SECTION 2.5 – CLINICAL OVERVIEW

EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (F/TAF FDC)

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
aGFR	actual glomerular filtration rate
AIDS	acquired immunodeficiency syndrome
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ANSM	National Agency of Medicine and Health Products Safety
ART	antiretroviral therapy
ARV	antiretroviral
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
B2M	beta-2-microglobulin
BHIVA	British HIV Association
BL	baseline
BMD	bone mineral density
BMI	body mass index
CatA	cathepsin A
CD4	cluster determinant 4
CFR	Code of Federal Regulations
CI	confidence interval
COBI, C	cobicistat (Tybost®)
CSR	clinical study report
C-telopeptide	type I collagen C-telopeptide
CYP	cytochrome P450 enzyme
CV	coefficient of variation
ddI	didanosine
DDI	drug-drug interaction
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
dNTP	2' deoxynucleoside triphosphate
DRV, D	darunavir
DTG	dolutegravir
DXA	dual-energy x-ray absorptiometry
EACS	European AIDS Clinical Society
EC_{50}	concentration of a compound inhibiting virus replication by 50%

EVG, E	elvitegravir (Vitekta®)
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EU	European Union
EVG, E	elvitegravir (Vitekta®)
F/TAF	emtricitabine/tenofovir alafenamide (coformulated)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC, F	emtricitabine (Emtriva®)
FTC-TP	emtricitabine 5′-triphosphate
Gilead	Gilead Sciences
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV, HIV-1, HIV-2	human immunodeficiency virus, type 1, type 2
IC_{50}	concentration that results in 50% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IND	Investigational New Drug (application)
INSTI	integrase strand-transfer inhibitor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
K_i	kinetic inhibition constant
LDL	low-density lipoprotein
LPV	lopinavir
LPV/r	ritonavir-boosted lopinavir
LOCF	last observation carried forward
LSM	least-squares mean
m	Module
MDZ	midazolam
MEB	Medicines Evaluation Board
M = F	missing = failure
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Medical Products Agency
MRP4	multidrug resistance-associated protein 4
mtDNA	mitochondrial DNA
MVC	maraviroc
N or n	number of subjects in a population (N) or subset (n)

NCEP	National Cholesterol Education Program
NDA	New Drug Application
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PI	protease inhibitor
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PP	per protocol
PRT	proximal renal tubulopathy
PSP	pediatric study plan
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
-R	resistant
RAL	raltegravir
RBP	retinol binding protein
RNA	ribonucleic acid
rNTP	ribonucleoside triphosphate
ROW	rest of world
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
STB	elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (coformulated; Stribild®)
TAF	tenofovir alafenamide
TAM	thymidine analog mutation
TBLH	total body less head
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate

TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
UACR	urine albumin to creatinine ratio
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
vs	versus

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

AUC	area under the plasma/PBMC concentration versus time curve
AUC_{inf}	area under the plasma/PBMC concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
$AUC_{0\text{-}last}$	area under the plasma/PBMC concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma/PBMC concentration versus time curve over the dosing interval
C_{max}	maximum observed plasma/serum concentration of drug
PBMC	peripheral blood mononuclear cell
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{max}	time (observed time point) of C_{max}

1. PRODUCT DEVELOPMENT RATIONALE

Gilead Sciences (Gilead) is submitting this dossier in support of a new marketing application for a fixed-dose combination (FDC) of emtricitabine (FTC; F) and tenofovir alafenamide (TAF). The F/TAF FDC is available in 2 tablet strengths, F/TAF 200/25 mg and F/TAF 200/10 mg. The proposed indication for the F/TAF FDC tablet is for use once daily in combination with other antiretroviral (ARV) agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients 12 years of age and older without any known resistance to the individual components.

This submission for F/TAF is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1473 and GS-US-311-1472) that provide a pharmacokinetic (PK) bridge between the 2 F/TAF FDC tablet strengths (200/25 mg and 200/10 mg) and Gilead's FDC tablet containing the HIV-1 integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), and the nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) FTC and TAF (E/C/F/TAF 150/150/200/10 mg). Clinical efficacy and safety of E/C/F/TAF have been established in a broad spectrum of patients including antiretroviral therapy (ART)-naive adults and adolescents, virologically suppressed subjects, and renally impaired subjects (E/C/F/TAF New Drug Application [NDA] 207561, Sequence 0000). In addition, the clinical efficacy and safety of F/TAF with COBI-boosted darunavir (DRV; D), administered as D/C/F/TAF, has been demonstrated in a Phase 2 study in ART-naive subjects.

This overview presents the clinical rationale for the development of F/TAF and reviews the information that is relevant to the benefit:risk assessment for the use of this FDC in the treatment of HIV-1 infection. This overview includes biopharmaceutic, clinical pharmacology, efficacy, and safety data that support the proposed labeling and patient information.

1.1. Scientific Background

1.1.1. HIV-1 Infection and Current Treatment Options

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide {27071}.

Standard of care for the treatment of HIV-1 infection uses combination ART to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. For ART-naive HIV-infected patients, treatment guidelines recommend that initial therapy consist of 2 N[t]RTIs and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an INSTI. Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {32519}, {27621}. All patient populations may benefit from once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {20372}.

1.1.2. Rationale for F/TAF Development

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non–AIDS-associated comorbidities. Clinical attention has become more focused on optimizing tolerability, long-term safety, and adherence {29705}.There remains a significant medical need for effective and safe therapies that take into consideration the aging patient population, non-HIV–related comorbidities, virologic resistance, and regimen simplification.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an oral prodrug of TFV that has advantages over other NRTIs, including a minimal propensity for mitochondrial toxicity (relative to zidovudine), no concern of life-threatening hypersensitivity reactions, or potentially inferior efficacy (except when combined with dolutegravir [DTG]) in patients with high pretreatment HIV-1 RNA levels (unlike abacavir [ABC]) {14803}. Consequently, TDF in combination with FTC is a guideline-recommended N(t)RTI backbone for ART-naive patients. The combination of FTC and TDF is used within several once-daily FDCs (Truvada® [TVD; FTC/TDF], Atripla® [ATR; efavirenz (EFV)/FTC/TDF], Complera® or Eviplera® [FTC/rilpivirine (RPV)/TDF], and Stribild® [STB; EVG/COBI/FTC/TDF]). In addition to use with the third agents in these FDCs, FTC/TDF may be combined with others to form a guideline-recommended regimen for ART-naive patients.

Despite its advantages over other NRTIs, TDF is associated with nephrotoxicity, which manifests as increased creatinine, increased protein loss (particularly tubular), and occasional cases of proximal renal tubulopathy (PRT) (including Fanconi syndrome). These TDF-associated renal risks necessitate increased renal monitoring, placing burden on the patient and healthcare provider. In addition, TDF is associated with early onset bone demineralization in adults, specifically reductions in bone mineral density (BMD); the decreases in BMD with TDF are larger than those seen with other NRTIs {26885}, {34210}.

TAF is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF. It achieves higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP) and > 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers an improved clinical profile compared with TDF.

Gilead proposes to address the unmet medical need for a highly efficacious N(t)RTI backbone that has an improved renal and bone safety profile compared with TDF-containing backbones, while maintaining the advantages of TDF over other NRTIs. Gilead has coformulated TAF with FTC (Emtriva®), an NRTI that is approved for use in combination with other agents for the treatment of HIV-1 infection in adults and children (generally 3 months of age or older) in the United States (US), Canada, European Union (EU), and other regions worldwide.

In ART-naive or virologically suppressed patients, an FDC that is a complete regimen (ie, single-tablet regimen) is generally preferred; however, a stand-alone NRTI backbone is important as it allows flexibility for clinicians to combine F/TAF with other third ARV agents to address individual patient's specific efficacy or safety/tolerability concerns.

The efficacy and safety of F/TAF have been established in Phase 2 and Phase 3 studies of E/C/F/TAF and are supported by a Phase 2 study of D/C/F/TAF. The key Phase 3 clinical data demonstrate the following for F/TAF-containing regimens:

- Highest virologic success rates than have been previously shown in studies of ART-naive, HIV-infected subjects, with low rate of treatment-emergent virologic resistance
- Maintenance of efficacy in subjects switching from standard-of-care regimens
- Improved bone safety profile as compared with TDF-containing regimens, specifically, less change in BMD at both the hip and spine for ART-naive subjects, and improvements in BMD for subjects who switched to a TAF-based regimen
- Improved renal safety profile as compared with TDF-containing regimens, specifically, less change in serum creatinine, proteinuria, and renal tubular proteinuria for ART-naive subjects compared with STB, and a reduction in serum creatinine levels and improvements in these renal tubular protein parameters for subjects who switched from a TDF-based regimen. Results support renal safety monitoring consistent with standard clinical practice (and with other non-TDF-containing ARV regimens).
- Efficacy and safety profile that supports the use of F/TAF without dose adjustment for renally impaired patients with an estimated glomerular filtration rate calculated using the Cockcroft-Gault equation (eGFR) as low as 30 mL/min
- Efficacy and safety profile in elderly subjects comparable with that from younger subjects
- Potent efficacy in ART-naive adolescents, with a renal safety profile consistent with that in adults, and no impact on bone mineralization relative to a reference population

1.2. Overview of the Clinical Development Program

This submission is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1472 and GS-US-311-1473) that demonstrated bioequivalent exposure of TAF and FTC between the F/TAF and E/C/F/TAF FDCs, and a comprehensive clinical pharmacology development program.

1.2.1. Clinical Pharmacology Development Program

A comprehensive program of clinical studies characterized the PK of F/TAF and its components. In total, 44 clinical studies provide PK (including drug-drug interaction [DDI] information and/or pharmacodynamic [PD]) data in support of this marketing application (m2.7.2, Section 1.2). Of these, 6 studies were conducted with F/TAF and 9 with TAF. The other studies were conducted with E/C/F/TAF, D/C/F/TAF, FTC, or FTC/TDF. Thirteen studies were conducted in HIV-infected subjects.

The TAF PK profile has been extensively characterized through clinical pharmacology studies with TAF, F/TAF, E/C/F/TAF, or D/C/F/TAF that entailed single and/or chronic dosing at

clinically relevant exposure of the drug(s) to assess PK, PK/PD relationships, and/or the effects of intrinsic and extrinsic factors. Drug-interaction studies were conducted using appropriate designs with adequate sample size to provide proper statistical comparisons and allow assessment of the clinical relevance of findings. Further details are provided in m2.7.2, Section 1.

1.2.2. Dose Selection

The recommended dose of F/TAF per the third ARV agent is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered as E/C/F/TAF, for which an extensive efficacy and safety database exists.

The different TAF dose (10 or 25 mg) is generally based on whether or not the coadministered third agent has any clinically relevant effect on TAF (eg, via inhibition of intestinal P-glycoprotein [P-gp]) (Section 3.5.7.3).

1.2.3. Clinical Efficacy and Safety Development Program

The efficacy and safety of F/TAF is based upon data from 6 clinical studies with E/C/F/TAF (Table 2) and is supported by 1 clinical study conducted with D/C/F/TAF, all in HIV-infected subjects.

Study populations that provided clinical efficacy and safety data for E/C/F/TAF were as follows:

- ART-naive, HIV-infected adults or adolescents with screening HIV-1 RNA ≥ 1000 copies/mL (Phase 3 Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0106) or ≥ 5000 copies/mL (Phase 2 Study GS-US-292-0102)

- Virologically suppressed adults taking a TDF-based regimen for 48 to more than 144 weeks (Phase 3 Study GS-US-292-0109)

- Adults with mild to moderate renal impairment (Phase 3Study GS-US-292-0112)

Across the 6 E/C/F/TAF studies, a total of 2394 subjects received at least 1 dose of E/C/F/TAF in the US, Europe, and Rest of World (including Asia, Africa, Australia, Canada, and Central and South America) (Table 1), including 2121 subjects in E/C/F/TAF Phase 3 studies and 273 subjects in the E/C/F/TAF Phase 2 study (including the randomized phase and open-label extension). For E/C/F/TAF overall, 2306 subjects (96.3%) were still on study treatment up to the applicable data cut date for each study (m2.7.3, Section 3.1.1).

Table 1. Number of Subjects Who Received E/C/F/TAF in Studies Included in the Submission by Region

	US	Europe	Rest of World (ROW)	Total Enrolled
Phase 3 Studies[a]	1360	311	450	2121
Phase 2 Studies[b]	273	0	0	273
TOTAL	**1633**	**311**	**450**	**2394**

a Phase 3 studies: GS-US-292-0104 (US:252; Europe: 74; ROW: 109), GS-US-292-0111 (US:280; Europe: 86; ROW: 65); GS-US-292-0109 (US:648; Europe: 125; ROW: 186); GS-US-292-0112 (US:171; Europe: 26; ROW: 51); GS-US-292-0106 (US:9; Europe: 0; ROW: 39)
b Phase 2 study: GS-US-292-0102
Source: m2.7.3, Table 1

The D/C/F/TAF (800/150/200/10 mg) Phase 2 study was a randomized, double-blinded, active-controlled study in HIV-infected, ART-naive subjects (Study GS-US-299-0102; m2.7.3, Section 2.2). The study population that provided clinical efficacy and safety data for D/C/F/TAF was treatment-naive, HIV-infected adults with screening HIV-1 RNA ≥ 5000 copies/mL. In the D/C/F/TAF Phase 2 study, a total of 103 subjects received at least 1 dose of D/C/F/TAF in the US. This study is also included in this submission because it demonstrated that D/C/F/TAF (800/150/150/10 mg) was noninferior to a standard-of-care regimen (DRV+COBI+FTC/TDF) when administered for 24 weeks using the US Food and Drug Administration (FDA) snapshot algorithm with HIV-1 RNA cutoff at 50 copies/mL, the primary endpoint of the study.

In the double-blind studies in ART-naive subjects for E/C/F/TAF (Studies GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111), the comparator group received STB because it allowed for a direct and exclusive comparison between TAF and TDF (as the other components of the regimens are identical). STB is a recommended standard of care regimen for initial therapy in the US Department of Health and Human Services (DHHS) guidelines, European AIDS Clinical Society (EACS) guidelines, International Antiviral Society-USA Panel HIV recommendations, and the British HIV Association (BHIVA) guidelines, {32519}, {32690}, {29697}, {27621}. In the study investigating subjects switching to E/C/F/TAF (Study GS-US-292-0109), subjects were virologically suppressed on the following FTC/TDF-containing regimens at baseline: STB, ATR, COBI-boosted atazanavir (ATV/co)+TVD, or RTV-boosted atazanavir (ATV/r)+TVD. In the Phase 2 D/C/F/TAF study (Study GS-US-299-0102), the 2 treatment groups received D/C/F/TAF or DRV+COBI+TVD. Therefore, the comparator groups in Studies GS-US-292-0109 and GS-US-299-0102 also allowed for comparison between TAF and TDF, and approved standard-of-care regimens.

For adolescent subjects, studies of E/C/F/TAF (Study GS-US-292-0106) and STB (Study GS-US-236-0112) provided a comparison between TAF and TDF via an integrated, cross-study analysis.

In addition to the data provided in the original E/C/F/TAF NDA submission (E/C/F/TAF NDA 207561, Sequence 0000), a safety update has been provided to the FDA (E/C/F/TAF Safety Update, Sequence 0008). The safety data were consistent with those in the original submission, and did not alter the positive benefit:risk profile of E/C/F/TAF.

Table 2. Studies Supporting Clinical Efficacy and Safety for the F/TAF FDC Marketing Application

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented
E/C/F/TAF Studies			
HIV-Infected, ART-Naive Adult Subjects			
GS-US-292-0104	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 435) STB + placebo-to-match E/C/F/TAF FDC (N = 432)	Week 48 efficacy, PK, and safety
GS-US-292-0111	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 431) STB + placebo-to-match E/C/F/TAF FDC (N = 435)	Week 48 efficacy, PK, and safety
GS-US-292-0102	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB Open-label extension phase allowed crossover from STB to E/C/F/TAF after the Week 48 visit and enrollment of virologically suppressed adult subjects who had received a DRV+COBI-containing regimen in Study GS-US-299-0102	Randomized phase: E/C/F/TAF FDC + placebo-to-match STB (N = 112) STB + placebo-to-match E/C/F/TAF FDC (N = 58) Open-label extension phase: Continued on E/C/F/TAF FDC (N = 105) Switch to E/C/F/TAF FDC (N = 161) from STB to E/C/F/TAF FDC (N = 53) from D/C/F/TAF to E/C/F/TAF FDC (N = 70) from DRV+COBI+TVD to E/C/F/TAF FDC (N = 38)	Week 48[b] efficacy, PK, and safety
HIV-Infected, Virologically Suppressed Adult Subjects			
GS-US-292-0109	Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to E/C/F/TAF FDC	Switch to E/C/F/TAF FDC (N = 959) Stay on TVD+3rd Agent (N = 477)	Week 48 efficacy and safety
HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment			
GS-US-292-0112	Phase 3, open-label, multicenter, multiple cohort study evaluated the safety, efficacy, and tolerability of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 248)	Week 24 efficacy and safety
HIV-Infected, ART-Naive, Adolescent Subjects			
GS-US-292-0106	Phase 2/3, open-label, multicenter, 2-part, single-group study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 48) PK substudy: N = 24	Week 24 efficacy, PK, and safety

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented
D/C/F/TAF Study			
HIV-Infected, ART-Naive Adult Subjects			
GS-US-299-0102	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+TVD	D/C/F/TAF FDC (N = 103) DRV+COBI+TVD (N = 50)	Week 48 efficacy, PK, and safety

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).
b The randomized phase was 48 weeks; most ART-naive subjects who continued E/C/F/TAF in the extension completed 96 weeks of treatment.
Source: m2.7.3, Table 2

1.2.4. Regulatory Guidelines and Advice

All studies conducted in the development program were conducted in accordance with International Conference on Harmonization (ICH) guidelines and therefore data should be interchangeable across regions. [redacted] All study designs were endorsed by the regulatory agencies of the countries in which the studies were conducted. As such, data are considered applicable across regions without need for further bridging studies.

All Phase 2 and Phase 3 studies included in this submission to support the F/TAF FDC were of an adequate design and duration, as recommended in applicable regulatory guidance (ICH E8 and E10; {28155}, {27447}, with well-established endpoints to characterize efficacy and safety in the treatment of HIV-1 infection{13932}. Advice on overall development was sought from the US FDA.

Scientific advice on the development of F/TAF was sought from the Medicinal Products Agency (MPA), Medicines and Healthcare products Regulatory Agency (MHRA), National Agency of Medicine and Health Products Safety (ANSM), and Medicines Evaluation Board (MEB), as well as in consultation with the US FDA. As a result of these discussions, and in accordance with the industry guidance, the registration strategy for F/TAF is based on 2 pivotal bioequivalence studies that pharmacokinetically bridge the exposure of the parent drugs, FTC and TAF, between each of the F/TAF FDC tablet strengths (F/TAF 200/25 mg and F/TAF 200/10 mg) to the E/C/F/TAF FDC tablet, which has been shown to be efficacious, safe, and well tolerated in a broad spectrum of HIV-infected patients (E/C/F/TAF NDA 207561, Sequence 0000). In addition, the use of F/TAF FDCs in combination with boosted DRV was evaluated and the need for specific dosing recommendations was assessed based on PK data and Phase 2 efficacy and safety data in the context of the D/C/F/TAF FDC.

The F/TAF clinical development program includes an Agreed Initial Pediatric Study Plan in the US and Paediatric Investigational Plan in the EU.

Gilead is seeking registration of the F/TAF FDC tablet in the EU, US, and other regions for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children 12 years of age and older.

2. OVERVIEW OF BIOPHARMACEUTICS

This submission is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1472 and GS-US-311-1473) that provide a pharmacokinetic bridge between the 2 F/TAF FDC tablet strengths (200/10 mg and 200/25 mg) and the E/C/F/TAF FDC, which has been shown to be efficacious, safe, and well tolerated in a broad spectrum of HIV-infected patients.
Study GS-US-311-1473 demonstrated bioequivalent exposure of TAF and FTC between F/TAF 200/25 mg and E/C/F/TAF, and Study GS-US-311-1472 demonstrated bioequivalent exposure of TAF and FTC between F/TAF 200/10 mg administered simultaneously with EVG and COBI compared with E/C/F/TAF (Section 3).

Biopharmaceutical studies are summarized in detail in m2.7.1. The formulation and dissolution profile of F/TAF is described in m2.7.1, Sections 1.1.1 and 1.1.2.

2.1. Formulation

F/TAF is an FDC product consisting of 2 active pharmaceutical ingredients, FTC and TAF fumarate. F/TAF FDC tablets are an immediate-release dosage form containing either 200 mg of FTC and 10 mg of TAF (F/TAF 200/10 mg) or 200 mg of FTC and 25 mg of TAF (F/TAF 200/25 mg).

F/TAF 200/10 mg tablets are gray, rectangular-shaped, film-coated tablets with “GSI” debossed on one side and “210” on the other. F/TAF 200/25 mg tablets are blue, rectangular-shaped, film-coated tablets with “GSI” debossed on one side and “225” on the other side. F/TAF tablets are manufactured through a series of unit processes: blending of FTC and TAF with excipients, [redacted] of the preblend, blending with lubricant, tablet compression, and nonfunctional film coating.

2.2. Dissolution Profile

The dissolution profile for the proposed commercial F/TAF FDC tablet formulations showed [redacted]% [redacted] minutes for the F/TAF 200/10-mg formulation, and [redacted]% [redacted] minutes for the F/TAF 200/25-mg formulation.

2.3. Bioavailability

The bioavailability of TAF when administered alone is estimated to be ≤ 40%, based on dog and human hepatic extraction data {23907}. TAF is transported by P-gp and metabolized by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI or RTV) reduces P-gp−mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. Cumulative results from Studies GS-US-311-1473, GS-US-292-0103, and GS-US-292-0101 indicated that TAF exposure following a 10-mg dose (either as a single agent coadministered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg either as a single agent or as a component of F/TAF.

FTC is rapidly and extensively absorbed after oral administration and peak plasma concentrations reaching a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1200 mg) and then followed an apparent multiexponential decay. Greater than 85% of an oral dose of FTC is absorbed with little first-pass elimination prior to reaching the systemic circulation, resulting in a high absolute bioavailability value (93% as shown in Study FTC-110; m2.7.2, Section 3.1.1.2).

2.4. Food Effect on Exposure

TAF

The effect of food on the absorption/bioavailability of TAF 25 mg was evaluated when given as part of F/TAF (200/25 mg; Study GS-US-311-1386 [m2.7.2, Section 2.5.1.2]), and the effect of food on the absorption/bioavailability of TAF 10 mg was evaluated when given as part of E/C/F/TAF (Study GS-US-292-0110 [m2.7.2, Section 2.5.3.1]).

In Study GS-US-311-1386, administration of F/TAF (200/25 mg) under fed conditions resulted in increased overall TAF exposure, lower C_{max}, and delayed T_{max}. Administration of F/TAF (200/25 mg) under fed conditions resulted in an increase in TAF exposure (AUC_{last}) by 77% compared with administration under fasting conditions, with a decrease of 15% in TAF C_{max} and delay in TAF T_{max} from 0.50 hours under fasting conditions to 1.00 hour under fed conditions. Given the wide range of efficacious and safe TAF exposure established in the Phase 3 E/C/F/TAF studies (predicted individual steady-state mean [95% CI, %CV] AUC 206.4 ng•h/mL [55.6 to 526.1 ng•h/mL, 71.8%]; and m2.7.2, Sections 3.3.1.1 and 3.3.2.1), the differences in TAF PK under fed and fasting conditions are not considered clinically relevant.

In Study GS-US-292-0110, administration of E/C/F/TAF under fed conditions did not affect overall TAF exposure, but resulted in a lower C_{max} and delayed T_{max}. Administration of E/C/F/TAF with a high-fat meal resulted in an increase of 17% in TAF exposure (AUC_{last}) compared with administration following an overnight fast, with a 37% decrease in TAF C_{max} and a delay in TAF T_{max} from 0.50 hours under fasting conditions to 1.00 hour under fed conditions. These differences in TAF PK parameters upon E/C/F/TAF administration with food (versus fasted) are not considered clinically relevant.

Based on the results from Studies GS-US-311-1386 and GS-US-292-0110, TAF may be administered without regard to food.

FTC

The effect of food on the absorption/bioavailability of FTC was evaluated when given as part of F/TAF (200/25 mg; Study GS-US-311-1386 [m2.7.2, Section 2.5.1.2]). Administration of F/TAF with a high-fat meal resulted in a decrease of 9% in FTC exposure (AUC_{inf} and AUC_{last}) compared with administration under fasting conditions, with a 27% decrease in FTC C_{max} and a delay in FTC T_{max} from 1.00 hour under fasting conditions to 2.00 hours under fed conditions. These findings are consistent with those from a previous study (Study FTC-111), which supports the current recommendation that FTC may be administered without regard to food.

Overall, F/TAF may be administered without regard to food.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This submission is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1472 and GS-US-311-1473) that provide a pharmacokinetic bridge between the 2 F/TAF FDC tablet strengths (200/10 mg and 200/25 mg) and the E/C/F/TAF FDC, which has been shown to be efficacious, safe, and well tolerated in a broad spectrum of HIV-infected patients.
Study GS-US-311-1473 demonstrated bioequivalent exposure of TAF and FTC between F/TAF 200/25 mg and E/C/F/TAF, and Study GS-US-311-1472 demonstrated bioequivalent exposure of TAF and FTC between F/TAF 200/10 mg administered simultaneously with EVG and COBI compared with E/C/F/TAF.

Additionally, the PK and PD data from clinical studies conducted with F/TAF and E/C/F/TAF are supported with data from clinical studies conducted with TAF or FTC, and with data from nonclinical studies. Data from studies conducted with the D/C/F/TAF FDC support dosing recommendations. The clinical studies characterizing the PK of F/TAF and its components are described in m2.7.2, Section 1.2. The analyses of the clinical PK data are described in detail in m2.7.2, Section 3.

The available nonclinical and clinical virology data in support of this submission are summarized in m2.7.2, Section 4; clinical virology data are incorporated with efficacy data in this overview (Section 4).

3.1. Mechanism of Action

Mechanism of action is summarized in m2.7.2, Sections 4.1.1.

3.1.1. TAF

TAF is a phosphonoamidate prodrug of TFV (2’-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation by cathepsin A (CatA), TAF is more efficient than TDF in loading TFV into peripheral blood mononuclear cells (PBMCs) (including lymphocytes, macrophages, and other HIV target cells). Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV-DP. TFV-DP inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain termination.

TFV has activity that is specific to HIV-1 and HIV-2 and hepatitis B virus (HBV). In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells. TFV-DP is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in vitro.

3.1.2. FTC

FTC, an NRTI, is converted intracellularly through 3 phosphorylation reactions to its active phosphorylated anabolite, FTC 5′-triphosphate (FTC-TP). FTC-TP inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxycytidine

triphosphate), and after incorporation into DNA, by DNA chain termination. FTC has activity that is specific to HIV (HIV-1 and HIV-2) and HBV. FTC-TP is a very weak inhibitor of mammalian DNA polymerases α, β, ε, and mitochondrial DNA polymerase γ. There was no evidence of toxicity to mitochondria in vitro and in vivo.

3.2. In Vitro Activity

Nonclinical virology is summarized in m2.7.2, Section 4.1.

3.2.1. TAF

The kinetic inhibition constant (K_i) values for TFV-DP against HIV-1 reverse transcription (RNA-dependent DNA synthesis) and the second strand DNA synthesis (DNA-dependent DNA synthesis) are 0.02 and 1.6 μM, respectively {1131}. TFV alone, or in combination with other NRTIs, ABC, didanosine, or lamivudine, has no effect on either the intracellular 2'-deoxynucleoside triphosphate (dNTP) or ribonucleoside triphosphate (rNTP) pool concentrations {8573}.

In resting human PBMCs in vitro, the $t_{1/2}$ of TFV-DP was approximately 50 hours; whereas, the $t_{1/2}$ in activated PBMCs was approximately 10 hours {1574}. Consistent with the in vitro studies, TFV is efficiently taken up by PBMCs in monkeys and is metabolized to TFV-DP, with the intracellular concentrations of the active metabolite TFV-DP reaching 0.9 μM. The $t_{1/2}$ of TFV-DP in the monkey PBMCs was > 50 hours and significant levels of TFV and its metabolites were observed in the lymph nodes 48 hours after dosing. The long intracellular $t_{1/2}$ supports once-daily dosing.

TAF showed broad anti-HIV activity in human PBMCs against all HIV-1 groups (M, N, O), including M subtypes A to G, with average EC_{50} values ranging from 0.10 to 12.0 nM and an overall mean EC_{50} of 3.6 nM. TAF also has potent antiviral activity against HIV-2, with EC_{50} values ranging from 0.91 to 2.63 nM.

As TAF is a prodrug of TFV, resistance analyses of the parent compound, TFV, are relevant to the TAF in vitro resistance profile. As expected, the HIV-1 resistance profile of TAF was nearly identical to that of TFV, under in vitro dose-escalation drug selection with wild-type HIV-1. Treatment with TAF or TFV led to the development of the reverse transcriptase (RT) mutation K65R ± S68N with moderate phenotypic resistance to TFV and no additional resistance after extended culturing time. In addition, limited viral evolution and phenotypic changes were observed after 6 months of resistance selection with either TAF or TFV in viruses with preexisting TFV-resistance mutations (K65R, 3TAMs, and Q151M complex), suggesting a lack of alternative resistance pathways for these viruses under selective pressure from TAF (or TFV). Interestingly, the K65R mutant reverted to wild type in the absence of TAF or TFV selection pressure after 6 months in culture. These results were confirmed and extended in phenotypic analyses with a panel of recombinant HIV-1 clinical isolates from ART-experienced patients. Susceptibility to TAF for this panel of HIV-1 mutants was almost identical to TFV, with fold change compared with wild-type virus ranging from 0.34- to 23-fold of the EC_{50} (correlation coefficient between TFV and TAF of 0.97).

Although the resistance profile for TAF was the same as that for TFV in in vitro drug resistance selection studies with wild-type or NRTI-resistant (NRTI-R) HIV-1 isolates, the in vivo resistance profile may differ between the 2 drugs since the level of TFV-DP achieved in vivo upon loading with TAF is significantly higher than that with TDF. When the in vivo condition was modeled, the results showed that physiologically relevant concentrations of TAF inhibited breakthrough for most of the viruses tested, including those with 3 thymidine analog mutations (TAMs), K65R, Q151M complex, 4 TAMs, or T69 insertion. In contrast, viral breakthrough was only inhibited for a few viruses in the presence of TFV. For viruses with the highest resistance (5 TAMs), neither TAF nor TFV could achieve inhibition of viral breakthrough. These results suggest that treatment with TAF may lead to antiviral efficacy against previously defined TDF-resistant viruses.

TAF also has shown potent antiviral activity against HIV-1 isolates resistant to other ARV drug classes (ie, NNRTI-R, PI-R and INSTI-R mutants and combination NRTI-R + NNRTI-R or NRTI-R + NNRTI-R + PI-R mutants), with fold changes in EC_{50} values between 0.1 and 5.4. For the viruses that contained NRTI-R plus other ARV class-resistant mutations, TAF showed a 2.1- and 5.4-fold reduced susceptibility associated with the presence of the following resistance mutations: 3 TAMs + M184V in the first isolate and MDR Q151M mutation complex + K65R + TAMs in the second isolate.

TFV is a potent and selective inhibitor of HBV and, in addition to assessing the use of TAF in HIV-1 infection for the currently proposed indication, Gilead is conducting clinical studies to evaluate the use of TAF in subjects infected with HBV.

TFV demonstrated additive to synergistic activity with a variety of other ARV drugs in vitro. The combination of TAF with TFV resulted in an additive effect, as expected since both deliver TFV-DP to cells. TAF exhibited moderate to high synergistic effects when combined with other N(t)RTIs or NNRTIs. The combination of TAF with PIs resulted in moderate synergy, and the combination of TAF with INSTIs resulted in the highest level of synergy. As expected, the combination of TAF with COBI, a pharmacokinetic enhancer coformulated with TAF in E/C/F/TAF and devoid of antiviral activity, resulted in an additive effect.

3.2.2. FTC

The EC_{50} of FTC against laboratory adapted strains of HIV-1 ranged from 0.0013 to 0.64 μM depending on cell type and virus strain used in the assay. With clinical isolates of HIV-1, EC_{50} values range from 0.002 to 0.028 μM. FTC displays antiviral activity in vitro against HIV-1 subtypes A, B, C, D, E, F, and G with EC_{50} values ranging from 0.002 to 0.075 μM, and shows activity against HIV-2 (with an EC_{50} of 0.007 to 1.5 μM). Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 reverse transcriptase (RT).

3.3. ADME Characteristics

TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and at the 10-mg dose contained within the E/C/F/TAF FDC tablet yields > 90% lower circulating levels of TFV relative to TDF.

3.3.1. Absorption

Absorption is described in detail in m2.7.2, Section 3.1.1.

TAF

TAF PK is characterized by rapid absorption, with a median plasma T_{max} of approximately 0.50 hours.

TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI or RTV) reduces P-gp mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. TAF exposure following a 10-mg dose (either as a single agent coadministered with COBI 150 mg or as a component of E/C/F/TAF) is comparable with that achieved following administration of TAF 25 mg either as a single agent or as a component of F/TAF.

Absorption in relation to administration of F/TAF with food is described in Section 2.4.

FTC

Following oral administration with food in HIV-infected patients, peak plasma concentrations were observed 3 hours postdose for FTC.

3.3.2. Distribution

Distribution is described in detail in m2.7.2, Section 3.1.2.

TAF

The protein binding of TAF was moderate in human plasma with percent unbound TAF values ranging from 14% to 23%.

FTC

In vitro binding of FTC to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

3.3.3. Metabolism and Elimination

Metabolism and elimination, interaction with drug transporters, and biotransformation are described in detail in m2.7.2, Section 3.1.3.

TAF

Metabolism is a major elimination pathway for TAF in humans, accounting for > 80% of an oral dose. TAF has a distinct metabolism profile designed to maximize both antiviral potency and clinical safety. Inside cells, TAF is converted by intracellular enzymes to form the pharmacologically active metabolite TFV-DP. Due to increased plasma stability and activation by CatA, as compared with TDF, TAF is more efficiently loaded into PBMCs (including lymphocytes and other HIV-target cells) and macrophages, which results in greater concentrations of TFV-DP in PBMCs and lower exposure of TFV, its major metabolite, to the systemic circulation and undesired tissues, including the kidney and bone. In human clinical studies, a 10-mg oral dose of TAF in E/C/F/TAF resulted in TFV-DP concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of TFV in plasma as compared with a 300-mg oral dose of TDF in STB.

In vitro, TAF had little or no inhibitory effect (concentration that resulted in 50% inhibition [IC_{50}] > 25 μM) on the human enzymes evaluated other than cytochrome P450 enzyme (CYP) 3A, the inhibition of which was relatively weak (IC_{50} ~7.5 μM). In primary human hepatocytes, TAF showed little or no potential for induction of CYP activity at clinically relevant concentrations. In assays with recombinant enzymes, TAF was not a substrate for CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6; metabolism of TAF with CYP3A4 was detectable in assays but was comparatively low. Based on the totality of data, TAF is not expected to have clinically meaningful CYP-mediated interaction potential.

TAF is eliminated following metabolism to its major metabolite TFV. TAF and TFV have a median plasma $t_{1/2}$ of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Renal excretion of intact TAF is a minor pathway with less than ≤2% of the dose eliminated in urine. In clinical PK studies, the pharmacologically active metabolite, TFV-DP, has a $t_{1/2}$ of 150 to 180 hours within PBMCs {8461}, {7878}.

FTC

In vitro studies indicate that FTC is not an inhibitor of human CYP450 enzymes. Following administration of [^{14}C]-FTC, complete recovery of the FTC dose was achieved in urine (~86%) and feces (~14%). The biotransformation of FTC includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable. The plasma FTC $t_{1/2}$ was approximately 10 hours. Following FTC dosing, the steady-state mean intracellular $t_{1/2}$ of FTC-TP (the active drug moiety) in PBMCs was 39 hours. FTC is primarily excreted by the kidney by both glomerular filtration and active tubular secretion.

3.4. Clinical Pharmacokinetics

Details on PK after single and multiple dose administration in HIV-infected and healthy subjects are presented in m2.7.2, Section 3.2.1.1.

3.4.1. Pharmacokinetics After Single and Multiple Dose Administration in HIV-Infected and Healthy Subjects

TAF

The TAF PK profile has been characterized following single doses and at steady state in healthy and HIV-infected individuals at doses ranging from 8 to 125 mg. Overall, TAF behaved dose proportionally and in a linear manner across the range of doses studied. The TAF PK profile is characterized by rapid absorption, with a median plasma T_{max} of approximately 0.50 hours, and rapid elimination, with a median plasma $t_{1/2}$ of approximately 0.40 hours and plasma concentrations below the limit of quantitation by approximately 5 hours postdose (Study GS-US-120-0104). Due to the short plasma $t_{1/2}$, TAF does not accumulate in plasma.

Bioequivalence between the TAF and FTC components of each F/TAF FDC tablet strength and the TAF and FTC components of E/C/F/TAF was established in 2 pivotal Phase 1 studies (GS-US-311-1473 and GS-US-311-1472). Study GS-US-311-1473 demonstrated bioequivalent exposure of TAF and FTC between F/TAF 200/25 mg and E/C/F/TAF, and Study GS-US-311-1472 demonstrated bioequivalent exposure of TAF and FTC between F/TAF 200/10 mg administered simultaneously with EVG and COBI compared with E/C/F/TAF.

Results from an integrated ad hoc PK analysis performed using data from studies conducted with TAF 25 mg and TAF 10 mg + COBI demonstrated that TAF (and TFV) exposures following administration of TAF 25 mg were similar to that observed following administration of TAF 10 mg + COBI.

TFV

The TFV PK profile is characterized by rapid emergence in plasma following TAF dosing, with a median plasma T_{max} ranging from 0.25 to 3 hours postdose, and slow elimination, with a median plasma $t_{1/2}$ of 32.37 hours.

Intracellular TFV-DP

Exploratory PK data from the ongoing Study GS-US-311-1089 in HIV-infected subjects provide a direct comparison of intracellular concentrations of the active phosphorylated metabolite TFV-DP between F/TAF and FTC/TDF in combination with various third agents (m2.7.2, Section 3.2.1.1.1). F/TAF administration resulted in intracellular TFV-DP concentrations that were > 4-fold higher relative to FTC/TDF administration. This finding is consistent with results from E/C/F/TAF studies (m2.7.2, Section 3.3.1.1).

FTC

The multiple-dose PK of FTC are dose proportional over the dose range of 25 to 200 mg.

3.4.2. Comparison of Exposure Between Healthy and HIV-Infected Subjects

TAF

HIV disease status did not have an effect on TAF exposure in healthy and HIV-infected subjects, and was not a statistically or clinically relevant covariate based on population PK analyses and an integrated ad hoc PK analysis that compared TAF 25 mg with TAF 10 mg plus COBI. Based on population PK covariate analyses, a statistically significant effect of HIV disease status on TFV PK parameters was observed; however, the range of TFV exposures across healthy and HIV-infected was comparable and the observed relationship between disease status and TFV exposure is therefore unlikely to be clinically relevant.

FTC

In general, FTC PK parameter estimates following oral administration are characterized by relatively low inter-subject variability, and consistent PK data have been observed between healthy volunteers and HIV-infected subjects.

3.5. Intrinsic Factors

The effects of intrinsic factors on PK of TAF are described in detail in m2.7.2, Section 3.2.2 and are summarized below.

3.5.1. Renal Impairment

Details on the PK in subjects with renal impairment are summarized in m2.7.2, Section 3.2.2.1.1.

TAF

No clinically relevant differences in TAF or TFV PK were observed between healthy subjects and subjects with severe renal impairment. Plasma TFV exposure in subjects with mild to moderate renal impairment were within or below the range of TFV plasma exposure after administration of TDF 300 mg in both healthy, HIV-uninfected subjects and in HIV-infected patients with normal renal function. Additionally, population PK analyses of TAF and TFV from pooled Phase 1, 2, and 3 study populations showed that baseline eGFR was not a statistically or clinically relevant covariate influencing TAF PK.

FTC

In an intensive PK substudy in Study GS-US-292-0112, the exposure of FTC following administration of E/C/F/TAF to HIV-infected subjects with eGFR rate calculated using the Cockcroft Gault equation ($eGFR_{CG}$) of 30 to 69 mL/min was comparable with that shown in subjects with mild renal impairment (50-80 mL/min) who do not require dose adjustment {23270}. In addition, the safety profile of FTC administered as E/C/F/TAF was comparable for subjects with $eGFR_{CG} < 50$ mL/min or $eGFR_{CG} \geq 50$ mL/min in Study GS-US-292-0112. As the study was conducted in the target population (ie, HIV-infected patients), these data are

considered robust enough to supplant the current recommendation to modify the dosing interval for FTC in patients with $eGFR_{CG}$ < 50 mL/min.

Overall, F/TAF may be administered once daily without dose adjustment in patients with mild to moderate renal impairment ($eGFR_{CG} \geq$ 30mL/min).

3.5.2. Hepatic Impairment

Details on the PK in subjects with hepatic impairment are summarized in m2.7.2, Section 3.2.2.1.2.

TAF

No clinically relevant differences in TAF or TFV PK were observed in subjects with mild to moderate hepatic impairment; therefore, no TAF dose adjustment is required in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the PK of TAF has not been studied.

FTC

The PK of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

3.5.3. Hepatitis B and/or Hepatitis C Virus Coinfection

Due to a lack of data with the appropriately suppressive dose of TAF for use in subjects with HBV coinfection, these subjects were excluded from the E/C/F/TAF clinical development program. Subjects with hepatitis C virus (HCV) coinfection were also excluded due to incomplete DDI data. As a result, there are no data yet available on the use of E/C/F/TAF in subjects with HBV or HCV coinfection.

The PK of FTC and TAF have not been fully evaluated in patients coinfected with HBV or HCV.

3.5.4. Pediatrics

Details on the PK in pediatric subjects are summarized in m2.7.2, Section 3.2.2.5.

TAF

The effect of age of pediatric subjects on the PK of TAF and TFV was assessed based on data from Study GS-US-292-0106, where E/C/F/TAF was administered to HIV-infected, ART-naive adolescents (12 to < 18 years). TAF and TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration, indicating that the 12- to < 18-year-old range had no relevant effects on the exposure of TAF. Additionally, in the pooled Phase 2 and Phase 3 study populations used for TAF population PK analyses, HIV-infected adolescent subjects had comparable TAF and TFV exposures versus HIV-infected adult subjects, respectively, again confirming that age (12- to < 18-year) was not a clinically relevant covariate.

FTC

There were no relevant effects of age (≥ 12 years) on the exposure of FTC.

3.5.5. Pharmacokinetics/Pharmacodynamics

Details on the PK/PD relationships are presented in m2.7.2, Section 3.3.

TAF

Based on PK/PD analysis for efficacy parameters TAF 25 mg is expected to provide near-maximal activity (HIV-1 RNA decreases of approximately 1.7 to 1.8 $\log_{10}$ copies/mL). Phase 2 data in Study GS-US-292-0102 with TAF 10 mg in the E/C/F/TAF FDC (which achieves exposure of TAF 25 mg) demonstrated efficacy, based on high proportions of subjects with plasma HIV-1 RNA < 50 copies/mL. The E/C/F/TAF FDC was shown to be effective with a favorable safety and tolerability profile in Phase 3 studies (Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106). Moreover, TAF PK/PD analyses evaluating TAF exposure versus response in the 2 pivotal Phase 3 studies (Studies GS-US-292-0104, GS-US-292-0111) using results from the FDA snapshot algorithm showed uniformly high virologic success across the quartile categories of TAF AUC_{tau} (AUC_{tau} from 47 to 1869 ng•h/mL) with no trends in exposure-response relationship observed.

FTC

The plasma and intracellular PK and PK-PD correlation, and long-term efficacy and safety data obtained from Phase 2/3 clinical studies and postmarketing experience, support the approved 200-mg once-daily dose for FTC.

3.5.6. Demographic Effects

Details on the effects of demographic factors on PK are presented in m2.7.2, Sections 3.2.1.2 and 3.2.2.

TAF

Population PK analyses indicated no statistically significant or clinically relevant influence on TAF exposure based on body size measures (body weight, body surface area, or body mass index, age (range 12 to 82 years), sex, race, $eGFR_{CG}$, and population (healthy subjects versus treatment-naive HIV subjects versus treatment-experienced HIV subjects). A modest, statistically significant effect of race (black versus non black) and sex on TFV PK parameters was observed. However, the range of TFV exposure across race and across males and females was comparable and, as such, these observed relationships are not considered to be clinically relevant.

In adolescents (n = 24), TAF and TFV exposures were comparable with historical values observed in HIV-infected, treatment-naive adults following E/C/F/TAF treatment. Similarly, in the population PK analyses, adolescent subjects had comparable TAF and TFV exposures versus HIV-infected adult subjects, confirming that age was not a clinically relevant covariate.

FTC

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for FTC. The PK of FTC have not been fully evaluated in the elderly (65 years of age and older).

3.5.7. Potential for Drug Interactions

Drug interaction information is summarized in m2.7.2, Section 3.2.3.2.

3.5.7.1. Potential for F/TAF to Affect Other Drugs

The potential for TAF and TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities. The inhibitory activity of TAF with human liver microsomal CYP isozymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed at concentrations up to 25 µM. The inhibition constant (IC_{50}) values calculated for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were greater than 25 µM. TAF weakly inhibited CYP3A-mediated oxidation of midazolam or testosterone with IC_{50} values of 7.6 and 7.4 µM, respectively. TFV at 100 µM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 was assessed at TAF concentration at 50 µM (AD-120-2040). There was no evidence for time- or cofactor-dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control.

Clinical evaluation of TAF as a CYP3A4 inhibitor or inducer (Study GS-US-120-1538) showed no clinically relevant differences in midazolam (MDZ) PK relative to MDZ alone following coadministration of MDZ (oral or intravenous) and TAF; these data indicate that multiple-dose TAF does not exhibit CYP3A inhibition or induction activity, either presystemically or systemically.

3.5.7.2. Potential for Other Drugs to Affect F/TAF

TAF is transported by P-gp and metabolized by esterases expressed in the intestine {21545}, {21546}. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly affect P-gp activity may lead to changes in TAF bioavailability. Coadministration with COBI or RTV can lead to near maximal inhibition of P-gp, which may result in an increase in TAF exposure. Coadministration with COBI-boosted EVG, ATV/r, or LPV/r resulted in an increase in TAF exposure of 122%, 91%, and 47%, respectively, compared with FTC+TAF or TAF single agent. Notably, coadministration with RTV- or COBI-boosted DRV had almost no effect on TAF exposure (6% increase and 2% decrease in AUC_{last}, respectively). Results from Study GS-US-311-1473, demonstrate bioequivalence in TAF exposure between F/TAF (200/25 mg) and E/C/F/TAF (150/150/200/10 mg); the results of the integrated ad hoc PK analysis support this conclusion.

COBI and RTV showed either weak or undetectable inhibition of organic anion transporter (OAT) 1, OAT3, and multidrug resistance-associated protein 4 (MRP4) in vitro (m2.6.4, Section 7.1.4). Consistently, transport of TFV by OAT1, OAT, and MRP4 was not meaningfully inhibited by COBI or RTV under physiological conditions and clinically relevant concentrations. In addition, COBI or RTV had no effect on the accumulation of TFV in human renal tissue slices at clinically relevant concentrations. Since both COBI and RTV are inhibitors of and TAF is a substrate of organic anion transporting polypeptide (OATP) transporters in vitro, the exposure to TAF may be affected by COBI or RTV via inhibition of hepatic uptake. The effects of differences in OATP1B1 and OATP1B3 activity are, however, not expected to be clinically relevant given the high passive permeability of TAF. Because of the highly restricted substrate specificity of the enzymes catalyzing the phosphorylation of FTC and TFV, inhibition of pharmacological activation by COBI or RTV is unlikely.

As TAF is not metabolized by CYP enzymes except for weak metabolism observed for CYP3A4 in vitro, CYP inducers are not expected to have a relevant effect on TAF PK; however, most CYP inducers are also P-gp inducers, and coadministration with P-gp inducers may decrease the absorption of TAF. Coadministration with a modest CYP3A inducer (ie, EFV) resulted in slightly lower TAF exposure (14% to 22%), and coadministration with a weak CYP3A inducer (ie, RPV) resulted in no change to TAF exposure. As such, no clinically meaningful effect is expected upon coadministration of F/TAF with modest or weak CYP3A inducers.

3.5.7.3. Dosing Recommendations for F/TAF

Drug interaction information (observed or predicted) for F/TAF with potential concomitant drugs is summarized in m2.7.2, Section 3.2.3.2.3.

The recommended dose of F/TAF per the third ARV agent is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered as E/C/F/TAF, for which an extensive efficacy and safety database exists. The different TAF dose (10 or 25 mg) is generally based on whether or not the coadministered third agent has any clinically relevant effect on TAF (eg, via inhibition of intestinal P-gp). Given the wide range of safe and efficacious TAF exposure established in the single-agent proof-of-concept study (Study GS-US-120-0104), in the Phase 2 study of D/C/F/TAF (Study GS-US-299-0102), and Phase 2 and Phase 3 studies of E/C/F/TAF, where specifically uniformly high rates of virologic success were observed across all quartiles of TAF exposures (AUC_{tau} from 47 to 1869 ng•h/mL) in ART-naive patients with no trends in exposure response relationship, the variability in TAF-equivalent dose by the third agent is considered acceptable.

Specifically, F/TAF 200/25 mg is recommended with third agents that do not have clinically relevant effect on TAF exposure (eg, EFV, RPV, DTG), and F/TAF 200/10 mg is recommended with third agents that substantially increase TAF exposure (eg, ATV+RTV, LPV/r, EVG+COBI [as E/C/F/TAF]). Although coadministration with boosted DRV (DRV+RTV or DRV+COBI) did not result in increased TAF absorption, clinical data from a Phase 2, randomized, double-blinded, active-controlled study in HIV-infected, ART-naive subjects (Study GS-US-299-0102; m2.7.3, Section 2) demonstrated that D/C/F/TAF (800/150/150/10 mg)

was noninferior to DRV+COBI+FTC/TDF when administered for 24 weeks using the US FDA snapshot algorithm with HIV-1 RNA cutoff at 50 copies/mL, the primary endpoint of the study. These data, together with characterization of DDI between DRV+RTV and DRV+COBI with TAF, as well as intracellular PBMC TFV-DP analysis, support the use of F/TAF 200/10 mg with boosted DRV. Although clinical studies were not conducted to evaluate the drug interaction potential, TAF does not affect the metabolic pathways relevant to the disposition of raltegravir (RAL), maraviroc (MVC), nevirapine (NVP), buprenorphine, methadone, naloxone, norbuprenorphine, or norgestimate/ethinyl estradiol and, as such, TAF is not expected to affect the PK of these agents. Similarly, since no clinically relevant P-gp inhibition is expected by these third agents, the PK profile of TAF should not be affected when these are coadministered.

The dosing recommendations for F/TAF (Table 3), were developed based on the totality of TAF plasma PK data from DDI studies, and the wide range of efficacious and safe TAF exposure established in the single-agent proof-of-concept study (Study GS-US-120-0104), in Phase 2 and Phase 3 studies of E/C/F/TAF (m2.7.2, Sections 3.2.1.2.1, 3.3.1.1, and 3.3.2.1), and the Phase 2 study of D/C/F/TAF (Study GS-US-299-0102). These dosing recommendations are further supported by intracellular TFV-DP data from subjects receiving F/TAF 200/25 mg with an unboosted third agent (ie, DTG, EFV, MVC, NVP, RAL, or RPV) or F/TAF 200/10 mg with a RTV-boosted PI in Study GS-US-311-1089, which tracked closely with TAF-equivalent dose (Table 3) and were several fold higher than the intracellular TFV-DP concentrations following FTC/TDF administration.

Table 3. Dose Recommendations for F/TAF with Potential Concomitant Antiretroviral Drugs

ARV Drug	Recommended F/TAF Dose (mg)	TAF-Equivalent Dose[a] (mg)
EFV	200/25	12[b]
RPV		24
DTG[c]		17[b]/30
RAL		—[d]
MVC		—[d]
NVP		—[d]
ATV+COBI	200/10	—[e]
ATV+RTV		19
DRV+COBI		11
DRV+RTV		11
LPV/r		15

a TAF-Equivalent Dose calculated based on percentage change in TAF AUC with/without coadministered drug (assuming that both drugs are administered concurrently). Expected exposure in fed state unless otherwise noted.
b Expected exposure in fasted state.
c Because DTG may be administered without regard to food, expected exposures are provided for both the fed and fasted states.
d No DDI study performed. Dosing recommendation based on the nonclinical profiles of TAF and the specified ARV.
e No DDI study performed. Dosing recommendation extrapolated based on nonclinical information and the DDI study between TAF and ATV+RTV.

3.6. Summary of Clinical Pharmacology

TAF is a prodrug with a distinct metabolic profile to TDF that results in > 90% lower circulating levels of TFV and > 4-fold higher intracellular levels of the active phosphorylated metabolite TFV-DP. This decreased systemic and increased target exposure is designed to maximize both antiviral potency and clinical safety.

TAF showed broad anti-HIV activity in human PBMCs against all HIV-1 groups and potent antiviral activity against HIV-2. TAF also has shown potent antiviral activity against HIV-1 isolates resistant to other ARV drug classes (ie, NNRTI-R, PI-R, and INSTI-R mutants and combination NRTI-R + NNRTI-R or NRTI-R + NNRTI-R + PI-R mutants).

The TAF and FTC components were bioequivalent between both doses of F/TAF (200/10 mg and 200/25 mg) and E/C/F/TAF; the lower dose of F/TAF was administered concurrently with EVG and COBI. The demonstration of bioequivalence enables the pharmacokinetic bridging of TAF and FTC between the F/TAF to E/C/F/TAF FDCs, for which efficacy and safety data have been established in a broad spectrum of patients. In combination with extensive evaluation of drug interactions and robust PK/PD analyses of TAF within E/C/F/TAF program, these bioequivalence data support the extrapolation of the clinical data for E/C/F/TAF to the clinical development program for F/TAF.

The PK profiles of F/TAF and its components have been well characterized in healthy subjects, HIV-infected subjects, and special populations. No clinically relevant differences in the PK of the individual components of F/TAF were observed with respect to demographic variables. Similarly, the PK of TAF in adolescents was consistent with the range of exposures associated with antiviral activity of E/C/F/TAF in adults, which supports the extrapolation of efficacy data from pediatrics to adult subjects and the use of F/TAF in patients > 12 years.

No dose adjustment of F/TAF is necessary in patients with estimated creatinine clearance greater or equal to 30 mL/min. No dose adjustment of F/TAF is necessary in patients with mild or moderate hepatic impairment as no clinically relevant changes in the PK were observed in these subjects. F/TAF or E/C/F/TAF FDC have not been studied in patients with severe hepatic impairment.

TAF PK/PD analyses evaluating TAF exposure versus response in the 2 pivotal Phase 3 studies (Studies GS-US-292-0104 and GS-US-292-0111) using results from the FDA snapshot algorithm showed uniformly high virologic success across the quartile categories of TAF AUC_{tau} with no trends in exposure-response relationship observed.

TAF is transported by P-gp. Therefore, drugs that induce P-gp activity may lead to a decreased plasma concentration of TAF, whereas, drugs that inhibit P-gp may increase the absorption and plasma concentration of TAF. Generally, F/TAF 200/25 mg is recommended with third agents that do not have clinically relevant effect on TAF exposure (eg, EFV, RPV, DTG), and F/TAF 200/10 mg is recommended with third agents that substantially increase TAF exposure (eg, ATV+RTV, LPV/r). The proposed prescribing information for F/TAF reflects these potential interaction concerns.

Clinical experience with F/TAF FDC including its DDI evaluations, are sufficient to provide guidance regarding potential clinically significant drug interactions in the HIV-infected population.

4. OVERVIEW OF EFFICACY

Evidence to support the clinical efficacy of F/TAF is provided by 6 clinical studies of E/C/F/TAF and 1 Phase 2 study of D/C/F/TAF (Study GS-US-299-0102) in combination with the demonstration of PK bioequivalence of F/TAF to E/C/F/TAF. Coadministration of F/TAF with certain third agents achieves TAF exposures that are lower than those observed following E/C/F/TAF administration (eg, F/TAF + COBI-boosted DRV) and, therefore, the demonstration of clinical efficacy in the Phase 2 Study GS-US-299-0102 supports the use of F/TAF with those third agents. These findings are supported by the TAF PK/PD analyses in the 2 pivotal Phase 3 studies (Studies GS-US-292-0104 and GS-US-292-0111), which demonstrated uniformly high virologic success across the quartile categories of TAF AUC_{tau} with no trends in exposure-response relationship observed.

This section provides an overview of the pooled analysis of efficacy that was conducted for the pivotal E/C/F/TAF Phase 3 studies in ART-naive subjects (Studies GS-US-292-0104 and GS-US-292-0111) and of the efficacy results of the remaining individual studies in ART-naive, virologically suppressed, renally impaired, or adolescent subjects (studies are described in Table 2; detailed descriptions of efficacy data are provided in m2.7.3, Section 3.2). Pooling of the efficacy data for Studies GS-US-292-0104 and GS-US-292-0111 is appropriate due to their identical study design, including eligibility criteria (m2.7.3, Section 2.1). Statistical methods for pooling and analysis of efficacy data are provided in the E/C/F/TAF Integrated Summary of Efficacy (ISE) statistical analysis plan (SAP). No other data were pooled (unless otherwise stated), due to differences in the subject populations studied, treatment durations, and randomization. The clinical virology analyses are described in m2.7.2, Section 4.2.

In the E/C/F/TAF clinical studies, demographic and baseline characteristics were generally similar between treatment groups within each randomized study; characteristics of the overall population are summarized below (m2.7.4, Section 1.3):

- The median ages of subjects who were ART-naive or virologically suppressed ranged from 33 to 41 years at baseline. Switch subjects (Cohort 1) in the renal impairment study had a median age of 58 years. Across studies, a total of 97 subjects were ≥ 65 years of age. The median age of adolescent subjects was 15 years and 23 adolescent subjects were in the Week 24 Full Analysis Set (FAS).

- Most subjects in each study were male (80%-90%), except for Study GS-US-292-0106 (41.7% male, 58.3% female); the proportion of women (~15%) was higher than in the Phase 3 studies for STB {21102}, {21057}.

- Across studies of adult subjects, the most common races were white (approximately 55% to 70%) and black (approximately 20% to 30%), and approximately 15% to 25% subjects were Hispanic or Latino. In adolescents, most subjects were black (~90%) and none were Hispanic or Latino.

Baseline disease characteristics were similar between treatment groups within each randomized study; characteristics of the overall population are summarized below (m2.7.4, Section 1.3):

- The median baseline HIV-1 RNA value in ART-naive subjects was approximately 4.5 $\log_{10}$ copies/mL and approximately 25% of subjects had baseline HIV-1 RNA above 100,000 copies/mL.

- Median baseline CD4 count was approximately 400 cells/μL in ART-naive subjects and approximately 650 cells/μL in virologically suppressed subjects.

- Most subjects in each study had asymptomatic HIV-1 infection.

The demographic and general baseline characteristics and baseline disease characteristics in the D/C/F/TAF Phase 2 study were consistent with the ART-naive E/C/F/TAF population (m2.7.4, Sections 1.3.1.2 and 1.3.2.2).

Generally, the studied populations are representative of both ART-naive and virologically suppressed HIV-infected subjects in the general population. In addition, clinical efficacy data were collected from a broad range of countries to support applicability across different geographical regions (Table 1).

4.1. Rationale for Primary Efficacy Endpoint

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm (at Week 48 for ART-naive and virologically suppressed subjects, and at Week 24 for subjects with renal impairment, for the randomized portion of the Phase 2 E/C/F/TAF Study GS-US-292-0102, and for the Phase 2 D/C/F/TAF Study GS-US-299-0102). The assay utilized to assess HIV-1 RNA levels was the sensitive, FDA-approved, COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, Version 2.0 (Roche). Secondary efficacy analyses including the percentage of subjects with HIV-1 RNA < 50 copies/mL using the missing = failure (M = F) method, the percentage of subjects with HIV-1 RNA < 20 copies/mL using the FDA snapshot algorithm, and changes in CD4 cell count, are summarized in this overview to support the primary efficacy endpoint results.

Noninferiority of investigational drug treatment versus active comparators (Section 1.2.3) was assessed using a 2-sided 95% confidence interval (CI) with a noninferiority margin of 12%. [redacted]

Noninferiority was assessed using the FAS and the Per Protocol (PP) Analysis Set in the randomized Phase 3 studies (m2.7.3, Section 3.1.3 for a detailed description of the analysis populations).

4.2. Efficacy in ART-Naive Adults

4.2.1. E/C/F/TAF Studies

Details on the individual efficacy results from the E/C/F/TAF Phase 2 Study GS-US-292-0102, and the Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 are provided in m2.7.3, Section 3.2.1.

The percentages of subjects with virologic success based on the pooled Phase 3 data (plasma HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) were as follows (Table 4):

- E/C/F/TAF 92.4%
- STB 90.4%

E/C/F/TAF was determined to be noninferior to STB because the lower bound of the 2-sided CI of the difference in the success rate (E/C/F/TAF – STB) was greater than the prespecified −12% margin (difference in percentages: 2.0%; 95% CI: −0.7% to 4.7%).

These pooled results confirmed those from the individual studies GS-US-292-0104 and GS-US-292-0111, where noninferiority of E/C/F/TAF versus STB was determined using the FAS (GS-US-292-0104: difference in percentages: 1.0%, 95.002% CI: −2.6% to 4.5%; GS-US-292-0111 difference in percentages: 3.1%, 95.002% CI −1.0% to 7.1%) and confirmed using the PP Analysis Set.

Table 4. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Pooled Data (FAS)

			E/C/F/TAF vs. STB	
	E/C/F/TAF (N=866)	**STB (N=867)**	**p-value**	**Difference in Percentages (95% CI)**
Virologic success at Week 48				
HIV-1 RNA < 50 copies/mL	800 (92.4%)	784 (90.4%)	0.13	2.0% (-0.7% to 4.7%)
Virologic failure at Week 48	31 (3.6%)	35 (4.0%)		
HIV-1 RNA >= 50 copies/mL	20 (2.3%)	23 (2.7%)		
Discontinued study drug due to lack of efficacy	2 (0.2%)	3 (0.3%)		
Discontinued study drug due to other reasons and last available HIV-1 RNA >= 50 copies/mL	8 (0.9%)	8 (0.9%)		
Added New ARV	1 (0.1%)	1 (0.1%)		
No virologic data in Week 48 window	35 (4.0%)	48 (5.5%)		
Discontinued study drug due to AE/death	8 (0.9%)	14 (1.6%)		
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL	21 (2.4%)	31 (3.6%)		
Missing data during window but on study drug	6 (0.7%)	3 (0.3%)		

Details of the analysis of the data provided in this table are described in m2.7.3, Section 3.2.1
Programming Details: .../version1/prog/t-snapshot-pooled.sas v9.2 Output file: t-snapshot-50-wk48-pooled.out [redacted]20[redacted]:15:51
Source: E/C/F/TAF ISE, Table 2

Results for subgroup analyses and key secondary efficacy endpoints were similar between treatment groups, as summarized below:

- In the pooled subgroup analysis, the rates of virologic success at Week 48 for the subgroups age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, region (US versus ex-US), or study drug adherence were similar for the E/C/F/TAF and STB groups. For female subjects and subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL, the lower bound of 95% CI for the virologic success was > 0, favoring the E/C/F/TAF group over the STB group. These results appeared to be mainly driven by data from Study GS-US-292-0111. Additional analyses of ART-naive, elderly subjects ≥ 65 years demonstrated 100% virologic success (4 of 4 subjects) in subjects administered E/C/F/TAF (m2.7.3, Section 3.3.1.4).

- The percentages of subjects with HIV-1 RNA < 50 copies/mL through Week 48 using the M = F method for the pooled data were as follows: E/C/F/TAF 93.0%; STB 92.3%.

- The percentages of subjects with HIV-1 RNA < 20 copies/mL at Week 48 using the FDA snapshot algorithm for the pooled data were as follows: E/C/F/TAF 84.4%; STB 84.0%.

- The emergence of resistance mutations was rare across the E/C/F/TAF and STB groups (E/C/F/TAF group 0.7%, 7 of 978 subjects; STB group 0.8%, 7 of 925 subjects) (integrated analysis of Studies GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111; m2.7.2, Section 4.2.2.5).

- The mean (SD) increases from baseline in CD4 cell counts through Week 48 (observed data) using the pooled data were as follows: E/C/F/TAF 230 [177.3] cells/μL; STB 211 [170.7] cells/μL (similar results were shown for the last observation carried forward [LOCF] analysis).

- The efficacy data from the Phase 2 Study GS-US-292-0102 supported those for the Phase 3 studies and demonstrated evidence of durable efficacy; 87.5% of subjects who received E/C/F/TAF from baseline achieved and maintained HIV-1 RNA < 50 copies/mL through Week 96 (M = F).

4.2.2. D/C/F/TAF Study

Key treatment outcomes for the Phase 2 Study GS-US-299-0102 are described below; full details are provided in m2.7.3, Section 3.2.2.

The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm) were as follows:

- D/C/F/TAF 74.8%

- DRV+COBI+TVD 74.0%

D/C/F/TAF was determined to be noninferior to DRV+COBI+TVD because the lower bound of the 2-sided CI of the difference in the success rate (D/C/F/TAF – DRV+COBI+TVD) was greater than the prespecified −12% margin (difference in percentages: 3.3%; 95% CI: −11.4% to 18.1%). Noninferiority of D/C/F/TAF versus DRV+COBI+TVD was confirmed by the analysis using the PP Analysis Set.

Results for subgroup analyses and key secondary efficacy endpoints were similar between treatment groups, as summarized below:

- The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) were as follows: D/C/F/TAF 76.7%, DRV+COBI+TVD 84.0%. The difference in rates of virologic success between treatment arms was primarily due to a difference in the numbers of subjects who discontinued study drug due to other reasons and had the last available HIV-1 RNA ≥ 50 copies/mL (D/C/F/TAF 8.7%, 9 subjects; DRV+COBI+TVD 4.0%, 2 subjects) or < 50 copies/mL (D/C/F/TAF 6.8%, 7 subjects; DRV+COBI+TVD 2.0%, 1 subject).

- Virologic success rates using the Week 24 FAS were balanced in both treatment groups for the subgroups age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, and study drug adherence rate.

- The percentages of subjects with HIV-1 RNA < 50 copies/mL through Week 48 using the M = F method were as follows: D/C/F/TAF 77.7%, DRV+COBI+TVD 86.0%.

- Development of resistance to any of the components of the ARV regimens used in the study was rare. No subjects developed primary protease resistance mutations during the study through the Week 48 analysis. One subject in the D/C/F/TAF group had NRTI-R mutations emerging at the unblinding visit after Week 48, with the emergence of a mutant/wild-type mixture at position K65 (K65K/R) and a mutant/wild-type mixture at position M184 (M184M/I). Phenotypic susceptibilities to both FTC and TAF/TFV were in the sensitive range despite the presence of those mutations.

- The mean (SD) increases from baseline in CD4 cell counts through Week 48 (observed data) D/C/F/TAF 231 (141.9) cells/μL; DRV+COBI+TVD 212 (151.5) cells/μL (similar results were shown for the LOCF analysis).

4.3. Efficacy in Virologically Suppressed Adults

Key treatment outcomes for Study GS-US-292-0109 are described below; full details are provided in m2.7.3, Section 3.2.1.2.

The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) were as follows (Table 5):

- E/C/F/TAF 95.6%

- FTC/TDF+3rd Agent 92.9%

Switching to E/C/F/TAF was determined to be noninferior to maintaining FTC/TDF+3rd Agent at Week 48 because the lower bound of the 2-sided CI of the difference in success rate (E/C/F/TAF − comparator) was greater than the prespecified −12% margin (difference in percentages: 2.7%, 95.01% CI: −0.3% to 5.6%). Noninferiority of E/C/F/TAF versus FTC/TDF+3rd Agent was confirmed by the analysis using the PP Analysis Set.

Table 5. GS-US-292-0109: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Week 48 FAS)

			E/C/F/TAF vs. FTC/TDF+3rd Agent	
	E/C/F/TAF (N=799)	FTC/TDF+3rd Agent (N=397)	p-value[a]	Difference in Percentages (95.01% CI)[b]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	764 (95.6%)	369 (92.9%)	0.051	2.7% (-0.3% to 5.6%)
Virologic Failure at Week 48	9 (1.1%)	5 (1.3%)		
HIV-1 RNA >= 50 copies/mL	6 (0.8%)	5 (1.3%)		
Discontinued Study Drug Due to Lack of Efficacy	1 (0.1%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[c]	0	0		
Added New ARV	2 (0.3%)	0		
No Virologic Data in Week 48 Window	26 (3.3%)	23 (5.8%)		
Discontinued Study Drug Due to AE/Death	8 (1.0%)	3 (0.8%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	5 (0.6%)	15 (3.8%)		
Missing Data During Window but on Study Drug	13 (1.6%)	5 (1.3%)		

Details of the analysis of the data provided in this table are described in GS-US-292-0109 CSR
Programming Details: .../version1/prog/t-snapshot.sas v9.2 Output file: t-snapshot-50-wk48.out [redacted]20[redacted]:14:11
Source: GS-US-292-0109 CSR, Section 15.1, Table 10.1

Results for subgroup analyses and key secondary efficacy endpoints were similar between treatment groups, as summarized below:

- Virologic success rates using the Week 48 FAS were balanced in both treatment groups for the age, sex, race, geographic regions, prior treatment regimen, and study drug adherence subgroups. Additional analyses of elderly subjects ≥ 65 years demonstrated 100% virologic success (10 of 10 subjects) in subjects administered E/C/F/TAF (m2.7.3, Section 3.3.1.4).

- The percentages of subjects with HIV-1 RNA < 50 copies/mL through Week 48 using the M = F method were as follows: E/C/F/TAF 96.4%, FTC/TDF+3rd Agent 94.7%.

- The percentages of subjects with HIV-1 RNA < 20 copies/mL at Week 48 using the FDA snapshot algorithm were as follows: E/C/F/TAF 92.2%; FTC/TDF+3rd Agent 90.4%.

- One subject (0.1%) from the E/C/F/TAF group (no subjects from the FTC/TDF+3rd Agent group) experienced confirmed virologic rebound; this subject did not have resistance detected to any study drug (m2.7.2, Section 4.2.1.1.4).

- The mean (SD) increases from baseline in CD4 cell counts through Week 48 (observed data) were as follows: E/C/F/TAF 33 (166.6) cells/μL; FTC/TDF+3rd Agent 27 (160.2) cells/μL (similar results were shown for the LOCF).

4.4. Efficacy in Adults with Mild to Moderate Renal Impairment

Key treatment outcomes for Study GS-US-292-0112 are described below; full details are provided in m2.7.3, Section 3.2.1.3.

The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm) were as follows:

- Cohort 1 (switch subjects) 95.0% (baseline $eGFR_{CG}$ < 50 mL/min: 95.0%; baseline $eGFR_{CG}$ ≥ 50 mL/min: 95.1%). Virologic success in Cohort 1 was maintained through Week 48 (93.7%).

- Cohort 2 (ART-naive subjects) 5 of 6 subjects.

Results for subgroup analyses and key secondary efficacy endpoints are summarized below:

- There were no clinically relevant differences in virologic success at Week 24 (FDA snapshot algorithm, HIV-1 RNA < 50 copies/mL) between subgroups (age, sex, race, region, or study drug adherence rate) for Cohort 1. Additional analyses of elderly subjects ≥ 65 years demonstrated that 92.1% (58 of 63 subjects) had virologic success (m2.7.3, Section 3.3.1.4).

- The percentage of subjects with HIV-1 RNA < 50 copies/mL through Week 24 using the M = F method was 97.5% in Cohort 1.

- The percentage of subjects with HIV-1 RNA < 20 copies/mL at Week 24 using the FAS was 93.0% for Cohort 1 (baseline $eGFR_{CG}$ < 50 mL/min 92.5%; baseline $eGFR_{CG}$ ≥ 50 mL/min 93.2%). Five of 6 subjects in Cohort 2 also had HIV-1 RNA < 20 copies/mL.

- In Cohort 1, 2 subjects (0.8%, 2 of 242) were analyzed and showed resistance to multiple drug classes; 1 subject had the same resistance documented in an historic genotype and 1 subject appeared to have had reinfection with a resistant virus. In Cohort 2, no subject met the criteria for resistance analysis (0%, 0 of 6) (m2.7.2, Section 4.2.1.1.5).

- CD4 cell counts remained stable during treatment with E/C/F/TAF for Cohort 1 (mean [SD] change from baseline in CD4 cell counts at Week 24 using the FAS [observed data] was −7 [159.2] cells/μL and at Week 48 [observed data] was 16 [158.0] cells/μL) and increased during treatment for Cohort 2 (mean [SD] change from baseline in CD4 cell count at Week 24 [observed data] was 126 [106.3] cells/μL and at Week 48 was 144 [169.7] cells/μL).

4.5. Efficacy in ART-Naive Adolescent Subjects

Key treatment outcomes for Study GS-US-292-0106 are described below; full details are provided in m2.7.3, Section 3.2.1.4.

The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 24 using FDA snapshot algorithm) was 91.3% (21 of 23 subjects in the Week 24 FAS).

Two subjects who had HIV-1 RNA > 50 copies/mL at Week 24 had HIV-1 RNA < 50 copies/mL at earlier visits and at Week 32.

Results for the key secondary endpoints are shown below:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL through Week 24 using the M = F method was identical to the primary endpoint: 91.3%.
- There was no virologic resistance to E/C/F/TAF in any subject.
- The mean (SD) increase from baseline in CD4 cell count was 212 (144.3) cells/μL.

4.6. Efficacy Discussion and Conclusions

In all HIV-infected populations studied, F/TAF-containing regimens produced high rates of virologic success as assessed using the FDA snapshot algorithm with HIV-1 RNA < 50 copies/mL.

In ART-naive adults, E/C/F/TAF FDC was noninferior to STB at the Week 48 primary endpoint (E/C/F/TAF 92.4%; STB 90.4% from pooled analysis of GS-US-292-0104 and GS-US-292-0111). These virologic success rates from the Phase 3 studies are the highest for any ART-naive population at Week 48, including other INSTI-based regimens (STB and DTG: Studies GS-US-236-0102 and GS-US-236-0103, {27389}, {28661}, {26002}, {18038}, {19639}, {19105}), and demonstrate the potent antiviral efficacy of an F/TAF-containing regimen against the current standard of care.

In the Phase 2 Study GS-US-292-0102 high rates of virologic suppression were achieved and maintained through 96 weeks of treatment, providing evidence for durable efficacy.

In virologically suppressed adults (Study GS-US-292-0109), switching to E/C/F/TAF was noninferior to continuing FTC/TDF+3rd Agent (STB, ATR, ATV/boosted+TVD) at Week 48 (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 92.9%). These results demonstrate that F/TAF maintains efficacy in subjects switching from standard-of-care regimens.

In subjects with mild to moderate renal impairment (Study GS-US-292-0112), those who switched to E/C/F/TAF maintained virologic suppression through Week 24 as evidenced by high rates of virologic success (E/C/F/TAF 95.0%). These results are consistent with those from Study GS-US-292-0109 in subjects with mildly impaired or normal renal function at baseline.

Importantly, these results demonstrate efficacy of F/TAF-containing regimens for subjects with moderate renal impairment, a population for whom no once daily NRTI backbone is currently approved.

In ART-naive adolescent subjects (Study GS-US-292-0106), high rates of virologic success were seen at Week 24 (91.3%). A high rate of virologic success was also seen for STB in adolescents in Study GS-US-236-0112 (85.7%). These results demonstrate that efficacy is similarly potent in ART-naive adolescents as in ART-naive adults.

In the Phase 2 Study GS-US-299-0102, D/C/F/TAF was noninferior to DRV+COBI+TVD when administered for 24 weeks. These findings are consistent with the PK/PD analysis conducted for the E/C/F/TAF clinical pharmacology program, which demonstrated that the rates of virologic success were uniformly high across a wide range of TAF AUC_{tau} (47 to 1869 ng•h/mL) with no trends in exposure-response relationship.

Across all studies, analyses of the secondary HIV-1 RNA endpoints supported the primary efficacy analyses. In addition, the immunologic benefits of treatment with F/TAF-containing regimens were demonstrated by improvements in CD4 cell counts. Generally, there was no difference in efficacy across the different subpopulations evaluated. In elderly subjects, virologic success rates were high and consistent with those from the overall study populations. Overall, these results indicate that F/TAF is efficacious in all populations without regard to demographic characteristics, baseline viral load, or underlying renal function.

In all subjects administered F/TAF-containing regimens, the emergence of resistance mutations for subjects experiencing virologic failure was rare. The cross-resistance profiles for the virologic failure subjects with emergent resistance to FTC and TAF were consistent with historical data. No novel TAF resistance mutations were observed.

Overall, these data demonstrate potent and durable efficacy of F/TAF for the treatment of HIV-1 in ART-naive adults and adolescents, virologically suppressed subjects, and subjects with mild to moderate renal impairment. The demonstration of PK bioequivalence of F/TAF (200/10 mg and 200/25 mg) to E/C/F/TAF (m2.7.2) in combination with the comprehensive demonstration of efficacy indicates that the F/TAF FDC will provide a highly effective treatment for HIV-1 in combination with other ARV agents.

5. OVERVIEW OF SAFETY

The clinical safety of F/TAF was primarily established through the E/C/F/TAF clinical development program. This section provides an overview of the pooled analysis of safety that was conducted for the pivotal Phase 3 studies in ART-naive subjects (Studies GS-US-292-0104 and GS-US-292-0111) and of the safety results of the remaining individual studies of E/C/F/TAF in ART-naive, virologically suppressed, renally impaired, and adolescent subjects (studies are described in Table 2; detailed descriptions of safety data are provided in m2.7.4, Section 2). In addition, safety results from the D/C/F/TAF study are presented. Key demographic and baseline characteristics across all populations are summarized in Section 4.

A comprehensive nonclinical pharmacology and virology, PK, and toxicology program for FTC and TAF was undertaken to support the clinical evaluation of the F/TAF FDC for the treatment of HIV-1 infection. No specific findings from the nonclinical program were confirmed as safety concerns in the clinical development program (m2.4, Section 1).

5.1. Extent of Exposure

A total of 2394 subjects received E/C/F/TAF in Phase 2 and Phase 3 studies at the proposed commercial dose of 150/150/200/10 mg, with a median (first quartile [Q1], third quartile [Q3]) exposure of 48.1 weeks (42.3, 60.0). In the D/C/F/TAF Phase 2 study, a total of 103 subjects received D/C/F/TAF, with a median (Q1, Q3) exposure of 68.0 weeks (65.4, 72.7). This population exposure exceeds the requirements of the ICH E1 guideline for the safety evaluation of drugs. The median exposure to E/C/F/TAF was similar in subjects who were ART-naive (Studies GS-US-292-0104 and GS-US-292-0111), subjects who were virologically suppressed (Study GS-US-292-0109), and subjects with mild to moderate renal impairment (Study GS-US-292-0112). The median (Q1, Q3) exposure was shorter in adolescent subjects in Study GS-US-292-0106 (12.1 weeks [4.1, 32.1]); however, approximately half of the subjects in the study received E/C/F/TAF for ≥ 24 weeks. In studies with comparators, exposure between groups was similar within each study.

The median (Q1, Q3) duration of exposure was 105.3 weeks (98.0, 108.1) for ART-naive subjects who received E/C/F/TAF through the extension phase of Study GS-US-292-0102, with the majority of subjects completing 96 weeks of treatment (92.0%, 103 subjects).

5.2. Criteria for Evaluation and Statistical Methods

Pooling of the safety data for Studies GS-US-292-0104 and GS-US-292-0111 was considered appropriate due to their identical study design, including eligibility criteria (m2.7.4, Section 1.1.3). No other data were pooled (unless otherwise stated), due to differences in the subject populations studied, treatment durations, and randomization.

For selected safety data (bone and renal parameters) in the randomized studies, comparisons between groups were performed using appropriate statistical tests.

To control for the overall type I error in the assessment of the primary efficacy endpoint and the key safety endpoints in the E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109; hypothesis testing was performed in sequential order. The primary hypothesis of noninferiority of E/C/F/TAF relative to the active comparator, with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (as defined by the FDA snapshot algorithm) was tested first. If noninferiority was established, multiplicity adjustments were performed for the following safety endpoints with a fallback procedure in the sequential order given below, with prespecified 2-sided alpha levels {23531}:

a) Hip BMD (alpha = 0.02)

b) Spine BMD (alpha = 0.01)

c) Serum creatinine (alpha = 0.01998 for Studies GS-US-292-0104 and GS-US-292-0111; and 0.0199 for Study GS-US-292-0109)

d) Treatment-emergent proteinuria for Studies GS-US-292-0104 and GS-US-292-0111; EFV-related symptom assessment score for Study GS-US-292-0109 (alpha = 0.00)

Further details on the statistical methods, safety data definitions, and grading scales are provided in E/C/F/TAF integrated summary of safety SAP (E/C/F/TAF ISS SAP) and are included in sections below when appropriate.

5.3. Overall Safety

The safety profile of F/TAF was consistent across all populations in the clinical development program. There was a preferential profile for F/TAF-containing regimens versus STB and versus other TDF-containing regimens for multiple measures of renal and bone safety.

The overall summaries of adverse events (AEs) for E/C/F/TAF and D/C/F/TAF are shown in Table 6 and Table 7.

Adverse Events

In E/C/F/TAF clinical studies, the AE profile was generally similar in ART-naive adults, virologically suppressed adults, adults with mild to moderate renal impairment, and ART-naive adolescents (Table 6). In ART-naive adults, the most commonly reported AEs were diarrhea, nausea, headache, and upper respiratory tract infection; events that are generally consistent with those from prior studies of STB and other TVD-based regimens {21102}, {21057}. Most subjects across all studies reported at least 1 AE. The percentage of subjects reporting any AE was generally as expected for the respective study populations and associated differences between studies in exposure to study drug. A similar percentage of subjects reported any AE between treatment groups within each randomized study. Across all studies, AEs leading to study drug discontinuation were uncommon.

Five ART-naive subjects died (E/C/F/TAF 2 subjects [embolic stroke and alcohol poisoning]; STB 3 subjects [cardiac arrest, recreational drug and alcohol overdose, and acute myocardial

infarction]). Two virologically suppressed subjects in the E/C/F/TAF group of Study GS-US-292-0109 died during the study (1 subject due to septic shock and 1 due to Stage 4 lung adenocarcinoma). None of the events that led to death were considered by the investigator as related to study drug.

Both E/C/F/TAF and STB were well tolerated in ART-naive subjects (Studies GS-US-292-0104 and GS-US-292-0111), with comparably low rates of Grade 3 or 4 AEs, serious adverse events (SAEs), SAEs considered related to study drugs, and AEs leading to drug discontinuations in both treatment groups.

As expected, among virologically suppressed subjects who were stable on their treatment regimen before participating in open-label Study GS-US-292-0109, subjects who switched to E/C/F/TAF had a higher incidence of any AE considered by the investigator as related to study drug than subjects who stayed on their existing regimen (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects). Most of the AEs considered related to study drug were Grade 1 in severity. The incidences of AEs related to study drug were lower in both treatment groups in Study GS-US-292-0109 than that in other studies.

With longer exposure to study drug in the open-label extension of Study GS-US-292-0102, the AE profile for the E/C/F/TAF group was consistent with that in the randomized phase.

No cases of proximal renal tubulopathy (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy were reported for subjects who received E/C/F/TAF or D/C/F/TAF.

In the D/C/F/TAF Phase 2 Study GS-US-299-0102, the frequency and type of reported AEs were generally similar to those in ART-naive adult subjects in the E/C/F/TAF studies. The percentage of subjects reporting any AE was generally as expected for the study population (m2.7.4, Section 2.1.2).

Key Safety Endpoints

Statistically significant differences (alpha protected using the fallback procedure described in Section 5.2) favoring E/C/F/TAF over STB or TDF-containing regimens were observed at Week 48 for all key secondary safety endpoints in both ART-naive and virologically suppressed subjects: mean percentage changes from baseline in hip BMD ($p < 0.001$ for both ART-naive and virologically suppressed subjects) and spine BMD ($p < 0.001$ for both ART-naive and virologically suppressed subjects; Section 5.5), mean change from baseline in serum creatinine ($p < 0.001$ for both ART-naive and virologically suppressed subjects), treatment emergent proteinuria (ART-naive subjects, $p = 0.022$), and change from baseline in EFV-related symptom assessment composite score (virologically suppressed subjects; $p < 0.001$; m2.7.4, Section 2.1.7.1).

Table 6. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Overall Summary of Adverse Events (Safety Analysis Set)

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Subjects with Renal Impairment		ART-Naive Adolescent Subjects
	GS-US-292-0104/ GS-US-292-0111		GS-US-292-0102[a]		GS-US-292-0109		GS-US-292-0112		GS-US-292-0106
Subjects Experiencing Any	E/C/F/TAF (N=866)	STB (N=867)	E/C/F/TAF (N=112)	STB (N=58)	E/C/F/TAF (N=959)	FTC/TDF+ 3rd Agent (N=477)	Cohort 1: ART-Experienced (N=242)	Cohort 2: ART-Naive (N=6)	E/C/F/TAF (N=48)
Adverse Event	778 (89.8%)	782 (90.2%)	107 (95.5%)	57 (98.3%)	764 (79.7%)	368 (77.1%)	209 (86.4%)	5 (83.3%)	39 (81.3%)
Grade 2, 3, or 4 Adverse Event	419 (48.4%)	380 (43.8%)	72 (64.3%)	29 (50.0%)	389 (40.6%)	177 (37.1%)	114 (47.1%)	3 (50.0%)	13 (27.1%)
Grade 3 or 4 Adverse Event	71 (8.2%)	75 (8.7%)	13 (11.6%)	3 (5.2%)	61 (6.4%)	32 (6.7%)	18 (7.4%)	0	4 (8.3%)
Study-Drug-Related Adverse Event	342 (39.5%)	364 (42.0%)	43 (38.4%)	19 (32.8%)	185 (19.3%)	61 (12.8%)	62 (25.6%)	1 (16.7%)	18 (37.5%)
Grade 2, 3, or 4 Study-Drug-Related Adverse Event	84 (9.7%)	75 (8.7%)	9 (8.0%)	1 (1.7%)	46 (4.8%)	20 (4.2%)	24 (9.9%)	1 (16.7%)	2 (4.2%)
Grade 3 or 4 Study-Drug-Related Adverse Event	12 (1.4%)	9 (1.0%)	1 (0.9%)	0	3 (0.3%)	6 (1.3%)	3 (1.2%)	0	1 (2.1%)
Serious Adverse Event	70 (8.1%)	59 (6.8%)	12 (10.7%)	3 (5.2%)	42 (4.4%)	21 (4.4%)	26 (10.7%)	0	4 (8.3%)
Study-Drug-Related Serious Adverse Event	3 (0.3%)	2 (0.2%)	0	0	0	1 (0.2%)	0	0	1 (2.1%)
Adverse Event Leading to Premature Study Drug Discontinuation	8 (0.9%)	13 (1.5%)	4 (3.6%)	0	9 (0.9%)	7 (1.5%)	8 (3.3%)	0	0
Death	2 (0.2%)	3 (0.3%)	0	0	2 (0.2%)	0	0	0	0

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. The AE profile of subjects in the open-label extension was similar to the AE profile observed in the randomized phase.

Source: m2.7.4, Table 16

Table 7. GS-US-299-0102: Overall Summary of Adverse Events (Safety Analysis Set)

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

Source: m2.7.4, Table 17

In the D/C/F/TAF study, differences favoring D/C/F/TAF over DRV+COBI+TVD in the categorical distribution of the clinical BMD status adjusted for baseline status was significantly different between treatment groups at Week 48 at the hip ($p = 0.010$) and at Weeks 24 and 48 at the spine ($p = 0.019$ at Week 24; $p = 0.024$ at Week 48) m2.7.4, Section 2.1.7.2.3. Increases from baseline in mean values for serum creatinine were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group ($p = 0.053$), and proteinuria was reported for a similar percentage of subjects in each group.

Clinical Laboratory Evaluations

In the E/C/F/TAF Phase 2 and Phase 3 studies, approximately 20% of subjects across all studies had a Grade 3 or 4 laboratory abnormality, with the exception of adolescent subjects in Study GS-US-292-0106 (4 subjects, 8.3%). Among the most common Grade 3 or 4 laboratory abnormalities across studies were creatine kinase, fasting low-density lipoprotein (LDL) (Section 5.8), and lipase. The results from the D/C/F/TAF Phase 2 study were consistent with those from the E/C/F/TAF studies in ART-naive subjects.

In ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111, there were no clinically relevant changes from baseline within groups, or differences between the treatment groups in median values for hematology or clinical chemistry parameters, and all median values were within normal ranges were reported. The majority of subjects had at least 1 laboratory abnormality, the majority of which were Grade 1 or 2. Grade 3 or 4 creatine kinase abnormalities (E/C/F/TAF 6.8%, 59 subjects; STB 5.7%, 49 subjects) occurred at a variety of time points, were not consistently present for individual subjects, and no case of clinical rhabdomyolysis was

reported. The incidence of Grade 3 or 4 creatine kinase abnormalities was similar across the 2 treatment groups in Study GS-US-292-0109.

Among virologically suppressed subjects in Study GS-US-292-0109, a lower percentage of subjects in the E/C/F/TAF group compared with the FTC/TDF+3rd Agent group had Grade 3 or 4 abnormalities (E/C/F/TAF 19.8%, FTC/TDF+3rd Agent 25.4%), predominantly driven by the higher incidence of Grade 3 or Grade 4 hyperbilirubinemia in the FTC/TDF+3rd Agent group (E/C/F/TAF 0.1%, 1 of 959 subjects; FTC/TDF+3rd Agent 14.3%, 68 of 477 subjects). Almost all cases (66 of 68) of Grade 3 or 4 hyperbilirubinemia in the FTC/TDF+3rd Agent group occurred in subjects taking ATV.

Among subjects with mild to moderate renal impairment in Study GS-US-292-0112, Grade 3 or 4 hypercholesterolemia, serum glucose (nonfasting, hyperglycemia), and urine glucose (glycosuria) were reported in a higher percentage of subjects than in other studies.

Lipase testing was only performed in subjects with serum amylase > 1.5 × upper limit of normal (ULN) and the overall numbers of subjects with Grade 3 or 4 lipase abnormalities was low.

5.4. Analysis of Adverse Drug Reactions

The key data source supporting the Adverse Reactions section of the F/TAF Prescribing Information is the Week 48 pooled data from the pivotal E/C/F/TAF Phase 3 studies in ART-naive subjects, Studies GS-US-292-0104 and GS-US-292-0111. Supporting data are also provided from studies of virologically suppressed adults switching treatment to E/C/F/TAF (Study GS-US-292-0109), adults with mild to moderate renal impairment (GS-US-292-0112), and ART-naive adolescents (GS-US-292-0106).

Adverse Drug Reactions

In Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects who discontinued study drug due to AEs, regardless of severity, were 0.9% (8 subjects) in the E/C/F/TAF group and 1.5% (13 subjects) in the STB group. The only AE (all Grades) considered related to study drug by the investigator that was reported in ≥ 10% of subjects in the E/C/F/TAF group was nausea (10.4%, 90 subjects).

Table 1 of the proposed F/TAF Prescribing Information, entitled *Adverse Reactions (Grades 2-4) Reported in ≥ 1% of HIV-1 Infected Treatment Naïve Adults in Any Treatment Arm in Studies 104 and 111 (Week 48 analysis)*, is based on all Grade 2 to 4 AEs considered related to study drug by the investigator and reported in ≥ 1% of subjects in either treatment group in the pooled dataset from Studies GS-US-292-0104 and GS-US-292-0111 (Table 8).

Five AEs considered related to study drug by the investigator that occurred less frequently than 1% (for Grades 2-4) in either treatment group in Studies GS-US-292-0104 and GS-US-292-0111 are also included as ADRs for F/TAF under Table 1 of the proposed Prescribing Information based on an assessment for a potential causal relationship: vomiting, abdominal pain, dyspepsia, flatulence, and rash.

Table 8. GS-US-292-0104 and GS-US-292-0111: Adverse Events Related to Study Drug (Grades 2-4) Reported in ≥ 1% of Subjects in Either Treatment Group (Week 48 analysis)

Adverse Events by System Organ Class and Preferred Term	E/C/F/TAF (N=866)	STB (N=867)
Gastrointestinal disorders		
Diarrhoea	11 (1.3%)	3 (0.3%)
Nausea	8 (0.9%)	11 (1.3%)
General disorders and administration site conditions		
Fatigue	9 (1.0%)	5 (0.6%)
Nervous system disorders		
Headache	9 (1.0%)	8 (0.9%)

Source: E/C/F/TAF ISS, Table 12

No additional adverse drug reactions (ADRs) to F/TAF were identified through Week 48 in virologically suppressed subjects (Study GS-US-292-0109) who switched from a TDF-containing regimen to E/C/F/TAF. In Study GS-US-292-0109, there were no AEs (Grades 2-4) considered related to study drug by the investigator that were reported in ≥ 1% of subjects in the E/C/F/TAF group.

Based on the data presented in m2.7.4, the safety profile of F/TAF in subjects with mild to moderate renal impairment from Study GS-US-292-0112 is similar to that in subjects with normal renal function, and the safety profile of F/TAF in ART-naive adolescent subjects aged 12 to < 18 years from Study GS-US-292-0106 is similar to that in adults.

Laboratory Abnormalities

The following Grade 3 or 4 laboratory abnormalities occurred in ≥ 2% of subjects in the E/C/F/TAF group in the pooled Week 48 dataset from Studies GS-US-292-0104 and GS-US-292-0111: creatine kinase (6.8%, 59 subjects); fasting LDL (5.0%, 42 subjects). For the creatine kinase abnormalities, there was no consistency in the timing of occurrences or degree of creatine kinase elevation and most elevations did not persist with continuation of study drug. Creatine kinase elevations were also noted at baseline prior to study drug initiation for some subjects. There were no cases of clinical rhabdomyolysis reported.

In the E/C/F/TAF group from Studies GS-US-292-0104 and GS-US-292-0111, 4 of 90 subjects (4.4%) who experienced lipase abnormalities had Grade 3 or 4 lipase abnormalities. Given that lipase testing was only performed in subjects with serum amylase > 1.5 × ULN and the low number of subjects with Grade 3 or 4 lipase abnormalities (4 subjects, all Grade 3), lipase abnormalities were not proposed for inclusion in the F/TAF Prescribing Information.

Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function (Study GS-US-216-0121). In the pooled dataset from Studies GS-US-292-0104 and GS-US-292-0111, increases in serum creatinine were observed by Week 2 for each treatment group, and remained stable through Week 48. Mean (SD) changes from baseline in the E/C/F/TAF group were 0.06 (0.105) mg/dL at Week 2 and 0.08 (0.124) mg/dL at Week 48.

Serum Lipids and Other

Mean changes from baseline in serum lipids from Studies GS-US-292-0104 and GS-US-292-0111 are presented in Table 3 of the proposed F/TAF Prescribing Information, entitled *Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving [TRADENAME] or STRIBILD in Studies 104 and 111* (m2.7.4, Section 3.3). In the E/C/F/TAF group, 4.4% of subjects (n = 32) were taking lipid modifying medications at study entry, and 3.6% of subjects (n = 31) initiated treatment during the study (E/C/F/TAF ISS, Tables Req6742.3.1 and Req6742.3.2). In the STB group, 5.0% of subjects (n = 43) were taking lipid modifying medications at study entry, and 2.9% of subjects (n = 25) initiated treatment during the study.

Comparison of alpha-protected bone and renal safety between treatment groups were secondary endpoints for the pivotal studies in ART-naive subjects and for the randomized study in virologically suppressed subjects. Results for these endpoints did not support their inclusion as ADRs for F/TAF. Thus, bone and renal safety data will be presented in the clinical trial experience section of the proposed F/TAF Prescribing Information.

5.5. Bone Safety

HIV-infected adults are at risk of low BMD, with up to 60% prevalence of osteopenia and up to 15% prevalence of osteoporosis {29584}. The initiation of treatment in ART-naive adults is associated with a decrease in BMD in the first 12 to 24 months of use {16915}, {14253}, {16604}, {14194}. The observed changes are similar whether the regimen includes an NNRTI, an INSTI, or a PI {10655}, {17561}; however, the decrease in BMD appears to be greater with TDF than with other NRTIs {11882}, {17735}, {29368}, {18854}.

HIV-1 treatment with TDF-containing regimens represents a concern for pediatric patients who initiate lifelong HIV therapy, particularly those in the pre- or peri-pubertal stage and those building bone mass. These concerns are illustrated in the DHHS guidelines for the treatment of HIV infection in children and adolescents which recommends against the use of TDF-containing regimens until Tanner stage 4 of development is reached {32519}.

As expected, decreases in hip and bone BMD were seen after initiation of E/C/F/TAF in ART-naive adults. The magnitude of these decreases were similar to those noted after initiation of treatment with other regimens including ABC and NRTI-sparing RAL and LPV {16658}, {25126}, {18370}, {27168}.

The totality of results from bone safety analyses in HIV-infected adult and adolescent subjects across the clinical development program demonstrated that treatment with F/TAF is associated

with a preferential bone safety profile compared with STB or with TDF-containing regimens, with statistically significant differences in multiple tests of bone metabolism. Specifically, the following results were noted (m2.7.4, Section 2.1.7.2):

- For ART-naive adults, significantly less BMD change from baseline at both the hip and spine was observed after treatment with E/C/F/TAF compared with STB (Table 9, Figure 1 [spine]). Compared with subjects receiving STB, fewer subjects in the E/C/F/TAF group had a > 3% decrease from baseline in BMD; more subjects in the E/C/F/TAF group had a > 3% increase from baseline in BMD. In addition, fewer subjects in the E/C/F/TAF group had worsening BMD clinical status from baseline (normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis).

- Observations in the Phase 2 Study GS-US-299-0102 were consistent with the E/C/F/TAF studies in ART-naive subjects. Decreases from baseline in BMD at the hip or spine were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group ($p < 0.001$ for the differences between the 2 groups in mean percentage changes from baseline in hip BMD at Weeks 24 and 48; $p < 0.001$ for the differences between the 2 groups in mean percentage changes from baseline in spine BMD at Week 24 and $p = 0.003$ at Week 48).

- For virologically suppressed adults who switched to E/C/F/TAF from a TDF-based regimen, improvements in both hip and spine BMD were observed (Table 10). Compared with subjects receiving TDF, fewer subjects in the E/C/F/TAF group had a > 3% decrease from baseline in BMD; more subjects in the E/C/F/TAF group had a > 3% increase from baseline in BMD. In addition, a higher percentage in the E/C/F/TAF group than the TDF group had an improvement in BMD clinical status, and a lower percentage of subjects in the E/C/F/TAF group than the TDF group had worsening BMD clinical status.

- Similar improvements in BMD were noted in virologically suppressed adults with renal impairment who switched to E/C/F/TAF from a TDF-based regimen, an older study population with a median age of 58 years. Moreover, minimal changes or small increases were observed in virologically suppressed subjects with renal impairment who switched to E/C/F/TAF from a non-TDF-based regimen, demonstrating the minimal effect of E/C/F/TAF itself on BMD.

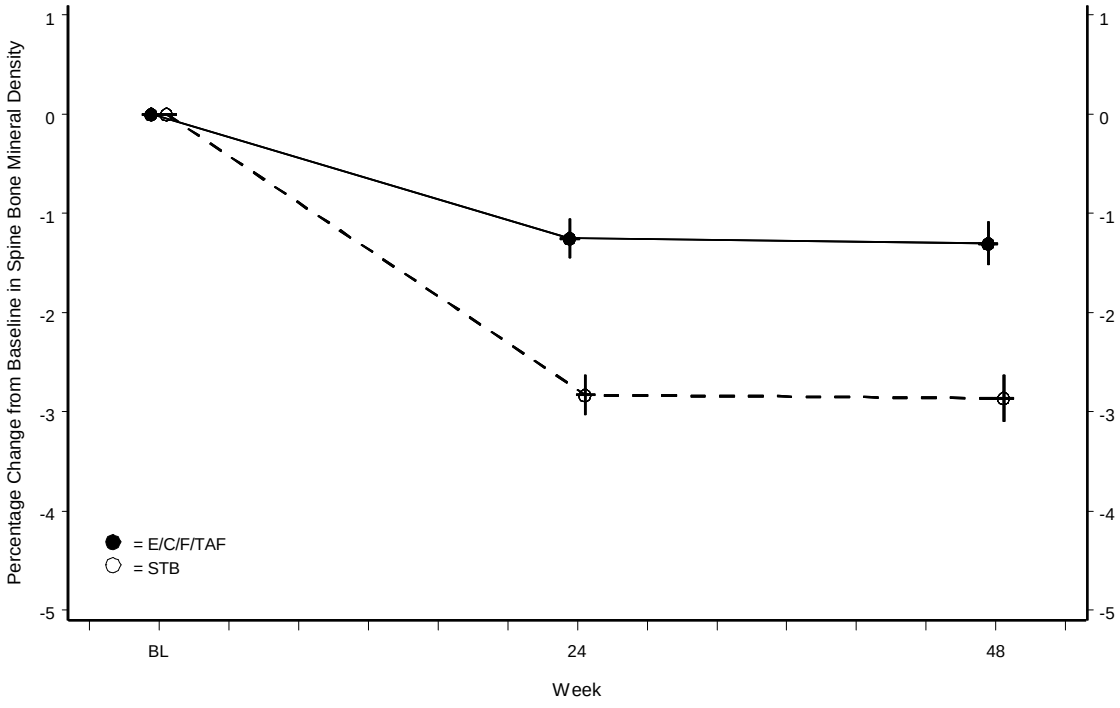
- In ART-naive adolescent subjects, treatment with E/C/F/TAF resulted in minimal changes from baseline in height-age adjusted spine (mean [SD] change: −0.08 [0.391]) and total body less head (TBLH) (mean [SD] change: −0.10 [0.256]) BMD Z-scores at Week 24. Results are supported by analyses in a subset of ART-naive adult subjects aged 18 to 25 years (from Studies GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111) who, like children and adolescents, have not yet achieved peak bone mass. Mean (SD) percentage decreases from baseline at Week 48 in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$). These results suggest that the improved BMD profile of E/C/F/TAF relative to STB observed in adults is applicable to adolescents who are undergoing pubertal development, rapid skeletal growth, and active bone mineralization.

- Across comparative studies, reduced bone turnover was observed with E/C/F/TAF compared with STB or TDF-regimens, as shown by less change in parathyroid hormone (PTH), type I collagen C telopeptide (C-telopeptide), and procollagen type 1 N-terminal propeptide (P1NP). Subjects who switched to E/C/F/TAF from a TDF-based regimen experienced a decrease from baseline in serum levels of the P1NP and PTH.

In a cross-study comparison of E/C/F/TAF (Study GS-US-292-0106) and STB in adolescents (Study GS-US-236-0112), there was no notable change from baseline in height- and age-adjusted spine BMD Z-score in the E/C/F/TAF group, compared with a decrease from baseline in the STB group (Z-score calculated using the Zemel method,
Integrated Pediatric Report BMD Addendum). At Week 24, the mean (SD) changes from baseline were as follows: E/C/F/TAF, −0.04 (0.422); STB, −0.37 (0.461). The difference between groups (E/C/F/TAF − STB) was as follows: analysis of variance (ANOVA) 0.33, 95% CI (0.05, 0.60), p = 0.020; analysis of covariance (ANCOVA) 0.24, 95% CI (−0.04, 0.53), p = 0.087. The results suggest no impact on bone mineralization relative to the reference population for E/C/F/TAF, but decreased mineralization relative to the reference population for the TDF-containing regimen.

These bone safety results demonstrate that treatment with F/TAF-containing regimens is associated with an improved bone profile, particularly relative to TDF-based regimens. This improved bone profile may benefit all HIV-infected patients, including those with risk factors for osteoporotic disease, including women and older patients.

Figure 1. **GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set)**



E/C/F/TAF (n=):	845	797	784
STB (n=):	850	816	773

BL = Baseline.
Only subjects with nonmissing spine BMD for the baseline visit were included in spine DXA analysis set.

Data Extracted: s292-0104: CRF,DXA Data: [redacted], Lab Data: [redacted], s292-0111: CRF,DXA Data: [redacted], Lab Data: [redacted]
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out [redacted]

Source: E/C/F/TAF ISS, Figure 3.2.2

Table 9. GS-US-292-0104 and GS-US-292-0111: Key Measures of BMD (Week 48 Analysis)

	E/C/F/TAF (N = 866)	STB (N = 867)	E/C/F/TAF vs STB[a]	
			p-value	Difference in LSM (95% CI)
Hip DXA Analysis	**(N = 780)**	**(N = 767)**		
Mean (SD) % Change in BMD	−0.657 (3.2646)	−2.948 (3.4095)	p < 0.001	2.291 (1.958 , 2.624)
Subjects with Categorical Change (%):				
> 3% Decrease in BMD	17%	50%	--	--
> 3% Increase in BMD	7%	3%		
Lumbar Spine DXA Analysis	**(N = 784)**	**(N = 773)**		
Mean % Change in BMD	−1.301 (3.0823)	−2.862 (3.2460)	p < 0.001	1.561 (1.247 , 1.876)
Subjects with Categorical Change (%):				
> 3% Decrease in BMD	27%	46%	--	--
> 3% Increase in BMD	7%	3%		

a P-values, difference in least squares means, and its 95% CI were from the analysis of variance (ANOVA) model including treatment as fixed effect.

Source: E/C/F/TAF ISS, Tables 20.1.2, 20.2.2, 22.1, and 22.2

Table 10. GS-US-292-0109: Key Measures of BMD (Week 48 Analysis)

	E/C/F/TAF (N = 902)	FTC/TDF+3rd Agent (N = 452)	E/C/F/TAF vs STB[a]	
			p-value	Difference in LSM (95% CI)
Hip DXA Analysis	**(N = 733)**	**(N = 350)**		
Mean Percent Change in BMD	1.949 (2.9956)	−0.136 (2.9890)	p < 0.001	2.078 (1.697 , 2.459)
Subjects with Categorical Change (%):				
>3% Decrease in BMD	2%	11%	--	--
>3% Increase in BMD	25%	9%		
Lumbar Spine DXA Analysis	**(N = 742)**	**(N = 356)**		
Mean Percent Change in BMD	1.861 (3.0889)	−0.110 (3.7415)	p < 0.001	1.970 (1.551 , 2.390)
Subjects with Categorical Change (%):				
>3% Decrease in BMD	6%	17%	--	--
>3% Increase in BMD	34%	14%		

a P-values, difference in least squares means, and its 95% CI were from the analysis of variance (ANOVA) model including treatment as fixed effect.

Source: GS-US-292-0109, Section 15.1, Tables 40.2 and 41.2

5.6. Renal Safety

Treatment with TDF in HIV-infected patients has been associated with nephrotoxicity, including an elevated risk of proteinuria and decline in kidney function, as well as proximal tubular dysfunction in some subjects {19884},{32519}, {22018}. Because of these associations and that between significant proteinuria and morbidity/mortality in the HIV-infected population {4195}, {17105}, {6964}, renal events and renal laboratory parameters were comprehensively evaluated for F/TAF-containing regimens.

Standard renal assessments of changes in serum creatinine, eGFR, and emergence of proteinuria (by dipstick) were complemented by more sensitive evaluations of tubular dysfunction, ie, quantitative assessment of proteinuria (urine protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR], urine retinol binding protein [RBP] to creatinine ratio, and beta-2-microglobulin [B2M] to creatinine ratio).

As expected, increases in serum creatinine were seen after initiation of E/C/F/TAF in ART-naive subjects. The magnitude of these increases was similar to those noted after initiation of treatment with other regimens including RTV and RPV {25886}, {18038}, {19105}, {28739}.

The totality of results from renal assessments in HIV-infected adult and adolescent subjects across the clinical development program demonstrated that treatment with F/TAF is associated with a preferential renal safety profile compared with STB or with TDF-containing regimens, with statistically significant differences in multiple tests of renal function. Specifically, the following results were noted (m2.7.4, Sections 2.1.5.2 and 2.1.5.3):

- In ART-naive adults, treatment with E/C/F/TAF was associated with less change in serum creatinine and eGFR and less proteinuria (by dipstick) compared with treatment with STB. In addition, decreases from baseline in proteinuria (UPCR) and albuminuria (UACR) were noted with E/C/F/TAF, while increases from baseline in UPCR and UACR were seen with STB. Similarly, treatment with D/C/F/TAF was associated with less change in serum creatinine and eGFR compared with treatment with DRV+COBI+TVD.

- For virologically suppressed adults who switched to E/C/F/TAF from a TDF-based regimen, there were minimal changes in serum creatinine and eGFR, and there were decreases in proteinuria and tubular proteinuria (RBP and B2M to creatinine ratios) (by dipstick). Decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria also occurred as soon as 1 week after switch to E/C/F/TAF from a TDF-containing regimen in renally impaired subjects, strongly suggesting a reduction in TFV-associated toxicity. Renally impaired subjects who switched from a non-TDF containing regimen had a mild increase in serum creatinine but had significant improvements in UPCR, UACR, and tubular proteinuria.

- An iohexol substudy of adult subjects with stable, mild to moderate renal impairment (eGFR ≥ 30 mL/min), subjects who switched to E/C/F/TAF had no change in aGFR through 24 weeks, regardless of baseline $eGFR_{CG}$ or pre-switch TDF use.

- In ART-naive adolescent subjects, changes in serum creatinine and eGFR calculated using the Schwartz formula were seen as early as Week 1 and subsequently stabilized and were nonprogressive. These changes are consistent with the known inhibitory effect of COBI on renal tubular creatinine secretion, which results in an increase in serum creatinine and a decrease in eGFR without an effect on aGFR.

- No cases of proximal renal tubulopathy (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy were reported for subjects who received E/C/F/TAF or D/C/F/TAF.

In a cross-study comparison of E/C/F/TAF (Study GS-US-292-0106) and STB in adolescents (GS-US-236-0112), the magnitude of change of serum creatinine and eGFR (by Schwartz) at Week 24 was similar in both E/C/F/TAF and STB groups (Integrated Pediatric Report). These changes were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration. Consistent with results in ART-naive adults, postbaseline incidence of proteinuria (by dipstick) was lower for subjects in the E/C/F/TAF group compared with the STB group (20.8%, 10 subjects vs 51.5%, 17 subjects, respectively).

Overall, across studies in different patient populations, there was a preferential renal safety profile for F/TAF, likely a result of the decrease in systemic TFV exposure relative to that with TDF-containing regimens. The extensive and consistent renal safety data support use of F/TAF without dose adjustment in HIV-infected patients with eGFR ≥ 30 mL/min.

5.7. Ocular Safety

Posterior uveitis was observed in a nonclinical study with dogs treated at a high dose of TAF, which was at 3.7- and 17-fold higher exposure to TAF and TFV, respectively, than that observed in human subjects administered a 25-mg dose (m2.4, Section 4.2.2.3). Therefore, in the E/C/F/TAF clinical program, analyses were conducted to evaluate the system organ class (SOC) term eye disorders to detect AEs where the symptoms reported may potentially represent posterior uveitis.

There have been no reports of posterior uveitis in human clinical studies to date.

Overall, in the E/C/F/TAF studies, similar incidence between treatment groups for events potentially related to uveitis, other eye disorders and conjunctivitis (m2.7.4, Section 2.1.7.4). Clinically, none of the AEs potentially related to uveitis in adults in the E/C/F/TAF groups were considered representative of an actual case of posterior uveitis. In an ophthalmologic substudy conducted as part of Study GS-US-292-0109, no subjects had fundoscopic findings consistent with uveitis. One adolescent subject treated with E/C/F/TAF developed intermediate uveitis. Symptoms and fundoscopic examination findings improved significantly with eye drops, and oral steroid and antihistamine therapy while treatment with E/C/F/TAF continued. In the D/C/F/TAF Phase 2 study, 6 subjects (5.8%) receiving D/C/F/TAF had nonserious AEs in the eye disorders SOC compared with none of the subjects in the DRV+COBI+TVD group. There were no AEs of uveitis during the study. No eye disorder resulted in discontinuation of study drug.

The general lack of eye findings in Phase 3 clinical studies indicates that the nonclinical finding in dogs is not of clinical relevance.

5.8. Fasting Glucose and Lipid Parameters

For ART-naive and virologically suppressed subjects in the randomized studies, greater increases in the fasting lipid parameters total cholesterol, direct LDL, high-density lipoprotein (HDL), total cholesterol to HDL ratio, triglycerides, and glucose were observed in subjects treated with E/C/F/TAF compared with those treated with a TDF-comparator (m2.7.4, Section 3.1). Higher percentages of subjects treated with E/C/F/TAF than those treated with a TDF-based comparator had categorical changes from baseline in the National Cholesterol Education Program (NCEP) ATP III lipid classifications; these categorical changes were clinically irrelevant and consistent with data from studies of ABC and other non-TDF-based regimens in ART-naive patients {15975} {11417}, {15585}, {18679}, {25972}, {26007}, {14803}. In the comparative E/C/F/TAF studies, the percentages of subjects who received concomitant lipid-modifying agents were comparable between treatment groups. A similar trend for fasting lipid results was seen in ART-naive adolescents who received E/C/F/TAF.

Changes in lipid parameters in the D/C/F/TAF Phase 2 study were generally consistent with those of the E/C/F/TAF studies in ART-naive subjects.

In renally impaired subjects, median changes from baseline in metabolic laboratory parameters demonstrated a trend toward increase in all parameters for subjects who switched to E/C/F/TAF from a TDF-containing regimen. Importantly, a trend toward a decrease in most parameters was seen for subjects who switched to E/C/F/TAF from a non-TDF-containing regimen, ie, suggesting that there is no lipidic effect associated with TAF.

The mechanism underlying the differences in metabolic laboratory parameters observed between treatment with E/C/F/TAF compared with TDF-containing regimens (including STB) is unknown but may be associated with the known lipid-lowering effect of TFV {27870}, {16173}, and the previously discussed markedly lower plasma concentrations of TFV in subjects receiving E/C/F/TAF.

5.9. Safety in Special Groups and Situations

Safety information pertinent to the use of F/TAF in special groups and situations is described in m2.7.4, Section 5, with appropriate information included in the proposed prescribing information. Key findings are as follows:

- The AE profile for subjects receiving F/TAF was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count. The safety profile for F/TAF is consistent with that for adults in both adolescents and in the elderly. Guidance is provided in the prescribing information that the F/TAF FDC should not be administered to patients under the age of 12 years or weighing < 35 kg.

- In Study GS-US-292-0112, subjects with $eGFR_{CG}$ < 50 mL/min had a similar safety profile compared with subjects with $eGFR_{CG} \geq 50$ mL/min.

- Based on available PK data (Section 3.5.2), no dose adjustment of F/TAF is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B). Treatment with F/TAF is not recommended for use in patients with severe hepatic impairment.

- Subjects who were hepatitis C antibody positive were excluded from all Phase 2 and Phase 3 studies of E/C/F/TAF. The exclusion criteria for Study GS-US-292-0104 were updated in Amendment 1 of the protocol to exclude subjects with positive HBV surface antigen. All of the other Phase 2 and Phase 3 studies of E/C/F/TAF excluded subjects with positive HBV surface antigen. Discontinuation of therapy with F/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis.

- No adequate and well-controlled studies of F/TAF or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of FTC or TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. F/TAF should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. F/TAF is assigned to Pregnancy Category B. No clinically relevant concerns are apparent from review of available pregnancy data in clinical studies.

- Because of the potential for HIV transmission, the potential for serious adverse reactions, and the risk for developing viral resistance to FTC in nursing infants, mothers should be instructed not to breastfeed if they are receiving F/TAF.

- No new safety issues have been identified regarding overdose.

5.10. Safety Discussion and Conclusions

The safety and tolerability profile of the F/TAF FDC is supported by a safety database, using Phase 2 and Phase 3 E/C/F/TAF studies and a Phase 2 D/C/F/TAF study, which is robust in terms of numbers of subjects receiving the recommended dose of each component and the length of treatment.

The proposed prescribing information for F/TAF is based on the Phase 3 E/C/F/TAF studies and, therefore, these data are discussed here.

Treatment with F/TAF was well tolerated across all patient populations evaluated, as demonstrated by the low overall incidences of SAEs considered related to drug or study drug discontinuation due to AEs. The most commonly reported AEs were diarrhea, nausea, and headache.

The AE profile for subjects receiving F/TAF was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count.

Treatment with F/TAF also demonstrated a preferential bone safety profile, as compared with TDF/STB, with statistically significant differences in multiple tests of bone metabolism. Specifically, the following results were noted:

- For ART-naive adults, E/C/F/TAF was associated with less change in BMD at both the hip and spine compared with STB. Fewer subjects in the E/C/F/TAF group had a > 3% decrease from baseline in hip and spine BMD; more subjects had a > 3% increase from baseline in hip and spine BMD; and fewer subjects with worsening hip and spine BMD clinical status from baseline compared with STB.

- For virologically suppressed adults, E/C/F/TAF was associated improvements in BMD compared with TDF-based regimens. Fewer subjects in the E/C/F/TAF group had a > 3% decrease from baseline in hip and spine BMD; more subjects had a > 3% increase from baseline in hip and spine BMD; more subjects with an improvement in hip and spine BMD clinical status; and fewer subjects with worsening hip and spine BMD clinical status from baseline compared with TDF-based regimens.

- Moreover, minimal changes or small increases in BMD were observed in virologically suppressed adults with renal impairment who switched to E/C/F/TAF from a non-TDF-based regimen, demonstrating the minimal effect of E/C/F/TAF itself on BMD.

- In ART-naive adolescent subjects, treatment with E/C/F/TAF resulted in minimal changes from baseline in height-age adjusted spine and TBLH BMD Z-scores at Week 24, demonstrating that E/C/F/TAF had no impact bone mineralization. In a cross-study comparison of E/C/F/TAF and STB in adolescents, there was no notable change from baseline in height- and age-adjusted spine BMD Z-score calculated using the Zemel method in the E/C/F/TAF group, compared with a decrease from baseline in the STB group.

- Across comparative studies, reduced bone turnover was observed with E/C/F/TAF compared with STB or TDF-regimens, as shown by less change in PTH, C-telopeptide, and P1NP.

These bone safety results demonstrate that exposure to F/TAF is associated with an improved bone safety profile, particularly relative to TDF-based regimens. This improved bone safety profile may benefit all HIV-infected patients, including those with risk factors for osteoporotic disease, including women and older patients. Compared with TDF-based regimens, treatment with E/C/F/TAF does not have a negative impact on bone health in HIV-infected adolescents, who are undergoing pubertal development, rapid skeletal growth, and active bone mineralization.

Treatment with the E/C/F/TAF FDC tablet also demonstrated a preferential renal safety profile, as compared with a TDF-based regimen (including STB), with statistically significant differences in multiple tests of renal function. Specifically, the following results were noted:

- In ART-naive adults and compared with STB, E/C/F/TAF was associated with less change in serum creatinine and eGFR and less proteinuria (by dipstick), and decreases from baseline in proteinuria (UPCR) and albuminuria (UACR) (versus increases in the STB group).

- For virologically suppressed adults and compared with a TDF-based regimen, E/C/F/TAF was associated with decreases or minimal changes in serum creatinine, increases in eGFR, decreases in proteinuria (by dipstick), and decreases from baseline in proteinuria (UPCR) and albuminuria (UACR) as soon as 1 week after switch, and no effect on aGFR.

- In ART-naive adolescent subjects, changes in serum creatinine and eGFR were consistent with the known inhibitory effect of COBI on renal tubular creatinine secretion.

- No cases of proximal renal tubulopathy (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy were reported for subjects who received E/C/F/TAF.

These renal safety results support standard clinical practice in monitoring for renal laboratory test abnormalities with F/TAF.

No findings related to ocular safety demonstrated any increased risk of uveitis associated with F/TAF compared with that with TDF-containing regimens.

Greater increases in the fasting lipid parameters total cholesterol, direct LDL, HDL, total cholesterol to HDL ratio, triglycerides, and glucose were seen in subjects treated with E/C/F/TAF compared with those treated with TDF-based regimens. These differences are considered to be associated with the lipid-lowering effect of TFV, and markedly lower plasma concentrations of TFV with E/C/F/TAF compared with TDF-based regimens. Importantly, a trend toward a decrease in most metabolic laboratory parameters was seen for subjects who switched to E/C/F/TAF from a non-TDF-containing regimen, ie, suggesting that there is no lipidic effect associated with TAF. Treatment with F/TAF is not considered to have an untoward effect on fasting glucose and lipid parameters.

Conclusions in relation to the use of F/TAF in special populations are as follows:

- The safety profile for F/TAF is consistent with that for adults in both adolescents and in the elderly. The F/TAF FDC should not be administered to patients under the age of 12 years or weighing less than 35 kg.

- Subjects with $eGFR_{CG} < 50$ mL/min had a similar safety profile compared with subjects with $eGFR_{CG} \geq 50$ mL/min; therefore, F/TAF can be used without dose adjustment for renally impaired patients with eGFR as low as 30 mL/min.

- F/TAF can be used without dose adjustment in patients with mild to moderate hepatic impairment. Treatment with F/TAF is not recommended for use in patients with severe hepatic impairment.

- The efficacy and safety of F/TAF have not been established in HIV-infected patients coinfected with HBV or HCV. Discontinuation of therapy with F/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis.

- The F/TAF FDC tablet should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

- Mothers should be instructed not to breastfeed if they are receiving F/TAF.

In conclusion, exposure to F/TAF has demonstrated an acceptable safety profile in HIV-infected subjects, along with a tolerability profile that offers renal and bone advantages compared with TDF-based regimens.

6. BENEFITS AND RISKS CONCLUSIONS

F/TAF FDC is a novel N(t)RTI backbone that can be used in combination with other ARV agents for the treatment of HIV infection. TAF is more stable in plasma than TDF. It achieves higher intracellular levels of the active phosphorylated metabolite TFV-DP and > 90% lower circulating levels of TFV relative to TDF. Therefore, the distinct metabolism of TAF offers an improved clinical profile compared with TDF. Therapy with the F/TAF FDC should be initiated by a physician experienced in the management of HIV infection. The following considerations support a favorable benefit:risk profile for the F/TAF FDC for the treatment of HIV-infected patients.

6.1. Benefits

For an individual patient living with HIV infection, the success of potent ART is based on many factors, including tolerability, convenience, adherence, resistance barrier, aging, and non-AIDS comorbidities. Non-AIDS comorbidities are increasingly accountable for morbidity and mortality. Consequently, clinical attention has become focused on the optimization of regimens and the development of novel therapies that address these critical factors {29705}. In addition, there remains a significant medical need for new safe and effective therapies for the treatment of pediatric patients, including adolescents.

F/TAF FDC tablets have many benefits for patients living with HIV infection including the following:

- **F/TAF is a Novel N(t)RTI Backbone that is Highly Effective in ART-Naive, Virologically Suppressed, and Renally Impaired Adults**

Treatment with F/TAF-containing regimens has demonstrated potent and durable ARV activity in 2 Phase 2 studies (Studies GS-US-292-0102 and GS-US-299-0102), and 4 Phase 3 studies (Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, and GS-US-292-0112). Using the FDA snapshot algorithm at Week 48, E/C/F/TAF was noninferior to standard of care based regimens in ART-naive and virologically suppressed patients. Results for virologic outcomes were consistent across multiple treatment populations and were supported by several sensitivity analyses. Immunologic benefits of treatment were demonstrated by increases in CD4 cell counts.

The virologic success rates at Week 48 in the pivotal studies in ART-naive subjects were the highest seen in clinical trials in ART-naive HIV-infected adult subjects, demonstrating potent antiviral efficacy of an F/TAF-containing regimen against a highly active comparator.

Efficacy analyses in subgroups revealed no meaningful differences in virologic success, supporting the F/TAF FDC as an effective treatment for the treatment of HIV-1 infection regardless of demographics and disease baseline characteristics.

- **F/TAF is Associated with a Low Frequency of Resistance Development**

The frequency of resistance development in subjects taking F/TAF-containing regimens was very low and comparable with that of comparator groups.

- **F/TAF is Well Tolerated in a Broad Spectrum of Patients**

Treatment with an F/TAF-containing regimen was well tolerated across a broad range of patient populations with different prior treatment paradigms (ART-naive or virologically suppressed), various degrees of renal function (normal function to moderate renal impairment), and a broad range of ages (12 through > 80 years), as demonstrated by the low overall incidences of SAEs considered related to study drug, or study drug discontinuation due to AEs. The most commonly reported adverse reactions for an F/TAF-containing FDC were diarrhea, headache, fatigue, and nausea.

- **F/TAF has an Improved Bone and Renal Safety Profile Compared with TDF-Containing Regimens**

Treatment with an F/TAF-containing regimen was associated with an improved bone safety profile, as compared with TDF-containing regimens. Specifically, treatment with F/TAF-containing regimens resulted in less change in BMD at both the hip and spine for ART-naive subjects, and improvements in BMD for subjects who switched from a TDF-based regimen. Patients with HIV have increased risk for bone disease and this improved bone profile represents a clinically meaningful advancement in therapeutic options, particularly for patients with other risks for osteoporotic bone disease, for patients aged more than 50 years, and for adolescents.

Treatment with F/TAF-containing regimens is associated with an improved renal safety profile, as compared with TDF-containing regimens. Specifically, treatment with F/TAF-containing regimens resulted in less change in serum creatinine for ART-naive subjects compared with STB and a reduction in serum creatinine levels for subjects who switched from a TDF-based regimen. Treatment with F/TAF-containing regimens is also associated with less proteinuria and less renal tubular proteinuria for ART-naive subjects compared with STB, and improvements in these renal protein parameters in subjects who switched from a TDF-based regimen.

- **F/TAF Maintains Virologic Suppression in Adult Patients with Mild to Moderate Renal Impairment, and Results in Improvements in Renal Function for Those who Switch from a TDF- Containing Regimen**

F/TAF offers an alternative, efficacious N(t)RTI backbone for subjects with baseline $eGFR_{CG}$ 30 to 69 mL/min. Multiple assessments of renal function in this population indicate that significant improvements in renal function occur as soon as 1 week after switch to an F/TAF-containing regimen and persist through 24 and/or 48 weeks. These included significant improvements in proteinuria, albuminuria, and tubular proteinuria. In addition, the safety profile of F/TAF was comparable for subjects with $eGFR_{CG} < 50$ mL/min or $eGFR_{CG} \geq 50$ mL/min. These data support the proposed recommendation that no dose adjustment of F/TAF is required in patients with $eGFR_{CG}$ 30 to 50 mL/min.

- **F/TAF has Potent Efficacy in ART-Naive Adolescents, with a Renal Safety Profile Consistent with that in Adults, and No Impact on Bone Mineralization Relative to a Reference Population.**

Based on PK analyses, the same proposed doses of F/TAF for adolescents as for adults are appropriate. Treatment with an F/TAF-containing regimen demonstrated potent efficacy, robust immunological response, and tolerability similar to results from studies in ART-naive adults. The lack of notable changes from baseline in height-age adjusted spine and TBLH BMD Z scores indicates that subjects mineralized bone at rates consistent with those of the reference population.

6.2. Risks

The clinical safety database is robust and includes data originating from the individual components of the F/TAF FDC as well as an in-depth and comprehensive clinical development program conducted in a broad range of HIV-infected subjects, including those who are ART-naive, virologically suppressed, or renally impaired, and adolescents.

Treatment with an F/TAF-containing regimen was well tolerated across all patient populations evaluated.

The F/TAF FDC may be used without dose adjustment in patients with estimated creatinine clearance greater than or equal to 30 mL/min. Treatment with F/TAF should not be initiated in patients with estimated creatinine clearance below 30 mL/min.

The F/TAF FDC may be used without dose adjustment in patients with mild or moderate hepatic impairment, but is not recommended for use in patients with severe hepatic impairment.

The efficacy and safety of F/TAF have not been established in HIV-infected patients coinfected with HBV or HCV. Discontinuation of therapy with F/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis.

The F/TAF FDC should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving F/TAF.

Precautionary language has been included in the proposed prescribing information as several adverse reactions have been noted as class effects for NRTIs or have been reported in patients receiving ART: lactic acidosis/severe hepatomegaly with steatosis, redistribution/accumulation of body fat, and immune reconstitution syndrome (including autoimmune disorders).

6.3. Conclusions

Both tablet strengths of the F/TAF FDC provide exposures to FTC and TAF that are bioequivalent to those from E/C/F/TAF that demonstrated potent antiviral efficacy and a favorable safety and tolerability profile. In addition, the comprehensive clinical pharmacology program establishes a wide range of TAF exposure that is efficacious and safe. These data

suggest that, when used in combination with other antiretroviral medications, F/TAF offers advantages over the existing recommended N(t)RTI backbone, meeting important unmet medical needs. The F/TAF FDC represents a new once-daily N(t)RTI backbone option for HIV-infected adults without any known mutations associated with resistance to the individual components of F/TAF, including those with mild to moderate renal impairment, and pediatric patients 12 years of age and older.

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