FDC vs control was to be concluded if the lower bound of the 2-sided 95% confidence interval of the stratum-adjusted Mantel-Haenszel difference between treatment groups (D/C/F/TAF FDC minus control) in the response rate was greater than -10% (ie, a margin of 10% is applied to noninferiority assessment).

e. Noninferiority of D/C/F/TAF FDC vs control was to be concluded if the upper bound of the 2-sided 95% confidence interval of the stratum-adjusted Mantel-Haenszel difference between treatment groups (D/C/F/TAF FDC minus control) in cumulative rebound rate was less than 4% (ie, a margin of 4% is applied to noninferiority assessment).

ANCOVA = analysis of covariance; ART = antiretroviral treatment; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; CD4 = clusters of differentiation 4; FDA = Food and Drug Administration; FDC = fixed-dose combination; HIV-1 = human immunodeficiency virus type 1; LS = least squares; NA = not applicable.

Source: Mod.2.7.3/Sec2.4.

For both Phase 3 studies with D/C/F/TAF FDC, an external, independent Data Monitoring Committee (DMC) was established to monitor the safety, tolerability, and efficacy information observed with the treatment regimens, to ensure the safety of the subjects enrolled in the studies, and to allow regular assessment of the risk/benefit profile, including a futility analysis for lack of (noninferior) efficacy and a blinded sample size re-estimation (the blinded sample size re-estimation did not warrant an adjustment in the studies' sample size; refer to Mod2.7.3/Sec2.4).

The safety and tolerability of the D/C/F/TAF FDC regimen up to 48 weeks of treatment was assessed based on reported AEs, clinical laboratory tests, vital sign measurements, and physical

examinations. In addition, bone investigations were performed in a subset of subjects in both Phase 3 studies with D/C/F/TAF FDC.

Special attention is given to deaths, other serious AEs (SAEs), AEs leading to discontinuation, grade 3 and 4 AEs, and AEs of interest. AEs of interest were AEs that 1) were considered relevant in the target population, 2) were considered class effects of ARVs, or 3) were identified as being of potential importance based on earlier clinical data.

The following AEs of interest were analyzed:

- AEs of interest reflecting safety concerns with TAF/TDF:
  - Renal events
  - Bone events
  - Ocular events
- AEs of interest reflecting mainly safety concerns with DRV:
  - Severe skin events
  - Rash events
  - Liver events (including the safety concern of hepatitis B virus flare after TAF/TDF discontinuation in co-infected subjects)
  - Hyperglycemia events
  - Lipid-related events
  - Immune reconstitution inflammatory events
  - Coronary artery events
- Other AEs of interest:
  - Pancreas events
  - Lipodystrophy events
  - Cardiac conduction events
  - Convulsion
  - Lactic acidosis/severe hepatomegaly with steatosis
  - Hemophilia/bleeding events

Narratives were provided as described in the methods sections of the clinical study reports (CSRs) (Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec3.9.5.1 and Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec3.9.5.1).

An overview of the relevant clinical studies supporting the safety profile of D/C/F/TAF FDC and the individual components, as applicable, is presented in:

- Table 1 for the Phase 3 and 2 studies with D/C/F/TAF FDC; and
- Mod2.7.4/Tab2 for the Phase 1 studies with D/C/F/TAF FDC, studies with individual components of the FDC, and studies with special populations.

For more details about the different safety, efficacy, and resistance assessments, refer to the Summary of Clinical Safety (Mod2.7.4), Summary of Clinical Efficacy (Mod2.7.3), and the Summary of Virology (Mod2.7.2/VirSum), respectively.

4.1.2. Critical Aspects of Phase 3 Studies

For the ongoing, randomized, active-controlled, double-blind, Phase 3 Study **TMC114FD2HTX3001** in HIV-1 infected, **ART-naïve** subjects who received either D/C/F/TAF FDC or DRV/COBI FDC co-administered with F/TDF FDC, no notable study limitations were identified by the Sponsor. This study has the following noteworthy aspects:

- In this double-blind study, no assessment could be made of the convenience of the single-tablet, once-daily regimen of the D/C/F/TAF FDC due to double-dummy matching placebo.
- This study allows a good characterization of the safety profile of D/C/F/TAF, because of the ART-naïve population studied and the double-blind design.

Noteworthy study design aspects of the ongoing, randomized, active-controlled, open-label, Phase 3 Study **TMC114IFD3013** in HIV-1 infected, **ART-experienced**, virologically-suppressed subjects who either switched to D/C/F/TAF FDC or continued their regimen consisting of a bPI combined with F/TDF are the following:

- As the loss of response is a more informative efficacy comparison than response rate in a population that is virologically suppressed at baseline, the primary objective was to demonstrate noninferiority of the tested drug (D/C/F/TAF FDC) compared to the reference treatment, using the proportion of virologic rebounders cumulative through Week 48 as primary efficacy endpoint instead of the conventional virologic suppression at Week 48 by the FDA snapshot approach. This was recommended by the FDA (refer to FDA communication of January 27th, 2015 in Mod1.6.3). This approach is more stringent in terms of identifying virologic failures than the conventional approach because:
  - the rebounds occurring at any time point through the entire treatment period up to the upper bound of the Week 48 window (ie, cumulative rebound rate) were used instead of the rebounds (HIV-1 RNA ≥50 copies/mL) occurring only within the Week 48 window. This cumulative assessment of virologic rebound therefore categorizes more subjects as rebounders than virologic failures by snapshot approach, making it a more strict endpoint (for further details see Mod.2.7.3/Sec2.4);
  - the definition of virologic rebound was broader as it not only included subjects with a confirmed HIV-1 RNA ≥50 copies/mL during treatment up to the upper bound of the Week 48 window, but also any subjects who discontinued prematurely (irrespective of reason) with a last available (single) HIV-1 RNA ≥50 copies/mL and any subject with last available on-treatment HIV-1 RNA ≥50 copies/mL at the study cut-off (Week 48).
- Treatment-experience and resistance inclusion criteria in this switch study with the D/C/F/TAF FDC were less strict than in other recent switch studies (eg, E/C/F/TAF,

bictegravir (B)/C/F/TAF, RPV/F/TAF, and DORI [RPV + dolutegravir] switch studies).[6,7,16,23] Note, that the subjects had to be treated for at least 6 months with a bPI and Truvada® (TVD [F/TDF]), and were virologically suppressed.

Subjects could enter the study even if they:

- were virologically suppressed for a minimum of only 2 months prior to screening;
- had once a viral load elevation between ≥50 copies/mL and <200 HIV-1 RNA copies/mL after previously reaching viral suppression, within 12 months prior to screening;
- had previous virologic failure on any ARV regimen (except for failure on a DRV-containing ART);
- had no historical genotypes. However, if historical genotypes were available, the only exclusion criterion was the presence of DRV RAMs (in line with once-daily indication of DRV in ART-experienced patients). Note that no screening/baseline genotypes could be generated due to suppressed viral loads at study entry.

- Subjects continuing their regimen in the control group are expected to tolerate their treatment and, therefore, present a better safety profile than those switching to a new ARV regimen. Therefore, compared to treatment-naïve subjects, subjects switching to D/C/F/TAF were less likely to experience:
  - early onset of adverse drug reactions (ADRs) to bPIs, such as rash and gastrointestinal events;
  - renal intolerance to TAF as they were already on TVD and tolerated the TDF component.

  However, the design of this study allows assessment of the improvement in renal parameters, following a switch from a F/TDF-based regimen to the F/TAF-based regimen.

- The open-label design may have influenced the safety assessments such as the AE reporting by the subjects, the causality assessment by the investigator, or the discontinuation decision by the subjects and/or the investigator.

- This study allows assessment of the benefit of the intake of a single pill vs 3 pills.

  Note that the design of the open-label Study TMC114IFD3013 allows comparison of drug accountability between treatment groups (intake of 1 pill vs 3 pills). This is not the case with the double-blind Study TMC114FD2HTX3001, in which all subjects had to take the same number of pills each day (including placebo). For completeness, the results for drug accountability of both Phase 3 studies are shown (Section 4.2.5).

4.2. Exposure, Subject Disposition, General Baseline Characteristics, and Drug Accountability

4.2.1. Extent of Exposure

An overview of the number of subjects in the Phase 3 and Phase 2 clinical studies supporting the D/C/F/TAF safety, efficacy, and resistance profile, by study drug and by study population, is presented in Table 1. The total number of HIV-1 infected subjects in these studies is 2,081, of whom 1,228 adult subjects received the D/C/F/TAF FDC (465 ART-naïve and

763 ART-experienced, virologically suppressed; refer to Mod2.7.4/Tab3).

The extent of exposure across these Phase 3 and Phase 2 studies by patient years of exposure and by mean weeks of exposure is presented in Mod2.7.3/Tab3. In Study TMC114FD2HTX3001, the median (Q1; Q3) duration of study drug intake was 48.1 (47.9; 48.7) weeks in the D/C/F/TAF group and 48.1 (48.0; 48.6) weeks in the control group. In Study TMC114IFD3013, the median (Q1; Q3) duration of study drug intake was 48.1 (48.0; 48.6) weeks in the D/C/F/TAF group and 48.1 (48.0; 48.9) weeks in the control group.

4.2.2. Subject Disposition and Reasons for Study Discontinuation

An overview of the subject disposition in the Phase 3 and 2 clinical studies supporting the D/C/F/TAF safety, efficacy, and resistance profile, by study population and by study drug, is presented in Mod2.7.3/Tab4.

In Study TMC114FD2HTX3001, the discontinuation rate up to Week 48 was 6.4% in the D/C/F/TAF group and 7.7% in the control group. In Study TMC114IFD3013, the discontinuation rate up to Week 48 was 4.5% in the D/C/F/TAF group and 5.3% in the control group. The main reasons for premature discontinuation of study drug in the Phase 3 studies were:

- Adverse event:
  - Study TMC114FD2HTX3001: 2.2% with D/C/F/TAF vs 4.1% with control;
  - Study TMC114IFD3013: 1.4% with D/C/F/TAF vs 1.1% with control.
- Withdrawal by subject:
  - Study TMC114FD2HTX3001: 1.1% with D/C/F/TAF vs 1.7% with control;
  - Study TMC114IFD3013: 1.3% with D/C/F/TAF vs 2.1% with control.
- Lost to follow-up:
  - Study TMC114FD2HTX3001: 1.4% with D/C/F/TAF vs 1.4% with control;
  - Study TMC114IFD3013: 0.7% with D/C/F/TAF vs 1.3% with control.

The following was observed in the Phase 3 studies for premature discontinuation of study drug for an efficacy-related reason:

- Study TMC114FD2HTX3001: 1 (0.3%) with D/C/F/TAF vs 0 with control;
- Study TMC114IFD3013: None.

4.2.3. Demographic and HIV Baseline Disease Characteristics

An overview of the demographic, HIV baseline disease characteristics, and general baseline characteristics of the subjects in the Phase 3 and Phase 2 clinical studies supporting the D/C/F/TAF safety, efficacy, and resistance profile, by study population and by study drug, is presented in Mod2.7.3/Sec2.3.3 and Sec2.3.4, and Mod2.7.4/Sec2.6.3.

No relevant differences in demographic, baseline HIV disease characteristics, and general baseline characteristics were observed between the treatment groups in each study, except for a slightly higher proportion of subjects with a medical history of cardiovascular (CV) disease,

chronic renal disorder, diabetes or hyperglycemia, in the D/C/F/TAF group compared to the control group of Study TMC114IFD3013.

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/m². There was only 1 (0.1%) subject aged more than 65 years, 11.7% females, 11.1% of subjects were black or African Americans, and 13.2% of subjects of Hispanic ethnicity. The majority of subjects was from Europe. Almost all (99.3%) subjects had viral load >1,000 copies/mL at screening, and 17.2% had a screening viral load ≥100,000 copies/mL. The majority of subjects had asymptomatic HIV-1 disease (84.4%). 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 at baseline. The mean time since HIV-1 diagnosis was about 19.5 months. Almost all subjects (99.7%) had a baseline eGFR based on serum creatinine ($eGFR_{CR}$; by Cockcroft-Gault [$eGFR_{CG}$]) ≥70 mL/min. The mean (SD) baseline eGFR based on serum cystatin C ($eGFR_{cyst}$; by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) was 113.6 (16.47) mL/min/1.73m^2. A total of 75 (10.3%) subjects had $eGFR_{cyst}$ Chronic Kidney Disease (CKD) stage 2 (between 60 and <90 mL/min/1.73 m^2), and 7 (1.0%) had $eGFR_{cyst}$ CKD stage 3 or 4 (between 15 and <60 mL/min/1.73 m^2). Refer to Mod5.3.5.1/TMC114FD2HTX3001_W48-CSR/Sec4.3 for more details.

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/m². There were 2.9% subjects aged more than 65 years, 18.0% females, 20.9% of subjects were black or African Americans, and 15.0% subjects of Hispanic ethnicity. The number of subjects was equally spread between regions (North America and EU). All subjects were virologically suppressed (HIV-1 RNA <50 copies/mL) at screening (or at screening re-test; n=5), and a minority (2.0%; n=23) had a baseline viral load ≥50 copies/mL. The majority of subjects had asymptomatic HIV-1 disease (68.1%). About 70% of subjects had CD4+ cell count >500 cells/mm^3 at baseline. The mean time since HIV-1 diagnosis was about 12 years. At baseline, 7.8% of subjects (89 subjects) had an $eGFR_{CG}$ <70 mL/min. The mean (SD) baseline $eGFR_{cyst}$ was 110.5 (17.22) mL/min/1.73m^2. A total of 133 (11.7%) subjects had $eGFR_{cyst}$ CKD stage 2 (between 60 and <90 mL/min/1.73 m^2), and 11 (1.0%) had $eGFR_{cyst}$ CKD stage 3 (between 30 and <60 mL/min/1.73 m^2). Refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec4.3 for more details.

4.2.4. Prior ARV Treatment

In the Phase 3 Study TMC114IFD3013 in HIV-1 infected, ART-experienced, virologically-suppressed subjects, the treatment groups were balanced for the use of bPI at screening (was a stratification factor) (refer to Mod5.3.5.1/TMC114IFD3013-W48-CSR/Sec4.4). DRV boosted with rtv or COBI was the most frequently used PI (overall used by 70.4% of the subjects at screening; overall use at screening of other PIs was 21.8% for ATV boosted with rtv or COBI, and 7.8% for lopinavir [LPV] boosted with rtv; COBI was used as PI booster in 14.8% of subjects).

Overall, 41.8% of subjects had never taken an ARV prior to their screening ARV regimen (bPI+F/TDF) and 58.2% had been exposed to ARVs prior to the screening ARV regimen.

There was no relevant difference in previous ARV use (excluding ARVs at screening) between the treatment groups; overall:

- 41.4% of subjects had previously taken ≥1 PI prior to their screening regimen;
- 41.5% of subjects had previously taken ≥1 NRTI prior to their screening regimen;
- 29.8% of subjects had previously taken ≥1 non-nucleoside reverse transcriptase inhibitor (NNRTI).

Overall, the reasons for discontinuing the prior ARVs (apart from the switch due to participation in the study, reported under 'Other reasons'), were most often for convenience (33.0%) or due to AEs (29.4%). A total of 14.8% of subjects discontinued prior ARVs due to virologic failure and 7.0% discontinued a prior PI due to virologic failure.

4.2.5. Drug Accountability

In the Phase 3 Study TMC114IFD3013 in HIV-1 infected, ART-experienced, virologically-suppressed subjects, treatment adherence was assessed by the drug accountability cumulative up to Week 48. There was a trend to a better adherence in the D/C/F/TAF group. In the analysis up to Week 48, the proportion of subjects with >95% adherence to ARV intake was 6.3% higher in the D/C/F/TAF group (1 pill/day) than in the control group (3 pills/day) (adherence to ARV intake of >95% was 91.6% with D/C/F/TAF vs 85.3% with control).

In the Phase 3 Study TMC114FD2HTX3001 in HIV-1 infected, ART-naïve subjects, treatment adherence was similar between both treatment groups (3 pills/day). The proportion of subjects with >95% adherence to ARV intake at Week 48 was 88.3% in both treatment groups (D/C/F/TAF and control).

5. OVERVIEW OF EFFICACY AND RESISTANCE PROFILE

The efficacy results of the Phase 3 Studies TMC114FD2HTX3001 and TMC114IFD3013 provide a robust proof of the efficacy profile of D/C/F/TAF FDC, with a high genetic barrier to resistance, in both ART-naïve and ART-experienced, virologically-suppressed, HIV-1 infected subjects:

- A comparable (noninferior) efficacy was observed with the D/C/F/TAF FDC vs reference treatment, on the primary endpoints.
- Results of secondary efficacy, sensitivity, and subgroup analyses all support the primary endpoints observed with the D/C/F/TAF FDC compared to reference treatment.
- No genotypic or phenotypic resistance was observed against DRV and TAF. Development of resistance to FTC was observed in only 1 subject.

The results of the Phase 2 Study GS-US-299-0102 are supportive and are not discussed here. The results of this Phase 2 Study in HIV-1 infected, ART-naïve adults showed similar virologic outcomes between the 2 treatment groups (D/C/F/TAF FDC and DRV+COBI+F/TDF) and noninferiority of D/C/F/TAF to DRV+COBI+F/TDF was determined (virologic response rate defined as HIV-1 RNA <50 copies/mL at Week 24, using the FDA snapshot approach). For further details, refer to Mod2.7.3/Sec3.1.2).

5.1. Efficacy in HIV-1 Infected, Adult Subjects

For an overview of the Phase 3 and 2 studies with the D/C/F/TAF FDC tablet in HIV-1 infected, adult subjects (including a summary of the study designs and primary endpoints), see Table 1 and Appendix 1.

5.1.1. Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve, Adult Subjects

The Week-48 results of this study in HIV-1 infected, ART-naïve subjects provide robust proof of efficacy and noninferiority of the D/C/F/TAF FDC compared to reference treatment as determined by the proportion of virologic responders (HIV-1 RNA <50 copies/mL at Week 48; FDA-defined snapshot approach) (refer to Mod2.7.3/Sec3.1.1).

5.1.1.1. Virologic Response and Virologic Failure (FDA Snapshot)

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 (see Table 6).

D/C/F/TAF was noninferior to the control (ie, lower limit of the stratified Mantel-Haenszel 95% confidence interval (CI) around the difference between D/C/F/TAF and control was above the protocol-defined noninferiority margin of -10%) with a treatment difference (95% CI) in virologic response between D/C/F/TAF and control of 2.7 (-1.6; 7.1) and a corresponding one-sided noninferiority p-value <0.001.

The virologic failure rate was low in each treatment group: 4.4% (16/362) in the D/C/F/TAF group vs 3.3% (12/363) in the control group.

Table 6: Proportion of Virologic Response (<50 Copies/mL) According to FDA Snapshot Approach at Week 48 (Study TMC114FD2HTX3001; ITT Population)

	D/C/F/TAF (N=362)		Control (N=363)		D/C/F/TAF vs Control	
	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	Difference in Proportions (95% CI)[b]	P-value for Non-inferiority
• Virologic success (ie, HIV-1 RNA <50 copies/mL at Week 48)	**331 (91.4%)**	**(88.1 ; 94.1)**	**321 (88.4%)**	**(84.7 ; 91.5)**	**2.7 (-1.6; 7.1)**	**<0.001[c]**
• Virologic failure:	**16 (4.4%)**	**(2.5 ; 7.1)**	**12 (3.3%)**	**(1.7 ; 5.7)**		
- HIV-1 RNA ≥50 copies/mL at Week 48	9 (2.5%)		9 (2.5%)			
- Virologic failure - leading to discontinuation	1 (0.3%)[d]		0			
- Virologic failure - discontinued due to other reason and last available HIV-1 RNA ≥50 copies/mL[e]	6 (1.7%)		3 (0.8%)			
• No viral load data in Week 48 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-1 RNA <50 copies/mL (or missing)[f]	4 (1.1%)		9 (2.5%)			
- Missing data during window but on study	3 (0.8%)		5 (1.4%)			

[a] Two-sided Exact Clopper-Pearson 95% CI.
[b] Based on stratum adjusted Mantel-Haenszel 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 noninferiority of D/C/F/TAF vs Control (margin = 10%).
[d] The subject reached a virologic endpoint per investigator's assessment. [redacted].
[e] 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).
[f] 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).

AE = adverse event; CI = confidence interval; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDA = Food and Drug Administration; HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat (population); N = number of subjects; n = number of subjects with that virologic response.

Source: Mod2.7.3/Sec3.1.1.1.1.

The results in the per protocol (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 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).

The results for virologic response were consistent across the sensitivity and subgroups analyses (by baseline disease, including baseline viral load and CD4+ cell counts, and demographic characteristics) (refer to Mod2.7.3/Sec3.1.1.1.2 and Sec3.1.1.1.3.1).

5.1.1.2. Immunology

At baseline, the mean (standard error [SE]) 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.

In both treatment groups, the mean CD4+ cell counts increased over time. At Week 48, changes from baseline in least squares (LS) means estimates (SE) 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. There was no statistically significant difference between treatment groups (p=0.213; refer to Mod2.7.3/Sec3.1.1.1.3.3).

5.1.2. Phase 3 Study TMC114IFD3013 in HIV-1 Infected, ART-experienced, Virologically-suppressed, Adult Subjects

The Week-48 results of this study in HIV-1 infected, ART-experienced, virologically-suppressed (HIV-1 RNA <50 copies/mL) subjects provide robust proof of efficacy.

For more information, refer to Mod2.7.3/Sec3.1.3.

5.1.2.1. Protocol-defined Virologic Rebound Cumulative Through Week 48

The protocol-defined virologic rebound rate cumulative through Week 48 (primary endpoint) was very low and similar in both treatment groups (2.5% [19/763] with D/C/F/TAF FDC vs 2.1% [8/378] with control; see Table 7).

D/C/F/TAF was noninferior to the control at Week 48 (ie, upper limit of the stratified Mantel-Haenszel 95% CI around the difference between D/C/F/TAF and control was below the protocol-defined noninferiority margin of 4%) with a treatment difference (95% CI) in cumulative rebound rate through Week 48 between D/C/F/TAF and control of 0.4 (-1.5; 2.2) and a corresponding one-sided noninferiority p-value <0.001.

Table 7: Proportion of Subjects With Protocol-defined Virologic Rebound (≥50 Copies/mL), Cumulative Through Week 48 (Study TMC114IFD3013; ITT Population)

		Cumulative Virologic Rebound Rate		D/C/F/TAF vs Control	
				Difference in Proportions [a]	
Treatment	N	n (%)	(95% CI) [b]	(95% CI)	Noninferiority P-value
D/C/F/TAF	763	19 (2.5%)	(1.5 ; 3.9)	0.4 (-1.5; 2.2)	<0.001 [c]
Control	378	8 (2.1%)	(0.9 ; 4.1)		

[a] Based on Mantel-Haenszel method 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 noninferiority of D/C/F/TAF vs Control (margin = 4%).

ATV = atazanavir; bPI = boosted protease inhibitor; CI = confidence interval; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; ITT = intent-to-treat (population); LPV = lopinavir; N = number of subjects; n = number of subjects with protocol-defined virologic rebound through Week 48; rtv = low-dose ritonavir.

Source: Mod2.7.3/Sec3.1.3.1.1.

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).

The results were consistent across various subgroups. Of note in this treatment-experienced population, results from subgroup analyses also showed that the bPI used at screening (DRV, ATV, or LPV boosted with either rtv or COBI) and the level of ART experience (number of

previous ARVs used; or previous ARV, PI, NRTI, or NNRTI virologic failure) did not affect the cumulative rebound rate through Week 48 in either treatment group (refer to Mod2.7.3/Sec3.1.3.1.2.3).

5.1.2.2. Virologic Response and Virologic Failure (FDA Snapshot)

At Week 48, the virologic response rate (HIV-1 RNA <50 copies/mL; FDA snapshot approach; key secondary endpoint) in the D/C/F/TAF group and the control group was similar (94.9% vs 93.7%, respectively; see Table 8). The virologic failure rate was very low in each treatment group (0.8% with D/C/F/TAF vs 0.5% with control; see Table 8) 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) (refer to Mod2.7.3/Sec3.1.3.1.2.1).

Table 8: Virologic Response (HIV-1 RNA <50 Copies/mL) According to Snapshot Approach at Week 48 (Study TMC114IFD3013; ITT Population)

n (%)	D/C/F/TAF (N=763)	Control (N=378)
• **Virologic success (ie, HIV-1 RNA <50 copies/mL at Week 48)**	**724 (94.9%)**	**354 (93.7%)**
• **Virologic failure:**	**6 (0.8%)**	**2 (0.5%)**
- HIV-1 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-1 RNA ≥50 copies/mL[a]	2 (0.3%)	0
• **No viral load data in Week 48 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-1 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%)

[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).

AE = adverse event; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; HIV-1 = human immunodeficiency virus type 1; ITT = intent-to-treat (population); N = number of subjects; n = number of subjects with that virologic response.

Source: Mod2.7.3/Sec3.1.3.1.2

The protocol-defined virologic rebound rate cumulative through Week 48 (primary endpoint; see Section 5.1.2.1) appeared to be predominantly driven by transient low-level viremia (refer to Mod2.7.3/Sec3.1.3.1.2):

- Most of the protocol-defined rebounders through Week 48 were re-suppressed at Week 48 following continuation of the assigned study treatment:
  - 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, FDA snapshot approach; see Mod5.3.5.1/TMC114IFD3013-W48-CSR/Tab22). Six rebounders were virologic failures at Week 48, and the remaining rebounder had missing viral load data in the Week-48 window.
  - 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, 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.

- Using the threshold of ≥200 HIV-1 RNA copies/mL (instead of the ≥50 HIV-1 RNA copies/mL), protocol-defined virologic rebound through Week 48 was observed in only 3 subjects (0.4%) in the D/C/F/TAF group and in 0 subjects in the control group.

5.1.2.3. Immunology

At baseline, the mean (SE) CD4+ count values were above 350 cells/mm^3, ie, 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.

In both treatment groups, the mean CD4+ cell counts increased over time, which was expected with continued virologic suppression. At Week 48 vs baseline, LS means estimates (SE) increased by 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. There were no statistically significant differences between treatment groups (p=0.148) (refer to Mod2.7.3/Sec3.1.3.2).

5.2. Efficacy in HIV-1 Infected, Adolescent Subjects

D/C/F/TAF FDC is expected to show the same high level of efficacy in adolescents (aged ≥12 to <18 years) as in adults, based on:

- efficacy results of clinical studies with boosted DRV (TMC114-C230) and E/C/F/TAF (GS-US-292-0106) in adolescents showing similar efficacy profiles of the adult doses of the components in adolescents (see Table 1 for an overview on the designs and primary endpoints, see Mod2.7.3/Sec3.2.1 and Sec3.2.2 for the efficacy results);
- PK data of boosted DRV and the other individual components of D/C/F/TAF FDC (see Section 3.6 and for more details refer to Mod2.7.2/ClinPharm/Sec3.3.1.2 and NDA021976/Mod2.7.2/ClinPharm/Sec3.14.2 [June 2012]).

These results are further supported by the recent results from a Phase 2/3 switch study (Study GS-US-216-0128) in HIV-1 infected, virologically-suppressed adolescents (aged ≥12 to <18 years). In this study, subjects switched from DRV plus rtv or ATV plus rtv to DRV plus COBI 150 mg once daily or ATV plus COBI 150 mg once daily in combination with 2 NRTIs. The results from this study support the use of COBI 150 mg as a pharmaco-enhancer of DRV in adolescents (see Section 3.6).[5,20]

5.3. Resistance Determination

5.3.1. In Vitro 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 virology research programs that were designed to provide information on the mechanism of drug action, in vitro antiviral activity, and in vitro drug resistance of DRV, COBI, FTC, and TAF, is presented in the Summary of Virology in Mod2.7.2/VirSum/Sec3, with references to the NDAs of the individual components, DRV/COBI and F/TAF.

Based on ARV drug combination studies in cell culture, no antagonistic antiviral effects of the components of D/C/F/TAF FDC are expected.

5.3.2. Clinical Resistance Data

Genotypic analyses were conducted at screening/baseline (Studies TMC114FD2HTX3001, GS-US-299-0102, TMC114-C230, and GS-US-292-0106), except for the switch study TMC114IFD3013 that enrolled virologically-suppressed subjects. In general, the prevalence of screening/baseline protease and reverse transcriptase resistance mutations was low and as expected in a treatment-naïve population and balanced between treatment groups (refer to Mod2.7.2/VirSum/Sec4).

- 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). All had HIV-1 RNA<50 copies/mL at Week 48 or at discontinuation (1 subject in Study TMC114FD2HTX3001 who discontinued due to "other reason" had no viral load data at discontinuation and had a last available HIV-1 RNA <50 copies/mL) by FDA snapshot approach (refer to Mod2.7.2/VirSum/Sec5).

Post-screening resistance testing was performed on samples from subjects experiencing protocol-defined virologic failure (refer to Mod2.7.2/VirSum/Sec4.1 and Sec4.2 for definitions/methodology). Resistance testing was conducted when HIV-1 RNA was ≥400 copies/mL (except for Study TMC114-C230 where attempts were made if the viral load was >50 copies/mL) and preferably at time of failure or at later timepoints.

Overall, in the Phase 3 studies included in this submission (Studies TMC114FD2HTX3001 and TMC114IFD3013), the following was observed in subjects receiving D/C/F/TAF (see Table 9):

- No DRV or primary PI RAMs were observed in any of the 1,125 subjects treated with D/C/F/TAF.
- No TAF RAMs were observed in any of the 1,125 subjects treated with D/C/F/TAF.
- 1 subject (0.1%) out of the 1,125 subjects treated with D/C/F/TAF developed an FTC RAM M184M/I/V, conferring phenotypic resistance to FTC.

Results from the Phase 2 studies included in this submission are in line with the Phase 3

resistance data (see Table 9).

Table 9: Development of Resistance in Phase 3 and 2 Clinical Studies Supporting D/C/F/TAF 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 [a]; n = 1**
	DRV/COBI+F/TDF	363	6 (1.7)	2 (0.6)	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
Total Phase 3	**D/C/F/TAF**	**1,125**	**27 (2.4)**	**8 (0.7)**	**0**	**1 (0.1)**
GS-US-299-0102	**D/C/F/TAF**	**103**	**6 (5.8)**	**6 (5.8)**	**0**	**K65K/R + M184M/I [b]; n=1**
	DRV+COBI+F/TDF	50	2 (4.0)	2 (4.0)	0	0
TMC114-C230	DRV/rtv + AZT/3TC or ABC/3TC	12	2 (16.7)	2 (16.7)	M46I [c]; n=1	K219Q [d]; n=1
GS-US-292-0106	E/C/F/TAF [e]	50	2 (4.0)	2 (4.0)	0	0
Total Phase 2 and 3	**D/C/F/TAF**	**1,228**	**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/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. Conferring phenotypic resistance to FTC and 3TC.

b. Mutations K65R and M184I are associated with resistance to TDF/TAF and FTC, respectively. However, phenotypic susceptibilities to both FTC and TDF/TAF were in the sensitive range despite the presence of these mutations.

c. M46I is a primary PI RAM, but not a DRV RAM; phenotypic assessment showed that the subject remained susceptible to all PIs, including DRV.

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.

Source: Mod2.7.2/VirSum/Sec5.

5.4. Long-term Efficacy

The Phase 3 studies with D/C/F/TAF are ongoing and from both studies data with D/C/F/TAF FDC will become available up to Week 96 (from the patients who continued in the extension phase) and beyond that time point (during the roll-over/follow-up phase).

Long-term efficacy of the single agents (at Week 96 or beyond) has been established (in studies TMC114-C211, GS-US-292-0104, GS-US-292-0111, GS-US-311-1089; refer to Mod2.7.3/Sec6).[1,16,28,29] In these studies, emergence of RAMs and phenotypic resistance against ARVs in the subjects' regimens were rare up to 144 and 192 weeks (refer to Mod2.7.3/Sec6).

5.5. Comparison of Efficacy and Resistance Results with Other Clinical Studies

Efficacy results at Week 48 (virologic response defined as HIV-1 RNA <50 copies/mL and virologic rebound, respectively) of the Phase 3 studies with the D/C/F/TAF FDC (TMC114FD2HTX3001 and TMC114IFD3013) compare favorably to the efficacy results from historical studies (see below).

Furthermore, the low-level development of resistance observed in the studies with the D/C/F/TAF FDC is in line with other studies investigating DRV 800 mg once-daily based regimens and studies investigating F/TAF vs F/TDF regimens (Mod2.7.2/VirSum/Sec5).

5.5.1. In HIV-1 Infected, ART-naïve Subjects

Efficacy results of the Week 48 primary analyses of the Phase 3 Study TMC114FD2HTX3001 (HIV-1 infected, ART-naïve subjects) with D/C/F/TAF FDC were comparable to the efficacy results from the following historical studies:

- Phase 3 studies with **DRV/rtv** (800/100 mg) once daily in combination with F/TDF in HIV-1 infected, ART-naïve subjects (Study TMC114-C211)[28] and with **DRV** 800 mg in combination with **COBI** 150 mg and 2 NRTIs (Study GS-US-216-0130), mainly in ART-naïve subjects[27];
- Phase 3 studies with **F/TAF** (administered as E/C/F/TAF 150/150/200/10 mg) in HIV-1 infected, ART-naïve subjects (Studies GS-US-292-0104 and GS-US-292-0111).[16]

5.5.2. In HIV-1 Infected, ART-experienced, Virologically-suppressed Subjects

Efficacy results at Week 48 (virologic response defined as HIV-1 RNA <50 copies/mL and virologic rebound) of Study TMC114IFD3013 in HIV-1 infected, ART-experienced, virologically-suppressed subjects were comparable with efficacy results from the following historical study:

- Phase 3 Study GS-US-311-1089 with subjects switching from F/TDF to F/TAF in combination with a 3rd agent in HIV-1 infected, ART-experienced, virologically-suppressed subjects.[8,26]

5.5.3. In HIV-1 Infected, ART-experienced, Virologically-failing Subjects

No data are available with the D/C/F/TAF (800/150/200/10 mg) FDC tablet in HIV-1 infected subjects who are ART-experienced, virologically-failing (HIV-1 RNA ≥50 copies/mL). The efficacy (and safety) of the D/C/F/TAF FDC tablet in ART-experienced, virologically-failing, HIV-1 infected patients can be extrapolated from the D/C/F/TAF Phase 3 studies and from historical data from individual components. In the Phase 3 studies with the D/C/F/TAF FDC tablet, exposures to DRV (TMC114FD2HTX3001 and TMC114IFD3013) and to TAF (TMC114FD2HTX3001) were consistent with historical PK data of boosted DRV and TAF administered as single agents (see Section 3.5 and refer to Mod2.7.2/ClinPharm/Sec3.2.2). These D/C/F/TAF FDC PK results permit extrapolation of the durable historical efficacy data of the individual D/C/F/TAF components to the D/C/F/TAF FDC tablet.[10,16,27,28]

6. OVERVIEW OF SAFETY

6.1. Nonclinical Data Relevant to the Clinical Use of the D/C/F/TAF FDC

Based on the nonclinical program and clinical experience to date with all 4 components, no additive or synergistic effects are expected for the D/C/F/TAF FDC beyond the expected PK boosting of DRV by COBI. Given the lack of significant overlapping toxicities of the individual components, nonclinical studies with the combination of the D/C/F/TAF FDC were not considered necessary. In Mod2.4, a summary of the nonclinical data is provided for the separate components as well as a nonclinical assessment on the combined use of DRV, COBI, FTC, and TAF. The comprehensive nonclinical programs of the individual components DRV, COBI, FTC, and TAF support the use of the D/C/F/TAF FDC tablet as proposed in the Prescribing Information in Mod1.14.1.

Based on nonclinical studies, the main potential clinical risks with D/C/F/TAF are with the TAF component. The primary target organs for TAF are bone and kidney; exacerbation of TAF effects on bone is not expected with the combination therapy.

6.2. Safety in HIV-1 Infected, Adult Subjects

For an overview of the Phase 3 and 2 studies with the D/C/F/TAF FDC tablet in HIV-1 infected, adult subjects (including a summary of the study designs), see Table 1 and Appendix 1.

In the Phase 3 and 2 studies with D/C/F/TAF FDC, 2,019 HIV-1 infected subjects were included. In these studies, a total of 1,228 subjects were treated with D/C/F/TAF FDC for 48 weeks.

The most prominent findings and conclusions of the 2 Phase 3 studies with D/C/F/TAF FDC are provided in the sections below. For more details refer to Mod2.7.4/Sec3.1.1.1 (safety data of Phase 3 Study TMC114FD2HTX3001) and Mod2.7.4/Sec3.1.1.2 (safety data of Phase 3 Study TMC114IFD3013). Results are presented separately for each study, as the safety data were not pooled (refer to Mod2.7.4/Sec2.1). The results of the Phase 2 Study GS-US-299-0102 are supportive and are not presented here (for details, refer to Mod2.7.4/Sec3.1.1.3).

6.2.1. Phase 3 Study TMC114FD2HTX3001 in HIV-1 Infected, ART-naïve, Adult Subjects

The Week-48 results of the Phase 3 Study TMC114FD2HTX3001 demonstrated that the D/C/F/TAF FDC tablet was well tolerated in 362 HIV-1 infected, ART-naïve adults over a mean (SD) exposure of 46.8 (8.4) weeks (refer to Mod2.7.4/Sec3.1.1.1.1).

Safety findings from Study TMC114FD2HTX3001 are consistent with the known safety profiles of the individual components of the D/C/F/TAF FDC. This study, where the only difference between the 2 treatment groups was the use of TAF rather than TDF, showed that the D/C/F/TAF FDC compared to DRV/COBI+F/TDF in treatment-naïve subjects has a better bone and renal safety profile. In addition, higher rates of abnormal fasting lipids were observed with D/C/F/TAF compared to DRV/COBI+F/TDF, consistent with the more pronounced lipid-lowering effect of TDF compared to TAF.

6.2.1.1. AE Overview in HIV-1 Infected, ART-naïve Adults

No deaths occurred up to the Week-48 visit (see Table 10 and refer to Mod2.7.4/Sec3.1.1.1.2). During the follow-up period, 1 subject in the control group experienced a fatal grade 4 SAE of sepsis after study drug interruption for a grade 4 sclerosing cholangitis. The event was considered not related to the study drug.

The incidence of SAEs was 4.7% in the D/C/F/TAF group vs 5.8% in the control group. SAEs were isolated events; by preferred term, no SAE was reported in more than 2 subjects per treatment group. No SAEs were considered related to the study drug in the D/C/F/TAF group.

The incidence of AEs leading to permanent discontinuation of the study drug was 1.9% in the D/C/F/TAF group vs 4.4% in the control group. AEs leading to discontinuation were isolated events. By preferred term, no AE leading to permanent discontinuation of the study drug was reported in more than 2 subjects per treatment group, except for rash, reported in 4 (1.1%) subjects in the D/C/F/TAF group and 5 (1.4%) subjects in the control group.

In the control group, there was a higher incidence of related AEs, of related SAEs and of AEs leading to discontinuation than in the D/C/F/TAF group (see Table 10).

Table 10: Adverse Events Summary Table (Study TMC114FD2HTX3001; ITT Population)

Number (%) of subjects with:	D/C/F/TAF (N=362)		Control (N=363)	
	Overall	Related	Overall	Related
≥1 AE	312 (86.2%)	126 (34.8%)	307 (84.6%)	151 (41.6%)
≥1 fatal AE	0	0	0	0
≥1 SAE	17 (4.7%)	0	21 (5.8%)	6 (1.7%)
≥1 AE for which study medication was permanently stopped	7 (1.9%)	7 (1.9%)	16 (4.4%)	14 (3.9%)
≥1 worst grade 3 AE	17 (4.7%)	5 (1.4%)	16 (4.4%)	3 (0.8%)
≥1 worst grade 4 AE	2 (0.6%)	1 (0.3%)	6 (1.7%)	2 (0.6%)

AE = adverse event, D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ITT = intent-to-treat; N = number of subjects per treatment group; SAE = serious adverse event.

Source: Mod2.7.4/Sec3.1.1.1.2 and Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab21.

There were no clinically relevant differences in incidence of the most frequent AEs by preferred term (reported in ≥5% of subjects in either treatment group) between both treatment groups (refer to Mod2.7.4/Sec3.1.1.1.2 and Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Tab22).

The majority of AEs were grade 1 or 2 (see Table 10 and refer to Mod2.7.4/Sec3.1.1.1.2). Grade 3 or 4 AEs were reported in 5.2% of subjects in the D/C/F/TAF group and in 6.1% of subjects in the control group. The most frequent (>2 (0.6%) subjects in either treatment group) grade 3 AE was low density lipoprotein (LDL) cholesterol increased in 4 (1.1%) subjects in the D/C/F/TAF group and no subjects in the control group. No grade 4 AE was reported for >1 subject in either treatment group except for suicide attempt in 2 (0.6%) subjects in the control group.

AEs considered at least possibly related to study drug were more frequently reported in the control group compared to the D/C/F/TAF group (see Table 10 and refer to Mod2.7.4/Sec3.1.1.1.2). The related AEs in the D/C/F/TAF group were mainly known ADRs for

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, rash, and nausea (reported in 5.5% to 8.6% of subjects).

The ADR profile of D/C/F/TAF based on this study with HIV-1 infected, ART-naïve adults is provided in Section 6.5.

6.2.1.2. Events of Interest in HIV-1 Infected, ART-naïve Adults

6.2.1.2.1. Renal Events

AEs From Renal System Organ Class (SOC)

Renal and urinary disorders were observed in 1.9% of subjects in the D/C/F/TAF group vs 5.9% in the control group (refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Att TSFAE02_EXT). In addition, relevant AEs were retrieved under the review category 'Renal events of interest' to search for potential cases of proximal renal tubulopathy (PRT). Renal events of interest were reported in 0.6% in the D/C/F/TAF group vs 2.2% in the control group and consisted, except for one event, of laboratory-related events. None were serious or led to study drug discontinuation. No AEs compatible with PRT, including Fanconi syndrome, were reported. For more information on renal events of interest, refer to Mod2.7.4/Sec3.1.1.1.3.

Glomerular Function

Estimated Glomerular Filtration Rate (eGFR) Based on Serum Cystatin C

- In both treatment groups, mean $eGFR_{cyst}$ (calculated using the CKD-EPI method) increased over time (LS means estimates at Week 48 vs baseline: +5.3 mL/min/1.73 m^2 with D/C/F/TAF vs +2.9 mL/min/1.73 m^2 with control). The mean increase from baseline at Week 48 of $eGFR_{cyst}$ was larger in the D/C/F/TAF group; the difference between treatment groups was statistically significant (p=0.001).
- At Week 48, compared to baseline, 8.2% of subjects (D/C/F/TAF) vs 8.5% (control) had an improvement in $eGFR_{cyst}$ CKD stage, 0.8% vs 2.8% had a worsened $eGFR_{cyst}$ CKD stage.

Serum Creatinine

- The mean increase from baseline at Week 48 of serum creatinine was smaller in the D/C/F/TAF group than in the control group (LS means estimates at Week 48 vs baseline: +4.8 µmol/L in the D/C/F/TAF group vs +8.2 µmol/L in the control group); the difference between treatment groups was statistically significant (p<0.001).

Estimated Glomerular Filtration Rate (eGFR) Based on Serum Creatinine

- Results of eGFR based on serum creatinine ($eGFR_{cr}$), as calculated either by the CKD-EPI formula ($eGFR_{CKD\text{-}EPI}$) or the Cockcroft-Gault (CG) formula ($eGFR_{CG}$), mirror the findings on serum creatinine.
- The mean decrease from baseline at Week 48 of $eGFR_{CG}$ was smaller in the D/C/F/TAF group than in the control group (LS means estimates at Week 48 vs baseline: -5.2 mL/min vs -11.2 mL/min); the difference between treatment groups was statistically significant

(p<0.001).

Proteinuria

In the D/C/F/TAF FDC group, there was an improvement of the proteinuria at Week 48 vs baseline, compared to the control group, as:

- Median levels of urine albumin to creatinine ratio (UACR) decreased at Week 48 in both treatment groups; the decreases were greater in the D/C/F/TAF group vs the control 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 Week 48.
- 3.8% (D/C/F/TAF) vs 5.5% (control) of subjects had clinically significant albuminuria (UACR ≥30 mg/g) at Week 48; 2.5% (D/C/F/TAF) vs 4.2% (control) 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 Week 48.
- Findings were similar for urine protein to creatinine ratio (UPCR).

Proximal Tubular Function

No AEs compatible with PRT, including Fanconi syndrome, were reported.

Renal events of interest were reported in 0.6% in the D/C/F/TAF group vs 2.2% in the control group and consisted, except for one event, of laboratory-related events. One clinical renal event of interest (0.3%) 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.

Subclinical Proximal Renal Tubulopathy

Throughout the entire treatment period, none of the subjects in the D/C/F/TAF group and 2 (0.6%) subjects in the control group met the study-defined criteria for a treatment-emergent potential subclinical PRT (ie, confirmed creatinine increase ≥0.4 mg/dL and abnormalities in at least 1 of the 3 other markers of proximal renal tubular dysfunction [hypophosphatemia, proteinuria, and normoglycemic glycosuria]). Neither of these 2 control subjects had AEs consistent with PRT reported. In addition, in the D/C/F/TAF group compared to the control group, consistently less subjects presented increases in any of the markers of proximal renal tubular dysfunction during the study.

Tubulopathy Markers

In the D/C/F/TAF FDC group, there were fewer abnormalities than in the control group of other markers of tubulopathy, such as retinol-binding protein (RBP) to creatinine ratio and beta-2-microglobulin to creatinine ratio (refer to Mod5.3.5.1/TMC114FD2HTX3001-W48-CSR/Sec6.3.1.3.5).

Levels of urine fractional excretion of phosphate ($FEPO_4$) increased in both treatment groups. There were no statistically significant differences between the treatment groups at Week 24 and Week 48. In the D/C/F/TAF group, less subjects with an $FEPO_4$ ≤20% at baseline had a worsening to an $FEPO_4$ >20% at Week 48 than in the control group.