SECTION 2.5 – CLINICAL OVERVIEW

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (E/C/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
ART	antiretroviral therapy
ARV	antiretroviral
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
BHIVA	British HIV Association
BMD	bone mineral density
BMI	body mass index
CD4	cluster determinant 4
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COBI, C	cobicistat (Tybost®)
CSR	clinical study report
C-telopeptide	type I collagen C-telopeptide
CYP	cytochrome P450 enzyme
ddI	didanosine
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
EASC	European AIDS Clinical Society
EC_{50}	concentration of a compound inhibiting virus replication by 50%
EOP2	End of Phase 2
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
ESRD	end-stage renal disease
EU	European Union
EVG, E	elvitegravir (Vitekta®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC, F	emtricitabine (Emtriva®)
FTC-DP	emtricitabine diphosphate
GCP	Good Clinical Practice
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_{95}	concentration that results in xx% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IN	integrase
IND	Investigational New Drug
INSTI	integrase strand-transfer inhibitor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
LDL	low-density lipoprotein
LOCF	last observation carried forward
LSM	least-squares mean
M = F	missing = failure
mtDNA	mitochondrial DNA
N or n	number of subjects in a population (N) or subset (n)
NCEP	National Cholesterol Education Program
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
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 Investigational 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
RBP	retinol binding protein
RNA	ribonucleic acid
rNTP	ribonucleoside triphosphate
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	selectivity index (ratio of CC_{50} to IC_{50})
SOC	system organ class
STB	elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (coformulated; Stribild®)
TAF	tenofovir alafenamide
TAF fumarate	tenofovir alafenamide fumarate
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_{inf}	area under the plasma/PBMC concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the plasma/PBMC concentration versus time curve over the dosing interval
C_{max}	maximum observed plasma/serum concentration of drug
C_{trough}	plasma concentration at the end of the dosing interval
F	estimated oral bioavailability of the drug (%), calculated as $100(AUC_{PO} \times Dose_{IV})/(AUC_{IV} \times Dose_{PO})$
PBMC	peripheral blood mononuclear cell
$t_{½}$	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)

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 elvitegravir (EVG, E), cobicistat (COBI, C), emtricitabine (FTC, F) and tenofovir alafenamide (TAF): the E/C/F/TAF FDC tablet (150/150/200/10 mg). The proposed indication for the E/C/F/TAF FDC tablet is for use once daily 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 overview presents the clinical rationale for the development of E/C/F/TAF and reviews the information that is relevant to the benefit/risk assessment for the use of the FDC tablet 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 antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI) {28776}, {27621}, {29584}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. 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 {21053}, {29702}.

1.1.2. Rationale for E/C/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 the optimization of tolerability, long-term safety, and adherence to potent ART regimens {29705}. There remains a significant medical need for new, effective therapies that take into consideration the non-HIV comorbidities, demographics of the aging HIV-infected population, antiretroviral (ARV) resistance, and regimen simplification.

Chronic kidney disease is important, since observational studies have demonstrated a relationship between kidney disease and progression to AIDS and death. Moreover, HIV-associated nephropathy present in up to 30% of patients, is a common cause of end-stage renal disease (ESRD) requiring dialysis {6964}, {17105}, {4195}, {10478}, {22038}.

ART with proven efficacy and safety in the both elderly and young patients is important; limited data and treatment options are available in both populations. The elderly have increased risks for comorbidities, including those related to renal and bone. There are specific and complex challenges for the treatment of adolescents, who also represent the population that will require ART for the longest time.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF, Viread®), an oral prodrug of TFV, has improved bioavailability, and delivers high systemic exposures of TFV with favorable efficacy and safety data. TDF is a preferred NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection {28776}, {27621}, {29584}.

While TDF is used broadly in the treatment of HIV-1 infection, an identified risk with its use is nephrotoxicity, which is associated with increased creatinine in some patients, increased protein loss (particularly tubular), and occasional cases of proximal renal tubulopathy (PRT) (including Fanconi syndrome). These risks necessitate increased renal monitoring with use of TDF-containing products, placing burden on the patient and healthcare provider. Early onset bone demineralization, specifically reductions in bone mineral density (BMD), has also been seen after treatment with TDF; decreases in BMD with TDF are larger than those seen with other NRTIs {26885}.

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

Gilead proposes to address the unmet medical need for a highly efficacious, complete regimen for the treatment of HIV-1 infection in ART-naive or virologically suppressed patients that has an improved renal and bone safety profile compared with TDF-containing regimens, including Stribild® (STB), and a low frequency of resistance development. Gilead has coformulated TAF with EVG, COBI, and FTC into an FDC tablet that is suitable for once-daily use. EVG, an HIV-1 INSTI that prevents integration of HIV-1 genetic material into the host-cell genome, is approved for use in combination with other agents for the treatment of HIV-1 infection in adults in the United States (US), Canada, and European Union (EU) (Vitekta®). COBI, a cytochrome P450 3A (CYP3A) inhibitor that boosts the exposure of CYP3A substrates, including EVG, is approved for use as a pharmacokinetic enhancer in adults in US, Canada, and EU (Tybost®). FTC, a NRTI, 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 US, Canada, EU, and other regions worldwide (Emtriva®).

Given the duration for which a newly diagnosed person with HIV may take an ART regimen throughout his or her lifetime, the E/C/F/TAF FDC tablet may provide the longevity of a single treatment that optimizes tolerability, long-term safety, and durable efficacy. For HIV-infected, ART-naive patients, E/C/F/TAF has significant advantages over existing marketed products, specifically significantly less proteinuria, less need for renal monitoring, and less impact on bone mineralization relative to TDF treatment. The relatively low dose of TAF (10 mg vs

TDF 300 mg) that is used in the E/C/F/TAF FDC also allows for coformulation with multiple other third ARV agents. This will allow HIV-infected, virologically suppressed patients to convert from a TDF-based regimen to receive a novel TFV prodrug coformulated with 2 active agents without any diminution of efficacy but with renal and bone safety advantages. E/C/F/TAF can provide a lifelong treatment option that can minimize impact on non-AIDS comorbidities that may be more important than AIDS-related opportunistic infections.

Described herein, clinical data demonstrate the following for E/C/F/TAF:

- Highest virologic success rates for both E/C/F/TAF and STB than have been previously shown in studies of ART-naive, HIV-infected subjects, with low rate of treatment-emergent virologic resistance.

- Improved bone safety profile as compared with TDF/STB, specifically, less change in BMD at both the hip and spine for ART-naive subjects, and improvements in BMD for subjects who switched to E/C/F/TAF from a TDF-based regimen.

- Improved renal safety profile as compared with TDF/STB, specifically, less change in serum creatinine, proteinuria, and renal tubular proteinuria for ART-naive subjects compared to STB, and a reduction in serum creatinine levels and improvements in these renal tubular protein parameters for subjects who switched to the E/C/F/TAF FDC from a TDF-based regimen. Results support inclusion of renal safety monitoring consistent with routine clinical practice (and with other non-TDF-containing ARV regimens) in the proposed prescribing information.

- Efficacy and safety profile that supports use without dose adjustment for renally impaired patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min.

- Efficacy and safety profile in elderly subjects (N > 75 subjects who were ≥ 65 years of age) comparable with that from younger subjects (12 to < 65 years of age).

- 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. E/C/F/TAF therefore has the potential to be the first INSTI-containing FDC available for pediatric patients 12 to < 18 years of age.

1.2. Overview of the Clinical Development Program

1.2.1. Clinical Pharmacology Development Program

A comprehensive program of clinical studies characterized the pharmacokinetics (PK) of E/C/F/TAF and its components. In total, 60 clinical studies provide PK data in support of this marketing application (m2.7.2, Section 1.2). Of these, 12 studies were conducted with E/C/F/TAF and 6 studies were conducted with F/TAF (1) or TAF (5). The other 42 studies were conducted with EVG, COBI, EVG+COBI, FTC, or STB. Twelve studies were conducted in HIV-infected subjects, including the 6 Phase 2 and 3 studies conducted with E/C/F/TAF that provide efficacy and safety data for adults and adolescent subjects.

Clinical pharmacology studies of E/C/F/TAF, individual component drugs, and/or STB entailed single and/or multiple dosing and clinically relevant exposure of the drug(s) to assess PK, PK/pharmacodynamic (PD) relationships, and/or the effects of intrinsic and extrinsic factors. Drug-interaction studies were performed 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 proposed commercial E/C/F/TAF FDC tablet contains EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg. The 150-mg dose of EVG is 1 of the 2 marketed doses of the product as a single agent (85 mg is the other dose). The 150-mg boosting dose of COBI is the marketed dose of COBI as a single agent, and the dose associated with boosting of the 150-mg dose of EVG. The 200-mg dose of FTC represents the marketed dose.

Cumulative assessment of exposure:response data from proof-of-concept
Study GS-US-120-0104 indicated that TAF 25-mg exposure provided potent and near-maximal antiviral activity. Relative to TDF 300 mg, TAF 25 mg demonstrated no loss in efficacy, but 90% reduction in TFV plasma levels that potentially translates into an improvement in off-target side effects. Pharmacokinetic data from Studies GS-US-292-0101 and GS-US-311-0101 indicated that TAF exposure from an 8- to 10-mg dose in combination with COBI (single agent or as E/C/F/TAF) were comparable with that from TAF 25 mg administered alone. Cumulative results from Studies GS-US-120-0104, GS-US-292-0101, and GS-US-311-0101 were used in selecting a 10-mg TAF dose for clinical development within the E/C/F/TAF FDC.

1.2.3. Clinical Efficacy and Safety Development Program

Efficacy and safety of E/C/F/TAF (150/150/200/10 mg) were evaluated in 6 clinical studies in HIV-infected subjects (Table 2). Study populations providing clinical efficacy and safety data were as follows:

- ART-naive, HIV-1 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 in Phase 2 study, GS-US-292-0102)

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

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

Across these 6 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 (EU)	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: Study GS-US-292-0102
Source: m2.7.3, Table 2

In the double-blind studies in ART-naive subjects (GS-US-292-0102, GS-US-292-0104, 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 preferred standard of care regimen for initial therapy in the US Department of Health and Human Services (DHHS) guidelines, European AIDS Clinical Society (EACS) guidelines, and the British HIV Association (BHIVA) guidelines, {26961}, {27621}, {27094}. In the study investigating subjects switching to E/C/F/TAF (GS-US-292-0109), subjects were virologically suppressed on the following FTC/TDF containing regimens at baseline: STB, Atripla® (ATR), COBI-boosted atazanavir (ATV/co)+Truvada® (TVD), or ritonavir (RTV)-boosted atazanavir (ATV/r)+TVD. This also provided a comparison between TAF and TDF in E/C/F/TAF and approved, standard of care regimens. For adolescent subjects, studies of E/C/F/TAF (GS-US-292-0106) and STB (GS-US-236-0112) provided a comparison between TAF and TDF via an integrated, cross-study analysis.

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

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	CSR and Narrative Locations
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	**CSR:** m5.3.5.1, GS-US-292-0104 **Narrative:** m2.7.3, Section 2.1.1
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	**CSR:** m5.3.5.1, GS-US-292-0111 CSR **Narrative:** m2.7.3, Section 2.1.2
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	**CSR:** m5.3.5.1, GS-US-292-0102 CSR **Narrative:** m2.7.3, Section 2.1.3
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 FTC/TDF+3rd Agent (N = 477)	Week 48 efficacy and safety	**CSR:** m5.3.5.1, GS-US-292-0109 CSR **Narrative:** m2.7.3, Section 2.2
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	**CSR:** m5.3.5.2, GS-US-292-0112 **Narrative:** m2.7.4, Section 1.1.4.1
HIV-Infected, ART-Naive, Adolescent Subjects				
GS-US-292-0106	Phase 2/3, open-label, multicenter, 2-part, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 48) PK substudy: N = 24	Week 24 efficacy, PK, and safety	**CSR:** m5.3.5.2, GS-US-292-0106 **Narrative:** m2.7.4, Section 1.1.4.2

ART = antiretroviral therapy; COBI = cobicistat; DRV = darunavir; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; FTC = emtricitabine; STB = Stribild; TDF = tenofovir disoproxil fumarate; TVD = Truvada (emtricitabine/tenofovir disoproxil fumarate)

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.

1.2.4. Regulatory Guidelines and Advice

All studies conducted in the E/C/F/TAF development program met the requirement for 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 E/C/F/TAF Phase 3 studies were of an adequate design and duration, as recommended in applicable regulatory guidance (ICH E8 and E10; {28155}, {27447}, {19051}), with well-established endpoints to characterize the efficacy and safety of the E/C/F/TAF FDC for the treatment of HIV-1 infection{13932}. Advice on overall development was sought from the US Food and Drug Administration (FDA).

The overall clinical development plan for the E/C/F/TAF FDC tablet for the treatment of HIV-1 infection was discussed with the US FDA at the [redacted] meeting on [redacted] 20[redacted] At the [redacted] meeting, the US FDA agreed that Study GS-US-292-0104 would support the registration of the E/C/F/TAF FDC in ART-naive, HIV-1 infected patients, together with an identical study (Study GS-US-292-0111), which would differ from Study GS-US-292-0104 only in the geographical area of the study. In the [redacted] meeting, the Agency also agreed that the use of a 12% margin for noninferior efficacy for studies would permit the efficacy contribution of TAF versus TDF to be adequately compared. Study GS-US-292-0109 was endorsed by the Agency to provide valuable safety information in patients who switch from a TDF-based regimen to the E/C/F/TAF FDC tablet. Further, it was agreed that a study in HIV-1 infected patients with mild to moderate renal function could potentially support the use of E/C/F/TAF in patients with eGFR of ≥ 30 mL/min (GS-US-292-0112), and that PK and safety data in adolescents could support an indication in pediatric patients 12 to < 18 years of age (Study GS-US-292-0106).

The E/C/F/TAF FDC tablet was granted Fast Track Designation on [redacted] 20[redacted]

The E/C/F/TAF clinical development program includes an Agreed Initial Pediatric Study Plan (PSP) in the US and Paediatric Investigational Plan (PIP) in the EU.

Based upon the clinical evidence provided from the clinical development described above, Gilead is seeking registration of the E/C/F/TAF FDC tablet in the EU, US and other regions for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of E/C/F/TAF.

2. OVERVIEW OF BIOPHARMACEUTICS

Administration of E/C/F/TAF results in equivalent exposures of EVG, COBI, and FTC relative to the single agents administered at the same dosages. The E/C/F/TAF FDC, which contains TAF 10 mg, provides equivalent exposures of both TAF and TFV relative to those attained with use of the TAF 25 mg single agent.

Relative to fasting conditions, the administration of E/C/F/TAF with a light meal (~400 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) did not affect overall exposures of TAF to a clinically meaningful extent (approximately 15% and 18% higher AUC with a light or high-fat meal, respectively, versus fasted). TAF (and COBI and FTC) can be administered without regard to food; however, E/C/F/TAF is recommended to be administered with food to achieve exposures of EVG that maintain a high inhibitory quotient against clinical viral isolates (m2.7.1, Section 3.2). This recommendation is consistent with those for EVG administered as a single agent, and for STB. E/C/F/TAF was administered with food in the Phase 2 and 3 clinical studies.

Biopharmaceutical studies of E/C/F/TAF are summarized in detail in m2.7.1.

2.1. Formulation

Two forms of the TAF drug substance were used in the development of TAF single agent and E/C/F/TAF FDC tablets: TAF monofumarate (GS-7340-02), synonym for GS-7340 as the monofumarate form (1:1 ratio of GS-7340 to fumarate), and TAF fumarate (GS-7340-03), synonym for the hemifumarate form (2:1 ratio of GS-7340 to fumarate) (m2.7.1, Section 1.1.1). TAF fumarate drug substance was selected for use in Phase 3 studies and in commercialization since it has enhanced purging capability of the process impurity GS-7339, increased thermodynamic stability in organic solvents, and improved thermal stability compared to the TAF monofumarate drug substance.

The proposed commercial E/C/F/TAF FDC tablet contains EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (as 11.2 mg of TAF fumarate). This tablet formulation was used in all primary and registration stability batches and in all pivotal Phase 3 clinical studies. EVG is fluid-bed granulated with intragranular excipients. FTC and TAF fumarate are dry-granulated with intragranular excipients. Both granulations are blended with COBI on silicone dioxide drug substance and extragranular excipients prior to compression into monolayer tablets. The E/C/F/TAF tablets are green, capsule shaped, film coated, and debossed with “GSI” on one side and “510” on the other side.

2.2. Dissolution Profile

The dissolution profile for the proposed commercial E/C/F/TAF FDC tablet formulation showed [redacted]% [redacted] minutes, [redacted]% [redacted] minutes (m2.7.1, Section 1.1.2).

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-glycoprotein (P-gp) and metabolized by esterases expressed in the intestine {21545}, {21546}. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases, so drugs that strongly inhibit P-gp activity increase TAF availability. Upon coadministration of TAF with COBI single agent, near maximal inhibition of P-gp by COBI is achieved, leading to increased availability of TAF (Study GS-US-311-0101, m2.7.2, Section 2.5.2.1). For the E/C/F/TAF FDC tablet that contains TAF 10 mg, TAF bioavailability is increased approximately 2.3-fold, consistent with the exposure that occurs with the TAF 25 mg single agent (Study GS-US-292-0103, m2.7.2, Section 2.2.1.2).

Following the administration of the E/C/F/TAF FDC tablet, the exposures of EVG, COBI, and FTC were equivalent to those observed following administration of EVG, COBI, or FTC single agents at the same dosages and consistent with those observed historically following administration of STB (Study GS-US-292-0103).

3. OVERVIEW OF CLINICAL PHARMACOLOGY

A comprehensive program of clinical studies characterizes the PK of E/C/F/TAF and its components. In total, 60 clinical studies provide PK data in support of this marketing application (m2.7.2, Section 1.2).

The available nonclinical and clinical virology data for E/C/F/TAF and its components are summarized in m2.7.2, Section 4; clinical virology data are incorporated with efficacy data in this overview (Section 4). The analyses of the clinical PK data are described in detail in m2.7.2, Section 3.

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, 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. EVG, COBI, and FTC

EVG is a low molecular weight, HIV-1 INSTI that prevents integration of the HIV-1 genetic material into the host-cell genome. EVG specifically inhibits HIV-1 integrase strand-transfer activity and the integration of viral DNA into host chromosomal DNA in cell culture. EVG does not inhibit human topoisomerases I or II.

COBI is devoid of HIV protease inhibition, unlike its structural analog, RTV. It is a potent, mechanism-based inhibitor of CYP3A and been shown in vitro to be a more specific CYP3A inhibitor than RTV. COBI increases the systemic levels of coadministered agents, whose bioavailability and elimination are affected by metabolism by CYP3A enzymes.

FTC, an NRTI, is converted intracellularly through 3 phosphorylation reactions to its active phosphorylated anabolite 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 (mtDNA) 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. When tested in cell culture, EVG, FTC, and TAF demonstrated synergistic antiviral activity that was maintained in the presence of COBI.

3.2.1. TAF

The 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, abacavir (ABC), didanosine (ddI), or lamivudine (3TC), 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 (≥ 5 times) 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. EVG, COBI, and FTC

EVG inhibited laboratory strains and various clinical isolates (wild-type and drug-resistant clones) of HIV-1 with a median EC_{50} value of 0.38 nM (range 0.02 to 1.3 nM) in human PBMCs in vitro. The EVG concentration that results in 50% cytotoxicity under the same conditions was 170 μM (selectivity index [SI] of > 100,000). EVG showed activity against multiple subtypes of HIV-1 and HIV-2. EVG showed broad anti-HIV activity against HIV-1 subtypes A, B, C, D, E, F, G, and O with average EC_{50} values ranging from 0.1 to 1.26 nM in PBMCs, and HIV-2 with an EC_{50} of 0.53 nM.

In vitro resistance selection experiments with EVG demonstrated that EVG can select 3 primary resistance mutations in HIV-1 integrase (IN), the T66I, E92Q, and Q148R mutations. The T66I,

E92Q, and Q148R mutations resulted in HIV-1 that had 15-, 36-, and 109-fold reduced susceptibility to EVG, respectively. The HIV-1 IN mutations selected by the metabolites, GS-9202 (M1) and GS-9200 (M4), are described in m2.7.2, Section 4.1.1.3.8.

The combination antiviral activity of EVG with other anti-HIV drugs did not show any antagonism. The antiviral activity of EVG in combination with TFV and FTC was synergistic, and the same level of synergy was observed in the presence of the pharmacokinetic enhancer COBI.

COBI has no detectable antiviral activity against HIV-1, HBV, or hepatitis C virus (HCV) and does not antagonize the antiviral effects of EVG, FTC, or TFV.

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 (Reports 462 v2 and 10498 v2), {4534}, {4541}, {4526}. With clinical isolates of HIV-1, EC_{50} values range from 0.002 to 0.028 μM (Report 462 v2). 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 (Reports 10498 v2 and 11419 v2), and shows activity against HIV-2 (with an EC_{50} of 0.007 to 1.5 μM).

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 approximately 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 is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by COBI reduces P-gp mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed. 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 alone.

Absorption in relation to administration of E/C/F/TAF with food is described in Section 2.

EVG, COBI, and FTC

Following oral administration with food in HIV-1 infected patients, peak plasma concentrations were observed ~ 4 hours postdose for EVG, 3 hours postdose for COBI, and 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 the percent unbound value of 20% based on multiple human ex vivo studies with the mean percent unbound TAF ranged 14% to 23%.

EVG, COBI, and FTC

EVG is 98-99% bound to human plasma proteins and binding is independent of drug concentration over the range of 1 ng/mL to 1.6 µg/mL. The mean plasma to blood drug concentration ratio was 1.37.

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

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. In vitro studies have shown that TAF is metabolized to TFV (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. In vivo, TAF is hydrolyzed within PBMCs and macrophages to form TFV (major metabolite), which is phosphorylated to the active metabolite, TFV-DP. 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 to a 300-mg oral dose of TDF in STB.

In vitro, TAF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or uridine diphosphate glucuronosyltransferase (UGT) 1A1. TAF is minimally metabolized by CYP3A4. Upon coadministration with the moderate CYP3A inducer probe efavirenz (EFV), TAF exposure was unaffected. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A in vitro.

TAF is 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 1% of the dose eliminated in urine. The pharmacologically active metabolite, TFV-DP, has a $t_{1/2}$ of 150-180 hours within PBMCs.

EVG, COBI, and FTC

EVG undergoes primarily oxidative metabolism via CYP3A, and is secondarily glucuronidated via UGT1A1/3 enzymes. Following oral administration of boosted [^{14}C]EVG, EVG was the predominant species in plasma, representing ~ 94% of the circulating radioactivity; 94.8% of the dose was recovered in feces, consistent with the hepatobiliary excretion of EVG; 6.7% of the administered dose was recovered in urine. Aromatic and aliphatic hydroxylation or glucuronidation metabolites are present in very low levels, displaying considerably lower antiviral activity against HIV-1 and do not contribute to the overall antiviral activity of EVG. The median $t_{1/2}$ of EVG following administration of STB is approximately 12.9 hours.

COBI is metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following oral administration of [^{14}C]COBI, 99% of circulating radioactivity in plasma was unchanged COBI; 86% and 8.2% of the dose were recovered in feces and urine, respectively. Low levels of metabolites are observed in urine and feces and do not contribute to the CYP3A inhibitory activity of cobicistat. The median $t_{1/2}$ of COBI following administration of STB is approximately 3.5 hours and the associated COBI exposures provide EVG C_{trough} approximately 10-fold above the protein binding-adjusted concentration that resulted in 95% inhibition (IC_{95}) for wild-type HIV-1 virus.

In vitro studies indicate that FTV 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 5'-triphosphate (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

Study GS-US-120-0104 evaluated the PK of TAF and TFV after single and multiple oral dosing of TAF 8, 25, or 40 mg monotherapy (Day 1 and Day 10) in HIV-infected subjects. TAF

exhibited linear PK and was rapidly absorbed in a dose proportional manner with a median $t_{1/2}$ of approximately 0.40 hours. The PK exposure parameters of TAF were similar within each dose group following single- and multiple-dose administration, as expected given the short plasma half-life of TAF. Consistent with linear PK, TFV single-dose exposures (AUC_{inf}) were comparable with steady-state exposures (AUC_{tau}).

In healthy subjects, the mean TAF exposure following single and multiple dosing of FTC+TAF 25 mg or E/C/F/TAF (GS-US-292-0103) was comparable (Day 1 vs Day 12), while the mean TFV exposure following single dosing (AUC_{inf}) was predictive of TFV multiple dose exposure (AUC_{tau}).

TAF has a distinct metabolism that maximizes both antiviral potency and clinical safety. This was confirmed by the pooled Phase 3 PK substudy data in which TAF was shown to be more stable in plasma than TDF and provided > 90% lower circulating levels of TFV. The distinct metabolism of TAF also provides > 4-fold higher intracellular levels of the active phosphorylated metabolite TFV-DP relative to TDF.

EVG, COBI, and FTC

EVG plasma exposures are nonlinear and less than dose-proportional, likely due to solubility-limited absorption.

COBI exposures are nonlinear and greater than dose-proportional over the range of 50 mg to 400 mg, consistent with a mechanism-based CYP3A inhibitor.

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. 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.

EVG, COBI, and FTC

EVG AUC_{tau}, C_{max}, and C_{trough} were comparable between healthy and HIV-infected subjects. In population PK analyses for EVG, COBI exposure was not associated with differences in EVG exposure at the 150-mg dose, confirming dose selection.

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 exposure was 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.

EVG, COBI, and FTC

No clinically relevant differences in EVG or COBI PK were observed between healthy subjects and subjects with severe renal impairment. In a population PK analysis of EVG, baseline eGFR was not a significant covariate, indicating no effect of eGFR on EVG PK. This was expected in view of the minimal renal excretion of EVG (~ 6 to 7%).

In an intensive PK substudy in Study GS-US-292-0112, the exposure of FTC following administration of E/C/F/TAF to subjects with $eGFR_{CG}$ 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 in Study GS-US-292-0112 was comparable for subjects with $eGFR_{CG} < 50$ mL/min or $eGFR_{CG} \geq 50$ mL/min.

Overall, E/C/F/TAF may be administered once daily without dose adjustment in patients with mild-to-moderate renal impairment (estimated glomerular filtration rate calculated using the Cockcroft-Gault equation [$eGFR_{CG}$] ≥ 30mL/min).

3.5.2. Hepatic Impairment

Details on the PK in subjects with renal 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.

EVG, COBI, and FTC

Both EVG and COBI are primarily metabolized and eliminated by the liver.

No clinically relevant differences in EVG or COBI PK were observed between subjects with moderate hepatic impairment and healthy subjects (Child-Pugh Class B). No dosage adjustment of EVG or COBI is necessary for patients with mild to moderate hepatic impairment. The PK of EVG and COBI in subjects with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

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 HCV coinfection were also excluded due to incomplete drug-drug interaction 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.

Pharmacokinetics of FTC and TAF have not been fully evaluated in patients coinfected with hepatitis B and/or C virus. Limited data from population pharmacokinetic analysis (n = 24) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of boosted EVG.

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. TAF and TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration, indicating no relevant effects of pediatrics (age ≥ 12 years) 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 was not a clinically relevant covariate.

EVG, COBI, and FTC

There were no relevant effects of age of pediatrics on the exposures of EVG, COBI, and 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) (m2.7.2, Section 3.3.1.1). Phase 2 data in Study GS-US-292-0102 with TAF 10 mg in the E/C/F/TAF FDC 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 (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 (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} with no trends in exposure-response relationship observed, confirming the dose selection of TAF 10 mg for the E/C/F/TAF FDC that provides equivalent exposure as TAF 25 mg single agent.

EVG, COBI, and FTC

EVG PK/PD analysis for efficacy parameters demonstrated that virologic response was uniformly high across the quartiles of EVG C_{trough} with no trends in exposure-response relationship observed (m2.7.2, Section 3.3.1). EVG exposures upon coadministration with COBI (STB) in HIV-1 infected subjects were associated with high rates of virologic response and corresponded to the plateau phase of its exposure-antiviral efficacy relationship.

The plasma and intracellular PK and PK-PD correlation, and long-term efficacy and safety data obtained from Phase 2/3 clinical studies, support the 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.

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 [BMI]), 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.

EVG, COBI, and FTC

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for COBI-boosted EVG, COBI or FTC. Pharmacokinetics of EVG, COBI, and 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.

EVG and COBI are both substrates of CYP3A and, therefore, agents which induce or inhibit CYP3A may alter the PK of EVG or COBI.

3.5.7.1. Potential for E/C/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.

Although TAF is a weak inhibitor of CYP3A, at clinically relevant concentrations, TAF is unlikely to affect hepatic CYP3A activity. While CYP3A activity may be affected in the intestine, where high levels of TAF can be achieved, the exposure to TAF in intestine should be transient and the potential for significant drug interaction is unlikely. In addition, since E/C/F/TAF contains COBI, a potent and specific CYP3A inhibitor, the effect caused by TAF, if any, is expected to be minimal. Moreover, any induction potential by TAF is countered by coadministration with COBI.

3.5.7.2. Potential for Other Drugs to Affect E/C/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 availability. However, upon coadministration with COBI in E/C/F/TAF, near maximal inhibition of P-gp by COBI is achieved, leading to increased availability of TAF with resulting exposure comparable with TAF 25 mg single agent. As such, TAF exposure following administration of E/C/F/TAF is not expected to be further increased when used in combination with another P-gp inhibitor. This is

supported by a clinical study with E/C/F/TAF and investigation agent GS-5816, a P-gp inhibitor, which showed no clinical relevant changes in TAF or TFV upon coadministration of E/C/F/TAF with GS-5816, relative to E/C/F/TAF alone (GS-US-342-1167). Because TAF was found to be a substrate for hepatic transporters organic anion transporting polypeptide (OATP) B1 and OATP1B3, exposure to TAF may be affected by inhibitors of OATP1B1 and OATP1B3 or by genetic polymorphisms affecting their transport activities. The effects of differences in OATP1B1 and OATP1B3 activity are, however, not expected to be clinically relevant given the high passive permeability of TAF.

Coadministration of TAF single agent with a modest CYP inducer, such as EFV, resulted in slightly lower TAF exposure (14%-22%) and a commensurate lowering of TFV exposure (GS-US-311-0101). As such, administration of E/C/F/TAF with a modest CYP3A inducer may result in lower TAF exposure. However, the magnitude of change in TAF and TFV would be expected to be less following E/C/F/TAF due to the presence of the potent CYP3A inhibitor COBI.

3.6. Summary of Clinical Pharmacology

TAF is a prodrug of TFV 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 PK profiles of E/C/F/TAF and its components have been well established in HIV-1 infected subjects and certain special populations. No clinically relevant differences in the PK of the E/C/F/TAF FDC were observed with respect to demographic variables. The PK of the individual components of E/C/F/TAF in adolescents were 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 E/C/F/TAF in patients > 12 years.

No dose adjustment of E/C/F/TAF is necessary in patients with estimated creatinine clearance greater or equal to 30 mL/min. No dose adjustment of E/C/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. The E/C/F/TAF FDC has not been studied in patients with severe hepatic impairment.

Based on PK/PD analysis for efficacy parameters, the exposure associated with TAF 25 mg (or ECFTAF 10 mg) is expected to provide near-maximal activity.

Based on the drug-drug interaction profile of EVG and COBI, the E/C/F/TAF FDC must not be coadministered with the following: 1) drugs with narrow therapeutic ranges that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated

with severe and/or life-threatening events, and 2) potent CYP3A inducers due to the potential for loss of virologic response and possible resistance to E/C/F/TAF.

Clinical experience with use of concomitant medications during treatment with the individual agents and E/C/F/TAF FDC in its clinical development program, including its drug-drug interaction evaluations, are sufficient to provide guidance regarding potential clinically significant drug interactions in the HIV-1 infected population.

4. OVERVIEW OF EFFICACY

This section provides an overview of the pooled analysis of efficacy that was conducted for the pivotal Phase 3 studies in ART-naive subjects (GS-US-292-0104 and GS-US-292-0111) and of the efficacy results of the remaining individual studies of E/C/F/TAF 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) in m5.3.5.3. No other data were pooled (unless otherwise stated), due to differences in the subject populations studied, treatment durations, and randomization. The clinical virology analyses conducted for the E/C/F/TAF development program are described in m2.7.2, Section 4.2.

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 425 cells/µL in ART-naive subjects and approximately 675 cells/µL in virologically suppressed subjects.

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

Generally, the studied populations are representative of both ART-naive and virologically suppressed HIV-1 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-defined snapshot algorithm (at Week 48 for ART-naive and virologically suppressed subjects, and at Week 24 for subjects with renal impairment and for the randomized portion of Study GS-US-292-0102). 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-defined snapshot algorithm, and changes in CD4 cell count, are summarized in this overview to support the primary efficacy endpoint results.

Noninferiority of treatment with E/C/F/TAF 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

Details on the individual efficacy results from the 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-defined snapshot algorithm) were as follows (Table 3):

- 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 3. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 48 Using FDA-Defined 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: m5.3.5.3, 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 3.3.4).

- 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-defined 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. It was numerically lower for the E/C/F/TAF group (0.4%, 4 of 978 subjects) compared to the 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); however, this difference did not achieve statistical significance.

- 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).

4.3. 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 3.2.2.

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

- 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 4. GS-US-292-0109: Virologic Outcome at Week 48 Using FDA-Defined 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 3.3.4).

- 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 using the FDA-defined 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 4.2.1.4).

- 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 3.2.3.

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 (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 3.3.4).

- 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 percentages 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 4.2.1.5).

- 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 3.2.4.

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, E/C/F/TAF produced high rates of virologic success as assessed using the FDA defined 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 dolutegravir [DTG]: Studies GS-US-236-0102 and GS-US-236-0103, {27389}, {28661}, {26002}, {18038}, {19639}, {19105}), and demonstrate the potent antiviral efficacy of E/C/F/TAF 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 (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 E/C/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 the E/C/F/TAF FDC for subjects with

moderate renal impairment, a population for whom no once daily single-tablet regimen 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.

Across all studies, analyses of the secondary HIV-1 RNA endpoints supported the primary efficacy analyses. In addition, the immunologic benefits of treatment with E/C/F/TAF 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 E/C/F/TAF is efficacious in all populations without regard to demographic characteristics, baseline viral load, or underlying renal function.

In all subjects administered E/C/F/TAF, 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 EVG, FTC, and TFV were consistent with historical data. No novel TAF resistance mutations were observed.

Overall, these data demonstrate potent and durable efficacy of the E/C/F/TAF FDC for the treatment of HIV-1 in ART-naive adults and adolescents, virologically suppressed subjects, and subjects with mild to moderate renal impairment.

5. OVERVIEW OF SAFETY

This section provides an overview of the pooled analysis of safety that was conducted for the pivotal Phase 3 studies in ART-naive subjects (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). Key demographic and baseline characteristics across all populations are summarized in Section 4.

A comprehensive nonclinical pharmacology and virology, PK, and toxicology program for EVG, COBI, FTC, and TAF was undertaken to support the clinical evaluation of the E/C/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 3 studies at the proposed commercial dose of 150/150/200/10 mg, with a median (Q1, Q3) exposure of 48.1 weeks (42.3, 60.0). This population exposure to E/C/F/TAF exceeds the requirements of the ICH E1 guideline for the safety evaluation of drugs. The median exposure was similar in subjects who were ART-naive (Studies GS-US-292-0104 and GS-US-292-0111), subjects who were virologically suppressed (GS-US-292-0109), and subjects with mild to moderate renal impairment (GS-US-292-0112). The median (first quartile [Q1], third quartile [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 in 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 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 m5.3.5.3, 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 E/C/F/TAF was consistent across all populations in the clinical development program. No unique safety signal for TAF or E/C/F/TAF was detected. There was a preferential profile for E/C/F/TAF versus STB and versus other TDF-containing regimens for multiple measures of renal and bone safety.

Adverse Events

The adverse event (AE) profile was generally similar in ART-naive adults, virologically suppressed adults, adults with mild to moderate renal impairment, and ART-naive adolescents (Table 5; m2.7.4, Section 2). 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 (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.

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; Section 5.6), change from baseline in 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 2.1.5.5.1).

Table 5. 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%)	8 (3.3%)	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 9

Clinical Laboratory Evaluations

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 creatinine kinase, fasting low-density lipoprotein (LDL) (Section 5.8), and lipase.

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 creatinine 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 creatinine 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 E/C/F/TAF Prescribing Information is the Week 48 pooled data from the pivotal 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 (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 proportion of subjects who discontinued study drug due to AEs, regardless of severity, was 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 2 of the proposed E/C/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 through 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 6).

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 E/C/F/TAF under Table 2 of the proposed Prescribing Information based on an assessment for a potential causal relationship: vomiting, abdominal pain, dyspepsia, flatulence, and rash.

Table 6. 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: m5.3.5.3, E/C/F/TAF ISS, Table 12

No additional ADRs to E/C/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 E/C/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 E/C/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 × upper limit of normal (ULN) and the low number of subjects with Grade 3 or 4 lipase abnormalities (4 subjects, all Grade 3), lipase abnormalities have not been proposed for inclusion in the E/C/F/TAF Prescribing Information.

Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function (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 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 3.1). 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 (m5.3.5.3, 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 E/C/F/TAF. Thus, bone and renal safety data will be presented in the clinical trial experience section of the proposed E/C/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 {28776}.

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 NTRI-sparing raltegravir and lopinavir {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 E/C/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 2.1.5.2):

- 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 7, Figure 1 [spine]). Compared to 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).

- 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 8). Compared to 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.

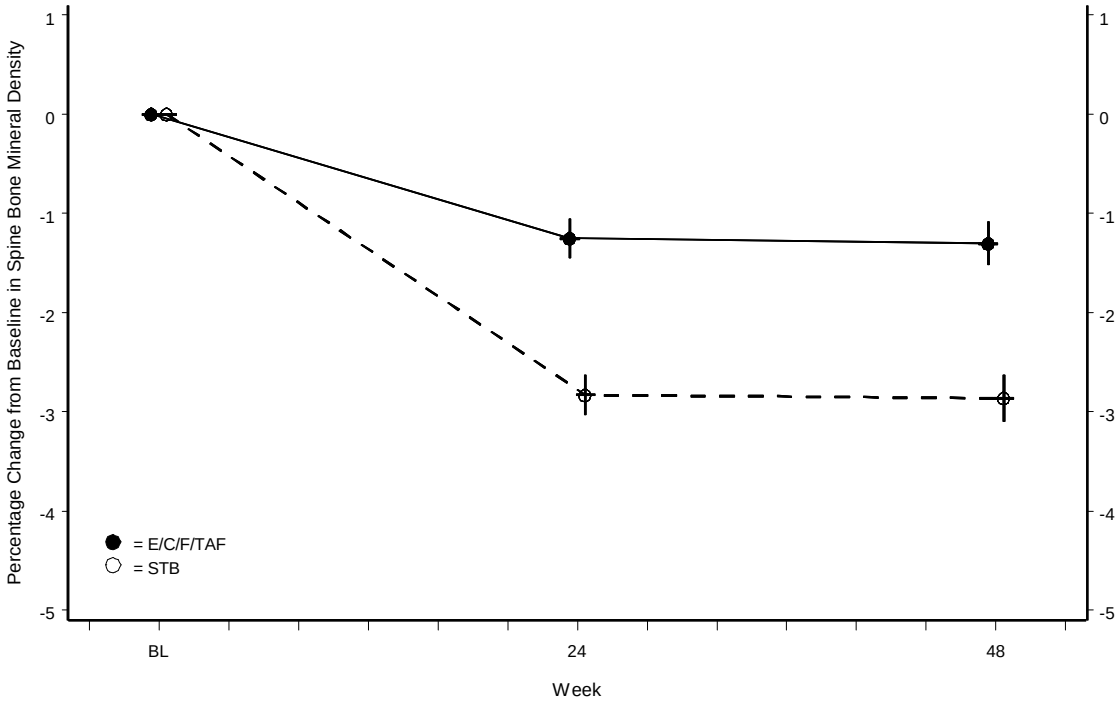
- In ART-naive adolescent subjects, treatment with E/C/F/TAF resulted in minimal changes from baseline in height-age adjusted spine (mean [SD] change: -0.08 [0.391]) and total body less head (TBLH) (mean [SD] change: -0.10 [0.256]) BMD Z-scores at Week 24. Results are supported by analyses in a subset 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 (GS-US-292-0106) and STB in adolescents (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, m5.3.5.3, 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: ANOVA 0.33, 95% CI (0.05, 0.60), $p = 0.020$; 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 E/C/F/TAF is associated with an improved bone profile, relative to other NRTI-based regimens and particularly 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]20[redacted], Lab Data: [redacted]20[redacted], s292-0111: CRF,DXA Data: [redacted]20[redacted], Lab Data: [redacted]20[redacted]
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out [redacted]20[redacted]:17:41

Source: m5.3.5.3, E/C/F/TAF ISS, Figure 3.2.2

Table 7. 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: m5.3.5.3, E/C/F/TAF ISS, Tables 20.1.2, 20.2.2, 22.1, 22.2

Table 8. GS-US-292-0109: Key Measures of BMD (Week 48 Analysis)

			E/C/F/TAF vs STB[a]	
	E/C/F/TAF (N = 902)	FTC/TDF+3rd Agent (N = 452)	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: m5.3.5.1, GS-US-292-0109, Section 15.1, Tables 40.2, 41.2

5.6. Renal Safety

Treatment with TDF in HIV-1 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}, {20402}, {22018}. In addition, COBI, a

component of E/C/F/TAF and STB, has been shown to inhibit tubular secretion of creatinine, thereby leading to an increase in serum creatinine and decrease in eGFR without an effect on actual GFR (aGFR). 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 in the E/C/F/TAF program.

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 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 rilpivirine (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 E/C/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 (Table 9; m2.7.4, Section 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.

- 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 B2MG 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 $\geq$ 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 E/C/F/TAF.

Table 9. GS-US-292-0104 and GS-US-292-0111: Key Renal Laboratory Parameters (Week 48 Analysis)

	E/C/F/TAF N=866	STB N=867	p-value
Serum Creatinine (mg/dL)[a]	0.08 (0.12)	0.11 (0.22)	< 0.001
$eGFR_{CG}$ (mL/min)[a]	-6.6 (15.37)	-11.2 (15.01)	< 0.001
Proteinuria by Urinalysis (Dipstick) (%)[b]	31.2%	36.7%	0.022
UPCR (mg/g)[c]	-3.4% (-34.5%, 42.6%)	19.8% (-23.0%, 75.8%)	< 0.001
UACR (mg/g) [c]	-4.7% (-32.9%, 35.6%)	7.1% (-26.5, 62.1%)	< 0.001
RBP to Urine Creatinine ratio (µg/g)[c]	9.2% (–23.0%, 48.6%)	51.2% (2.9%, 132.9%)	< 0.001
Beta-2-microglobulin to Urine Creatinine ratio (µg/g)[c]	−31.7% (–57.3%, 3.7%)	24.1% (–33.8%, 167.9%)	< 0.001

a Mean (SD) change from baseline
b Treatment-emergent graded events
c Median percent change (Q1, Q3)
Source: m5.3.5.3, E/C/F/TAF ISS, Tables 26.2, 27.1, 28, 29.1 to 29.4

In a cross-study comparison of E/C/F/TAF (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 (m5.3.5.3, 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 to the STB group (20.8%, 10 subjects vs 51.5%, 17 subjects, respectively).

Overall, the extensive and consistent renal safety data support use of E/C/F/TAF without dose adjustment in HIV-infected patients with eGFR ≥ 30 mL/min. Across studies in different patient populations, there was a preferential profile for E/C/F/TAF, likely a result of the decrease in systemic TFV exposure relative to that with TDF-containing regimens. Proposed prescribing information includes renal safety monitoring consistent with routine clinical practice and other non-TDF-containing ARV regimens.

5.7. Ocular Safety

Posterior uveitis was observed in a nonclinical study with dogs treated at 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 4.2.5.3). 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, similar incidence between treatment groups for events potentially related to uveitis, other eye disorders and conjunctivitis (m2.7.4, Section 2.1.5.4). 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.

The general lack eye findings in Phase 2 and 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.

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 E/C/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 E/C/F/TAF was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count. The safety profile for E/C/F/TAF is consistent with that for

adults in both adolescents and in the elderly. Guidance is provided in the prescribing information that the E/C/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 $eGFR_{CG}$ ≥ 50 mL/min.

- Based on available PK data (Section 3.5.2), no dose adjustment of E/C/F/TAF is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B). Treatment with E/C/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 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 E/C/F/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC and TAF components.

- No adequate and well-controlled studies of E/C/F/TAF or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of EVG, COBI, FTC, or TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. The E/C/F/TAF FDC tablet should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. The E/C/F/TAF FDC tablet 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 E/C/F/TAF.

- No new safety issues have been identified regarding overdose.

5.10. Safety Discussion and Conclusions

The safety and tolerability profile of the E/C/F/TAF FDC is supported by a safety database that is robust in terms of numbers of subjects receiving the recommended dose of each component and the length of treatment.

Treatment with E/C/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 for E/C/F/TAF were diarrhea, nausea, headache, and upper respiratory tract infection.

Treatment with E/C/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 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 treatment with E/C/F/TAF is associated with an improved bone profile, relative to other NRTI-based regimens and particularly 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. Compared to 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 E/C/F/TAF.

These renal safety results support routine clinical practice in monitoring for renal laboratory test abnormalities with E/C/F/TAF. In addition, results confirm that treatment with E/C/F/TAF can be administered without dose adjustment to HIV-infected patients with eGFR ≥ 30 mL/min.

No findings related to ocular safety demonstrated any increased risk of uveitis associated with E/C/F/TAF compared to 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 E/C/F/TAF is not considered to have an untoward effect on fasting glucose and lipid parameters.

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

- The AE profile for subjects receiving E/C/F/TAF was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count. The safety profile for E/C/F/TAF is consistent with that for adults in both adolescents and in the elderly. The E/C/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 $eGFR_{CG}$ ≥ 50 mL/min; therefore, E/C/F/TAF can be used without dose adjustment for renally impaired patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min.

- Treatment with E/C/F/TAF is not recommended for use in patients with severe hepatic impairment.

- The E/C/F/TAF FDC is not indicated for the treatment of HIV-1 in subjects with chronic HBV or HCV infection. Discontinuation of therapy with E/C/F/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis.

- The E/C/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 E/C/F/TAF.

In conclusion, E/C/F/TAF has demonstrated an acceptable safety profile in HIV-1 infected subjects, along with a tolerability profile that offers renal and bone advantages compared with TDF-based regimens.

6. BENEFITS AND RISKS CONCLUSIONS

The E/C/F/TAF FDC combines an INSTI (EVG boosted by COBI) with the standard of care, preferred-agent NRTI (FTC), and a novel TFV prodrug, TAF, in a once-daily tablet. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite TFV-DP, and approximately 90% lower circulating levels of TFV relative to TDF. Therefore, the distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF. Therapy with the E/C/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 E/C/F/TAF for the treatment of HIV-1 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.

A considerable challenge in achieving long term virologic suppression is the avoidance of development of drug resistance. Incomplete or partial adherence to treatment regimens is a critical factor contributing to the development of resistance and treatment failure is often particularly problematic for HIV-1 infected adolescents. FDC regimens have been shown to provide increased adherence and improved clinical and virologic outcomes {21053}, {29702}.

The E/C/F/TAF FDC tablet has many benefits for patients living with HIV infection including the following:

- **E/C/F/TAF is Highly Efficacious in ART-Naive, Virologically Suppressed, and Renally Impaired Adults**

The E/C/F/TAF FDC has demonstrated potent and durable ARV activity in 1 Phase 2 study (GS-US-292-0102), and 5 Phase 3 studies (GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, GS-US-292-0112, GS-US-292-0106). Using the FDA-defined snapshot methodology at Week 48, E/C/F/TAF was noninferior to standard of care based regimens in the active comparator studies. Results were consistently strong across multiple treatment populations and were and supported by several sensitivity analyses and immunologic benefits of treatment were demonstrated by increases in CD4 cell counts.

The virologic success rates at Week 48 for both the E/C/F/TAF FDC and the STB groups in the pivotal studies in ART-naive subjects were the highest seen in clinical trials in ART-naive HIV-1 infected adult subjects, demonstrating the potent antiviral efficacy of the E/C/F/TAF FDC against a highly active comparator.

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

- **E/C/F/TAF is an FDC with a Low Frequency of Resistance Development**

The development of drug resistance and loss of regimen efficacy is a risk of ART. Generally, the risk of resistance development is dependent on the efficacy, tolerability, and adherence to an ART regimen. The frequency of resistance development in subjects taking the E/C/F/TAF FDC was very low and comparable to that of comparator groups.

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

Treatment with the E/C/F/TAF FDC was well tolerated across various 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 spectrum 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 AEs for the E/C/F/TAF FDC were diarrhea, nausea, headache, and upper respiratory tract infection, which were generally consistent with AEs from prior studies of STB and other TVD-based regimens.

- **E/C/F/TAF Has a Preferential Bone and Renal Safety Profile Compared with TDF-Containing Regimens, including STB**

Treatment with the E/C/F/TAF FDC is associated with a preferential bone safety profile, as compared with TDF-based regimens (including STB), with statistically significant differences in tests of bone metabolism. Specifically, the E/C/F/TAF FDC resulted in less change in BMD at both the hip and spine for ART-naive subjects, and improvements in BMD for subjects who switched to the E/C/F/TAF FDC 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 the E/C/F/TAF FDC is associated with preferential renal safety profile, as compared with TDF-based regimens (including STB), with statistically significant differences in multiple tests of renal function. Specifically, the E/C/F/TAF FDC resulted in less change in serum creatinine for ART-naive subjects compared to STB and a reduction in serum creatinine levels for subjects who switched to the E/C/F/TAF FDC from a TDF-based regimen. Treatment with the E/C/F/TAF FDC is also associated with less proteinuria and less renal tubular proteinuria for ART-naive subjects compared to STB, and improvements in these renal protein parameters in subjects who switched to E/C/F/TAF from a TDF-based regimen. Proposed prescribing information includes renal safety monitoring consistent with routine clinical practice and other non-TDF-containing ARV regimens. At initiation and during treatment, patients may simply be monitored in accordance with their local standard of care.

- **E/C/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-Based Regimen**

As virologic control was maintained through 24 weeks in subjects who switched treatment, the E/C/F/TAF FDC offers an alternative, efficacious regimen 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 E/C/F/TAF and persist through 24 and/or 48 weeks. These included significant improvements in proteinuria, albuminuria, tubular proteinuria, and fractional excretion of uric acid. The E/C/F/TAF FDC is the first complete ARV regimen with robust data demonstrating the safety and efficacy of use in patients with an eGFR as low as 30 mL/min without dose adjustment, providing a safe and effective INSTI-containing FDC alternative.

- **E/C/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. E/C/F/TAF is the First INSTI-containing FDC for use in Pediatric Patients 12 to < 18 years of Age.**

Based on PK analyses, the dose of E/C/F/TAF (150/150/200/10 mg) is appropriate for adolescent use. Treatment with E/C/F/TAF demonstrated potent efficacy, robust immunological response, and tolerability similar to results from studies in ART-naive adults. Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and 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.

Treatment with the E/C/F/TAF FDC offers specific safety advantages relative to the only currently approved FDC in adolescents (Atripla; which is associated with central nervous system (CNS) and severe rash side effects) and, therefore, may improve treatment adherence for adolescents. In addition to offering patients a regimen without CNS and rash side effects, the E/C/F/TAF FDC offers patients a regimen without known teratogenicity risks and with no impact on bone mineralization relative to the reference population for E/C/F/TAF (compared with decreased mineralization relative to the reference population for the TDF-containing regimen, in the peri-pubescent period.

6.2. Risks

The clinical safety database is robust and includes data originating from the individual components of the E/C/F/TAF FDC as well as an in-depth and comprehensive E/C/F/TAF clinical development program conducted in HIV-1 infected, ART-naive and virologically suppressed subjects.

Treatment with the E/C/F/TAF FDC was well tolerated across all patient populations evaluated (See Section 6.1).

Treatment with E/C/F/TAF may increase the plasma concentrations of drugs metabolized by CYP3A. The potential for clinically significant drug-drug interactions with narrow therapeutic index drugs that are highly dependent on CYP3A for their clearance are included as contraindications for use with E/C/F/TAF. The E/C/F/TAF FDC is proposed for use as treatment of HIV-1 infection in adults and pediatric patients 12 years of age or older with no known resistance to the individual components. Because no data are currently available to inform the use of E/C/F/TAF with other ARTs, use of E/C/F/TAF in conjunction with other antiretroviral products is not recommended. The E/C/F/TAF FDC should not be administered with other medicinal products containing its components or products with similar components such as 3TC or RTV, or with adefovir dipivoxil.

The E/C/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 E/C/F/TAF.

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

The E/C/F/TAF FDC is not indicated for the treatment of chronic HBV or HCV infection, and safety and efficacy have not been established in patients coinfected with HBV or HCV and HIV-1. Discontinuation of therapy with E/C/F/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC and TAF components of E/C/F/TAF.

Precautionary language has also been included in the proposed prescribing information as several adverse reactions have been noted as class effects for one or more of the individual components of E/C/F/TAF: lactic acidosis/severe hepatomegaly with steatosis, redistribution/accumulation of body fat, and immune reconstitution syndrome (including autoimmune disorders).

6.3. Conclusions

The E/C/F/TAF FDC has demonstrated both potent antiviral efficacy and a safety and tolerability profile that offer advantages over existing recommended ARV regimens, meeting important unmet medical needs. The E/C/F/TAF FDC represents a favorable new therapeutic once-daily option for HIV-infected adults, including those with mild to moderate renal impairment, and pediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of E/C/F/TAF.

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