SECTION 2.7.1—SUMMARY OF BIOPHARMACEUTICAL STUDIES AND ASSOCIATED ANALYTICAL METHODS

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

Gilead Sciences

[redacted] **20**[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

1'-OH MDZ	midazolam metabolite (1′-hydroxymidazolam)
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ATV	atazanavir
BCS	Biopharmaceutics Classification System
BMD	bone mineral density
CD	cluster determinant
CI	confidence interval
COBI, C	cobicistat (Tybost®)
CSR	clinical study report
CV	coefficient of variation
DRV, D	darunavir
DTG	dolutegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
EFV	efavirenz
EVG, E	elvitegravir (Vitekta®)
FDC	fixed-dose combination
F/TAF	emtricitabine/tenofovir alafenamide (coformulated)
FTC, F	emtricitabine (Emtriva®)
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HIV, HIV-1	human immunodeficiency virus, type 1
HPLC-UV	high-performance liquid chromatography with ultraviolet detection
INSTI	integrase strand-transfer inhibitor
LC-MS	liquid chromatography/mass spectrometry
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LLOQ	lower limit of quantitation
LPV	lopinavir
LTSS	long-term storage stability
m	Module
MDZ	midazolam
NF	National Formulary
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopeia
PI	protease inhibitor
PK	pharmacokinetic(s)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

[redacted]	[redacted]
RE	relative error
RPV	rilpivirine
RTV	ritonavir
SPE	solid phase extraction
TAF	tenofovir alafenamide (GS-7340)
TDF	tenofovir disoproxil fumarate (Viread®)
TFV-DP	tenofovir diphosphate
TFV	tenofovir
TVR	telaprevir
USA	United States of America
USP	United States Pharmacopeia

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

AUC_{last}	area under the plasma/serum/PBMC concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma/serum/PBMC concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$
C_{max}	maximum observed plasma/serum/PMBC concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
PBMC	peripheral blood mononuclear cell
T_{max}	time (observed time point) of C_{max}

1. SUMMARY OF BIOPHARMACEUTICAL STUDIES AND ASSOCIATED ANALYTICAL METHODS

1.1. Background and Overview

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.

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

For ART-naive HIV-infected patients, treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI). Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {27621}, {32519}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an oral prodrug of TFV. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs {26885}, {34210}.

TDF in combination with emtricitabine (FTC; F) forms a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients that can be combined with different third agents. The combination of FTC and TDF is used within several once-daily fixed-dose combinations (FDCs) (Truvada® [TVD; FTC/TDF], Atripla® [ATR; efavirenz (EFV)/FTC/TDF], Complera®/Eviplera® [FTC/rilpivirine (RPV)/TDF], and Stribild® [elvitegravir (EVG; E)/cobicistat (COBI; C)/FTC/TDF]). Availability of a stand-alone NRTI backbone is important when there is a medical need to use a third agent that is not part of an FDC (eg, ritonavir [RTV]-boosted PIs), and particularly to provide a range of treatment options in patients with virologic resistance to their third agent but not to the backbone.

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

Gilead Sciences (Gilead) has coformulated TAF (as TAF fumarate) with FTC into an FDC tablet available in 2 doses, F/TAF 200/25 mg and F/TAF 200/10 mg. Because TAF is a substrate of intestinal efflux transporters (ie, P-glycoprotein [P-gp]) and hepatic transporters (ie, organic anion transporting polypeptide [OATP]1B1 and OATP1B3), TAF exposure may be increased upon coadministration with inhibitors of these transporters with the effect apparently driven predominantly by P-gp inhibition (ie, by RTV or COBI; m2.7.2, Section 3.2.3.2.2). Therefore, the recommended F/TAF dose (200/25 mg or 200/10 mg based on third agent) is generally based on whether or not the coadministered agent has any clinically relevant effect on TAF exposure (eg, via inhibition of intestinal P-gp). Specifically, F/TAF 200/25 mg is recommended with unboosted third agents and F/TAF 200/10 mg is recommended with boosted third agents.

This submission for the N(t)RTI backbone F/TAF is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1472 and GS-US-311-1473) that pharmacokinetically bridge each F/TAF FDC tablet strength (200/25 mg or 200/10 mg) to Gilead's FDC tablet containing the HIV-1 INSTI EVG, the pharmacoenhancer COBI, FTC, and TAF (E/C/F/TAF 150/150/200/10 mg), for which clinical safety and efficacy have been established in a broad range of patient populations.

The pharmacokinetic (PK) and pharmacodynamic data from clinical studies conducted with F/TAF and E/C/F/TAF are supported with data from clinical studies conducted with TAF and FTC, and with data from nonclinical studies. Data from studies conducted with the darunavir (DRV; D)/C/F/TAF FDC support dosing recommendations.

A summary of the bioanalytical methods for quantitation of the components of F/TAF in the clinical development program are described in Section 1.1.3 with links to the current method validation reports.

A list of clinical studies presenting the analyte, biological matrix, current validation report, name of analytical method, calibration ranges, and a link to sample analysis reports (Appendix 16.1.10 of the corresponding clinical study reports [CSRs]) is included in Appendix 4.4.

A tabular summary of the long-term storage stability (LTSS) program for the analytes of F/TAF is presented in Section 1.1.5. A detailed tabular summary presented by clinical study that includes the analyte, biological matrices, study sample collection dates, study sample analysis dates, and transpired time (calculated time between the date of the first sample collection and the date of the last sample analysis), and the supporting LTSS data are provided in Appendix 4.5.

Bioanalytical methods for quantitation of coadministered drugs are summarized in Appendix 4.6.

1.1.1. Formulation Development

The commercial drug product is an FDC tablet containing 200 mg of FTC and 10 mg of TAF (F/TAF 200/10 mg), or 200 mg of FTC and 25 mg of TAF (F/TAF 200/25 mg). TAF is incorporated into the drug product as the hemifumarate form (referred to as TAF fumarate). Both tablet strengths contain the same active ingredients and excipients and differ only in the percent active and the composition of the film coating material.

FTC and TAF fumarate are blended, [redacted] with intragranular excipients, and lubricated with magnesium stearate to produce F/TAF final powder blends containing either [redacted]% w/w of TAF fumarate and [redacted]% w/w of FTC, or [redacted]% of TAF fumarate and [redacted]% of FTC. These F/TAF final powder blends are compressed into F/TAF 200/10 mg core tablets, or F/TAF 200/25 mg core tablets, respectively. Both tablet strengths have an identical tablet core weight of [redacted] mg. The F/TAF 200/10 mg tablet cores are film coated using [redacted] to produce F/TAF 200/10 mg film coated tablets. The F/TAF 200/25 mg tablet cores are film coated using [redacted] to produce F/TAF 200/25 mg film coated tablets.

The F/TAF tablet formulation evolved throughout clinical development. F/TAF tablet core formulations containing 200 mg of FTC and 25 mg of TAF, and 200 mg of FTC and 40 mg of TAF, were initially developed at a total core tablet weight of 450 mg and manufactured to evaluate the drug-drug interaction potential of F/TAF with efavirenz and with COBI-boosted DRV (GS-US-311-0101). Based on clinical demonstration of the ability of COBI to boost TAF exposure, the 40 mg dose of TAF was discontinued in favor of a 10 mg TAF dose. Tablet formulation compositions were then adjusted to accommodate the lower 10 mg TAF dose and to increase relative drug load, resulting in a total weight of 350 mg for both F/TAF 200/10 mg and F/TAF 200/25 mg core tablets. Higher relative drug load was shown to improve the solid-state chemical stability of TAF.

The commercial F/TAF 200/10 mg tablets are gray, rectangular-shaped, film-coated tablets with "GSI" debossed on one side and "210" on the other. F/TAF 200/10 mg tablets contain 200 mg of FTC and 10 mg of TAF and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The film-coat contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide black.

The commercial F/TAF 200/25 mg tablets are blue, rectangular-shaped, film-coated tablets with "GSI" debossed on one side and "225" on the other. F/TAF 200/25 mg tablets contain 200 mg of FTC and 25 mg of TAF and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The film-coat contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Blue #2/indigo carmine aluminum lake.

Commercial formulations are identical to formulations used in pivotal bioequivalence studies (GS-US-311-1472 and GS-US-311-1473), in the Phase 3 study (GS-US-311-1089), and in registration stability batches. The quantitative composition of F/TAF tablets is summarized in Appendix 4.1.

1.1.2. Dissolution Profile

According to the Biopharmaceutics Classification System (BCS), FTC is a high solubility, high permeability (BCS 1) compound. TAF is a high solubility, low permeability (BCS 3) compound.

Dissolution of the proposed commercial product was performed using a [redacted] rpm. [redacted] mL [redacted] pH [redacted] °C. The amount of each active ingredient dissolved was [redacted]

[redacted]

Dissolution profiles for commercial tablet formulations of F/TAF 200/10 mg tablets (Lot CR1308B) and F/TAF 200/25 mg tablets (CR1305B) are summarized in Appendix 4.2. The dissolution profile showed that [redacted]% [redacted] minutes for F/TAF 200/10 mg tablets and [redacted]% [redacted] minutes for F/TAF 200/25 mg tablets.

1.1.3. Bioanalytical Methods

1.1.3.1. Determination of TAF in Human Plasma

The TAF bioanalytical method was validated at [redacted], United States of America [USA]) for the determination of TAF in human plasma. The method involved protein precipitation extraction of TAF and its internal standard ([redacted]) from human plasma followed by liquid chromatography/tandem mass spectrometry (LC-MS/MS) with positive ionization. Bioanalytical method validation parameters are summarized in Table 1.

Table 1. Bioanalytical Method Validation for Determination of TAF in Human Plasma at [redacted]

	TAF
Calibrated Range (ng/mL)	1 to 1000
Lower Limit of Quantitation (ng/mL)	1
Interassay Precision Range (%CV)	1.8% to 7.3%
Interassay Accuracy Range (%RE)	−3.7% to 6.5%
Studies Supported	GS-US-120-0104, GS-US-120-0107, GS-US-120-0108, GS-US-120-0109, GS-US-120-0114, GS-US-120-0117, GS-US-120-0118, GS-US-120-1538, GS-US-120-1554, GS-US-292-0101, GS-US-292-0102, GS-US-292-0103, GS-US-292-0104, GS-US-292-0106, GS-US-292-0108, GS-US-292-0109, GS-US-292-0110, GS-US-292-0111,GS-US-292-0112, GS-US-292-1316, GS-US-299-0102, GS-US-311-0101, GS-US-311-1088, GS-US-311-1386, GS-US-311-1472, GS-US-311-1473, and GS-US-342-1167

Source: [redacted] 60-1115 Amendment 5

1.1.3.2. Determination of TFV in Human Plasma

The initial bioanalytical method for the determination of TFV in human plasma was developed and validated at [redacted]. The method involved solid phase extraction (SPE) of TFV and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 2.

Table 2. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted] ([redacted] Method 60-1116)

	TFV
Calibrated Range (ng/mL)	0.3 to 300
Lower Limit of Quantitation (ng/mL)	0.3
Interassay Precision Range (%CV)	2.7% to 8.4%
Interassay Accuracy Range (%RE)	0.0% to 3.0%
Studies Supported	GS-US-120-0104, GS-US-120-0107, GS-US-120-0108, GS-US-120-0109, GS-US-120-0117, GS-US-292-0101, GS-US-292-0102, GS-US-292-0103, GS-US-292-0104, GS-US-292-0108, GS-US-299-0102, GS-US-311-0101, and GS-US-342-1167

Source: [redacted] 60-1116 Amendment 3

The initial TFV bioanalytical method for the determination of TFV in human plasma was improved and validated at [redacted] using the improved liquid chromatographic separation method to support the F/TAF program. The method involved SPE of TFV and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 3.

Table 3. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted] ([redacted] Method 60-1352)

	TFV
Calibrated Range (ng/mL)	0.3 to 300
Lower Limit of Quantitation (ng/mL)	0.3
Interassay Precision Range (%CV)	1.7% to 7.9%
Interassay Accuracy Range (%RE)	−2.7% to 2.7%
Studies Supported	GS-US-120-0114, GS-US-120-0118, and GS-US-292-0110

Source: [redacted] 60-1352

The initial TFV bioanalytical method for the determination of TFV in human plasma was improved and validated at [redacted] using a smaller sample volume and an improved liquid chromatographic separation method to support the F/TAF program. This method involved SPE of TFV and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 4.

Table 4. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted] ([redacted] Method 60-1368)

	TFV
Calibrated Range (ng/mL)	0.3 to 300
Lower Limit of Quantitation (ng/mL)	0.3
Interassay Precision Range (%CV)	1.8% to 4.8%
Interassay Accuracy Range (%RE)	−2.7% to 2.7%
Studies Supported	GS-US-120-1538, GS-US-120-1554, GS-US-292-0104, GS-US-292-0106, GS-US-292-0109, GS-US-292-0111, GS-US-292-0112, GS-US-292-1316, and GS-US-311-1088

Source: [redacted] 60-1368

1.1.3.3. Determination of TAF and TFV in Human Urine

The bioanalytical method for the simultaneous determination of TAF and TFV in human urine was developed and validated at [redacted]. The method involved protein precipitation extraction of TAF, TFV, and internal standards ([redacted] and [redacted], respectively) from human urine followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 5.

Table 5. Bioanalytical Method Validation for Determination of TAF and TFV in Human Urine at [redacted]

	TAF	TFV
Calibrated Range (ng/mL)	2 to 1000	10 to 5000
Lower Limit of Quantitation (ng/mL)	2	10
Interassay Precision Range (%CV)	2.5% to 15.2%	2.6% to 9.2%
Interassay Accuracy Range (%RE)	−0.4% to 3.6%	−0.5% to 1.3%
Studies Supported	GS-US-120-0108 and GS-US-120-0109	

Source: [redacted] 60-1220 Amendment 1

1.1.3.4. Determination of TFV and FTC in Human Plasma

The TFV and FTC bioanalytical method was developed and validated at Gilead for the determination of TFV and FTC in human plasma. The method involved the extraction of TFV, FTC, and internal standards ([redacted] and [redacted]) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 6.

Table 6. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma at Gilead

	TFV	FTC
Calibrated Range (ng/mL)	10 to 1000	5 to 2000
Lower Limit of Quantitation (ng/mL)	10	5
Interassay Precision Range (%CV)	4.37% to 7.85%	3.98% to 9.47%
Interassay Accuracy Range (%RE)	−5.2% to 4.0%	−1.7% to 8.0%
Studies Supported	FTC-114 and GS-US-174-0105	

Source: Gilead 15401v9

The combined TFV and FTC bioanalytical method was improved and validated at [redacted] for the determination of TFV and FTC in human plasma. The method involved the extraction of TFV, FTC, and stable isotope internal standards ([redacted] and [redacted], respectively) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 7.

Table 7. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma at [redacted]

	TFV	FTC
Calibrated Range (ng/mL)	5 to 3000	5 to 3000
Lower Limit of Quantitation (ng/mL)	5	5
Interassay Precision Range (%CV)	2.4% to 6.5%	1.4% to 5.7%
Interassay Accuracy Range (%RE)	−4.7% to 2.0%	−7.8% to 2.4%
Studies Supported	GS-US-292-0101, GS-US-292-0102, GS-US-292-0104, GS-US-292-0106, GS-US-292-0111, GS-US-292-0112, and GS-US-292-1316, and GS-US-342-1167 GS-US-292-0103, GS-US-292-0108, and GS-US-311-0101 (FTC only)	

Source: [redacted] 42-0831 Amendment 5

1.1.3.5. Determination of FTC in Human Plasma

The initial FTC human plasma bioanalytical method was developed and validated at Gilead for the analysis of all FTC clinical study samples except for 1 study conducted by [redacted] in 19[redacted] (Study 143-001). The proprietary method used by [redacted] to analyze plasma samples collected in Study 143-001 was a high-performance liquid chromatography with UV detection (HPLC-UV) assay with a lower limit of quantitation (LLOQ) of 80 ng/mL. Gilead does not have access to validation reports from [redacted] and is unable to provide additional information.

The initial Gilead (formerly [redacted]) FTC plasma method involved SPE of FTC and its internal standard ([redacted]) from human plasma followed by

LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 8.

Table 8. Bioanalytical Method Validation for Determination of FTC in Human Plasma at Gilead

	FTC
Calibrated Range (ng/mL)	5 to 5000
Lower Limit of Quantitation (ng/mL)	5
Interassay Precision Range (%CV)	4.89% to 10.69%[a]
Interassay Accuracy Range (%RE)	0.0% to 5.2%[a]
Studies Supported	FTC-101, FTC-106, FTC-107, FTC-108, FTC-109, FTC-110, FTC-111, and FTC-203 FTC-107 (human dialysate)

a Included lower limit of quantitation data.
Source: [redacted] 7536v6

1.1.3.6. Determination of FTC and Emivirine in Human Plasma

A combined FTC and emivirine bioanalytical method was developed and validated at Gilead for the determination of FTC and emivirine in human plasma. The method involved SPE of FTC, emivirine, and internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 9.

Table 9. Bioanalytical Method Validation for Determination of FTC and Emivirine in Human Plasma at Gilead

	FTC	Emivirine
Calibrated Range (ng/mL)	10 to 2500	20 to 10,000
Lower Limit of Quantitation (ng/mL)	10	20
Interassay Precision Range (%CV)	3.7% to 9.2%	3.2% to 4.3%
Interassay Accuracy Range (%RE)	−0.4% to 1.8%	−3.7% to 6.2%
Studies Supported	FTC-102, FTC-303, and FTCB-101	

Source: [redacted] 6879v4

1.1.3.7. Determination of FTC, Zidovudine, and Stavudine in Human Plasma

A combined FTC, zidovudine, and stavudine bioanalytical method was developed and validated at Gilead for the determination of FTC, zidovudine, and stavudine in human plasma. The method involved SPE of FTC, zidovudine, and stavudine, and internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 10.

Table 10. Bioanalytical Method Validation for Determination of FTC, Zidovudine, and Stavudine in Human Plasma at Gilead

	FTC	Zidovudine	Stavudine
Calibrated Range (ng/mL)	10 to 3500	10 to 3500	50 to 3500
Lower Limit of Quantitation (ng/mL)	10	10	50
Interassay Precision Range (%CV)	3.52% to 8.04%	6.17% to 9.15%	7.50% to 11.85%
Interassay Accuracy Range (%RE)	−5.9% to 4.8%	−1.6% to 3.6%	−6.6% to 2.9%
Studies Supported	FTC-103		

Source: [redacted] 7969v1

1.1.3.8. Determination of FTC in Human Urine

The initial FTC human urine bioanalytical method was developed and validated at Gilead for the analysis of all FTC clinical study samples except for 1 study (Study 143-001) conducted by [redacted] in 19[redacted]. The proprietary method used by [redacted] to analyze urine samples collected from Study 143-001 was an HPLC-UV assay with an LLOQ of 1000 ng/mL. Gilead does not have access to validation reports from [redacted] and is unable to provide additional information.

The initial FTC urine bioanalytical method involved SPE of FTC and its internal standard ([redacted]) from human urine followed by LC-MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 11.

Table 11. Bioanalytical Method Validation for Determination of FTC in Human Urine at Gilead ([redacted] Method 2638)

	FTC
Calibrated Range (ng/mL)	250 to 5000
Lower Limit of Quantitation (ng/mL)	250
Intraassay Precision Range (%CV)	Not performed
Intraassay Accuracy Range (%RE)	−19.2% to 0.4%
Studies Supported	FTC-101

Source: [redacted] 2638v1

The initial FTC urine bioanalytical method was improved by changing it to an LC-MS/MS method for the determination of FTC in human urine. The method involved protein precipitation extraction of FTC and its internal standard ([redacted]) from human urine followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 12.

Table 12. Bioanalytical Method Validation for Determination of FTC in Human Urine at Gilead ([redacted] Method 8361)

	FTC
Calibrated Range (ng/mL)	2500 to 250,000
Lower Limit of Quantitation (ng/mL)	2500
Interassay Precision Range (%CV)	5.2% to 9.7%
Interassay Accuracy Range (%RE)	−4.0% to 3.3%
Studies Supported	FTC-106, FTC-107, FTC-108, and FTC-110

Source: [redacted] 8361v2

1.1.4. Cross-Validations

Transfer of bioanalytical methods between different bioanalytical laboratories included refinements in the chromatographic conditions, implementation of stable isotope-labeled internal standards, and qualification of new calibrated ranges, as applicable. Cross validations with spiked matrix standards and pooled subject samples were conducted at each bioanalytical laboratory to establish interlaboratory reliability. All of the methods met the precision and accuracy run acceptance criteria stated in method validation standard operating procedures.

1.1.5. Long-Term Storage Stability

Analytical support for the F/TAF program includes extensive LTSS studies (Table 13), including combination stability of TAF, TFV, and FTC (Table 14) within biological matrices studied.

Table 13. Long-Term Storage Stability of TAF, TFV, and FTC

Analyte	Matrix	LTSS Data Available	Most Current Validation Report
TAF	Plasma	520 days at −70°C	[redacted] 60-1115 Amendment 5
TAF	Urine	103 days at −70°C	[redacted] 60-1220 Amendment 1
TFV	Plasma	1092 days at −70°C	[redacted] 60-1116 Amendment 3
TFV	Urine	225 days at −70°C	[redacted] 60-1270 Amendment 2
FTC	Plasma	1426 days at −80°C	Gilead 15401v9
FTC	Urine	664 days at −70°C	[redacted] 42-1236 Amendment 2

Table 14. Combination Stability of TAF, TFV, and FTC

Primary Analyte	Primary Analyte in the Presence of:	Matrix	LTSS Data Available	Most Current Validation Report
TAF	FTC TFV EVG COBI EFV RPV ATV DRV	Plasma	487 days at −70°C	[redacted] 60-1325 Amendment 1
TFV[a]	TAF FTC EVG COBI EFV RPV ATV DRV	Plasma	485 days at −70°C	[redacted] 60-1325 Amendment 1
FTC	TAF TFV EVG COBI EFV RPV ATV DRV	Plasma	485 days at −70°C	[redacted] 60-1325 Amendment 1
TFV[b]	TAF FTC EVG COBI EFV RPV ATV DRV	Plasma	485 days at −70°C	[redacted] 60-1325 Amendment 1

LTSS = long-term storage stability
a At a calibrated range of 5 to 3000 ng/mL.
b At a calibrated range of 0.3 to 300 ng/mL as a metabolite of TAF.
Non-Gilead/pertinent analytes (eg, EFV, RPV, ATV, DRV) are included and tested as ongoing potential combination drug programs.
Source: [redacted] 60-1325 Amendment 1

In the F/TAF program, all reported data are from samples analyzed within the timeframe supported by LTSS data.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Summaries of clinical studies included in this marketing application are presented in m2.7.2 for clinical pharmacology studies, m2.7.3 for clinical efficacy studies, and m2.7.4 for clinical safety studies.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Bioavailability

3.1.1. Bioavailability of TAF

Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (~ 40%). TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI or RTV) reduces P-gp-mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. Cumulative results from Studies GS-US-311-1473 (m2.7.2, Section 2.2.1.3), GS-US-292-0103 (m2.7.2, Section 2.2.3.2), and GS-US-292-0101 (m2.7.2, Section 2.2.3.1), indicated that TAF exposure following a 10-mg dose (either as a single agent coadministered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg either as a single agent or as a component of F/TAF. Results from Study GS-US-311-1473 (Table 15) demonstrate bioequivalence in TAF exposure between F/TAF (200/25 mg) and E/C/F/TAF (150/150/200/10 mg); the results of the integrated ad hoc PK analysis support this conclusion (m2.7.2, Section 3.2.1.4.1, Table 55).

As TAF is not metabolized by CYP enzymes except for weak metabolism observed for CYP3A4 in vitro, CYP inducers are not expected to have a relevant effect on TAF PK; however, most CYP inducers are also P-gp inducers, and coadministration with P-gp inducers may decrease the absorption of TAF. Coadministration with a modest CYP3A and P-gp inducer (ie, EFV) resulted in slightly lower TAF exposure (14% to 22%; m2.7.2, Section 3.2.3.2.2), and coadministration with a weak CYP3A and P-gp inducer (ie, RPV) resulted in no change to TAF exposure. As such, minimal effect on TAF exposure is expected upon coadministration of F/TAF with a modest or weak CYP3A/P-gp inducer. Coadministration of F/TAF with potent CYP3A/P-gp inducers is not recommended.

3.1.2. Bioavailability of FTC

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

3.2. Bioequivalence of F/TAF Tablet to E/C/F/TAF Tablet

Bioequivalence between the TAF and FTC components of each F/TAF FDC and the TAF and FTC components of E/C/F/TAF was established in 2 pivotal Phase 1 bioequivalence studies (GS-US-311-1473 and GS-US-311-1472). Both of these studies were randomized, open-label, single-dose, 2-way, crossover studies in healthy subjects.

Statistical comparisons of plasma TAF and FTC PK parameters AUC_{last}, AUC_{inf}, and C_{max} are presented in Table 15 for F/TAF (200/25 mg) versus E/C/F/TAF (150/150/200/10 mg) and in Table 16 for F/TAF (200/10 mg) + EVG+COBI versus E/C/F/TAF (150/150/200/10 mg).

Study GS-US-311-1473 demonstrated bioequivalent TAF exposure between F/TAF 200/25 mg and E/C/F/TAF, and Study GS-US-311-1472 demonstrated bioequivalent TAF exposure between F/TAF 200/10 mg administered simultaneously with EVG and COBI and E/C/F/TAF. In each study, the geometric least-squares mean (GLSM) ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria specified for bioequivalence. Further details for Studies GS-US-311-1473 and GS-US-311-1472 are presented in m2.7.2, Section 2.2.1.3 and Section 2.2.1.2, respectively.

Table 15. Study GS-US-311-1473: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (TAF or FTC PK Analysis Set)

TAF PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32 (96.48, 104.31)
AUC_{inf} (ng•h/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54 (94.61, 102.62)
C_{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63 (95.46, 112.49)
FTC PK Parameter	**Test**		**Reference**		**GLSM Ratio (90% CI), %**
	n	**Mean (%CV)**	**n**	**Mean (%CV)**	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	116	9423.9 (19.3)	116	10475.3 (19.7)	90.01 (88.88, 91.16)
AUC_{inf} (ng•h/mL)	116	9654.6 (19.3)	116	10706.6 (19.6)	90.20 (89.06, 91.35)
C_{max} (ng/mL)	116	1577.4 (26.8)	116	1601.7 (19.6)	97.26 (94.57, 100.03)

Source: m5.3.1.2, GS-US-311-1473, Section 15.1, Tables 4.2.1, 4.2.2, 5.1, 5.3.1, and 5.3.2

Table 16. Study GS-US-311-1472: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (TAF or FTC PK Analysis Set)

TAF PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/10 mg) +EVG+COBI (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	97	336.6 (33.9)	99	340.2 (33.8)	97.96 (94.69,101.34)
AUC_{inf} (ng•h/mL)	97	351.8 (31.0)	99	354.1 (32.9)	98.34 (94.81,101.99)
C_{max} (ng/mL)	97	301.6 (48.8)	99	310.3 (48.7)	96.86 (89.36,104.99)
FTC PK Parameter	**Test**		**Reference**		**GLSM Ratio (90% CI), %**
	n	**Mean (%CV)**	**n**	**Mean (%CV)**	
F/TAF (200/10 mg) +EVG+COBI (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	97	10,159.2 (17.2)	99	10,086.8 (15.9)	99.84 (98.41,101.29)
AUC_{inf} (ng•h/mL)	97	10,535.1 (27.0)	99	10,294.4 (15.8)	100.67 (98.24,103.16)
C_{max} (ng/mL)	97	1660.8 (20.6)	99	1662.6 (19.1)	99.57 (96.78,102.44)

Source: m5.3.1.2, GS-US-311-1472, Section 15.1, Tables 4.1.1, 4.1.2, 5.3.1I, and 5.3.2I

3.3. Bioequivalence of F/TAF to TAF and FTC Single Agents

An additional bioequivalence study, Study GS-US-311-1088 with F/TAF (200/25 mg), was conducted to establish the bioequivalence of F/TAF FDC to FTC and TAF coadministered as individual agents. This study was a Phase 1, randomized, open-label, single-dose, 2-way crossover study in healthy subjects.

Statistical comparisons of plasma TAF and FTC PK parameters AUC_{last}, AUC_{inf}, and C_{max} (F/TAF versus FTC+TAF) are presented in Table 17.

The GLSM ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria specified for bioequivalence, demonstrating the bioequivalence of F/TAF (200/25 mg) FDC tablet and FTC and TAF coadministered as individual agents.

Table 17. Study GS-US-311-1088: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

	Mean (%CV) by Treatment		
	F/TAF (Test) (N = 55)	FTC+TAF (Reference) (N = 55)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{last} (ng•h/mL)	265.1 (42.9)	253.6 (33.7)	102.68 (95.78, 110.09)
AUC_{inf} (ng•h/mL)	273.8 (45.4)[a]	257.9 (34.4)[b]	105.77 (97.26, 115.01)
C_{max} (ng/mL)	232.4 (51.9)	248.1 (44.7)	92.59 (82.31, 104.16)
FTC PK Parameter			
AUC_{last} (ng•h/mL)	9175.8 (17.4)	9596.0 (22.9)	96.16 (94.29, 98.08)
AUC_{inf} (ng•h/mL)	9387.7 (17.3)	9821.6 (22.5)	96.09 (94.24, 97.96)
C_{max} (ng/mL)	1873.5 (27.2)	1767.6 (22.8)	104.98 (100.75, 109.39)

a n = 43
b n = 48
Source: m5.3.1.2, GS-US-311-1088, Section 15.1, Tables 5.1, 5.2, and 6.1

3.4. Effect of Food

3.4.1. TAF

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

In Study GS-US-311-1386, a randomized, open-label, single-dose, 2-treatment, 2-period, crossover study of the effect of food on the PK of the TAF component of F/TAF (200/25 mg), administration of F/TAF under fed conditions resulted in increased overall TAF exposure, lower C_{max}, and delayed T_{max}. Administration of F/TAF (200/25 mg) under fed conditions resulted in an increase in TAF exposure (AUC_{last}) by 77% compared with administration under fasting conditions, with a decrease of 15% in TAF C_{max} and delay in TAF T_{max} from 0.50 hour under fasting conditions to 1.00 hour under fed conditions. Given the wide range of safe and efficacious TAF exposure established in the Phase 3 E/C/F/TAF studies (predicted individual steady-state mean [95% CI, %CV] AUC 206.4 ng•h/mL [55.6 to 526.1 ng•h/mL, 71.8%] and m2.7.2 Sections 3.3.1.1 and 3.3.2.1), the differences in TAF PK under fed and fasting conditions are not considered clinically relevant.

In Study GS-US-292-0110, a randomized, open-label, single-dose, 3-treatment, 3-period, 6-sequence, crossover study of the effect of food on the PK of the TAF component of E/C/F/TAF, administration of E/C/F/TAF under fed conditions did not affect overall TAF exposure, but resulted in a lower C_{max} and delayed T_{max}. Administration of E/C/F/TAF with a high-fat meal resulted in an increase of 17% in TAF exposure (AUC_{last}) compared with

administration following an overnight fast, with a 37% decrease in TAF C_{max} and a delay in TAF T_{max} from 0.50 hour under fasting conditions to 1.00 hour under fed conditions. These differences in TAF PK parameters upon E/C/F/TAF administration with food (versus fasted) are not considered clinically relevant.

The differential effect of food observed between Studies GS-US-311-1386 and GS-US-292-0110 is likely due to the oral bioavailability of TAF when administered in the absence or presence of a boosting agent. Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (~ 40%). TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI or RTV) reduces P-gp-mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. As a result, the effect of food on TAF absorption is smaller when administered in the presence of a boosting agent.

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

3.4.2. FTC

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

3.5. Conclusions

The bioavailability of TAF is estimated to be ~ 40%. Drugs that strongly inhibit P-gp activity increase TAF bioavailability; for example, inhibition of P-gp by boosting agents such as COBI or RTV increase the fraction of the TAF dose absorbed to approximately 90%. Minimal effect on TAF exposure is expected upon coadministration of F/TAF with a modest or weak CYP3A/P-gp inducer, but coadministration of F/TAF with potent CYP3A/P-gp inducers is not recommended. Exposure to TAF may be affected by inhibitors of OATP1B1 and OATP1B3 or by genetic polymorphisms affecting their transport activities; however, these effects are not expected to be clinically relevant given the high passive permeability of TAF.

The bioequivalence of F/TAF to E/C/F/TAF or F/TAF to FTC and TAF coadministered as individual agents in support of the marketing application was evaluated in Studies GS-US-311-1473 (F/TAF 200/25 mg vs E/C/F/TAF), GS-US-311-1472 (F/TAF 200/10 mg + COBI+EVG vs E/C/F/TAF), and GS-US-311-1088 (F/TAF 200/25 mg vs FTC 200 mg + TAF 25 mg). The results of these studies demonstrated that:

- The FTC and TAF components of F/TAF FDC (200/25 mg) are bioequivalent to E/C/F/TAF FDC (150/150/200/10 mg)

- The FTC and TAF components of F/TAF FDC (200/10 mg) administered simultaneously with EVG and COBI are bioequivalent to E/C/F/TAF FDC (150/150/200/10 mg)

- The FTC and TAF components of F/TAF FDC (200/25 mg) are bioequivalent to its individual components administered simultaneously

The effect of food on FTC and TAF PK has been evaluated in Studies GS-US-292-0110 (TAF 10 mg + COBI [as part of E/C/F/TAF]) and GS-US-311-1386 (TAF 25 mg [as part of F/TAF]). The results of these 2 studies demonstrated differences in FTC and TAF PK under fasted and fed conditions that are not considered clinically relevant; therefore, F/TAF may be administered without regard to food.

4. APPENDICES

Appendix Number	Appendix Title
4.1	Quantitative Composition of the Proposed Commercial Formulation of F/TAF FDC Tablets
4.2	Summary of In Vitro Dissolution Profiles for the Formulation of F/TAF FDC Tablets Lot No. CP[redacted]01B
4.3	Tabular Summary of Biopharmaceutic Studies
4.4	Summary of Analytical Methods for Individual Studies
4.5	Summary of Long-Term Storage Stability Data for Individual Studies
4.6	Determination of Coadministered Drugs in Human Plasma Supporting F/TAF Studies

4.1. Quantitative Composition of the Proposed Commercial Formulation of F/TAF FDC Tablets

Ingredient	F/TAF 200/10 mg		F/TAF 200/25 mg		Quality Standard	Function
	% w/w	mg/tablet	% w/w	mg/tablet		
Intragranular						
Emtricitabine[a]	[redacted]	200.0	[redacted]	200.0	In-house	Active Ingredient
Tenofovir Alafenamide Fumarate[a]	[redacted]	11.2[b]	[redacted]	28.0[c]	In-house	Active Ingredient
Microcrystalline Cellulose[a]	[redacted]	[redacted]	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Croscarmellose Sodium	[redacted]	[redacted]	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Magnesium Stearate	[redacted]	[redacted]	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Extragranular						
Magnesium Stearate	[redacted]	[redacted]	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Total	100	[redacted]	100	[redacted]	--	--
Film-Coat						
[redacted]	[redacted]	[redacted]			In-house	[redacted]
[redacted]			[redacted]	[redacted]	In-house	[redacted]
[redacted]	--	--	--	--	USP, Ph. Eur.	[redacted]

NF = National Formulary; Ph. Eur. = European Pharmacopeia; TAF = tenofovir alafenamide; USP = United States Pharmacopeia

a [redacted]

b 11.2 mg of tenofovir alafenamide fumarate corresponds to 10 mg of tenofovir alafenamide.

c 28.0 mg of tenofovir alafenamide fumarate corresponds to 25 mg of tenofovir alafenamide.

d [redacted] contains [redacted] % w/w ([redacted] mg) Polyvinyl Alcohol-part hydrolyzed [redacted] % w/w ([redacted] mg) Titanium Dioxide [redacted] % w/w ([redacted] mg) Macrogol/PEG [redacted] [redacted] % w/w ([redacted] mg) Talc [redacted] % w/w ([redacted] mg) Iron Oxide, Black [redacted].

e [redacted] contains [redacted] % w/w ([redacted] mg) Polyvinyl Alcohol-part hydrolyzed [redacted] % w/w ([redacted] mg) Titanium Dioxide [redacted] % w/w ([redacted] mg) Macrogol/PEG [redacted] [redacted] % w/w ([redacted] mg) Talc [redacted] % w/w ([redacted] mg) FD&C Blue #2/Indigo Carmine Aluminum Lake.

f [redacted].

Source: m3.2.P.1, Table 1

4.2. Summary of In Vitro Dissolution Profiles of FTC and TAF From F/TAF 200/10 mg Tablets (CR[redacted]08B) and F/TAF 200/25 mg Tablets (CR[redacted]05B)

Time (minutes)	% Dissolved			
	F/TAF 200/10 mg CR[redacted]08B		F/TAF 200/25 mg CR[redacted]05B	
	FTC	TAF	FTC	TAF
5	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]

Dissolution condition: 50 mM sodium citrate buffer pH 5.5, 500 mL 37 ºC, 75 rpm
Source: m3.2.P.5.4, Table 8 and Table 13

4.3. Tabular Summary of Biopharmaceutic Studies

Tabular summaries of biopharmaceutic studies included in this marketing application are provided in m2.7.2.

4.4. Summary of Analytical Methods for Individual Studies

A tabular summary of the analytical methods, method validation reports, and sample analysis reports for individual studies are provided below for studies conducted to support the F/TAF clinical development program. Study numbers shown in **bold** have not been previously submitted to regulatory agencies.

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
143-001	Human Plasma	FTC	Method documents not available (property of [redacted])	HPLC-UV	80 ng/mL (LLOQ)	Sample analysis reports not available (property of [redacted])
	Human Urine	FTC		HPLC-UV	1000 ng/mL (LLOQ)	
FTC-101	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 8200v4
	Human Urine	FTC	[redacted] 2638v1	LC/MS (SIM)	250-5000 ng/mL	
FTC-102	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS	10-2500 ng/mL	[redacted] 7027v3
FTC-103	Human Plasma	FTC	[redacted] 7969v1	LC-MS/MS	10-3500 ng/mL	[redacted] 8206v3
		Zidovudine			10-3500 ng/mL	
		Stavudine			50-3500 ng/mL	
FTC-106	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 8603v2
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS	2.5-250 µg/mL	

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
FTC-107	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 10824v1
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS	2.5-250 µg/mL	
	Human Dialysate	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	
FTC-108	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 11088v1
		Penciclovir	[redacted] V-01-BIO-TP0260-01	LC-MS/MS	25-2000 ng/mL	
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS	2500-250,000 ng/mL	
		Penciclovir	[redacted] V-01-BIO-TP0260-01	LC-MS/MS	2500-250,000 ng/mL	
FTC-109	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 8737v2
FTC-110	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 11694v1
	Human Urine	FTC	[redacted] 8361v2	LC/MS-MS	2500-250,000 ng/mL	
FTC-111	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 11378v1
FTC-114	Human Plasma	FTC	Gilead 15401v9	LC-MS/MS	5-2000 ng/mL	[redacted] 15408v1
		TFV			10-1000 ng/mL	
FTC-203	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-2000 ng/mL	Gilead 15289v2

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
FTC-303	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS	10-2500 ng/mL	[redacted] 6564v3
FTCB-101	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS	10-2500 ng/mL	[redacted] 6525v2
GS-US-120-0104	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1128A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1128B
		TFV	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1128C
GS-US-120-0107	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1230A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1230B
GS-US-120-0108	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1269A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1269B
	Human Urine	TAF	[redacted] 60-1220 Amendment 1	LC-MS/MS	2-1000 ng/mL	[redacted] 60-1269C
		TFV			10-5000 ng/mL	
GS-US-120-0109	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1245A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1245B
	Human Urine	TAF	[redacted] 60-1220 Amendment 1	LC-MS/MS	2-1000 ng/mL	[redacted] 60-1245C
		TFV			10-5000 ng/mL	
GS-US-120-0114	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1344A
		TFV	[redacted] 60-1352	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1344B Amendment 1
GS-US-120-0117	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1330A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1330B Amendment 1
		RPV	[redacted] 42-1102 Amendment 3	LC-MS/MS	1-500 ng/mL	[redacted] 60-1330C

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
GS-US-120-0118	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1369A Amendment 1
		TFV	[redacted] 60-1352	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1369B Amendment 1
		ATZ	[redacted] 42-0830 Amendment 3	LC-MS/MS	10-5000 ng/mL	[redacted] 60-1369C
		DRV	[redacted] 42-0902 Amendment 3	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1369D
		LPV	[redacted] 42-1359 Amendment 1	LC-MS/MS	100-20,000 ng/mL	[redacted] 60-1369E
		DTG	[redacted] 42-1369 Amendment 2	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1369F
GS-US-120-1538	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1463A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1463B
		MDZ	[redacted] 42-0624 Addendum 3	LC-MS/MS	0.1-100 ng/mL	[redacted] 60-1463C
		1'-OH MDZ				
GS-US-120-1554	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1460A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1460B
		RPV	[redacted] 42-1408	LC-MS/MS	1-500 ng/mL	[redacted] 60-1460C
GS-US-174-0105	Human Plasma	FTC	Gilead 15401v9	LC-MS/MS	5-2000 ng/mL	Gilead Sciences S-174-01
		TFV	Gilead 15401v9	LC-MS/MS	10-1000 ng/mL	
	Human Whole Blood	Tacrolimus	[redacted] 6332-138 original and Amendment 1	LC-MS/MS	0.1-10 ng/mL	[redacted] 6511-218
GS-US-292-0101	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1119A
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1119B
		TFV				
		TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1119C
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1119D

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
GS-US-292-0102	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1222A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1222B
		COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1222C
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1222D [redacted] 60-1222E
		TFV				
GS-US-292-0103	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1142A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1142B
		COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1142C
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1142D
GS-US-292-0104	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1312A Amendment 1
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1312B
		TFV	[redacted] 60-1368	LC-MS/MS		
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1312C
		TFV				
GS-US-292-0106	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1314A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1314B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1314C
		TFV				
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1314D
		COBI			5-2500 ng/mL	

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
GS-US-292-0108	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-12103A
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-12103B
		TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-12103C
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-12103D
GS-US-292-0109	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1315A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1315B
GS-US-292-0110	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1358A
		TFV	[redacted] 60-1352	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1358B
GS-US-292-0111	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1313A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1313B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1313C
		TFV				
GS-US-292-0112	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1316A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1316B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1316C
		TFV				
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1316D
		COBI			5-2500 ng/mL	
		Iohexol	[redacted] 2100-775	LC-MS/MS	1000-500,000 ng/mL	[redacted] 8283389

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
GS-US-292-1316	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1411A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1441B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1411C
		TFV				
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1411D
		COBI			5-2500 ng/mL	
		Sertraline	[redacted] 42-1402	LC-MS/MS	0.2-200 ng/mL	[redacted] 60-1411E
GS-US-299-0102	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1223A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1223B
		COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1223C
		DRV	[redacted] 42-0902 Amendment 3	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1223D
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1223E
		TFV				[redacted] 60-1223F
GS-US-311-0101	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1125A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1125B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1125C
		DRV	[redacted] 42-0902 Amendment 3	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1125D
		EFV	[redacted] 42-0827 Amendment 3	LC-MS/MS	5-5000 ng/mL	[redacted] 60-1125E
		COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1125F
GS-US-311-1088	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-13100A
		TFV	[redacted] 60-1368	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-13100B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-13100C

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
GS-US-311-1386	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1423A
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-14223B
GS-US-311-1472	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1442A
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1442B Amendment 1
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1442C Amendment 1
		COBI	[redacted] 60-1343 Amendment 2	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1442C Amendment 1
GS-US-311-1473	Human Plasma	TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1443A
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1443B
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1443C
		COBI	[redacted] 60-1343 Amendment 2	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1443C
GS-US-342-1167	Human Plasma	SOF	[redacted] 60-1323 Amendment 2	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1390A
		GS-566500			10-5000 ng/mL	
		GS-331007			10-5000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1390B
		TFV				[redacted] 60-1390C
		EFV	[redacted] 42-1216 Amendment 1	LC-MS/MS	5-5000 ng/mL	[redacted] 60-1390D
		RPV	[redacted] 42-1102 Amendment 3	LC-MS/MS	1-500 ng/mL	[redacted] 60-1390E
		DTG	[redacted] 42-1369 Amendment 2	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1390F
		TAF	[redacted] 60-1115 Amendment 5	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1390G
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1390H
		COBI	[redacted] 60-1343 Amendment 2	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1390I

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Calibration Range	Sample Analysis Report
		EVG			20-10,000 ng/mL	
		GS-5816	[redacted]-102TRA1	LC-MS/MS	1-1000 ng/mL	[redacted]-278

1'-OH MDZ = midazolam metabolite (1′-hydroxymidazolam); ATV = atazanavir; COBI = cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HPLC-UV = high-performance liquid chromatography with ultraviolet detection; LC-MS/MS = liquid chromatography/tandem mass spectrometry; LPV = lopinavir; MDZ = midazolam; [redacted]; RPV = rilpivirine; TAF = tenofovir alafenamide; TFV = tenofovir

a Study numbers shown in **bold** have not been previously submitted to regulatory agencies.

b The most current validation reports are listed. Validation reports included in the corresponding CSRs were those in effect at the time of final approval of the CSR.

4.5. Summary of Long-Term Storage Stability Data for Individual Studies

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
FTC-103	Human Plasma	FTC	[redacted]19 through [redacted]19	[redacted]19 through [redacted]19	68 days at −70°C	1426 days at −80°C	Gilead 15401v9	[redacted] 8206v2
		Zidovudine	[redacted]19 through [redacted]19	[redacted]19 through [redacted]19	68 days at −70°C	87 days at −70°C	[redacted] 42-0415	[redacted] 8206v2
		Stavudine	[redacted]19 through [redacted]19	[redacted]19 through [redacted]19	68 days at −70°C	87 days at −70°C	[redacted] 42-0415	[redacted] 8206v2
FTC-107	Human Plasma	FTC	[redacted]19 through [redacted]20	[redacted]20 through [redacted]20	373 days at −80°C	1426 days at −80°C	Gilead 15401v9	[redacted] S-01-TP0006-01
	Human Urine	FTC	[redacted]19 through [redacted]20	[redacted]20 through [redacted]20	373 days at −80°C	664 days at −70°C	[redacted] 42-1236 Amendment 2	
	Human Dialysate	FTC	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	275 days at −80°C	460 days at −80°C	[redacted] 20050v1_V_FTC_DDI_ Human_Plasma_V1	
FTC-108	Human Plasma	FTC	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	154 days at −80°C	1426 days at −80°C	Gilead 15401v9	[redacted] S-01-TP0006-03
		Penciclovir	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	236 days at −80°C	Not reported	[redacted] V-01-BIO-TP0260-01	
	Human Urine	FTC	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	222 days at −80°C	294 days at −80°C	[redacted] 8361v2	
		Penciclovir	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	258 days at −80°C	Not reported	[redacted] V-01-BIO-TP0260-01	

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
FTC-111	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	57 days at −80°C	1426 days at −80°C	Gilead 15401v9	[redacted] S-01-BIO-TP0006-05
FTC-114	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	57 days at −80°C	1426 days at −80°C	Gilead 15401v9	[redacted] S-03-BIO-TP0006-05
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	44 days at −80°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] S-03-BIO-TP0006-05
FTC-203	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	1298 days at −70°C	1426 days at −80°C	Gilead 15401v9	[redacted] S-03-BIO-TP0006-02
FTC-303	Human Plasma	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	[redacted] 19[redacted] through [redacted] 19[redacted]	334 days at −80°C	1426 days at −80°C	Gilead 15401v9	[redacted] 6564v3
GS-US-120-0104	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	228 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1128A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	258 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1128B
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	251 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1128C
GS-US-120-0107	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	102 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1230A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	116 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1230B

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-120-0108	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	95 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1269A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	98 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1269B
	Human Urine	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	103 days at −70°C	103 days at −70°C	[redacted] 60-1220 Amendment 1	[redacted] 60-1269C
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	103 days at −70°C	225 days at −70°C	[redacted] 60-1270 Amendment 2	
GS-US-120-0109	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	43 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1245A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	30 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1245B
	Human Urine	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	29 days at −70°C	103 days at −70°C	[redacted] 60-1220 Amendment 1	[redacted] 60-1245C
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	29 days at −70°C	225 days at −70°C	[redacted] 60-1270 Amendment 2	
GS-US-120-0114	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	87 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1344A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	106 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1344B Amendment 1

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-120-0117	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	30 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1330A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	41 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1330B Amendment 1
		RPV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	41 days at −70°C	783 days at −70°C	[redacted] 42-1102 Amendment 3	[redacted] 60-1330C
GS-US-120-0118	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	51 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1369A Amendment 01
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	46 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1369B Amendment 01
		ATZ	[redacted]p 2013 through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	24 days at −70°C	721 days at −70°C	[redacted] 42-0830 Amendment 3	[redacted] 60-1369C
		DRV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	23 days at −70°C	1635 days at −70°C	[redacted] 42-0902 Amendment 3	[redacted] 60-1369D
		LPV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	12 days at −70°C	43 days at −70°C	[redacted] 42-1359 Amendment 1	[redacted] 60-1369E
		DTG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	20 days at −70°C	77 days at −70°C	[redacted] 42-1369 Amendment 2	[redacted] 60-1369F

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-120-1538	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	29 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1463A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	26 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1463B
		MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	35 days at −70°C	135 days at −70°C	[redacted] 42-0624 Addendum 3	[redacted] 60-1463C
		1'-OH MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	35 days at −70°C	135 days at −70°C		
GS-US-120-1554	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	29 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1460A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	438 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1460B
		RPV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	35 days at −70°C	783 days at −70°C	[redacted] 42-1102 Amendment 3	[redacted] 60-1460C
GS-US-174-0105	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	151 days at −80°C	1426 days at −80°C	Gilead 15401v9	Gilead Sciences S-174-01
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	151 days at −80°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	
	Human Whole Blood	Tacrolimus	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	168 days at −80°C	1369 days at −60°C to −80°C	[redacted] 6332-138 Amendment 1	[redacted] 6511-218

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-292-0101	Human Plasma	COBI	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	81 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1119A
		EVG	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	81 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	88 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1119B
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	88 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	67 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1119C
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	86 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1119D
GS-US-292-0102	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	446 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1222A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	451 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1222B
		COBI	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	457 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1222C
		EVG	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	457 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	449 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1222D
		FTC-TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	194 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1222E

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-292-0103	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	45 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1142A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	292 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1142B
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	70 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1142C
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	70 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1142C
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	45 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1142D
GS-US-292-0104	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	479 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1312A Amendment 1
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	472 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1312B
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	401 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1312C
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	57 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1312E
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	57 days at −70°C	1297 days at –60°C to −80°C	[redacted] 60-1343 Amendment 2	

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-292-0106	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	408 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1314A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	400 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1314B
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	406 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1314C
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	407 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1314D
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	407 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	
GS-US-292-0108	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	71 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-12103A
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	71 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	47 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-12103B
		TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	80 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-12103C
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	74 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-12103D

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-292-0109	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	386 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1315A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	380 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1315B
GS-US-292-0110	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	45 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1358A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	49 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1358B
GS-US-292-0111	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	430 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1313A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	430 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1313B
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	403 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1313C

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-292-0112	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	434 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1316A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	438 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1316B
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	441 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1316C
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	497 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1316D
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	497 days at −70°C	1297 days at –60°C to −80°C	[redacted] 60-1343 Amendment 2	
		Iohexol	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	458 days at −70°C	1260 days at −60°C to −80°C	[redacted] 2100-775	[redacted] 8283389

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-292-1316	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	63 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1411A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	66 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1411B
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	32 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1411C
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	15 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1411D
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	15 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 5	
		Sertraline	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	27 days at −70°C	74 days at −70°C	[redacted] 42-1402	[redacted] 60-1411E

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-299-0102	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	471 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1223A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	457 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1223B
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	469 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1223C
		DRV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	471 days at −70°C	1635 days at −70°C	[redacted] 42-0902 Amendment 3	[redacted] 60-1223D
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	412 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1223E
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	184 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1223F

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-311-0101	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	63 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1125A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	62 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1125B
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	73 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1125C
		DRV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	40 days at −70°C	301 days at −70°C	[redacted] 42-0902 Amendment 3	[redacted] 60-1125D
		EFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	40 days at −70°C	1301 days at −70°C	[redacted] 42-0827 Amendment 3	[redacted] 60-1125E
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	48 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1125F
		DRV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	40 days at −70°C	301 days at −70°C	[redacted] 42-0902 Amendment 3	[redacted] 60-1125D
GS-US-311-1088	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	50 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-13100A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	54 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-13100B
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	38 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-13100C

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-311-1386	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	37 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1423A
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	50 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-14223B
GS-US-311-1472	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	51 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1442A
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	57 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1442B Amendment 1
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	56 days at −70°C	585 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1442C Amendment 1
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	56 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1442C Amendment 1
GS-US-311-1473	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	50 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1443A
	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	47 days at −70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1443B
	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	56 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1443C
	Human Plasma	COBI	[redacted] 20[redacted] through [redacted]ug 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	51 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1443C

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
GS-US-342-1167	Human Plasma	SOF GS-566500 GS-331007	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	46 days at –70°C	813 days at −70°C 747 days at −70°C 813 days at −70°C	[redacted] 60-1323 Amendment 2	[redacted] 60-1390A
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	52 days at –70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1390B
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	44 days at –70°C	1426 days at −80°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1390C
		EFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	24 days at –70°C	1301 days at –70°C	[redacted] 42-1216 Amendment 1	[redacted] 60-1390D
		RPV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	44 days at –70°C	783 days at –70°C	[redacted] 42-1102 Amendment 3	[redacted] 60-1390E
		DTG	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	62 days at –70°C	77 days at –70°C	[redacted] 42-1369 Amendment 2	[redacted] 60-1390F
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	55 days at –70°C	520 days at –70°C	[redacted] 60-1115 Amendment 5	[redacted] 60-1390G
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	42 days at –70°C	369 days at –70°C	[redacted] 60-1368	[redacted] 60-1390H
		COBI EVG	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	54 days at –70°C	585 days at –70°C 1297 days at –60°C to –80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1390I
		GS-5816	[redacted] 20 to [redacted] 20	[redacted] 20 to [redacted] 20	64 days at –70°C	570 days at –70°C	[redacted]-102TRA1	[redacted]-278

1'-OH MDZ = midazolam metabolite (1′-hydroxymidazolam); COBI = cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LPV = lopinavir; LTSS = long-term storage stability; MDZ = midazolam; RPV = rilpivirine; [redacted]; TAF = tenofovir alafenamide; TFV = tenofovir

a Transpired time was the calculated time between the date of the first sample collection and the date of the last sample analysis.

b The most current validation reports are listed. Validation reports included in the corresponding CSRs were those in effect at the time of final approval of the CSR.

4.6. Determination of Coadministered Drugs in Human Plasma Supporting F/TAF Studies

This section describes the analytical methods used to determine coadministered drugs in human plasma and the corresponding validation data that support F/TAF clinical studies. The validation reports for the F/TAF studies in this section were current at the time of this summary module.

4.6.1. Determination of EVG and COBI in Human Plasma

A combined EVG and COBI bioanalytical method was developed and validated at [redacted] for the determination of EVG and COBI in human plasma. The method involved the extraction of EVG, COBI, and stable isotope internal standards ([redacted] and [redacted], respectively) from human plasma using SPE followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 18.

Table 18. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma at [redacted]

	EVG	COBI
Calibrated Range (ng/mL)	20 to 10,000	5 to 2500
Lower Limit of Quantitation (ng/mL)	20	5
Interassay Precision Range (%CV)	2.8% to 8.1%	3.9% to 8.3%
Interassay Accuracy Range (%RE)	−8.0% to 5.7%	−0.3% to 9.7%
Studies Supported	GS-US-292-0101, GS-US-292-0102, GS-US-292-0103, GS-US-292-0104, and GS-US-292-0108 GS-US-311-0101 (COBI only)	

Source: [redacted] 60-0949 Amendment 5

This combined EVG and COBI bioanalytical method was improved and validated at [redacted] using the improved liquid chromatographic separation method to support the F/TAF program. This method involved protein precipitation extraction of EVG, COBI, and stable isotope internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 19.

Table 19. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma at [redacted]

	EVG	COBI
Calibrated Range (ng/mL)	20 to 10,000	5 to 2500
Lower Limit of Quantitation (ng/mL)	20	5
Interassay Precision Range (%CV)	4.0% to 6.7%	3.4% to 5.7%
Interassay Accuracy Range (%RE)	−0.6% to 9.3%	−3.0% to 2.0%
Studies Supported	GS-US-292-0106, GS-US-292-0112, GS-US-292-1316	

Source: [redacted] 60-1343 Amendment 2

4.6.2. Determination of Penciclovir in Human Plasma and Urine

The bioanalytical method for the determination of penciclovir in human plasma and urine was developed and validated at Gilead. The method involved protein precipitation extraction of penciclovir and its internal standard ([redacted]) from human plasma and urine followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 20.

Table 20. Bioanalytical Method Validation for Determination of Penciclovir in Human Plasma and Urine at Gilead

	Penciclovir (Plasma)	Penciclovir (Urine)
Calibrated Range (ng/mL)	25 to 2000	2500 to 200,000
Lower Limit of Quantitation (ng/mL)	25	2500
Interassay Precision Range (%CV)	8.46% to 18.22%	2.75% to 19.23%[a]
Interassay Accuracy Range (%RE)	−12.7% to 2.0%	−16.0% to 6.8%[a]
Studies Supported	FTC-108	

a Intraday values.
Source: [redacted] V-01-BIO-TP0260-01

4.6.3. Determination of ATV and RTV in Human Plasma

A commercially available atazanavir (ATV) and ritonavir (RTV) bioanalytical method was developed at [redacted] for the simultaneous determination of ATV and RTV in human plasma. The method involved the extraction of ATV, RTV, and internal standards ([redacted] and [redacted], respectively) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 21.

Table 21. Bioanalytical Method Validation for Determination of ATV and RTV in Human Plasma at [redacted]

	ATV	RTV
Calibrated Range (ng/mL)	10 to 5000	5 to 2500
Lower Limit of Quantitation (ng/mL)	10	5
Interassay Precision Range (%CV)	3.8% to 5.5%	4.0% to 8.4%
Interassay Accuracy Range (%RE)	−2.4% to −0.1%	−6.6 % to −0.5%
Studies Supported	GS-US-120-0118 (ATV only)	

Source: [redacted] 42-0830 Amendment 3

4.6.4. Determination of RTV and LPV in Human Plasma

RTV and LPV bioanalytical method was developed and validated at [redacted] for the simultaneous determination of RTV and LPV in human plasma. The method involved the protein precipitation extraction of RTV and LPV, and internal standards ([redacted] and [redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 22.

Table 22. Bioanalytical Method Validation for Determination of RTV and LPV in Human Plasma at [redacted]

	RTV	LPV
Calibrated Range (ng/mL)	25 to 4000	100 to 20,000
Lower Limit of Quantitation (ng/mL)	25	100
Interassay Precision Range (%CV)	1.7 to 1.9	1.2 to 1.4
Interassay Accuracy Range (%RE)	-3.7 to -0.4	-6.3 to -3.3
Studies Supported	GS-US-120-0118 (LPV only)	

Source: [redacted] 42-1359 Amendment 1

4.6.5. Determination of DTG in Human Plasma

A commercial bioanalytical method for the determination of dolutegravir (DTG) in human plasma was validated at [redacted]. This method involved the protein precipitation extraction of DTG and internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 23.

Table 23. Bioanalytical Method Validation for Determination of DTG in Human Plasma at [redacted]

	DTG
Calibrated Range (ng/mL)	20 to 20,000
Lower Limit of Quantitation (ng/mL)	20
Interassay Precision Range (%CV)	2.1% to 4.6%
Interassay Accuracy Range (%RE)	−2.7% to 1.1%
Studies Supported	GS-US-120-0118

Source: [redacted] 42-1369 Amendment 2

4.6.6. Determination of EFV in Human Plasma

An efavirenz (EFV) commercial bioanalytical method was developed and validated at [redacted] for determination of EFV in human plasma. This method involved liquid-liquid extraction of EFV and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 24.

Table 24. Bioanalytical Method Validation for Determination of EFV in Human Plasma at [redacted] ([redacted] Method 42-0827)

	EFV
Calibrated Range (ng/mL)	5 to 5000
Lower Limit of Quantitation (ng/mL)	5
Interassay Precision Range (%CV)	5.0% to 11.4%
Interassay Accuracy Range (%RE)	−3.3% to 0.5%
Studies Supported	GS-US-311-0101

Source: [redacted] 42-0827 Amendment 3

An EFV commercial bioanalytical method was later improved and validated at [redacted] for determination of EFV in human plasma. This method involved liquid-liquid extraction of EFV and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 25.

Table 25. Bioanalytical Method Validation for Determination of EFV in Human Plasma at [redacted] ([redacted] Method 42-1216)

	EFV
Calibrated Range (ng/mL)	5 to 5000
Lower Limit of Quantitation (ng/mL)	5
Interassay Precision Range (%CV)	1.5 % to 6.3%
Interassay Accuracy Range (%RE)	−5.2% to 7.5%
Studies Supported	GS-US-342-1167

Source: [redacted] 42-1216 Amendment 1

4.6.7. Determination of RPV in Human Plasma

A commercial bioanalytical method for determination of RPV in human plasma was developed and validated at [redacted]. This method involved liquid-liquid extraction of RPV and its internal standard ([redacted]) from human plasma followed by LC/MS/MS with positive ionization Bioanalytical method validation parameters are summarized in Table 26.

Table 26. Bioanalytical Method Validation for Determination of RPV in Human Plasma

	RPV
Calibrated Range (ng/mL)	1 to 500
Lower Limit of Quantitation (ng/mL)	1
Interassay Precision Range (%CV)	2.8% to 5.7%
Interassay Accuracy Range (%RE)	−7.2% to 2.2%
Studies Supported	GS-US-120-0117 and GS-US-342-1167

Source: [redacted] 42-1102 Amendment 3

Another commercial bioanalytical method for determination of RPV in human plasma was developed and validated at [redacted]. This method involved liquid-liquid extraction of RPV and its internal standard ([redacted]) from human plasma followed by LC/MS/MS with positive ionization Bioanalytical method validation parameters are summarized in Table 27.

Table 27. Bioanalytical Method Validation for Determination of RPV in Human Plasma

	RPV
Calibrated Range (ng/mL)	1 to 500
Lower Limit of Quantitation (ng/mL)	1
Interassay Precision Range (%CV)	3.4 to 4.9
Interassay Accuracy Range (%RE)	-3.5 to -2.3
Studies Supported	GS-US-120-1554

Source: [redacted] 42-1408

4.6.8. Determination of DRV in Human Plasma

A commercially available DRV method involving the extraction of DRV and its internal standard ([redacted]) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Table 28.

Table 28. Bioanalytical Method Validation for Determination of DRV in Human Plasma at [redacted]

	DRV
Calibrated Range (ng/mL)	20 to 10,000
Lower Limit of Quantitation (ng/mL)	20
Interassay Precision Range (%CV)	2.8% to 10.6%
Interassay Accuracy Range (%RE)	−3.9% to −1.0%
Studies Supported	GS-US-120-0117, GS-US-120-1554, and GS-US-311-0101

Source: [redacted] 42-0902 Amendment 3

4.6.9. Determination of Iohexol in Human Plasma

A commercially available iohexol bioanalytical method involving the extraction of iohexol and its internal standard ([redacted]) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Table 29.

Table 29. Bioanalytical Method Validation for Determination of Iohexol in Human Plasma at [redacted]

	Iohexol
Calibrated Range (ng/mL)	1000 to 500,000
Lower Limit of Quantitation (ng/mL)	1000
Interassay Precision Range (%CV)	4.2% to 8.3%
Interassay Accuracy Range (%RE)	-5.5% to 5.0%
Studies Supported	GS-US-292-0112

Source: [redacted] 2100-775

4.6.10. Determination of MDZ and 1′-OH MDZ in Human Plasma

A commercially available midazolam (MDZ) bioanalytical method involving the extraction of MDZ, midazolam metabolite (1′-hydroxymidazolam; 1′-OH MDZ), and internal standards ([redacted] and [redacted], respectively) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Table 30.

Table 30. Bioanalytical Method Validation for Determination of MDZ and 1′-OH MDZ in Human Plasma at [redacted]

	MDZ	1′-OH MDZ
Calibrated Range (ng/mL)	0.1 to 100	0.1 to 100
Lower Limit of Quantitation (ng/mL)	0.1	0.1
Interassay Precision Range (%CV)	2.4% to 7.1%	3.0% to 8.2%
Interassay Accuracy Range (%RE)	−2.7% to −1.0%	−3.0% to −1.3%
Studies Supported	GS-US-120-1538	

Source: [redacted] 42-0624 Addendum 3

4.6.11. Determination of Sertraline in Human Plasma

A commercially available sertraline bioanalytical method involving the extraction of sertraline and its internal standard ([redacted]) from human plasma using protein precipitation followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Table 31.

Table 31. Bioanalytical Method Validation for Determination of Sertraline in Human Plasma at [redacted]

	Sertraline
Calibrated Range (ng/mL)	0.2 to 200
Lower Limit of Quantitation (ng/mL)	0.2
Interassay Precision Range (%CV)	2.3% to 3.7%
Interassay Accuracy Range (%RE)	−5.8% to −0.8%
Studies Supported	GS-US-292-1316

Source: [redacted] 42-1402

4.6.12. Determination of Tacrolimus in Human Whole Blood

A commercially available tacrolimus bioanalytical method involving the extraction of tacrolimus and its internal standard ([redacted]) from human whole blood using protein precipitation followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Table 32.

Table 32. Bioanalytical Method Validation for Determination of Tacrolimus in Human Whole Blood at [redacted]

	Tacrolimus
Calibrated Range (ng/mL)	0.1 to 10
Lower Limit of Quantitation (ng/mL)	0.1
Interassay Precision Range (%CV)	3.0% to 6.7%
Interassay Accuracy Range (%RE)	−5.8% to 3.7%
Studies Supported	GS-US-174-0105

Source: [redacted] 6332-138 original and Amendment 1

4.6.13. Determination of SOF, GS-566500, and GS-331007 in Human Plasma

The bioanalytical method for determination of SOF and its 2 predominant human metabolites, GS-566500 and GS-331007, in human plasma was later improved and validated at [redacted]. This method involved protein precipitation extraction of SOF, GS-566500, and GS-331007 and internal standards ([redacted], [redacted], and [redacted]) from human plasma followed by LC/MS/MS with negative ionization. Bioanalytical method validation parameters are summarized in Table 33.

Table 33. Bioanalytical Assay Validation for SOF, GS-566500 and GS-331007 in Human Plasma at [redacted] ([redacted] 60-1323)

	SOF	GS-566500	GS-331007
Calibrated range (ng/mL)	5 to 2500	10 to 5000	10 to 5000
Lower Limit of Quantitation (ng/mL)	5	10	10
Interday precision range (%CV)	2.4% to 9.7%	5.1% to 7.7%	2.5% to 7.2%
Interday accuracy range (%RE)	−5.1% to 3.4%	−2.2% to 2.9%	−1.0% to 2.5%
Studies Supported	GS-US-342-1167		

Source: [redacted] 60-1323 Amendment 2

4.6.14. Determination of GS-5816 in Human Plasma

The bioanalytical method for quantitation of GS-5816 in human plasma was also developed and validated at [redacted]. The method involved solid phase extraction of GS-5816 and internal standard [redacted] from human plasma followed by LC/MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 34.

Table 34. Bioanalytical Method Validation for Determination of GS-5816 in Human Plasma at [redacted]

	GS-5816
Calibrated Range (ng/mL)	1 to 1000
Lower Limit of Quantitation (ng/mL)	1
Interassay Precision Range (%CV)	1.7% to 4.9%
Interassay Accuracy Range (%RE)	−1.5% to 4.1%
Studies Supported	GS-US-342-1167

Source: [redacted]-102TRA1

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SECTION 2.7.2—SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

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

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ΔΔQTc	time-matched, baseline-adjusted, placebo-corrected QTc
ΔΔQTcF	time-matched, baseline-adjusted, placebo-corrected QTcF
ΔQTcF	time-matched, baseline-adjusted QTcF
µCi	microcurie(s)
1′-OH MDZ	midazolam metabolite (1′-hydroxymidazolam)
3TAM	3 thymidine analog-associated mutations
3TC	lamivudine
3TC-TP	lamivudine 5′-triphosphate
AAUCMB	average area under the curve minus baseline
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AF	assay failure
AIC	Akaike information criterion
AIDS	acquired immunodeficiency syndrome
AK	adenylate kinase
ALT	alanine aminotransferase
ANOVA	analysis of variance
APV	amprenavir
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV	atazanavir, atazanavir sulfate
BA	bioavailability
BCRP	breast cancer resistance protein
BE	bioequivalence
BHAP	bis(heteroaryl) piperazine
BID	twice daily
BL	baseline
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
BSEP	bile salt excretory pump
CatA	cathepsin A
CBV-TP	carbovir triphosphate
CC_{50}	concentration that resulted in 50% cytotoxicity
CCHG_QTcF	time-matched, baseline-adjusted, placebo-corrected QTcF (see ΔΔQTcF)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

CD4	cluster determinant 4
cDNA	complementary DNA
CI	confidence interval
CL_{cr}	creatinine clearance
COBI, C	cobicistat (GS-9350; Tybost®)
+COBI	cobicistat boosted (not coformulated)
CPT	Child-Pugh-Turcotte
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450 enzyme
d4T	stavudine
d4T-TP	stavudine triphosphate
dATP	deoxyadenosine triphosphate
$DAVG_{11}$	time-weighted average change from baseline at Day 11
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
L-dC	beta-L-2′-deoxycytidine
dCTP	deoxycytidine triphosphate
ddATP	dideoxyadenosine triphosphate
ddC	zalcitabine
ddCTP	dideoxycytidine triphosphate
ddI	didanosine
DDI	drug-drug interaction
dGTP	deoxyguanosine triphosphate
DLV	delavirdine
DNA	deoxyribonucleic acid
dNTP	2′-deoxynucleoside triphosphate
DRV, D	darunavir
L-dT	beta-L-2′-deoxythymidine
DTG	dolutegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
ECG	electrocardiogram
EC_{XX}	concentration inhibiting viral replication by XX%
ED_{XX}	dose that produced a therapeutic response in XX% of subjects
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
$eGFR_{CKD\text{-}EPI,\ cysC}$	estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

$eGFR_{MDRD}$	estimated glomerular filtration rate calculated using the modification of diet in renal disease equation
ELISA	enzyme-linked immunosorbent assay
E_{max}	maximum (pharmacodynamic) effect
ESDD	early study drug discontinuation
EVG, E	elvitegravir (GS-9137; Vitekta®)
F	female
f inc	relative efficiency of incorporation
FAS	Full Analysis Set
FC	fold change
FDA	Food and Drug Administration
FDC	fixed-dose combination
F/TAF	emtricitabine/tenofovir alafenamide (coformulated)
FTC, F	emtricitabine (GS-9019; Emtriva®)
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®/Eviplera®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
FTC-TP	emtricitabine 5′-triphosphate
GI	gastrointestinal
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
GMR	geometric mean ratio
GS-7340	tenofovir alafenamide
GS-331007	metabolite of sofosbuvir
GS-566500	metabolite of sofosbuvir
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HC/HF	high-calorie/high-fat
HCMV	human cytomegalovirus
HCV	hepatitis C virus
HIV, HIV-1, HIV-2	human immunodeficiency virus, type 1, type 2
HSA	human serum albumin
HSV, HSV-1, HSV-2	herpes simplex virus, type 1, type 2
IAS-USA	International Antiviral Society-USA
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IC_{XX}	concentration that resulted in XX% inhibition
ID	identification
IDV	idinavir
IN	integrase

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

ins	insertion
INSTI	integrase strand-transfer inhibitor
IQR	interquartile range
IV	intravenous(ly)
k_{cat}	enzyme catalytic constant
K_d	equilibrium binding or affinity constant
K_i	kinetic inhibition constant
K_m	Michaelis-Menton constant
k_{pol}	incorporation rate
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LF	light-fat
LPV	lopinavir
LPV/r	ritonavir-boosted lopinavir (coformulated)
LS	least-squares
m	Module
M	male
MATE	multidrug and toxin extrusion protein
Max	maximum
MDM	monocyte-derived macrophage
MDZ	midazolam
MDZ_{IV}	intravenously administered midazolam
MDZ_{oral}	orally administered midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MOI	multiplicity of infection
MRP	multidrug resistance associated protein
MVC	maraviroc
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
NAM	nucleoside-associated mutation
NC	not calculable
ND	not determined or not done
NFV	nelfinavir
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OAT	organic anion transporter
OATP	organic anion transporting polypeptide

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

OCT	organic cation transporter
PBMC	peripheral blood mononuclear cell
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
PD	pharmacodynamic
P-gp	P-glycoprotein
PHA	phytohemagglutinin
PI	protease inhibitor
PK	pharmacokinetic(s)
PMPA	tenofovir (see TFV)
PMPAp	tenofovir monophosphate (see TFV-MP)
PMPApp	tenofovir diphosphate (see TFV-DP)
PNP	purine nucleoside phosphorylase
Pol	polymerase
PR	protease
Q1, Q2, Q3, Q4	first quartile, second quartile, third quartile, fourth quartile
QD	once daily
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
QTcI	QT interval corrected for heart rate using the individual correction formula
QTcN	QT interval corrected for heart rate using population-specific correction formula
-R	resistant, resistance
+RTV	ritonavir boosted (not coformulated)
R^2	coefficient of determination
RAL	raltegravir
RAM	resistance-associated mutation
RAP	Resistance Analysis Population
RBV	ribavirin
rIFN-α	recombinant interferon α
RNA	ribonucleic acid
rNTP	ribonucleoside triphosphate
RPV	rilpivirine
RSV	respiratory syncytial virus
RT	reverse transcriptase
RT-PCR	reverse transcription polymerase chain reaction

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

RTV	ritonavir
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SI	selectivity index
SIV	simian immunodeficiency virus
SOC	system organ class
SOF	sofosbuvir (Solvaldi®)
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
STR	single-tablet regimen
T-20	enfuvirtide
TAF	tenofovir alafenamide (GS-7340)
TAM	thymidine analog-associated mutation
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TFV	tenofovir (M12; previously referred to as PMPA)
TFV-DP	tenofovir diphosphate (previously referred to as PMPApp)
TFV-MP	tenofovir monophosphate (previously referred to as PMPAp)
TIBO	tetrahydro-imidazo-benzodiazepine-one
TVD	emtricitabine/tenofovir disoproxil fumarate (Truvada®)
UTP	uridine triphosphate
V_{max}	apparent relative maximum velocity
VZV	varicella zoster virus
WHsAg	woodchuck hepatitis virus surface antigen
WHV	woodchuck hepatitis virus
WT	wild-type
ZDV	zidovudine

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

A_e	amount of unchanged drug excreted in urine
AUC	area under the plasma/PBMC concentration versus time curve
AUC_{0-12}	area under the plasma/PBMC concentration versus time curve from time zero through 12 hours
AUC_{inf}	area under the plasma/PBMC concentration versus time curve extrapolated to infinite time
AUC_{last}	area under the plasma/PBMC concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma/PBMC concentration versus time curve over the dosing interval
C_{24h}	observed plasma/PBMC concentration at time 24 hours
CL	systemic clearance after intravenous administration
CL/F	apparent oral clearance
CL_r	renal clearance of unchanged drug
CL_{ss}/F	apparent steady-state clearance
C_{max}	maximum observed plasma/PBMC concentration
$C_{max,ss}$	maximum observed plasma/PBMC concentration at steady-state
C_{min}	minimum observed plasma/PBMC concentration over the dosing interval
$C_{min,ss}$	minimum observed plasma/PBMC concentration over the dosing interval at steady-state
C_{tau}	observed plasma/PBMC concentration at the end of the dosing interval
F	absolute bioavailability
$t_{1/2}$	estimated terminal elimination half-life in plasma/PBMC
T_{max}	time (observed time point) of C_{max}
$T_{max,ss}$	time (observed time point) of C_{max} at steady-state
V_c/F	apparent volume of the central compartment
V_p/F	apparent volume of the peripheral compartment
V_{ss}	steady-state volume of distribution
V_z	volume of distribution after intravenous administration
V_z/F	apparent volume of distribution

1. BACKGROUND AND OVERVIEW

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.

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

For ART-naive HIV-infected patients, treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI). Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {32519}, {27621}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an oral prodrug of TFV. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs {26885}, {34210}.

TDF in combination with emtricitabine (FTC; F) forms a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients that can be combined with different third agents. The combination of FTC and TDF is used within several once-daily fixed-dose combinations (FDCs) (Truvada® [TVD; FTC/TDF], Atripla® [ATR; efavirenz (EFV)/FTC/TDF], Complera®/Eviplera® [FTC/rilpivirine (RPV)/TDF], and Stribild® [STB; elvitegravir (EVG; E)/cobicistat (COBI; C)/FTC/TDF]). Availability of a stand-alone NRTI backbone is important when there is a medical need to use a third agent that is not part of an fixed-dose combination (FDC) (eg, ritonavir [RTV]-boosted PIs), and particularly to provide a range of treatment options in patients with virologic resistance to their third agent but not to the backbone.

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

Gilead Sciences (Gilead) has coformulated TAF (as TAF fumarate) with FTC into an FDC tablet available in 2 doses, F/TAF 200/25 mg and F/TAF 200/10 mg. Because TAF is a substrate of intestinal efflux transporters (ie, P-glycoprotein [P-gp]) and hepatic transporters (ie, organic anion transporting polypeptide [OATP]1B1 and OATP1B3), TAF exposure may be increased

upon coadministration with inhibitors of these transporters, with the effect apparently driven predominantly by P-gp inhibition (ie, by RTV or COBI; Section 3.2.3.2.2). Therefore, the recommended F/TAF dose (200/25 mg or 200/10 mg based on third agent) is generally based on whether or not the coadministered agent has any clinically relevant effect on TAF exposure (eg, via inhibition of intestinal P-gp). Specifically, F/TAF 200/25 mg is recommended with unboosted third agents and F/TAF 200/10 mg is recommended with boosted third agents.

This submission for the N(t)RTI backbone F/TAF is based on 2 pivotal bioequivalence (BE) studies (Studies GS-US-311-1473 and GS-US-311-1472) that pharmacokinetically bridge each F/TAF FDC tablet strength (200/25 mg or 200/10 mg) to Gilead's FDC tablet containing the HIV-1 INSTI EVG, the pharmacoenhancer COBI, FTC, and TAF (E/C/F/TAF 150/150/200/10 mg), for which clinical safety and efficacy have been established in a broad range of patient populations.

The PK and PD data from clinical studies conducted with F/TAF and E/C/F/TAF are supported with data from clinical studies conducted with TAF and FTC, and with data from nonclinical studies. Data from studies conducted with the darunavir (DRV; D)/C/F/TAF FDC support dosing recommendations.

The clinical studies that provide PK and/or PD data to support this marketing application are listed and briefly described in Section 1.2, with the results from individual studies conducted with TAF or a TAF-containing FDC presented in Section 2. A discussion of data across all studies is presented in Section 3, including a discussion of integrated data. The nonclinical and clinical virology studies supporting the clinical development of F/TAF are summarized in Sections 4.1 and 4.2, respectively. In addition to individual summaries of virology resistance data from 6 E/C/F/TAF studies and 1 D/C/F/TAF study presented in Section 4.2.1, an integrated analysis of the virology resistance data from 1 Phase 2 E/C/F/TAF study (GS-US-292-0102) and 2 Phase 3 E/C/F/TAF studies (GS-US-292-0104 and GS-US-292-0111) is presented in Section 4.2.2.

1.1. Human Biomaterials Studies

Studies pertinent to the PK of F/TAF using human biomaterials are discussed in detail and in the context of PK data in other species in the Nonclinical Pharmacokinetics Written Summary (m2.6.4). References to using human biomaterials pertinent to clinical PK are included in this summary as appropriate (Section 3.1).

1.2. Clinical Pharmacology Studies

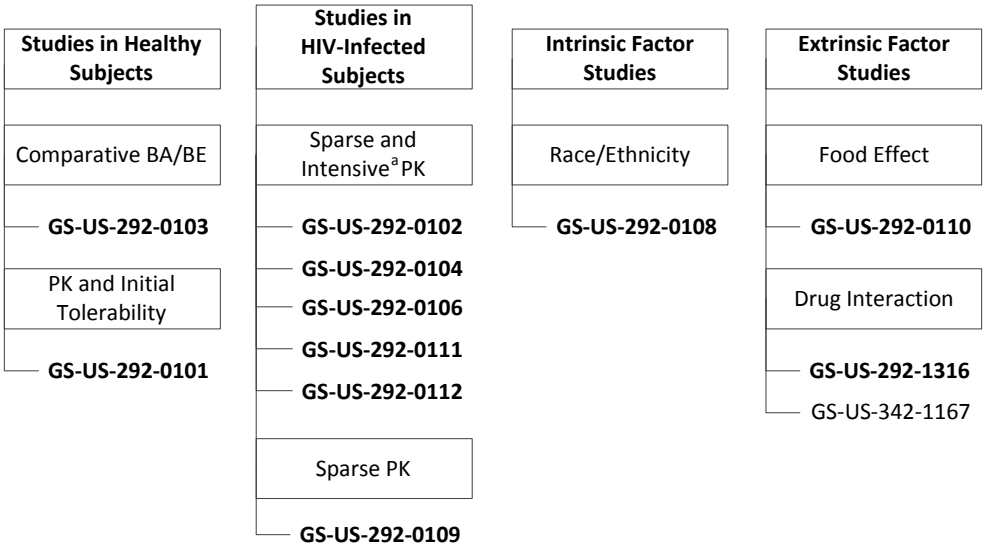
A comprehensive program of clinical studies characterizes the PK of F/TAF and its components. The 44 clinical studies that provide PK and/or PD data in support of this marketing application are listed in Table 1, with the dosage form, lot number, dose, number of subjects who were administered drug, and hyperlinks to select study narratives. Throughout this document, unless otherwise specified, the dosage of E/C/F/TAF was 150/150/200/10 mg, and the dosages of single-agent EVG and single-agent COBI were each 150 mg.

Two pitoval BE studies were conducted to pharmacokinetically bridge each F/TAF tablet strength to the E/C/F/TAF FDC:

- Study GS-US-311-1473 evaluated the BE of F/TAF (200/25 mg) versus E/C/F/TAF
- Study GS-US-311-1472 evaluated the BE of F/TAF (200/10 mg)+COBI+EVG versus E/C/F/TAF

Based on the BE of each F/TAF FDC to E/C/F/TAF, data collected using E/C/F/TAF are considered relevant to the characterization of F/TAF PK; these data comprise the majority of this submission, as shown in Figure 1.

Figure 1. Summary of E/C/F/TAF Studies Contributing to the Summary of Clinical Pharmacology



a Intensive PK sampling was conducted in PK substudies.

Single-agent studies are included in the submission to characterize the following:

- Clinical pharmacology profile of TAF (Study GS-US-120-0104) and FTC (Studies 143-001, FTC-101, FTC-102, FTC-203, and FTC-303)
- The absorption, metabolism, distribution, and elimination (ADME) of TAF and FTC (Studies GS-US-120-0109 and FTC-106, respectively).
- The effect of TAF on QT/QTc interval (Study GS-US-120-0107)
- The effect of the following intrinsic factors on TAF and FTC PK:
  - Renal impairment (Studies GS-US-120-0108 and FTC-107, respectively)
  - Hepatic impairment (Studies GS-US-120-0114 and FTCB-101, respectively)

- Drug-drug interaction (DDI) potential between TAF and midazolam (MDZ; Study GS-US-120-1538) or RPV (Study GS-US-120-1554)

- DDI potential between FTC and zidovudine (ZDV) or stavudine (d4T; Study FTC-103 for both), and between FTC and famciclovir (Study FTC-108) or TDF (Study FTC-114).

The effect of food on TAF and FTC exposure in the absence of a boosting agent was evaluated in Study GS-US-311-1386 using the F/TAF (200/25 mg) FDC. The effect of food on TAF and TFV exposure in the presence of a boosting agent was evaluated in Study GS-US-292-0110 using E/C/F/TAF. The results of Study FTC-111, which evaluated the effect of food on FTC exposure, are consistent with those from Study GS-US-311-1386.

The following studies are included in the submission to characterize DDI potential and/or to support dosing recommendations:

- Study GS-US-311-0101 evaluated the DDI potential between F/TAF and EFV, between F/TAF and DRV+COBI, and between TAF and COBI.

- Study GS-US-120-0118 evaluated the DDI potential between TAF 10 mg + FTC and RTV-boosted atazanavir (ATV+RTV), RTV-boosted DRV (DRV+RTV), ritonavir-boosted lopinavir (coformulated; LPV/r), or dolutegravir (DTG).

- Study GS-US-174-0105 evaluated the DDI potential between FTC (in the context of the FTC/TDF FDC) and tacrolimus.

- Two studies conducted with D/C/F/TAF (Studies GS-US-299-0101 and GS-US-299-0102) support dosing recommendations. Study GS-US-299-0101 evaluated formulations of the D/C/F/TAF FDC that contained either 10 or 25 mg TAF, and Study GS-US-299-0102 demonstrated the efficacy and safety of the D/C/F/TAF (800/150/150/10 mg) FDC.

To characterize the PK of the active metabolite, intracellular peripheral blood mononuclear cell (PBMC) concentrations of TFV-DP were measured in HIV-infected subjects receiving F/TAF 200/25 mg + an unboosted third agent, F/TAF 200/10 mg + a boosted PI, or FTC/TDF + third agent as part of the ongoing Study GS-US-311-1089.

Table 1. Overview of Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

Study Number Phase	Test Treatment(s)		Reference Treatment(s)
	Dose and Formulation (Lot Number[a])	n[b]	Dose and Formulation
Comparative Bioavailability/Bioequivalence			
GS-US-311-1088 Phase 1	**F/TAF** 200/25-mg tablet (CR[redacted]05B2)	56	**FTC** 200-mg capsule + **TAF** 25-mg tablet
GS-US-311-1472 Phase 1	**F/TAF** 200/10-mg tablet (CR[redacted]08B2) + **EVG** 150-mg tablet + **COBI** 150-mg tablet	99	**E/C/F/TAF** 150/150/ 200/10-mg tablet

Study Number Phase	Test Treatment(s) Dose and Formulation (Lot Number[a])	n[b]	Reference Treatment(s) Dose and Formulation
GS-US-311-1473 Phase 1	**F/TAF** 200/25-mg tablet (CR[redacted]05B2)	116	**E/C/F/TAF** 150/150/ 200/10-mg tablet
GS-US-292-0103 Phase 1	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]05B1)	33	**EVG** 150-mg tablet + **COBI** 150-mg tablet **FTC** 200-mg capsule + **TAF** 25-mg tablet
GS-US-299-0101 Phase 1	**D/C/F/TAF** Formulation 1, 800/150/200/25-mg, monolayer tablet (DB[redacted]02B1) **D/C/F/TAF** Formulation 2, 800/150/200/25-mg, bilayer tablet (DB[redacted]01B1) **D/C/F/TAF** Formulation 3, 800/150/200/10-mg, monolayer tablet (DB[redacted]03B1) 2 × **DRV** 400-mg tablet + **COBI** 150-mg tablet + **FTC/TDF** 200/300-mg tablet	101	2 × **DRV** 400-mg tablet + **COBI** 150-mg tablet **FTC/TDF** 200/300-mg tablet **FTC** 200-mg capsule + **TAF** 25-mg tablet
FTC-109 Phase 1	2 × **FTC** 100-mg capsule (TP-0006-99099) **FTC** 200-mg capsule (TP-0006-99125)	12	Not applicable
Bioavailability			
FTC-110 Phase 1	**FTC** 200-mg capsule (TP-0006-00205) **FTC** 10-mg/mL oral solution (TP-0006-00211) **FTC** 10-mg/mL IV solution (TP-0006-00093)	12	Not applicable
Mass Balance (PK, Metabolism, and Excretion)			
GS-US-120-0109 Phase 1	**TAF** [^{14}C]-labeled, 25-mg capsule (each containing a mixture of unlabeled TAF and 100 µCi [^{14}C]TAF) ([^{14}C]TAF: GS002-035-057-C-20[redacted]-PVA; TAF: 7340-03-AC-1P; Capsules: CM[redacted]04A)	8	Not applicable
FTC-106 Phase 1	**FTC** 200-mg in oral solution containing 250 µCi [^{14}C]FTC (TP-0006-99044, TP-0006/96/WW, TP-0006-99084 [3361001])	6	2 × **FTC** 100-mg capsule
Effect on QT/QTc Interval			
GS-US-120-0107 Phase 1	**TAF** 25-mg tablet (CM[redacted]02B1) 5 × **TAF** 25-mg tablet (CM[redacted]02B1)	58	5 × placebo-to-match TAF **Moxifloxacin** 400-mg tablet
Study Supporting PK and Initial Tolerability in Healthy Subjects			
GS-US-292-0101 Phase 1	**E/C/F/TAF** 150/150/200/25-mg tablet (Formulation 1: CP[redacted]03B1, Formulation 2: CP[redacted]01B1) **E/C/F/TAF** 150/150/200/40-mg tablet (Formulation 1: CP[redacted]04B1, Formulation 2: CP[redacted]02B1)	38	**STB** 150/150/200/300-mg tablet **TAF** 25-mg tablet

Study Number Phase	Test Treatment(s) Dose and Formulation (Lot Number[a])	n[b]	Reference Treatment(s) Dose and Formulation
Controlled Multiple-Dose Studies with Intensive PK Sampling in HIV-Infected Subjects			
GS-US-292-0102 Phase 2	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]05B1, CP[redacted]05B2, CP[redacted]01B1, CP[redacted]03B1R, CP[redacted]08B1, CP[redacted]05B1, CP[redacted]11B1) + placebo-to-match STB	112[c]	**STB** 150/150/200/300-mg tablet + placebo-to-match E/C/F/TAF
GS-US-292-0104 Phase 3	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]04B1, CP[redacted]08B1, CP[redacted]09B1, CP[redacted]07B1, CP[redacted]08B1, CP[redacted]11B1, CP[redacted]13B1, CP[redacted]14B1) + placebo-to-match STB	435	**STB** 150/150/200/300-mg tablet + placebo-to-match E/C/F/TAF
GS-US-292-0111 Phase 3	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]05B1, CP[redacted]08B1, CP[redacted]09B1, CP[redacted]05B1, CP[redacted]07B1, CP[redacted]11B1, CP[redacted]13B1, CP[redacted]14B1) + placebo-to-match STB	431	**STB** 150/150/200/300-mg tablet + placebo-to-match E/C/F/TAF
FTC-303 Phase 3	2 × **FTC** 100-mg capsule (TP-0006/96/JJ, TF-0006/96/PP, TP-0006/96V V, TP-0006/96/ZZ, TP-0006/96/RRR, TP-0006-99044, TP-0006-99097) + background ARV regimen	294	**3TC** 150-mg tablet + background ARV regimen
Controlled Multiple-Dose Studies with Sparse PK Sampling in HIV-Infected Subjects			
GS-US-292-0109 Phase 3	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]05B1, CP[redacted]08B1, CP[redacted]09B1, CP[redacted]07B1, CP[redacted]08B1, CP[redacted]10B1, CP[redacted]13B1, CP[redacted]14B1, CP[redacted]15B1)	959	**FTC/TDF+3rd Agent** regimen (STB, ATR, ATV+COBI+FTC/TDF, or ATV+RTV+FTC/TDF)
GS-US-299-0102 Phase 2	**D/C/F/TAF** 800/150/200/10-mg tablet (DB[redacted]03B1, DB[redacted]03B2, DB[redacted]01B1, DB[redacted]04B1) + 2 × placebo-to-match DRV + placebo-to-match COBI + placebo-to-match FTC/TDF	103	2 × **DRV** 400-mg tablet + **COBI** 150-mg tablet + **FTC/TDF** 200/300-mg tablet + placebo-to-match D/C/F/TAF
Studies Supporting PK and Initial Tolerability in HIV-Infected Subjects (Including PD and PK/PD Relationships)			
GS-US-311-1089 Phase 3	**F/TAF** 200/25 mg-tablet (CR[redacted]05B1, CR[redacted]08B1) + **unboosted 3rd Agent** + placebo-to-match FTC/TDF **F/TAF** 200/10 mg-tablet (CR[redacted]08B1, CR[redacted]07B1) + **boosted 3rd Agent** + placebo-to-match FTC/TDF	333	**FTC/TDF** 200/300 mg-tablet + **3rd Agent** + placebo-to-match F/TAF
GS-US-120-0104 Phase 1	**TAF** 8-mg tablet (CM[redacted]02B1) **TAF** 25-mg tablet (CM[redacted]03B1) **TAF** 40-mg tablet (CM[redacted]04B1)	25	**TDF** 300-mg tablet Placebo-to-match TAF tablet
143-001 Phase 1	**FTC** 100-mg capsule (2T2722) 2 × **FTC** 100-mg capsule (2T2722) 4 × **FTC** 100-mg capsule (2T2722) 8 × **FTC** 100-mg capsule (2T2722) 12 × **FTC** 100-mg capsule (2T2722)	12	Placebo-to-match FTC

Study Number Phase	Test Treatment(s) Dose and Formulation (Lot Number[a])	n[b]	Reference Treatment(s) Dose and Formulation
FTC-101 Phase 1	**FTC** 25-mg capsule (25947) **FTC** 100-mg capsule (26172) 2 × **FTC** 100-mg capsule (26172)	41	Not applicable
FTC-102 Phase 1/2	**FTC** 25-mg capsule (29087) **FTC** 100-mg capsule (29408) 2 × **FTC** 100-mg capsule (29408)	60	**3TC** 150-mg tablet
Studies Evaluating the Effect of Intrinsic Factors			
Studies of the Effect of Renal Impairment			
GS-US-292-0112 Phase 3; HIV-infected subjects	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]04B1, CP[redacted]08B1, CP[redacted]03B1, CP[redacted]07B1, CP[redacted]10B1, CP[redacted]11B1, CP[redacted]13B1, CP[redacted]14B1, CP[redacted]02B1)	248	Not applicable
GS-US-120-0108 Phase 1; non–HIV-infected subjects	**TAF** 25-mg tablet (CM[redacted]02B1, CM[redacted]02B1, CM[redacted]02B1-A)	27	Not applicable
FTC-107 Phase 1; non–HIV-infected subjects	2 × **FTC** 100-mg capsule (TP-0006-99044)	29	Not applicable
Studies of the Effect of Hepatic Impairment			
GS-US-120-0114 Phase 1; non–HIV-infected subjects	**TAF** 25-mg tablet (CM[redacted]08B1)	40	Not applicable
FTCB-101 Phase 1; HBV-infected, non–HIV-infected subjects	**FTC** 25-mg capsule (TP-0006/96/AA) 2 × **FTC** 25-mg capsule (TP-0006/96/AA) **FTC** 100-mg capsule (TP-0006/96/BB) 2 × **FTC** 100-mg capsule (TP-0006/96/BB) 3 × **FTC** 100-mg capsule (TP-0006/96/BB)	49	Not applicable
Study of the Effect of Race/Ethnicity in Healthy (Japanese and Caucasian) Subjects			
GS-US-292-0108 Phase 1	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]01B1)	20	Not applicable
Studies in HIV-Infected Pediatric Subjects			
GS-US-292-0106 Phase 2/3; 12 to < 18 years of age	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]05B1, CP[redacted]03B1, CP[redacted]08B1, CP[redacted]10B1, CP[redacted]11B1, CP[redacted]13B1)	48	Not applicable

Study Number Phase	Test Treatment(s) Dose and Formulation (Lot Number[a])	n[b]	Reference Treatment(s) Dose and Formulation
FTC-203 Phase 2; ≥ 3 months and ≤ 17 years of age	**FTC** 200 mg capsule (TP-0006-00133 [66-382-AR], TP-0006-00205 [70-035-4Q], TP-0006-01031 [75-042-4Q], W302A1 [96-074-4Q-21]) or 10 mg/mL oral solution (TP-0006-00175 [68-002-4P], TP-0006-00211 [72-010-4T], TP-0006-00216 [73-011-4T], TP-0006-01015 [74-012-4T], TP-0006-03003 [96-017-4T]) + background ARV regimen	116	Not applicable
Studies Evaluating the Effect of Extrinsic Factors			
Studies of the Effect of Food in Healthy Subjects			
GS-US-311-1386 Phase 1	**F/TAF** 200/25-mg tablet (CR[redacted]05B2)	40	Not applicable
GS-US-292-0110 Phase 1	**E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]09B1)	43	Not applicable
FTC-111 Phase 1	2 × **FTC** 100-mg capsule (TP-0006-00120) **FTC** 200-mg capsule (TP-0006-00205)	24	Not applicable
Studies of Potential Drug-Drug Interaction in Healthy Subjects			
GS-US-311-0101 Phase 1	**F/TAF** 200/40-mg tablet (CR[redacted]07B1) + **EFV** 600-mg tablet **F/TAF** 200/25-mg tablet (CR[redacted]06B1) + 2 × **DRV** 400-mg tablet + **COBI** 150-mg tablet **TAF** 8-mg tablet (CM[redacted]02B1) + **COBI** 150-mg tablet	50	**F/TAF** 200/40-mg tablet **F/TAF** 200/25-mg tablet 2 × **DRV** 400-mg tablet + **COBI** 150-mg tablet **TAF** 8-mg tablet
GS-US-292-1316 Phase 1	**Sertraline** 50-mg tablet + **E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]10B1)	19	**Sertraline** 50-mg tablet **E/C/F/TAF** 150/150/200/10-mg tablet
GS-US-342-1167 Phase 1	**SOF/GS-5816** 400/100-mg tablet + **EFV/FTC/TDF** 600/200/300-mg tablet **SOF/GS-5816** 400/100-mg tablet + **FTC/RPV/TDF** 200/25/300-mg tablet **SOF/GS-5816** 400/100-mg tablet + **DTG** 50-mg tablet **SOF/GS-5816** 400/100-mg tablet + **E/C/F/TAF** 150/150/200/10-mg tablet (CP[redacted]09B1)	101	**SOF/GS-5816** 400/100-mg tablet **EFV/FTC/TDF** 600/200/300-mg tablet **FTC/RPV/TDF** 200/25/300-mg tablet **DTG** 50-mg tablet **E/C/F/TAF** 150/150/200/10-mg tablet
GS-US-120-0117 Phase 1	**TAF** 25-mg tablet (CM[redacted]08B1) + **RPV** 25-mg tablet	36	**TAF** 25-mg tablet **RPV** 25-mg tablet

Study Number Phase	Test Treatment(s) Dose and Formulation (Lot Number[a])	n[b]	Reference Treatment(s) Dose and Formulation
GS-US-120-0118 Phase 1	**TAF** 10-mg tablet (CM[redacted]07B1) + **FTC** 200-mg capsule **ATV** 300-mg capsule + **RTV** 100-mg tablet 2 × **DRV** 400-mg tablet + **RTV** 100-mg tablet **LPV/r** 4 × 200/50-mg tablet **DTG** 50-mg tablet	40	**TAF** 10-mg tablet + **FTC** 200-mg capsule **ATV** 300-mg capsule + **RTV** 100-mg tablet 2 × **DRV** 400-mg tablet + **RTV** 100-mg tablet **LPV/r** 4 × 200/50-mg tablet **DTG** 50-mg tablet
GS-US-120-1538 Phase 1	**TAF** 25-mg tablet (CM[redacted]06B2) + **MDZ** 2.5-mg oral syrup **TAF** 25-mg tablet (CM[redacted]06B2) + **MDZ** 1-mg solution for injection	18	**TAF** 25-mg tablet
GS-US-120-1554 Phase 1	**TAF** 25-mg tablet (CM[redacted]06B2) **RPV** 25-mg tablet **TAF** 25-mg tablet (CM[redacted]06B2) + **RPV** 25-mg tablet	34	Not applicable
FTC-103 Phase 1	2 × **FTC** 100-mg capsule (26295)	13	**ZDV** 3 × 100-mg capsule **d4T** 40-mg capsule
FTC-108 Phase 1	**FTC** 2 × 100-mg capsule (TP-0006-99099) **Famciclovir** 500-mg tablet **FTC** 2 × 100-mg capsule (TP-0006-99099) + **Famciclovir** 500-mg tablet	12	Not applicable
FTC-114 Phase 1	**FTC** 200-mg capsule (TP-0006-01048 [75-044-4Q]) **TDF** 300-mg tablet **FTC** 200-mg capsule (TP-0006-01048 [75-044-4Q]) + **TDF** 300-mg tablet	19	Not applicable
GS-US-174-0105 Phase 1	**FTC/TDF** 200/300-mg tablet (V403B1) + **Tacrolimus** 0.5-mg or 1.0-mg capsules	27	**FTC/TDF** 200/300-mg tablet **Tacrolimus** 0.5-mg or 1.0-mg capsules

a Lot number provided only for TAF-containing products, for FTC in FTC studies, and for FTC/TDF in Study GS-US-174-0105.
b Number of subjects who were administered any test treatment.
c Includes the 112 subjects who received E/C/F/TAF during the randomized phase of the study. An additional 161 subjects received at least 1 dose of E/C/F/TAF in the open-label extension phase of the study.

1.3. Bioanalytical Methods

The bioanalytical methods used for the determination of plasma concentrations of TAF, TFV, and FTC during the clinical development programs are described in m2.7.1, Section 1.1.3. An overview of the validated bioanalytical methods used for the determination of plasma concentrations of TAF and FTC, as well as all other analytes, in the individual clinical studies is provided in m2.7.1, Appendix 4.4.

1.4. Absorption, Distribution, Metabolism, and Elimination

The results from in vitro or nonclinical and clinical studies for the ADME of F/TAF and its components are described in Section 3.1.

1.5. Population Pharmacokinetics

1.5.1. TAF

To evaluate the population PK of TAF and identify intrinsic factors influencing TAF PK, population PK analyses were performed using pooled data from healthy subjects and 1543 HIV-infected subjects following E/C/F/TAF administration in the Phase 1, Phase 2, and Phase 3 studies listed in Table 2. A mixed-effect modeling approach using NONMEM Version 7.3 software was applied and the results of the population PK analyses are discussed in Section 3.2.1.2. Similar analyses were performed to evaluate to the population PK of TAF's major metabolite, TFV, and to identify intrinsic factors influencing TFV PK. Select findings from the population PK analyses are included in the discussion of the effect of intrinsic factors (Section 3.2.2).

Further details on the population PK model are described in the TAF Population PK Report.

Table 2. Studies Used in the Population PK Analysis of TAF Administered as E/C/F/TAF

Study	Phase	Population	Sampling (Intensive/Sparse)
GS-US-292-0103	1	Healthy	Intensive
GS-US-292-0108	1	Healthy	Intensive
GS-US-292-0110	1	Healthy	Intensive
GS-US-292-0102	2	HIV-infected	Intensive[a], sparse
GS-US-292-0106	2/3	HIV-infected	Intensive[a], sparse
GS-US-292-0104	3	HIV-infected	Intensive[a], sparse
GS-US-292-0111	3	HIV-infected	Intensive[a], sparse
GS-US-292-0109	3	HIV-infected	Sparse
GS-US-292-0112	3	HIV-infected	Intensive[a], sparse

a Intensive PK sampling was conducted in PK substudies.
Source: TAF Population PK Report

1.5.2. FTC

To identify individual intrinsic factors that significantly correlate with key PK parameter estimates of FTC, simple linear regression analysis and analysis of variance (ANOVA) were first performed on pooled data from healthy and HIV-infected subjects following oral administration of FTC 200 mg, including 108 healthy subjects and 16 HIV-infected subjects (13542v1). The steady-state PK parameters were obtained from Studies FTC-101 (Day 10) and FTC-303, and

included 20 HIV-infected subjects. Stepwise multiple linear regression analysis was then performed to evaluate the relationship of 1 or more independent demographic variables with a single dependent PK parameter estimate of FTC. The results of these analyses are discussed in Section 3.2.1.2. Select findings from the population PK analyses are included in the discussion of the effect of intrinsic factors (Section 3.2.2). These findings were previously submitted in support of the clinical pharmacology of FTC.

1.6. Integrated Ad Hoc PK Analysis of TAF 25 mg and TAF 10 mg + COBI

In support of the Population PK analyses and to further characterize TAF single- and multiple-dose PK and the effect of covariates on TAF exposure, an integrated ad hoc PK analysis was performed using data from studies conducted with TAF 25 mg or TAF 10 mg + COBI. For these analyses, data were pooled from studies (Table 3) conducted in healthy or HIV-infected subjects who were administered single-agent TAF 25 mg, F/TAF 200/25 mg, E/C/F/TAF, or F/TAF 200/10 mg + COBI and who had at least 1 nonmissing PK parameter (ie, AUC_{last} or C_{max}) for the respective analyte. Initial exploratory analyses revealed a confounding effect of boosting on food effect; as such, this analysis was performed separately for data collected in the presence and absence of a boosting agent. A mixed-effect modeling approach using stepwise model selection was applied for each of the PK parameters of interest. Covariates were entered into a multivariate model in a forward stepwise fashion based on the Akaike information criterion (AIC) fit statistic.

Findings from these supportive analyses are presented in Section 3.2.1.3 and included in the comparison of exposure between healthy and HIV-infected subjects (Section 3.2.1.4.1) and in the discussion of the effect of intrinsic factors (Section 3.2.2).

Table 3. Studies Used in Integrated Ad Hoc PK Analysis of TAF 25 mg and TAF 10 mg + COBI

Study	TAF Formulation	Phase	N	Population	Sampling (Intensive or Sparse)
Single-Dose Pharmacokinetic Data With TAF 25 mg					
GS-US-311-1088	F/TAF (200/25 mg)	1	55	Healthy	Intensive
GS-US-311-1386	F/TAF (200/25 mg)	1	40	Healthy	Intensive
GS-US-311-1473[a]	F/TAF (200/25 mg)	1	116	Healthy	Intensive
GS-US-120-0107	TAF 25 mg	1	58	Healthy	Intensive
GS-US-120-0108	TAF 25 mg	1	13	Healthy	Intensive
GS-US-120-0109	TAF 25 mg	1	8	Healthy	Intensive
GS-US-120-0114	TAF 25 mg	1	20	Healthy	Intensive
GS-US-120-0117	TAF 25 mg	1	18	Healthy	Intensive
GS-US-120-0104	TAF 25 mg	1	8	HIV-infected	Intensive
		Total	**336**		

Study	TAF Formulation	Phase	N	Population	Sampling (Intensive or Sparse)
Multiple-Dose Pharmacokinetic Data With TAF 25 mg					
GS-US-311-0101	F/TAF 200/25 mg	1	12	Healthy	Intensive
GS-US-292-0101	TAF 25 mg	1	37	Healthy	Intensive
GS-US-292-0103[b]	TAF 25 mg	1	20	Healthy	Intensive
GS-US-120-1538	TAF 25 mg	1	18	Healthy	Intensive
GS-US-120-1554	TAF 25 mg	1	17	Healthy	Intensive
GS-US-120-0104	TAF 25 mg	1	8	HIV-infected	Intensive
		Total	**112**		
Single-Dose Pharmacokinetic Data With TAF 10 mg + COBI					
GS-US-311-1472[c]	F/TAF (200/10 mg) + COBI and E/C/F/TAF	1	100	Healthy	Intensive
GS-US-311-1473[a]	E/C/F/TAF	1	116	Healthy	Intensive
GS-US-292-0108[d]	E/C/F/TAF	1	20	Healthy	Intensive
GS-US-292-0110	E/C/F/TAF	1	42	Healthy	Intensive
		Total	**278**		
Multiple-Dose Pharmacokinetic Data With TAF 10 mg + COBI					
GS-US-292-0108[d]	E/C/F/TAF	1	17	Healthy	Intensive
GS-US-292-0103[b]	E/C/F/TAF	1	33	Healthy	Intensive
GS-US-292-1316	E/C/F/TAF	1	19	Healthy	Intensive
GS-US-292-0102	E/C/F/TAF	2	19	HIV-infected	Intensive[e], sparse
GS-US-292-0104	E/C/F/TAF	3	15	HIV-infected	Intensive[e], sparse
GS-US-292-0111	E/C/F/TAF	3	20	HIV-infected	Intensive[e], sparse
		Total	**123**		

a In Study GS-US-311-1473, subjects received both TAF 25 mg and E/C/F/TAF. Subjects were counted once for each study treatment received.
b In Study GS-US-292-0103, subjects may have received TAF 25 mg or both TAF 25 mg and E/C/F/TAF. Subjects were counted once for each study treatment received.
c In Study GS-US-311-1472, subjects received both F/TAF (200/10 mg) + COBI and E/C/F/TAF. Subjects were counted only once.
d Study GS-US-292-0108 conducted PK sampling after a single dose and after multiple doses. Subjects were counted once for each type of data obtained.
e Intensive PK sampling was conducted in PK substudies.
Source: m5.3.5.3, Integrated Ad Hoc PK Analysis Table 1.1

1.7. Pharmacokinetics/Pharmacodynamics

Results of analyses evaluating potential relationships between efficacy parameters and the PK/PD of TAF and FTC in HIV-infected subjects are presented in Section 3.3.1, and those evaluating potential relationships between safety parameters and the PK/PD of TAF and FTC are presented in Section 3.3.2.

1.8. Virology

A comprehensive program of nonclinical experiments and clinical studies characterized the antiviral activity of F/TAF and its individual components, as described in Sections 1.8.1 and 1.8.2, respectively.

1.8.1. Nonclinical Virology

Nonclinical virology studies characterized the antiviral activity of the F/TAF components, TAF and FTC, as well as TFV and TDF against laboratory strains and various clinical isolates (wild-type and drug-resistant strains) of HIV-1 and other viruses in target cell lines and primary cell cultures (eg, PBMCs). These studies characterized the following specific PD characteristics, the results of which are provided in Sections 4.1.1, 4.1.2, and 4.1.2.3, respectively.

- Primary pharmacodynamics: mechanism of action and antiviral activity against HIV-1 (wild-type and drug-resistant strains), including drug-resistance selection
- Secondary pharmacodynamics: effect against host enzymes (eg, DNA polymerases and proteases) and non-HIV viruses
- Pharmacodynamic drug interactions

Conclusions from these nonclinical virology studies are provided in Section 4.1.3.2.

1.8.2. Clinical Virology

Clinical virology analyses were performed for HIV-infected subjects with clinical virology data from 6 E/C/F/TAF Phase 2 and Phase 3 studies (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) and 1 D/C/F/TAF Phase 2 study (GS-US-299-0102). Resistance analyses were performed on plasma HIV-1 isolates from all subjects who met prespecified criteria.

Integrated virology analyses were performed for HIV-infected subjects with clinical virology data from 1 Phase 2 E/C/F/TAF study (GS-US-292-0102) and 2 Phase 3 E/C/F/TAF studies (GS-US-292-0104 and GS-US-292-0111).

Results from these analyses are provided in Section 4.2.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

A tabular listing of clinical pharmacology studies is provided in Appendix 6.1. Narratives for studies that contribute information to this Summary of Clinical Pharmacology and that were conducted using TAF or a TAF-containing FDC are provided in Sections 2.2 to 2.5, except E/C/F/TAF Studies GS-US-292-0102, GS-US-292-0104, GS US-292-0109, and GS-US-292-0111, and D/C/F/TAF Study GS-US-299-0102 for which narratives are provided in m2.7.3, Section 2; E/C/F/TAF Studies GS-US-292-0106 and GS-US-292-0112, for which narratives are provided in m2.7.4, Section 1.

2.1. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Studies pertinent to the PK of F/TAF using human biomaterials are discussed in detail and in the context of PK data in other species in the Nonclinical Pharmacokinetics Written Summary (m2.6.4). References to using human biomaterials pertinent to clinical PK are also included in this summary as appropriate (Section 3.1).

2.2. Studies in Healthy Subjects

2.2.1. F/TAF Studies

2.2.1.1. Study GS-US-311-1088

Title

A Phase 1, Randomized, Open-Label, Single-Dose, Two-way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet

Objectives

The primary objective of this study was as follows:

- To evaluate the BE between F/TAF FDC tablets and FTC+TAF coadministered as the individual agents

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of single oral doses of FTC and TAF administered as F/TAF FDC tablets or coadministered as the individual agents

Study Design

This Phase 1, randomized, open-label, single-dose, 2-way crossover study evaluated the BE between F/TAF and FTC+TAF coadministered as individual agents in healthy subjects. Following screening and Day −1 procedures, eligible subjects were randomized to 1 of 2 treatment sequences (ie, AB or BA) and received the following treatments (1 on Day 1 and 1 on Day 15):

- Treatment A: Single dose of F/TAF (200/25 mg) administered orally under fed conditions
- Treatment B: Single dose of FTC 200 mg + TAF 25 mg administered orally under fed conditions

Subjects were admitted to the study clinic on Day −1 and remained confined to the clinic until the morning of Day 7. Subjects returned to the clinic for readmission on Day 14 and remained

confined until the morning of Day 21. Subjects received follow-up phone calls on Days 10 and 29.

Further details on the design and results of this study are available in the clinical study report (CSR; m5.3.1.2, GS-US-311-1088).

Study Population

A total of 56 subjects were randomized in this study, and 54 subjects completed the study. One subject was discontinued due to a protocol violation (positive drug screen during the washout period). A second subject withdrew consent on Day 29 prior to completion of all scheduled PK assessments.

In the Safety Analysis Set, the median age of subjects was 35 years (range: 20 to 45 years). Half of the subjects were male. The majority of subjects were white (82.1%) and the remainder were black (17.9%); 92.9% were Hispanic/Latino. At baseline, the median (first quartile [Q1], third quartile [Q3]) body mass index (BMI) of subjects was 26.2 (23.8, 27.8) kg/m^2. The median (Q1, Q3) estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) at baseline was 125.0 (108.7, 139.9) mL/min.

Pharmacokinetic Results

Statistical comparisons of plasma TAF and FTC PK parameters AUC_{last}, AUC_{inf}, and C_{max} (F/TAF versus FTC+TAF) are presented in Table 4.

Table 4. F/TAF Study GS-US-311-1088: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

	Mean (%CV) by Treatment		
	F/TAF (Test) (N = 55)	FTC+TAF (Reference) (N = 55)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{last} (ng•h/mL)	265.1 (42.9)	253.6 (33.7)	102.68 (95.78, 110.09)
AUC_{inf} (ng•h/mL)	273.8 (45.4)[a]	257.9 (34.4)[b]	105.77 (97.26, 115.01)
C_{max} (ng/mL)	232.4 (51.9)	248.1 (44.7)	92.59 (82.31, 104.16)
FTC PK Parameter			
AUC_{last} (ng•h/mL)	9175.8 (17.4)	9596.0 (22.9)	96.16 (94.29, 98.08)
AUC_{inf} (ng•h/mL)	9387.7 (17.3)	9821.6 (22.5)	96.09 (94.24, 97.96)
C_{max} (ng/mL)	1873.5 (27.2)	1767.6 (22.8)	104.98 (100.75, 109.39)

a n = 43
b n = 48
Source: m5.3.1.2, GS-US-311-1088, Section 15.1, Tables 5.1, 5.2, and 6.1

The profiles were comparable between treatments. All parameters were within the prespecified BE boundary of 80% to 125%.

Safety Results

No serious adverse events (SAEs), deaths, or pregnancies occurred during this study, and no subject discontinued the study drug due to an adverse event (AE).

The percentage of subjects with any AE was 10.7% (6 of 56 subjects) with F/TAF administration and 14.5% (8 of 55 subjects) with FTC+TAF administration. No AE occurred in more than 1 subject following F/TAF administration. The only AE reported in more than 1 subject following FTC+TAF administration was iatrogenic injury (2 subjects with traumatic venipuncture, 3.6%).

All AEs were Grade 1. No AEs were considered related to study drug.

No clinically relevant changes in laboratory or vital sign parameters were observed during this study.

Conclusions

The overall conclusions of this study were as follows:

- F/TAF 200 /25 mg is bioequivalent to FTC 200 mg + TAF 25 mg single agents administered simultaneously.
- F/TAF 200 /25 mg and FTC 200 mg + TAF 25 mg were generally safe and well tolerated in healthy subjects.

2.2.1.2. Study GS-US-311-1472

Title

A Phase 1, Randomized, Open-Label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine/Tenofovir Alafenamide (200/10 mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets

Objectives

The primary objective of this study was as follows:

- To evaluate the BE of FTC and TAF administered as F/TAF (200/10 mg) + EVG+COBI or as E/C/F/TAF

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of single oral doses of EVG, COBI, FTC, and TAF administered as FDC tablets (E/C/F/TAF and F/TAF) or as single agents (EVG and COBI)

Study Design

This was a randomized, open-label, single-dose, 2-way, crossover study to determine the BE of FTC and TAF, administered as F/TAF (200/10 mg) + EVG+COBI or as E/C/F/TAF. Following screening and Day −1 procedures, subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received a single dose of 1 of the following treatments (A or B) on Days 1 and 7:

- Treatment A: Single dose of F/TAF (200/10 mg) administered simultaneously with EVG 150-mg and COBI 150-mg tablets orally under fed conditions
- Treatment B: Single dose of E/C/F/TAF (150/150/200/10 mg) administered orally under fed conditions

Subjects were admitted to the study clinic on Day –1 and remained confined to the clinic until Day 13. Subjects received a follow-up phone call on Day 21 ± 2 days (14 [± 2] days after the last dose of study drug).

Further details on the design and results of this study are available in the CSR (m5.3.1.2, GS-US-311-1472).

Study Population

A total of 100 subjects were randomized and received at least 1 dose of study drug. Two subjects did not complete the study (ie, 1 subject had an AE leading to discontinuation, and 1 subject withdrew consent). Approximately half of subjects were male (52.0%), and the majority of subjects were white (85.0%) and Hispanic or Latino (73.0%). At baseline, the median age was 32 years (range: 18 to 45 years), median (Q1, Q3) BMI was 26.4 (23.5, 28.1) kg/m^2, and median (Q1, Q3) $eGFR_{CG}$ was 135.4 (116.8, 150.2) mL/min.

Pharmacokinetic Results

Statistical comparisons of plasma TAF and FTC PK parameters AUC_{last}, AUC_{inf}, and C_{max} (F/TAF [200/10 mg] + EVG+COBI versus E/C/F/TAF) are presented in Table 5.

Table 5. F/TAF Study GS-US-311-1472: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (TAF or FTC PK Analysis Set)

TAF PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/10 mg) +EVG+COBI (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	97	336.6 (33.9)	99	340.2 (33.8)	97.96 (94.69,101.34)
AUC_{inf} (ng•h/mL)	97	351.8 (31.0)	99	354.1 (32.9)	98.34 (94.81,101.99)
C_{max} (ng/mL)	97	301.6 (48.8)	99	310.3 (48.7)	96.86 (89.36,104.99)
FTC PK Parameter	**Test**		**Reference**		**GLSM Ratio (90% CI), %**
	n	**Mean (%CV)**	**n**	**Mean (%CV)**	
F/TAF (200/10 mg) +EVG+COBI (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	97	10,159.2 (17.2)	99	10,086.8 (15.9)	99.84 (98.41,101.29)
AUC_{inf} (ng•h/mL)	97	10,535.1 (27.0)	99	10,294.4 (15.8)	100.67 (98.24,103.16)
C_{max} (ng/mL)	97	1660.8 (20.6)	99	1662.6 (19.1)	99.57 (96.78,102.44)

Source: m5.3.1.2, GS-US-311-1472, Section 15.1, Tables 4.1.1, 4.1.2, 5.3.1I, and 5.3.2I

The geometric least-squares mean (GLSM) ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria for BE. The median T_{max} for TAF was 1.50 hours following F/TAF+EVG+COBI and 1.00 hours following E/C/F/TAF. The median T_{max} for FTC was 2.02 hours following F/TAF+EVG+COBI and 2.00 hours following E/C/F/TAF.

Safety Results

No deaths, SAEs, or Grade 4 AEs were reported. One AE of macular rash leading to premature study drug discontinuation was reported following administration of E/C/F/TAF; this event was Grade 2 and considered related to study drug by the investigator. With the exception of 1 Grade 3 AE of arthralgia (considered not related to study drug), all other AEs were Grade 1 or 2 in severity.

Adverse events were reported in 30 of 99 subjects (30.3%) following F/TAF+EVG+COBI (Treatment A) and in 27 of 100 subjects (27.0%) following E/C/F/TAF (Treatment B). The most common AEs reported for any study treatment were headache (Treatment A: 9 subjects, Treatment B: 10 subjects), nausea (Treatment A: 9 subjects, Treatment B: 6 subjects), diarrhea (Treatment A: 4 subjects, Treatment B: 2 subjects).

No Grade 4 and 6 Grade 3 laboratory abnormalities were observed during this study. All Grade 3 abnormalities were occult blood on urinalysis in female subjects (4 of 6 subjects had confirmed menses). All other laboratory abnormalities observed were Grade 1 or 2.

There were no clinically relevant changes from baseline in renal laboratory parameters (serum creatinine, $eGFR_{CG}$, or serum phosphate) in any treatment group. Additionally, there were no clinically relevant changes from baseline in uric acid levels, the primary metabolite of TAF.

No clinically significant changes in vital sign measurements were observed during this study. No pregnancies occurred during this study.

Conclusions

The overall conclusions of this study are as follows:

- The FTC and TAF components of F/TAF (200/10 mg), when administered simultaneously with EVG and COBI, are bioequivalent to the FTC and TAF components of E/C/F/TAF.
- Administration of single doses of F/TAF (200/10 mg) + EVG+COBI and E/C/F/TAF were generally well tolerated in this study.

2.2.1.3. Study GS-US-311-1473

Title

A Phase 1, Randomized, Open-Label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine/Tenofovir

Alafenamide (200/25 mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets

Objectives

The primary objective of this study was as follows:

- To evaluate the BE of FTC and TAF administered as F/TAF (200/25 mg) or as E/C/F/TAF

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of a single oral dose of FTC and TAF administered as F/TAF (200/25 mg) and a single oral dose of EVG, COBI, FTC, and TAF administered as E/C/F/TAF

Study Design

This was a randomized, open-label, single-dose, 2-way, crossover study to determine the BE of FTC and TAF, administered as F/TAF (200/25 mg) or as E/C/F/TAF. Following screening and Day −1 procedures, subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received a single dose of 1 of the following treatments (A or B) on Days 1 and 7:

- Treatment A: Single dose of F/TAF (200/25 mg) administered orally under fed conditions
- Treatment B: Single dose of E/C/F/TAF (150/150/200/10 mg) administered orally under fed conditions

Subjects were admitted to the study clinic on Day –1 and remained confined to the clinic until Day 13. Subjects received a follow-up phone call on Day 21 ± 2 days (14 [±2] days after the last dose of study drug).

Further details on the design and results of this study are available in the CSR (m5.3.1.2, GS-US-311-1473).

Study Population

A total of 116 subjects were randomized, received at least 1 dose of study drug, and completed the study. The population was 65.5% male, 53.4% white, and 54.3% Hispanic/Latino. At baseline, the median age was 33 years (range: 18 to 45 years), median (Q1, Q3) BMI was 25.9 (24.0, 27.9) kg/m^2, and median (Q1, Q3) $eGFR_{CG}$ (ie, creatinine clearance) was 112.2 (101.0, 132.9) mL/min.

Pharmacokinetic Results

Statistical comparisons of plasma TAF and FTC PK parameters AUC_{last}, AUC_{inf}, and C_{max} (F/TAF [200/25 mg] versus E/C/F/TAF) are presented in Table 6.

Table 6. F/TAF Study GS-US-311-1473: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Test and Reference Treatments (TAF or FTC PK Analysis Set)

TAF PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32 (96.48, 104.31)
AUC_{inf} (ng•h/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54 (94.61, 102.62)
C_{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63 (95.46, 112.49)
FTC PK Parameter	**Test**		**Reference**		**GLSM Ratio (90% CI), %**
	n	**Mean (%CV)**	**n**	**Mean (%CV)**	
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	116	9423.9 (19.3)	116	10475.3 (19.7)	90.01 (88.88, 91.16)
AUC_{inf} (ng•h/mL)	116	9654.6 (19.3)	116	10706.6 (19.6)	90.20 (89.06, 91.35)
C_{max} (ng/mL)	116	1577.4 (26.8)	116	1601.7 (19.6)	97.26 (94.57, 100.03)

Source: m5.3.1.2, GS-US-311-1473, Section 15.1, Tables 4.2.1, 4.2.2, 5.1, 5.3.1, and 5.3.2

The GLSM ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria specified for BE. The median T_{max} for TAF was the same (1.50 hours), while the median T_{max} for FTC was 2.00 hours following administration of F/TAF (200/25 mg) compared with 3.00 hours following administration of E/C/F/TAF.

Safety Results

Safety was comparable between the 2 study drugs in this study. No deaths, AEs leading to premature study drug discontinuation, or Grade 4 AEs were reported. One SAE of peritoneal hemorrhage was reported following F/TAF administration; this event was Grade 3 and considered not related to study drug by the investigator. With the exception of the Grade 3 AE of peritoneal hemorrhage, all other AEs were Grade 1 or 2 in severity.

Adverse events reported in > 1 subject during any study treatment were nausea, headache, constipation, vomiting, diarrhea, dizziness, tension headache, and toothache. Nausea was reported in 5 (4.3%) subjects while receiving F/TAF and in 6 (5.2%) subjects while receiving E/C/F/TAF; all other AEs were reported in < 3% of subjects.

One Grade 4 and 2 Grade 3 laboratory abnormalities were observed during this study. One subject had a Grade 4 laboratory abnormality of increased lipase (with a Grade 2 amylase elevation on the same day) but no AE was reported. Two female subjects had Grade 3 occult blood in urine, one of whom had confirmed menses at the time. All other laboratory abnormalities observed were Grade 1 or 2.

There were no clinically relevant changes from baseline in renal laboratory parameters (serum creatinine, $eGFR_{CG}$, or serum phosphate) in any treatment group. Additionally, there were no clinically relevant changes from baseline in uric acid levels, the primary metabolite of TAF.

No clinically significant changes in vital sign measurements were observed during this study. No pregnancies occurred during this study.

Conclusions

- The FTC and TAF components of F/TAF (200/25 mg) are bioequivalent to the FTC and TAF components of E/C/F/TAF.
- Administration of single doses of F/TAF (200/25 mg) and E/C/F/TAF were generally well tolerated in this study.

2.2.2. TAF Studies

2.2.2.1. Study GS-US-120-0107

Title

A Phase 1, Partially-Blinded, Randomized, Placebo- and Positive-Controlled Study to Evaluate the Effect of GS-7340 on the QT/QTc Interval in Healthy Subjects

Objectives

The primary objective of this study was as follows:

- To evaluate the effects of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on time-matched, baseline-adjusted, placebo-corrected QTcF (corrected QT calculated using the Fridericia formula)

The secondary objectives of this study were as follows:

- To explore the effect of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on corrected QT using other approaches, including QTcB (corrected QT calculated using the Bazett formula), and QTcN (corrected QT calculated using population correction formula)
- To determine the PK of TAF and its metabolite TFV
- To explore the relationship between ΔΔQTc (time-matched, baseline-adjusted, placebo-corrected QTc) and plasma concentrations of TAF and its metabolite TFV
- To explore the effect of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on other electrocardiogram (ECG) parameters, including PR interval
- To evaluate the safety and tolerability of TAF in healthy subjects at the doses administered

Study Design

This was a partially-blinded, randomized, placebo- and positive-controlled, 4-period, single-dose, crossover study to evaluate the effect of TAF on time-matched, baseline-adjusted, and placebo-corrected QTcF, QTcB, and QTcN, and exploring the effect of TAF on ECG parameters in healthy subjects. The following treatments were administered during the study:

- Treatment A (therapeutic exposure): TAF 25 mg (1 × 25-mg TAF tablet + 4 × TAF placebo-to-match)
- Treatment B (supratherapeutic exposure): TAF 125 mg (5 × 25-mg TAF tablets)
- Treatment C (placebo control): 5 × TAF placebo-to-match
- Treatment D (positive control): 1 × moxifloxacin 400 mg

Placebo and TAF study drugs in Treatments A, B, and C were administered double blind. Moxifloxacin given in Treatment D was administered open label.

Subjects were admitted to the study clinic on Day 0 and remained confined to the clinic until the morning of Day 40. Subjects completed 4 dosing periods; each period consisted of 1 day of dosing with 1 of 4 study drug treatments. Dosing in the first 3 periods was followed by a washout period of 11 days to avoid carryover effects. Subjects returned to the clinic 7 days after the last dose for an in-clinic follow-up visit.

Further details on the design and results of this study are available in the CSR (GS-US-120-0107).

Study Population

A total of 48 subjects were to be enrolled in the study to obtain a total of 40 evaluable subjects. A total of 59 subjects were randomized into the study, and 58 subjects completed the study. One subject was discontinued during the first treatment period and was replaced. Ten subjects were replaced due to damaged ECG flash cards in the third period. These 11 subjects were included in the safety analysis set, but were excluded from PK, PD, and PK/PD analysis sets due to incomplete ECG data (the primary endpoint).

Subjects in the PD analysis set were predominantly male (66.7%), white (81.3%), of Hispanic/Latino ethnicity (93.8%), and had a median age of 38 years (range: 18 to 44 years).

Pharmacokinetic Results

Pharmacokinetic parameters for TAF and TFV following single oral doses of TAF 25 or 125 mg were approximately proportional to dose (Table 7).

Table 7. TAF Study GS-US-120-0107: Statistical Analysis of Dose Proportionality

	Mean (%CV)		
	TAF 125 mg (Test) (N = 48)	TAF 25 mg (Reference) (N = 48)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{last} (ng•h/mL)	1214.3 (33.2)	225.9 (44.0)	551.85 (525.61, 579.40)
AUC_{inf} (ng•h/mL)	1228.0 (32.6)[a]	228.2 (43.4)	542.04 (517.16, 568.13)
C_{max} (ng/mL)	859.0 (35.1)	174.3 (59.1)	522.37 (475.94, 573.33)
TFV PK Parameter			
AUC_{last} (ng•h/mL)	1144.4 (20.5)	196.1 (24.7)	587.35 (566.51, 608.96)
AUC_{inf} (ng•h/mL)	1543.1 (22.8)	258.7 (28.5)	602.04 (578.15, 626.92)
C_{max} (ng/mL)	50.8 (26.0)	8.7 (29.9)	585.28 (556.34, 615.71)

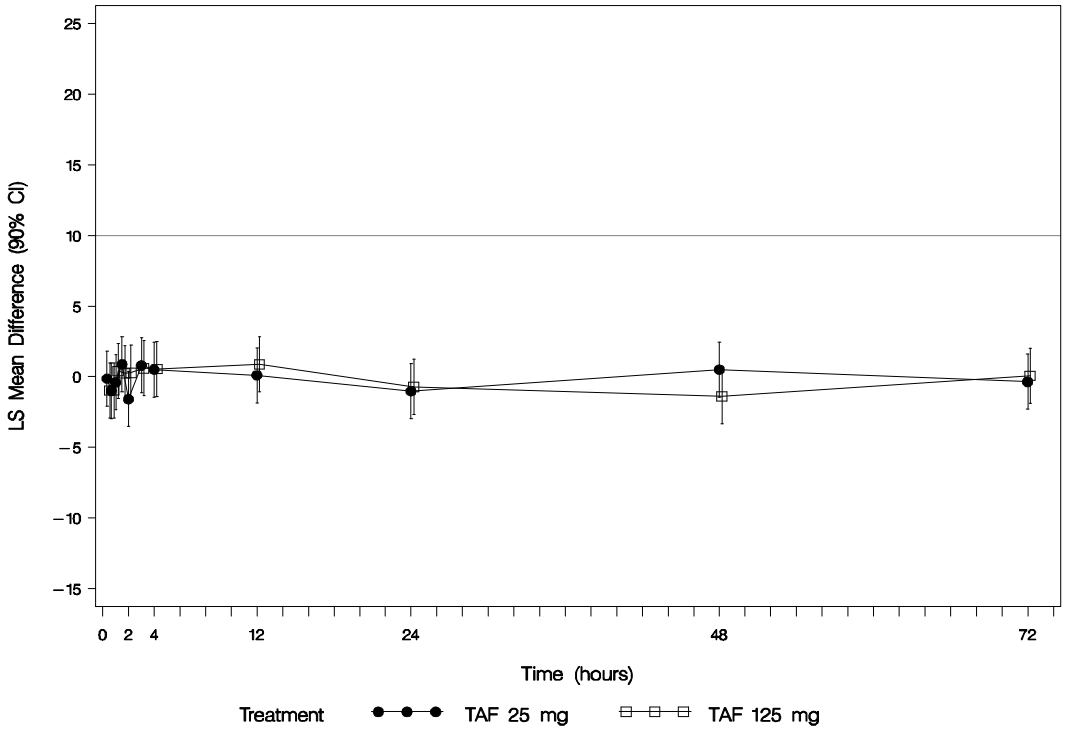
a n = 47
Source: GS-US-120-0107, Section 15.1, Tables 14.1, 14.2, and 15

Pharmacodynamic Results

Assay Sensitivity: Time-matched, baseline-adjusted, placebo-corrected change from predose baseline in QTcF was evaluated for a single dose of moxifloxacin to demonstrate assay sensitivity. In this analysis, the lower bound of the 2-sided 90% CI for the mean difference between moxifloxacin and placebo was greater than 5 msec at 2 time points (3 and 4 hours) after dosing, thereby establishing assay sensitivity.

Noninferiority Analyses: For the primary analysis, TAF was concluded to have no QTcF prolongation effect as the upper bounds of the 2-sided 90% CIs for the mean difference between therapeutic or supratherapeutic doses of TAF and placebo were below 10 msec at all time points after dosing (Figure 2). Small negative changes in QTcF were observed at both dose levels. Results from the analyses of secondary endpoints, QTcB, QTcN, and QTcI (QT interval corrected using the individual correction formula) values, were consistent with those from the primary analysis.

Figure 2. **TAF Study GS-US-120-0107: Noninferiority Evaluation for Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF (PD Analysis Set)**



Source: GS-US-120-0107, Section 15.1, Figure 2.1

Categorical Analyses: Results from categorical analyses of QTcF, QTcB, QTcN, and QTcI are summarized in Table 8. No subject had a treatment-emergent absolute QTc interval > 500 msec at any postdose assessment, or a change from predose baseline QTc > 60 msec with any correction factor following any treatment. No subject had a treatment-emergent absolute QTc interval > 480 msec or a change from predose baseline > 30 msec following a therapeutic (25 mg) or supratherapeutic (125 mg) dose of TAF.

Table 8. **TAF Study GS-US-120-0107: Categorical Analysis of QTc (msec) by Treatment (PD Analysis Set)**

	TAF 25 mg (N = 48)	TAF 125 mg (N = 48)	Placebo (N = 48)	Moxifloxacin 400 mg (N = 48)
Observed Value				
> 500 msec	0	0	0	0
> 480 msec	0	0	0	QTcB (n = 1)
> 450 msec	QTcB (n = 3) QTcI (n = 1)	QTcB (n = 1)	0	QTcF (n = 2) QTcB (n = 4) QTcN (n = 2) QTcI (n = 2)
Change from Predose/Baseline				
> 60 msec	0	0	0	0
> 30 msec	0	0	0	QTcB (n = 3)

QTcI = QT interval corrected for heart rate using the individual correction formula; QTcN = QT interval corrected for heart rate using the population-specific correction formula
Source: GS-US-120-0107, Section 15.1, Tables 3.6, 4.6, 5.6, and 6.6

Pharmacokinetic/Pharmacodynamic Results

There was no consistent, pharmacologically meaningful association between time-matched, baseline-adjusted, placebo-corrected QTc and TAF or TFV plasma concentrations.

Safety Results

At least 1 treatment-emergent AE was reported for 13.8%, 17.2%, 15.3%, and 17.2% of subjects in the TAF 25-mg, TAF 125-mg, placebo, and moxifloxacin 400-mg groups, respectively. The majority of AEs were reported as Grade 1 in severity. No deaths or pregnancies occurred during this study, and no subject discontinued the study due to an AE. There were no SAEs during the TAF or placebo treatment periods. One subject had multiple SAEs during the moxifloxacin treatment period (gastritis, erosive duodenitis, gastric ulcer, and *Helicobacter* infection); all were considered unrelated to study drug. Three subjects had AEs that could be associated with cardiac disease. These included palpitations associated with no ECG changes in 1 subject during the TAF 25-mg treatment, dizziness (concurrent with nausea and headache) associated with ST segment depression on ECG in 1 subject during the TAF 125-mg treatment, and presyncope (described as a mild vasovagal reaction) with no associated clinically significant ECG changes in 1 subject during the moxifloxacin treatment. There were no clinically relevant changes in any hematology or chemistry parameter for any treatment. No clinically significant changes in vital signs or safety ECGs were observed for any treatment during this study. Specifically, there were no clinically significant changes in safety ECGs for the 10 subjects who were replaced due to damaged ECG flash cards in the third period.

Conclusions

- Exposures of TAF and TFV were approximately proportional to dose.
- The expected increase in QTc upon administration of 400-mg moxifloxacin demonstrated assay sensitivity. TAF, administered at doses of 25 and 125 mg, did not lead to changes in the QTc interval in healthy adults. Thus, this study is a negative thorough QT study as defined by International Conference on Harmonisation (ICH) guidance.
- There was no pharmacologically meaningful association between time-matched, baseline-adjusted, placebo-corrected QTcF and TAF or TFV plasma concentrations.
- Single doses of TAF administered at therapeutic (25 mg) and supratherapeutic (125 mg) doses were generally well tolerated in these healthy subjects. Most AEs were considered Grade 1 and unrelated to study drug.

2.2.2.2. Study GS-US-120-0109

Title

A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism and Excretion of GS-7340

Objectives

The primary objective of this study was as follows:

- To determine the mass balance of TAF following administration of a single, oral dose of radiolabeled carbon-14 ([^{14}C])TAF

The secondary objectives of this study were as follows:

- To evaluate the PK of TAF, and its metabolite TFV, and safety following administration of a single, oral dose of radiolabeled [^{14}C]TAF
- To determine the metabolite profile of TAF in humans following administration of a single, oral dose of radiolabeled [^{14}C]TAF

Study Design

This was an open-label, Phase 1, mass balance study conducted at a single study center in the United States to evaluate the PK, metabolism, and excretion of TAF following administration of a single, oral dose of radiolabeled [^{14}C]TAF in healthy subjects.

Further details on the design and results of this study are available in the CSR (GS-US-120-0109).

Study Population

A total of 8 subjects were planned to be enrolled to obtain 6 evaluable subjects. Eight subjects were enrolled, completed study drug administration, and included in the safety and PK analysis sets. Six subjects completed the study, and 2 subjects withdrew consent.

All subjects were men, and most (7 subjects [87.5%]) were white. The median age was 29 years (range: 19 to 45 years). The median BMI was 25.9 kg/m^2 (range: 22.6 to 29.3 kg/m^2), and the median $eGFR_{CG}$ was 117.5 mL/min (range: 87.7 to 198.2 mL/min).

Pharmacokinetic Results

The results of this mass balance study confirmed that TAF was extensively metabolized in urine and feces. The total mean ± SD recovery of [^{14}C]-radioactivity in feces plus urine was 84.4% ± 2.45% (N = 7), with the percentage of radioactive dose recovered from feces at 47.2% ± 4.62% (N = 7) and the percentage of radioactive dose recovered from urine at 36.2% ± 5.62% (N = 8). The predominant species detected in feces and urine was TFV, accounting for 99% of the radioactivity recovered in feces, and 86% of the radioactivity recovered in urine. All other metabolites detected in the feces and urine were in trace amounts, with no values exceeding 2%

of the administered radioactive dose. Only 1.41% ± 0.561% of the total radioactive dose was identified in urine as TAF, suggesting very low renal TAF clearance. No radioactive TAF was detected in feces.

There were 2 concentration peaks present in the plasma [^{14}C]-radioactivity time profile. At the first maximal plasma radioactivity concentration around 2 hours postdose, the predominant species was TAF, accounting for 72.6% of the total [^{14}C]-radioactivity quantified. At the second maximal plasma radioactivity concentration around 24 to 48 hours postdose, the predominant species was uric acid, accounting for 97.6% of the total [^{14}C]-radioactivity quantified. Over the 96-hour period following TAF administration, the predominant species circulating in plasma was uric acid, which accounted for 73.9% of the total [^{14}C]-radioactivity AUC over the 96-hour period; TAF and TFV AUC represented 1.8% and 1.5% of the total [^{14}C]-radioactivity AUC, respectively.

In addition to TFV and uric acid, additional low quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine. They are identical to the endogenous products of purine metabolism and should not cause any safety risk.

Safety Results

Two subjects (25.0%) had ≥ 1 treatment-emergent AE. All treatment-emergent AEs were assessed as Grade 1 in severity. No deaths or other SAEs occurred during this study, and no subject discontinued the study due to an AE. No subject had a treatment-emergent laboratory abnormality. There were no clinically relevant changes from baseline in renal laboratory parameters during the study (serum creatinine or serum phosphate). Additionally, the formation of the primary metabolite from TAF administration (uric acid) did not alter the uric acid level in plasma in these subjects. No clinically significant changes in vital signs or safety ECG results were observed during this study.

Conclusions

- TAF was extensively metabolized and eliminated in urine and feces. The mean ± SD cumulative urinary and fecal recovery of [^{14}C]-radioactivity was 84.4% ± 2.45% (N = 7), with the percentage of radioactive dose recovered from feces at 47.2% ± 4.62% (N = 7) and the percentage of radioactive dose recovered from urine at 36.2% ± 5.62% (N = 8). The predominant species detected in feces and urine was TFV. Renal excretion of TAF as parent drug was a very minor pathway for elimination.

- The predominant species circulating in plasma was uric acid, which accounted for 73.9% of the total [^{14}C]-radioactivity AUC over the 96-hour period. At the first maximal plasma radioactivity concentration around 2 hours postdose, the predominant species was TAF. At the second maximal plasma radioactivity concentration around 24 to 48 hours postdose, the predominant species was uric acid. Additional low quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine, which were identical to the endogenous products of purine metabolism.

- TAF 25-mg capsules, administered together with a tracer dose of [^{14}C]-radiolabeled TAF as a single oral capsule, were well tolerated.

2.2.3. E/C/F/TAF Studies

2.2.3.1. Study GS-US-292-0101

Title

A Phase 1, Multiple-Dose Study Evaluating the Relative Bioavailability of Two Elvitegravir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Formulations vs Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen and GS-7340

Objectives

The primary objective of this study was as follows:

- To evaluate the relative bioavailability of EVG, COBI, FTC, and TFV when administered as 1 of 2 FDC formulations (previously referred to as single-tablet regimen [STR]) of E/C/F/TAF versus STB or TAF, respectively

The secondary objective of this study was as follows:

- To evaluate the safety of administration of STB, TAF, and 2 formulations of E/C/F/TAF

Study Design

This was a Phase 1, open-label, crossover, randomized, multiple-dose, multiple-cohort, single-center study designed to evaluate the relative bioavailability of 2 formulations of E/C/F/TAF (containing 25 or 40 mg TAF) versus STB or TAF 25 mg alone in healthy male and female subjects. The PK of EVG, COBI, FTC, TFV, and TAF were assessed.

Subjects were assigned to 1 of 2 cohorts and randomized to 1 of 4 treatment sequences (I, II, III, or IV) within each cohort. On Days 1 through 54, subjects were administered study treatment (Treatment A, B, C, D, E, or F) according to their assigned treatment sequence. Each of the 4 study treatments in Cohorts 1 and 2 were administered for 12 days with a 2-day washout period between treatments. Subjects were discharged from the study clinic on Day 57, and a follow-up evaluation was performed 14 days after the last dose of study drug.

The following study treatments were administered in Cohort 1:

- Treatment A: E/C/F/TAF FDC Formulation 1 (150/150/200/25 mg)
- Treatment B: E/C/F/TAF FDC Formulation 1 (150/150/200/40 mg)
- Treatment C: STB (150/150/200/300 mg)
- Treatment D: 25-mg TAF tablet

Subjects in Cohort 1 were randomized to 1 of the 4 treatment sequences as follows:

	Days 1-12	Days 15-26	Days 29-40	Days 43-54
Sequence I	A	B	C	D
Sequence II	B	D	A	C
Sequence III	C	A	D	B
Sequence IV	D	C	B	A

The following study treatments were administered in Cohort 2:

- Treatment E: E/C/F/TAF FDC Formulation 2 (150/150/200/25 mg)
- Treatment F: E/C/F/TAF FDC Formulation 2 (150/150/200/40 mg)
- Treatment C: STB (150/150/200/300 mg)
- Treatment D: 25-mg TAF tablet

Subjects in Cohort 2 were randomized to 1 of the 4 treatment sequences as follows:

	Days 1-12	Days 15-26	Days 29-40	Days 43-54
Sequence I	E	F	C	D
Sequence II	F	D	E	C
Sequence III	C	E	D	F
Sequence IV	D	C	F	E

Further details on the design and results of this study are available in the CSR (GS-US-292-0101).

Study Population

A total of 40 subjects were planned to be enrolled (20 per cohort) with a target of 16 evaluable subjects per cohort. Of the 40 enrolled subjects, 36 (90%) received all planned doses of study drug and completed the study: 19 of 20 subjects (95%) in Cohort 1 and 17 of 20 subjects (85%) in Cohort 2. Of the 4 subjects who did not complete study drug dosing, 3 did so because of a protocol violation (1 subject in Cohort 1 and 2 subjects in Cohort 2), and 1 subject (Cohort 2) discontinued study drug dosing because of an AE.

In Cohort 1, 10 (50%) were male, and the median age was 38 years (range: 25 to 45 years). Seventeen of the subjects (85%) were white and 3 (15%) were black; all were Hispanic/Latino. Median values for weight, height, and a BMI at screening were 78.8 kg, 168.5 cm, and 27.8 kg/m^2, respectively. Median baseline $eGFR_{CG}$ was 136.9 mL/min (range: 102.5 to

170.0 mL/min) and median baseline eGFR by modification of diet in renal disease ($eGFR_{MDRD}$) was 110.0 mL/min/1.73 m^2 (range: 79.6 to 146.0 mL/min/1.73 m^2).

In Cohort 2, 10 (50%) were male, and the median age was 38 years (range: 26 to 45 years). Seventeen of the subjects (85%) were white and 3 (15%) were black; 19 (95%) were Hispanic/Latino. Median values for weight, height, and BMI at screening were 74.3 kg, 167.5 cm, and 26.2 kg/m^2, respectively. Median baseline $eGFR_{CG}$ was 123.5 mL/min (range: 84.3 to 154.6 mL/min) and median baseline $eGFR_{MDRD}$ was 105.5 mL/min/1.73 m^2 (range: 71.3 to 169.2 mL/min/1.73 m^2).

Pharmacokinetic Results

Pharmacokinetic parameters of TAF, TFV, EVG, COBI, and FTC are presented in Table 9, Table 10, Table 11, Table 12, and Table 13, respectively. Comparisons of exposure parameters are made primarily for treatments containing TAF 25 mg, which represent the target exposures that provide robust antiviral activity (Study GS-US-120-0104).

Table 9. E/C/F/TAF Study GS-US-292-0101: Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test	Reference	
Cohort 1: E/C/F/TAF Formulation 1 (150/150/200/25 mg; Test) vs TAF 25 mg (Reference) (N = 19)			
AUC_{last} (ng•h/mL)	552.1 (40.5)	242.4 (42.4)	221.78 (199.99, 245.95)
C_{max} (ng/mL)	506.9 (54.2)	215.4 (55.0)	222.62 (187.11, 264.87)
Cohort 2: E/C/F/TAF Formulation 2 (150/150/200/25 mg; Test) vs TAF 25 mg (Reference) (N = 18)			
AUC_{last} (ng•h/mL)	558.7 (28.6)	244.9 (34.0)	230.93 (205.52, 259.50)
C_{max} (ng/mL)	472.4 (57.4)	210.8 (43.7)	223.01 (188.40, 263.97)

Source: GS-US-292-0101, Section 15.1, Tables 4.1.5, 4.2.5, 5.1, and 5.2; GS-US-292-0101, Section 15.1, Listing 8.2

Table 10. E/C/F/TAF Study GS-US-292-0101: Statistical Comparisons of TFV PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

TFV PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test	Reference	
Cohort 1: E/C/F/TAF Formulation 1 (150/150/200/25 mg; Test) vs STB (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	834.9 (17.6)	3737.3 (22.3)	22.62 (21.39, 23.91)
C_{max} (ng/mL)	65.9 (50.9)	444.7 (28.9)	14.02 (12.20, 16.11)
C_{tau} (ng/mL)	28.1 (20.3)	73.2 (25.1)	38.93 (36.54, 41.47)
Cohort 1: E/C/F/TAF Formulation 1 (150/150/200/25 mg; Test) vs TAF 25 mg (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	834.9 (17.6)	273.4 (23.5)	306.92 (290.34, 324.45)
C_{max} (ng/mL)	65.9 (50.9)	16.3 (24.8)	367.68 (319.98, 422.50)
C_{tau} (ng/mL)	28.1 (20.3)	9.4 (25.9)	301.52 (283.03, 321.22)
Cohort 2: E/C/F/TAF Formulation 2 (150/150/200/25 mg; Test) vs STB (Reference) (N = 18)			
AUC_{tau} (ng•h/mL)	897.8 (12.7)	4089.6 (21.7)	22.47 (21.11, 23.91)
C_{max} (ng/mL)	71.9 (57.3)	505.3 (27.1)	13.54 (11.62, 15.77)
C_{tau} (ng/mL)	31.3 (15.0)	81.6 (22.2)	39.13 (36.46, 41.99)
Cohort 2: E/C/F/TAF Formulation 2 (150/150/200/25 mg; Test) vs TAF 25 mg (Reference) (N = 18)			
AUC_{tau} (ng•h/mL)	897.8 (12.7)	300.3 (13.4)	299.23 (281.25, 318.37)
C_{max} (ng/mL)	71.9 (57.3)	17.5 (15.1)	370.45 (318.17, 431.34)
C_{tau} (ng/mL)	31.3 (15.0)	10.5 (16.7)	300.33 (279.91, 322.24)

Source: GS-US-292-0101, Section 15.1, Tables 4.1.4, 4.2.4, 5.1, and 5.2; GS-US-292-0101, Section 15.1, Listing 8.2

Table 11. E/C/F/TAF Study GS-US-292-0101: Statistical Comparisons of EVG PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

EVG PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test	Reference	
Cohort 1: E/C/F/TAF Formulation 1 (150/150/200/25 mg; Test) vs STB (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	25243.0 (24.7)	22732.0 (27.4)	111.30 (103.88, 119.24)
C_{max} (ng/mL)	2458.5 (31.4)	2162.6 (31.3)	112.80 (103.57, 122.84)
C_{tau} (ng/mL)	426.3 (40.3)	419.2 (39.9)	102.30 (93.80, 111.57)
Cohort 2: E/C/F/TAF Formulation 2 (150/150/200/25 mg; Test) vs STB (Reference) (N = 18)			
AUC_{tau} (ng•h/mL)	24332.1 (28.4)	23693.1 (23.9)	101.31 (95.30, 107.71)
C_{max} (ng/mL)	2218.4 (33.2)	2178.7 (30.0)	100.24 (91.03, 110.38)
C_{tau} (ng/mL)	439.8 (44.7)	453.5 (37.1)	95.00 (87.88, 102.70)

Source: GS-US-292-0101, Section 15.1, Tables 4.1.1, 4.2.1, 5.1, and 5.2; GS-US-292-0101, Section 15.1, Listing 8.2

Table 12. E/C/F/TAF Study GS-US-292-0101: Statistical Comparisons of COBI PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

COBI PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test	Reference	
Cohort 1: E/C/F/TAF Formulation 1 (150/150/200/25 mg; Test) vs STB (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	11212.4 (25.8)	10486.3 (31.4)	108.56 (104.22, 113.08)
C_{max} (ng/mL)	1552.1 (23.8)	1426.4 (28.7)	110.15 (103.89, 116.79)
C_{tau} (ng/mL)	34.6 (57.2)	37.1 (71.3)	102.10 (88.06, 118.37)
Cohort 2: E/C/F/TAF Formulation 2 (150/150/200/25 mg; Test) vs STB (Reference) (N = 18)			
AUC_{tau} (ng•h/mL)	12024.6 (21.9)	11847.6 (24.7)	102.05 (96.67, 107.72)
C_{max} (ng/mL)	1630.7 (17.1)	1582.2 (23.0)	103.94 (98.35, 109.83)
C_{tau} (ng/mL)	38.5 (95.8)	39.1 (112.7)	105.22 (94.66, 116.95)

Source: GS-US-292-0101, Section 15.1, Tables 4.1.2, 4.2.2, 5.1, and 5.2; GS-US-292-0101, Section 15.1, Listing 8.2

Table 13. E/C/F/TAF Study GS-US-292-0101: Statistical Comparisons of FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

FTC PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test	Reference	
Cohort 1: E/C/F/TAF Formulation 1 (150/150/200/25 mg; Test) vs STB (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	11907.0 (18.3)	11977.6 (17.2)	99.13 (95.51, 102.89)
C_{max} (ng/mL)	1984.0 (18.7)	1910.4 (15.7)	103.53 (97.36, 110.09)
C_{tau} (ng/mL)	93.5 (24.6)	93.3 (22.2)	99.67 (92.24, 107.70)
Cohort 2: E/C/F/TAF Formulation 2 (150/150/200/25 mg; Test) vs STB (Reference) (N = 18)			
AUC_{tau} (ng•h/mL)	12552.2 (17.1)	13134.0 (15.1)	95.48 (92.33, 98.74)
C_{max} (ng/mL)	2019.5 (15.6)	2096.6 (20.9)	97.19 (91.34, 103.41)
C_{tau} (ng/mL)	109.7 (26.7)	110.1 (27.7)	99.65 (93.00, 106.77)

Source: GS-US-292-0101, Section 15.1, Tables 4.1.3, 4.2.3, 5.1, and 5.2; GS-US-292-0101, Section 15.1, Listing 8.2

Following administration of E/C/F/TAF Formulations 1 and 2 (containing 25 mg TAF), geometric mean TAF and TFV exposures were substantially higher relative to TAF 25-mg single agent. With both formulations of E/C/F/TAF containing 25 mg TAF, TAF AUC_{last} and C_{max} were approximately 2.2- and 2.3-fold higher, respectively, while TFV AUC_{tau} and C_{max} were approximately 3.1- and 3.7-fold higher, respectively. A comparable increase in exposure was observed for TAF and TFV exposures in Study GS-US-311-0101 (Section 2.5.1.1) when dosed as TAF 8 mg + COBI versus TAF 8 mg single agent; TAF AUC_{last} and C_{max} were approximately 2.7- and 2.8-fold higher, respectively, while TFV AUC_{tau} and C_{max} were approximately 3.3- and 3.3-fold higher, respectively. These data suggest that the interaction is COBI-mediated, likely due to inhibition of P-gp–mediated intestinal secretion of TAF. TAF and TFV exposures were generally dose-proportional following E/C/F/TAF (containing 40 mg TAF) versus E/C/F/TAF

(containing 25 mg TAF). TFV exposure parameters were lower following administration of E/C/F/TAF Formulations 1 and 2 (containing 25 or 40 mg TAF) and TAF single agent compared with STB in Cohorts 1 and 2, respectively; mean TFV exposure (AUC_{tau} and C_{max}) following TAF single agent was > 90% lower compared with STB.

Following administration of E/C/F/TAF Formulations 1 and 2 (containing 25 or 40 mg TAF), the geometric mean ratio (GMR) and 90% CIs of AUC_{tau}, C_{max}, and C_{tau} for EVG, COBI, and FTC were contained within the protocol-defined lack of interaction boundary of 70% to 143%, versus administration of STB, indicating no clinically relevant differences. The stricter 80% to 125% boundary criterion for BE was also met for EVG, COBI, and FTC exposures. Exposures of EVG, COBI, and FTC were consistent with historical data from previous studies.

Safety Results

Treatment-emergent AEs were reported in 5 of 19 subjects (26.3%) in Treatment A, 4 of 19 subjects (21.1%) in Treatment B, 12 of 39 subjects (30.8%) in Treatment C, 12 of 37 subjects (32.4%) in Treatment D, 7 of 18 subjects (38.9%) in Treatment E, and 3 of 18 subjects (16.7%) in Treatment F. All except 1 treatment-emergent AE were assessed as Grade 1 or Grade 2 in severity. No deaths or SAEs occurred during the study. One subject discontinued from the study because of a nonserious AE of Grade 3 increased creatine phosphokinase that was assessed as related to study drug. The incidence of treatment-emergent laboratory abnormalities was similar across treatment groups. There were no clinically relevant changes in vital signs, physical examination findings, or ECGs during the study.

Conclusions

- Administration of E/C/F/TAF Formulations 1 and 2 resulted in substantially higher TAF and TFV exposures relative to TAF 25-mg single agent, while mean TFV exposure (AUC_{tau} and C_{max}) following TAF 25-mg single agent was > 90% lower compared with STB.
- Administration of E/C/F/TAF Formulations 1 and 2 (containing 25 or 40 mg TAF) provided similar EVG, COBI, and FTC exposures compared with STB.
- E/C/F/TAF Formulations 1 and 2, as well as STB and TAF alone, were generally safe and well tolerated in healthy subjects.

2.2.3.2. Study GS-US-292-0103

Title

A Phase 1, Multiple-Dose Study Evaluating the Relative Bioavailability of Elvitegravir/Cobicistat/Emtricitabine/GS-7340 STR Relative to the Administration of Individual Components Cobicistat-Boosted Elvitegravir, Emtricitabine, and GS-7340

Objectives

The primary objective of this study was as follows:

- To evaluate the PK and relative bioavailability of EVG, COBI, FTC, TAF, and TFV administered as E/C/F/TAF relative to the administration of the individual components: EVG, COBI, FTC, and TAF

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of administration of E/C/F/TAF and the individual components EVG, COBI, FTC, and TAF

Study Design

This was a single-center, randomized, open-label, multiple-dose, multiple-cohort, 2-period, crossover study in healthy adult subjects. Eligible subjects were assigned to Cohort 1 or Cohort 2 such that there was an approximately even distribution of healthy male and nonpregnant, nonlactating female subjects aged 18 to 45 years in each. Study treatments were as follows:

Cohort 1

Treatment A: E/C/F/TAF (150/150/200/10 mg)

Treatment B: EVG 150 mg + COBI 150 mg

Cohort 2

Treatment A: E/C/F/TAF (150/150/200/10 mg)

Treatment C: FTC 200 mg + TAF 25 mg

Each treatment was administered orally once daily, in the morning, with food, for 12 days.

Within each cohort, subjects were randomized in a 1:1 ratio to receive treatments in Sequence I or Sequence II, as follows:

	Period 1	Period 2	
Cohort 1	**Days 1-12**	**Days 13-24**	**Day 34**
Sequence I	A	B	Follow-up
Sequence II	B	A	
Cohort 2			
Sequence I	A	C	
Sequence II	C	A	

Further details on the design and results of this study are available in the CSR (GS-US-292-0103).

Study Population

A total of 34 subjects (14 in Cohort 1 and 20 in Cohort 2) were planned to be enrolled to obtain a total of 12 and 16 evaluable subjects in Cohorts 1 and 2, respectively. A total of 34 healthy subjects were enrolled in the study and assigned to Cohort 1 (14 subjects) or Cohort 2 (20 subjects) as planned. All subjects in each cohort received ≥ 1 dose of study drug. All subjects in Cohort 1, and 19 of 20 subjects in Cohort 2, received all planned doses of study drugs and completed the study. One subject in Cohort 2 withdrew consent to continued participation in the study after receiving single doses of FTC and TAF 25 mg (Treatment C) and was excluded from the EVG, COBI, FTC, TAF, and TFV PK analysis sets.

The median ages of subjects in Cohort 1 and Cohort 2 were 26 years (range: 18 to 42 years) and 36 years (range: 20 to 45 years), respectively, and the percentages of non-Hispanic/Latino subjects were 57% and 65%, respectively. With regard to other characteristics, the 2 cohorts were comparable in terms of sex (approximately 71% male), race (approximately 59% white, 41% black), weight (overall median at baseline: 76.0 kg), BMI (overall median at baseline: 25.5 kg/m^2), and $eGFR_{CG}$ (overall median at baseline: 125.8 mL/min).

Pharmacokinetic Results

Primary PK exposure parameters of TAF, TFV, EVG, COBI, and FTC following administration of E/C/F/TAF, EVG+COBI, and EVG+TAF 25 mg, and statistical comparisons of each between treatments, are presented in Table 14.

Table 14. E/C/F/TAF Study GS-US-292-0103: Statistical Comparisons of TAF, TFV, EVG, COBI, and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 2: E/C/F/TAF (Test) vs FTC+TAF 25 mg (Reference) (N = 19)			
AUC_{last} (ng•h/mL)	250.2 (24.7)	278.2 (28.8)	91.42 (84.12, 99.35)
C_{max} (ng/mL)	176.9 (35.1)	179.5 (33.9)	98.68 (84.57, 115.13)
TFV PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 2: E/C/F/TAF (Test) vs FTC+TAF 25 mg (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	324.2 (15.4)	265.9 (22.2)	123.63 (116.97, 130.67)
C_{max} (ng/mL)	19.6 (13.9)	19.2 (76.0)	114.16 (97.52, 133.64)
C_{tau} (ng/mL)	11.4 (17.8)	9.2 (23.5)	125.37 (117.72, 133.51)
EVG PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 1: E/C/F/TAF (Test) vs EVG+COBI (Reference) (N = 14)			
AUC_{tau} (ng•h/mL)	22,067.1 (26.3)	23,099.2 (22.7)	94.87 (91.51, 98.36)
C_{max} (ng/mL)	1943.5 (23.9)	2161.0 (27.0)	90.32 (85.07, 95.89)
C_{tau} (ng/mL)	422.2 (54.4)	418.6 (42.2)	97.83 (88.39, 108.27)
COBI PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 1: E/C/F/TAF (Test) vs EVG+COBI (Reference) (N = 14)			
AUC_{tau}(ng•h/mL)	11,209.8 (27.4)	10,931.2 (25.5)	102.00 (98.10, 106.06)
C_{max} (ng/mL)	1560.7 (26.1)	1489.4 (23.2)	104.07 (99.41, 108.94)
C_{tau} (ng/mL)	34.6 (85.5)	26.7 (62.1)	116.43 (102.05, 132.83)
FTC PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 2: E/C/F/TAF (Test) vs FTC+TAF 25 mg (Reference) (N = 19)			
AUC_{tau}(ng•h/mL)	12,352.6 (13.5)	10,520.9 (13.8)	117.57 (113.72, 121.55)
C_{max} (ng/mL)	1947.0 (21.2)	1788.8 (19.2)	108.99 (102.81, 115.55)
C_{tau} (ng/mL)	107.4 (25.8)	87.5 (20.6)	121.26 (114.66, 128.24)

Source: GS-US-292-0103, Section 15.1, Tables 4.1.1, 4.1.2, 4.2.3, 4.2.5, 4.2.7, and 5

In the present study, TAF and resultant TFV exposures following administration of the reduced dose TAF 10 mg as a constituent of E/C/F/TAF were comparable with those observed following administration of the TAF 25-mg dose (coadministered with FTC), confirming the 2- to 3-fold change in exposure observed previously when TAF was dosed with COBI or as a constituent of E/C/F/TAF relative to its administration as a single agent (GS-US-311-0101 [Section 2.5.1.1] and GS-US-292-0101 [Section 2.2.3.1]). This increased exposure is likely due to inhibition by COBI of P-gp–mediated intestinal secretion of TAF (GS-US-311-0101 and GS-US-292-0101).

Specifically, following the administration of E/C/F/TAF (test treatment), the 90% CIs of the GLSM ratios for TAF and TFV exposures relative to FTC+TAF 25 mg (reference treatment) were contained within the protocol-defined 70% to 143% lack-of-effect boundary. Mean (%CV) TFV exposure parameters (AUC and C_{max}) following multiple doses of E/C/F/TAF and FTC+TAF 25 mg were > 90% lower than observed following administration of STB (mean [%CV] AUC_{tau} and C_{max} for TFV were 4066.2 [24.1] ng•h/mL and 485.6 [31.1] ng/mL, respectively).

Following the administration of E/C/F/TAF, the GLSM ratios and 90% CIs for EVG, COBI, and FTC were all contained within the protocol-defined 70% to 143% lack-of-effect boundary relative to EVG+COBI or FTC+TAF 25 mg, indicating no clinically relevant differences. The stricter 80% to 125% boundary was also met for the relevant EVG, COBI, and FTC exposure parameters, consistent with previous findings from Study GS-US-292-0101.

Overall, the data support the selection of a 10-mg dose of TAF for clinical development of E/C/F/TAF.

Safety Results

Adverse events were reported for 19 of 33 subjects (57.6%) in Cohorts 1 and 2 while receiving E/C/F/TAF (Treatment A), 7 of 14 subjects (50.0%) in Cohort 1 while receiving EVG+COBI (Treatment B), and 8 of 20 subjects (40.0%) in Cohort 2 while receiving FTC+TAF 25 mg (Treatment C). Adverse events were almost exclusively Grade 1 and there were no Grade 3 or Grade 4 AEs. There were no deaths and no SAEs, and no subject prematurely discontinued study drug because of an AE. No subject had a graded serum creatinine abnormality during the course of the study. There were no clinically relevant changes from baseline in mean values for serum phosphate while subjects were receiving any study treatment. No subject had a graded treatment-emergent serum phosphate abnormality during the study. No subject had a positive urine glucose test at any stage during the study. There were no clinically relevant changes in any vital signs parameter, physical examination finding, or ECG profile during the course of the study.

Conclusions

- While mean TFV exposure (AUC_{tau} and C_{max}) following E/C/F/TAF or FTC+TAF 25 mg was markedly lower than historical TFV exposure following administration of STB, administration of E/C/F/TAF resulted in comparable TAF and TFV exposures relative to FTC+TAF 25 mg.

- Administration of E/C/F/TAF provided EVG, COBI, and FTC exposures comparable with those observed following administration of EVG+COBI and EVG+TAF 25 mg, and to those observed historically following administration of STB.

- E/C/F/TAF was generally safe and well tolerated by healthy subjects.

2.2.4. D/C/F/TAF Study

2.2.4.1. Study GS-US-299-0101

Title

A Phase 1, Adaptive-Design, Multiple-Dose Study Evaluating the Bioavailability of 3 Formulations of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen (STR) Relative to the Administration of Individual Components Cobicistat-Boosted Darunavir, Emtricitabine, and GS-7340

Objectives

The primary objectives of this study were as follows:

Part 1:

- To evaluate the PK of DRV, COBI, FTC, TAF, and TFV when administered as a D/C/F/TAF FDC in 2 TAF doses and 3 formulations in order to propose the Phase 2 dose and formulation

Part 2:

- To evaluate the PK and BA (bioavailability) of DRV, COBI, FTC, and TFV when administered as COBI-boosted DRV (DRV+COBI) plus FTC/TDF relative to the administration of the individual components: DRV+COBI or FTC/TDF

Part 3:

- To evaluate the PK and BA of DRV, COBI, FTC, TAF, and TFV when administered as the proposed Phase 2 D/C/F/TAF FDC tablet relative to the administration of the individual components: DRV+COBI or FTC+TAF 25 mg.

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of administration of D/C/F/TAF and the individual components DRV+COBI, FTC, FTC/TDF, and TAF 25 mg.

Study Design

This was an adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple-cohort, single-center study. In Part 1, 3 formulations of the D/C/F/TAF FDC were evaluated to select a

formulation for further investigation in Part 3 of the study. In Part 2, drug-drug interaction (DDI) effects were evaluated between DRV+COBI coadministered with FTC/TDF versus administration of DRV+COBI or administration of FTC/TDF alone. In Part 3, the PK and BA of D/C/F/TAF Formulation 3 (Treatment C, a monolayer FDC containing 10 mg TAF) were compared with DRV+COBI and with FTC+TAF 25 mg.

In each part/cohort, subjects were enrolled with an approximate equal distribution between male and female subjects. Assignment to part (and cohort) was made at the screening visit; subjects were not allowed to participate in more than 1 part of the study. Treatments were administered by part and cohort as described below.

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

Subjects assigned to Part 1 were randomized (in a 1:1:1 ratio) to 1 of the following 3 treatments:

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

Part 2: Assessment of DDI Potential between DRV+COBI and FTC/TDF

Subjects assigned to Part 2 were assigned to 1 of the following 2 cohorts, and, within each cohort, randomized (in a 1:1 ratio) to treatment sequence:

Cohort 1

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

Cohort 2

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

Part 3: PK and Bioavailability of Selected FDC Formulation

Upon review of the PK and safety data from Part 1, Treatment C was selected for evaluation in Part 3. Subjects assigned to Part 3 were assigned to 1 of the following 2 cohorts, and, within each cohort, randomized (in a 1:1 ratio) to treatment sequence:

Cohort 1

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

Cohort 2

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

Further details on the design and results of this study are available in the CSR (m5.3.1.2, GS-US-299-0101).

[redacted]

All subjects completed all treatments and procedures in Parts 1 and 2, and all but 1 subject completed all treatments and procedures in Part 3. Subject *AA (Part 3, Cohort 1, Sequence EC) discontinued due to an AE during her first treatment period.

All subjects in this study were healthy subjects; 53.3% of subjects were male. In all parts of the study, subjects were predominantly white and Hispanic/Latino, ranging in age from 20 to 45 years. For all subjects at baseline, the range of BMI was 20.1 to 29.9 kg/m^2, and the range of eGFR was 88.4 to 193.2 mL/min.

Pharmacokinetic Results

Pharmacokinetic results for the primary exposure parameters of TAF, TFV, DRV, COBI, and FTC following administration of the test or reference treatments are summarized below by study part and analyte.

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

Exposures of plasma TAF and intracellular TFV-DP following administration of all 3 D/C/F/TAF FDC formulations were in a range associated with potent antiviral activity of TAF administered as a single agent (Study GS-US-120-0104). The TAF exposures (AUC_{last} and C_{max}) were higher (~30% to 50%) following a single dose of each D/C/F/TAF FDC formulation, as compared with exposures following multiple doses, consistent with a mixed inhibitory/inductive effect on TAF absorption. The TAF and TFV exposures were consistent across Days 12 and 21, indicating that PK assessments on Day 12 are representative of steady-state. Summary results for Day 12 are presented in Table 15 (as the mean [%CV]). The TFV exposure at steady-state following the administration of both D/C/F/TAF FDC formulations containing 25 mg TAF (Formulations 1 and 2) was consistent with the findings following DRV+COBI+FTC/TAF (200/25 mg; Study GS-US-311-0101). TAF 25 mg in the presence of DRV+COBI (from the FDC or individual components) resulted in approximately 3-fold higher than historical TFV exposures following administration of single-agent TAF 25 mg (Studies GS-US-120-0104, GS-US-292-0101, and GS-US-292-0103). Steady-state TFV levels following administration of the D/C/F/TAF FDC formulation containing 10 mg TAF (Formulation 3) were proportionally lower compared with the D/C/F/TAF FDC formulations containing 25 mg TAF. The resulting TFV levels from the FDC with 10 mg TAF were approximately 90% less than levels following administration of STB or following administration of TDF with boosted PIs. TAF exposure from the FDC with 10 mg TAF was within the range associated with potent antiviral activity as

demonstrated in the proof-of-concept Study GS-US-120-0104 (Section 2.3.2.1). Accordingly, D/C/F/TAF FDC Formulation 3, containing 10 mg TAF, was selected for evaluation in Part 3 of this study. Systemic exposures of DRV, COBI, and FTC were consistent with historical data.

Table 15. D/C/F/TAF Study GS-US-299-0101: Summary of Steady-State PK Parameter Estimates for Plasma TAF, Plasma TFV, and Intracellular TFV-DP Following Once-Daily Dosing of D/C/F/TAF FDC Formulations 1, 2, or 3 (PK Analysis Sets)

	Day 12 – Mean (%CV) by Treatment		
	D/C/F/TAF Formulation 1 (N = 10)	**D/C/F/TAF Formulation 2 (N = 10)**	**D/C/F/TAF Formulation 3 (N = 10)**
TAF PK Parameter			
AUC_{last} (ng•h/mL)	314.6 (26.9)	326.6 (20.0)	116.4 (26.0)
C_{max} (ng/mL)	328.3 (30.5)	344.1 (27.3)	130.7 (39.2)
TFV PK Parameter			
AUC_{tau} (ng•h/mL)	903.4 (16.7)	1020.6 (22.3)	359.1 (11.2)
C_{max} (ng/mL)	51.3 (25.3)	54.6 (21.5)	20.7 (14.5)
C_{tau} (ng/mL)	28.4 (17.0)	36.5 (27.0)	11.5 (10.3)
Intracellular TFV-DP PK Parameter			
AUC_{0-12} (μM•h)	22.8 (46.1)	31.3 (55.0)	9.3 (61.9)

Formulation 1 was a monolayer tablet with 25 mg TAF; Formulation 2 was a bilayer tablet with 25 mg TAF; Formulation 3 was a monolayer tablet with 10 mg TAF
Source: m5.3.1.2, GS-US-299-0101, Section 15.1, Tables 4.1.4, 4.1.5, and 4.1.6

Part 2: Assessment of DDI Potential between DRV+COBI and FTC/TDF

DRV+COBI+FTC/TDF is a comparator treatment in clinical studies of D/C/F/TAF in HIV-infected subjects. Following the administration of DRV+COBI+FTC/TDF, exposures of DRV, COBI, and FTC were comparable, relative to the administration of DRV+COBI or FTC/TDF alone, indicating no clinically relevant differences (see statistical comparisons summarized in Table 16). Tenofovir AUC_{tau} was ~17% higher following administration of DRV+COBI+FTC/TDF versus administration of FTC/TDF alone, consistent with observations/TFV exposures following administration of STB or following administration of TDF with boosted PIs. Exposures of DRV, COBI, FTC, and TFV were consistent with historical data (Studies GS-US-311-0101, GS-US-236-0101, and GS-US-236-0110).

Table 16. D/C/F/TAF Study GS-US-299-0101: Statistical Comparisons of TFV, DRV, COBI, and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
TFV PK Parameter: DRV+COBI+FTC/TDF (Test) vs FTC/TDF (Reference) (N = 16)			
AUC_{tau} (ng•h/mL)	3402.1 (17.5)	2887.8 (15.7)	117.36 (111.23, 123.81)
C_{max} (ng/mL)	356.8 (33.2)	323.0 (28.0)	109.29 (93.36, 127.94)
C_{tau} (ng/mL)	68.5 (21.1)	55.2 (18.7)	123.47 (115.82, 131.63)
DRV PK Parameter: DRV+COBI+FTC/TDF (Test) vs DRV+COBI (Reference) (N = 20)			
AUC_{tau} (ng•h/mL)	108,767.2 (16.3)	109,387.6 (17.6)	99.56 (94.06, 105.39)
C_{max} (ng/mL)	9536.4 (10.6)	9577.1 (7.7)	99.29 (96.01, 102.67)
C_{tau} (ng/mL)	1789.1 (54.8)	1939.1 (52.0)	86.20 (71.10, 104.52)
COBI PK Parameter: DRV+COBI+FTC/TDF (Test) vs DRV+COBI (Reference) (N = 20)			
AUC_{tau}(ng•h/mL)	10,853.3 (24.2)	11,037.6 (22.6)	98.04 (94.40, 101.81)
C_{max} (ng/mL)	1427.0 (23.8)	1423.3 (19.7)	99.55 (95.41, 103.88)
C_{tau} (ng/mL)	23.4 (53.1)	25.3 (73.1)	94.89 (81.45, 110.54)
FTC PK Parameter: DRV+COBI+FTC/TDF (Test) vs FTC/TDF (Reference) (N = 16)			
AUC_{tau} (ng•h/mL)	11,173.5 (12.7)	9575.2 (10.2)	116.38 (111.62, 121.34)
C_{max} (ng/mL)	1988.8 (19.1)	1831.5 (21.4)	108.94 (100.54, 118.04)
C_{tau} (ng/mL)	83.0 (22.2)	70.5 (24.2)	118.09 (111.24, 125.36)

Source: m5.3.1.2, GS-US-299-0101, Section 15.1, Tables 4.2.1, 4.2.2, 4.2.7, 4.2.8, and 5.2

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

In order to evaluate the relative BA of the selected Phase 2 D/C/F/TAF FDC formulation (Formulation 3, containing 10 mg TAF), the exposures of TAF, TFV, DRV, COBI, and FTC were assessed following the administration of the FDC relative to FTC + TAF 25 mg or DRV+COBI (Table 17). The observed TAF exposures were in a range associated with antiviral activity of TAF administered as a single agent (Study GS-US-120-0104). The 90% CIs of the GLSM ratios for exposure parameters were below the protocol-defined 70% to 143% no-effect boundary relative to FTC+TAF 25 mg (reference treatment). Exposures of TFV were 41% to 51% higher relative to FTC+TAF 25 mg (reference treatment), and were ~88% lower than TFV exposure observed following DRV+COBI+FTC/TDF in Part 2. Following the administration of D/C/F/TAF FDC Formulation 3, DRV, COBI, and FTC exposures were comparable relative to DRV+COBI or FTC+TAF 25 mg, indicating no clinically relevant differences. Overall, based on the maintenance of TAF in a range corresponding to antiviral activity and the substantially lower TFV exposures versus TDF-containing regimens, these data support the TAF dose selection (ie, 10 mg) for subsequent clinical development of the FDC.

Table 17. D/C/F/TAF Study GS-US-299-0101: Statistical Comparisons of TAF, TFV, DRV, COBI, and FTC PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
TAF PK Parameter: D/C/F/TAF (Test) vs FTC+TAF (Reference) (N = 16)			
AUC_{last} (ng•h/mL)	166.7 (30.0)	320.0 (30.8)	52.10 (46.53, 58.33)
C_{max} (ng/mL)	184.0 (35.8)	317.2 (41.6)	58.95 (48.30, 71.95)
TFV PK Parameter: D/C/F/TAF (Test) vs FTC+TAF (Reference) (N = 16)			
AUC_{tau} (ng•h/mL)	421.1 (19.3)	280.2 (17.2)	149.81 (143.48, 156.43)
C_{max} (ng/mL)	24.2 (17.4)	17.2 (16.9)	141.21 (134.20, 148.59)
C_{tau} (ng/mL)	14.6 (20.9)	9.6 (18.3)	151.16 (143.55, 159.18)
DRV PK Parameter: D/C/F/TAF (Test) vs DRV+COBI (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	102,288.7 (26.3)	102,149.3 (28.5)	100.47 (95.65, 105.53)
C_{max} (ng/mL)	9233.0 (20.2)	9320.8 (13.5)	98.29 (94.21, 102.54)
C_{tau} (ng/mL)	1621.7 (61.7)	1508.4 (62.0)	107.39 (91.52, 126.00)
COBI PK Parameter: D/C/F/TAF (Test) vs DRV+COBI (Reference) (N = 19)			
AUC_{tau}(ng•h/mL)	9229.9 (18.9)	9229.0 (18.9)	99.97 (94.83, 105.39)
C_{max} (ng/mL)	1237.3 (15.4)	1245.8 (16.9)	99.47 (95.18, 103.95)
C_{tau} (ng/mL)	21.3 (89.7)	17.0 (71.0)	113.27 (97.82, 131.16)
FTC PK Parameter: D/C/F/TAF (Test) vs FTC+TAF (Reference) (N = 16)			
AUC_{tau} (ng•h/mL)	13,444.1 (20.6)	11,556.9 (18.6)	115.96 (112.94, 119.07)
C_{max} (ng/mL)	2362.8 (17.4)	2207.3 (23.1)	108.22 (103.06, 113.64)
C_{tau} (ng/mL)	97.6 (37.4)	79.6 (28.6)	119.93 (112.86, 127.43)

The TAF dose was 10 mg in the D/C/F/TAF FDC (test) and 25 mg in the FTC+TAF (reference).
Source: m5.3.1.2, GS-US-299-0101, Section 15.1, Tables 4.3.1, 4.3.2, 4.3.10, 4.3.12, 4.3.15, and 5.3

Safety Results

In this study, there were no deaths or SAEs. One subject discontinued the study in Part 3 due to a Grade 1 and nonserious drug rash that occurred after 10 days of treatment with DRV+COBI.

The overall incidence of AEs in Part 1 (n = 10 by treatment) was 60.0% for D/C/F/TAF FDC Formulations 1 and 2 (containing 25 mg TAF) and 30.0% for D/C/F/TAF FDC Formulation 3 (containing 10 mg TAF). In Part 1, constipation and headache were the only AEs reported in more than 1 subject during any treatment. Study drug-related AEs did not occur during treatment with Formulations 1 or 2, and occurred in 30.0% of subjects during treatment with Formulation 3. All AEs in Part 1 were considered to be of Grade 1 severity by the investigator.

The overall incidence of AEs in Parts 2 and 3 (DRV+COBI, n = 40; DRV+COBI+FTC/TDF, n = 36; D/C/F/TAF FDC Formulation 3, n = 35; FTC/TDF, n = 16; and FTC+TAF, n = 16) ranged from 10.0% during treatment with DRV+COBI to 25.0% during treatment with FTC+TAF. In Parts 2 and 3, constipation was the only AE reported in more than 1 subject during any treatment, and was reported by 2 subjects during DRV+COBI + FTC/TDF treatment, by 1 subject during D/C/F/TAF FDC Formulation 3 treatment, and by no subject during the other 3 treatments. Study-drug related AEs were recorded for 12.5%, 8.3%, and 2.5% of subjects receiving FTC/TDF, DRV+COBI+FTC/TDF, and DRV+COBI, respectively. Study drug-related AEs were not reported during treatment in Parts 2 and 3 with D/C/F/TAF FDC Formulation 3 (containing 10 mg TAF) or FTC + TAF. Adverse events in 2 subjects in Parts 2 and 3 were considered to be of Grade 2 severity (related AEs of hypoesthesia and paresthesia in 1 subject during FTC/TDF treatment and an unrelated AE of tooth abscess in 1 subject during DRV+COBI + FTC/TDF treatment); all other AEs in Parts 2 and 3 were considered to be of Grade 1 severity by the investigator.

Treatment-emergent laboratory abnormalities in individual subjects were generally Grade 1 or Grade 2. There was no evident treatment-related pattern in the overall occurrence of treatment-emergent graded laboratory abnormalities. One subject in Part 3 who received D/C/F/TAF FDC Formulation 3 followed by FTC+TAF had Grade 4 increased creatine kinase (likely exercise-induced), Grade 3 increased aspartate aminotransferase (AST), and Grade 2 increased alanine aminotransferase (ALT) at the follow-up visit after completing the study. Other Grade 3 findings included transient hypoglycemia in 1 subject on Day 1 of DRV+COBI treatment, transient Grade 3 elevated lipase (accompanied by Grade 2 elevated amylase) in 1 subject on Day 9 of FTC/TDF treatment, and Grade 3 blood in urine (at various time points and with no treatment-related pattern) in 5 female subjects.

No clinically relevant changes in vital sign parameters or ECG findings were observed during this study.

Conclusions

- Administration of the D/C/F/TAF FDC containing 10 mg TAF resulted in TAF exposures associated with potent antiviral activity of TAF administered as a single agent and markedly lower systemic TFV levels, as compared with administration of TDF as a single agent, as STB, or as TDF with boosted PIs.

- Administration of the D/C/F/TAF FDC containing 10 mg TAF provided comparable DRV, COBI, and FTC exposures, as compared with DRV+COBI or FTC+TAF 25 mg.

- Administration of DRV+COBI+FTC/TDF provided comparable DRV, COBI, and FTC exposures versus DRV+COBI or FTC/TDF alone, while TFV exposure was modestly higher, consistent with its exposures with boosted PIs.

- Multiple D/C/F/TAF FDC formulations with 10 or 25 mg TAF were well tolerated in this study. Additionally, administration of FTC/TDF alone or coadministered with DRV+COBI was well tolerated.

- There were no clinically relevant changes from baseline in renal function parameters of serum creatinine, eGFR, serum phosphate, urine glucose, and urine protein during any treatment.

- Based on TAF exposures associated with antiviral activity and TFV exposures that were substantially less versus TDF-containing regimens, the 10-mg TAF dose was selected for subsequent clinical development of the FDC in treatment-naive subjects.

2.3. Study in HIV-Infected Subjects

2.3.1. F/TAF Study

2.3.1.1. Study GS-US-311-1089

Title

A Phase 3, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects Who are Virologically Suppressed on Regimens Containing FTC/TDF

Objectives

The primary objective of Study GS-US-311-1089 is as follows:

- To evaluate the efficacy of switching to F/TAF versus maintaining FTC/TDF in HIV-infected subjects who are virologically suppressed on regimens containing FTC/TDF, as determined by the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives of Study GS-US-311-1089 are as follows:

- To evaluate the bone safety of 2 regimens as determined by the percentage change from baseline in hip and spine BMD at Week 48

- To evaluate the efficacy, safety, and tolerability of 2 regimens through Week 48 and Week 96

- To evaluate the PK of TAF and TFV

Study Design

Study GS-US-311-1089 is an ongoing, randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy and safety of switching to F/TAF versus maintaining FTC/TDF in HIV-infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing FTC/TDF for ≥ 6 consecutive months prior to screening. Eligible subjects were randomized in a 1:1 ratio to 1 of the following 2 treatments:

- Treatment 1: F/TAF (200/25 mg or 200/10 mg based on third agent) + placebo-to-match FTC/TDF; third agent remains the same

- Treatment 2: FTC/TDF + placebo-to-match F/TAF; third agent remains the same

Randomization was stratified by the third agent in a subject's existing regimen (boosted PI versus any other protocol-allowed third agent [unboosted regimens]).

Trough blood samples were collected at Week 4 (20 to 24 hours postdose) to determine intracellular TFV-DP concentrations in PBMCs.

Study Population

At the time of this interim analysis, 663 subjects (333 subjects in the F/TAF group and 330 subjects in the FTC/TDF group) had been treated with at least 1 dose of study drug (Appendix 6.4, Table 3). Of these, 579 subjects were included in the PBMC PK Analysis Set, including 308 subjects in the F/TAF group and 271 subjects in the FTC/TDF group.

In the Safety Analysis Set, the majority of subjects were male (84.6% overall; Appendix 6.4, Table 5). The median age was 48 years (range: 22 to 78 years) in the F/TAF group and 49 years (range: 22 to 79 years) in the FTC/TDF group (p = 0.83). Overall, the most common races were white (75.0%) and black or African American (20.5%), and most subjects were not Hispanic or Latino (81.0%). The overall median (Q1, Q3) value for BMI at baseline was 26.3 (23.7, 29.7) kg/m^2.

Pharmacokinetic Results

This study allows for a direct comparison of intracellular concentrations of the active phosphorylated metabolite TFV-DP between F/TAF and FTC/TDF in combination with various third agents (boosted by RTV or unboosted). Intracellular PBMC TFV-DP concentrations were greater than 4-fold higher in the subjects who received F/TAF than in those who received FTC/TDF (Geometric mean [95% CI] 114.001 [100.899, 128.804] $pg/10^6$ cells for the F/TAF group and 27.781 [24.799, 31.122] $pg/10^6$ cells for the FTC/TDF group; GLSM ratio of 416.100%; Table 48).

In the analysis of intracellular PBMC TFV-DP concentration by third agent (boosted by RTV or unboosted), geometric mean concentrations in subjects receiving F/TAF ranged from 54.224 to 268.000 $pg/10^6$ cells, with the number of subjects in each subgroup varying from n = 1 to n = 82 (Appendix 6.4, Table 58.1). Although the sample sizes are small, concentrations of intracellular TFV-DP appear to track with the changes in TAF plasma exposure observed upon coadministration with various third agents in clinical studies.

Conclusions

The conclusions from this analysis are as follows:

- F/TAF administration resulted in intracellular TFV-DP concentrations that were greater than 4-fold higher relative to FTC/TDF and consistent with previous E/C/F/TAF findings.

- Intracellular PBMC TFV-DP concentrations track with anticipated TAF plasma exposure.

2.3.2. TAF Study

2.3.2.1. Study GS-US-120-0104

Title

A Phase 1, Randomized, Partially-Blinded, Active and Placebo-Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-7340 Monotherapy in Subjects with HIV-1

Objectives

The primary objective of this study was as follows:

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

The secondary objectives of this study were as follows:

- To investigate the safety of TAF 8 mg, 25 mg, and 40 mg as compared with TDF 300 mg and placebo-to-match TAF
- To investigate the plasma and intracellular PK of TAF and/or TFV following single and multiple doses of TAF and TDF
- To investigate the viral dynamics of HIV-1 with the use of TAF and TDF
- To investigate the correlation between the intracellular concentrations of TFV in PBMCs and the antiviral effect
- To investigate the effect of TAF and TDF on bone and renal biomarkers during and following 10 days of monotherapy

Study Design

This was a randomized, partially-blinded, active- and placebo-controlled study to evaluate the safety, PK, and antiviral activity of TAF monotherapy in HIV-infected subjects.

Subjects were randomized in a 2:2:2:1:2 ratio to one of the following 5 treatment groups:

Treatment Group 1: TAF 8 mg

Treatment Group 2: TAF 25 mg

Treatment Group 3: TAF 40 mg

Treatment Group 4: TDF 300 mg

Treatment Group 5: Placebo-to-match TAF tablet

Treatments 1, 2, 3 and 5 (TAF and matched placebo) were blinded, while Treatment 4 (TDF) was open label.

Further details on the design and results of this study are available in the CSR (GS-US-120-0104).

Study Population

A total of 36 subjects were planned to be enrolled in this study. A total of 40 eligible subjects were randomized into the study. Two subjects were randomized and never dosed (1 subject each in the TAF 40-mg treatment group and placebo-to-match TAF treatment group). Nine subjects received TAF 8 mg, 8 subjects received TAF 25 mg, 8 subjects received TAF 40 mg, 6 subjects received open-label TDF 300 mg, and 7 subjects received placebo-to-match TAF. A total of 37 subjects completed the study; 1 subject was lost to follow-up.

Of the 38 randomized and treated subjects, 37 (97.4%) were male, 20 (52.6%) were white, and 14 (36.8%) were black. The median age was 39 years (range: 20 to 57 years), the median BMI was 26.6 kg/m^2 (range: 19.9 to 37.3 kg/m^2), and the median $eGFR_{CG}$ was 113.8 mL/min (range: 64.2 to 173.9 mL/min). At baseline, no subjects showed resistance to NRTIs or PIs; 2 subjects showed resistance to NNRTIs.

Efficacy Results

Median $DAVG_{11}$ for plasma HIV-1 RNA (log_{10} copies/mL) levels showed significantly greater decreases in the TAF treatment groups and TDF 300-mg treatment group compared with the placebo-to-match TAF treatment group (TAF 8 mg [−0.76 versus −0.01], 25 mg [−0.94 versus −0.01], and 40 mg [−1.08 versus −0.01], p = 0.001 each TAF treatment group and TDF 300 mg [−0.48 versus −0.01], p = 0.038). The median $DAVG_{11}$ (log_{10} copies/mL) in the TAF 25-mg and 40-mg treatment groups showed significantly greater decreases compared with the TDF 300-mg treatment group (−0.94 and −1.08 versus −0.48, p = 0.017 and p = 0.006, respectively) with a statistically significant difference also observed between the TAF 8-mg and 40-mg treatment groups (−0.76 versus −1.08, p = 0.003).

The decrease in plasma HIV-1 RNA levels from baseline to Day 11 was significantly greater for groups that received TAF 25 mg (p = 0.024) and TAF 40 mg (p = 0.003) compared with the group that received TDF 300 mg.

The first phase decay slopes for plasma HIV-1 RNA for the TAF-25 mg and TAF-40 mg treatment groups were significantly steeper than for the TDF 300-mg treatment group (p = 0.012 and p = 0.006, respectively).

There was no statistically significant difference in changes from baseline in CD4 cell count when comparing treatment groups at any visit during the study.

Virology Results

Viral resistance to TAF or TDF did not develop in this study. Postbaseline data were available for 37 of the 38 subjects (97.4%); none of whom developed NRTI-resistance (-R), NNRTI-R, or PI-R mutations by standard genotypic analyses.

Pharmacokinetic/Pharmacodynamic Results

Pharmacokinetic parameters of plasma TAF, plasma TFV, and intracellular TFV-DP (previously abbreviated PMPApp) are presented in Table 18, Table 19, and Table 20, respectively.

Table 18. TAF Study GS-US-120-0104: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF (TAF PK Analysis Set)

	TAF Multiple-Dose PK Day 10		
TAF PK Parameter	**TAF 8 mg (n = 9)**	**TAF 25 mg (n = 8)**	**TAF 40 mg (n = 8)**
AUC_{last} (ng•h/mL), Mean (%CV)	54.7 (92.6)	115.2 (33.4)	308.9 (33.6)
AUC_{last} (ng•h/mL), Median (Q1, Q3)	27.5 (20.3, 103.3)	109.1 (101.4, 132.9)	344.2 (213.4, 383.4)
C_{max} (ng/mL), Mean (%CV)	85.8 (116.3)	223.6 (58.8)	629.5 (57.0)
C_{max} (ng/mL), Median (Q1, Q3)	41.5 (24.9, 80.2)	177.2 (131.0, 318.3)	606.4 (299.6, 948.4)
T_{max} (h), Median (Q1, Q3)	0.50 (0.50, 0.50)	0.50 (0.50, 0.75)	0.50 (0.38, 0.50)
$t_{1/2}$ (h), Median (Q1, Q3)	0.38 (0.26, 0.50)[a]	0.39 (0.34, 0.54)	0.42 (0.32, 0.49)

a n = 8
AUC_{last} is presented for multiple-dose PK because TAF concentrations are BLQ by approximately 5 hours postdose and utilizing AUC_{last} instead of AUC_{inf} or AUC_{tau}, respectively, provides a more appropriate measure of exposure assessment. To account for the variability in the data, the mean and median AUC_{last} and C_{max} are presented.
Source: GS-US-120-0104, Section 15.1, Table 21.1

Table 19. TAF Study GS-US-120-0104: Summary of Single-Dose and Steady-State PK Parameter Estimates for TFV Following Once-Daily Dosing of TAF (TFV PK Analysis Set)

	TFV Single-Dose PK[a] Day 1				TFV Multiple-Dose PK Day 10			
TFV PK Parameter	**TAF 8 mg (n = 9)**	**TAF 25 mg (n = 8)**	**TAF 40 mg (n = 8)**	**TDF 300 mg (n = 6)**	**TAF 8 mg (n = 9)**	**TAF 25 mg (n = 8)**	**TAF 40 mg (n = 8)**	**TDF 300 mg (n = 6)**
AUC[b], Mean (%CV)	49.4 (30.3)	195.9 (27.2)	287.3 (33.7)	1719.2 (57.9)	65.5 (23.5)	267.7 (26.7)	405.8 (12.7)	1918.0 (39.4)
C_{max} (ng/mL), Mean (%CV)	2.0 (31.1)	6.5 (40.1)	14.0 (20.3)	181.2 (50.5)	4.2 (24.7)	15.7 (22.1)	28.3 (8.7)	252.1 (36.6)
C_{tau} (ng/mL), Mean (%CV)	0.7 (19.8)	2.4 (23.5)	4.0 (27.2)	23.9 (57.5)	2.1 (33.8)	9.21 (26.1)	13.3 (16.0)[c]	38.7 (44.7)
T_{max} (h), Median (Q1, Q3)	1.00 (1.00, 2.00)	1.50 (1.03, 1.75)	1.00 (0.75, 1.00)	1.25 (0.53, 1.50)	1.50 (1.00, 1.98)	1.50 (1.25, 1.75)	1.29 (1.04, 1.50)	1.25 (0.58, 2.00)
$t_{1/2}$ (h), Median (Q1, Q3)	23.85 (18.32, 37.17)[c]	29.83 (26.87, 44.00)[c]	24.55 (20.33, 28.25)	15.56 (14.17, 17.07)	30.77 (26.90, 55.61)[d]	40.19 (28.98, 44.84)	35.95 (26.38, 42.90)[c]	14.86 (12.18, 16.81)

a AUC_{inf} and C_{24h} are presented for single-dose PK
b AUC_{inf} is presented for single-dose PK and AUC_{tau} is presented for multiple-dose PK
c n = 7
d n = 8
Source: GS-US-120-0104, Section 15.1, Table 21.2

Table 20. TAF Study GS-US-120-0104: Summary of Steady-State PK Parameter Estimates for Intracellular TFV-DP Following Once-Daily Dosing of TAF (TFV-DP PK Analysis Set)

Intracellular TFV-DP PK Parameter	Intracellular TFV-DP Multiple-Dose PK Day 10			
	TAF 8 mg (n = 6)	TAF 25 mg (n = 4)	TAF 40 mg (n = 7)	TDF 300 mg (n = 4)
AUC_{tau} (μM•h), Mean (%CV)	3.5 (77.1)	21.4 (76.9)	74.5 (92.7)	3.0 (119.6)
AUC_{tau} (μM•h), Median (Q1, Q3)	2.5 (1.6, 5.8)	15.8 (9.6, 33.2)	53.4 (28.3, 104.7)	1.6 (1.0, 4.9)

To account for the variability in the data, the mean and median AUC_{tau} are presented.
Source: GS-US-120-0104, Section 15.1, Table 21.3

Following administration of TAF 8 mg, 25 mg, or 40 mg, TAF was rapidly absorbed with detectable levels at the first sampling time point (0.25 hours) and a median T_{max} of approximately 0.50 hours. TAF $t_{1/2}$ was approximately 0.40 hours and plasma concentrations were below the limit of quantitation (BLQ) by approximately 5 hours postdose. Pharmacokinetic exposure parameters of TAF were similar within each dose group following single- and multiple-dose administration, as expected given the short plasma $t_{1/2}$ of TAF.

Following administration of TAF 8 mg, 25 mg, 40 mg, or TDF 300 mg (TFV equivalent dose of 4.8 mg, 15.1 mg, 24.1 mg, and 135.6 mg, respectively), the highest TFV plasma concentrations were observed when given as TDF. TFV plasma levels were greater within each dose group following multiple dosing, relative to single dose administration, indicating accumulation, and in general, single-dose exposure (AUC_{inf}) was comparable with steady-state exposure (AUC_{tau}). TFV exposure following administration of TDF 300 mg was consistent with historical data and substantially higher than when given as TAF. At steady-state, following multiple-dose administration of TAF 8 mg, 25 mg, or 40 mg, the mean TFV AUC_{tau} values were 97%, 86%, and 79% lower, respectively, while mean TFV C_{max} values were 98%, 94%, and 89% lower, respectively, as compared with the mean TFV AUC_{tau} and C_{max} observed when dosed as TDF 300 mg. Intracellular PBMC TFV-DP AUC_{tau} was similar when given as TAF 8 mg or TDF 300 mg. Following multiple-dose administration of TAF 25 mg and 40 mg, mean intracellular TFV-DP AUC_{tau} values were approximately 7-fold and approximately 25-fold higher, respectively, relative to TDF 300 mg.

Safety Results

Similar frequencies of treatment-emergent AEs occurred while receiving TAF 8 mg (6 of 9 subjects [66.7%]), TAF 25 mg (3 of 8 subjects [37.5%]), TAF 40 mg (5 of 8 subjects [62.5%]), TDF 300 mg (2 of 6 subjects [33.3%]), and placebo-to-match TAF (5 of 7 subjects [71.4%]). Most treatment-emergent AEs experienced by subjects during the study were Grade 1 in severity. A treatment-emergent SAE was reported in 1 of 8 subjects (12.5%) receiving TAF 25 mg (chest pain). This SAE was not considered by the investigator to be related to study drug. An SAE

(cellulitis) was reported in 1 subject in the placebo-to-match TAF group; however, the subject was not dosed with study drug or part of the safety analysis set. No deaths, pregnancies, or AEs leading to premature study drug discontinuation occurred during this study. The majority of treatment-emergent laboratory abnormalities were reported as Grade 1 or Grade 2 as the highest toxicity grade for a given parameter. There were no clinically relevant changes from baseline in renal laboratory parameters (serum creatinine, $eGFR_{CG}$, or serum phosphate) or bone or renal biomarkers in any treatment group. No clinically relevant changes in vital signs measurements or ECG results were reported during this study and no abnormal physical findings were reported as AEs.

Conclusions

- The antiviral effect of TAF 8 mg was similar to TDF 300 mg, and increased with higher doses of TAF. As measured by change from baseline in HIV-1 RNA and $DAVG_{11}$, statistically greater decreases were observed between the 25-mg ($p = 0.017$) and 40-mg ($p = 0.006$) doses of TAF compared with the TDF 300-mg treatment group. The decrease in plasma HIV-1 RNA levels from baseline to Day 11 was significantly greater for groups that received TAF 25 mg ($p = 0.024$) and TAF 40 mg ($p = 0.003$) compared with the group that received TDF 300 mg. Analysis of early decline in plasma HIV-1 RNA indicates that the 25-mg and 40-mg doses of TAF may be more potent than TDF 300 mg. There was no statistically significant difference in changes from baseline in CD4 cell count when comparing treatment groups at any visit during the study. Viral resistance to TAF or TDF did not develop in this study. Postbaseline data were available for 37 of the 38 subjects (97.4%); none of whom developed NRTI-R, NNRTI-R, or PI-R mutations by standard genotypic analyses.

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

- The 8-mg, 25-mg, and 40-mg doses of TAF were well tolerated during this clinical study of HIV-infected subjects and showed safety profiles similar to that of the TDF 300-mg treatment group.

2.4. Intrinsic Factor Pharmacokinetic Studies

2.4.1. TAF Studies

2.4.1.1. Study GS-US-120-0108

Title

A Phase 1, Open-Label, Parallel-Design Study to Evaluate the Pharmacokinetics of GS-7340 in Subjects with Severe Renal Impairment

Objectives

The primary objective of this study was as follows:

- To evaluate the PK of TAF and its metabolite TFV following administration of TAF in subjects with severe renal impairment and matched healthy subjects (control group)

The secondary objective of this study was as follows:

- To evaluate the safety of TAF and its metabolite TFV in subjects with severe renal impairment and matched healthy subjects (control group)

Study Design

This was an open-label, parallel-design, single-dose, PK study of TAF in subjects with severe renal impairment (defined as having a calculated creatinine clearance [CL_{cr}] of $15 \leq CL_{cr} \leq 29$ mL/min at screening [severe renal impairment group]) and matched healthy subjects with normal renal function (control group). Calculated CL_{cr} was determined using the Cockcroft-Gault formula ($eGFR_{CG}$). Following screening procedures and baseline assessments (Day 0), eligible subjects in each of the 2 groups (severe renal impairment and control) received a single dose of TAF 25 mg (1 × 25-mg tablet) administered orally on Day 1. Enrollment of subjects in the control group began after the corresponding matched subject in the severe renal impairment group had completed PK assessments.

Subjects were confined from Day 0 through completion of assessments on Day 7. Subjects returned to the clinic for a follow-up visit for safety assessments, including calculated CL_{cr}, on Day 14.

Serial blood and urine samples were collected before dosing and following TAF dosing in order to determine TAF and TFV concentrations and estimate plasma PK parameters and plasma protein binding. Specimen collection occurred over 144 hours at the time points listed below.

Blood collection: 0 hours (before dosing) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dosing.

Urine collection: 0 hours (before dosing) and within the intervals 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, and 120-144 hours after dosing. The stop time of the predose urine void was considered the start time of the 144-hour urine collection.

Further details on the design and results of this study are available in the CSR (GS-US-120-0108).

Study Population

A total of 28 subjects were planned to be enrolled to obtain 24 evaluable subjects (12 in each group). A total of 14 subjects with severe renal impairment ($eGFR_{CG}$ 15-29 mL/min) and 13 matched control subjects with normal renal function ($eGFR_{CG} \geq 90$ mL/min) were enrolled, received a single oral dose of TAF 25 mg, and completed the study. All 27 subjects were included in the PK and safety analysis sets.

Demographics were similar between treatment groups. Eight subjects (57.1%) in the severe renal impairment group and 7 subjects (53.8%) in the normal renal function group were women, and most were white (11 subjects [78.6%] with severe renal impairment and 12 subjects [92.3%] with normal renal function). Median age was 66 years (range: 46 to 73 years) in the severe renal impairment group and 64 years (range: 53 to 74 years) in the normal renal function group. Median $eGFR_{CG}$ at predose was 25.5 mL/min (range: 13.1 to 32.6 mL/min) in the severe renal impairment group and was 94.2 mL/min (range: 84.3 to 140.2 mL/min) in the normal renal function group.

Pharmacokinetic Results

Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure as assessed by AUC_{inf} relative to subjects with normal renal function (Table 22). This difference was not considered clinically relevant, as it is less than a 2-fold difference.

Subjects with severe renal impairment had a 6.05-fold mean increase in systemic TFV exposure as assessed by AUC_{inf} relative to subjects with normal renal function (Table 22). The TFV exposure encountered in subjects with severe renal impairment in this study after a single dose of TAF 25 mg was within or below the range of TFV plasma exposures measured in other studies after administration of TDF 300 mg in subjects and patients with normal renal function.

TAF plasma protein binding measured at 1 and 4 hours was similar between subjects with severe renal impairment and subjects with normal renal function (Table 21; mean percentage unbound was approximately 20% at 1 hour and approximately 14% at 4 hours in both groups). TFV plasma protein binding measured at 2 and 24 hours was also similar between subjects with severe renal impairment and subjects with normal renal function (mean percentage unbound ranged from 97% to 99% at both time points in both groups).

Table 21. TAF Study GS-US-120-0108: Summary of PK Parameter Estimates for TAF and TFV Following a Single Dose of TAF 25 mg in Subjects with Severe Renal Impairment or Normal Renal Function

Mean (%CV)	Severe Renal Impairment (n = 14)	Normal Renal Function (n = 13)
TAF		
AUC_{inf} (ng•h/mL)	513.2 (47.3)	267.3 (49.2)
AUC_{last} (ng•h/mL)	510.6 (47.4)	265.9 (49.5)
C_{max} (ng/mL)	363.7 (65.7)	198.8 (62.1)
$t_{1/2}$ (h)	0.75 (51.8)	0.53 (22.8)
CL/F (mL/h)	61,717.8 (56.8)	117,633.1 (53.9)
CL_r (mL/min)	4.2 (77.6)	35.8 (51.7)
Percent of dose recovered in urine (%)	0.47 (95.6)	2.00 (34.6)
A_e (ng)	117,230.4 (95.6)	500,408.6 (34.6)
TFV		
AUC_{inf} (ng•h/mL)	2073.8 (47.1)	342.6 (27.2)
AUC_{last} (ng•h/mL)	1694.9 (43.1)	298.0 (26.1)
C_{max} (ng/mL)	26.4 (32.4)	9.5 (36.5)
$t_{1/2}$ (h)	56.53 (19.6)	51.28 (12.2)
CL/F (mL/h)	8531.4 (36.4)	47,013.8 (26.3)
CL_r (mL/min)	51.4 (40.1)	209.4 (24.6)
Percent of dose recovered in urine (%)	30.12 (24.6)	24.17 (23.3)
A_e (ng)	4,548,490 (24.6)	3,650,168 (23.3)

Source: GS-US-120-0108, Section 15.1, Tables 4.1, 4.2, 5.1, and 5.2

Table 22. TAF Study GS-US-120-0108: Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

	GLSM Ratio (90% CI), % Severe Renal Impairment (Test) (N = 14) vs Normal Renal Function (Reference) (N = 13)	
PK Parameter	**TAF**	**TFV**
AUC_{inf} (ng•h/mL)	191.89 (137.81, 267.18)	573.76 (457.21, 720.01)
AUC_{last} (ng•h/mL)	192.26 (137.81, 268.21)	545.91 (442.82, 672.99)
C_{max} (ng/mL)	179.43 (123.73, 260.20)	279.31 (231.48, 337.02)

Source: GS-US-120-0108, Section 15.1, Table 6.1

Safety Results

At least 1 treatment-emergent AE was reported for 6 subjects (42.9%) with severe renal impairment and 7 subjects (53.8%) with normal renal function. All treatment-emergent AEs were assessed by the investigator as Grade 1 in severity. No deaths or SAEs occurred during this study, and no subject discontinued the study due to an AE. No pregnancies were reported during the study.

There were no clinically meaningful changes from baseline in median values for any chemistry or hematology parameter during the study. Five subjects (35.7%) in the severe renal impairment group and no subjects in the normal renal function group had a Grade 3 treatment-emergent laboratory abnormality; all other treatment-emergent laboratory abnormalities were Grade 1 or 2 in severity. For specific indices of renal function, there were no clinically meaningful changes in median serum creatinine, eGFR, or phosphate in either treatment group. Treatment-emergent graded abnormalities in serum creatinine (Grade 2-3) were noted for 3 subjects in the severe renal impairment group. None of these 3 subjects had an increase in serum creatinine of ≥ 0.5 mg/dL from predose (using the lowest value observed predose) on 2 consecutive measurements postdose. No clinically significant changes in vital signs or safety ECGs were observed during this study.

Conclusions

- Plasma TAF exposure in subjects with severe renal impairment was less than 2-fold higher than TAF exposure in matched controls with normal renal function. Plasma TFV exposure in subjects with severe renal impairment, while higher, was within or below the range of TFV exposures achieved as part of a TDF-containing regimen in historical subjects with normal renal function. There were no differences in the protein binding of TAF and TFV between subjects with severe renal impairment and subjects with normal renal function.

- Single doses of TAF 25 mg were well tolerated in subjects with severe renal impairment and in subjects with normal renal function in this study. All AEs were considered Grade 1.

- Given the extensive safety data available for TDF and the observation that TFV exposure in subjects with severe renal impairment in this study was within or below the range of those from TDF in subjects with normal renal function, TAF dose or schedule modification may not be required and warrants further study.

2.4.1.2. Study GS-US-120-0114

Title

A Phase 1, Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of Tenofovir Alafenamide in Subjects with Normal and Impaired Hepatic Function

Objectives

The primary objective of this study was as follows:

- To evaluate the PK of TAF in subjects with normal and impaired hepatic function

The secondary objective of this study was as follows:

- To evaluate the safety of TAF in subjects with normal and impaired hepatic function

Study Design

This was a 2-cohort, open-label, multicenter, single-dose, parallel-group study of the safety, tolerability, and PK of TAF in subjects with normal and impaired hepatic function. Subjects were enrolled in 1 of the following 2 cohorts, each containing a group of subjects with impaired hepatic function and a group of normal, matched controls:

Cohort 1

- Group 1: Subjects with mild hepatic impairment (Child-Pugh-Turcotte [CPT] Class A score of 5 to 6) (n = 10)
- Group 2: Subjects with normal hepatic function (n = 10)

Cohort 2

- Group 1: Subjects with moderate hepatic impairment (CPT Class B score of 7 to 9) (n = 10)
- Group 2: Subjects with normal hepatic function (n = 10)

All subjects received a single, oral dose of TAF 25 mg on Day 1. Subjects were confined at the study center from Day −1 until completion of PK and safety assessments on Day 7.

Further details on the design and results of this study are available in the CSR (GS-US-120-0114).

Study Population

A total of 40 subjects (10 subjects each in the mild or moderate hepatic impairment group and 20 subjects in the normal hepatic function group, each matched to a mildly or moderately impaired subject, respectively) were planned to be enrolled in this study. Forty subjects were enrolled in and completed the study.

Demographic and baseline characteristics were generally similar between each hepatic impairment group and its matched control group.

For subjects with mild hepatic impairment and subjects in the matched control group, there was an even distribution of male and female subjects (50.0% in each group). Subjects with mild hepatic impairment had a median age of 58 years (range: 51 to 63 years) while subjects in the matched control group had a median age of 55 years (range: 49 to 67 years). For subjects with mild hepatic impairment and subjects in the matched control group, most subjects were white (70.0% and 50.0%, respectively).

For subjects with moderate hepatic impairment and subjects in the matched control group, most subjects were male (70.0% in each group). Subjects with moderate hepatic impairment had a median age of 55 years (range: 46 to 64 years) while subjects in the matched control group had a median age of 53 years (range: 46 to 65 years). For subjects with moderate hepatic impairment and subjects in the matched control group, most subjects were white (90.0% and 80.0%, respectively).

Pharmacokinetic Results

The means (%CV) and GLSM ratios (%; 90% CI) of TAF and TFV plasma exposure parameters following a single dose of TAF to subjects with hepatic impairment and to normal matched control subjects are shown in Table 23 and Table 24.

Table 23. TAF Study GS-US-120-0114: Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Subjects With Mild Hepatic Impairment and Subjects With Normal Hepatic Function

	Mean (%CV)		
	Mild Hepatic Impairment (Test) (N = 10)	Normal Matched Control (Reference) (N = 10)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{inf} (ng•h/mL)	227.6 (47.7)	239.1 (39.8)	92.48 (66.25, 129.09)
AUC_{last} (ng•h/mL)	223.3 (49.3)	235.4 (40.6)	91.83 (65.15, 129.43)
C_{max} (ng/mL)	170.5 (55.5)	180.9 (54.2)	89.01 (57.69, 137.33)
TFV PK Parameter			
AUC_{inf} (ng•h/mL)	275.5 (37.8)	306.5 (36.9)	89.16 (67.20, 118.30)
AUC_{last} (ng•h/mL)	245.7 (38.8)	269.9 (34.3)	89.31 (67.30, 118.53)
C_{max} (ng/mL)	8.2 (31.3)	8.4 (27.9)	97.03 (75.93, 124.00)

GLSMs were obtained using a mixed-effects model.
Source: GS-US-120-0114, Section 15.1, Tables 4.3.1.1, 4.3.2.1, and 5.1.1

Table 24. TAF Study GS-US-120-0114: Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function

	Mean (%CV)		
	Moderate Hepatic Impairment (Test) (N = 10)	Normal Matched Control (Reference) (N = 10)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{inf} (ng•h/mL)	205.9 (37.8)	181.4 (30.8)	112.69 (87.29, 145.47)
AUC_{last} (ng•h/mL)	203.5 (37.8)	176.5 (31.9)	115.06 (88.50, 149.57)
C_{max} (ng/mL)	132.5 (37.1)	124.0 (64.2)	118.70 (78.94, 178.47)
TFV PK Parameter			
AUC_{inf} (ng•h/mL)	247.9 (38.0)	240.7 (15.1)	97.22 (77.03, 122.70)
AUC_{last} (ng•h/mL)	217.8 (37.8)	214.8 (15.4)	95.55 (75.20, 121.42)
C_{max} (ng/mL)	7.3 (24.2)	8.4 (30.4)	87.56 (70.49, 108.76)

GLSMs were obtained using a mixed-effects model.
Source: GS-US-120-0114, Section 15.1, Tables 4.3.1.1, 4.3.2.1, and 5.1.1

TAF Exposure

In subjects with mild hepatic impairment, the plasma exposure parameters of TAF were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 7.52%, 8.17%, and 10.99% lower, respectively) relative to matched control subjects with normal hepatic function. The upper bounds of the 90% CIs were below the protocol-defined clinically significant increase of 100% in TAF AUC_{inf}, AUC_{last}, or C_{max} for subjects with mild hepatic impairment compared with normal matched control subjects, and the observed decreases are not considered to be clinically relevant.

In subjects with moderate hepatic impairment, the plasma exposure parameters of TAF were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 12.69%, 15.06%, and 18.70% higher, respectively) relative to matched control subjects with normal hepatic function. The upper bounds of the 90% CIs were below the protocol-defined clinically significant increase of 100% in TAF AUC_{inf}, AUC_{last}, or C_{max} for subjects with moderate hepatic impairment compared with normal matched control subjects, and the observed increases are not considered to be clinically relevant.

TFV Exposure

In subjects with mild hepatic impairment, the plasma exposure parameters of TFV were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 10.84%, 10.69%, and 2.97% lower, respectively) relative to matched control subjects with normal hepatic function. The upper bounds of the 90% CIs were below the protocol-defined clinically significant increase of 100% in TFV AUC_{inf}, AUC_{last}, or C_{max} for subjects with mild hepatic impairment compared with normal matched control subjects, and the observed decreases are not considered to be clinically relevant.

In subjects with moderate hepatic impairment, the plasma exposure parameters of TFV were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 2.78%, 4.45%, and 12.44% lower, respectively) relative to matched control subjects with normal hepatic function. The upper bounds of the 90% CIs were below the protocol-defined clinically significant increase of 100% in TFV AUC_{inf}, AUC_{last}, or C_{max} for subjects with moderate hepatic impairment compared with normal matched control subjects, and the observed decreases are not considered to be clinically relevant.

Protein Binding

TAF plasma protein binding was measured in all subjects at the nominal sampling times of 1 and 4 hours postdose. The mean ± SD percentage unbound TAF ranged from 16% to 19% in subjects with mild hepatic impairment and their matched controls at the 1-hour and 4-hour postdose time points. The mean ± SD percentage unbound TAF ranged from 14% to 23% in subjects with moderate hepatic impairment and their matched controls at the 1-hour and 4-hour time points. These data are consistent with historical data; in Study GS-US-120-0108 (Section 2.4.1.1), the percentage of unbound TAF ranged from 14% to 20% across the 1-hour and 4-hour time points in both subjects with normal renal function and severe renal impairment. The observed differences in protein binding are not considered to be clinically relevant.

TFV plasma protein binding was measured in all subjects at the nominal sampling times of 2 and 24 hours postdose. The mean ± SD percentage unbound TFV was > 99% in subjects with mild or moderate hepatic impairment as well as in the matched controls. These data are consistent with historical data; in Study GS-US-120-0108, the percentage of unbound TFV ranged from 97% to

99% across the 2-hour and 24-hour time points in both subjects with normal renal function and severe renal impairment.

Exploratory analyses indicated no clinically relevant correlations between the TAF or TFV exposure versus CPT score or its individual laboratory components (ie, albumin, total bilirubin, prothrombin time, and international normalized ratio).

Safety Results

At least 1 treatment-emergent AE was reported for 3 subjects in the mild hepatic impairment group and 4 subjects in the matched control group. At least 1 treatment-emergent AE was reported for 2 subjects in the moderate hepatic impairment group and 3 subjects in the matched control group. No SAEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE. Most AEs were Grade 1 in severity and considered unrelated to treatment. No clinically relevant changes in any hematology or chemistry parameter for any group were noted. No clinically significant changes in vital signs or safety ECGs were observed during this study.

Conclusions

- No clinically relevant changes in TAF or TFV PK were observed in subjects with mild or moderate hepatic impairment compared with the normal matched control subjects following administration of a single dose of TAF. There were no clinically relevant differences in protein binding of TAF and TFV between hepatically impaired subjects and their matched controls. No clinically relevant correlation between TAF or TFV exposure parameters (AUC_{inf}, AUC_{last}, and C_{max}) and CPT score or its individual laboratory components were observed. Accordingly, the results from this study indicate that no dose adjustment of TAF is necessary in subjects with mild or moderate hepatic impairment.
- Single doses of TAF 25 mg were generally well tolerated in subjects with mild or moderate hepatic impairment and in subjects with normal hepatic function. Most AEs were considered Grade 1 and unrelated to study drug.

2.4.2. E/C/F/TAF Study

2.4.2.1. Study GS-US-292-0108

Title

A Phase 1 Single and Multiple Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single Tablet Regimen (STR) in Healthy Japanese and Caucasian Subjects

Objectives

The primary objective of this study was as follows:

- To investigate the PK of EVG, COBI, FTC, TAF, and TFV when administered as E/C/F/TAF in healthy Japanese and Caucasian subjects

The secondary objective of this study was as follows:

- To assess the safety and tolerability of E/C/F/TAF in healthy Japanese and Caucasian subjects

Study Design

This was an open-label, sequential, single- and multiple-dose study to evaluate the PK, safety, and tolerability of E/C/F/TAF in healthy Japanese and Caucasian subjects. Following completion of screening and baseline (Day −1) procedures, eligible subjects received a single dose of study treatment on the morning of Day 1, followed by a washout (until the morning of Day 8), and then once-daily morning doses of study treatment on Days 8 to 19. No study treatment was administered on Days 2 to 7.

Subjects were confined from Day −1 through the completion of assessments on Day 23 and returned to the clinical study unit at 10 (± 2) days after the last dose for a follow-up safety visit.

Serial plasma and urine samples were collected before and after dosing in order to determine EVG, COBI, FTC, TAF, and TFV concentrations and estimate PK parameters. On Days 1 and 19, serial plasma PK samples were collected predose (≤ 5 minutes) and at the following postdose time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 12, 18, 24, 36, 48, and 72 hours. Trough plasma PK samples were collected predose on Days 13, 15, and 17. On Days 1 and 19, subjects were asked to empty their bladders prior to dosing and all urine was collected at the following intervals: 0-6, 6-12, 12-24, 24-48, 48-72, and 72-96 hours after dosing. Samples were collected from pooled urine at each collection interval.

Safety assessments were performed throughout the study, including laboratory analyses, physical examinations, vital signs and weight measurements, ECG, and reporting of AEs and concomitant medications.

In addition, for subjects who provided consent, an additional blood sample was obtained for possible genetic discovery research to identify or validate genetic markers that may predict the natural history of disease, response to therapy, and/or the tolerability of medical therapies.

Further details on the design and results of this study are available in the CSR (GS-US-292-0108).

Study Population

A total of 20 subjects (10 Japanese and 10 Caucasian) were enrolled in this study as planned. Of those, 3 were withdrawn prematurely from the study: 2 Caucasian subjects and 1 Japanese subject. One Caucasian subject was withdrawn due to AEs (headache, urticaria, and pruritus) and 2 subjects withdrew consent.

Japanese subjects were of first generation descent, born in Japan, and able to trace maternal and paternal Japanese ancestry of parents and grandparents. Japanese subjects had not lived outside Japan > 5 years and had a lifestyle, including diet that had not changed significantly since leaving Japan. Caucasian subjects were not of Japanese or Asian descent, with parents and grandparents not born in Japan or in any Asian country. The median age (range) in each group was 36 years (23 to 51 years) for Caucasians and 42 years (26 to 51 years) for Japanese. There were similar percentages of male and female subjects in the Caucasian (5 of each) and Japanese (6 male; 4 female) groups.

Pharmacokinetic Results

The PK of EVG, COBI, FTC, TAF, and TFV were comparable between Japanese and Caucasian subjects, both after a single dose of E/C/F/TAF and upon multiple dosing of E/C/F/TAF (Table 25). The PK data generated were consistent with historical data following the administration of E/C/F/TAF.

Table 25. E/C/F/TAF Study GS-US-292-0108: Summary of Single-Dose and Steady-State PK Parameter Estimates for EVG, COBI, FTC, TAF, and TFV Following Once-Daily Dosing of E/C/F/TAF in Japanese and Caucasian Subjects

	Japanese Subjects		Caucasian Subjects	
	Single Dose N = 10	Multiple Dose N = 9	Single Dose N = 10	Multiple Dose N = 8
EVG PK Parameter, Mean (%CV)				
AUC[a] (ng•h/mL)	24,629.2 (19)	31,194.5 (38)	31,144.1 (41)	35,803.7 (29)
AUC_{last} (ng•h/mL)	23,377.9 (22)	NA	30,453.0 (43)	NA
C_{max} (ng/mL)	2143.4 (16)	2964.1 (33)	2495.9 (43)	3698.2 (32)
C_{tau} (ng/mL)	NA	379.6 (64)	NA	557.6 (40)
COBI PK Parameter, Mean (%CV)				
AUC[a] (ng•h/mL)	6273.4 (38)	8228.2 (19)	5680.0 (56)	10,643.7 (39)
AUC_{last} (ng•h/mL)	6220.3 (38)	NA	5615.2 (57)	NA
C_{max} (ng/mL)	958.4 (37)	1293.1 (17)	809.7 (44)	1456.6 (35)
C_{tau} (ng/mL)	NA	17.8 (28)	NA	28.5 (47)
FTC PK Parameter, Mean (%CV)				
AUC[a] (ng•h/mL)	12,019.8 (13)	13,142.1 (12)	12,646.9 (17)	14,827.0 (23)
AUC_{last} (ng•h/mL)	11,792.5 (13)	NA	12,277.4 (17)	NA
C_{max} (ng/mL)	2652.4 (21)	2944.6 (12)	2381.2 (21)	2744.3 (15)
C_{tau} (ng/mL)	NA	75.4 (29)	NA	101.6 (44)
TAF PK Parameter, Mean (%CV)				
AUC[a] (ng•h/mL)	242.1 (22)	253.7 (26)	235.8 (30)	292.0 (28)
AUC_{last} (ng•h/mL)	240.7 (22)	NA	233.6 (30)	NA
C_{max} (ng/mL)	359.8 (29)	317.3 (19)	258.6 (39)	319.0 (45)
C_{last} (ng/mL)	NA	2.1 (46)	NA	2.4 (63)
TFV PK Parameter, Mean (%CV)				
AUC[a] (ng•h/mL)	338.7 (19)	330.6 (12)	337.5 (16)	411.8 (37)
AUC_{last} (ng•h/mL)	215.3 (10)	NA	227.8 (19)	NA
C_{max} (ng/mL)	20.3 (55)	24.5 (32)	11.5 (39)	23.1 (31)
C_{tau} (ng/mL)	NA	11.1 (16)	NA	14.9 (29)

a AUC for single dose is AUC_{inf}; for multiple dose is AUC_{tau} for all analytes except TAF where on multiple dosing AUC_{last} is presented.

Source: GS-US-292-0108, Section 15.1, Tables 4.1.1 to 4.1.5 and 4.2.1 to 4.2.5

Safety Results

Nine Caucasian subjects and 6 Japanese subjects experienced treatment-emergent AEs. No Grade 2, 3, or 4 treatment-emergent AEs or SAEs were reported. One Caucasian subject was discontinued from the study due to treatment-emergent AEs (Grade 2 headache, Grade 2 urticaria, and Grade 1 pruritus). No Grade 4 laboratory abnormalities were reported during the study. One Grade 3 abnormality (urine blood) was reported. Two Grade 2 laboratory abnormalities were reported (both hyperglycemia). No laboratory abnormalities were reported as treatment-emergent AEs. No subjects had clinically significant vital signs or ECG results during the study.

Conclusions

- The PK of EVG, COBI, FTC, TAF, and TFV were comparable between Japanese and Caucasian subjects in this study, and supports dosing of E/C/F/TAF in both Japanese and non-Japanese subjects

- E/C/F/TAF was well tolerated in this study. No significant differences in safety parameters between Caucasian and Japanese subjects were noted.

2.5. Extrinsic Factor Pharmacokinetic Studies/Drug-Drug Interaction Pharmacokinetic Studies

2.5.1. F/TAF Studies

2.5.1.1. Study GS-US-311-0101

Title

A Phase 1 Study Evaluating the Drug Interaction Potential Between Once-Daily FTC/GS-7340 Fixed Dose Combination and Efavirenz or Cobicistat-Boosted Darunavir

Objectives

The primary objectives of this study were as follows:

- To evaluate the PK of TAF, TFV, and FTC, following once-daily coadministration of F/TAF (200/40 mg) + EFV relative to administration of F/TAF alone (Cohort 1)

- To evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF (200/25 mg) + DRV+COBI relative to administration of F/TAF alone and DRV+COBI alone (Cohorts 2 and 3)

- To evaluate the PK of TAF, TFV, and COBI following once-daily coadministration of TAF 8 mg and COBI relative to administration of TAF 8 mg alone (Cohort 4)

The secondary objectives of this study were as follows:

- To evaluate the safety of F/TAF administered alone or in combination with EFV (Cohort 1)
- To explore the PK of EFV following its coadministration with F/TAF (Cohort 1)
- To evaluate the safety of F/TAF + DRV+COBI when administered as F/TAF alone or DRV+COBI alone or when administered in combination (Cohorts 2 and 3)
- To evaluate the safety of TAF administered alone or in combination with COBI (Cohort 4)

Study Design

This was an open-label, crossover, nonrandomized, multicohort, single-center, multiple-dose study designed to evaluate the drug interaction potential between once-daily F/TAF and EFV or DRV+COBI, and between TAF as a single agent and COBI in healthy subjects. Following completion of screening and baseline (Day 0) procedures, eligible subjects were assigned to a cohort (1, 2, 3, or 4) with an approximately even distribution of males and females to each cohort. The following study treatments were administered in this study once daily in the morning:

Cohort 1	Days 1 to 12: Treatment A, F/TAF 200/40-mg tablet, fasted	Days 13 to 26: Treatment B, F/TAF 200/40-mg tablet + EFV 600-mg tablet, fasted
Cohort 2	Days 1 to 12: Treatment C, F/TAF 200/25-mg tablet, fed	Days 13 to 22: Treatment D, F/TAF 200/25-mg tablet + 2 × DRV 400-mg tablets + COBI 150-mg tablet, fed
Cohort 3	Days 1 to 10: Treatment E, 2 × DRV 400-mg tablets + COBI 150-mg tablet, fed	Days 11 to 22: Treatment F, F/TAF 200/25-mg tablet + 2 × DRV 400-mg tablets + COBI 150-mg tablet, fed
Cohort 4	Days 1 to 12: Treatment G, TAF 8-mg tablet, fed	Days 13 to 22: Treatment H, TAF 8-mg tablet + COBI 150-mg tablet, fed

Cohort 1: Study treatments were administered in the morning under fasted conditions (no food or liquids, except water, for at least 8 hours) at approximately the same time each day with 240 mL of water. On the days of PK assessments (Days 12 and 26), subjects were restricted from food intake until after collection of the 4-hour PK blood draw, relative to study drug dosing. Subjects were restricted from water consumption 1 hour before and 2 hours after dosing, except for the 240 mL given with the study treatment. A meal (standardized lunch) was provided to subjects after the 4-hour postdose blood draw.

Cohorts 2, 3, and 4: Study treatments were administered within 5 minutes of completion of a standard meal, at approximately the same time each day with 240 mL of water. On the days of PK assessments (Cohorts 2 and 4: Days 1, 12, 13, and 22; Cohort 3: Days 10 and 22), study treatments were administered in the morning under fed conditions (within 5 minutes of completion of a meal) following an overnight fast (no food or liquids, except water, for at least

8 hours). A standard meal was provided. Subjects then refrained from food intake until after collection of the 4-hour PK blood draw, relative to study drug dosing. Subjects were restricted from water consumption 1 hour before and 2 hours after dosing, except for the 240 mL given with the study treatment. A meal was provided to subjects after the 4-hour postdose blood draw.

Further details on the design and results of this study are available in the CSR (GS-US-311-0101).

Study Population

A total of 50 subjects (12 subjects each in Cohorts 1, 2, and 4; 14 subjects in Cohort 3) were planned to be enrolled in this study. Fifty subjects were enrolled and received study drug. Two subjects (4.0%) did not complete the study due to AEs. One subject in Cohort 1 (treatment sequence AB) discontinued on Day 14 because of Grade 2 anxiety after receiving 1 dose of Treatment B (F/TAF [200/40 mg] + EFV), and 1 subject in Cohort 2 (treatment sequence CD) discontinued on Day 7 because of joint abscess (left knee) after receiving 6 daily doses of Treatment C (F/TAF [200/25 mg]). All other subjects received both doses of study drug as planned.

Of the 50 enrolled subjects, 29 (58.0%) were male, 40 (80.0%) were white, and 10 (20.0%) were black. Ninety-four percent of subjects were Hispanic/Latino. The median age was 36 years (range: 21 to 45 years), the median BMI was 27.2 kg/m^2 (range: 20.4 to 31.0 kg/m^2), and the median $eGFR_{CG}$ was 128.6 mL/min (range: 87.2 to 190.7 mL/min).

Pharmacokinetic Results

Pharmacokinetic results for the primary exposure parameters of TAF, TFV, COBI, FTC, and DRV following administration of the test and reference treatments are summarized in Table 26, Table 27, Table 28, Table 29, and Table 30, respectively, by cohort.

Table 26. F/TAF Study GS-US-311-0101: Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (TAF PK Analysis Set)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: F/TAF (200/40 mg) + EFV, Day 26 (Test) vs F/TAF (200/40 mg), Day 12 (Reference) (N = 11)			
AUC_{last} (ng•h/mL)	285.8 (46.4)	344.0 (60.9)	85.54 (72.08, 101.52)
C_{max} (ng/mL)	390.8 (62.2)	499.4 (82.8)	77.92 (57.68, 105.25)
Cohort 2: F/TAF (200/25 mg) + DRV+COBI, Day 22 (Test) vs F/TAF (200/25 mg), Day 12 (Reference) (N = 11)			
AUC_{last} (ng•h/mL)	239.3 (41.0)	245.6 (41.9)	97.64 (80.38, 118.62)
C_{max} (ng/mL)	215.0 (59.2)	208.3 (40.2)	93.43 (72.16, 120.98)
Cohort 4: TAF 8 mg + COBI, Day 22 (Test) vs TAF 8 mg, Day 12 (Reference) (N = 12)			
AUC_{last} (ng•h/mL)	213.3 (37.7)	81.2 (43.9)	265.06 (229.00, 306.80)
C_{max} (ng/mL)	189.9 (45.6)	71.0 (72.9)	283.31 (219.65, 365.43)

Source: GS-US-311-0101, Section 15.1, Tables 4.1 and 5

Table 27. F/TAF Study GS-US-311-0101: Statistical Comparisons of TFV PK Parameter Estimates Between Test and Reference Treatments (TFV PK Analysis Set)

TFV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: F/TAF 200/40 mg + EFV, Day 26 (Test) vs F/TAF 200/40 mg, Day 12 (Reference) (N = 11)			
AUC_{tau} (ng•h/mL)	350.2 (31.7)	430.9 (24.0)	79.72 (73.34, 86.65)
C_{max} (ng/mL)	24.0 (34.7)	31.1 (26.2)	75.49 (66.65, 85.50)
C_{tau} (ng/mL)	11.4 (32.4)	13.6 (22.5)	81.61 (74.74, 89.10)
Cohort 2: F/TAF 200/25 mg + DRV+COBI, Day 22 (Test) vs F/TAF 200/25 mg, Day 12 (Reference) (N = 11)			
AUC_{tau} (ng•h/mL)	953.4 (20.0)	299.3 (29.3)	323.88 (302.11, 347.21)
C_{max} (ng/mL)	57.4 (23.2)	18.3 (27.8)	316.03 (300.13, 332.76)
C_{tau} (ng/mL)	33.7 (19.7)	10.8 (33.2)	320.56 (290.05, 354.27)
Cohort 4: TAF 8 mg + COBI, Day 22 (Test) vs TAF 8 mg, Day 12 (Reference) (N = 12)			
AUC_{tau} (ng•h/mL)	286.9 (21.9)	86.1 (19.4)	330.88 (310.20, 352.93)
C_{max} (ng/mL)	19.3 (20.5)	5.8 (19.5)	334.09 (301.98, 369.62)
C_{tau} (ng/mL)	10.3 (24.4)	3.0 (19.9)	334.86 (312.43, 358.91)

Source: GS-US-311-0101, Section 15.1, Tables 4.2 and 5

Table 28. F/TAF Study GS-US-311-0101: Statistical Comparisons of COBI PK Parameter Estimates Between Test and Reference Treatments (COBI PK Analysis Set)

COBI PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 3: F/TAF 200/25 mg + DRV+COBI, Day 22 (Test) vs DRV+COBI, Day 10 (Reference) (N = 14)			
AUC_{tau} (ng•h/mL)	11,786.9 (21.9)	10,797.0 (18.6)	108.63 (102.75, 114.85)
C_{max} (ng/mL)	1428.4 (12.8)	1356.7 (16.5)	105.83 (100.12, 111.87)
C_{tau} (ng/mL)	43.6 (61.0)	38.1 (56.2)	110.71 (98.01, 125.06)

Source: GS-US-311-0101, Section 15.1, Tables 4.4 and 5

Table 29. F/TAF Study GS-US-311-0101: Statistical Comparisons of FTC PK Parameter Estimates Between Test and Reference Treatments (FTC PK Analysis Set)

FTC PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: F/TAF 200/40 mg + EFV, Day 26 (Test) vs F/TAF 200/40 mg, Day 12 (Reference) (N = 11)			
AUC_{tau} (ng•h/mL)	10,339.5 (16.8)	11,251.2 (14.7)	91.63 (87.38, 96.09)
C_{max} (ng/mL)	2344.7 (22.5)	2643.7 (26.7)	89.66 (81.30, 98.86)
C_{tau} (ng/mL)	59.5 (20.6)	64.7 (20.1)	91.94 (86.05, 98.22)
Cohort 2: F/TAF 200/25 mg + DRV+COBI, Day 22 (Test) vs F/TAF 200/25 mg, Day 12 (Reference) (N = 11)			
AUC_{tau} (ng•h/mL)	12,308.7 (20.1)	9861.8 (16.9)	124.17 (117.26, 131.49)
C_{max} (ng/mL)	2268.9 (20.6)	2023.7 (24.1)	112.74 (102.27, 124.29)
C_{tau} (ng/mL)	90.1 (21.9)	68.2 (14.6)	130.81 (123.95, 138.06)

Source: GS-US-311-0101, Section 15.1, Tables 4.3 and 5

Table 30. F/TAF Study GS-US-311-0101: Statistical Comparisons of DRV PK Parameter Estimates Between Test and Reference Treatments (DRV PK Analysis Set)

DRV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 3: F/TAF 200/25 mg + DRV+COBI, Day 22 (Test) vs DRV+COBI, Day 10 (Reference) (N = 14)			
AUC_{tau} (ng•h/mL)	115,736.3 (31.2)	116,150.0 (28.3)	99.11 (91.54, 107.30)
C_{max} (ng/mL)	10,215.2 (21.2)	10,023.8 (22.8)	102.25 (95.61, 109.36)
C_{tau} (ng/mL)	2401.0 (56.1)	2380.0 (41.6)	96.81 (81.51, 114.98)

Source: GS-US-311-0101, Section 15.1, Tables 4.5 and 5

Following administration of F/TAF 200/40 mg + EFV in Cohort 1, the GLSM ratio and 90% CIs for TAF AUC_{last} and TFV AUC_{tau} and C_{tau} were within the protocol-defined lack of interaction boundary, relative to F/TAF dosed alone. However, the lower limit of the 90% CI for TAF C_{max} and TFV C_{max} fell slightly below the lower bound of 70%. The changes were not considered to be clinically meaningful, as the TAF exposure observed in the presence of EFV following TAF 40 mg (and expected following TAF 25 mg) was in the range of exposures associated with potent antiviral activity (GS-US-120-0104 [Section 2.3.2.1]), while the TFV exposure observed in the presence of EFV following treatment with TAF 40 mg or 25 mg would represent a substantial reduction in circulating TFV as compared with TDF 300 mg. The GLSM ratio and 90% CIs for FTC were within the protocol-defined lack of interaction boundary. EFV exposure was comparable with historical data. As such, there were no clinically relevant drug interactions between EFV and F/TAF.

Following administration of F/TAF 200/25 mg + DRV+COBI in Cohort 2, the GLSM ratio and 90% CIs for TAF and FTC were within the lack of interaction boundary, relative to F/TAF dosed

alone. However, the GLSM ratios for TFV AUC_{tau} and C_{max} were 323.88% and 316.03%, respectively, consistent with the higher TFV exposure observed in Cohort 4 of this study (TAF 8 mg + COBI versus TAF 8 mg alone) and with E/C/F/TAF versus TAF 25 mg single agent in Study GS-US-292-0101 (Section 2.2.3.1). The increase in TFV exposure, without a change in TAF exposure, upon multiple-dose coadministration with DRV+COBI is indicative of a mixed inhibitory/inductive effect on P-gp influencing TAF absorption. An increase in TAF exposure (AUC_{last} and C_{max}) following a single dose of F/TAF+DRV+COBI, as compared with a single dose of F/TAF alone, suggested the presence of an inhibitory drug interaction resulting in increased availability of TAF following a single dose that is abated following multiple dosing. The comparable exposure of TAF following multiple-dose coadministration with DRV+COBI versus TAF alone may be due to an inductive effect of DRV on P-gp.

Following administration of F/TAF 200/25 mg + DRV+COBI in Cohort 3, the GLSM ratio and 90% CIs for DRV and COBI were within the lack of interaction boundary, relative to DRV+COBI dosed alone. The stricter 80% to 125% boundary criterion for BE was also met for DRV and COBI, with the exception of COBI C_{tau} (125.06%), which was slightly above the upper limit. TAF and TFV exposures were comparable with those observed when dosed as DRV+COBI + F/TAF 200/25 mg in Cohort 2. COBI and FTC exposures were consistent with historical data from previous studies.

Following coadministration of TAF 8 mg + COBI in Cohort 4, the GLSM ratio and 90% CIs for TAF and TFV were above the lack of interaction boundary, relative to TAF dosed alone. The GLSM ratios of TAF AUC_{last} and C_{max} (265.06% and 283.31%, respectively) and TFV AUC_{tau} and C_{max} (330.88% and 334.09%, respectively) were consistent with the higher TAF and TFV exposures observed with E/C/F/TAF versus TAF single agent in Study GS-US-292-0101, indicating the presence of a COBI-mediated interaction, likely due to inhibition of P-gp-mediated intestinal secretion of TAF. COBI exposure was in the range of those observed previously (Studies GS-US-216-0112 and GS-US-216-0124).

Safety Results

Overall, treatment-emergent AEs were reported for ≥ 1 subject during each treatment, except during administration of DRV+COBI (Cohort 3: no AE reported). Except for headache (2 of 12 subjects during Treatment B [F/TAF 200/40 mg + EFV], 2 of 25 subjects during Treatment D/F [F/TAF 200/25 mg +DRV+COBI]), *Escherichia coli* urinary tract infection (2 of 12 subjects during Treatment B [F/TAF 200/40 mg + EFV]), constipation (2 of 12 subjects during Treatment G [TAF 8 mg]), and vessel puncture site pain (2 of 12 subjects during Treatment H [TAF 8 mg + COBI]), no AE was reported in > 1 subject for a treatment. All AEs were Grade 1 or 2 in severity. No SAEs, death, or pregnancies occurred in this study. Two subjects discontinued study drug because of an AE (Grade 2 anxiety with treatment sequence AB [F/TAF 200/40 mg then F/TAF 200/40 mg + EFV] and Grade 2 joint abscess with Treatment C [F/TAF 200/25 mg]). The Grade 2 anxiety was considered by the investigator to be related to the study drug. All but 1 of the treatment-emergent laboratory abnormalities were Grade 1 or 2. There were no clinically relevant changes from baseline in renal laboratory parameters (serum creatinine, CL_{cr}, or serum phosphate) in any treatment group. No treatment-emergent graded serum creatinine, serum phosphate, or urine glucose abnormalities were reported in any subject

during any treatment. No clinically meaningful changes from baseline were observed in clinical laboratory test values, vital signs, physical findings, or safety ECGs.

Conclusions

- Administration of F/TAF+EFV resulted in no clinically relevant changes in FTC, TFV, or TAF exposure, as compared with F/TAF dosed alone. Based on these data, it is concluded that no dose adjustments are needed when EFV is coadministered with F/TAF or TAF single agent.

- Administration of F/TAF+DRV+COBI resulted in comparable exposures of TAF and FTC, but substantially higher TFV exposure, relative to F/TAF dosed alone.

- Administration of F/TAF+DRV+COBI resulted in comparable exposures of DRV and COBI, relative to DRV+COBI dosed alone.

- Administration of TAF+COBI resulted in substantially higher TAF and TFV exposures relative to TAF dosed alone, with COBI exposure in the range of historical data.

- Multiple doses of F/TAF, administered alone or coadministered with EFV or DRV+COBI, were well tolerated in this study. One study drug-related AE of anxiety led to discontinuation. This AE occurred after the first dose of F/TAF 200/40 mg + EFV. EFV has been shown to have central nervous system-related side effects. Additionally, multiple doses of TAF 8 mg administered alone or coadministered with COBI were well tolerated.

2.5.1.2. Study GS-US-311-1386

Title

A Phase 1, Randomized, Open-Label Study to Determine the Effect of Food on the Pharmacokinetics of Tenofovir Alafenamide When Administered as Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Tablet in Healthy Volunteers

Objectives

The primary objectives of this study were as follows:

- To evaluate the effect of food on the PK of TAF when administered as F/TAF

- To evaluate the effect of food on the PK of FTC when administered as F/TAF

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of F/TAF administered under fed and fasted conditions

Study Design

This was a randomized, open-label, single-dose, 2-treatment, 2-period, crossover, food-effect study. Following screening and Day −1 assessments, eligible subjects were randomized (1:1) to 1 of 2 treatment sequences (AB or BA) and received the following study drug treatments (first treatment on Day 1 and second treatment on Day 8).

- Treatment A (fasted): Single dose of F/TAF (200/25 mg), administered orally under fasted conditions in the morning
- Treatment B (fed): Single dose of F/TAF (200/25 mg), administered orally under fed conditions in the morning

Subjects were admitted to the study center on Day -1 and remained confined to the clinic until the morning of Day 14. Subjects received a follow-up telephone call on Day 22 ± 2 days.

Further details on the design and results of this study are available in the CSR (m5.3.3.4, GS-US-311-1386).

Study Population

A total of 40 subjects were randomized, and all received at least 1 dose of study drug. Of these, 38 subjects (95.0%) received both doses of study drug, and 2 discontinued after receiving F/TAF under fasted conditions (Treatment A) only; the reasons for discontinuation of study drug (and study) were AE and pregnancy, respectively. One of the 38 subjects who completed study drug discontinued the study early due to withdrawal of consent; therefore, 37 subjects (92.5%) completed the study.

The majority of subjects in the Safety Analysis Set were male (60.0%, 24 subjects). The median age was 28 years (range: 20 to 45). The majority of subjects were white (72.5%) and were not Hispanic or Latino (97.5%). At baseline, the median (Q1, Q3) BMI was 26.5 (24.1, 27.8) kg/m^2, and the median (Q1, Q3) $eGFR_{CG}$ was 121.8 (108.5, 132.5) mL/min.

Pharmacokinetic Results

Table 31 presents TAF and FTC plasma PK parameters AUC_{inf}, AUC_{last}, and C_{max}, and the statistical comparisons of these parameters following the administration of F/TAF under fasted conditions and fed conditions (high-calorie, high-fat meal). When administered under fed conditions, the mean (%CV) C_{max} value was 207.2 (63.2) ng/mL (with an SD of 131.03 [value not shown]) and mean (%CV) AUC_{last} value was 254.5 (42.6) ng•h/mL (with an SD of 108.40 [value not shown]).

TAF AUC_{inf} and AUC_{last} increased by 75% and 77%, respectively, when administered under fed conditions compared with fasted conditions. TAF C_{max} decreased by 15% when administered under fed conditions compared with fasted conditions and was accompanied by a delay in median T_{max} (increase from 0.50 hours under fasted conditions to 1.00 hour under fed conditions). FTC AUC_{inf} and AUC_{last} decreased by 9% and FTC C_{max} decreased by 27%, when

administered under fed conditions compared with fasted conditions, and there was a delay in median T_{max} (increase from 1.00 hour under fasted conditions to 2.00 hours under fed conditions).

Table 31. F/TAF Study GS-US-311-1386: Statistical Comparisons of TAF and FTC PK Parameter Estimates Between Study Treatments (PK Analysis Sets)

	Mean (%CV) by Treatment		
	F/TAF Fed (Test) (N = 38)	F/TAF Fasted (Reference) (N = 40)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{inf} (ng•h/mL)	266.8 (42.0)[a]	147.0 (42.5)	175.38 (163.93, 187.63)
AUC_{last} (ng•h/mL)	254.5 (42.6)	145.8 (42.9)	176.57 (166.19, 187.60)
C_{max} (ng/mL)	207.2 (63.2)	230.1 (36.2)	84.53 (74.92, 95.37)
FTC PK Parameter			
AUC_{inf} (ng•h/mL)	9181.9 (15.6)	10,122.6 (15.5)	91.11 (88.84, 93.44)
AUC_{last} (ng•h/mL)	8964.4 (15.6)	9876.4 (15.6)	91.22 (88.90, 93.60)
C_{max} (ng/mL)	1551.2 (22.6)	2097.8 (19.1)	73.50 (69.26, 78.00)

a n = 33; TAF AUC_{inf} could not be calculated in 5 subjects.
Source: m5.3.3.4, GS-US-311-1386, Section 15.1, Tables 4.1, 4.2 and 5

Safety Results

No deaths were reported during this study. One subject had a confirmed pregnancy after she had received a dose of F/TAF administered under fasted conditions, and study drug was discontinued. The subject subsequently had a spontaneous abortion approximately 2 weeks after dosing. This was an SAE and considered by the investigator to be related to study drug.

One subject discontinued study drug due to an AE of neutropenia. After administration of F/TAF under fasted conditions on Day 1, neutrophil levels decreased on Day 3 to Grade 1, falling further on Days 4 and 5 to Grade 3, followed by Grade 2 on Days 6 through 8, and then resolving to within the normal range on Day 9. The investigator considered the AE to be related to study drug.

The percentage of subjects with any AE was 30.0% (12 of 40 subjects) following F/TAF administered under fasted conditions and 26.3% (10 of 38 subjects) following F/TAF administered under fed conditions. AEs that were considered by the investigator as related to study drug were reported in 20.0% (8 subjects) and 18.4% (7 subjects), respectively.

The most common AEs were nausea and headache (each reported in 7.5% [3 subjects] following F/TAF administered under fasted conditions and 5.3% [2 subjects] following F/TAF

administered under fed conditions), and chills (5.3% [2 subjects] following F/TAF administered under fed conditions only).

The majority of AEs were Grade 1 (mild). Two subjects had a Grade 3 (severe) AE (neutropenia and spontaneous abortion), both following F/TAF administered under fasted conditions and considered by the investigator as related to study drug.

There were no clinically relevant changes in clinical laboratory parameters, vital signs, or body weight during the study.

Conclusions

The overall conclusions of this study are as follows:

- Overall TAF exposure (AUC_{inf}) increased by 75% when F/TAF (200/25 mg) was administered under fed conditions compared with fasted conditions. The wide range of TAF exposure associated with potent antiviral activity established in Study GS-US-120-0104 and with safety and efficacy in the E/C/F/TAF clinical program (predicted individual steady-state mean [95% CI, %CV] AUC 206.4 ng•h/mL [55.6 to 526.1 ng•h/mL, 71.8%]) indicates that the TAF PK differences upon F/TAF administration with or without food are not clinically relevant.

- Overall FTC exposure (AUC_{inf}) decreased by 9% when F/TAF (200/25 mg) was administered under fed conditions compared with fasted conditions. These findings are consistent with those from a previous study (FTC-111), which supports the current recommendation that FTC can be administered without regard to food.

- Single doses of F/TAF, administered under fed and fasted conditions, were generally well tolerated in this study.

- Overall, the differences in TAF or FTC exposures upon administration with food are not expected to result in clinically relevant differences in efficacy or safety; therefore, F/TAF can be administered without regard to food.

2.5.2. TAF Studies

2.5.2.1. Study GS-US-120-0117

Title

A Phase 1 Single-Dose Study Evaluating the Pharmacokinetic Drug Interaction Potential between Rilpivirine and Tenofovir Alafenamide

Objectives

Study GS-US-120-0117 was conducted to evaluate the PK drug interaction potential between RPV and TAF.

The primary objective of this study was as follows:

- To evaluate the PK of RPV and TAF following single-dose administration of RPV and TAF alone and in combination in healthy subjects

The secondary objective of this study was as follows:

- To evaluate the safety of single-dose administration of RPV and TAF alone and in combination in healthy subjects

Study Design

This was an open-label, single-center, single-dose, crossover study in healthy adult subjects. Subjects were enrolled in 1 of the following 2 cohorts to receive 2 treatments in a randomized sequence with a 10-day washout period between treatments:

Cohort 1:

Treatment A: TAF 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal

Treatment B: TAF 25 mg + RPV 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal

Cohort 2:

Treatment B: TAF 25 mg + RPV 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal

Treatment C: RPV 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal

Subjects were confined at the study center from Day −1 until completion of PK and safety assessments on Day 17.

Further details on the design and results of this study are available in the CSR (GS-US-120-0117).

Study Population

All 36 randomized subjects completed the study (18 subjects in Cohort 1 and 18 subjects in Cohort 2). All subjects were included in the safety analysis set and all PK analysis sets.

Subjects had a median age of 30 years in Cohort 1 (range: 19 to 43 years) and 32 years in Cohort 2 (range: 19 to 44 years), and there was an even distribution of male and female subjects (50% in each cohort). Subjects were either white (38.9% in Cohort 1 and 72.2% in Cohort 2) or black (61.1% in Cohort 1 and 27.8% in Cohort 2). Overall, 38.9% and 55.6% of subjects were of Hispanic/Latino ethnicity in Cohort 1 and Cohort 2, respectively.

Pharmacokinetic Results

There is no clinically meaningful drug interaction between TAF and RPV, as the 90% CIs of the GMRs are all contained in the predefined no-drug interaction boundary of 70% to 143% in exposure or C_{max} of TAF, TFV, or RPV when TAF is coadministered with RPV versus when TAF or RPV is administered alone (Table 32).

Table 32. TAF Study GS-US-120-0117: Statistical Comparisons of TAF, TFV, and RPV PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

	Mean (%CV) by Treatment			
TAF PK Parameter	**TAF+RPV Cohort 1 (N = 18)**	**TAF+RPV Cohort 2 (N = 18)**	**TAF Cohort 1 (N = 18)**	**GLSM Ratio (90% CI), %**
AUC_{inf} (ng•h/mL)	262.4 (54.6)	247.8 (27.3)	263.4 (42.7)	95.91 (83.65, 109.97)
AUC_{last} (ng•h/mL)	260.1 (55.3)	245.2 (27.2)	261.4 (43.1)	95.55 (82.89, 110.13)
C_{max} (ng/mL)	231.8 (91.9)	200.9 (45.6)	201.4 (54.3)	101.19 (82.76, 123.71)
	Mean (%CV) by Treatment			
TFV PK Parameter	**TAF+RPV Cohort 1 (N = 18)**	**TAF+RPV Cohort 2 (N = 18)**	**TAF Cohort 1 (N = 18)**	**GLSM Ratio (90% CI), %**
AUC_{inf} (ng•h/mL)	279.5 (27.1)	268.9 (22.1)	257.3 (27.9)	108.75 (102.43, 115.46)
AUC_{last} (ng•h/mL)	238.4 (26.1)	237.1 (21.9)	222.4 (25.8)	106.99 (101.69, 112.58)
C_{max} (ng/mL)	8.7 (33.8)	8.1 (27.1)	7.2 (25.3)	118.10 (107.33, 129.96)
	Mean (%CV) by Treatment			
RPV PK Parameter	**TAF+RPV Cohort 1 (N = 18)**	**TAF+RPV Cohort 2 (N = 18)**	**RPV Cohort 2 (N = 18)**	**GLSM Ratio (90% CI), %**
AUC_{inf} (ng•h/mL)	3201.7 (45.2)	3677.9 (40.0)	3949.8 (30.2)	89.18 (76.15,104.44)
AUC_{last} (ng•h/mL)	2425.2 (41.0)	2662.3 (32.9)	2767.3 (26.2)	93.46 (80.70,108.23)
C_{max} (ng/mL)	89.3 (36.5)	104.3 (40.2)	105.9 (30.1)	94.50 (79.74,112.00)

Source: GS-US-120-0117, Section 15.1, Tables 4.1.1 to 4.1.3, 4.2.1 to 4.2.3, and 5

Safety Results

No SAEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE.

At least 1 treatment-emergent AE was reported for 0.0%, 11.1%, and 27.8% of subjects during TAF 25 mg, TAF 25 mg + RPV, and RPV treatments, respectively. Adverse events reported in at least 2 subjects for each treatment included headache (3 of 36 subjects [8.3%] with TAF+RPV

treatment and 2 subjects [11.1%] with RPV treatment), nausea and vomiting (2 subjects each [5.6%] with TAF+RPV treatment); and constipation (2 subjects [11.1%] with RPV treatment).

All AEs were reported as Grade 1 (mild) in severity. No Grade 2, 3, or 4 events were reported.

Adverse events in 3 subjects were considered by the investigator to be possibly related to study drug: nausea and vomiting were each reported by 2 (5.6%) subjects with TAF+RPV treatment, and abdominal pain was reported for 1 (5.6%) subject with RPV treatment.

There were no clinically relevant changes in any hematology or chemistry parameter for any treatment (including TAF, TAF+RPV, and RPV). One subject had a Grade 3 abnormality of hematuria (following TAF+RPV treatment). The site confirmed that the subject was on her menses; therefore, the investigator did not repeat the laboratory assessment [data on file].

No clinically significant changes in vital signs or safety ECGs were observed during this study.

Conclusions

- Rilpivirine and TAF coadministration does not result in clinically relevant changes in RPV, TAF, or TFV exposure and no dose adjustments are necessary.
- Single doses of TAF 25 mg, TAF 25 mg + RPV, and RPV were generally well tolerated in these healthy subjects. All AEs were considered Grade 1 and most AEs were considered unrelated to study drug.

2.5.2.2. Study GS-US-120-0118

Title

A Pharmacokinetic Study Evaluating the Drug Interaction Potential of Tenofovir Alafenamide with a Boosted Protease Inhibitor or Unboosted Integrase Inhibitor in Healthy Subjects

Objectives

The primary objectives of this study were as follows:

- To evaluate the effect of common boosted PIs ATV+RTV; DRV+RTV; LPV/r, or the INSTI DTG on the PK of TAF
- To evaluate the PK of ATV, DRV, LPV, and DTG alone and in combination with FTC and TAF

The secondary objectives of this study were as follows:

- To evaluate the safety of administration of FTC and TAF plus ATV+RTV, DRV+RTV, LPV/r, and DTG
- To evaluate PK of TFV following the coadministration of FTC and TAF plus ATV+RTV DRV+RTV, LPV/r, and DTG, relative to the administration of FTC and TAF alone

Study Design

This was an open-label study of the PK drug interaction potential of TAF with the RTV-boosted PIs ATV+RTV, DRV+RTV, and LPV/r, or the INSTI DTG, in 40 healthy adult subjects. Subjects received a single dose of TAF 10 mg + FTC 200 mg, followed by 13 days of daily dosing of ATV+RTV, DRV+RTV, LPV/r, or DTG, followed by an additional single dose of TAF 10 mg + FTC 200 mg administered in the presence of steady-state RTV-boosted PI or unboosted DTG. Serial PK samples were collected to evaluate the relevant PK parameters for TAF and TFV or ATV, DRV, LPV, and DTG, administered alone or in combination. Subjects were enrolled in 1 of 4 treatment cohorts. The study was planned to enroll 40 subjects (10 subjects per cohort) to obtain 32 evaluable subjects (8 subjects per cohort). The following study treatments were administered:

- Treatment A = Treatment F: FTC 200 mg + TAF 10 mg once, administered in the morning with food
- Treatment B: ATV 300 mg + RTV 100 mg once daily, administered in morning with food
- Treatment C: DRV 800 mg + RTV 100 mg once daily, administered in morning with food
- Treatment D: 4 × LPV/r 200/50 mg once daily, administered in morning with food
- Treatment E: DTG 50 mg once daily, administered in the morning with food

	Day 1	Days 2–14	Day 15
Cohort	**Reference 1**	**Reference 2**	**Test**
1	A	B	A + B
2	A	C	A + C
3	A	D	A + D
4	F	E	F + E

Subjects were confined at the study center from Day −1 until completion of PK and safety assessments on Day 16.

Further details on the design and results of this study are available in the CSR (m5.3.3.4, GS-US-120-0118).

Study Population

Forty subjects were enrolled in the study to receive study drug (10 subjects in each of the 4 cohorts). Thirty-nine of the 40 subjects completed the study. One subject assigned to Cohort 4 (FTC+TAF, DTG, and FTC+TAF+DTG treatment) withdrew consent prior to study completion.

The median age in Cohorts 1, 2, 3, and 4 was 32, 35, 34, and 36 years, respectively (overall range: 23 to 45 years). Of the 40 subjects enrolled, 27 were males and 13 were female. The majority of subjects were white (30 of 40 subjects) and of Hispanic/Latino ethnicity (34 of 40 subjects).

Pharmacokinetic Results

Coadministration of ATV+RTV or LPV/r with FTC+TAF increased TAF exposures approximately 91% and 47%, respectively, versus FTC+TAF alone (Table 33). Following dosing with DRV+RTV or DTG, the TAF exposure was unchanged.

Table 33. TAF Study GS-US-120-0118: Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	164.8 (18.1)	91.6 (39.9)	188.92 (155.37, 229.71)
AUC_{last} (ng•h/mL)	162.6 (18.8)	89.5 (40.8)	191.06 (155.08, 235.40)
C_{max} (ng/mL)	146.5 (46.9)	76.8 (29.4)	176.72 (128.19, 243.63)
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	80.5 (30.4)	80.0 (41.8)	104.34 (84.14, 129.39)
AUC_{last} (ng•h/mL)	78.6 (30.9)	77.4 (43.6)	106.27 (83.59, 135.10)
C_{max} (ng/mL)	102.3 (46.5)	73.4 (49.4)	141.80 (96.11, 209.22)
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	122.5 (42.7)	82.7 (34.0)	144.75 (114.15, 183.55)
AUC_{last} (ng•h/mL)	120.8 (43.9)	80.0 (34.1)	146.73 (116.60, 184.65)
C_{max} (ng/mL)	157.5 (39.4)	68.7 (28.7)	218.97 (171.88, 278.97)
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	105.1 (31.7)	100.9 (51.2)	116.62 (93.49, 145.48)
AUC_{last} (ng•h/mL)	103.0 (30.6)	98.5 (53.3)	119.02 (95.83, 147.82)
C_{max} (ng/mL)	83.4 (30.6)	79.9 (60.6)	123.64 (87.79, 174.13)

Source: m5.3.3.4, GS-US-120-0118, Section 15.1, Tables 4.1.1, 4.2.1, 4.3.1, 4.4.1, 5.1, 5.2, 5.3, and 5.4

Coadministration of ATV+RTV, DRV+RTV, or LPV/r with FTC+TAF increased TFV exposures approximately 162%, 105%, and 316%, respectively, versus FTC+TAF alone (Table 34). Following dosing with DTG, TFV exposures were unchanged.

Table 34. TAF Study GS-US-120-0118: Statistical Comparisons of TFV PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

TFV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	285.9 (22.1)	113.7 (36.0)	261.59 (213.95, 319.84)
AUC_{last} (ng•h/mL)	102.1 (18.0)	41.7 (22.4)	247.77 (216.82, 283.14)
C_{max} (ng/mL)	8.8 (20.9)	4.3 (30.7)	212.35 (185.83, 242.65)
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	258.9 (21.5)	137.2 (49.2)	204.61 (153.78, 272.25)
AUC_{last} (ng•h/mL)	103.8 (12.7)	43.5 (24.2)	242.74 (207.17, 284.41)
C_{max} (ng/mL)	9.2 (21.2)	3.9 (34.1)	241.54 (198.10, 294.51)
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	409.8 (22.0)	98.2 (23.6)	416.36 (349.56, 495.93)
AUC_{last} (ng•h/mL)	129.0 (12.5)	40.3 (16.2)	322.01 (298.02, 347.93)
C_{max} (ng/mL)	12.7 (25.6)	3.4 (21.1)	374.52 (319.28, 439.30)
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{inf} (ng•h/mL)	114.9 (16.9)	94.2 (27.6)	124.94 (106.46, 146.62)
AUC_{last} (ng•h/mL)	43.0 (19.8)	41.7 (20.0)	104.25 (98.74, 110.08)
C_{max} (ng/mL)	3.8 (23.1)	3.7 (44.3)	109.91 (96.39, 125.32)

Source: m5.3.3.4, GS-US-120-0118, Section 15.1, Tables 4.1.2, 4.2.2, 4.3.2, 4.4.2, 5.1, 5.2, 5.3, and 5.4

Coadministration of TAF 10 mg + FTC 200 mg had no effect on the PK of RTV-boosted PIs or DTG (Table 35).

Table 35. TAF Study GS-US-120-0118: Statistical Comparisons of ATV, DRV, LPV, and DTG PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

ATV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (90% CI), %
Cohort 1: FTC+TAF 10 mg +ATV+RTV (Test) vs ATV+RTV (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	64,035.2 (47.0)	64,692.1 (46.3)	98.73 (96.35, 101.18)
C_{tau} (ng/mL)	1636.9 (91.7)	1619.0 (91.3)	100.08 (96.04, 104.29)
C_{max} (ng/mL)	5730.2 (17.3)	5946.9 (21.7)	97.55 (88.98, 106.94)
DRV PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 2: FTC+TAF 10 mg +DRV+RTV (Test) vs DRV+RTV (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	97,486.1 (23.9)	97,646.2 (27.1)	100.63 (95.70, 105.81)
C_{tau} (ng/mL)	2598.0 (45.9)	2374.1 (47.6)	112.83 (95.20, 133.73)
C_{max} (ng/mL)	8472.5 (16.6)	8567.7 (18.7)	99.09 (90.85, 108.08)
LPV PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 3: FTC+TAF 10 mg +LPV/r (Test) vs LPV/r (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	179,207 (30.1)	176,925 (24.3)	100.41 (92.38, 109.15)
C_{tau} (ng/mL)	2004.9 (88.2)	1954.4 (73.1)	97.58 (85.00, 112.02)
C_{max} (ng/mL)	14,662.6 (19.2)	14,592.3 (17.4)	100.29 (95.05, 105.83)
DTG PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (90% CI), %**
Cohort 4: FTC+TAF 10 mg +DTG (Test) vs DTG (Reference) (N = 10)			
AUC_{tau} (ng•h/mL)	77,932.9 (19.3)	74,127.5 (16.0)	102.31 (97.09, 107.81)
C_{tau} (ng/mL)	2063.8 (30.3)	1949.3 (25.1)	104.88 (97.17, 113.19)
C_{max} (ng/mL)	5894.9 (6.7)	5148.0 (17.6)	115.29 (104.48, 127.22)

Source: m5.3.3.4, GS-US-120-0118, Section 15.1, Tables 4.1.3, 4.2.3, 4.3.3, 4.4.3, 5.1, 5.2, 5.3, and 5.4

Safety Results

No SAEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE.

The percentage of subjects with at least 1 AE was: FTC+TAF (4 of 40 subjects), ATV+RTV (10 of 10 subjects), FTC+TAF+ATV+RTV (1 of 10 subjects), DRV+RTV (2 of 10 subjects), LPV/r (9 of 10 subjects), DTG (3 of 10 subjects), and FTC+TAF+DTG (1 of 9 subjects). No

AEs were reported during the following treatments: FTC+TAF+DRV+RTV and FTC+TAF+LPV/r. Adverse events reported in at least 2 subjects for each treatment included ocular icterus (10 of 10 subjects [100%] with ATV+RTV treatment), diarrhea (5 of 10 subjects [50%] with LPV/r treatment), dry mouth (5 of 10 subjects [50%] with LPV/r treatment), dysgeusia (3 of 10 subjects [30%] with LPV/r treatment), and headache (2 of 10 subjects [20%] with DTG treatment).

All AEs were reported as Grade 1 (mild) or Grade 2 (moderate). No Grade 3 or 4 events were reported.

Adverse events considered by the investigator to be possibly related to study drug: 1 of 10 subjects (2.5%) with FTC+TAF treatment (flatulence, n = 1; nausea, n = 1), 10 of 10 subjects (100%) with ATV+RTV treatment (ocular icterus, n = 10; jaundice, n = 1), and 5 of 10 subjects (50%) with LPV/r treatment (diarrhea, n = 5; vomiting, n = 1).

Increases from baseline in median values for total bilirubin were observed during ATV+RTV treatment (median increases of 3.8 mg/dL on Day 8 and 2.9 mg/dL on Day 14). No other clinically relevant changes from baseline in median values were observed for any hematology or chemistry parameter, and median values for all other parameters were within normal range before and after dosing.

No clinically significant changes in vital signs were observed during this study.

Conclusions

- Coadministration of FTC+TAF with DTG does not result in clinically relevant changes in TAF or TFV exposure. Coadministration of FTC+TAF with ATV+RTV or LPV/r resulted in increased TAF and TFV exposures. Coadministration of FTC+TAF with DRV+RTV does not result in clinically relevant changes in TAF, but resulted in increased TFV exposures.
- Coadministration of FTC+TAF with ATV+RTV, DRV+RTV, LPV/r, and DTG was generally well tolerated in these healthy subjects. All AEs were considered Grade 1 or Grade 2. Except for AEs associated with ATV+RTV and LPV/r, most AEs were considered unrelated to study drug.

2.5.2.3. Study GS-US-120-1538

Title

A Fixed-Sequence, Open-Label, Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Midazolam (Oral and Intravenous) in Healthy Volunteers

Objectives

The primary objective of this study was as follows:

- To evaluate the effect of TAF on the PK of oral midazolam (MDZ_{oral}) and intravenous (IV) midazolam (MDZ_{IV})

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of TAF, MDZ_{oral} and MDZ_{IV} administered together or separately

Study Design

This Phase 1, open-label, fixed-sequence, multiple-dose, single-center study evaluated PK and potential drug interactions between TAF and MDZ (oral and IV) in healthy subjects. Following screening and Day –1 procedures, eligible subjects began study treatments in a fixed-sequence. All study drugs were administered in the morning under fed conditions as follows:

Day 1	Day 2	Day 3	Days 4–15	Day 16	Day 17	Day 18
MDZ_{oral}	X	MDZ_{IV}	TAF 25 mg	TAF+ MDZ_{oral}	TAF 25 mg	TAF+ MDZ_{IV}

MDZ_{oral} = 2.5 mg oral syrup; MDV_{IV} = 1 mg solution for injection (slow IV push over 1 minute); TAF+MDZ_{IV} = TAF 25 mg tablet + 1 mg solution for injection (slow IV push over 1 minute) administered within 5 minutes of each other; TAF+MDZ_{oral} = TAF 25 mg tablet + 2.5 mg oral syrup coadministered

Subjects were admitted to the study clinic on Day –1 and remained confined in the clinic until the morning of Day 19 after completion of study procedures. Subjects received a follow-up telephone call on Day 25 ± 2 days (7 ± 2 days after the final dose of study drug).

Further details on the design and results of this study are available in the CSR (m5.3.3.4, GS-US-120-1538).

Study Population

Of 28 screened subjects, 18 subjects were enrolled in the study. Each of the 18 enrolled subjects (100%) completed study treatment in the protocol-specified sequence, and all completed the study. The median age of subjects was 39 years (range: 24 to 45), and 50% of the subjects were male. The majority of subjects were white (88.9%) and the remainder were black or African American (11.1%); all of the subjects (100%) were Hispanic/Latino. At baseline, the median (Q1, Q3) BMI value of subjects was 27.4 (25.5, 28.6) kg/m^2, and the median (Q1, Q3) $eGFR_{CG}$ was 119.5 (109.1, 132.8) mL/min.

Pharmacokinetic Results

Following administration of TAF+MDZ_{oral} compared with MDZ alone, the 90% CIs of the AUC_{last}, AUC_{inf}, and C_{max} GLSMs for MDZ and a midazolam metabolite (1′-OH MDZ; 1′-hydroxymidazolam) were within the lack-of-interaction bounds (70% to 143%; Table 36). Following administration of TAF+MDZ_{IV} compared with MDZ_{IV} alone, the 90% CIs of the AUC_{last}, AUC_{inf}, and C_{max} GLSMs for MDZ and 1′-OH MDZ were also within the lack-of-interaction bounds (Table 37). These data suggest that multiple-dose TAF does not affect presystemic or systemic CYP3A activity.

Table 36. TAF Study GS-US-120-1538: Statistical Comparisons of MDZ_{oral} and 1′-OH MDZ_{oral} PK Parameter Estimates Between Study Treatments (MDZ_{oral} PK Analysis Set)

	Mean (%CV) by Treatment		
	TAF+MDZ_{oral} (Test) (N = 18)	MDZ_{oral} (Reference) (N = 18)	GLSM Ratio (90% CI), %
MDZ_{oral} PK Parameter			
AUC_{last} (ng•h/mL)	46.5 (31.8)	41.3 (30.8)	112.28 (103.05, 122.33)
AUC_{inf} (ng•h/mL)	49.4 (32.0)	43.7 (31.4)	112.97 (103.61, 123.17)
C_{max} (ng/mL)	8.9 (22.5)	8.8 (26.9)	101.87 (91.96, 112.84)
1′-OH MDZ_{oral} PK Parameter			
AUC_{last} (ng•h/mL)	12.9 (29.7)	13.4 (26.1)	95.13 (86.05, 105.16)
AUC_{inf} (ng•h/mL)	14.3 (34.8)	14.3 (24.9)	97.75 (88.02, 108.56)
C_{max} (ng/mL)	3.0 (32.2)	3.3 (33.4)	90.65 (76.64, 107.22)

Source: m5.3.3.4, GS-US-120-1538, Section 15.1, Tables 4.2.2, 4.2.3, and 5.1

Table 37. TAF Study GS-US-120-1538: Statistical Comparisons of MDZ_{IV} and 1′-OH MDZ_{IV} PK Parameter Estimates Between Study Treatments (MDZ_{IV} PK Analysis Set)

	Mean (%CV) by Treatment		
	TAF+MDZ_{IV} (Test) (N = 18)	MDZ_{IV} (Reference) (N = 18)	GLSM Ratio (90% CI), %
MDZ_{IV} PK Parameter			
AUC_{last} (ng•h/mL)	41.6 (21.4)	38.4 (22.3)	108.47 (103.57, 113.61)
AUC_{inf} (ng•h/mL)	43.8 (21.7)	40.4 (21.9)	108.45 (103.72, 113.40)
C_{max} (ng/mL)	23.8 (21.9)	24.4 (27.8)	99.19 (88.51, 111.15)
1′-OH MDZ_{IV} PK Parameter			
AUC_{last} (ng•h/mL)	5.7 (26.4)	5.3 (25.3)	108.49 (100.75, 116.83)
AUC_{inf} (ng•h/mL)	6.8 (27.2)	6.1 (27.9)	110.71 (102.31, 119.79)
C_{max} (ng/mL)	1.9 (39.5)	1.9 (31.6)	96.45 (85.67, 108.59)

Source: m5.3.3.4, GS-US-120-1538, Section 15.1, Tables 4.2.4, 4.2.5, and 5.1

Safety Results

No Grade 3 or 4 AEs, SAEs, or AEs leading to discontinuation were reported; and no pregnancy or death occurred during the study.

The most frequently reported AEs by treatment were dizziness (16.7%), vessel puncture site hemorrhage (11.1%), and vessel puncture site pain (11.1%) while subjects were receiving MDZ_{IV}; contact dermatitis (11.1%) while subjects were receiving TAF; and infusion site pain (11.1%), while subjects were receiving TAF+MDZ_{IV}. No AEs were reported while subjects were receiving MDZ_{oral}, TAF, or TAF+MDZ_{oral}.

The majority of AEs were Grade 1 in severity and were in the SOC general disorders and administration site conditions. The number of subjects with AEs considered related to study drug or study procedure was low; all related AEs were Grade 1 and occurred while subjects were receiving MDZ_{IV} or TAF+MDZ_{IV}.

Two subjects had graded laboratory abnormalities during the study: 1 subject with Grade 1 decreased bicarbonate and Grade 3 blood in urine (menses confirmed), and 1 (female) subject with Grade 1 blood in urine. None of these graded laboratory abnormalities was reported as an AE. There were no clinically relevant changes from baseline in vital signs.

Conclusions

- Following coadministration of MDZ (oral or IV) and TAF relative to MDZ alone, no clinically relevant differences in MDZ exposures were observed, indicating that multiple dose TAF does not inhibit or induce CYP3A in vivo, either presystemically or systemically.

- TAF administered alone or with MDZ (IV or oral) was well tolerated with few AEs and clinical laboratory abnormalities and no Grade 3 or 4 AEs, SAEs, or discontinuations due to AEs.

2.5.2.4. Study GS-US-120-1554

Title

A Fixed-Sequence, Randomized, Open-Label, 2-Cohort, 2-Period, Multiple-Dose Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Rilpivirine in Healthy Subjects

Objectives

The primary objectives of this study were as follows:

- To evaluate the effect of TAF on the PK of RPV

- To evaluate the effect of RPV on the PK of TAF

The secondary objectives of this study were as follows:

- To evaluate the effect of RPV on the PK of TFV, the metabolite of TAF

- To evaluate the safety and tolerability of TAF and RPV, administered together and separately

Study Design

This was an open-label, fixed-sequence, randomized, 2-cohort, 2-period, multiple-dose, single-center, Phase 1 study to evaluate the PK and drug interaction potential between TAF and RPV in healthy adult subjects. Subjects were randomized (1:1) to 1 of 2 treatment cohorts. The study was planned to enroll 34 subjects (17 subjects per cohort) to obtain 30 evaluable subjects (15 subjects per cohort). The following study treatments were administered:

- Treatment A: TAF 25 mg, administered orally once daily in the morning, under fed conditions
- Treatment B: RPV 25 mg, administered orally once daily in the morning, under fed conditions
- Treatment C: TAF 25 mg + RPV 25 mg, administered orally once daily in the morning, under fed conditions

	Days 1-14	Days 15-28
Cohort 1	Treatment A	Treatment C
Cohort 2	Treatment B	Treatment C

Following screening and Day –1 procedures, eligible subjects were confined at the study center until completion of PK and safety assessments on Day 29. A follow-up telephone call was scheduled 7 ± 2 days after the last dose of study drug.

Further details on the design and results of this study are available in the CSR (m5.3.3.4, GS-US-120-1554).

Study Population

A total of 34 subjects were randomized to receive study drug: 17 subjects in Cohort 1 (TAF-TAF+RPV) and 17 subjects in Cohort 2 (RPV-TAF+RPV). Thirty-two of the 34 subjects (94.1%) completed the study. Two subjects assigned to Cohort 2 (RPV-TAF+RPV) did not complete the study: 1 subject discontinued study drug due to an AE (increased hepatic enzymes) and 1 subject withdrew consent prior to completing study drug.

The majority of subjects were male (21 subjects; 61.8%), white (70.6%), and of Hispanic or Latino ethnicity (82.4%). At baseline, the median age was 35 years (range: 20 to 45), the median (Q1, Q3) BMI was 26.9 (24.3, 29.0) kg/m^2, the median (Q1, Q3) $eGFR_{CG}$ was 115.9 (105.1, 133.5) mL/min, and the median (Q1, Q3) $eGFR_{CKD\text{-}EPI,\ cysC}$ was 124.9 (121.4, 128.9) mL/min/1.73 m^2.

Pharmacokinetic Results

The steady-state plasma PK parameters of TAF, TFV and RPV following administration of TAF alone, RPV alone, or TAF+RPV are shown in Table 38.

Table 38. TAF Study GS-US-120-1554: Statistical Comparisons of TAF, TFV, and RPV PK Parameter Estimates Between Study Treatments (PK Analysis Sets)

	Mean (%CV) by Treatment		
	TAF+RPV (Test) (N = 32)	**TAF (Reference) (N = 17)**	**GLSM Ratio (90% CI), %**
TAF PK Parameter			
AUC_{tau} (ng•h/mL)	335.6 (29.9)	307.6 (18.4)	101.43 (93.93, 109.52)
AUC_{last} (ng•h/mL)	334.1 (30.0)	306.3 (18.4)	101.31 (93.77, 109.46)
C_{max} (ng/mL)	242.8 (38.2)	238.2 (25.5)	101.26 (84.23, 121.73)
TFV PK Parameter			
AUC_{tau} (ng•h/mL)	267.6 (16.9)	237.9 (14.0)	110.66 (107.32, 114.11)
C_{max} (ng/mL)	16.5 (35.9)	14.4 (12.9)	112.27 (102.19, 123.33)
C_{tau} (ng/mL)	9.4 (17.4)	7.9 (16.9)	117.72 (112.85, 122.80)
	Mean (%CV) by Treatment		
RPV PK Parameter	**TAF+RPV (Test) (N = 32)**	**RPV (Reference) (N = 16)**	**GLSM Ratio (90% CI), %**
AUC_{tau} (ng•h/mL)	3052.2 (31.6)	3264.7 (34.3)	101.27 (96.42, 106.36)
C_{max} (ng/mL)	202.6 (31.0)	227.3 (35.3)	92.91 (87.44, 98.72)
C_{tau} (ng/mL)	123.4 (37.7)	122.2 (40.1)	112.77 (103.58, 122.77)

Source: m5.3.3.4, GS-US-120-1554, Section 15.1, Tables 4.1.1, 4.2.1, 4.3.1, 5.1.1, 5.2.1, and 5.3.1

Safety Results

No deaths, SAEs, or pregnancies were reported during this study. One AE leading to premature study drug discontinuation (Grade 2 increased hepatic enzymes) was reported for 1 subject assigned to Cohort 2 (RPV-TAF+RPV), which accounted for the only AE that was considered by the investigator as related to study drug (RPV).

Adverse events were reported for 2 of 17 subjects (11.8%) following administration of RPV alone and for 5 of 33 subjects (15.2%) following administration of TAF+RPV. No AEs were reported for any subject following administration of TAF alone. Headache was the only AE reported in > 1 subject. No Grade 3 or Grade 4 AEs were reported; all AEs were Grade 1 or 2 in severity.

Grade 3 laboratory abnormalities were reported in 4 subjects and Grade 4 laboratory abnormalities were reported for 1 subject. One subject had Grade 3 AST and Grade 4 ALT, beginning after multiple-dose RPV and continuing after a single dose of TAF+RPV; this subject experienced the Grade 2 AE of increased hepatic enzymes on Day 14 that led to study drug

discontinuation. Three female subjects had Grade 3 occult blood on dipstick urinalysis, all of whom had confirmed menses at the time. All other laboratory abnormalities observed were Grade 1 or 2.

There were no clinically relevant changes from baseline in renal laboratory parameters (serum creatinine, $eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ cysC,}$ or serum phosphate) for any treatment.

No clinically significant changes in vital sign measurements were observed during this study.

Conclusions

- Following multiple-dose administration of TAF 25 mg and RPV 25 mg, there were no clinically relevant changes in TAF, TFV, or RPV exposure; no dose adjustment of either agent is necessary when TAF and RPV are administered together. TAF and RPV can be chronically administered together.

- Study drugs were generally well tolerated in this study. There were no new or unexpected safety findings in this short-term, multiple-dose study in healthy subjects.

2.5.3. E/C/F/TAF Studies

2.5.3.1. Study GS-US-292-0110

Title

A Phase 1, Randomized, Open-Label Study to Determine the Effect of Food on the Pharmacokinetics of Tenofovir Alafenamide When Administered as a Single Tablet Regimen Containing Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in Healthy Volunteers

Objectives

The primary objective of this study was as follows:

- To evaluate the effect of food (high-calorie/high-fat meal or light/low-fat meal) on the PK of TAF when administered as E/C/F/TAF

The secondary objectives of this study were as follows:

- To evaluate the effect of food (high-calorie/high-fat meal or light/low-fat meal) on the PK of TFV when administered as E/C/F/TAF

- To evaluate the safety of administration of E/C/F/TAF under fed and fasted conditions

Study Design

This was a Phase 1, randomized, open-label, single-center, 3-treatment, 3-period, 6-sequence, crossover, food-effect study evaluating the PK of TAF and TFV when given as part of E/C/F/TAF under fasted conditions and 2 different fed conditions (high-calorie/high-fat meal [approximately 800 kcal, approximately 50% fat] and light/low-fat meal [approximately 400 kcal, approximately 20% fat]). The study consisted of a 15-day treatment phase (serial blood samples drawn on Days 1, 8, and 15) and a 14-day follow-up phase. Subjects were confined at the study center from Day −1 until completion of PK and safety assessments on Day 17.

Further details on the design and results of this study are available in the CSR (GS-US-292-0110).

Study Population

A total of 42 subjects were planned to be enrolled to obtain 36 evaluable subjects. Forty-three subjects were randomized to the study and received ≥ 1 study treatment. One subject received 1 dose of study drug on Day 1, but discontinued the study prematurely at the investigator's discretion and did not receive additional treatments. Forty-two of the 43 randomized subjects received all 3 study treatments.

Most subjects were male (69.8%) and white (51.2%). Subjects had a median age of 34 years (range: 21 to 45 years).

Pharmacokinetic Results

Administration of E/C/F/TAF under fed conditions did not affect the overall exposure of TAF, but resulted in a lower C_{max} and delayed T_{max} (Table 39). When administered with a high-calorie/high-fat meal, the mean (%CV) C_{max} value was 210.7 (47.0) ng/mL (with an SD of 99.01 [value not shown]) and mean (%CV) AUC_{last} value was 251.4 (30.4) ng•h/mL (with an SD of 76.37 [value not shown]). The GLSM ratios of the AUC_{last} of TAF when administered with a light/low-fat or high-calorie/high-fat were 115% (90% CI: 107% to 124%) and 117% (90% CI: 108% to 126%), respectively (Table 40). The GLSM ratios of the C_{max} of TAF were 68% (90% CI: 59% to 79%) and 63% (90% CI: 55% to 73%) when administered under light/low-fat or high-calorie/high-fat conditions, respectively. This approximately 35% decrease in TAF plasma C_{max} when administered with food was accompanied by a delay in median T_{max}, from 0.50 hours to 1.00 hour when administered with either a light/low-fat or high-calorie/high-fat meal.

Similarly, food did not affect the overall TFV exposure (Table 39). The TFV AUC_{inf} GLSM ratios when E/C/F/TAF was administered with a light/low-fat or high-calorie/high-fat meal were 114% (90% CI: 108% to 119%) and 113% (90% CI: 107% to 118%), respectively (Table 40). Likewise, food administration, irrespective of content, resulted in a decrease of C_{max} (approximately 15%) with a corresponding delay of median T_{max} (from 0.75 hours to 1.50 hours).

These modest changes in TAF and TFV PK parameters upon E/C/F/TAF administration with food (versus fasted) were not considered clinically relevant.

Table 39. E/C/F/TAF Study GS-US-292-0110: Summary of PK Parameter Estimates for TAF and TFV Following a Single-Dose of E/C/F/TAF (PK Analysis Sets)

	Mean (%CV) by Treatment Condition		
	E/C/F/TAF Light/LF Meal (N = 42)	**E/C/F/TAF HC/HF Meal (N = 42)**	**E/C/F/TAF Fasted (N = 42)**
TAF PK Parameter			
AUC_{inf} (ng•h/mL)	252.2 (32.3)	254.5 (29.6)	223.9 (44.9)
AUC_{last} (ng•h/mL)	250.3 (32.7)	251.4 (30.4)	222.5 (45.2)
C_{max} (ng/mL)	219.5 (43.7)	210.7 (47.0)	329.1 (47.0)
TFV PK Parameter			
AUC_{inf} (ng•h/mL)	322.7 (20.3)	319.5 (19.2)	285.4 (22.3)
AUC_{last} (ng•h/mL)	180.6 (17.8)	180.2 (16.1)	179.0 (19.6)
C_{max} (ng/mL)	12.9 (38.3)	13.1 (44.1)	15.3 (36.5)

Source: GS-US-292-0110, Section 15.1, Tables 4.1 and 4.2

Table 40. E/C/F/TAF Study GS-US-292-0110: Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Study Treatment Conditions (PK Analysis Sets)

	GLSM ratio (90% CI), %		
	Light/LF Meal (Test) vs Fasted (Reference)	**HC/HF Meal (Test) vs Fasted (Reference)**	**HC/HF Meal (Test) vs Light/LF Meal (Reference)**
TAF PK Parameter			
AUC_{inf} (ng•h/mL)	115.22 (107.14, 123.91)	117.53 (109.28, 126.39)	102.00 (94.85, 109.69)
AUC_{last} (ng•h/mL)	114.95 (106.82, 123.69)	116.65 (108.40, 125.52)	101.48 (94.30, 109.20)
C_{max} (ng/mL)	68.04 (58.96, 78.52)	63.20 (54.76, 72.93)	92.88 (80.49, 107.18)
TFV PK Parameter			
AUC_{inf} (ng•h/mL)	113.54 (108.23, 119.11)	112.68 (107.40, 118.21)	99.24 (94.60, 104.11)
AUC_{last} (ng•h/mL)	101.38 (97.77, 105.13)	101.39 (97.77, 105.13)	100.00 (96.44, 103.70)
C_{max} (ng/mL)	84.11 (75.71, 93.45)	83.76 (75.39, 93.05)	99.58 (89.63, 110.63)

GLSMs were obtained using a mixed-effects model.
Source: GS-US-292-0110, Section 15.1, Table 5

Safety Results

At least 1 treatment-emergent AE was reported for 3 subjects (7.0%) after administration of E/C/F/TAF after a light/low-fat meal, for 2 subjects (4.8%) after administration of E/C/F/TAF after a high-calorie/high-fat meal, and for 2 subjects (4.8%) after administration of E/C/F/TAF under fasted conditions. All AEs were Grade 1 or 2 in severity and were considered by the Investigator to be unrelated to treatment. No SAEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE. No clinically relevant changes in any hematology or chemistry parameter for any group were noted. No clinically significant changes in vital signs or safety ECGs were observed during this study.

Conclusions

- The modest changes in TAF and TFV PK parameters upon E/C/F/TAF administration with food (versus fasted) were not considered clinically relevant. TAF can be administered without regard to food, and these findings can be extrapolated to all TAF presentations.

- Single doses of E/C/F/TAF, given under fasted conditions and 2 different fed conditions (light/low-fat meal and high-calorie/high-fat meal), were generally well tolerated in this sample of 43 healthy subjects.

2.5.3.2. Study GS-US-292-1316

Title

A Phase 1, Open-Label, Fixed Sequence Study Evaluating the Pharmacokinetics and Drug Interaction Potential Between Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen and Sertraline in Healthy Subjects

Objectives

The primary objective of this study was as follows:

- To evaluate the PK of EVG, TAF, and sertraline following the coadministration of E/C/F/TAF and sertraline relative to the administration of E/C/F/TAF or sertraline alone

The secondary objectives of this study were as follows:

- To evaluate the PK of COBI, FTC, and TFV following the coadministration of E/C/F/TAF and sertraline relative to the administration of E/C/F/TAF or sertraline alone

- To evaluate the safety and tolerability of administration of E/C/F/TAF or sertraline alone or in combination as E/C/F/TAF + sertraline

Study Design

This was a Phase 1, open-label, 3-period, fixed-sequence, single-center study to evaluate the PK and drug interaction potential between E/C/F/TAF and sertraline in healthy adult subjects. Following completion of screening and Day −1 procedures, eligible subjects were enrolled. The following study treatments were administered:

- Treatment A: sertraline 50 mg, single dose, administered orally in the morning with food
- Treatment B: E/C/F/TAF (150/150/200/10 mg), single dose, administered orally in the morning with food for 12 days
- Treatment C: sertraline 50 mg, single dose + E/C/F/TAF (150/150/200/10 mg), single dose, administered orally in the morning with food

Subjects were admitted to the study clinic on Day −1 and remained confined to the clinic until the morning of Day 15. Subjects received a follow-up phone call 7 days after the last study drug administration.

Further details on the design and results of this study are available in the CSR (GS-US-292-1316).

Study Population

A total of 20 subjects were planned to be enrolled to obtain 18 evaluable subjects. Twenty subjects were enrolled and received a single dose of sertraline (Treatment A) and ≥ 1 dose of E/C/F/TAF (Treatment B). Nineteen of the 20 subjects received E/C/F/TAF+ sertraline (Treatment C). One subject withdrew consent prior to study completion (Day 3).

Of the 20 subjects enrolled, 12 (60%) were males and 8 (40%) were female, with a median age of 36 years (range: 23 to 44 years). The majority of subjects were white (18 subjects [90%]) and of Hispanic/Latino ethnicity (18 subjects [90%]). The median (range) value for BMI at baseline was 26.4 (20.8, 30.3) kg/m^2.

Pharmacokinetic Results

The mean and %CV of the primary PK parameters for EVG, COBI, FTC, TAF, TFV, and sertraline following the administration E/C/F/TAF and sertraline alone or in combination, and the results of the statistical analysis, are summarized in Table 41.

Table 41. E/C/F/TAF Study GS-US-292-1316: Statistical Comparisons of EVG, COBI, FTC, TAF, TFV, and Sertraline PK Parameter Estimates Between Test and Reference Treatments (All PK Analysis Set)

	Mean (%CV) by Treatment		
	E/C/F/TAF+Sertraline (Test) (N = 19)	E/C/F/TAF (Reference) (N = 19)	GLSM ratio (90% CI), %
EVG PK Parameter			
AUC_{tau} (ng•h/mL)	20,600.2 (19.3)	22,077.5 (20.2)	93.54 (89.46, 97.81)
C_{max} (ng/mL)	1812.1 (17.3)	2112.6 (27.3)	87.50 (82.25, 93.09)
C_{tau} (ng/mL)	346.2 (32.3)	349.1 (37.2)	99.21 (93.45, 105.34)
COBI PK Parameter			
AUC_{tau} (ng•h/mL)	11,862.1 (28.5)	11,873.4 (28.7)	99.92 (97.00, 102.92)
C_{max} (ng/mL)	1905.8 (20.0)	1804.2 (19.9)	105.67 (101.28, 110.24)
C_{tau} (ng/mL)	26.9 (117.8)	27.8 (97.1)	86.81 (79.41, 94.90)
FTC PK Parameter			
AUC_{tau} (ng•h/mL)	9186.4 (15.9)	10,935.7 (18.8)	84.35 (81.11, 87.73)
C_{max} (ng/mL)	1922.6 (26.6)	2126.8 (24.8)	89.61 (82.03, 97.90)
C_{tau} (ng/mL)	73.8 (42.3)	77.9 (39.6)	94.15 (89.93, 98.56)
TAF PK Parameter			
AUC_{last} (ng•h/mL)	254.3 (35.7)	269.7 (38.5)	95.63 (89.18, 102.54)
C_{max} (ng/mL)	287.9 (52.2)	303.9 (61.4)	100.16 (86.45, 116.05)
TFV PK Parameter			
AUC_{tau} (ng•h/mL)	316.8 (19.9)	311.3 (20.5)	101.80 (99.95, 103.68)
C_{max} (ng/mL)	22.4 (38.6)	19.8 (25.0)	109.94 (100.27, 120.53)
C_{tau} (ng/mL)	10.8 (24.1)	10.7 (25.2)	101.01 (98.91, 103.15)
Sertraline PK Parameter			
AUC_{last} (ng•h/mL)	258.3 (25.1)	256.5 (33.6)	109.17 (90.03, 132.37)
AUC_{inf} (ng•h/mL)	379.7 (29.8)	440.3 (38.7)	93.31 (77.04, 113.00)
C_{max} (ng/mL)	19.4 (25.4)	18.6 (32.5)	113.68 (93.67, 137.98)

Source: GS-US-292-1316, Section 15.1, Tables 4.1.1 to 4.1.5, 4.1.6.1, and 5

Following the coadministration of E/C/F/TAF and sertraline, no clinically relevant alterations in the PK of EVG, COBI, FTC, TAF, TFV, or sertraline were observed relative to the administration of E/C/F/TAF or sertraline alone. The 90% CIs for the relevant PK parameters of EVG, COBI, FTC, TAF, TFV, and sertraline were within the protocol-specified no-PK-alteration boundary of 70% to 143%, indicating a lack of CYP-mediated drug interaction upon coadministration of E/C/F/TAF and sertraline. Overall, the exposures of all analytes following

E/C/F/TAF and/or sertraline were consistent with historical data. Based on these study results, no dose adjustment is needed when coadministering E/C/F/TAF and sertraline.

Safety Results

Onset of ≥ 1 AE was reported for 10.0% (2 of 20) of subjects after a single-dose administration of sertraline alone, for 15.0% (3 of 20) of subjects during treatment with E/C/F/TAF, and for 31.6% (6 of 19) of subjects after a single-dose administration of E/C/F/TAF + sertraline. All AEs were Grade 1. No SAEs, deaths, or pregnancies occurred during this study, and no subject discontinued the study due to an AE. One subject withdrew consent due to AEs. No clinically relevant changes from baseline in any hematology or chemistry parameters were observed during this study.

Conclusions

- Coadministration of E/C/F/TAF with sertraline had no effect on the PK of sertraline, EVG, COBI, FTC, TAF, or TFV.
- Coadministration of sertraline with E/C/F/TAF had no effect on the PK of EVG, COBI, FTC, TAF, or TFV.
- Coadministration of E/C/F/TAF with sertraline was generally well tolerated in these healthy subjects.
- Since no clinically relevant drug interactions were observed upon coadministration of E/C/F/TAF and sertraline, no dose adjustments are needed when coadministering E/C/F/TAF and sertraline. This recommendation can be extrapolated to F/TAF based on the nonclinical profile of TAF.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. ADME Characteristics

3.1.1. Absorption

3.1.1.1. In Vitro/Nonclinical Studies

The PK of TAF has been extensively characterized in vitro and in nonclinical species, and is characterized by rapid absorption across species with a T_{max} of 0.08 hours in mouse and dog and 0.5 hours in monkey. In all rat plasma samples, TAF was undetectable. Following oral administration in dog and monkey, TAF plasma concentrations decline rapidly, with a $t_{1/2}$ of < 1 hour and concentrations undetectable in plasma by 5 hours postdose. Concomitant with the rapid decline in TAF concentrations in plasma, the predominant metabolite TFV was formed and persisted in plasma over the dosing interval. Consistent with dose-dependent permeability observed in vitro, the oral BA of TAF increased with increasing dose in dogs and the observed oral BA was 14.3% at the 10-mg/kg dose {23907}. Following a 15-mg/kg oral dose of [^{14}C]TAF to bile duct-cannulated dog, the fraction absorbed was at least 41% based on excretion in urine and bile. Therefore, hepatic extraction was calculated to be approximately 65%.

FTC is rapidly and extensively absorbed after oral administration in mice, rats, and cynomolgus monkeys, with oral BA ranging from 58% to 97%. Exposure is roughly dose-proportional over most of the range explored. Therefore, absorption of FTC is likely rapid and complete in humans over the clinical dose range. FTC is not extensively metabolized; therefore, its BA is likely to be governed only by absorption, with little or no first-pass metabolism in the intestinal wall or liver.

The results of nonclinical studies investigating absorption are discussed in detail in the Nonclinical Pharmacokinetics Written Summary (m2.6.4).

3.1.1.2. Clinical Studies

TAF

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

Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (~40%). TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI or RTV) reduces P-gp−mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. Cumulative results from Studies GS-US-311-1473 (Section 2.2.1.3), GS-US-292-0103 (Section 2.2.3.2), and GS-US-292-0101 (Section 2.2.3.1), indicated that TAF exposure following a 10-mg dose (either as a single agent coadministered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg either as a single agent or as a component of F/TAF.

The effect of food on TAF absorption was evaluated in 2 Phase 1 studies: 1) when given as part of F/TAF (200/25 mg; GS-US-311-1386 [Section 2.5.1.2]) and 2) when given as part of E/C/F/TAF (GS-US-292-0110 [Section 2.5.3.1]). Food has an effect on TAF absorption; however, the observed differences are not considered clinically relevant given the wide range of safe and efficacious TAF exposure established (Sections 3.3.1.1 and 3.3.2.1). Compared with administration under fasting conditions, administration of a single dose of TAF following a high-fat meal resulted in a decreased C_{max} (15% when administered as F/TAF [200/25 mg] and 37% when administered as E/C/F/TAF) and an increased AUC_{last} (77% when administered as F/TAF [200/25 mg] and 17% when administered as E/C/F/TAF). Food effect is described further in Section 3.2.3.1.

FTC

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

The effect of food on the absorption of FTC was evaluated when given as part of F/TAF (200/25 mg; GS-US-311-1386 [Section 2.5.1.2]). The findings from this study were consistent with those from a previous study (FTC-111), which supports the current recommendation that FTC can be administered without regard to food.

Urinary excretion data provide evidence that FTC is extensively absorbed after single or repeated oral doses administered in either the capsule or solution formulations. Urinary recovery of unchanged FTC averaged 47% to 74% (Table 42) in these studies following oral administration of 200 mg FTC as a single dose or at steady-state following once-daily administration. Total recovery of unchanged FTC and its metabolites in urine as determined in a [^{14}C]FTC mass balance study (FTC-106) averaged 85.8% of the administered oral dose, providing the evidence of extensive oral absorption. The remainder of the [^{14}C]FTC dose recovered in feces (13.7%) exclusively as unchanged FTC, primarily over the 48- to 96-hour postdose period.

At the FTC therapeutic dose (200 mg once daily given as the capsule formulation), the steady-state peak plasma FTC concentration averaged approximately 2 µg/mL. FTC disposition follows linear, first-order kinetics, with steady-state plasma FTC concentration-time profiles predictable based on single-dose data. The steady-state plasma AUC over the 24 hour dosing interval following 200 mg once-daily dose averaged 10 µg•h/mL, which is the same as the AUC_{inf} value following a single-dose administration. The steady-state condition was generally achieved following 4 consecutive daily doses of FTC (3 days). The T_{max}, $t_{1/2}$ estimates, and urinary excretion data were similar between the single-dose and steady-state conditions, ie, indicating linear kinetics. In general, C_{max} value (approximately 2 µg/mL) did not show substantial increase following multiple-dose administration, reflecting a small accumulation index in the absorption phase. The steady-state trough plasma FTC concentration following a 200 mg once-daily dose averaged approximately 0.075 µg/mL, which is approximately 5-fold higher than the mean in vitro concentration that resulted in 90% inhibition (IC_{90}) value

(0.014 µg/mL) for inhibition of HIV-1 replication. In Study FTC-101, plasma concentrations of FTC (C_{max}, AUC, and C_{min}) increased in a dose-proportional manner following both single- and multiple-dose administration over the dose range of 25 to 200 mg given once or twice daily.

Table 42. Mean Urinary Recovery and Renal Clearance Estimates for FTC

Study No.	Number of Subjects (M/F) Type Age: Mean (range)	Dose (Oral Capsule Unless Noted)	% Dose Excreted as FTC	CL_r (mL/min)[a]
143-001[a]	12 (12M/0F) HIV-infected 36 (24-55) years	100 mg	47.2 (20%)	3.04 (32%)[a]
		200 mg	49.7 (20%)	2.65 (26%)[a]
		400 mg	56.5 (17%)	2.90 (25%)[a]
		800 mg	67.4 (31%)	3.32 (30%)[a]
		1200 mg	56.7 (23%)	2.86 (31%)[a]
FTC-101	8 (8M/0F) HIV-infected 35 (28-50) years	25 mg twice daily	59.5 (42%)	253 (41%)
	8 (7M/1F) HIV-infected 40 (27-59) years	100 mg twice daily	72.8 (27%)	244 (38%)
	8 (6M/2F) HIV-infected 33 (25-41) years	200 mg twice daily	74.2 (36%)	334 (47%)
	8 (6M/2F) HIV-infected 37 (27-48) years	100 mg once daily	67.6 (28%)	305 (24%)
	8 (8M/0F) HIV-infected 37 (29-42) years	200 mg once daily	65.2 (7%)	319 (15%)
FTC-106	6 (6M/0F) Healthy subjects 38 (33-43) years	200 mg (Day 1)	58.7 (16%)	194 (18%)
	5 (5M/0F) Healthy subjects 37 (33-42) years	200 mg once daily (Day 11[b])	62.1 (14%)	207 (14%)
FTC-107	6 (5M/1F) Healthy subjects 60 (47-74) years	200 mg	70.9 (36%)	213 (42%)
FTC-108	12 (9M/3F) Healthy subjects 35 (19-47) years	200 mg	47.0 (25%)	146 (32%)
FTC-110	12 (7M/5F) Healthy subjects 32 (21-44) years	200 mg	68.6 (20%)	228 (22%)
		200 mg oral solution	55.4 (15%)	240 (27%)
		200 mg IV	72.9 (6%)	227 (21%)

a Single oral dose for Study 143-001. CL_r values for Study 143-001 reported as mL/min/kg.
b 20 mL of 10 mg/mL FTC solution containing 250 µCi ^{14}C-labeled FTC.
Data are presented as mean (%CV). Urine collection interval of 24 hours for multiple-dose studies; and 24 hours for Study 143-001 and 48 hours for other single-dose studies.
Source: 143-001; FTC-101; FTC-106; FTC-107; FTC-108; FTC-110

3.1.2. Distribution

3.1.2.1. In Vitro/Nonclinical Studies

Protein binding of TAF was moderate in dog and human plasma with percentage unbound values of 48.0% and 46.8%, respectively. These in vitro values were higher than those observed in multiple human ex vivo studies with the mean percentage unbound TAF ranging from 14% to 23% in all subjects. Following oral administration of [^{14}C]TAF to rat, mouse, and dog, [^{14}C]TAF-derived radioactivity was widely distributed to most of the tissues in all species. Distribution studies in dogs showed 5.7- to 15-fold higher ^{14}C-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of [^{14}C]-TAF relative to [^{14}C]-TDF (D990173-BP; 97-DDM-4331-001) {7415}. Consistent with high hepatic extraction, high levels of radioactivity were observed in the liver; high radioactivity was also measured in the kidney. Low levels of radioactivity were observed in brain and testis in mouse. No melanin binding was observed in rats. Distribution trends in the pigmented uveal tract of the eye and pigmented skin suggested that [^{14}C]TAF-related radioactivity was not selectively associated with melanin-containing tissues in the pigmented mouse.

FTC is widely distributed in the body. After oral administration, the highest concentrations are found in the intestine and kidneys, consistent with its absorption and elimination via these tissues. Levels in central nervous system tissues reach approximately 2% to 9% of those in plasma.

The results of nonclinical studies investigating the distribution of FTC and TAF are discussed in detail in the Nonclinical Pharmacokinetics Written Summary (m2.6.4).

3.1.2.2. Clinical Studies

TAF

The protein binding of TAF was moderate in human plasma (based on human ex vivo studies), with mean percentage unbound TAF values ranging from 14% to 23% in Studies GS-US-120-0108 [Section 2.4.1.1] and GS-US-120-0114 [Section 2.4.1.2]. In a human ADME study, following administration of an oral 25-mg dose of [^{14}C]TAF in healthy subjects, the whole blood-to-plasma concentration ratio of ^{14}C-radioactivity increased from 0.6 at 0.25 hours postdose to 2.4 at 216 hours postdose, suggesting a relatively slower clearance of ^{14}C-radioactivity from blood cells relative to the plasma ^{14}C-radioactivity time-course (GS-US-120-0109 [Section 2.2.2.2]).

The distribution of TAF into compartments other than plasma (eg, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated.

FTC

The apparent volume of distribution of FTC determined in a number of studies is quite large with average V_z/F values ranging from 128 to 385 L following administration of 200 mg FTC in

capsules. Since the absolute BA (F) value for FTC given in the capsule formulation is close to 1 (0.93), the V_z/F value approximates the V_z value. This is reflected by the observation that the apparent volume of distribution after intravenous (IV) dosing (V_z), 242 L, is within the range of the V_z/F estimates following oral administration. The steady-state volume of distribution (V_{ss}) of FTC as determined following IV administration in Study FTC-110 averaged 109 L (or 1.43 L/kg), much larger than the total body water in a person with an average body weight of 70 kg (ie, 40 L). These data indicate that FTC is widely distributed throughout the body and it distributes to both the intracellular and extracellular fluid spaces.

After IV administration of FTC at a dose of 200 mg given by infusion over 60 minutes (Study FTC-110), FTC is eliminated from plasma with a $t_{1/2}$ of 9 hours, consistent with that observed after oral administration. The systemic clearance (CL) of FTC averaged 307 mL/min (4.03 mL/min/kg), and the estimated V_{ss} averaged 109 L (1.43 L/kg). The V_{ss} estimate is within the range estimated in animal species, but the CL estimate in man is 3- to 6-fold smaller than that in animals. The CL estimate as compared with hepatic blood flow indicates that FTC is a low extraction-ratio drug, as evidenced by its high absolute BA (93%).

Protein binding studies, reported in Study TBZZ/93/0025, revealed that the fraction of unbound FTC in plasma is > 96% in human plasma over a wide concentration range (0.02 to 200 µg/mL). This low level of protein binding for FTC suggests that drug interactions due to altered protein binding are unlikely to occur for FTC. FTC and its minor metabolites did not have a high affinity for red blood cells (Study FTC-106) since the plasma to blood concentration ratios for the parent drug and metabolites were about 1.0.

FTC appeared to be well distributed into white blood cells (Studies FTC-101 and FTC-106) since high levels of FTC 5′-triphosphate (FTC-TP; the intracellular anabolite of FTC) were measured in PBMCs, an active site for the antiviral action. FTC also has good penetration into semen as evidenced by 4-fold higher semen concentrations (approximately 5 µg/mL on average) than plasma concentrations determined at 1.5 to 3.5 hours postdose.

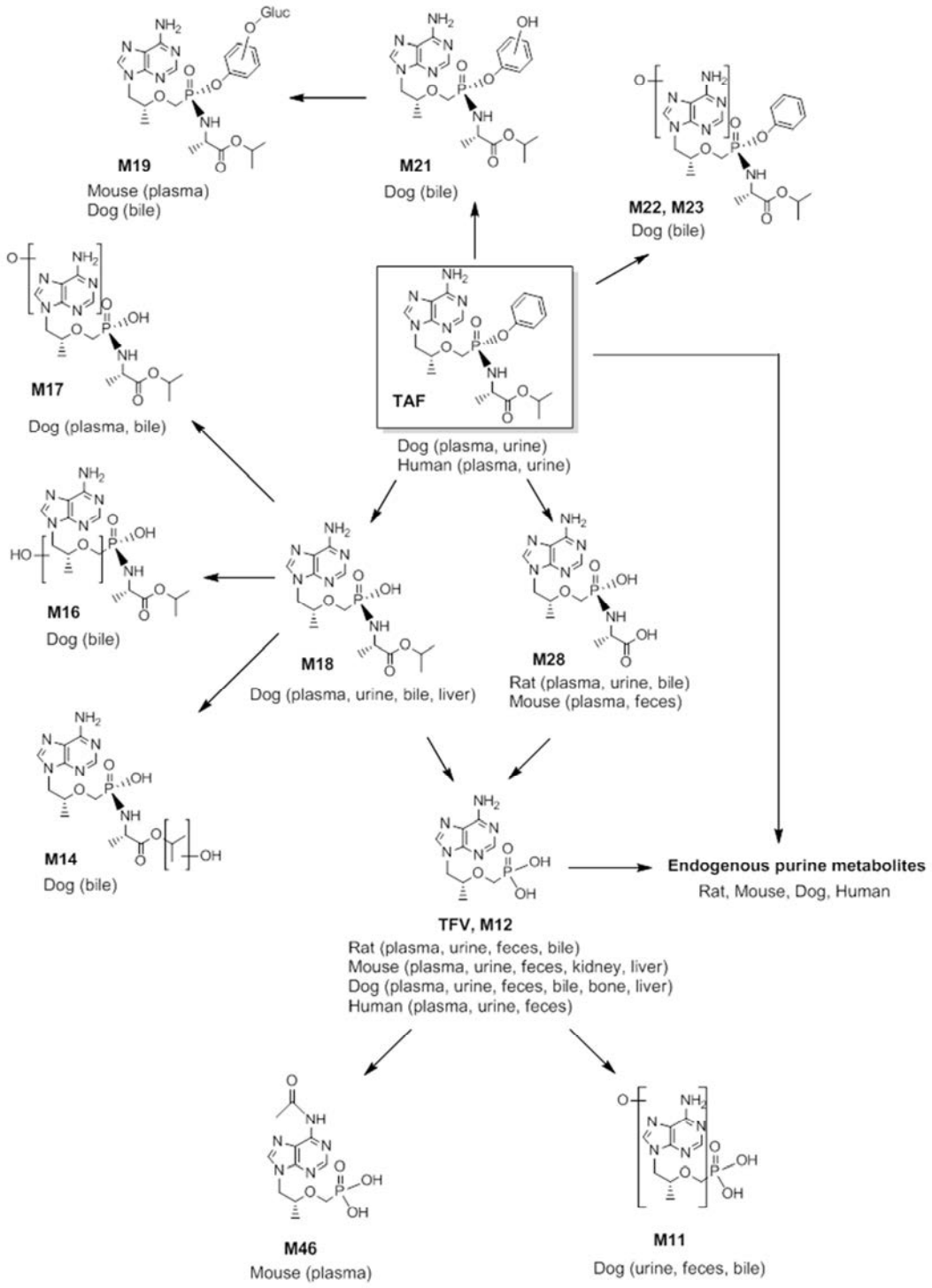
3.1.3. Metabolism and Elimination

3.1.3.1. In Vitro/Nonclinical Studies

The biotransformation of TAF was studied in mice, rats, dogs, and humans (Figure 3). Endogenous purine metabolites including hypoxanthine, xanthine, allantoin, and uric acid were observed in all species, including humans. TFV accounted for a majority of drug-related material in plasma, urine, and feces from all species, except for human plasma in which uric acid was the predominant metabolite, accounting for 73.9% of the total AUC over 96 hours. The major metabolite in rat bile was M18, which accounted for 63% of total radioactivity recovered in bile. M18 and its oxidized metabolite, M16, were the major metabolites in dog bile accounted for 29% and 38% of total radioactivity recovered in bile. Various oxidative metabolites were found in dog bile. No metabolites unique to human were observed. Following oral dosing of mice, rats, and dogs with [^{14}C]TAF, the majority of radiolabel was recovered in the feces or urine in all species. The elimination of a large amount of radioactivity in bile of bile duct-cannulated dogs indicates that biliary excretion is a major route of elimination of [^{14}C]TAF-derived radioactivity in dogs. Total recovery of radiolabel was high for all species.

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

Figure 3. Biotransformation Pathway of TAF



In radiolabel studies in mice, rats, and cynomolgus monkeys, metabolism accounts for only a minor percentage of FTC elimination. Only trace levels of metabolites were found in feces. Over 90% of the radioactivity in mouse and rat urine, and 64% of the radioactivity in monkey urine was unchanged drug. In human, unchanged FTC with 3 minor metabolites in urine accounted for essentially the entire dose recovered in urine (approximately 86%). The 3 putative metabolites were 2 sulfoxides (M1 and M2) and a glucuronide (M3) and they were also identified in other nonclinical species. Thus, FTC is not extensively metabolized and is eliminated primarily as unchanged drug by renal excretion. Based on these observations, it is unlikely that FTC will be subject to significant first pass metabolism, or to changes in clearance due to hepatic disease or metabolic drug interactions.

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

The results of nonclinical studies investigating metabolism and excretion are discussed in detail in the Nonclinical Pharmacokinetics Written Summary (m2.6.4).

3.1.3.2. Clinical Studies

TAF

TAF has a distinct metabolism profile designed to maximize both antiviral potency and clinical safety. Inside cells, TAF is converted by intracellular enzymes to form the pharmacologically active metabolite TFV-DP. Due to increased plasma stability and activation by CatA, as compared with TDF, TAF is more efficiently loaded into PBMCs (including lymphocytes and other HIV-target cells) and macrophages, which results in greater concentrations of TFV-DP in PBMCs and lower exposure of TFV to the systemic circulation and undesired tissues, including the kidney and bone.

Study GS-US-120-0109 evaluated the mass balance and PK of TAF following an oral dose of [^{14}C]TAF to healthy subjects (Section 2.2.2.2). TAF was extensively metabolized (> 80% of an oral dose) and excreted in feces and urine as the major metabolite, TFV. Metabolism of TAF to TFV was rapid, with median TAF plasma $t_{1/2}$ of 0.51 hours and a median TFV T_{max} of 3.25 hours postdose. TFV had a median plasma $t_{1/2}$ of 32.37 hours. The predominant species detected in feces (Table 43) and urine (Table 44) was TFV, with all other metabolites detected in trace amounts (no value exceeding 2% of the administered radioactive dose). Renal excretion of TAF as parent drug was a minor pathway (≤ 2%) (GS-US-120-0108, Section 2.4.1.1).

Human data are consistent with the established nonclinical profile of TAF.

Table 43. TAF Study GS-US-120-0109: Percent of Total ^{14}C-Radioactivity Present as [^{14}C]TAF Metabolites in Pooled Feces From All Sampling Intervals by High-Performance Liquid Chromatography

[^{14}C]TAF Metabolite	Mean (SD) Percent of Total Radioactivity
TFV	31.4 (10.4)
M29	0.224 (0.328)
M43	0.0628 (0.178)

Source: GS-US-120-0109, Section 15.1, Table 8.1

Table 44. TAF Study GS-US-120-0109: Percent of Total ^{14}C-Radioactivity Present as [^{14}C]TAF Metabolites in Pooled Urine From All Sampling Intervals by High-Performance Liquid Chromatography

[^{14}C]TAF Metabolite	Mean (SD) Percent of Total Radioactivity
TFV	22.2 (4.47)
M27B	1.93 (1.72)
M7/M8	0.258 (0.372)
TAF	1.41 (0.561)

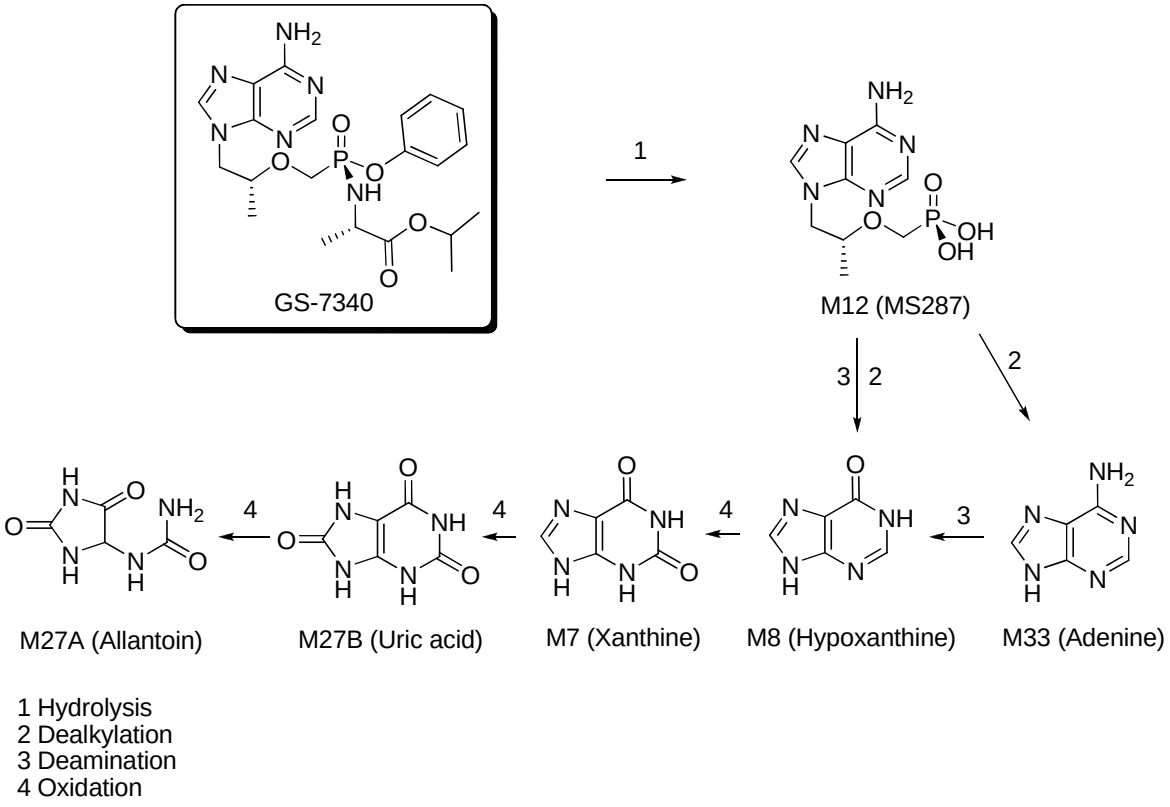
Source: GS-US-120-0109, Section 15.1, Table 7.1

Following administration of TAF, plasma ^{14}C-radioactivity showed a time-dependent profile with TAF as the most abundant species in the initial few hours and uric acid in the remaining period.

With regard to [^{14}C]TAF metabolites, in addition to TFV and uric acid, low quantities of other metabolites were formed, including xanthine, hypoxanthine, and adenine. They are identical to the endogenous products of purine metabolism and, as such, are not associated with safety risk.

A proposed biotransformation pathway for [^{14}C]TAF is shown in Figure 4. TAF is primarily metabolized via the purine catabolic pathway following conversion to TFV.

Figure 4. Proposed Biotransformation Pathway of TAF in Humans

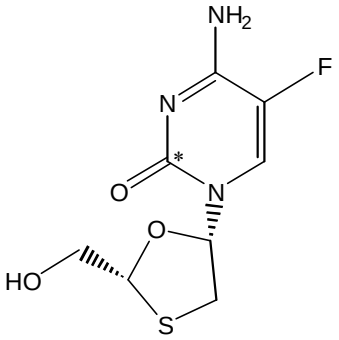


Pathways are proposed based on general knowledge of metabolism and do not imply definitive pathways. Direct experimentation was not performed.
Source: GS-US-120-0109, Appendix 16.10, Figure 11

FTC

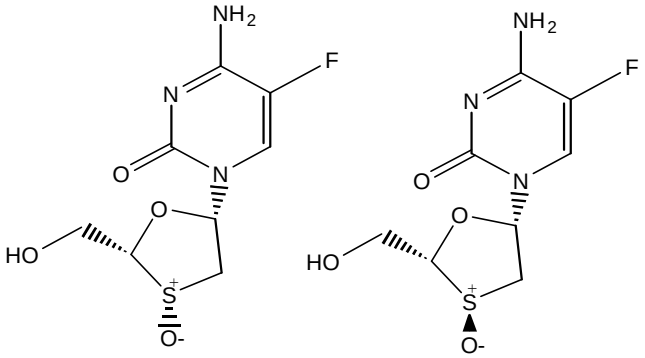
FTC is primarily eliminated from the plasma via renal excretion as unchanged drug (approximately 65% of an oral dose and approximately 73% of an IV dose). Metabolism is a minor route of elimination. In a mass balance study with [^{14}C]FTC, an average of 65% to 70% of an oral FTC dose was excreted in urine as unchanged drug, accounting for ~80% of the total radioactivity present in urine (Study FTC-106). Approximately 13% of an oral dose was recovered in the urine (12.9%) and in feces (0.01%) as metabolites. Three putative metabolites were isolated, with structures tentatively identified by mass spectrometry (Figure 5).

Figure 5. Putative Metabolites of FTC

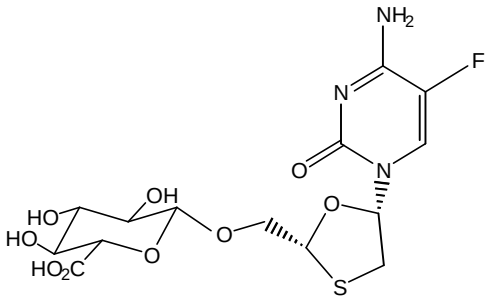


Emtricitabine (FTC)

*:indicates the site of ^{14}C label



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



M3 (2′-O-Glucuronide of Emtricitabine)

Source: FTC-106, Section 3.6.5.3, Figure A

Metabolite M2 was the predominant metabolite of the 3, with its urinary recovery accounting for 8.7% of the dose administered. M2 was sporadically quantifiable in plasma samples of 2 of 5 subjects, and when measurable, plasma M2 concentrations were 30- to 50-fold lower than plasma FTC concentrations at corresponding time points. Urinary recoveries of metabolites M1 and M3 accounted for only 0.3% and 4% of the dose administered, respectively. These 3 metabolites along with unchanged FTC in urine accounted for essentially the entire dose recovered in urine (~86%).

Two clinical studies (FTC-101 and FTC-106) also show that FTC is effectively metabolized intracellularly in PBMCs (the active site for the anti-HIV action) to form its active metabolite, FTC-TP. In Study FTC-106, 99.6% of the total radioactive dose was recovered in urine and feces, and 91.5% of the dose was accounted for as FTC and 3 identifiable metabolites. The remaining ~8% of the dose in urine/feces could represent the unidentifiable metabolites resulting from the intracellular catabolism of FTC-TP.

Studies in animals and humans have shown that FTC undergoes little metabolism; therefore, coadministered drugs known to affect drug metabolism, especially pathways mediated by CYP, would not be expected to have a significant effect on the metabolism of FTC. Furthermore it is unlikely that FTC is an inducer or inhibitor of CYP as other structurally related nucleoside analogs, such as lamivudine (3TC), are not known to affect drug metabolism of coadministered agents.

The results of a second in vitro study lend further support to the low level of metabolism observed in in vivo studies conducted in rats, monkeys, and humans (15396v1). The study investigated the metabolism of FTC using complementary DNA (cDNA)-expressed human CYP isoenzymes and pooled human liver microsomes. At 2 concentrations (5 and 50 μM), FTC was incubated with various cDNA-expressed human CYP isoenzymes to detect the formation of the metabolites in a time-dependent manner, thus allowing the identification of the major human CYP isoenzyme(s) responsible for its metabolism. To confirm this identification, a second approach was used in which the metabolism of FTC was investigated with incubations of pooled human liver microsomes in the presence and absence of selective inhibitors of the major human CYPs (15247).

The results show that FTC was relatively stable in the incubation medium. One minor metabolite (~1%) was detected in cDNA-expressed CYP 3A4 incubations only. It was not formed by any other isoenzyme investigated (CYP 1A2, 2A6, 2B6, 2D6, 2E1, 2C8, 2C9, or 2C19), indicating that CYP 3A4 was the sole CYP isoenzyme responsible for the metabolism of FTC. Microsomal incubations in the presence and absence of selective inhibitors of various CYPs confirmed the low rate of FTC metabolism, and also suggest the possible involvement of flavin adenine dinucleotide-containing monooxygenase enzymes in the metabolism of FTC.

The results of in vitro studies confirm that FTC is a poor substrate for the human CYP system, and lacks inhibitory activity for the major CYP isoenzymes.

FTC is primarily eliminated from plasma as unchanged FTC in urine (about 65% to 70% of an oral dose), with an elimination $t_{1/2}$ of 9 to 10 hours. Due to the multiexponential (generally triphasic) decay characteristics of the plasma FTC concentration versus time curves, plasma $t_{1/2}$ estimates for FTC could vary depending on the duration of plasma sampling period and the time points chosen for log-linear regression analysis. The terminal $t_{1/2}$ of FTC could be as long as 29 hours in plasma when sampling time was extended to 108 hours postdose at steady-state. However, the $t_{1/2}$ estimate determined over the steady-state daily (24-hour) dosing interval, averaging 9 to 10 hours, appeared to be the most clinically relevant plasma $t_{1/2}$ estimate for FTC. This $t_{1/2}$ estimate is consistent with the observation that steady-state condition for FTC was achieved within 3 days (Study FTC-106).

The average percentage of an FTC dose excreted as unchanged drug in urine ranged from 47% to 74% (averaging ~65%) in adults with normal renal function (Table 42).

Mean renal clearance values for FTC ranged from 146 to 334 mL/min (averaging ~210 mL/min) across all studies and over a wide dose range. The ratio between renal clearance and total body clearance (210/307 = 0.68) is consistent with the fraction of dose excreted in urine as the unchanged drug. Renal clearance values in subjects with normal renal function were consistently greater than the estimated CL_{cr} values. Thus, the observed renal clearance values are consistent with net renal tubular secretion of FTC.

Fecal excretion accounted for an average of 13.7% of the administered radioactive dose in Study FTC-106. Unchanged FTC represented 96% of the total radioactivity recovered in feces. The majority (~86%) of the radioactive dose recovered in the feces was excreted in the 48- to

96-hour interval after dosing. This delayed excretion of radioactivity, primarily as FTC, in feces (intestinal tract) suggests that intestinal secretion of FTC occurs via an efflux transporter.

The fact that FTC is primarily eliminated in urine as unchanged drug with very little metabolism, especially very minor Phase 1 oxidative metabolism, suggests that this drug presents a low potential for PK drug interactions at the level of hepatic or other organ metabolism.

3.1.3.3. Cytochrome P450 Interaction Potential

The potential for TAF, or its major metabolite TFV, to inhibit or induce major human drug metabolizing CYPs was examined in vitro using hepatic microsomal fractions and enzyme selective activities (AD-120-2003 and V990172-104). Of the human enzymes evaluated, TAF had little or no inhibitory effect (concentration that resulted in 50% inhibition [IC_{50}] > 25 μM) on any other than CYP3A, the inhibition of which was relatively weak (IC_{50} ~ 7.5 μM). In primary human hepatocytes, TAF showed little or no potential for induction of CYP activity at clinically relevant concentrations. In assays with recombinant enzymes, TAF was not a substrate for CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6; metabolism of TAF with CYP3A4 was detectable in assays but was comparatively low (AD-120-2004). Based on the totality of data, TAF is not expected to have clinically meaningful CYP-mediated interaction potential.

The results of in vitro studies confirm that FTC is a poor substrate for the human CYP system, and lacks inhibitory activity for the major CYP isoenzymes. Based on the totality of data, FTC administered as F/TAF does not have CYP-mediated interaction potential.

The clinical DDI potential of F/TAF is discussed further in Section 3.2.3.2.

3.1.3.4. Inhibition Potential of F/TAF Components on Human Drug Transporters

Results from all transporter substrate studies are summarized in Table 45. In addition to being a substrate of P-gp (as discussed in Section 3.1.1.2), TAF is a substrate of breast cancer resistance protein (BCRP), OATP1B1, and OATP1B3.

Table 45. Transporter Substrate Assessment of F/TAF Components

	Substrate Assessment (yes/no)		
Transporter	**FTC**	**TAF**	**TFV**
P-gp	no	yes	no
BCRP	no	yes	no
OATP1B1	ND	yes	ND
OATP1B3	ND	yes	ND
OAT1	no	no	yes
OAT3	yes	no	yes
OCT1	ND	no	no
OCT2	no	ND	no
MRP1	ND	ND	no
MRP2	no	ND	no
MRP4	ND	ND	yes

Source: m2.6.4, Section 7

Results from all transporter inhibition studies are summarized in Table 46. Because at clinically relevant concentrations TAF, TFV, and FTC do not inhibit any of the transporters tested in vitro, they are unlikely to be perpetrators of transporter-mediated drug interactions.

Table 46. Transporter Inhibition Assessment of F/TAF Components

Transporter	IC_{50} (μM)		
	TAF	TFV	FTC
P-gp	> 100	> 1000	> 100
BCRP	> 100	> 100	> 100
BSEP	> 100	> 100	> 100
OATP1B1	> 100	> 100	> 100
OATP1B3	> 100	> 100	> 100
MATE1	> 100	> 300	> 100
MATE2-K	ND	ND	ND
OAT1	> 100	33.8[a]	> 100
OAT3	> 100	> 1000	> 100
OCT1	> 100	> 100	> 100
OCT2	> 100	> 300	> 100
OCTN1	ND	ND	ND
MRP1	ND	> 500	ND
MRP2	ND	> 100	> 100
MRP4	ND	> 1000[b]	> 100

a Binding constant for uptake into CHO cells {2520}.
b {10260}
Source: m2.6.4, Section 7

3.2. Pharmacokinetics

3.2.1. Pharmacokinetic Profile

3.2.1.1. Single- and Multiple-Dose Pharmacokinetics

3.2.1.1.1. Pharmacokinetics of TAF After Single- and Multiple-Dose Administration in HIV-Infected and Healthy Subjects

TAF

The PK profile of TAF has been evaluated in 21 Phase 1 studies, 2 Phase 2 studies, 1 Phase 2/3 study, and 4 Phase 3 studies. The TAF PK profile has been characterized following single doses and at steady-state in healthy and HIV-infected individuals at doses ranging from 8 to 125 mg. Overall, TAF behaved dose proportionally and in a linear manner across the range of doses

studied. The TAF PK profile is characterized by rapid absorption, with a median plasma T_{max} of approximately 0.50 hours, and rapid elimination, with a median plasma $t_{1/2}$ of approximately 0.40 hours and BLQ plasma concentrations by approximately 5 hours postdose (Study GS-US-120-0104). Due to the short plasma $t_{1/2}$, TAF does not accumulate in plasma.

Bioequivalence between the TAF and FTC components of each F/TAF FDC and the TAF and FTC components of E/C/F/TAF was established in 2 pivotal Phase 1 BE Studies GS-US-311-1473 and GS-US-311-1472. Study GS-US-311-1473 demonstrated bioequivalent TAF exposure between F/TAF 200/25 mg and E/C/F/TAF, and Study GS-US-311-1472 demonstrated bioequivalent TAF exposure between F/TAF 200/10 mg administered simultaneously with EVG and COBI and E/C/F/TAF (Table 47).

Table 47. F/TAF Studies GS-US-311-1473 and GS-US-311-1472: Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (TAF PK Analysis Sets)

TAF PK Parameter	Test		Reference		GLSM Ratio (90% CI), %
	n	Mean (%CV)	n	Mean (%CV)	
F/TAF Study GS-US-311-1473					
F/TAF (200/25 mg; Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32 (96.48, 104.31)
AUC_{inf} (ng•h/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54 (94.61, 102.62)
C_{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63 (95.46, 112.49)
F/TAF Study GS-US-311-1472					
F/TAF (200/10 mg) +EVG+COBI (Test) vs E/C/F/TAF (Reference)					
AUC_{last} (ng•h/mL)	97	336.6 (33.9)	99	340.2 (33.8)	97.96 (94.69,101.34)
AUC_{inf} (ng•h/mL)	97	351.8 (31.0)	99	354.1 (32.9)	98.34 (94.81,101.99)
C_{max} (ng/mL)	97	301.6 (48.8)	99	310.3 (48.7)	96.86 (89.36,104.99)

Source: Table 5 and Table 6

TFV

The PK profile of TFV, the major metabolite of TAF, has been evaluated in 18 Phase 1 studies, 2 Phase 2 studies, 1 Phase 2/3 study, and 4 Phase 3 studies. The TFV PK profile is characterized by rapid emergence in plasma following TAF dosing, with a median plasma T_{max} ranging from 0.25 to 3 hours postdose, and slow elimination, with a median plasma $t_{1/2}$ of 32.37 hours.

Intracellular TFV-DP

Exploratory PK data from the ongoing Study GS-US-311-1089 in HIV-infected subjects provide a direct comparison of intracellular concentrations of the active phosphorylated metabolite TFV-DP between F/TAF and FTC/TDF in combination with various third agents (Table 48). F/TAF administration resulted in intracellular TFV-DP concentrations that were > 4-fold higher relative to FTC/TDF administration. This finding is consistent with results from E/C/F/TAF studies (Section 3.3.1.1).

Table 48. F/TAF Study GS-US-311-1089: Statistical Comparisons of Intracellular PBMC TFV-DP Concentrations Between Test and Reference Treatments (PBMC PK Analysis Set)

	Intracellular PBMC TFV-DP Concentration (pg/10^6 cells)[a]	
	F/TAF[b] (Test) (N = 304)[c]	FTC/TDF (Reference) (N = 265)[c]
Geometric Mean (95% CI)	114.001 (100.899, 128.804)	27.781 (24.799, 31.122)
GLSM	113.541	27.287
GLSM Ratio (90% CI), %	416.100 (362.390,477.771)	

a For each subject, a trough blood sample was collected at Week 4, Week 8, or Week 12.
b One subject, whose third agent was RAL, was incorrectly enrolled into the F/TAF 10-mg stratum and received randomized study drug. This subject was excluded in this summary.
c Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie, sample age ≥ 61 days)
Source: Appendix 6.4, Table 54.1 and Table 57.1

Intracellular TFV-DP concentrations for subjects who received F/TAF in Study GS-US-311-1089 are summarized by third agent in Table 49 (unboosted third agents) and Table 50 (RTV-boosted PIs). Of note, the number of subjects in each subgroup varied from n = 1 to n = 82; the intracellular TFV-DP concentration in subgroups with only a small number of subjects (ie, EFV, maraviroc [MVC], or RPV) should be interpreted with caution. Overall, geometric mean intracellular TFV-DP concentrations ranged from 54.224 to 268.000 pg/10^6 cells. These results suggest that intracellular TFV-DP loading tracks closely with plasma TAF exposures upon coadministration with various third agents, which served as basis for F/TAF dose recommendations (Sections 3.2.3.2.4 and 3.2.3.2.5).

Table 49. F/TAF Study GS-US-311-1089: Summary of Intracellular PBMC TFV-DP Concentrations for Subjects Who Received F/TAF (200/25 mg) by Unboosted Third Agent (PBMC PK Analysis Set)

	Geometric Mean (95% CI) by Unboosted Third Agent						
	+ DTG (N=24)	+ EFV (N=8)	+ MVC (N=1)	+ NVP (N=65)	+ RAL (N=55)	+ RPV (N=3)	Total (N=156)
Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	106.571 (70.145, 161.913)	54.224 (20.281, 144.976)	268.000 (NA)	137.937 (102.738, 185.196)	167.293 (122.471, 228.519)	161.478 (1.146, 22,750.113)	136.257 (113.167, 164.058)

Source: Appendix 6.4, Table 56.1.2

Table 50. F/TAF Study GS-US-311-1089: Summary of Intracellular PBMC TFV-DP Concentrations for Subjects Who Received F/TAF (200/10 mg) by RTV-Boosted Third Agent (PBMC PK Analysis Set)

	Geometric Mean (95% CI) by RTV-Boosted Third Agent			
	+ ATV+RTV (N=50)	+ DRV+RTV (N=82)	+ LPV/r (N=16)	Total (N=148)
Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	126.292 (96.649, 165.027)	78.879 (64.028, 97.175)	96.052 (66.029, 139.725)	94.465 (81.047, 110.103)

Source: Appendix 6.4, Table 56.1.1

3.2.1.1.2. Pharmacokinetics of FTC After Single- and Multiple-Dose Administration in Healthy Subjects

Single- and multiple-dose PK studies have shown that FTC is rapidly and extensively absorbed after oral administration. Plasma FTC concentrations were measurable at the earliest sampling time (15 minutes postdose) and reached a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1200 mg) and then followed an apparent multiexponential decay from the plasma. Greater than 85% of an oral dose of FTC is absorbed with little first-pass elimination prior to reaching the systemic circulation, resulting in a high absolute bioavailability value (93% as shown in Study FTC-110). FTC PK parameter estimates after a single oral 200 mg dose are summarized in Table 51 and the steady-state PK parameter estimates of FTC following 200-mg once-daily dosing, the therapeutic dose within the F/TAF FDCs, are summarized in Table 52.

At the therapeutic dose (200 mg once daily given as the capsule formulation), the steady-state peak plasma FTC concentration averaged approximately 2 µg/mL FTC disposition follows linear, first-order kinetics, with steady-state plasma FTC concentration-time profiles predictable based on single-dose data. The steady-state plasma AUC over the 24-hour dosing interval following 200 mg once daily averaged 10 µg•h/mL, which was comparable with the $AUC_{0\text{-inf}}$ value following a single-dose administration and was consistent with the PK principle.

Table 51. Summary of PK Parameter Estimates for FTC Following a Single Dose of FTC 200 mg Administered as the Capsule Formulation in Healthy and HIV-Infected Subjects

Study No.	$AUC_{0\text{-inf}}$ (µg•h/mL)	C_{max} (µg/mL)	T_{max} (h)	$t_{1/2}$ (h)
143-001 (N = 12)	9.16 (15)	2.12 (30)	1.27 (42)	2.84 (21)
FTC-101 (N = 16)	6.72 (18)	1.59 (30)	1.70 (56)	2.90 (12)
FTC-106 (N = 6)	10.42 (6)	2.14 (15)	1.17 (22)	11.97 (23)
FTC-107 (N = 6)	11.78 (25)	2.20 (29)	1.84 (51)	14.19 (24)
FTC-108 (N = 12)	11.30 (10)	2.35 (20)	1.17 (21)	11.00 (9)
FTC-109 (N = 12)	10.95 (14)	2.40 (18)	1.13 (34)	6.76 (15)
FTC-110 (N = 12)	10.37 (17)	2.24 (19)	1.21 (32)	8.89 (12)
FTC-111 (N = 24)	9.66 (21)	2.01 (26)	1.08 (27)	5.89 (18)

Data are presented as mean (%CV).
Source: 143-001; FTC-101; FTC-106; FTC-107; FTC-108; FTC-109; FTC-110; FTC-111

Table 52. Summary of Steady-State PK Parameter Estimates for FTC Following Once-Daily Dosing of FTC 200 mg

Study No.	AUC_{tau} (h•µg/mL)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$T_{max,ss}$ (h)	$t_{1/2}$ (h)
FTC-101 (N = 8)	8.00 (15)	1.72 (53)	0.05 (24)	2.00 (48)	8.24 (31)
FTC-106 (N = 5)	10.04 (18)	1.72 (16)	0.07 (28)	1.00 (0)	10.2 (19)
FTC-303 (N = 12)	11.31 (29)	1.94 (24)	0.11 (71)	1.80 (58)	8.08 (32)

Data are presented as mean (%CV).
Source: FTC-101; FTC-106; FTC-303

Additionally, the PK of FTC has been extensively characterized previously and FTC exposures were shown to be comparable with STB across E/C/F/TAF Phase 1 and Phase 2 studies (Table 53). As such, only the PK of the new study drug TAF was evaluated in the Phase 3 pivotal studies.

Table 53. Summary of Steady-State PK Parameter Estimates for FTC Following Once-Daily STB or E/C/F/TAF Administration

FTC PK Parameter	STB Phase 2 and 3 (N = 62)	E/C/F/TAF Phase 1 (N = 19)	E/C/F/TAF Phase 2 (N = 19)
AUC_{tau} (ng•h/mL)	12,737.0 (35.3)[a]	12,352.6 (13.5)	11,714.1 (16.6)
C_{max} (ng/mL)	1884.8 (27.1)	1947.0 (21.2)	2056.3 (20.2)
C_{tau} (ng/mL)	142.0 (174.2)[a]	107.4 (25.8)	95.2 (46.7)

a n = 61; AUC_{tau} and C_{tau} were not calculated for Subject *AB for any analyte because concentration values were missing for some postdose time points.
Data are presented as mean (%CV).
Source: STB PK/PD Table 2.3; GS-US-292-0103, Section 15.1, Table 4.2.3; GS-US-292-0102, Section 15.1, Table 51.3

3.2.1.2. Population Pharmacokinetics

3.2.1.2.1. TAF

TAF

The final population model that best described TAF PK was a 2-compartment model with absorption lag time and sequential zero- and first-order absorption.

The typical apparent systemic TAF CL/F was estimated to be 56.3 L/h, the apparent volume of the central compartment (V_c/F) was 10.3 L, and the apparent volume of peripheral compartment (V_p/F) was 447 L. TAF was absorbed at a typical rate of 1.83 h^{-1} with a lag time of 0.134 hours.

Population PK covariate analyses indicated no statistically significant or clinically relevant influence on TAF exposure based on body size measures (body weight, body surface area, or BMI), age, sex, race, $eGFR_{CG}$ at baseline, or population (healthy subjects versus ART-naive HIV-infected subjects versus ART-experienced HIV-infected subjects) (Section 3.2.2).

For population PK analyses, the intersubject variability in TAF exposure varied across studies depending on whether intensive or sparse sampling was employed (%CV: 26% to 34% across Phase 1 studies and 58% to 118% across Phase 2 and Phase 3 studies).

For a typical reference subject (nonblack, male, HIV-infected subject, CL_{cr} =100 mL/min), the predicted steady-state TAF PK values were 188.1 ng•h/mL for AUC and 165.6 ng/mL for C_{max}. In the pitoval E/C/F/TAF studies (GS-US-292-0104 and GS-US-292-0111), the mean (95% CI, %CV) predicted individual steady-state TAF PK values were 206.4 ng•h/mL (55.6 to 526.1 ng•h/mL, 71.8%) for AUC and 162.2 ng/mL (46.5 to 340 ng/mL, 51.1%) ng/mL for C_{max}.

TFV

The final population model that best described TFV (the major metabolite of TAF) was a 2-compartment model with sequential zero- and first-order absorption. The typical apparent systemic TFV CL/F was estimated to be 30.2 L/h, the V_c/F was 1600 L, and the V_p/F was 1670 L. TFV was absorbed at a typical rate of 2.33 h^{-1}.

Based on population PK analyses, the main covariate that influenced the PK of TFV was, as expected based on its renal route of elimination, baseline $eGFR_{CG}$. For subjects with $eGFR_{CG}$ of 50 mL/min, CL/F, V_c/F, and V_p/F were 44%, 44%, and 65% lower, respectively, than for typical subjects ($eGFR_{CG}$ of 100 mL/min), while in subjects with $eGFR_{CG}$ of > 150 mL/min, the respective values were 40%, 40%, and 85% higher, respectively, than for typical subjects. In addition, CL/F was 11% lower in males versus females and 12% higher in blacks versus nonblacks. The V_c/F and V_p/F were 67% and 36% lower, respectively, in healthy subjects compared with HIV-infected subjects. The influence of the remainder of the statistically significant covariates on TFV exposure (AUC, C_{max}, and C_{min}) were minor and not considered to be clinically meaningful, as the systemic TFV exposure following E/C/F/TAF is > 90% lower compared with STB.

For population PK analyses, the intersubject variability in TFV exposure was generally modest/low and comparable across studies (%CV: 18% to 41% across Phase 2 and Phase 3 studies).

For a typical reference subject (nonblack, male, HIV-infected subject, CL_{cr} =100 mL/min), the predicted steady-state TFV PK values were 331.2 ng•h/mL for AUC, 16.9 ng/mL for C_{max}, and 12.1 ng/mL for C_{min}. In the pitoval E/C/F/TAF studies (GS-US-292-0104 and GS-US-292-0111), the mean (95% CI, %CV) predicted individual steady-state TFV PK values were 292.6 ng•h/mL (179.8 to 445.7 ng•h/mL, 27.4%) for AUC, 15.2 ng/mL (9.3 to 23.1 ng/mL, 26.1%) for C_{max}, and 10.6 ng/mL (6.4 to16.6 ng/mL, 28.5%) for C_{min}.

Further details on the population PK for TAF and TFV are presented in the population PK report (TAF Population PK Report).

3.2.1.2.2. FTC

As expected from the renal elimination pathway of FTC and based on simple linear regression analysis and ANOVA, followed by stepwise multiple linear regression analysis, $eGFR_{CG}$ was the most important covariate affecting the overall plasma exposure to FTC. The effect of renal impairment on FTC PK is discussed in Section 3.2.2.1.1.2. Additional covariates involved in the calculation of $eGFR_{CG}$ value, including age, sex, and body weight, were secondarily important in influencing FTC exposures due to their effect on $eGFR_{CG}$ and consequently overall clearance. No other clinically relevant effects of intrinsic or extrinsic factors were observed on FTC PK.

Further details on the population PK for FTC are presented in the population PK report (13542v1).

3.2.1.3. Integrated Ad Hoc PK Analysis of TAF 25 mg Compared With TAF 10 mg + COBI

In support of the Population PK analyses and to further characterize TAF and TFV single- and multiple-dose PK, an integrated ad hoc PK analysis was performed using data from studies conducted with TAF 25 mg and TAF 10 mg + COBI (Section 1.6). The overall findings from the integrated ad hoc PK analysis were consistent with and supportive of those from the population PK analysis.

TAF

Based on the integrated ad hoc PK analysis, TAF exposure following administration of TAF 25 mg was similar to that observed following administration of TAF 10 mg + COBI, with mean AUC_{last} values between 251.8 and 322.0 ng•h/mL and mean C_{max} values between 209.8 and 289.0 ng/mL (m5.3.5.3, Integrated Ad Hoc PK Analysis, Table In-text1). There was no evidence of accumulation or time-dependent kinetics.

TFV

Based on the integrated ad hoc PK analysis, TFV exposure following administration of TAF 25 mg was similar to that observed following administration of TAF 10 mg + COBI, with mean AUC values between 260.2 and 318.5 ng•h/mL and mean C_{max} values between 8.2 and 18.3 ng/mL (m5.3.5.3, Integrated Ad Hoc PK Analysis, Table In-text2). Consistent with linear PK, TFV single-dose exposures (AUC_{inf}) were comparable with exposures following multiple dosing (AUC_{tau}).

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

3.2.1.4.1. TAF

TAF

Using population PK modeling, data from HIV-infected subjects (pivotal E/C/F/TAF Phase 3 Studies GS-US-292-0104 and GS-US-292-0111) were compared with those from healthy subjects (E/C/F/TAF Studies GS-US-292-0103, GS-US-292-0108, and GS-US-292-0110) following multiple-dose administration of E/C/F/TAF.

Based on population PK analyses, HIV disease status did not have an effect on TAF exposure and was not a statistically significant or clinically relevant covariate (Table 54; TAF Population PK Report).

Table 54. Population PK Analysis: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF by Subject Population

TAF PK Parameter	E/C/F/TAF	
	Healthy Subjects (N = 79)[a]	HIV-Infected Subjects (N = 539)[b]
AUC_{last} (ng•h/mL)	250 (31.6)	206 (71.8)
C_{max} (ng/mL)	178 (46.4)	162 (51.1)

a Subjects from Studies GS-US-292-0103, GS-US-292-0108, and GS-US-292-0110
b Subjects from Studies GS-US-292-0104 and GS-US-292-0111
Data are presented as mean (%CV).
Source: TAF Population PK Report

In support of the population PK analyses, an integrated ad hoc PK analysis was performed using data from studies conducted with TAF 25 mg or TAF 10 mg + COBI (Table 3).

Based on descriptive summaries of TAF PK parameters from the integrated ad hoc PK analysis, there were no clinically relevant differences in TAF exposure between healthy and HIV-infected subjects (Table 55).

Table 55. Integrated PK Analysis: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF 25 mg or TAF 10 mg + COBI by Subject Population (TAF PK Analysis Set)

TAF PK Parameter	TAF 25 mg		TAF 10 mg + COBI	
	Healthy Subjects (N = 432)	HIV-Infected Subjects (N = 8)	Healthy Subjects (N = 330)	HIV-Infected Subjects (N = 54)
AUC_{last} (ng•h/mL)	270.2 (48.95)	127.4 (48.96)	311.1 (40.06)	239.8 (56.04)
C_{max} (ng/mL)	220.3 (58.57)	227.7 (66.42)	279.0 (52.69)	228.6 (60.80)

Data are presented as mean (%CV).
Source: m5.3.5.3, Integrated Ad Hoc PK Analysis, Table In-text3

TFV

Based on population PK covariate analyses of data from healthy and HIV-infected subjects who were administered E/C/F/TAF (Table 2), 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 as shown in Table 56. As such, the observed relationship between disease status and TFV exposure is not considered to be clinically relevant.

Table 56. Population PK Analysis: Summary of PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF by Subject Population

TFV PK Parameter	E/C/F/TAF	
	Healthy Subjects (N = 79)[a]	HIV-Infected Subjects (N = 841)[b]
AUC_{tau} (ng•h/mL)	307 (22.7)	293 (27.4)
C_{max} (ng/mL)	21.2 (23.9)	15.2 (26.1)
C_{min} (ng/mL)	10.0 (27.6)	10.6 (28.5)

a Subjects from Studies GS-US-292-0103, GS-US-292-0108, and GS-US-292-0110
b Subjects from Studies GS-US-292-0104 and GS-US-292-0111
Data are presented as mean (%CV).
Source: TAF Population PK Report

3.2.1.4.2. FTC

In general, FTC PK parameter estimates following oral administration are characterized by relatively low intersubject variability, and consistent PK data have been observed between healthy subjects and HIV-infected subjects (Table 57). This is likely a result of the high oral bioavailability and the fact that FTC is primarily excreted unchanged in the urine (~65% to 70% of an oral dose) rather than metabolized (< 13% of an oral dose).

Table 57. Summary of Steady-State PK Parameter Estimates for FTC Following Once-Daily Dosing of FTC 200 mg

Study No	Number (M/F) Type Age: Mean (range)	$C_{max,ss}$ (µg/mL)	$T_{max,ss}$ (h)	$C_{min,ss}$ (µg/mL)	AUC_{tau} (h•µg/mL)	$t_{1/2}$ (h)	CL_{ss}/F (mL/min)
FTC-101	8 (8M/0F) HIV-infected subjects 37 (29-42) years	1.72 (53%)	2.00 (48%)	0.05 (24%)	8.00 (15%)	8.24 (31%)	425 (15%)
FTC-106	5 (5M/0F) Healthy subjects 37 (33-42) years	1.72 (16%)	1.00 (0%)	0.07 (28%)	10.04 (18%)	10.2 (19%)	339 (20%)
FTC-303	12 (1M/11F) HIV-infected subjects 38 (21-61) years	1.94 (24%)	1.80 (58%)	0.11 (71%)	11.31 (29%)	8.08 (32%)	317 (27%)

Data are presented as mean (%CV).
Source: FTC-101; FTC-106; FTC-303

3.2.2. Effect of Intrinsic Factors

3.2.2.1. End Organ Dysfunction

3.2.2.1.1. Renal Impairment

3.2.2.1.1.1. TAF

Pharmacokinetic data, and relevant safety data, support administration of F/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min).

TAF

An open-label study was performed to evaluate the PK of TAF and its metabolite TFV in non−HIV-infected subjects with severe renal impairment (defined as subjects with $eGFR_{CG}$ between 15 mL/min and 29 mL/min [inclusive] who were not on dialysis) and in age- and sex-matched non−HIV-infected subjects with normal renal function ($eGFR_{CG} \geq 90$ mL/min) following a single dose of TAF (Study GS-US-120-0108).

Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure (as assessed by AUC_{inf}) relative to age- and sex-matched subjects with normal renal function (Table 58). These data supported the conduct of a clinical study to evaluate the safety and efficacy of E/C/F/TAF in HIV-infected subjects with mild to moderate renal impairment (Study GS-US-292-0112).

Table 58. TAF Study GS-US-120-0108: Statistical Comparisons of TAF PK Parameter Estimates in Non–HIV-Infected Between Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

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

Source: GS-US-120-0108, Section 15.1, Tables 4.1 and 6.1

A Phase 3 PK substudy (n = 30) evaluating the PK of TAF following administration of E/C/F/TAF was performed in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min at screening, and showed mean (%CV) TAF exposure (AUC) of 254.2 (54.1) ng•h/mL (n = 29 for this parameter; Study GS-US-292-0112). The TAF exposure was numerically higher in subjects with baseline $eGFR_{CG} < 50$ versus ≥ 50 mL/min. These Phase 3 data are consistent with results from the renal impairment study, GS-US-120-0108.

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, baseline $eGFR_{CG}$ was not a statistically significant or clinically relevant covariate influencing TAF PK (TAF Population PK Report). Although TAF exposure was higher in HIV-infected subjects with lower baseline $eGFR_{CG}$ relative to those with normal renal function (> 90 mL/min), the difference between those with moderate renal impairment ($30 \leq eGFR_{CG} < 60$ mL/min; mean [%CV] AUC 305.0 [112.5] ng•h/mL; C_{max} 208.6 [53.0] ng/mL) and those with normal renal function was less than 50% (mean [%CV] AUC 210.4 [94.1] ng•h/mL; C_{max}158.9 [57.1] ng/mL; Table 59).

Table 59. Population PK Analysis: Summary of PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Baseline Renal Function

	E/C/F/TAF			
TAF PK Parameter	**26[a] ≤ $eGFR_{CG}$ < 50 mL/min (N = 69)**	**30 ≤ $eGFR_{CG}$ < 60 mL/min (N = 133)**	**60 ≤ $eGFR_{CG}$ < 90 mL/min (N = 204)**	**$eGFR_{CG}$ ≥ 90 mL/min (N = 769)**
AUC (ng•h/mL)	343.7 (126.1)	305.0 (112.5)	223.9 (86.8)	210.4 (94.1)
C_{max} (ng/mL)	222.4 (50.3)	208.6 (53.0)	166.2 (43.7)	158.9 (57.1)

a All subjects in the renal impairment study, GS-US-292-0112, had $eGFR_{CG}$ > 30 mL/min at screening.
Data are presented as mean (%CV).
Source: TAF Population PK Report and E/C/F/TAF PK/PD, Ad Hoc Table 6919.1.1

TFV

Following a single dose of TAF, non–HIV-infected subjects with severe renal impairment (Study GS-US-120-0108) had a 6.05-fold mean increase in systemic TFV exposure (as assessed by AUC_{inf}) relative to age- and sex-matched non–HIV-infected subjects with normal renal function (Table 60). The plasma TFV exposure observed in this study in subjects with severe renal impairment was within or below the ranges of exposure observed in historical studies after administration of TDF 300 mg in both HIV-infected and non–HIV-infected subjects with normal renal function (3300 ng•h/mL) {26885},{34210}.

Table 60. TAF Study GS-US-120-0108: Statistical Comparisons of TFV PK Parameter Estimates in Non−HIV-Infected Between Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

	Mean (%CV)		
TFV PK Parameter	**Test Severe Renal Impairment (N = 14)**	**Reference Normal Renal Function (N = 13)**	**GLSM Ratio (90% CI), %**
AUC_{inf} (ng•h/mL)	2073.8 (47.1)	342.6 (27.2)	573.76 (457.21, 720.01)
AUC_{last} (ng•h/mL)	1694.9 (43.1)	298.0 (26.1)	545.91 (442.82, 672.99)
C_{max} (ng/mL)	26.4 (32.4)	9.5 (36.5)	279.31 (231.48, 337.02)

Source: GS-US-120-0108, Section 15.1, Tables 4.2 and 6.1

A Phase 3 PK substudy (n = 30) evaluating the PK of TFV following administration of E/C/F/TAF was performed in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min at screening, and showed mean (%CV) TFV exposure (AUC) of 552.7 (32.0) ng•h/mL (n = 29 for this parameter; Study GS-US-292-0112). The TFV exposure was numerically higher in subjects with baseline $eGFR_{CG}$ < 50 versus ≥ 50 mL/min. These Phase 3 data are consistent with results from the renal impairment study, GS-US-120-0108.

Based on population PK analyses of pooled data from Phase 1, Phase 2, and Phase 3 studies in healthy and HIV-infected subjects, a statistically significant effect of baseline $eGFR_{CG}$ on TFV exposure was observed based on covariate analyses; this result was expected with TFV being primarily renally eliminated. Although TFV exposure was higher in HIV-infected subjects with lower baseline $eGFR_{CG}$ relative to those with normal renal function (Table 61), the TFV exposure observed in subjects with $eGFR_{CG}$ < 50 mL/min (775.6 ng•h/mL) was within or below the ranges of exposure observed in historical studies after administration of TDF 300 mg in both HIV-infected and non–HIV-infected subjects with normal renal function (3300 ng•h/mL) {26885},{34210}.

Table 61. Population PK Analysis: Summary of PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Baseline Renal Function

	E/C/F/TAF			
TFV PK Parameter	**26[a] ≤ $eGFR_{CG}$ < 50 mL/min (N = 81)**	**30 ≤ $eGFR_{CG}$ < 60 mL/min (N = 155)**	**60 ≤ $eGFR_{CG}$ < 90 mL/min (N = 264)**	**$eGFR_{CG}$ ≥ 90 mL/min (N = 1053)**
AUC (ng•h/mL)	775.6 (31.4)	669.7 (29.2)	421.4 (30.2)	285.5 (27.1)
C_{max} (ng/mL)	38.3 (31.1)	33.2 (28.7)	21.6 (33.4)	14.9 (25.4)
C_{min} (ng/mL)	27.9 (31.6)	24.2 (29.4)	15.3 (30.6)	10.4 (28.6)

a All subjects in the renal impairment study, GS-US-292-0112, had $eGFR_{CG}$ > 30 mL/min at screening.
Data are presented as mean (%CV).
Source: TAF Population PK Report and E/C/F/TAF PK/PD, Ad Hoc Table 6919.1.2

3.2.2.1.1.2. FTC

Because renal excretion of the unchanged drug is the principal route of elimination for FTC, it is anticipated that the PK profiles of FTC in subjects with altered or deficient renal function may vary or deviate from those in subjects with normal renal function. Adult subjects with varying degrees of renal impairment (or insufficiency), as determined by estimated $eGFR_{CG}$ values, were evaluated in Study FTC-107.

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

The percentage of dose excreted as unchanged FTC in urine for the normal and mild renal impairment groups ($eGFR_{CG}$ 50-80 mL/min) was similar to that observed with healthy subjects (FTC-106) and HIV-infected subjects with normal renal function (FTC-101). However in subjects with moderate and severe impairment ($eGFR_{CG}$ < 50 mL/min), the urinary recovery was lower (approximately 30%-50% of the dose) over a 72-hour collection period, primarily due to slower excretion of FTC by the impaired kidneys, which, in the absence of clinical experience of FTC in HIV-infected subjects with $eGFR_{CG}$ less than 60 mL/min, led to a dose interval adjustment recommendation (FTC-107 Dosing Interval Report).

A Phase 3 safety and efficacy study was conducted to evaluate the effect of the E/C/F/TAF on renal parameters in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min (Study GS-US-292-0112 [m2.7.4, Section 1]). This study included an intensive PK substudy evaluating the PK of FTC following administration of E/C/F/TAF in subjects with $eGFR_{CG}$ of 30 to 69 mL/min (n = 30) and showed mean (%CV) FTC exposure AUC and C_{max} of 20,968.6 (25.5) ng•h/mL and 2645.3 (27.7) ng/mL, respectively, which were in the range of exposures where dose modification was not warranted in FTC-107. Importantly, the mean FTC AUC and C_{max} observed in GS-US-292-0112 subjects with $eGFR_{CG}$ of 30 to 69 mL/min is comparable with the AUC and C_{max} of 19,900 (6.2) ng•h/mL and 3800 (2.3) ng/mL, respectively, for subjects with $eGFR_{CG}$ of 50 to 80 mL/min who do not require dose adjustment {23270}, {30162}. Subjects with $eGFR_{CG}$ < 50 mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG}$ > 50 mL/min, and the observed laboratory abnormalities were consistent between the two groups.

The totality of these data supports the recommendation that F/TAF may be safely administered once daily without dose adjustment in patients with renal impairment ($eGFR_{CG}$ 30 to 69 mL/min).

3.2.2.1.2. Hepatic Impairment and Effect of Hepatitis B and/or Hepatitis C Coinfection

3.2.2.1.2.1. TAF

The PK of TAF and its metabolite TFV was evaluated in non–HIV-infected subjects with mild or moderate hepatic impairment (CPT Class A or B) and in age- and sex-matched non−HIV-infected subjects with normal hepatic function following a single dose of TAF (Study GS-US-120-0114; Section 2.4.1.2). The effect of severe hepatic impairment on the PK of TAF has not been studied.

Subjects with hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection were excluded from the E/C/F/TAF clinical development program.

TAF

In non−HIV-infected subjects with mild or moderate hepatic impairment, TAF plasma PK exposure parameters were comparable with those in subjects with normal hepatic function. In subjects with mild hepatic function (CPT Class A score of 5 to 6), AUC_{inf}, AUC_{last}, and C_{max} were 7.52%, 8.17%, and 10.99% lower, respectively, than those of subjects with normal hepatic function. In subjects with moderate hepatic impairment (CPT Class B score of 7 to 9), AUC_{inf},

AUC_{last}, and C_{max} were 12.69%, 15.06%, and 18.70% higher, respectively, than those of subjects with normal hepatic function. The upper bounds of the 90% CIs for the TAF AUC_{inf}, AUC_{last}, or C_{max} GLSM ratios were below the protocol-defined clinically significant increase of 100% and the observed increases were not considered clinically relevant. Accordingly, no dose adjustment is necessary for patients with mild to moderate hepatic impairment (CPT Class A or B).

TFV

In non−HIV-infected subjects with mild or moderate hepatic impairment, TFV plasma PK exposure parameters were comparable with those in subjects with normal hepatic function. In subjects with mild hepatic impairment, AUC_{inf}, AUC_{last}, and C_{max} were 10.84%, 10.69%, and 2.97% lower, respectively, than those of subjects with normal hepatic function. In subjects with moderate hepatic impairment, AUC_{inf}, AUC_{last}, and C_{max} were 2.78%, 4.45%, and 12.44% lower, respectively, than those in subjects with normal hepatic function. The upper bounds of the 90% CIs for the TFV AUC_{inf}, AUC_{last}, or C_{max} GLSM ratios were below the protocol-defined clinically significant increase of 100% and the observed decreases were not considered clinically relevant.

3.2.2.1.2.2. FTC

The PK of FTC has not been studied in hepatically impaired subjects. Renal excretion of unchanged drug is the major route of elimination of FTC in man with metabolism representing a minor pathway for the elimination (< 13% of oral dose) (Study FTC-106). Therefore, in patients with various degrees of hepatic dysfunction, little change in FTC clearance is expected.

The PK of FTC has been evaluated in a Phase 1 study in subjects with chronic HBV (Study FTCB-101). Study FTCB-101 was an open-label, dose-escalation study to evaluate the safety, tolerance, PK, and anti-HBV activity of multiple repeated doses of 5 once-daily dosage regimens (25, 50, 100, 200, and 300 mg once daily) of FTC monotherapy for 56 days (8 weeks) in HBV-infected subjects. At least 8 (up to 11) subjects were enrolled in each dose cohort. Full-profile plasma PK of FTC (0- to 24-hour sampling) were evaluated on Day 1 following the first dose administration and then on Day 28 at steady-state.

FTC was rapidly and well absorbed following oral administration, with peak plasma FTC concentrations generally occurring within 1.5 hours postdose. Plasma concentrations of FTC (C_{max} and AUC) increased in a dose-proportional manner following both single- and multiple-dose administration. Plasma trough concentrations at steady-state increased in a dose-linear manner. The mean total body clearance (CL/F) value of FTC was relatively constant across various doses and averaged ~300 mL/min. An average plasma elimination $t_{1/2}$ of ~8.5 hours was determined for FTC across dose levels. Based on the steady-state data from FTCB-101, FTC PK in HBV-infected subjects are generally similar to those determined previously in healthy subjects and in HIV-infected subjects as shown in Table 62.

The data show that mean $C_{max,ss}$ and AUC_{tau} values of FTC in HBV-infected subjects (receiving 200-mg dose in capsule) appeared to be comparable with those in healthy subjects (receiving 200-mg dose in solution). The mean $C_{max,ss}$ and AUC_{tau} values of FTC in HBV-infected subjects

were slightly higher than those in the HIV-infected subjects; however, the small differences are not likely to be clinically significant.

Subjects with HBV or HCV coinfection were excluded from the E/C/F/TAF clinical development program so the effect of HBV or HCV coinfection was not analyzed.

Table 62. Summary of Steady-State PK Parameter Estimates for FTC Following Once-Daily Dosing of FTC 200 mg in Various Populations

Study No.	Number of Subjects (M/F) Type Age: Mean (range)	$C_{max,ss}$ (µg/mL)	$T_{max,ss}$ (h)	$C_{min,ss}$ (µg/mL)	AUC_{tau} (µg•h/mL)	$t_{1/2}$ (h)	CL_{ss}/F (mL/min)
FTC-106	5 (5M/0F) Healthy subjects 37 (33–42) years	1.72 (16%)	1.00 (0%)	0.07 (28%)	10.04 (18%)	10.2 (19%)	339 (20%)
FTC-303	12 (1M/11F) HIV-infected 38 (21–61) years	1.94 (24%)	1.80 (58%)	0.11 (71%)	11.31 (29%)	8.08 (32%)	317 (27%)
FTCB-101	9 (6M/3F) HBV-infected 30 (29–45) years	3.00 (26%)	1.50 (69%)	0.07 (31%)	12.80 (27%)	6.96 (21%)	277 (25%)

Data are presented as mean (%CV)
Source: FTC-106; FTC-303; and FTCB-101

3.2.2.2. Age

3.2.2.2.1. TAF

In the E/C/F/TAF pooled Phase 2 and Phase 3 study population used for the population PK analyses, median (Q1, Q3) age was 38 (28, 49) years, with a range of 12 to 82 years, and 227 subjects were ≥ 55 years of age (TAF Population PK Report and E/C/F/TAF PK/PD, Ad Hoc Table 6919.2).

Subjects younger than 18 years are discussed under pediatrics in Section 3.2.2.4.2.

TAF

Using population PK modeling, age did not have an effect on TAF exposure in HIV-infected subjects and was not a statistically significant or clinically relevant covariate (Table 63).

Descriptive summaries of TAF PK parameters from the integrated ad hoc PK analysis are presented in Table 64 by age group (18 to < 55 years of age; ≥ 55 years of age). No clinically relevant differences were observed between age groups.

For both the TAF Population PK analysis and the integrated ad hoc PK analysis, age (as a continuous covariate) did not have an effect on TAF exposure in healthy or HIV-infected subjects, and was not statistically significant.

Table 63. Population PK Analysis: Summary of PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Age Group

TAF PK Parameter	E/C/F/TAF	
	18 to < 55 Years of Age (N = 915)	≥ 55 Years of Age (N = 197)
AUC_{tau} (ng•h/mL)	221.5 (104)	239.2 (72.8)
C_{max} (ng/mL)	164.2 (55.8)	178.2 (51.8)

Data are presented as mean (%CV).
Source: TAF Population PK Report

Table 64. Integrated Ad Hoc PK Analysis: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF 25 mg or TAF 10 mg + COBI in Healthy or HIV-Infected Subjects by Age Group (TAF PK Analysis Set)

TAF PK Parameter	TAF 25 mg		TAF 10 mg + COBI	
	18 to < 55 Years of Age (N = 418)	≥ 55 Years of Age (N = 22)	18 to < 55 Years of Age (N = 382)	≥ 55 Years of Age (N = 2)
AUC_{last} (ng•h/mL)	268.5 (49.88)	207.6 (45.88)	304.4 (41.84)	269.6 (44.01)
C_{max} (ng/mL)	224.1 (58.36)	145.4 (47.16)	274.4 (53.59)	210.5 (44.68)

Data are presented as mean (%CV).
Source: m5.3.5.3, Integrated Ad Hoc PK Analysis, Table In-text3

TFV

As age is often correlated with renal function and TFV is primarily renally eliminated, an effect of age on TFV exposure was expected (Table 65); however, age was not found to be a statistically significant covariate after adjusting for $eGFR_{CG}$. Moreover, this age-dependent exposure difference was not considered clinically relevant because TFV exposure in subjects ≥ 55 years of age receiving E/C/F/TAF was at least 80% lower than TFV exposure observed following STB administration (Table 90).

Table 65. Population PK Analysis: Summary of PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Age Group

TFV PK Parameter	E/C/F/TAF	
	18 to < 55 Years of Age (N = 1251)	≥ 55 Years of Age (N = 227)
AUC_{tau} (ng•h/mL)	322.3 (44.2)	522.9 (37.1)
C_{max} (ng/mL)	16.7 (42.9)	26.2 (35.6)
C_{min} (ng/mL)	11.7 (44.6)	18.9 (37.0)

Data are presented as mean (%CV).
Source: TAF Population PK Report

3.2.2.2.2. FTC

There were no relevant differences with respect to range and distribution of AUC values between the 2 age groups examined for FTC PK (13542v1). Subjects > 40 years had slightly higher (< 10%) mean/median AUC and C_{max} values than subjects ≤ 40 years of age. There were no major differences in the overall range and distribution of $t_{1/2}$ values between the 2 age groups. However, subjects > 40 years of age had a longer mean or median $t_{1/2}$ than subjects ≤ 40 years by 26% or 30%.

3.2.2.3. Weight/Body Mass Index/Body Surface Area

3.2.2.3.1. TAF

The effect of body weight, BMI, and body surface area were considered during covariate assessment in the population PK analyses.

In the pooled Phase 2 and Phase 3 study populations used for TAF population PK analyses, the median (Q1, Q3) weight was 75 (66, 86) kg, with a range of 35 to 219 kg (E/C/F/TAF PK/PD, Ad Hoc Table 6919.2).

TAF

Using population PK modeling, weight did not have an effect on TAF exposure in healthy or HIV-infected subjects and was not a statistically significant or clinically relevant covariate (Table 66).

Descriptive summaries of TAF PK parameters from the integrated ad hoc PK analysis are presented in Table 67 by weight group (≤ 75 kg; > 75 kg). No clinically relevant differences were observed between weight groups.

For both the TAF Population PK analysis and the integrated ad hoc PK analysis, weight (as a continuous covariate) did not have an effect on TAF exposure in healthy or HIV-infected subjects, and was not statistically significant. Additionally, body surface area did not have an effect on TAF in HIV-infected subjects and was not a statistically significant or clinically relevant covariate based on TAF population PK analyses (TAF Population PK Report).

Table 66. Population PK Analysis: Summary of PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Weight Range

TAF PK Parameter	E/C/F/TAF			
	Weight ≤ 66 kg (N = 301)	66 < Weight ≤ 75 kg (N = 260)	75 < Weight ≤ 86 kg (N = 263)	Weight > 86 kg (N = 288)
AUC_{tau} (ng•h/mL)	237.2 (68.8)	248.7 (124)	208.4 (85.9)	204.6 (104)
C_{max} (ng/mL)	176.7 (50.2)	169.4 (52.6)	162.3 (44.4)	157.6 (70.4)

Data are presented as mean (%CV).
Source: TAF Population PK Report

Table 67. Integrated Ad Hoc PK Analysis: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF 25 mg or TAF 10 mg + COBI in Healthy or HIV-Infected Subjects by Weight Range (TAF PK Analysis Set)

TAF PK Parameter	TAF 25 mg		TAF 10 mg + COBI	
	Weight ≤ 75 kg (N = 200)	Weight > 75 kg (N = 240)	Weight ≤ 75 kg (N = 205)	Weight > 75 kg (N = 179)
AUC_{last} (ng•h/mL)	298.4 (50.37)	239.4 (46.16)	327.6 (41.61)	275.6 (39.45)
C_{max} (ng/mL)	241.3 (61.09)	203.8 (54.31)	280.4 (54.59)	266.5 (52.09)

Data are presented as mean (%CV).
Source: m5.3.5.3, Integrated Ad Hoc PK Analysis, Table In-text3

TFV

There was a modest dependence of TFV exposure on weight (Table 68) but this was not found to be a statistically significant covariate after adjusting for $eGFR_{CG}$. Moreover, this weight-dependent exposure difference was not considered clinically relevant because TFV exposure observed in subjects ≤ 66 kg receiving E/C/F/TAF was > 80% lower than TFV exposure observed following STB administration (Table 90).

Table 68. Population PK Analysis: Summary of PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Weight Range

TFV PK Parameter	Weight ≤ 66 kg (N = 384)	66 < Weight ≤ 75 kg (N = 355)	75 < Weight ≤ 86 kg (N = 366)	Weight > 86 kg (N = 373)
AUC_{tau} (ng•h/mL)	422.2 (48.4)	355.5 (42.5)	331.9 (37.1)	300.3 (51.8)
C_{max} (ng/mL)	21.7 (48.3)	18.2 (40.6)	17.1 (34.3)	15.5 (46.6)
C_{min} (ng/mL)	15.3 (47.6)	12.9 (42.7)	12.1 (37.9)	10.9 (53.5)

Data are presented as mean (%CV).
Source: TAF Population PK Report

3.2.2.3.2. FTC

The summary data of AUC and C_{max} values distinguishing body weight groups showed that there were no major differences in the overall range and distribution of AUC and C_{max} values between the 2 body weight groups. However, subjects with a body weight ≤ 75 kg had about 10% to 15% higher mean/median AUC and C_{max} values than subjects with a body weight > 75 kg. There were no major differences in the overall range and distribution of $t_{1/2}$ values between the 2 weight groups. Subjects with a body weight ≤ 75 kg tended to have slightly shorter (< 10%) median $t_{1/2}$ than subjects with a body weight > 75 kg.

3.2.2.4. Race/Ethnicity

3.2.2.4.1. TAF

In the pooled Phase 1, Phase 2, and Phase 3 study populations used for TAF population PK analyses, 59.2% of subjects were white, 24.7% were black, and 16.2% were "other."

TAF

Using population PK modeling, race did not have an effect on TAF exposure in HIV-infected subjects and was not a statistically significant or clinically relevant covariate (Table 69).

Descriptive summaries of TAF PK parameters from the integrated ad hoc PK analysis are presented in Table 70 by race (white; black; other). No clinically relevant differences were observed between race groups.

For both the TAF Population PK analysis and the integrated ad hoc PK analysis, race did not have an effect on TAF exposure in healthy or HIV-infected subjects, and was not a statistically significant covariate.

Table 69. Population PK Analysis: Summary of PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Race

	E/C/F/TAF		
TAF PK Parameter	**White (N = 655)**	**Black (N = 265)**	**Other (N = 192)**
AUC_{tau} (ng•h/mL)	226.0 (98.9)	229.9 (111)	212.7 (73.0)
C_{max} (ng/mL)	168.1 (57.1)	159.9 (49.8)	170.9 (54.4)

Data are presented as mean (%CV).
Source: TAF Population PK Report

Table 70. Integrated Ad Hoc PK Analysis: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF 25 mg or TAF 10 mg + COBI in Healthy or HIV-Infected Subjects by Race (TAF PK Analysis Set)

	TAF 25 mg			TAF 10 mg + COBI		
TAF PK Parameter	**White (N = 304)**	**Black (N = 128)**	**Other (N = 8)**	**White (N = 249)**	**Black (N = 112)**	**Other (N = 23)**
AUC_{last} (ng•h/mL)	265.2 (51.86)	272.5 (45.66)	197.0 (30.22)	316.7 (40.87)	286.3 (45.00)	255.4 (28.84)
C_{max} (ng/mL)	221.2 (62.03)	221.5 (50.76)	187.7 (45.79)	282.1 (54.86)	243.4 (53.39)	309.2 (35.77)

Data are presented as mean (%CV).
Source: m5.3.5.3, Integrated Ad Hoc PK Analysis, Table In-text3

TFV

Based on covariate analyses, a statistically significant effect of race (black versus nonblack) on TFV PK parameters was observed (Table 71). However, the range of TFV exposure across races was comparable and overall > 80% lower than TFV exposure observed following STB administration (Table 90). As such, the observed relationship between race and TFV exposure is not considered clinically relevant.

Table 71. Population PK Analysis: Summary of PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Race

	E/C/F/TAF		
TFV PK Parameter	**White (N = 871)**	**Black (N = 368)**	**Other (N = 239)**
AUC_{tau} (ng•h/mL)	358.6 (48.0)	310.3 (37.9)	398.7 (50.4)
C_{max} (ng/mL)	18.3 (45.1)	16.2 (35.1)	20.5 (51.9)
C_{min} (ng/mL)	13.1 (48.3)	11.2 (38.7)	14.4 (49.2)

Data are presented as mean (%CV).
Source: TAF Population PK Report

3.2.2.4.2. FTC

There were no major differences in the overall range and distribution or in the mean/median values for any of the key FTC PK parameter estimates (AUC, C_{max} and $t_{1/2}$) between the Caucasian and non-Caucasian groups.

3.2.2.5. Pediatrics

The effect of age for pediatric subjects on the PK of TAF, TFV, and FTC was assessed based on data from Study GS-US-292-0106 (m2.7.4, Section 1), where E/C/F/TAF was administered to HIV-infected, ART-naive adolescents.

The effect of age for adult subjects is discussed in Section 3.2.2.2.

3.2.2.5.1. TAF

TAF

TAF exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration (PK substudy in Study GS-US-292-0102 [m2.7.3, Section 2]), indicating no relevant effects of pediatrics (age ≥ 12 years) on the exposure of TAF (Table 72).

Table 72. E/C/F/TAF Studies GS-US-292-0106 Versus GS-US-292-0102: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

	E/C/F/TAF	
TAF PK Parameter	**Adolescent Subjects (N = 24)**	**Adult Subjects (N = 19)**
AUC_{last} (ng•h/mL)	188.9 (55.8)	227.5 (47.3)
C_{max} (ng/mL)	166.8 (64.4)	232.8 (64.6)

Data are presented as mean (%CV).
Source: GS-US-292-0106, Section 15.1, Table 49.1; GS-US-292-0102, Section 15.1, Table 51.4

Additionally, in the pooled Phase 2 and Phase 3 study populations used for TAF population PK analyses, HIV-infected adolescent subjects had comparable TAF exposures versus HIV-infected adult subjects as shown in Table 73, again confirming that age was not a clinically relevant covariate.

Table 73. Population PK Analysis: Summary of PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Adolescent and Adult Subjects

	E/C/F/TAF	
TAF PK Parameter	**Adolescent Subjects (N = 23)[a]**	**Adult Subjects (N = 539)[b]**
AUC_{last} (ng•h/mL)	242.8 (57.8)	206.4 (71.8)
C_{max} (ng/mL)	121.7 (46.2)	162.2 (51.1)

a Adolescent subjects from Study GS-US-292-0106.
b Adult subjects from Studies GS-US-292-0104 and GS-US-292-0111.
Data are presented as mean (%CV).
Source: TAF Population PK Report

TFV

TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration (PK substudy in Study GS-US-292-0102 [m2.7.3, Section 2]), indicating no relevant effects of pediatrics (age ≥ 12 years) on the exposure of TFV (Table 74).

Table 74. E/C/F/TAF Studies GS-US-292-0106 Versus GS-US-292-0102: Summary of Steady-State PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

	E/C/F/TAF	
TFV PK Parameter	**Adolescent Subjects (N = 24)**	**Adult Subjects (N = 19)**
AUC_{tau} (ng•h/mL)	287.6 (18.8)	326.2 (14.8)
C_{max} (ng/mL)	17.6 (23.7)	18.2 (12.4)
C_{tau} (ng/mL)	10.0 (21.4)	11.4 (17.9)

Data are presented as mean (%CV).
Source: GS-US-292-0106, Section 15.1, Table 49.5; GS-US-292-0102, Section 15.1, Table 51.5

Additionally, in the pooled Phase 2 and Phase 3 study populations used for TFV population PK analyses, HIV-infected adolescent subjects had comparable TFV exposures versus HIV-infected adult subjects as shown Table 75, again confirming that age was not a clinically relevant covariate.

Table 75. Population PK Analysis: Summary of PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Adolescent and Adult Subjects

	E/C/F/TAF	
TFV PK Parameter	**Adolescent Subjects (N = 23)[a]**	**Adult Subjects (N = 841)[b]**
AUC_{tau} (ng•h/mL)	275.8 (18.4)	292.6 (27.4)
C_{max} (ng/mL)	14.6 (20.0)	15.2 (26.1)
C_{min} (ng/mL)	10.0 (19.6)	10.6 (28.5)

a Adolescent subjects from Study GS-US-292-0106.
b Adult subjects from Studies GS-US-292-0104 and GS-US-292-0111.
Data are presented as mean (%CV).
Source: TAF Population PK Report

3.2.2.5.2. FTC

FTC is approved for use in the pediatric population; however, the effect of age on the PK of FTC in E/C/F/TAF was also assessed based on data from Study GS-US-292-0106, where FTC 200 mg as a part of E/C/F/TAF was administered to HIV-infected, ART-naive adolescents. FTC exposure was comparable with values observed in HIV-infected, ART-naive adults following E/C/F/TAF (GS-US-292-0102), indicating no relevant effects of pediatrics (age ≥ 12 years) on the exposures of FTC (Table 76).

Table 76. E/C/F/TAF Studies GS-US-292-0106 Versus GS-US-292-0102: Summary of Steady-State PK Parameter Estimates for FTC Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

	E/C/F/TAF	
FTC PK Parameter	**Adolescent Subjects (N = 24)**	**Adult Subjects (N = 19)**
AUC_{tau} (ng•h/mL)	14,424.4 (23.9)	11,714.1 (16.6)
C_{max} (ng/mL)	2265.0 (22.5)	2056.3 (20.2)
C_{tau} (ng/mL)	102.4 (38.9)[a]	95.2 (46.7)

a n = 23
Data are presented as mean (%CV).
Source: GS-US-292-0106, Section 15.1, Table 49.4; GS-US-292-0102, Section 15.1, Table 51.3

3.2.2.6. Sex

3.2.2.6.1. TAF

In the pooled Phase 1, Phase 2, and Phase 3 study populations used for TAF population PK analyses, 16.3% of subjects were female.

TAF

Using population PK modeling, sex did not have an effect on TAF exposure in HIV-infected subjects and was not a statistically significant or clinically relevant covariate (Table 77).

Descriptive summaries of TAF PK parameters from the integrated ad hoc PK analysis are presented in Table 78 by sex. Based on the integrated ad hoc PK analysis, a statistically significant effect of sex on TAF PK parameters was observed, with higher exposure in females (mean [%CV] AUC_{last} TAF 25 mg 305.7 [47.69] ng•h/mL; TAF 10 mg + COBI 355.9 [36.30] ng/mL) than in males (mean [%CV] AUC_{last} TAF 25 mg 241.8 [49.02] ng•h/mL; TAF 10 mg + COBI 276.1 [42.40] ng/mL). Because of the wide range of safe and efficacious TAF exposure established (Sections 3.3.1.1 and 3.3.2.1) and the larger and more robust dataset used for population PK analyses, which concluded no effect of sex on TAF PK, the relationship between sex and TAF exposure is not considered clinically relevant.

Table 77. Population PK Analysis: Summary of PK Parameter Estimates for TAF Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Sex

	E/C/F/TAF	
TAF PK Parameter	**Male (N = 934)**	**Female (N = 178)**
AUC_{tau} (ng•h/mL)	218.9 (92.7)	254.9 (117)
C_{max} (ng/mL)	165.2 (55.1)	174.3 (55.1)

Data are presented as mean (%CV).
Source: TAF Population PK Report

Table 78. Integrated Ad Hoc PK Analysis: Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF 25 mg or TAF 10 mg + COBI in Healthy or HIV-Infected Subjects by Sex (TAF PK Analysis Set)

TAF PK Parameter	TAF 25 mg		TAF 10 mg + COBI	
	Male (N = 271)	Female (N = 169)	Male (N = 257)	Female (N = 127)
AUC_{last} (ng•h/mL)	241.8 (49.02)	305.7 (47.69)	276.1 (42.40)	355.9 (36.30)
C_{max} (ng/mL)	206.6 (61.06)	243.7 (54.28)	262.9 (54.40)	294.8 (51.54)

Data are presented as mean (%CV).
Source: m5.3.5.3, Integrated Ad Hoc PK Analysis, Table In-text3

TFV

Based on covariate analyses, a statistically significant effect of sex on TFV PK parameters was observed. However, the range of TFV exposure across males and females was comparable as shown in Table 79. As such, the observed relationship between sex and TFV exposure is not considered clinically relevant.

Table 79. Population PK Analysis: Summary of PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Sex

TFV PK Parameter	E/C/F/TAF	
	Male (N = 1248)	Female (N = 230)
AUC_{tau} (ng•h/mL)	340.5 (44.7)	421.2 (53.3)
C_{max} (ng/mL)	17.6 (43.0)	21.2 (51.5)
C_{min} (ng/mL)	12.3 (44.9)	15.4 (52.5)

Data are presented as mean (%CV).
Source: TAF Population PK Report

3.2.2.6.2. FTC

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

3.2.3. Effect of Extrinsic Factors

The assessment of potential effects of extrinsic factors on the PK of F/TAF, TAF, TFV, or FTC included food effect and DDIs.

3.2.3.1. Effect of Food

TAF

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

In a randomized, open-label, single-dose, 2-treatment, 2-period, crossover study of the effect of food on the PK of the TAF component of F/TAF (200/25 mg; Study GS-US-311-1386), administration of F/TAF under fed conditions resulted in increased overall TAF exposure, lower C_{max}, and delayed T_{max}. Administration of F/TAF (200/25 mg) under fed conditions resulted in an increase in TAF exposure (AUC_{last}) by 77% compared with administration under fasting conditions, with a decrease of 15% in TAF C_{max} and delay in TAF T_{max} from 0.50 hour under fasting conditions to 1.00 hour under fed conditions. Given the wide range of safe and efficacious TAF exposure established in the Phase 3 E/C/F/TAF studies (predicted individual steady-state mean [95% CI, %CV] AUC 206.4 ng•h/mL [55.6 to 526.1 ng•h/mL, 71.8%] and Sections 3.3.1.1 and 3.3.2.1), the differences in TAF PK under fed and fasting conditions are not considered clinically relevant.

In a randomized, open-label, single-dose, 3-treatment, 3-period, 6-sequence, crossover study of the effect of food on the PK of the TAF component of E/C/F/TAF (Study GS-US-292-0110), administration of E/C/F/TAF under fed conditions did not affect overall TAF exposure, but resulted in a lower C_{max} and delayed T_{max}. Administration of E/C/F/TAF with a high-fat meal resulted in an increase of 17% in TAF exposure (AUC_{last}) compared with administration following an overnight fast, with a 37% decrease in TAF C_{max} and a delay in TAF T_{max} from 0.50 hour under fasting conditions to 1.00 hour under fed conditions. These differences in TAF PK parameters upon E/C/F/TAF administration with food (versus fasted) are not considered clinically relevant.

The differential effect of food observed between Studies GS-US-311-1386 and GS-US-292-0110 is likely due to the oral bioavailability of TAF when administered in the absence or presence of a boosting agent. Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (~40%). TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI or RTV) reduces P-gp−mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. As a result, the effect of food on TAF absorption is smaller when administered in the presence of a boosting agent.

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

FTC

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

3.2.3.2. Drug Interaction Potential

The results from nonclinical and clinical studies have defined the potential of F/TAF or its components as perpetrators or victims of DDIs.

The results from in vitro evaluation of F/TAF or its components as perpetrators or victims of DDIs are described in more detail in the Nonclinical Pharmacokinetics Written Summary (m2.6.4).

Results and recommendations pertinent to F/TAF are presented below.

3.2.3.2.1. Potential for F/TAF to Affect Other Drugs

TAF

The potential for TAF to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (AD-120-2003). The inhibitory activity of TAF with human liver microsomal CYP isoenzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed at concentrations up to 25 µM. The IC_{50} values calculated for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were greater than 25 µM. TAF weakly inhibited CYP3A-mediated oxidation of MDZ or testosterone with IC_{50} values of 7.6 and 7.4 µM, respectively.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A was assessed at TAF concentration at 50 µM (AD-120-2040). There was no evidence for time- or cofactor-dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control.

Clinical evaluation of TAF as a CYP3A4 inhibitor or inducer (Study GS-US-120-1538; Section 2.5.2.3) showed no clinically relevant differences in MDZ PK relative to MDZ alone following coadministration of MDZ (oral or IV) and TAF; these data indicate that TAF does not exhibit CYP3A inhibition or induction activity, either presystemically or systemically.

TFV

The potential for TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (V990172-104). TFV at 100 µM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

3.2.3.2.2. Potential for Other Drugs to Affect F/TAF

TAF is transported by P-gp and metabolized by esterases expressed in the intestine {21545}, {21546}. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly affect P-gp activity (eg, COBI and RTV) may lead to changes in TAF bioavailability. Coadministration with COBI or RTV can lead to near maximal inhibition of P-gp, resulting in an increase in TAF exposure (Table 80). Coadministration with COBI-boosted EVG, RTV-boosted ATV, or RTV-boosted LPV resulted in an increase in TAF exposure of 122%, 91%, and 47%, respectively, compared with FTC+TAF or TAF single agent. Notably, coadministration with RTV- or COBI-boosted DRV had almost no effect on TAF plasma exposure (6% increase and 2% decrease in AUC_{last}, respectively). It was because of the effect of P-gp inhibitors on TAF exposure that 2 F/TAF FDC tablet strengths were developed. Results from Study GS-US-311-1473 (Table 6) demonstrate bioequivalence in TAF exposure between F/TAF (200/25 mg) and E/C/F/TAF (150/150/200/10 mg); the results of the integrated ad hoc PK analysis (Table 55) support this conclusion.

As TAF is not metabolized by CYP enzymes except for weak metabolism observed for CYP3A4 in vitro, CYP inducers are not expected to have a relevant effect on TAF PK; however, most CYP inducers are also P-gp inducers, and coadministration with P-gp inducers may decrease the absorption of TAF. Coadministration with a modest CYP3A and P-gp inducer (ie, EFV) resulted in slightly lower TAF exposure (14% to 22%; Table 80), and coadministration with a weak CYP3A and P-gp inducer (ie, RPV) resulted in no change to TAF exposure. As such, minimal effect on TAF exposure is expected upon coadministration of F/TAF with a modest or weak CYP3A/P-gp inducer. Coadministration of F/TAF with potent CYP3A/P-gp inducers is not recommended.

Because TAF was found to be a substrate for hepatic transporters OATP1B1 and OATP1B3 (Section 3.1.3.4), 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.

Table 80. Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

TAF PK Parameter	Mean (%CV)		GLSM Ratio (90% CI), %
	Test	Reference	
F/TAF Study GS-US-311-0101			
TAF 8 mg + COBI, Day 22 (Test) vs TAF 8 mg, Day 12 (Reference) (N = 12)			
AUC_{last} (ng•h/mL)	213.3 (37.7)	81.2 (43.9)	265.06 (229.00, 306.80)
C_{max} (ng/mL)	189.9 (45.6)	71.0 (72.9)	283.31 (219.65, 365.43)
F/TAF (200/25 mg) + DRV+COBI, Day 22 (Test) vs F/TAF (200/25 mg), Day 12 (Reference) (N = 11)			
AUC_{last} (ng•h/mL)	239.3 (41.0)	245.6 (41.9)	97.64 (80.38, 118.62)
C_{max} (ng/mL)	215.0 (59.2)	208.3 (40.2)	93.43 (72.16, 120.98)
F/TAF (200/40 mg) + EFV, Day 26 (Test) vs F/TAF (200/40 mg), Day 12 (Reference) (N = 11)			
AUC_{last} (ng•h/mL)	285.8 (46.4)	344.0 (60.9)	85.54 (72.08, 101.52)
C_{max} (ng/mL)	390.8 (62.2)	499.4 (82.8)	77.92 (57.68, 105.25)
E/C/F/TAF Study GS-US-292-0101			
E/C/F/TAF Formulation 1 (150/150/200/25 mg; Test) vs TAF 25 mg (Reference) (N = 19)			
AUC_{last} (ng•h/mL)	552.1 (40.5)	242.4 (42.4)	221.78 (199.99, 245.95)
C_{max} (ng/mL)	506.9 (54.2)	215.4 (55.0)	222.62 (187.11, 264.87)
TAF Study GS-US-120-0118			
FTC+TAF 10 mg +ATV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{last} (ng•h/mL)	162.6 (18.8)	89.5 (40.8)	191.06 (155.08, 235.40)
C_{max} (ng/mL)	146.5 (46.9)	76.8 (29.4)	176.72 (128.19, 243.63)
FTC+TAF 10 mg +LPV/r (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{last} (ng•h/mL)	120.8 (43.9)	80.0 (34.1)	146.73 (116.60, 184.65)
C_{max} (ng/mL)	157.5 (39.4)	68.7 (28.7)	218.97 (171.88, 278.97)
FTC+TAF 10 mg +DRV+RTV (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{last} (ng•h/mL)	78.6 (30.9)	77.4 (43.6)	106.27 (83.59, 135.10)
C_{max} (ng/mL)	102.3 (46.5)	73.4 (49.4)	141.80 (96.11, 209.22)
FTC+TAF 10 mg +DTG (Test) vs FTC+TAF 10 mg (Reference) (N = 10)			
AUC_{last} (ng•h/mL)	103.0 (30.6)	98.5 (53.3)	119.02 (95.83, 147.82)
C_{max} (ng/mL)	83.4 (30.6)	79.9 (60.6)	123.64 (87.79, 174.13)
TAF Study GS-US-120-1554			
TAF 25 mg +RPV (Test) (N = 32) vs TAF 25 mg (Reference) (N = 17)			
AUC_{last} (ng•h/mL)	334.1 (30.0)	306.3 (18.4)	101.31 (93.77, 109.46)
C_{max} (ng/mL)	242.8 (38.2)	238.2 (25.5)	101.26 (84.23, 121.73)

Source: Table 9, Table 26, Table 33, and Table 38

3.2.3.2.3. Management of Known and Potential Drug-Drug Interactions

Based on results from clinical studies evaluating the DDI potential between various drugs (or drug combinations) and TAF (or TAF-containing FDCs), changes in TAF exposure upon coadministration with various drugs are summarized in Table 81.

Table 81. Changes in TAF PK with Concomitant Drugs

Drug	% Change in TAF PK Parameter (90% CI) With Coadministered Drug[a]		Data Source
	AUC	C_{max}	
COBI	↑165 (↑129 to ↑207)	↑183 (↑120 to ↑265)	Study GS-US-311-0101
EVG+COBI	↑122 (↑100 to ↑146)	↑123 (↑87 to ↑165)	Study GS-US-292-0101
ATV+RTV	↑91 (↑55 to ↑135)	↑77 (↑28 to ↑144)	Study GS-US-120-0118
LPV/r	↑47 (↑17 to ↑85)	↑119 (↑72 to ↑179)	Study GS-US-120-0118
DTG	↑19 (↓4 to ↑48)	↑24 (↓12 to ↑74)	Study GS-US-120-0118
DRV+RTV	↑6 (↓16 to ↑35)	↑42 (↓4 to ↑109)	Study GS-US-120-0118
Sertraline[b]	↓4 (↓11, ↑3)	0 (↓14, ↑16)	Study GS-US-292-1316
DRV+COBI	↓2 (↓20, ↑19)	↓7 (↓28, ↑21)	Study GS-US-311-0101
SOF/GS-5816[c]	↓13 (↓19, ↓6)	↓20 (↓32, ↓6)	Study GS-US-342-1167
EFV	↓14 (↓28 to ↑2)	↓22 (↓42 to ↑5)	Study GS-US-311-0101
RPV	↑1 (↓6, ↑10)	↑1 (↓16, ↑22)	Study GS-US-120-1554

a Difference from 100% in the GLSM ratio (Test/Reference).
b Study conducted using E/C/F/TAF. Conclusion may be extrapolated to the F/TAF FDCs based on nonclinical information.
c Study conducted using E/C/F/TAF.

Based on results from clinical studies evaluating the DDI potential between various drugs (or drug combinations) and TAF (or TAF-containing FDCs), changes in TAF exposure upon coadministration with various drugs are summarized in Table 82.

Table 82. Changes in Drug PK With Concomitant TAF

Drug	% Change in Drug PK Parameter (90% CI) With Coadministered TAF[a]		Data Source
	AUC	C_{max}	
EVG	↓5 (↓8, ↓2)	↓10 (↓15, ↓4)	Study GS-US-292-0103
COBI (+EVG)	↑2 (↓2, ↑6)	↑4 (↓1, ↑9)	Study GS-US-292-0103
ATV (+RTV)	↓1 (↓4, ↑1)	↓2 (↓11, ↑7)	Study GS-US-120-0118
DRV (+RTV)	↑1 (↓4, ↑6)	↓1 (↓9, ↑8)	Study GS-US-120-0118
LPV (+RTV)	0 (↓8, ↑9)	0 (↓5, ↑6)	Study GS-US-120-0118
DTG	↑2 (↓3, ↑8)	↑15 (↑4, ↑27)	Study GS-US-120-0118
RPV	↑1 (↓4, ↑6)	↓7 (↓13, ↓1)	Study GS-US-120-1554

Drug	% Change in Drug PK Parameter (90% CI) With Coadministered TAF[a]		Data Source
	AUC	C_{max}	
Sertraline[b]	↑9 (↓10, ↑32)	↑14 (↓6, ↑38)	Study GS-US-292-1316
DRV (+COBI)	↓1 (↓8, ↑7)	↑2 (↓4, ↑9)	Study GS-US-311-0101
COBI (+DRV)	↑9 (↑3, ↑15)	↑6 (0, ↑12)	Study GS-US-311-0101
SOF[b]	↑37 (↑24, ↑52)	↑23 (↑7, ↑42)	Study GS-US-342-1167
GS-5816[b]	↑50 (↑35, ↑66)	↑30 (↑17, ↑45)	Study GS-US-342-1167
MDZ	↑12 (↑3, ↑22)	↑2 (↓8, ↑13)	Study GS-US-120-1538

a Difference from 100% in the GLSM ratio (Test/Reference).
b Study conducted with E/C/F/TAF.

Based on results from clinical studies evaluating the DDI potential between various drugs (or drug combinations) and FTC (or FTC-containing FDCs), changes in FTC exposure upon coadministration with various drugs are summarized in Table 83.

Table 83. Changes in FTC PK with Potential Concomitant Drugs

Drug	% Change in FTC PK Parameter (90% CI) With Coadministered Drug[a]		Data Source
	AUC	C_{max}	
d4T	↑1 (↓7, ↑10)	↑4 (↓6, ↑16)	Study FTC-103
ZDV	↑13 (↑4, ↑22)	↓1 (↓35, ↑52)	Study FTC-103
TDF	↑7 (0, ↑14)	↓4 (↓13, ↑6)	Study FTC-114
EFV	↓8 (↓13, ↓4)	↓10 (↓19, ↓1)	Study GS-US-311-0101
DRV+COBI	↑24 (↑17, ↑31)	↑13 (↑2, ↑24)	Study GS-US-311-0101
Sertraline	↓16 (↓19, ↓12)	↓10 (↓18, ↓2)	Study GS-US-292-1316
SOF/GS-5816	↑1 (↓2, ↑4)	↑2 (↓3, ↑6)	Study GS-US-342-1167
Tacrolimus	↓5 (↓9, ↓1)	↓11 (↓17, ↓5)	Study GS-US-174-0105
Famciclovir	↓8 (↓14, ↓1)	↓10 (↓20, ↑1)	Study FTC-108

a Difference from 100% in the GLSM ratio (Test/Reference).

Based on in vitro and in vivo absorption, metabolism, and elimination properties, and clinical PK of F/TAF (or its components), various clinical DDI studies were performed using commonly administered concomitant medications, CYP3A inhibitors or inducers, P-gp inhibitors or inducers. Drug interaction information (observed or predicted) and dosing recommendations for F/TAF with potential concomitant drugs are summarized in Table 84.

Table 84. Drug Interaction Information for F/TAF with Potential Concomitant Drugs

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered.
Antifungals: itraconazole ketoconazole	↑ TAF	Coadministration of itraconazole or ketoconazole, both of which are P-gp inhibitors, may increase plasma concentrations of tenofovir alafenamide. No dose adjustment is required.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of rifampin, rifabutin, and rifapentine, all of which are P-gp inducers, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of F/TAF with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St John's wort *(Hypericum perforatum)*	↓ TAF	Coadministration of St John's wort, a P-gp inducer, may decrease TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of F/TAF with St John's wort is not recommended.

This table is not all inclusive.
a ↑ = Increase, ↓ = Decrease, ↔ = No Effect

3.2.3.2.4. Effect of Drug-Drug Interactions on Active and Major Metabolites

TFV

Coadministration of TAF with a modest CYP3A inducer (ie, EFV) resulted in slightly lower TFV exposure (20% to 25%; GS-US-311-0101 [Section 2.5.1.1]), likely due to P-gp induction. As such, administration of F/TAF with a modest CYP3A inducer may result in lower TFV exposure. Coadministration of TAF with a weak CYP inducer (ie, RPV) resulted in no clinically relevant change in TFV exposure (GS-US-120-1554 [Section 2.5.2.4]). As such, no effect on TFV exposure is expected upon coadministration of F/TAF with a weak CYP3A inducer.

Intracellular metabolic activation of TAF in PBMCs or other lymphatic tissues involves conversion to TFV by catA (m2.6.2), {10427}, {13119}. In contrast, TAF was primarily hydrolyzed by carboxylesterase 1 in primary hepatocytes as described. Tenofovir is then further phosphorylated to TFV-DP by cellular nucleotide kinases. These steps are high capacity and low affinity and are not readily inhibited by other xenobiotics.

Intracellular TFV-DP

As described in Section 3.2.1.1.1, F/TAF administration (irrespective of third agent) resulted in intracellular TFV-DP concentrations that were > 4-fold higher relative to FTC/TDF. This finding is consistent with results from E/C/F/TAF studies (Section 3.3.1.1).

When analyzed by third agent (boosted by RTV or unboosted), F/TAF administration resulted in intracellular TFV-DP concentrations that were 1.7- to 9.5-fold higher relative to FTC/TDF (Table 85). As described further in Section 3.2.3.2.5, intracellular PBMC TFV-DP concentrations track closely with anticipated TAF plasma exposure (ie, TAF-equivalent dose; Table 86).

Table 85. F/TAF Study GS-US-311-1089: Statistical Comparisons of Intracellular TFV-DP Concentrations Between Test and Reference Treatments by Coadministered Third Agent (PBMC PK Analysis Set)

Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	F/TAF (Test)		FTC/TDF (Reference)		GLSM Ratio (90% CI), %
	n	Geometric Mean (95% CI)	n	Geometric Mean (95% CI)	
+DTG	24	106.571 (70.145, 161.913)	19	32.724 (20.960, 51.091)	325.664 (198.902,533.213)
+EFV	8	54.224 (20.281, 144.976)	6	32.002 (13.222, 77.459)	169.441 (64.761,443.327)
+MVC	1	268.000 (NA)	5	28.276 (11.792, 67.799)	947.810 (233.900,3840.727)
+NVP	65	137.937 (102.738, 185.196)	56	31.464 (25.240, 39.223)	438.402 (323.162,594.737)
+RAL	55	167.293 (122.471, 228.519)	57	29.920 (22.720, 39.403)	559.127 (396.255,788.945)
+RPV	3	161.478 (1.146, 22,750.113)	5	36.695 (14.161, 95.089)	440.057 (42.736,4531.321)
+ATV+RTV	50	126.292 (96.649, 165.027)	34	23.208 (17.062, 31.569)	544.164 (389.197,760.833)
+DRV+RTV	82	78.879 (64.028, 97.175)	69	23.317 (18.927, 28.725)	338.294 (264.774,432.228)
LPV/r	16	96.052 (66.029, 139.725)	14	31.070 (13.040, 74.029)	309.144 (146.581,651.992)

Source: Appendix 6.4, Table 56.1.1, Table 56.1.2, Table 56.1.3, Table 56.1.4, and Table 58.1

3.2.3.2.5. Analysis of Clinical Pharmacology Information Relevant to Dosing Recommendations

Coadministration of TAF had no clinically relevant effect on the PK of ritonavir-boosted atazanavir (ATV+RTV), lopinavir (LPV/r), or darunavir (DRV+RTV), COBI-boosted darunavir (DRV+COBI) or elvitegravir (EVG+COBI), rilpivirine (RPV), or dolutegravir (DTG; Table 82). Therefore, no dose adjustment of these ARVs is required when coadministered with F/TAF. The effect of TAF on EFV PK has not been assessed.

The recommended dose of F/TAF (200/25 mg or 200/10 mg based on third agent) is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered as E/C/F/TAF, for which an extensive safety and efficacy database exists. The different TAF dose (10 or 25 mg) is generally based on whether or not the coadministered third agent has any clinically relevant

effect on TAF exposure (eg, via inhibition of intestinal P-gp; Table 81). Given the wide range of safe and efficacious TAF exposure established in the single-agent, proof-of-concept study (GS-US-120-0104), in Phase 2 and Phase 3 studies of E/C/F/TAF (Sections 3.2.1.2.1, 3.3.1.1, and 3.3.2.1), and the Phase 2 study of D/C/F/TAF (Study GS-US-299-0102), the variability in TAF-equivalent dose by third agent is considered acceptable.

Specifically, F/TAF 200/25 mg is recommended with third agents that do not have clinically relevant effect on TAF exposure (eg, EFV, RPV, DTG), and F/TAF 200/10 mg is recommended with third agents that substantially increase TAF exposure (eg, ATV+RTV, LPV/r, EVG+COBI [as E/C/F/TAF]). Although coadministration with boosted DRV (DRV+RTV or DRV+COBI) did not result in increased TAF absorption, clinical data from a Phase 2, randomized, double-blinded, active-controlled study in HIV-infected, ART-naive subjects (Study GS-US-299-0102; m2.7.3, Section 2) demonstrated that D/C/F/TAF (800/150/150/10 mg) was noninferior to DRV+COBI+FTC/TDF when administered for 24 weeks using the United States Food and Drug Administration (FDA) snapshot algorithm with HIV-1 RNA cutoff at 50 copies/mL, the primary endpoint of the study. These data support the use of F/TAF 200/10 mg with boosted DRV (either DRV+RTV or DRV+COBI). Although clinical studies were not conducted to evaluate the drug interaction potentials between TAF and the following drugs, none is expected based on nonclinical information (Sections 3.1.3 and 3.2.3.2.1): raltegravir (RAL), maraviroc (MVC), nevirapine (NVP), buprenorphine, methadone, naloxone, norbuprenorphine, or norgestimate/ethinyl estradiol.

The dosing recommendations for F/TAF, outlined in Table 86, were developed based on the totality of TAF plasma PK data from DDI studies, and the wide range of safe and efficacious TAF exposure established in the single-agent, proof-of-concept study (GS-US-120-0104), in Phase 2 and Phase 3 studies of E/C/F/TAF (Sections 3.2.1.2.1, 3.3.1.1, and 3.3.2.1), and the Phase 2 study of D/C/F/TAF (Study GS-US-299-0102). These dosing recommendations are further supported by intracellular TFV-DP data from subjects receiving F/TAF 200/25 mg with an unboosted third agent (ie, DTG, EFV, MVC, NVP, RAL, or RPV) or F/TAF 200/10 mg with a RTV-boosted PI in Study GS-US-311-1089, which tracked closely with TAF-equivalent dose (Table 86) and were several-fold higher than the intracellular TFV-DP concentrations following FTC/TDF administration.

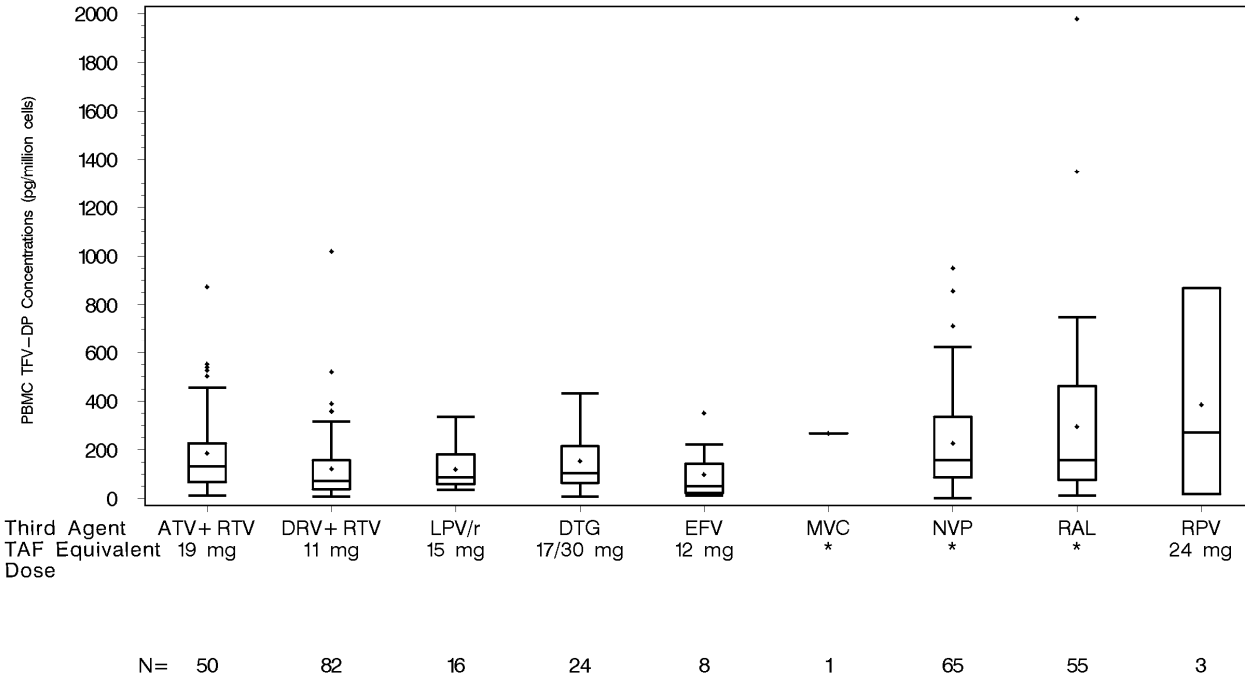
Table 86. Dose Recommendations for F/TAF with Potential Concomitant Antiretroviral Drugs

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

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

Study GS-US-311-1089 is an ongoing study in HIV-infected subjects evaluating F/TAF administered in accordance with the proposed dosing recommendations (Table 86). Figure 6 presents intracellular TFV-DP concentrations (mean and range at steady-state pre-dose) by third agent with the respective TAF-equivalent doses from Table 86. These data are supportive of the F/TAF dosing recommendations and suggest that intracellular TFV-DP loading track closely with plasma TAF exposure upon coadministration with various third agents (based on TAF-equivalent dose).

Figure 6. F/TAF Study GS-US-311-1089: Box Plot of Intracellular TFV-DP Concentration for Subjects Who Received F/TAF by Third Agent (PBMC PK Analysis Set)



Source: Appendix 6.4, Figure req7762.1

3.3. Pharmacokinetics/Pharmacodynamics

Tables, figures, and listings related to PK/PD analyses are presented in E/C/F/TAF PK/PD and STB PK/PD.

3.3.1. Pharmacokinetic-Pharmacodynamic Relationship for Efficacy Parameters

3.3.1.1. TAF

The PK/PD analysis sets for TAF and TFV included all subjects who (1) were randomized and received at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111, and (2) had at least 1 nonmissing TAF or TFV PK parameter, respectively, (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.

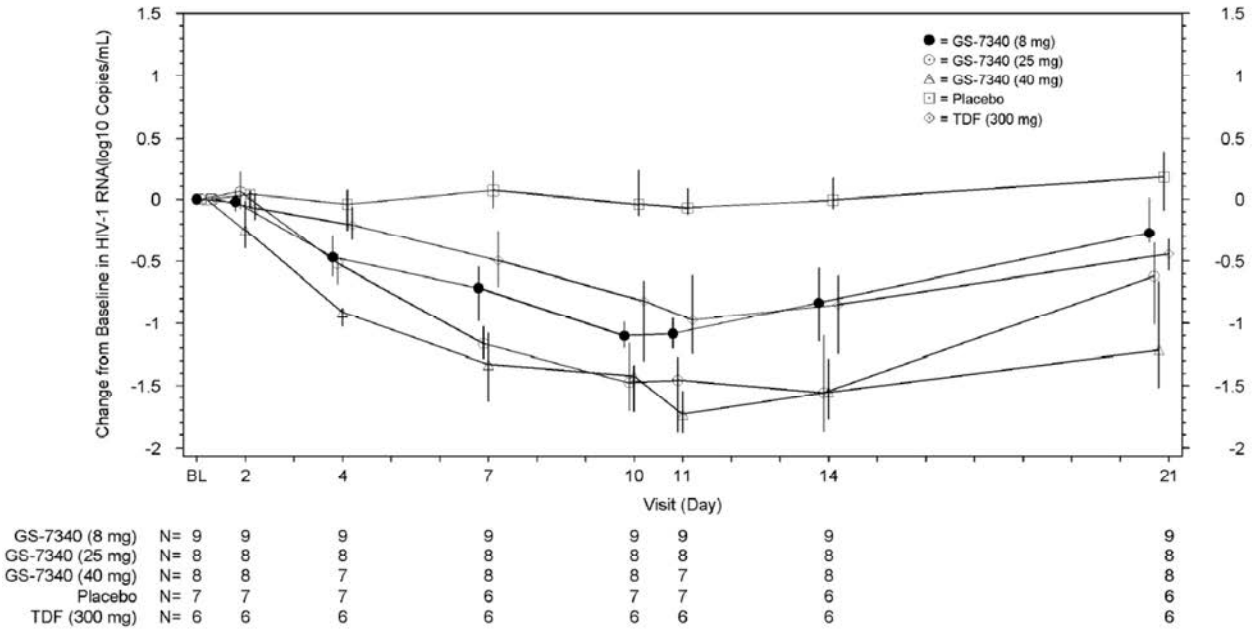
The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot algorithm. Analyses were performed between available TAF AUC_{tau} and C_{max} (estimated from population PK modeling for TAF) for the primary efficacy endpoint.

TAF

In the proof-of-concept Study GS-US-120-0104 (Section 2.3.2.1), following once-daily administration of single-agent TAF 8, 25, 40 mg, or TDF 300 mg, the median (Q1, Q3) $DAVG_{11}$

values (the primary efficacy endpoint) were −0.76 (−0.86, −0.57), −0.94 (−1.12, −0.76), −1.08 (−1.35, −0.97), and −0.48 (−0.57, −0.34) log_{10} copies/mL, respectively. The median $DAVG_{11}$ (log_{10} copies/mL) in the TAF 25-mg and 40-mg treatment groups showed significantly greater decreases compared with the TDF 300-mg treatment group (−0.94 and −1.08 versus −0.48, p = 0.017 and p = 0.006, respectively) with a statistically significant difference also observed between the TAF 8-mg and 40-mg treatment groups (−0.76 versus −1.08, p = 0.003). Median (Q1, Q3) change from baseline to Day 11 in HIV-1 RNA values were −1.08 (−1.20, −0.96), −1.46 (−1.88, −1.28), −1.73 (−1.88, −1.55) and −0.97 (−1.24, −0.62) log_{10} copies/mL for TAF 8, 25, 40 mg, and TDF 300 mg, respectively (Figure 7). The decreases in median viral load for both TAF 25 mg and TAF 40 mg were statistically significantly greater than that observed for TAF 8 mg (p = 0.030 and 0.002, respectively).

Figure 7. TAF Study GS-US-120-0104: Median (Q1, Q3) of Change from Baseline in HIV-1 RNA (log_{10} copies/mL) by Visit (Full Analysis Set)



Baseline HIV-1 RNA was defined to be the geometric mean of the last 2 available nonmissing HIV-1 RNA values before the first dose.
Source: GS-US-120-0104, Section 15.1, Figure 2.1.2

The PK/PD relationship between TAF plasma exposure and antiviral activity was explored using a maximum (PD) effect (E_{max}) model, where Effect = (E_{max} × log_{10} PK parameter)/(log_{10} PK parameter 50 + log PK parameter). Day 10 C_{max}, AUC, and change from baseline in HIV-1 RNA were fit to E_{max} models that investigated both fixed (hill = 1) and variable hill slopes. Models were evaluated using goodness of fit to select the most appropriate model. Results showed that TAF AUC fits well with an E_{max} model, resulting in an E_{max} of ~1.7 to 1.8 log_{10} copies/mL decline from baseline and a concentration of drug inhibiting virus replication by 50% (EC_{50}) value of ~32 ng•h/mL. A similar fit and E_{max} estimate was obtained using TAF C_{max}, which was somewhat expected given the relatively brief plasma circulation time of TAF (driven by a short half-life) and the resulting contribution of C_{max} to the overall AUC. Compared with the antiviral

activity of TAF 40 mg, TAF 25 mg is expected to provide near-maximal activity (~1.7 to 1.8 log_{10} copies/mL).

The PK/PD relationship between TAF plasma exposure and efficacy was also explored using data from the Phase 3 E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111.

The TAF PK/PD analysis sets included all subjects who (1) were randomized and received at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111, and (2) had at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot algorithm. Analyses were performed using available TAF AUC_{tau} and C_{max} values (estimated from population PK modeling for TAF) for the primary efficacy endpoint; results using quartiles of PK exposure are presented in Table 87.

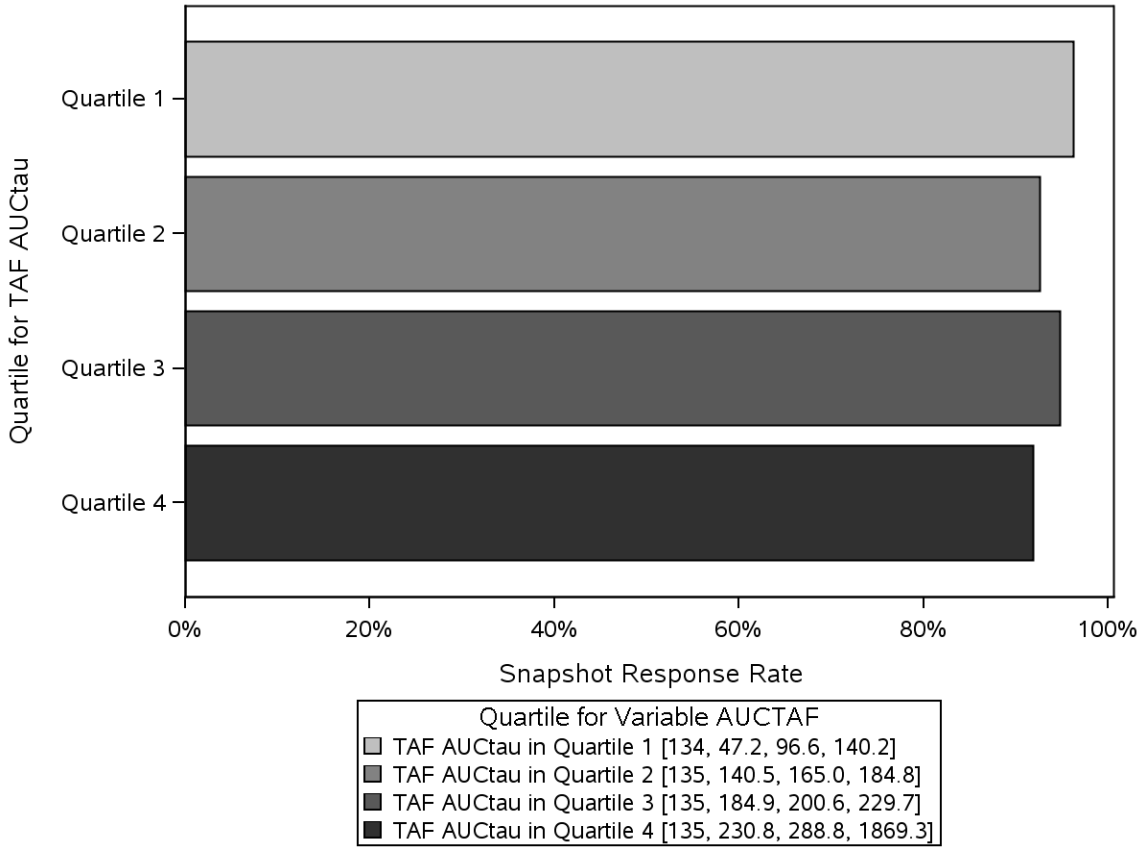
Virologic success was uniformly high across the categories of TAF AUC_{tau}, with no trends in exposure-response relationship observed. These results are consistent with the careful and data-driven dose selection of TAF 10 mg for the E/C/F/TAF FDC, which provides equivalent exposure to TAF 25 mg.

Table 87. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Percentage of Virologic Success at Week 48 Across Quartiles of TAF Exposure (TAF PK/PD Analysis Set)

Quartile	N	TAF AUC_{tau} (ng•h/mL)	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) (%)
Q1	134	47.2 to 140.2	96.3
Q2	135	140.5 to 184.8	92.6
Q3	135	184.9 to 229.7	94.8
Q4	135	230.8 to 1869.3	91.9

Source: E/C/F/TAF PK/PD, Table 2.1

Figure 8. **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, FDA Snapshot Algorithm) by TAF AUC_{tau} (ng•h/mL) Quartile Subgroup (TAF PK/PD Analysis Set)**



The TAF PK/PD analysis set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.
Source: E/C/F/TAF PK/PD, Figure 1.1.1

These results are also in accordance with the findings from the TAF population PK analyses that identified no statistically significant or clinically relevant covariates on TAF PK/exposure (Section 3.2.1.2.1) and the comparable and high rates of efficacy observed across demographic characteristics (m2.7.3, Section 3.3).

TFV

The PK/PD relationship between TFV plasma exposures and antiviral activity was explored using an E_{max} model, where Effect = (E_{max} × $\log_{10}$ PK parameter)/($\log_{10}$ PK parameter 50 + log PK parameter). Plasma TFV exposure, which was substantially lower with TAF versus TDF, did not correlate with antiviral activity.

Intracellular TFV-DP

Pooled Phase 3 data from the PK substudies in the pivotal E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 allowed for a direct comparison of intracellular TFV-DP concentrations following administration with E/C/F/TAF versus STB in HIV-infected subjects. The distinct metabolism of TAF, described in Section 3.1.3.2, provides stable and > 4-fold higher intracellular levels of TFV-DP relative to TDF (Table 88 and Figure 9).

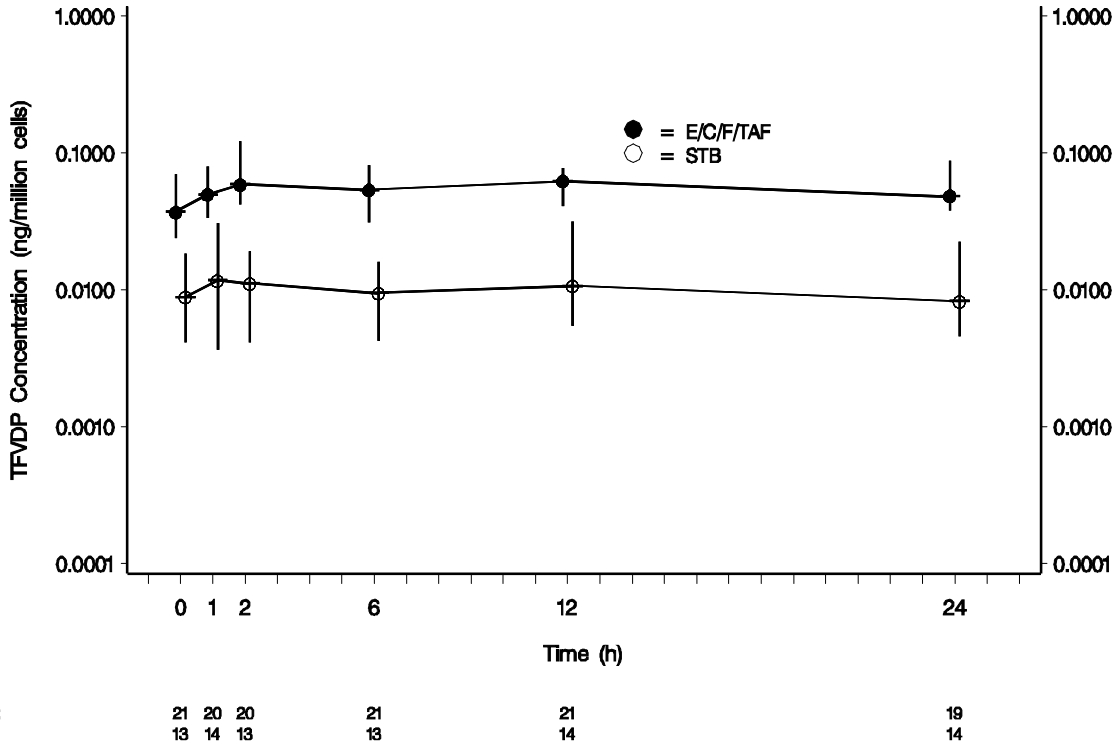
In a pooled analysis that included PK data from the Phase 2 Study GS-US-292-0102 in addition to those from the 2 pivotal Phase 3 studies (GS-US-292-0104 and GS-US-292-0111), all of which evaluated E/C/F/TAF versus STB in HIV-infected subjects, results were consistent with those in Table 88 (intracellular TFV-DP AUC_{tau} GLSM ratio of 437.25% [90% CI: 285.57%, 669.49%]) (E/C/F/TAF PK/PD, Ad Hoc Table 6875.3).

Table 88. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Statistical Comparisons of Intracellular TFV-DP PK Parameter Estimate Between Test and Reference Treatments (PK Substudy Analysis Set)

Intracellular TFV-DP PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 21)	STB (N = 14)		
AUC_{tau} (μM•h/L)	12.56	3.06	410.59	233.64, 721.55

Source: E/C/F/TAF PK/PD, Ad Hoc Table 6905.3

Figure 9. **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Median (Q1, Q3) Intracellular PBMC TFV-DP Concentrations: Intracellular TFV-DP PK Profile After Administration of E/C/F/TAF or STB (Semilogarithmic Scale, PK Substudy Analysis Set)**



Source: E/C/F/TAF PK/PD, Ad Hoc Figure 6905.4

3.3.1.2. FTC

Effects on Plasma HIV-1 RNA Levels

Two short-term studies (FTC-101 and FTC-102) were conducted to determine the dose-response relationship and to define a dosage regimen for FTC in Phase 3 studies. Study FTC-101 was an open-label, sequential, dose-ranging trial evaluating the in vivo antiviral activity of FTC in HIV-infected subjects given 14 days of monotherapy at 25 mg twice daily, 100 mg once daily, 100 mg twice daily, 200 mg once daily, and 200 mg twice daily. A total of 41 subjects (N = 8 or 9 per dose group) naive to 3TC and abacavir (ABC) were enrolled. At screening, CD4 cell count ranged from 198 to 1071 cells/mm^3 and plasma HIV-1 RNA ranged from 3.9 to 5.9 log_{10} copies/mL. Plasma HIV-1 RNA was measured at baseline and frequently over the 14 days of treatment. Pharmacokinetics of FTC in plasma and FTC-TP in PBMCs were also evaluated.

Potent ARV suppression occurred in all dosage cohorts, with a strong trend toward greater activity at the higher doses. Viral suppression in the 200-mg once-daily group was as good as in the 200-mg twice-daily group. The 200-mg once-daily dose group showed a median change in

plasma HIV-1 RNA from baseline at Day 15 of 1.9 log_{10} as compared with 1.3, 1.5, 1.7, and 1.9 log_{10} for the 25-mg twice-daily, 100-mg once-daily, 100-mg twice-daily, and 200-mg twice-daily dose groups, respectively. The onset of anti-HIV activity occurred within 48 hours of initiating FTC dosing, with the most rapid viral load decline occurring between Days 3 and 8. Results of statistical analyses of HIV-1 RNA average area under the curve minus baseline (AAUCMB), change from baseline at Day 15 (last day on study treatment), and maximum change from baseline consistently supported the dose-response relationship and the maximal antiviral effect at the 200-mg once-daily and 200-mg twice-daily doses.

Study FTC-102 was an open-label, randomized, parallel-group study evaluating 3 once-daily dosage regimens of FTC (25, 100, and 200 mg once daily) and the 3TC 150-mg twice-daily regimen during 10 days of monotherapy. A total of 81 subjects, naive to 3TC and ABC, were randomized to 1 of the 4 treatment regimens. At screening, median CD4 cell count ranged from 350 to 431 cells/mm^3 and median plasma HIV-1 RNA ranged from 4.3 to 4.7 log_{10} copies/mL. Plasma HIV-1 RNA levels were measured at baseline and frequently over the 10 days of treatment.

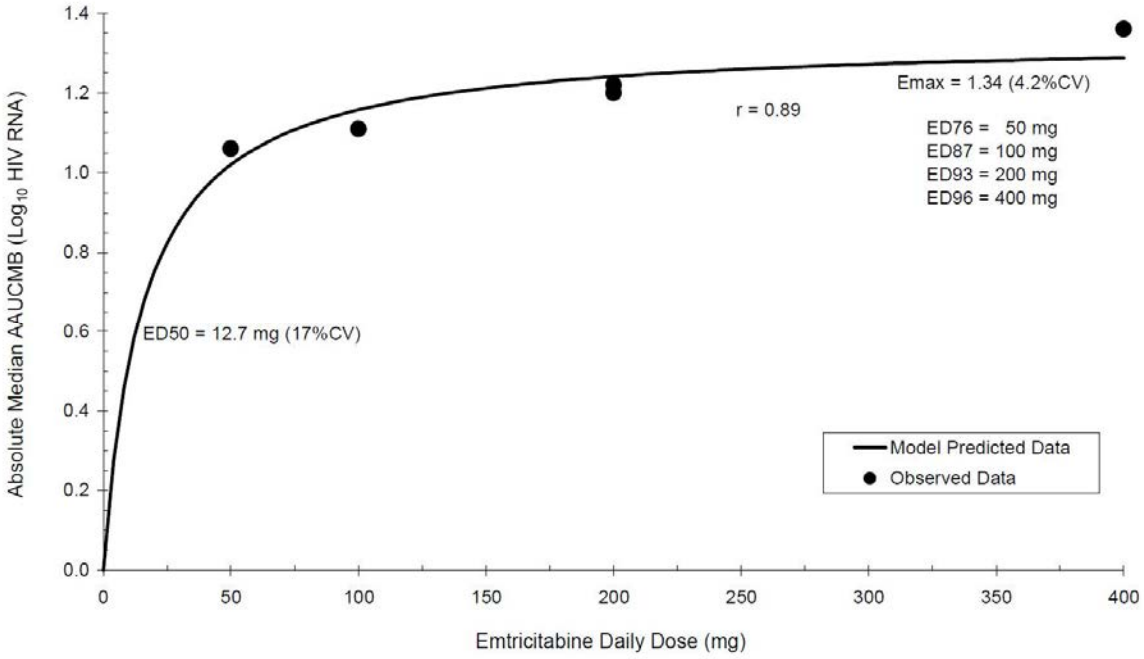
This randomized, controlled study confirmed the dose-response results of Study FTC-101, with the greatest antiviral activity occurring in the FTC 200-mg once-daily dose group. Median change in plasma HIV-1 RNA from baseline at Day 11 was 1.50, 1.58, and 1.69 log_{10} for the 25-, 100-, and 200-mg once-daily FTC doses, respectively, and was 1.48 log_{10} for the 3TC 150-mg twice-daily dose. Results from statistical analyses of HIV-1 RNA AAUCMB, change from baseline at Day 11 (last day on study treatment), and maximum change from baseline consistently distinguish 200 mg once daily from the lower FTC doses. There was a greater percentage of subjects who had HIV-1 RNA suppressed to the limit of assay detection (400 copies/mL) or who had a 2-log_{10} decrease in HIV-1 RNA from baseline receiving the FTC 200-mg once-daily dose.

The dose-response relationship was further evaluated by correlating plasma HIV-1 RNA AAUCMB with FTC daily dose from Study FTC-101 using a pharmacological E_{max} model, ie, Effect = (E_{max} × Dose)/(dose that produced a therapeutic response in 50% of subjects [ED_{50}] + Dose). The pharmacological dose-response curve (Figure 10) shows that the effect of FTC on HIV-1 RNA suppression had reached the maximal effect at doses > 200 mg per day.

The parameter estimates determined by the model are summarized as follows. The dose-response relationship of the anti-HIV activity of FTC determined by the E_{max} model shows that the antiviral effect of FTC reaches a plateau as dose increases, with little difference in the activity between the 200- and 400-mg doses. The maximal anti-HIV activity (as determined by median AAUCMB) is estimated to be 1.34 log_{10}. At a dose of 200 mg, the observed median AAUCMB, ie, 1.22 log_{10}, is approaching the maximum activity estimate. This dose-response relationship analysis indicates that the antiviral activity of FTC at a dose of 200 mg per day would have already achieved close to 95% of the maximal antiviral activity with little additional (~3%) activity observed at the 400-mg dose per day (by doubling the dose). Since the 100-mg daily dose of FTC produces anti-HIV activity that is < 90% of the maximal activity, the 200-mg daily dose is expected to be more active or robust than the 100-mg dose. Based on the totality of the

PK/PD data of FTC in plasma and FTC-TP in PBMCs, the exposure in subjects with $eGFR_{CG}$ < 50 mL/min is expected to result in near maximal antiviral activity.

Figure 10. FTC Study FTC-101: Dose-Response Relationship of Anti-HIV Activity of FTC: Plots of Log_{10} HIV-1 RNA AAUCMB Versus FTC Daily Dose



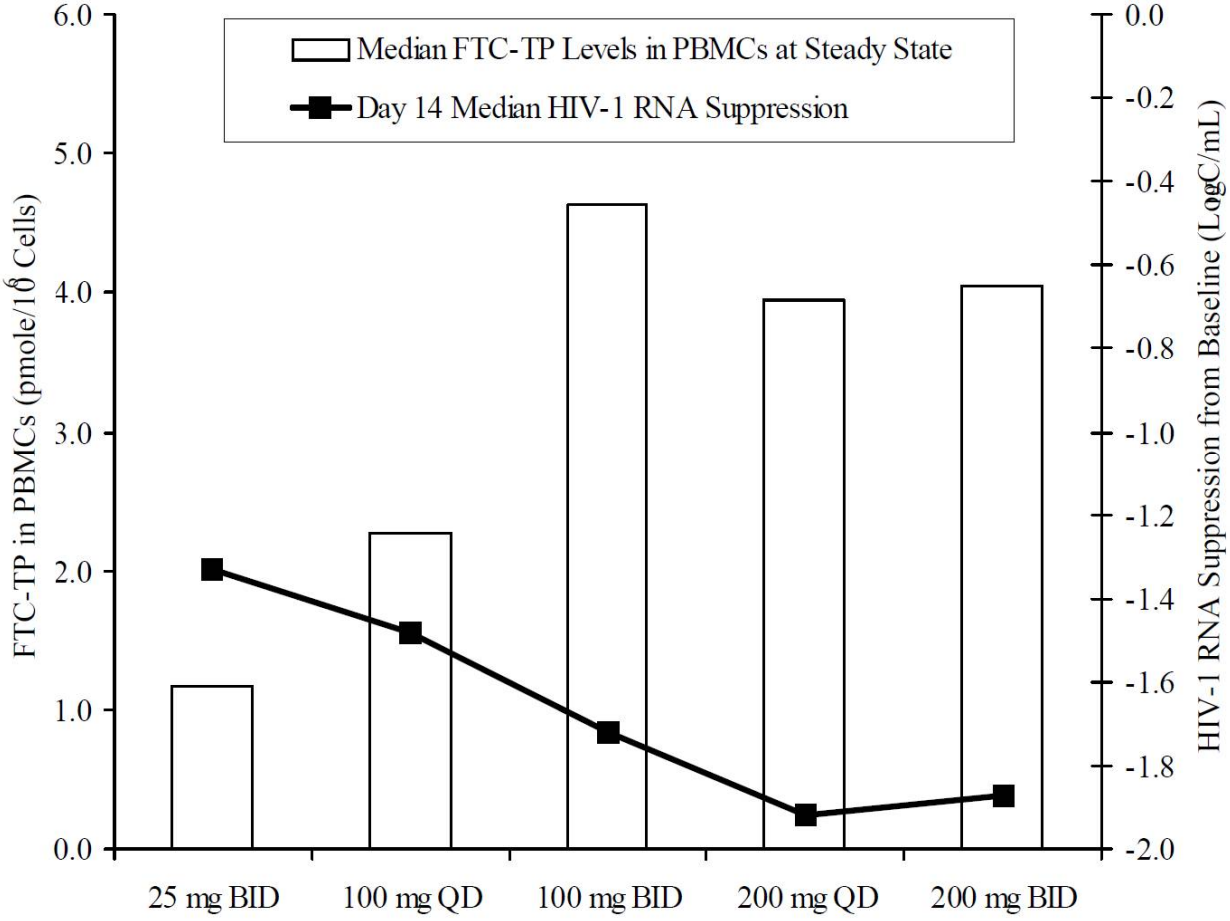
Source: {4975}

Pharmacokinetic-Pharmacodynamic Relationship

The PK and PD relationship for FTC as determined by intracellular FTC-TP concentrations versus plasma HIV-1 RNA suppression has been characterized in Study FTC-101.

In Study FTC-101, the steady-state intracellular FTC-TP concentrations in PBMCs increased in a dose-related fashion, reaching an apparent plateau level at FTC daily doses of 200 mg or greater (Figure 11). The median steady-state FTC-TP concentrations following administration of 200-mg dose twice daily were similar to those following administration of 200-mg dose once daily. This phenomenon is consistent with the saturable enzyme kinetics of intracellular FTC phosphorylation in vitro. Similarly, HIV-1 RNA suppression also increased with FTC dose and reached an apparent plateau at doses between 200 and 400 mg per day. The median viral suppression following administration of a 200-mg dose once daily was similar to that following a 200-mg dose twice daily.

Figure 11. FTC Study FTC-101: Correlation of Antiviral Activity of FTC and FTC-Triphosphate Levels in PBMCs



Source: FTC-101, Appendix 16 PK Analysis Report, Figure 12

3.3.2. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

3.3.2.1. TAF

The safety endpoints for the PK/PD analyses based on population PK estimates were:

- Presence or absence of diarrhea, nausea, vomiting, and gastrointestinal (GI) and abdominal pains (excluding oral and throat) (which included: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, and GI pain)
- Percent change from baseline at Week 48 in hip and spine BMD
- Maximum increase from baseline through Week 48 in serum creatinine
- Change from baseline at Week 48 for select fasted lipids (total cholesterol, low-density lipoprotein, and high-density lipoprotein)

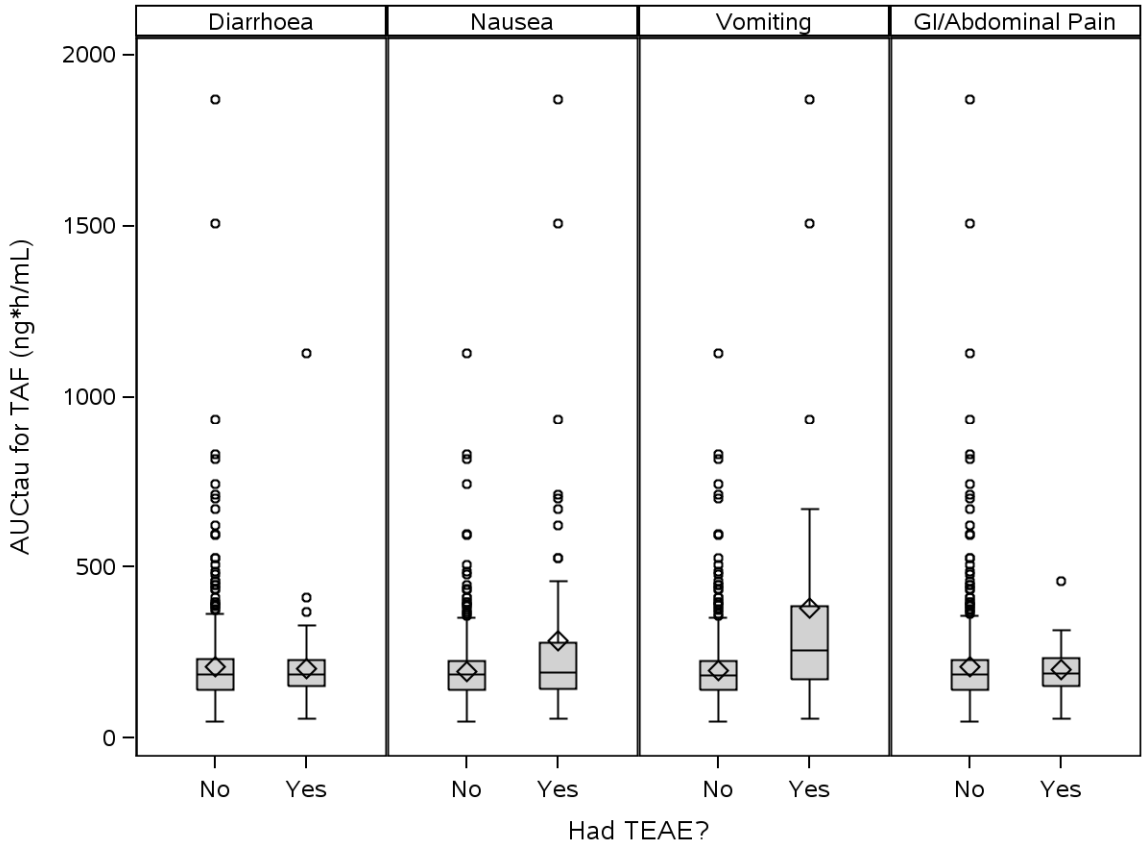
Analyses were performed between the exposure parameters (ie, AUC_{tau} and C_{max}) of TAF or TFV (estimated from population PK modeling for TAF or TFV).

The relationships between plasma TAF and TFV concentrations and ΔΔQTcF were evaluated in a thorough QT/QTc study of TAF single agent.

TAF

The PK-PD analyses of the TAF exposure-safety relationship were performed in ART-naive HIV-infected subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 using TAF exposures derived from population PK modeling versus safety parameters that included commonly observed AEs, namely diarrhea and nausea (very common ≥ 10%), and vomiting and GI/abdominal pain (common ≥ 1% and < 10%). The relationships between TAF exposure and incidence of AEs (present = yes; absent = no) are shown in Figure 12 for AUC_{tau} and in Figure 13 for C_{max}.

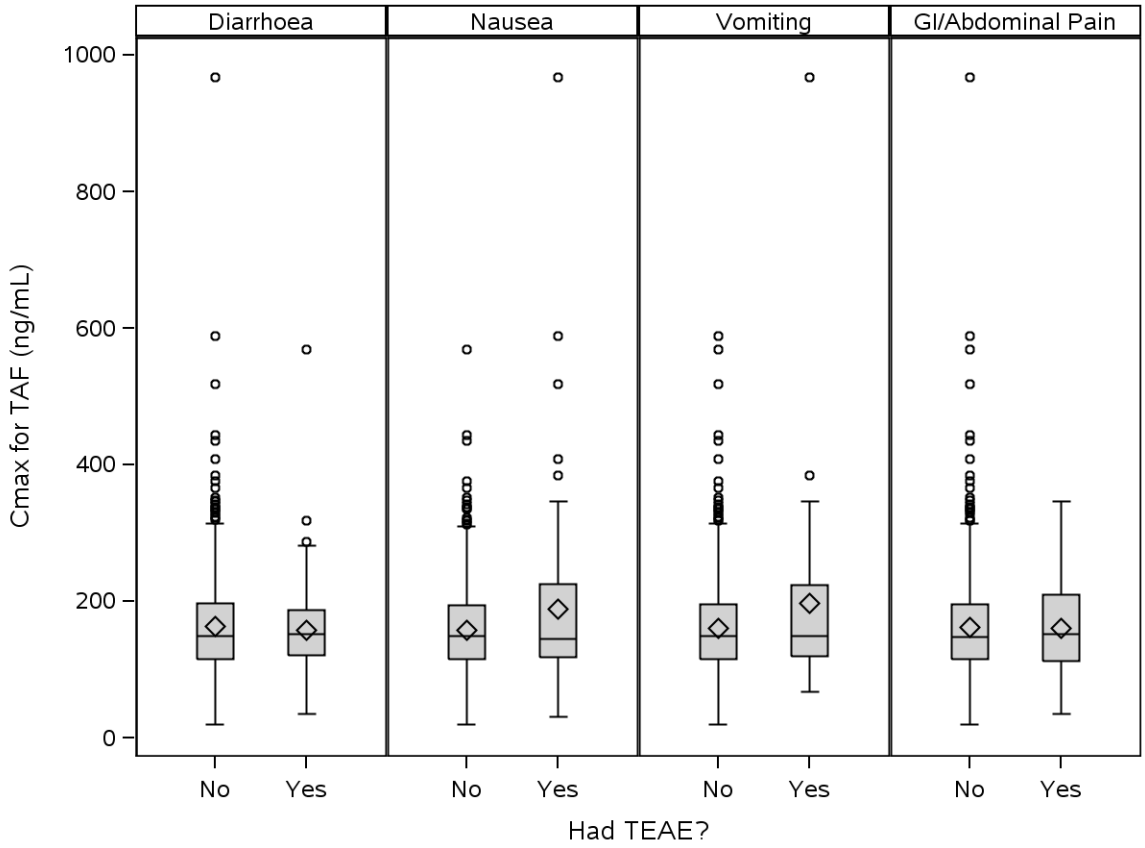
Figure 12. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of TAF AUC_{tau} (ng•h/mL) by Selected Adverse Events (TAF PK/PD Analysis Set)



Diarrhea: No (n = 454), Yes (n = 85); Nausea: No (n = 463), Yes (n = 76); Vomiting: No (n = 508), Yes (n = 31); GI/Abdominal Pains: No (n = 512), Yes (n = 27)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.

The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
AEs were coded using MedDRA Version 17.0.
Diarrhoea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).
Source: E/C/F/TAF PK/PD, Table 4.1.1 and Figure 2.1.1

Figure 13. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of TAF C_{max} (ng/mL) by Selected Adverse Events Subgroup (TAF PK/PD Analysis Set)



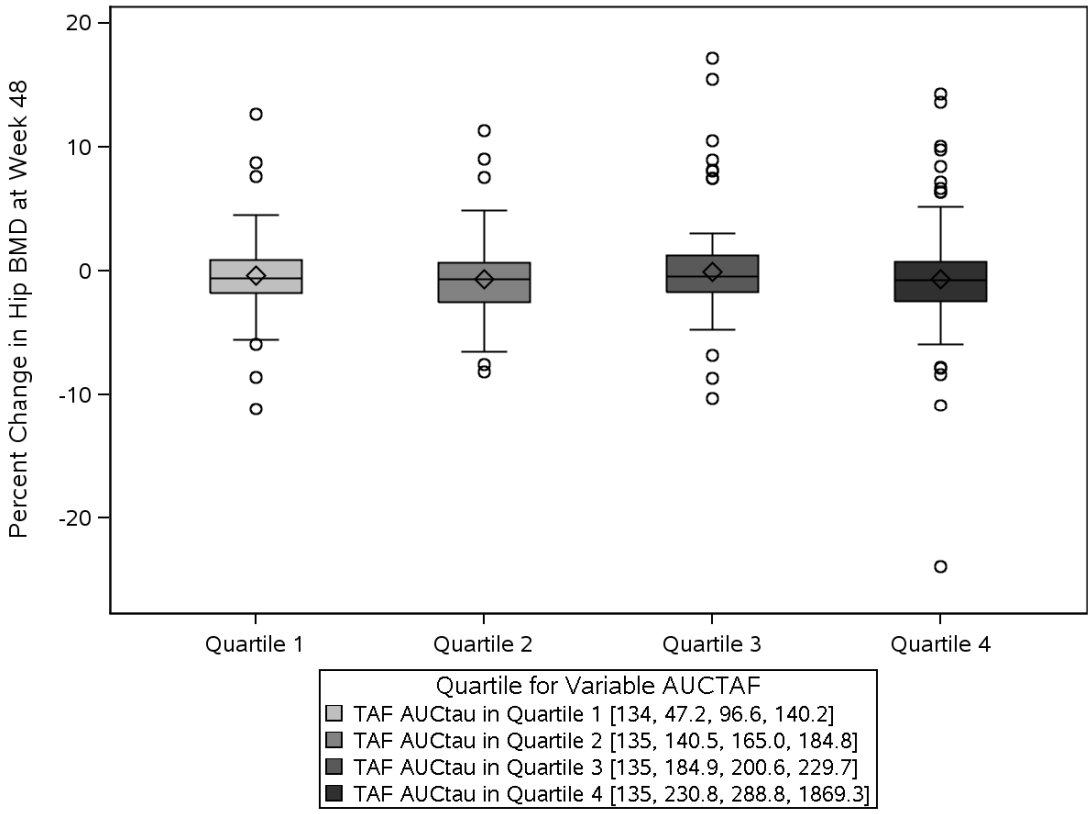
Diarrhea: No (n = 454), Yes (n = 85); Nausea: No (n = 463), Yes (n = 76); Vomiting: No (n = 508), Yes (n = 31); GI/Abdominal Pains: No (n = 512), Yes (n = 27)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
AEs were coded using MedDRA Version 17.0.
Diarrhoea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).
Source: E/C/F/TAF PK/PD, Table 4.1.1 and Figure 2.1.2

For diarrhea and GI/abdominal pain, TAF exposure was comparable regardless of the presence or absence of either of those symptoms and no exposure-AE trends were observed with these AEs.

TAF exposure was generally comparable in the presence or absence of nausea and vomiting, but logistic regression analysis showed a trend between the highest TAF exposure and the presence of these AEs (nausea correlated with the highest 4% of TAF exposure; vomiting correlated with the highest 19% of TAF exposure) (E/C/F/TAF PK/PD, Ad Hoc Tables 6918.1.1.1 to 6918.1.2.2 and 6921.1). No trend was observed between exposure and severity (E/C/F/TAF PK/PD, Ad Hoc Tables 6918.2.1.1 to 6918.2.2.2). The overall incidence of nausea and vomiting was similar between treatment groups in Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF ISS, Table 7).

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were also key safety endpoints in Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TAF exposure quartiles and changes in BMD at the hip and spine were evaluated and results of the analysis are shown in Figure 14 for hip BMD and in Figure 15 for spine BMD. The percentage change from baseline at Week 48 was comparable across TAF AUC_{tau} quartiles for both hip and spine BMD; no exposure-changes in BMD trends were noted.

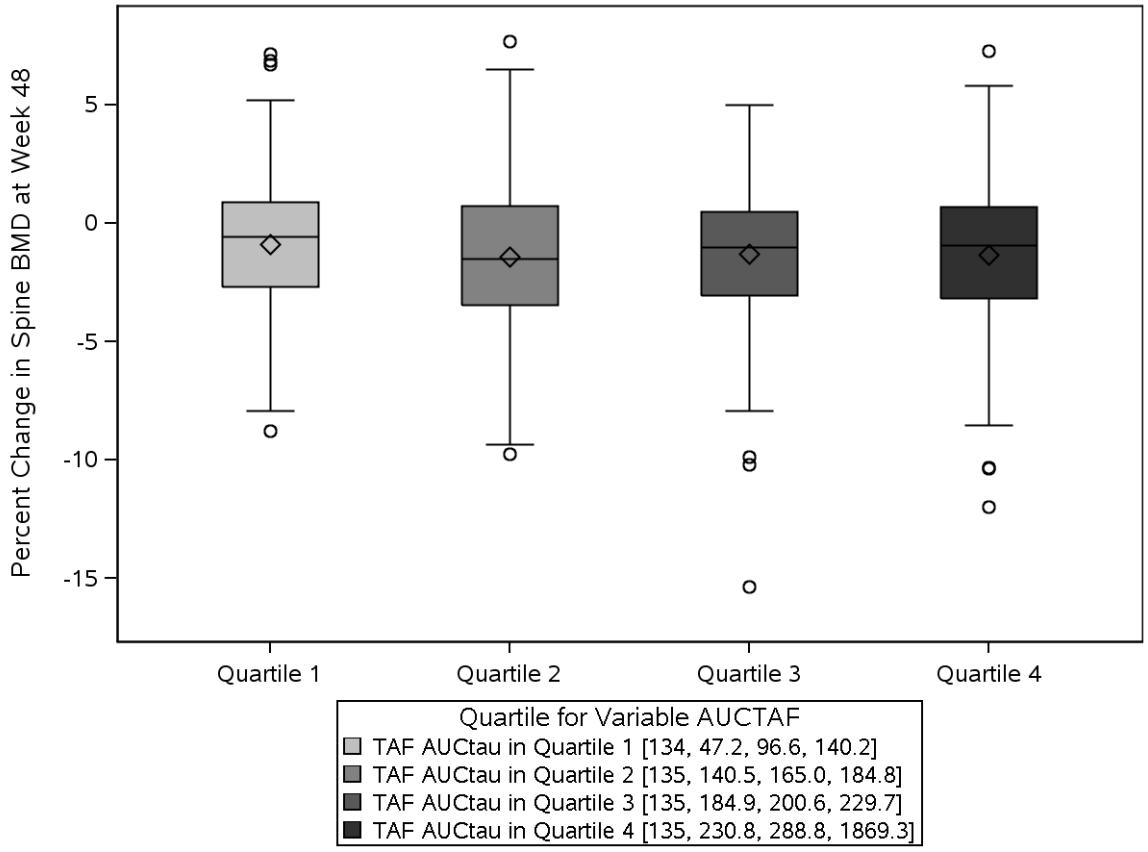
Figure 14. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.

Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.
Source: E/C/F/TAF PK/PD, Figure 6.1.1.1

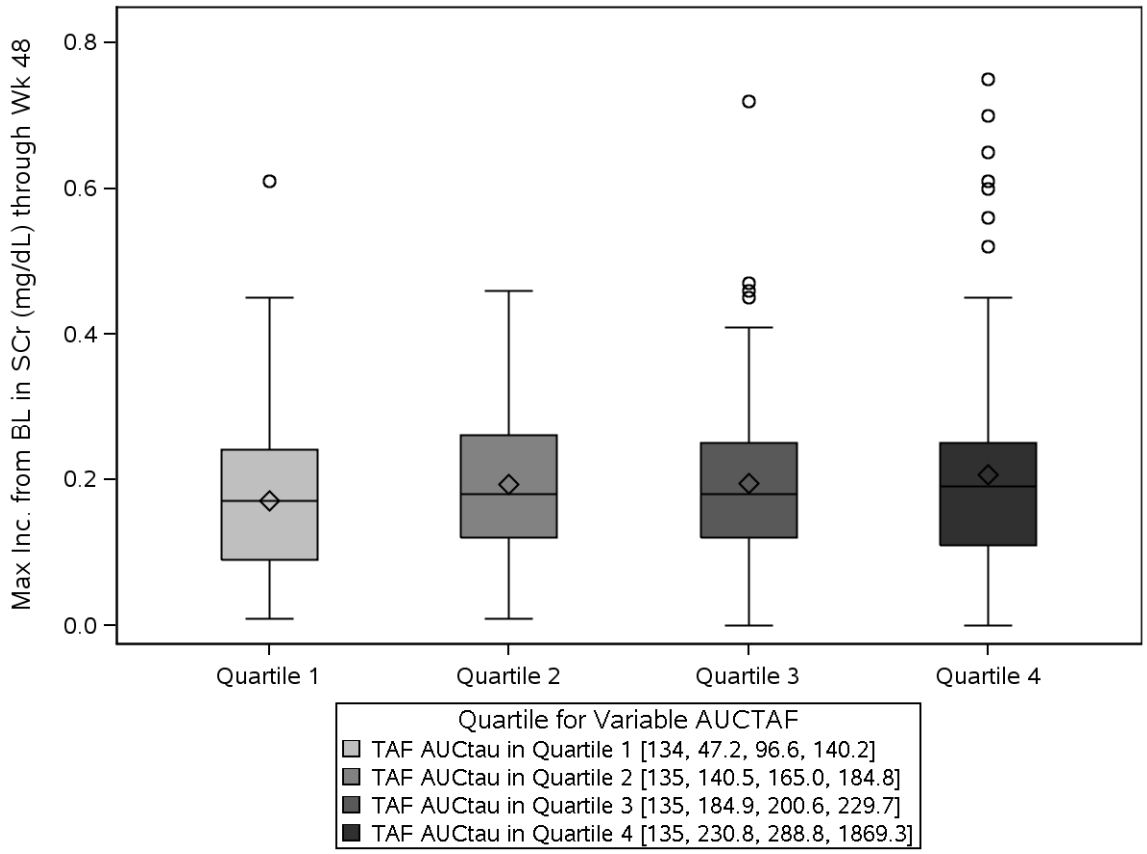
Figure 15. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.
Source: E/C/F/TAF PK/PD, Figure 6.1.1.2

Change from baseline in serum creatinine at Week 48 was a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. The relationship between TAF exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated and results of the analysis are shown in Figure 16. Maximum increase from baseline in serum creatinine was comparable across TAF AUC_{tau} quartiles; no exposure changes in serum creatinine trends were noted.

Figure 16. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TAF PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TAF AUC_{tau} for subjects included in the corresponding quartile.
Source: E/C/F/TAF PK/PD, Figure 4.1.1

A linear mixed-effect model was used to quantify the relationship between plasma concentrations of TAF and ΔΔQTcF with gender as a fixed effect and subject as a random effect. The statistical analyses of the relationship between TAF plasma concentrations and ΔΔQTcF are summarized in Table 89, the relationship between TAF plasma concentrations and ΔΔQTcF is depicted graphically in Figure 17, and the relationship between TAF plasma concentrations and ΔΔQTcF at T_{max} is depicted graphically in Figure 18. The results suggest that there is no statistically significant or pharmacologically meaningful association between TAF plasma concentration and ΔΔQTcF interval.

At the observed TAF C_{max} (174.3 ng/mL) following administration of TAF 25 mg, mean ΔΔQTcF is predicted to be –0.373 msec (the upper 95% 1-sided CI = 0.686). At the observed

TAF C_{max} (859.0 ng/mL) following administration of TAF 125 mg, mean ΔΔQTcF is predicted to be 0.389 msec (the upper 95% 1-sided CI = 1.930). Both upper limits of the 1-sided 95% CIs were far below the ICH E14 recommended threshold of 10 msec.

Similar analyses were performed to evaluate the relationship between TAF plasma concentrations and ΔQTcF, and the relationship between TAF plasma concentrations and raw QTcF. The results suggest that there is a statistically significant, small, negative association between TAF plasma concentrations and ΔQTcF and raw QTcF interval. This very weak association was maintained upon adjustment for gender.

Table 89. TAF Study GS-US-120-0107: Statistical Analysis of the Relationship between TAF Plasma Concentrations and Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF (TAF PK/PD Analysis Set)

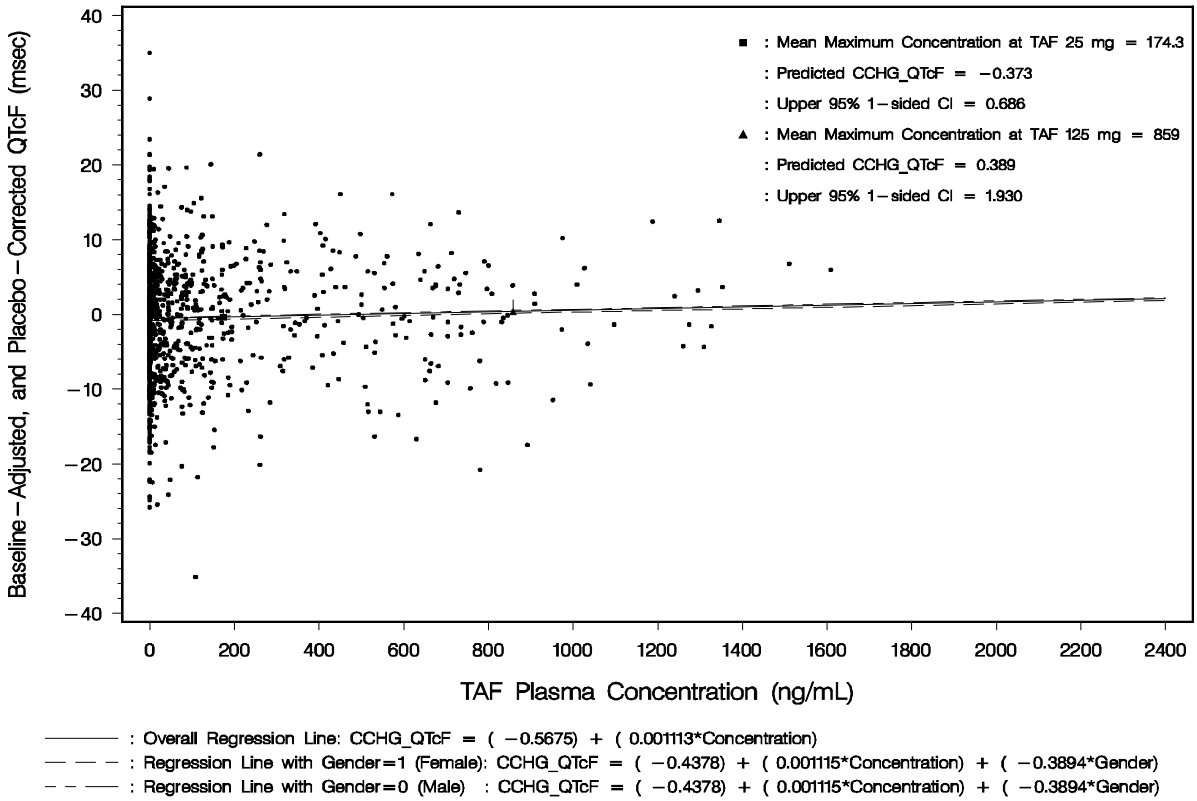
QTcF	Estimate	Standard Error	95% Confidence Interval		p-value
			Lower	Upper	
Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF					
Overall Regression Equation: ΔΔQTcF = a + (b × Concentration)					
Intercept (a)	-0.5675	0.6509	-1.8769	0.7420	0.39
Concentration (b)	0.001113	0.000921	-0.00069	0.002920	0.23
Regression Equation with Gender as a Fixed Effect: ΔΔQTcF = a + (b × Concentration) + (c × Gender[a])					
Intercept (a)	-0.4378	0.8006	-2.0494	1.1737	0.59
Concentration (b)	0.001115	0.000921	-0.00069	0.002922	0.23
Gender (c)	-0.3894	1.3746	-3.1563	2.3775	0.78

a For the regression equation with gender as a fixed effect, "Gender" was defined as 0 for male subjects and 1 for female subjects.

Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect. PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.

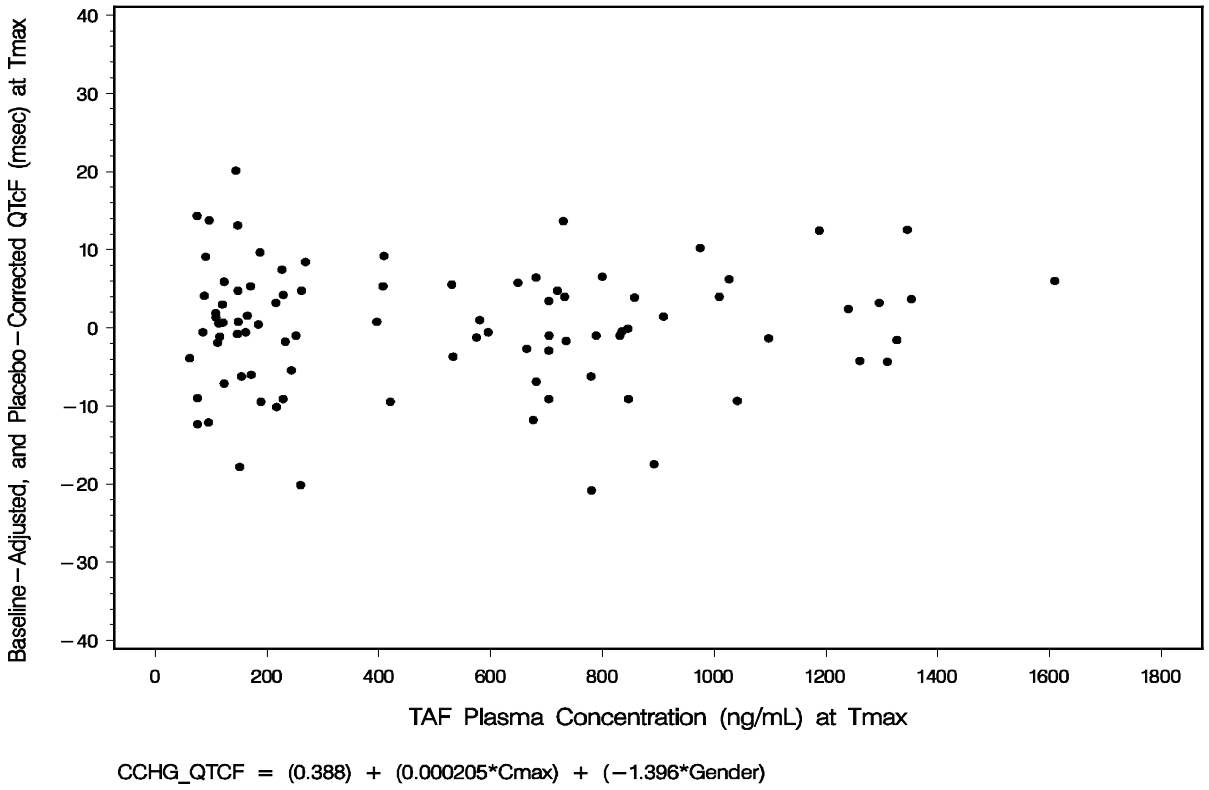
Source: GS-US-120-0107, Section 15.1, Table 16.1

Figure 17. TAF Study GS-US-120-0107: Scatter Plot of Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF versus TAF Plasma Concentration (TAF PK/PD Analysis Set)



Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect.
PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.
Upper 95% 1-sided CI was calculated based on overall PK/PD regression model.
Source: GS-US-120-0107, Section 15.1, Figure 6.1

Figure 18. TAF Study GS-US-120-0107: Scatter Plot of Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF at T_{max} versus TAF Plasma Concentration at T_{max} (TAF PK/PD Analysis Set)



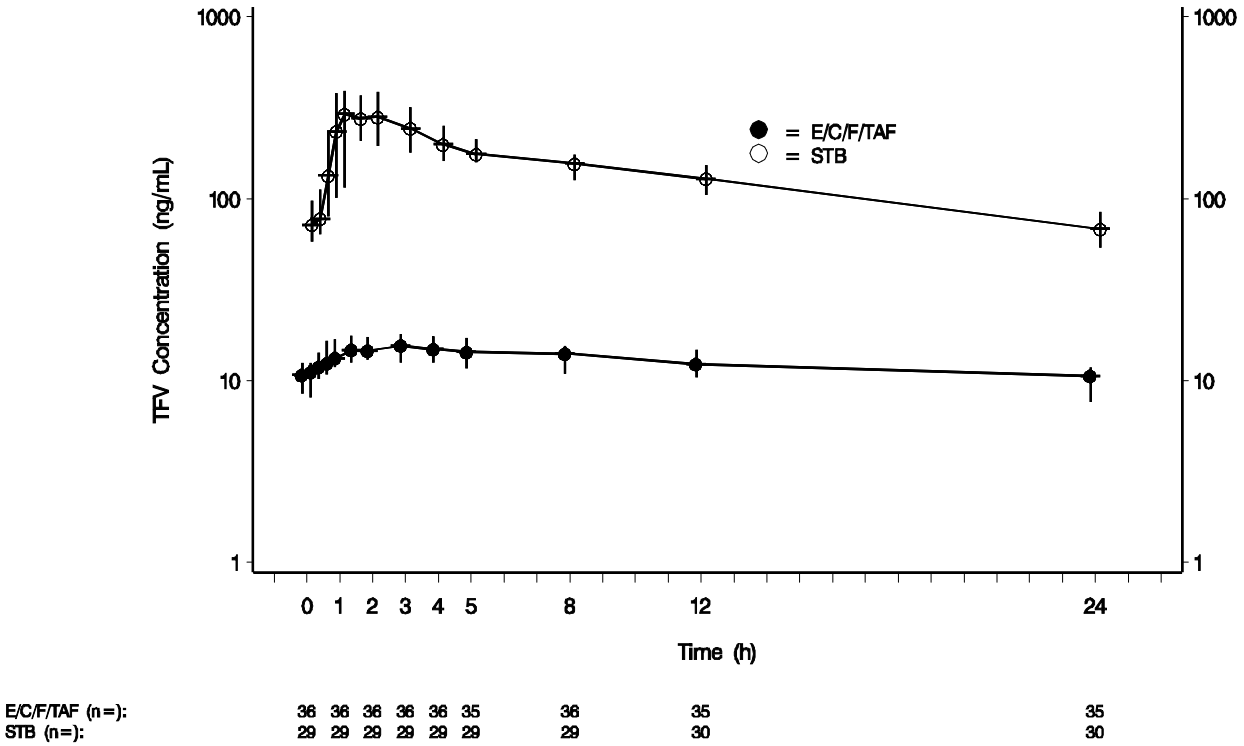
PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.
Source: GS-US-120-0107, Section 15.1, Figure 6.3

TFV

As described in Section 3.1.3.2, TAF has a distinct metabolism designed to maximize both antiviral potency and clinical safety. Pooled Phase 3 data from the PK substudies in the pivotal Studies GS-US-292-0104 and GS-US-292-0111 allowed for a direct comparison of plasma TFV concentration following administration with E/C/F/TAF versus STB in HIV-infected subjects. TAF is more stable in plasma than TDF and provides a relative reduction in circulating levels of TFV of more than 90% (Figure 19 and Table 90).

In a pooled analysis that included PK data from the Phase 2 Study GS-US-292-0102 in addition to those from the 2 pivotal Phase 3 studies (GS-US-292-0104 and GS-US-292-0111), all of which evaluated E/C/F/TAF versus STB in HIV-infected subjects, results were consistent with those in Table 90 (plasma TFV AUC_{tau} GLSM ratio of 8.90% [90% CI: 8.20%, 9.65%]; E/C/F/TAF PK/PD, Ad Hoc Table 6875.3).

Figure 19. **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Median (Q1, Q3) Plasma TFV Concentrations: TFV PK Profile After Administration of E/C/F/TAF or STB (Semilogarithmic Scale, PK Substudy Analysis Set)**



Source: E/C/F/TAF PK/PD, Ad Hoc Figure 6905.3

Table 90. **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Statistical Comparisons of TFV PK Parameter Estimates Between Test and Reference Treatments (PK Substudy Analysis Set)**

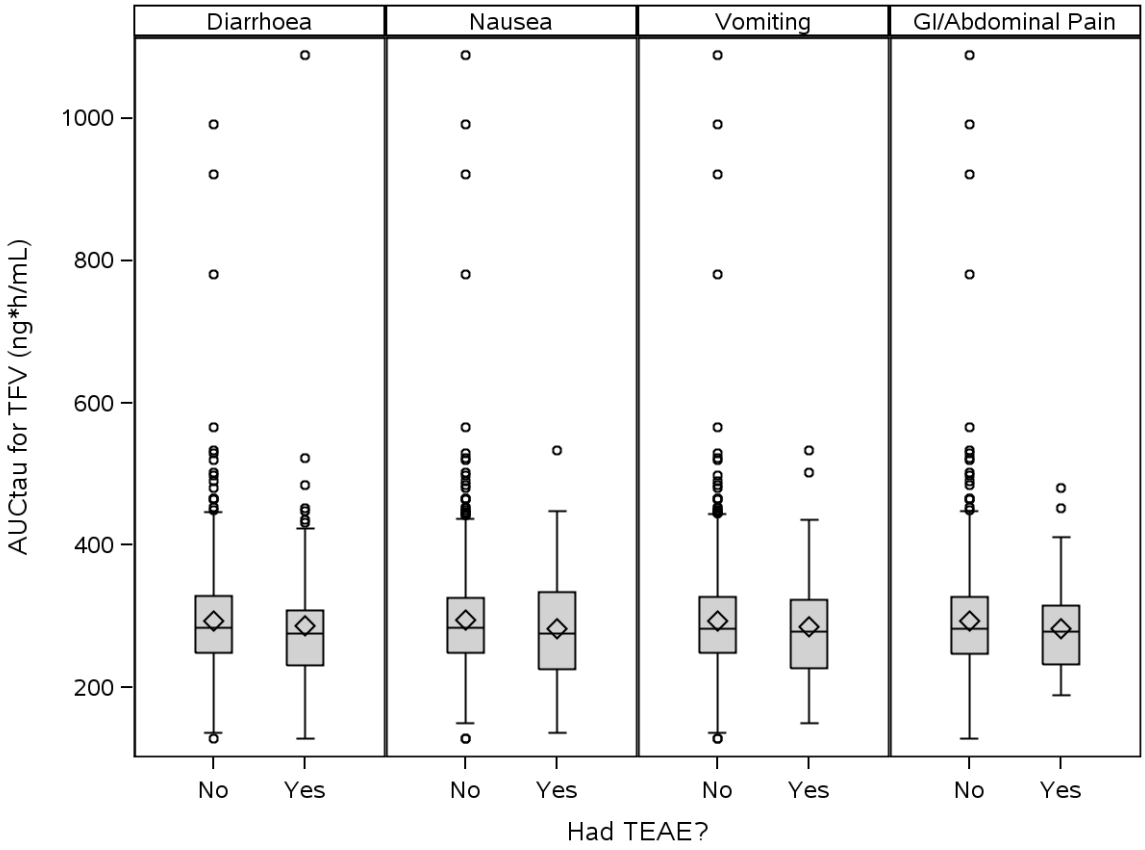
TFV PK Parameter	GLSMs by Treatment		GLSM Ratio (90% CI),%
	E/C/F/TAF (N = 36)	STB (N = 30)	
AUC_{tau} (ng•h/mL)	290.25	3308.04[a]	8.77 (7.94, 9.69)
C_{max} (ng/mL)	16.52	399.12[a]	4.14 (3.69, 4.64)
C_{tau} (ng/mL)	9.70[b]	65.61	14.79 (13.08, 16.73)

a N = 29
b N = 35
Source: E/C/F/TAF PK/PD, Ad Hoc Table 6905.3

The PK-PD analyses of the TFV exposure-safety relationship were performed in ART-naive HIV-infected subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 using TFV exposures derived from population PK modeling versus safety parameters that included

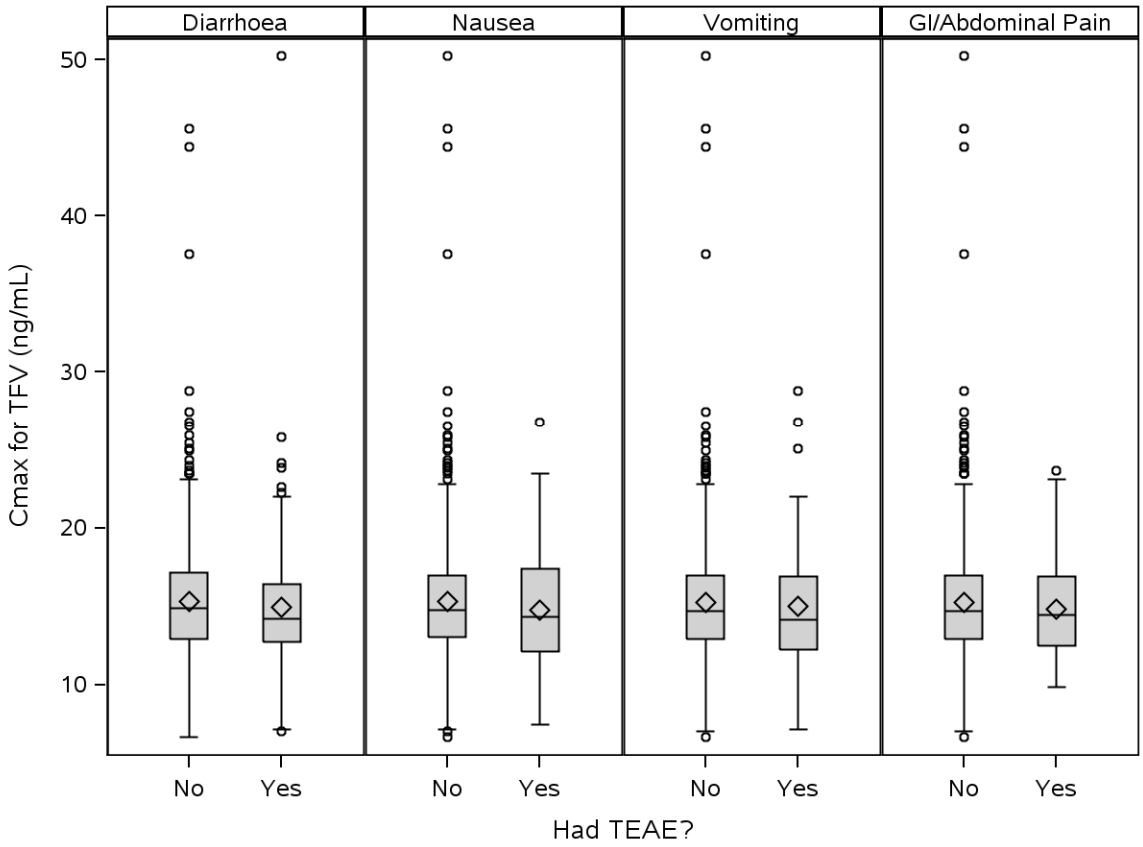
commonly observed AEs, namely diarrhea and nausea (very common ≥ 10%), and vomiting and GI/abdominal pain (common ≥ 1% and < 10%). The relationships between TFV exposure and incidence of AEs (present = yes; absent = no) are shown in Figure 20 for AUC_{tau} and in Figure 21 for C_{max}.

Figure 20. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of TFV AUC_{tau} (ng•h/mL) by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set)



Diarrhea: No (n = 696), Yes (n = 145); Nausea: No (n = 715), Yes (n = 126); Vomiting: No (n = 781), Yes (n = 60); GI/Abdominal Pains: No (n = 788), Yes (n = 53)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
AEs were coded using MedDRA Version 17.0.
Diarrhoea, nausea, and vomiting refer to MedDRA preferred terms; GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).
Source: E/C/F/TAF PK/PD, Table 4.2.1 and Figure 2.2.1

Figure 21. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of TFV C_{max} (ng/mL) by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set)



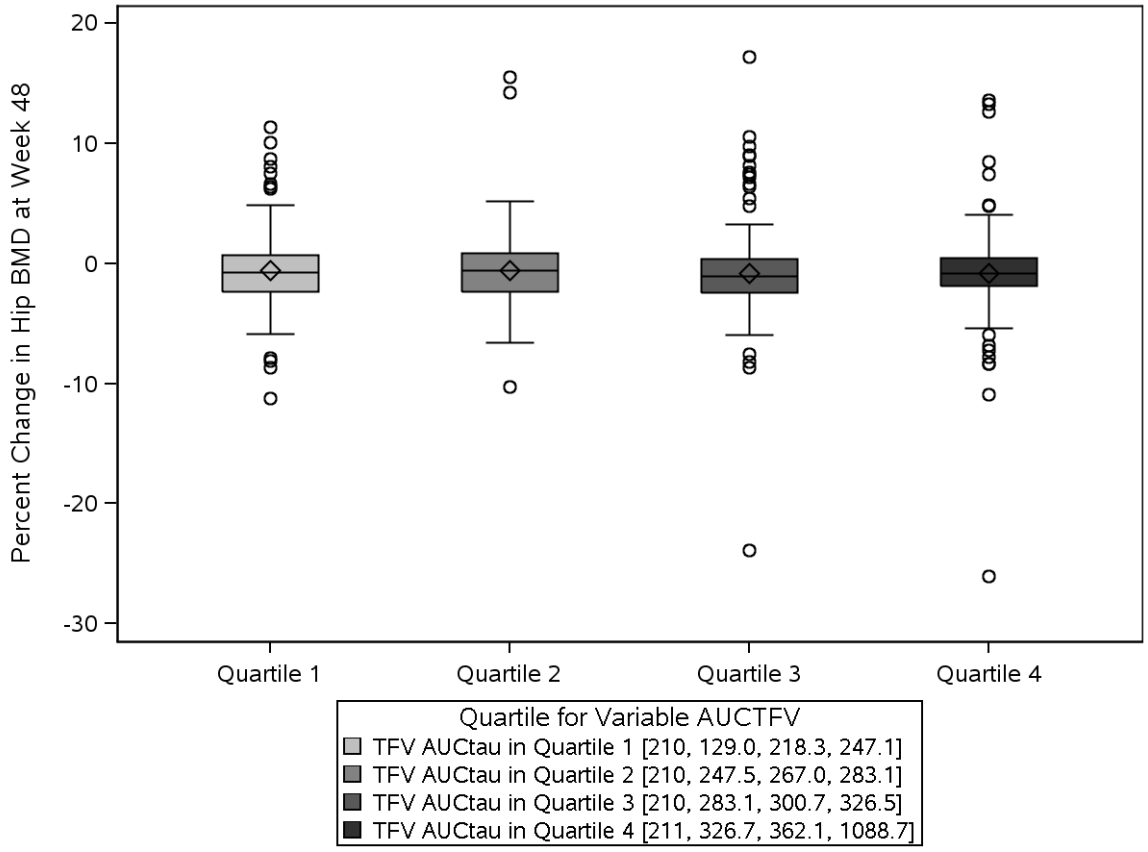
Diarrhea: No (n = 696), Yes (n = 145); Nausea: No (n = 715), Yes (n = 126); Vomiting: No (n = 781), Yes (n = 60); GI/Abdominal Pains: No (n = 788), Yes (n = 53)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
AEs were coded using MedDRA Version 17.0.
Diarrhoea, nausea, and vomiting refer to MedDRA preferred terms, GI/abdominal pain refers to the MedDRA high-level term GI and abdominal pains (excluding oral and throat).
Source: E/C/F/TAF PK/PD, Table 4.2.1 and Figure 2.2.2

For diarrhea, GI/abdominal pain, nausea, and vomiting, TFV exposure was comparable regardless of the presence or absence of those symptoms and no exposure-AE trends were observed with these AEs.

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were also key safety endpoints in Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TFV exposure quartiles and changes in BMD at the hip and spine were evaluated and results of the analysis are shown in Figure 22 for hip BMD and in Figure 23 for

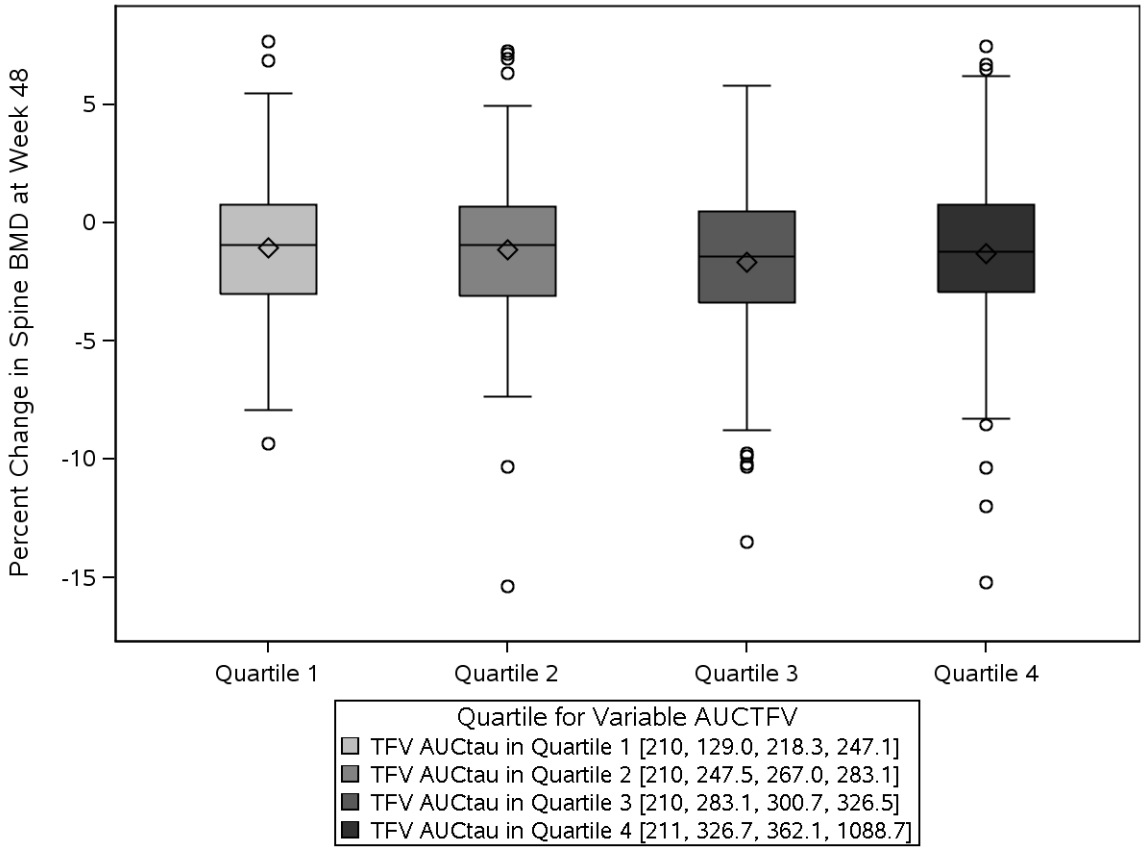
spine BMD. The percentage change from baseline at Week 48 was comparable across all TFV AUC_{tau} quartiles for both hip and spine BMD; no exposure-changes in BMD trends were noted.

Figure 22. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TFV AUC_{tau} for subjects included in the corresponding quartile.
Source: E/C/F/TAF PK/PD, Figure 6.2.1.1

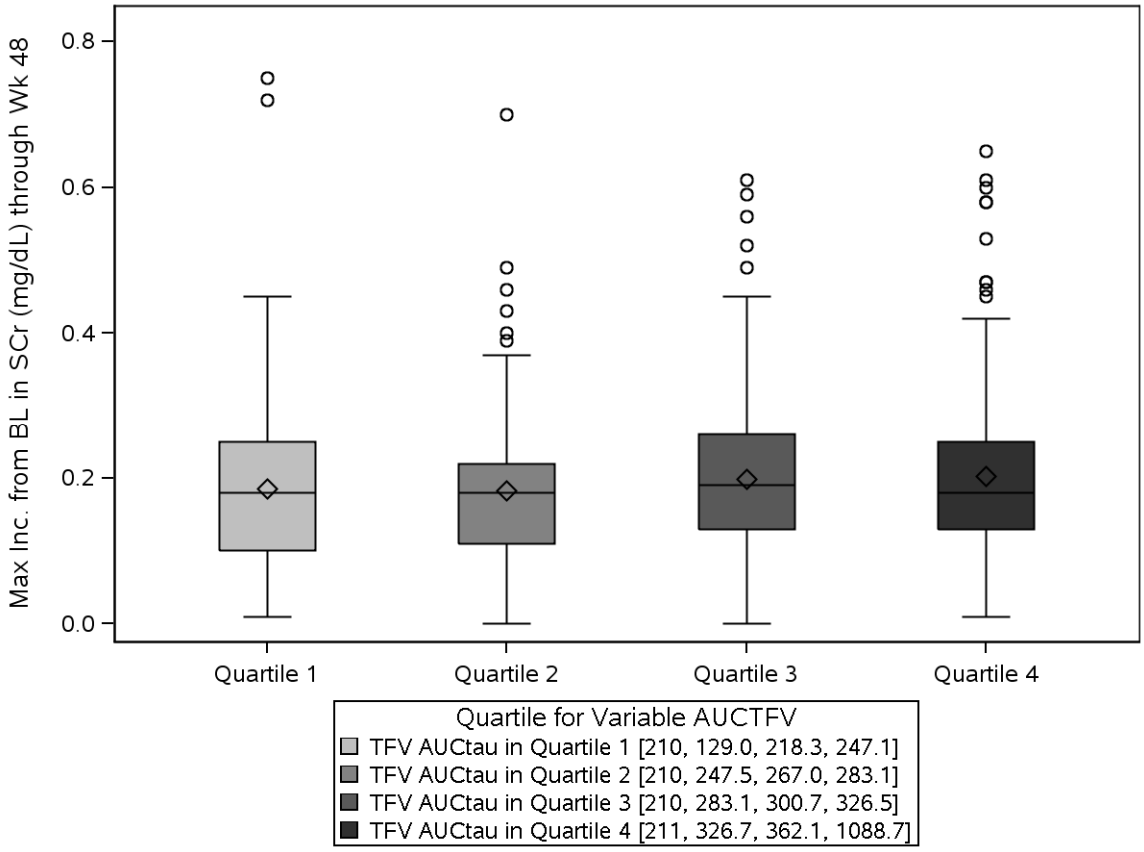
Figure 23. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TFV AUC_{tau} for subjects included in the corresponding quartile.
Source: E/C/F/TAF PK/PD, Figure 6.2.1.2

Change from baseline in serum creatinine at Week 48 was a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. The relationship between TFV exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated and results of the analysis are shown in Figure 24. Maximum increase from baseline in serum creatinine was comparable across TFV AUC_{tau} quartiles; no exposure-changes in serum creatinine trends were noted.

Figure 24. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)



Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TFV PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 or GS-US-292-0111 and at least 1 nonmissing TFV PK parameter (ie, AUC_{tau} or C_{max}) estimated from the TAF population PK analysis.
Numbers presented in the square brackets are the sample size, minimum, median, and maximum of TFV AUC_{tau} for subjects included in the corresponding quartile.
Source: E/C/F/TAF PK/PD, Figure 4.2.1

A linear mixed-effect model was used to quantify the relationship between plasma concentrations of TFV and ΔΔQTcF with gender as a fixed effect and subject as a random effect. The statistical analyses of the relationship between TFV plasma concentrations and ΔΔQTcF are summarized in Table 91, the relationship between TFV plasma concentrations and ΔΔQTcF is depicted graphically in Figure 25, and the relationship between TFV plasma concentrations and ΔΔQTcF at T_{max} is depicted graphically in Figure 26. The results suggest that there is a statistically significant, small, positive association between TFV plasma concentration and ΔΔQTcF interval. This small association was not considered clinically meaningful because the predicted population mean increases in ΔΔQTcF at the mean maximum plasma concentrations with therapeutic and supratherapeutic doses were far below the ICH E14 recommended threshold of 10 msec. This very weak association was maintained upon adjustment for gender.

At the observed TFV C_{max} (8.7 ng/mL) following administration of TAF 25 mg, mean ΔΔQTcF is predicted to be –0.570 msec (the upper 95% 1-sided CI = 0.487). At the observed TFV C_{max} (50.8 ng/mL) following administration of TAF 125 mg, mean ΔΔQTcF is predicted to be 0.877 msec (the upper 95% 1-sided CI = 2.259). Both upper limits of the 1-sided 95% CIs were far below the ICH E14 recommended threshold of 10 msec.

Similar analyses were performed to evaluate the relationship between TFV plasma concentrations and ΔQTcF, and the relationship between TFV plasma concentrations and raw QTcF. The results suggest that there is a statistically significant, small, negative association between TFV plasma concentrations and ΔQTcF and raw QTcF interval. This very weak association was maintained upon adjustment for gender.

Although there appears to be a statistically significant, positive association between plasma concentrations of TFV and ΔΔQTcF, the estimated slope is very small and the predicted population mean increase in ΔΔQTcF at the mean maximum plasma concentration under therapeutic and supratherapeutic doses are far below the ICH E14 recommended threshold of 10 msec. Taking into account the fact that TFV concentrations seem negatively associated with ΔQTcF and raw QTcF, we conclude that there is no pharmacologically meaningful association between plasma concentrations of TFV and ΔΔQTcF, ΔQTcF, or raw QTcF.

Table 91. TAF Study GS-US-120-0107: Statistical Analysis of the Relationship between TFV Plasma Concentrations and Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF (PK/PD Analysis Set)

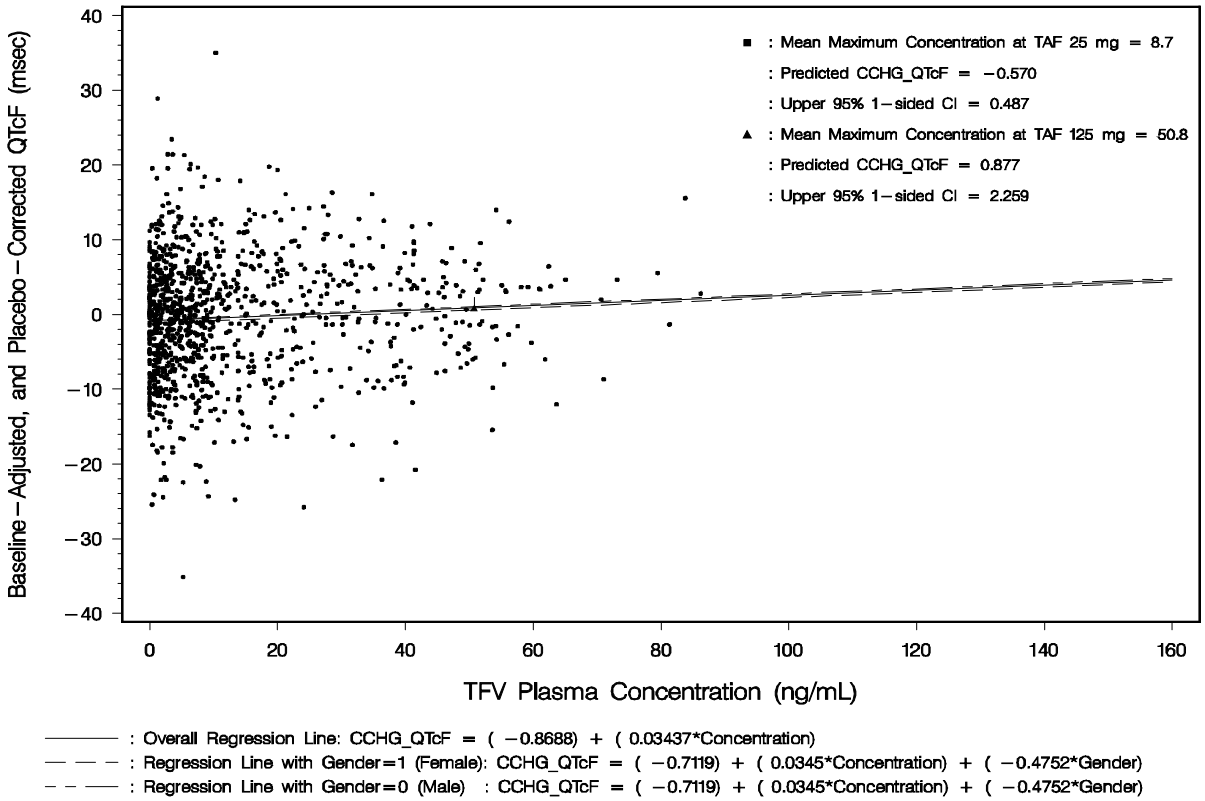
QTcF	Estimate	Standard Error	95% Confidence Interval		p-value
			Lower	Upper	
Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF					
Overall Regression Equation: ΔΔQTcF = a + (b × Concentration)					
Intercept (a)	-0.8688	0.6641	-2.2047	0.4671	0.20
Concentration (b)	0.03437	0.01424	0.006429	0.06231	0.016
Regression Equation with Gender as a Fixed Effect: ΔΔQTcF = a + (b × Concentration) + (c × Gender[a])					
Intercept (a)	-0.7119	0.8076	-2.3376	0.9138	0.38
Concentration (b)	0.03450	0.01424	0.006547	0.06245	0.016
Gender (c)	-0.4752	1.3696	-3.2320	2.2816	0.73

a For the regression equation with gender as a fixed effect, "Gender" was defined as 0 for male subjects, 1 for female subjects.

Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect. PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.

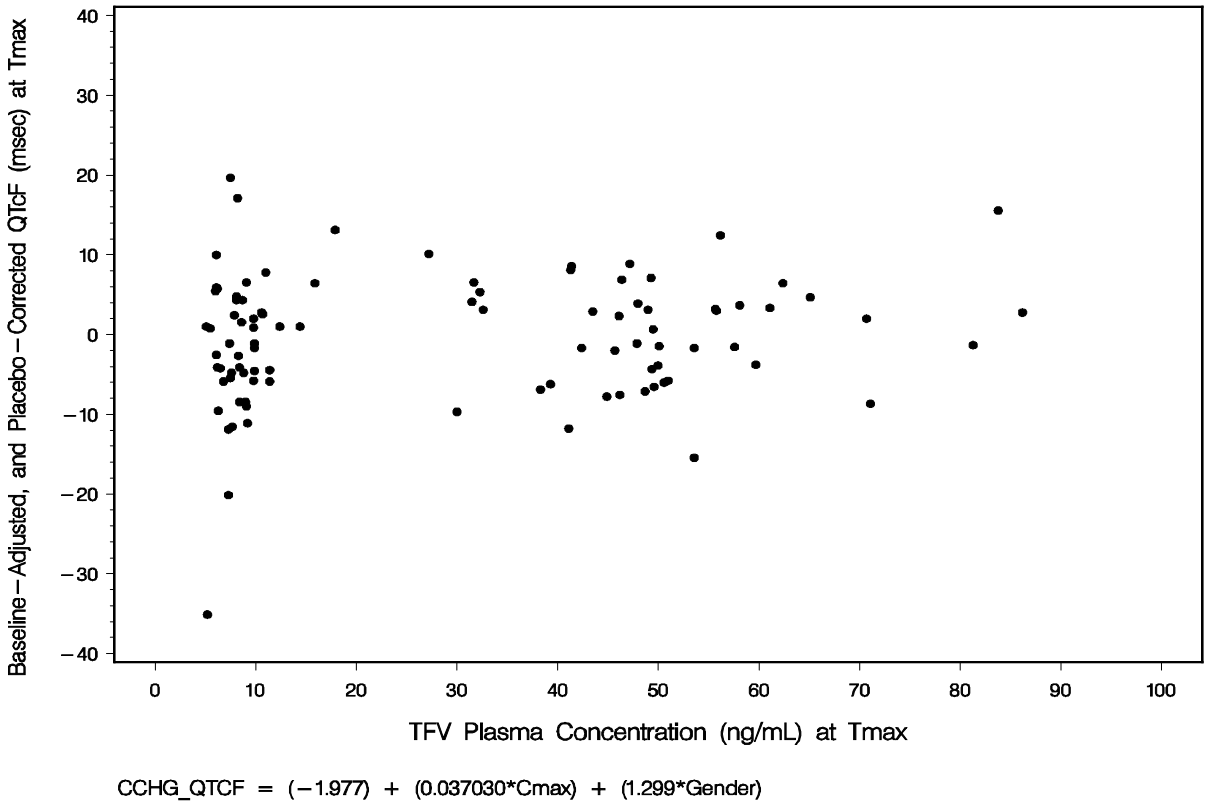
Source: GS-US-120-0107, Section 15.1, Table 16.2

Figure 25. TAF Study GS-US-120-0107: Scatter Plot of Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF versus TFV Plasma Concentration (TFV PK/PD Analysis Set)



Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect. PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.
Upper 95% 1-sided CI was calculated based on overall PK/PD regression model.
Source: GS-US-120-0107, Section 15.1, Figure 6.2

Figure 26. TAF Study GS-US-120-0107: Scatter Plot of Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF at T_{max} versus TFV Plasma Concentrations at T_{max} (TFV PK/PD Analysis Set)

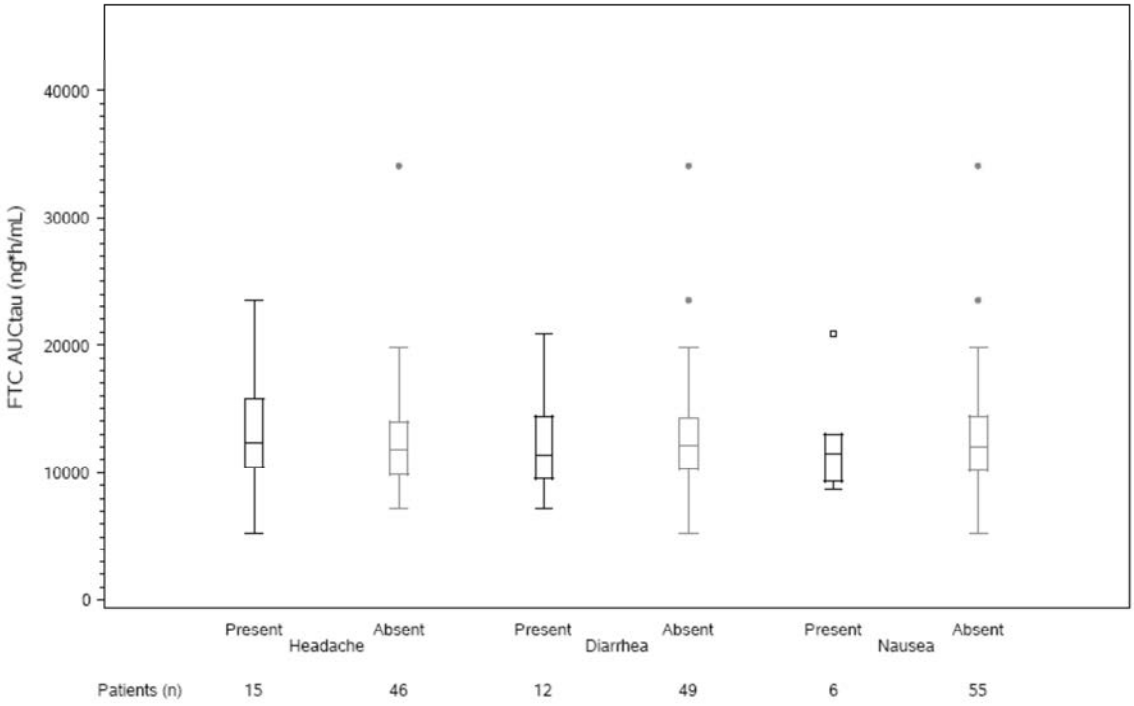


PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.
Source: GS-US-120-0107, Section 15.1, Figure 6.4

3.3.2.2. FTC

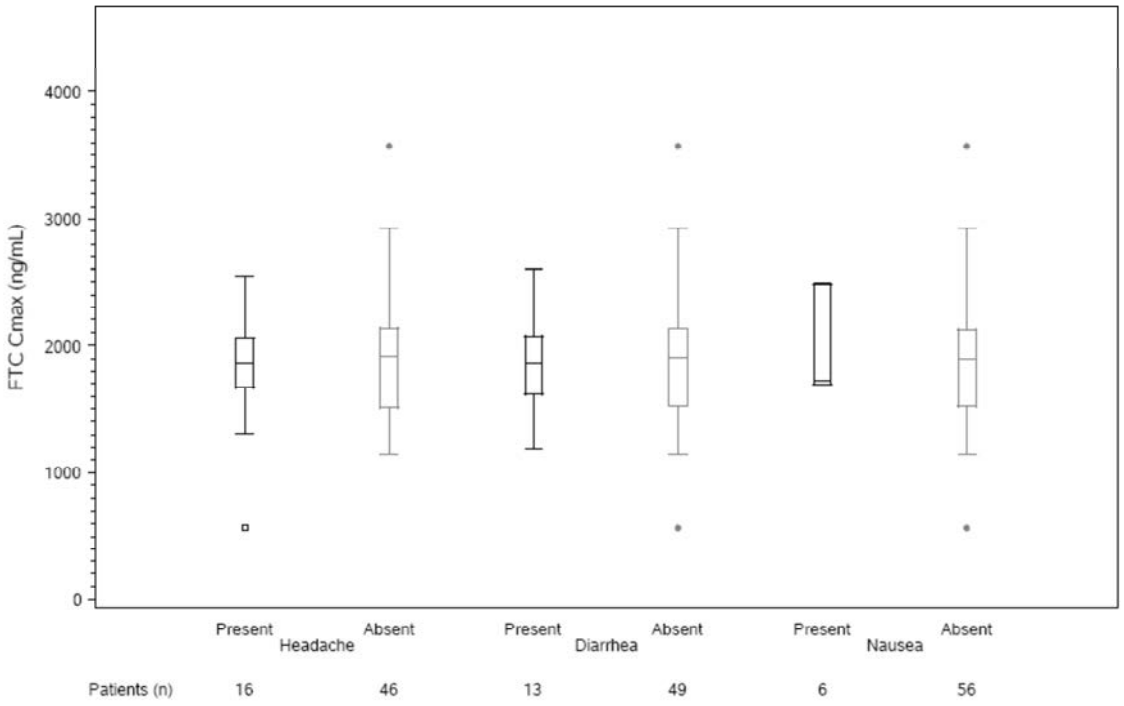
Pharmacokinetic-pharmacodynamic analyses of the FTC exposure-safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2/3 studies using FTC exposures derived from intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea. The relationships between FTC exposure and incidence of AEs (present/absent) are shown in Figure 27 for AUC_{tau} and in Figure 28 for C_{max}. FTC exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed.

Figure 27. Box Plot of FTC AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set)



Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Source: STB PK/PD Figure 4.1

Figure 28. Box Plot of FTC C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set)

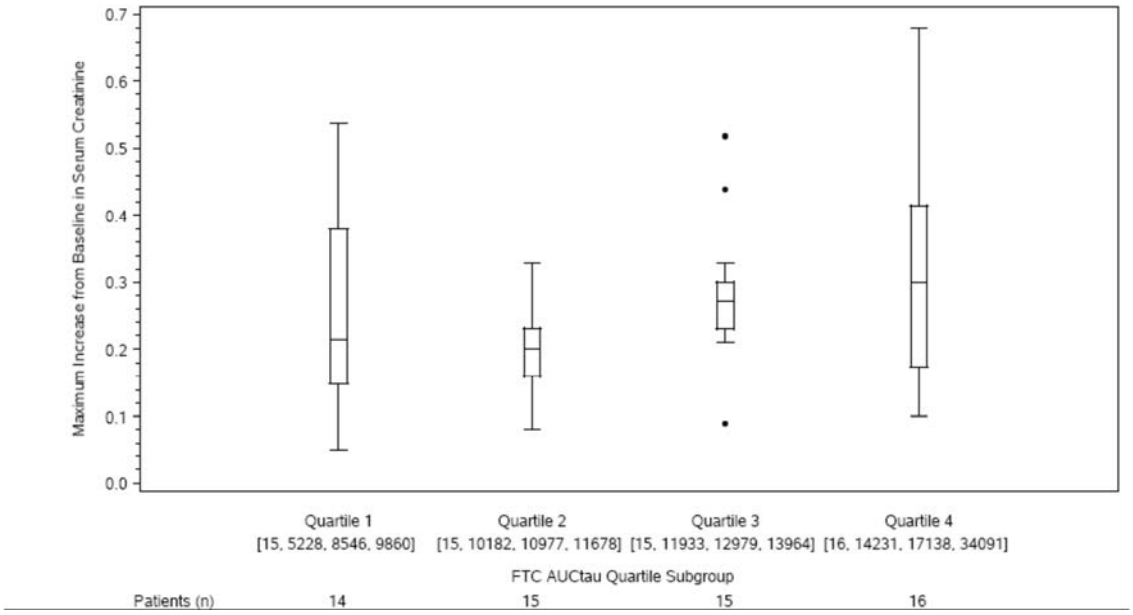


Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Source: STB PK/PD Figure 4.2

The relationship between FTC exposure quartiles and changes in renal laboratory parameters was also evaluated; exposure versus serum creatinine change is shown in Figure 29. As observed for the other agents, across all FTC AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable, and no trends in exposure-changes in laboratory parameters were noted.

Importantly, the range of FTC exposures explored in these PK/PD analyses covered the individual FTC exposures observed in the renally-impaired, HIV-infected subjects with $eGFR_{CG}$ < 50 mL/min receiving E/C/F/TAF in Phase 3 Study GS-US-292-0112. Moreover, as demonstrated in Study GS-US-292-0112, subjects with $eGFR_{CG}$ < 50 mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG} \geq 50$ mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

Figure 29. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by FTC AUC_{tau} (ng•h/mL) Quartile Subgroup (FTC PK/PD Analysis Set)



Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Subject *AC with a maximum increase from baseline in serum creatinine of 2.95 mg/dL in the Quartile 4 subgroup was excluded from the figure for better visualization purposes.
Numbers presented in the square brackets were the sample size, minimum, median, and maximum of FTC AUC_{tau} for subjects included in that subgroup.
Sample size reported at the bottom of the figure was the number of subjects with nonmissing values for both the selected PK parameter and the selected safety endpoint.
Source: STB PK/PD Figure 8.1

4. VIROLOGY SUMMARY

4.1. Nonclinical Virology

A tabular listing of nonclinical virology studies is provided in Appendix 6.3.

4.1.1. Primary Pharmacodynamics

4.1.1.1. TAF: In Vitro Pharmacodynamics

4.1.1.1.1. Mechanism of Action and Activity Against HIV-1 Reverse Transcriptase

4.1.1.1.1.1. Intracellular Metabolism

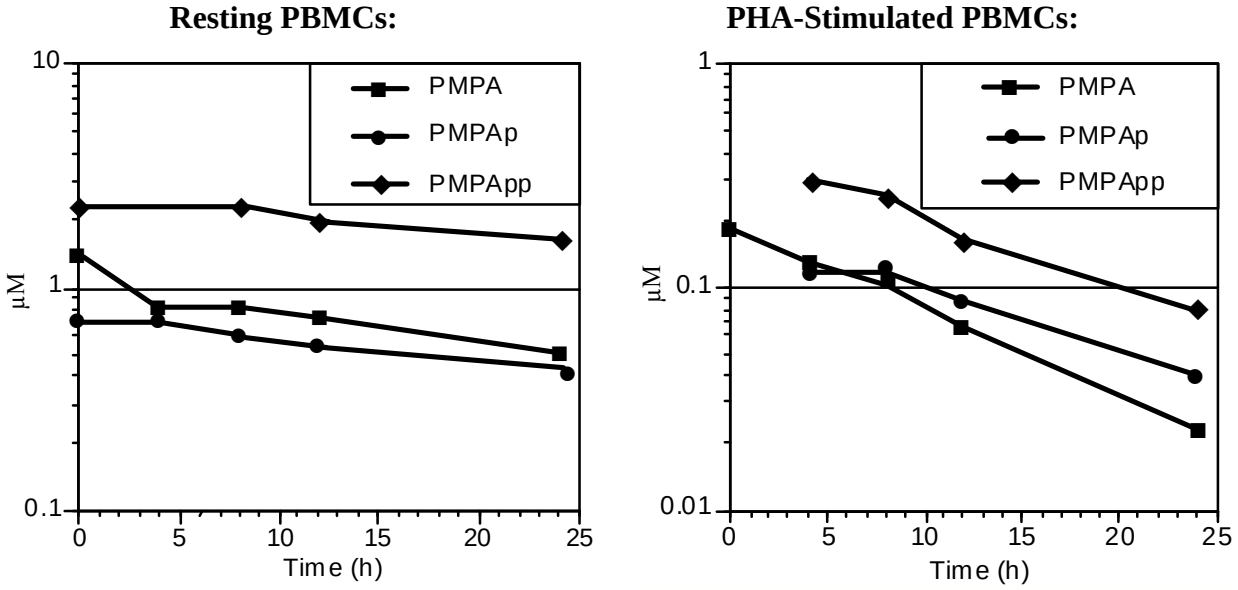
In Vitro

TFV is a nucleotide analog (ie, a nucleoside monophosphate analog) and, therefore, not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, TFV-DP. In some cells, intracellular concentrations of nucleoside kinases are cell-cycle dependent. The cellular enzymes responsible for TFV metabolism to the phosphorylated forms are adenylate kinase (AK) {13} and nucleotide diphosphate kinase, which are highly active and ubiquitous. Adenylate kinase exists as 2 isoenzymes, AK1 and AK2, with the phosphorylation of TFV mediated more efficiently by AK2.

The intracellular metabolism of TFV was studied in PBMCs {1574}. The intracellular $t_{1/2}$ of TFV and the phosphorylated metabolites TFV monophosphate (TFV-MP, previously abbreviated PMPAp) and TFV-DP differs in resting cells versus activated PBMCs, as presented in Figure 30. In resting human PBMCs, the $t_{1/2}$ of TFV-DP was found to be approximately 50 hours, whereas the $t_{1/2}$ in phytohemagglutinin (PHA)-stimulated PBMCs was found to be approximately 10 hours. This long intracellular $t_{1/2}$ supports once-daily dosing.

The intracellular phosphorylation of TFV and ABC to their active metabolites, TFV-DP and carbovir triphosphate (CBV-TP), respectively, was investigated in vitro in CEM-SS cells for potential antagonism (PC-104-2008). The results demonstrate no difference in the intracellular phosphorylation of either compound when present in combination as compared with when given alone (Table 92 and Table 93). These in vitro results indicate that there is no overlap between the anabolic routes of these NRTIs and thus limited potential for a drug interaction. These results are in agreement with combination results that show additive anti-HIV activity of these compounds and a lack of antiviral antagonism.

Figure 30. TFV Intracellular Metabolism in Human PBMCs



Source: {1574}

Table 92. Metabolism of 10 μM TFV Either Alone or in Combination with 10 μM Abacavir

Time	TFV Alone (pmol/million cells)[a]			TFV+ABC (pmol/million cells)[a]		
(h)	TFV	TFV-MP	TFV-DP	TFV	TFV-MP	TFV-DP
2	1.27 ± 0.18	0.05 ± 0.01	0.17 ± 0.01	1.13 ± 0.03	0.05 ± 0.01	0.14 ± 0.02
24	1.71 ± 0.33	0.45 ± 0.02	1.54 ± 0.12	1.59 ± 0.14	0.41 ± 0.01	1.57 ± 0.04

a Values determined by LC/MS/MS.
Source: PC-104-2008

Table 93. Metabolism of 10 μM Abacavir Either Alone or in Combination with 10 μM TFV

Time	ABC Alone (pmol/million cells)[a]	ABC+TFV (pmol/million cells)[a]
(h)	CBV-TP[b]	CBV-TP[b]
2	0.03 ± 0.01	0.05 ± 0.02
24	0.17 ± 0.01	0.24 ± 0.03

a Values determined by LC/MS/MS.
b CBV-TP is the active anabolite of ABC.
Source: PC-104-2008

Coadministration of TDF and didanosine (ddI) has been clinically associated with increased plasma concentrations of ddI. In vitro studies showed that TFV-MP and TFV-DP can inhibit purine nucleoside phosphorylase (PNP), which is involved in the metabolic degradation of ddI

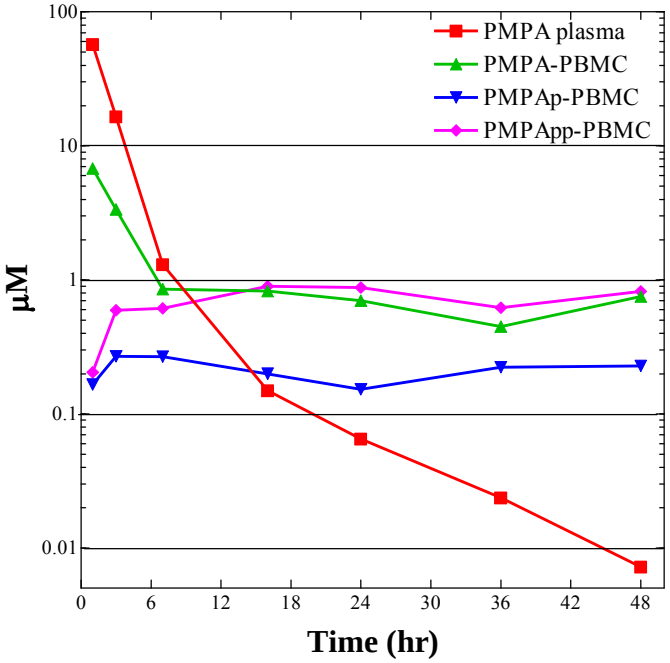
{6054}. Thus, the clinical observation of increased ddI plasma concentrations appears to be due to inhibition of its degradation via inhibition of PNP by TFV.

In order to assess the potential effect of TFV on the natural pools of 2′-deoxynucleoside triphosphates (dNTPs) and ribonucleoside triphosphates (rNTPs), the T-cell line CEM-CCRF was treated with TFV, either alone or in combination with other NRTIs {8573}. There was no effect of TFV alone, or TFV plus ABC, ddI, or 3TC on either the intracellular dNTP or rNTP pool concentrations. The only tested NRTI that significantly altered dNTP pools was ZDV. Incubation of 10 μM ZDV, either alone or in combination with other NRTIs, increased deoxyadenosine triphosphate (dATP), deoxyguanosine triphosphate (dGTP), and thymidine triphosphate levels by up to 44%. In contrast to a control potent PNP inhibitor, TFV was unable to alter intracellular dNTP pools upon addition of exogenous 2′-deoxyguanosine. While inhibition of PNP-dependent ddI degradation is the most plausible mechanism for the drug interaction between ddI and TFV, TFV does not appear to be a potent enough inhibitor of PNP to cause changes in the other nucleotide pools.

In Vivo

The kinetics of intracellular TFV metabolism were studied in monkeys that received a single dose of 30 mg/kg [^{14}C]TFV subcutaneously. After dosing, serial blood samples were obtained and analyzed. Plasma TFV levels and PBMC intracellular TFV and TFV metabolite concentrations were determined (P2001025). The TFV concentration in plasma reached a maximum of approximately 50 μM and declined with a $t_{1/2}$ of 5 to 7 hours. Consistent with the in vitro studies, TFV is efficiently taken up by PBMCs 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 this experiment was > 50 hours (Figure 31).

Figure 31. **Plasma TFV Concentrations and Concentrations of TFV, TFV-MP, and TFV-DP in PBMCs After Administration of a Single Dose of [^{14}C]TFV to Monkeys**



Source: P2001025

To assess the metabolism of TFV in lymph nodes, axillary, inguinal, and mesenteric lymph nodes were obtained at 48 hours after dosing of [^{14}C]TFV in the monkey. As observed in PBMCs, significant intracellular concentrations of TFV and its metabolites were observed in lymph node mononuclear cells from all 3 sites (Table 94).

Table 94. **TFV and Metabolites in Selected Lymph Nodes of a Monkey 48 Hours After Administration of a Single Dose of [^{14}C]TFV**

	Intracellular Concentration (µM)		
Node	**TFV**	**TFV-MP**	**TFV-DP**
Axillary	0.37	0.26	0.27
Inguinal	1.3	0.65	ND
Mesenteric	5.2	0.17	0.13

Source: P2001025

4.1.1.1.1.2. HIV-1 Reverse Transcriptase

Inside the cells, TFV is converted to its active metabolite TFV-DP. TFV-DP efficiently inhibits both RNA- and DNA-directed HIV-1 reverse transcriptase (RT) DNA polymerization. It competes with dATP for incorporation into DNA and, since it lacks a 3′-hydroxyl group, causes premature termination of DNA synthesis upon its incorporation into the nascent DNA chain. The kinetic inhibition constant (K_i) for TFV-DP against HIV-1 RT were determined using both RNA and DNA templates (Table 95). The K_i values for 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}. The removal of incorporated TFV can occur by wild-type RT and RT with mutations that enhance excision (notably T215F/Y or T69SSS) by both pyrophosphorolysis and adenosine triphosphate (ATP)-mediated excision mechanisms; however, TFV-terminated primers are efficiently translocated, which can result in partial protection from the excision process {7583}, {11304}.

Table 95. Kinetic Inhibition Constants of TFV-DP Against HIV-1 Reverse Transcriptase

Template	K_i (μM)	K_m dATP (μM)	K_i/K_m
RNA Template	0.02	0.05	0.40
DNA Template	1.6	4.6	0.35

Source: {1131}

4.1.1.1.2. In Vitro Evaluation of TAF on HIV Clinical Isolates

4.1.1.1.2.1. Activity Against HIV-1 Subtypes

The antiviral activity of TAF was assessed in fresh human PBMCs against a panel of 26 wild-type HIV-1 clinical isolates representing all HIV-1 groups (M, N, O), including M subtypes A to G (PC-120-2004). Virus and activated PBMCs were mixed in the presence of TAF and incubated for 7 days before antiviral effect (ie, inhibition of RT activity) and cytotoxicity were assessed. In this in vitro experiment, PBMC viability remained high throughout the incubation period; thus virus-infected cells were used for the assessment of both antiviral activity and cytotoxicity. ZDV was included as a positive control drug.

Overall, TAF showed potent antiviral activity against the HIV-1 groups/subtypes evaluated (Table 96). The EC_{50} values for the 26 isolates ranged from 0.10 to 12.0 nM, with an overall mean EC_{50} of 3.6 nM. No significant differences were observed between the mean TAF EC_{50} values for any of the HIV-1 subtypes/groups evaluated. No cytotoxicity was observed with TAF or ZDV at the concentrations evaluated (concentration that results in 50% cytotoxicity [CC_{50}] > 500 and > 1000 nM, respectively).

Table 96. TAF Antiviral Activity Against Primary HIV-1 Isolates

Primary HIV-1 Isolates				EC_{50} (nM)	
Type	**Group**	**Subtype**	**Isolate**	**TAF**	**ZDV**
HIV-1	M	A	92UG029	8.75	26.4
			92UG037	0.69	2.12
			92RW016	0.71	1.53
		B	93BR021	9.69	48.0
			JR-CSF	1.05	1.95
			90US873	3.87	6.03
		C	92BR025	4.16	9.00
			98BR004	1.75	7.56
			93IN101	1.50	5.49
		D	92UG001	3.79	11.3
			92UG046	0.99	3.33
			92UG024	6.27	7.21
		E	93TH073	1.18	3.54
			CMU06	1.36	4.09
			CMU08	5.88	13.1
		F	93BR019	0.73	4.87
			92BR024	5.97	17.1
			93BR029	0.14	1.28
			93BR020	2.22	7.41
		G	G3	5.34	14.0
			RU570	12.0	66.4
			JV1083	9.85	27.4
	N	NA	YBF30	1.98	5.23
	O	NA	BCF02	1.30	1.23
			BCF03	3.01	7.20
			BCF07	0.10	3.81

Source: PC-120-2004

4.1.1.1.2.2. Effect of Serum Proteins

The protein binding of TAF was moderate in human plasma, with 20% unbound based on multiple human ex vivo studies; the mean percentage of unbound TAF ranged from 14% to 23% in all subjects (GS-US-120-0108 [Section 2.4.1.1] and GS-US-120-0114 [Section 2.4.1.2]). The protein binding of TFV was studied in the presence or absence of human plasma and human serum (P0504-00039.1). The percentages of TFV that remained unbound in human plasma and human serum were 99.3% and 92.8%, respectively.

4.1.1.1.3. In Vitro HIV-1 Resistance

4.1.1.1.3.1. TFV Resistance Background

Resistance analyses of the parent compound, TFV, are relevant to the TAF in vitro resistance profile since TAF is a prodrug of TFV.

In a previous experiment, site-directed recombinant virus expressing the K65R mutation showed 3-fold reduced susceptibility to TFV, 3- to 12-fold reduced susceptibility to ABC, ddI, FTC, 3TC, zalcitabine (ddC), and d4T, but full susceptibility to ZDV (TPI 15883). The K65R mutation has also been selected in vitro by ddC, d4T, and ABC; and in vivo by ddI, ddC, and ABC {1003}, {1004}, {1793}, {2141}, {4573}. However, in clinical studies, the K65R mutation is infrequently observed to develop with these ARV drugs and is observed in the plasma HIV of 2% to 4% of ART-experienced patients {2187}, {3799}, {12143}.

4.1.1.1.3.2. TAF In Vitro Resistance Selections with Wild-Type HIV-1 Isolates

The resistance profile of TAF was studied in parallel with that of the parent drug TFV in a series of dose-escalation resistance selection experiments in MT-2 cells (PC-120-2011). The effect of the increasing selective pressure on the wild-type HIV-1_{IIIB} from TAF and TFV was assessed by analyzing the genotypic and phenotypic changes in the virus over time.

Successive passage of wild-type HIV-1_{IIIB} in increasing concentrations of TAF or TFV led to the emergence of the K65R mutation in RT at drug concentrations between 4- and 15-times EC_{50}, independent of the drug used. Importantly, attempts to increase the drug concentrations beyond 16 times the EC_{50} of each drug (to 24-times EC_{50} [336 nM] for TAF and 24-times EC_{50} [84 µM] for TFV) over > 5 weeks did not yield additional resistance or viable virus. The K65R mutation was accompanied by an S68N mutation in 3 of 4 selections performed, either as a full mutation or mixture. The development of the S68N mutation alongside K65R has been observed previously in TDF/TFV clinical and in vitro studies {10769}, {9312} where it is likely playing a role in partially restoring reduced replication capacity induced by the K65R mutation {12688}. A transient K70E mutation as a mixture with wild-type virus was also observed along with a K65R mutation as a mixture with wild-type virus in the second experiment with TAF, but was not detected at subsequent time points. A transient K70E mutation has been observed previously in clinical studies of TDF and is associated with minor decreases in TFV susceptibility in phenotypic assays {11303}, {9312}.

The phenotypic resistance of TAF was also similar to TFV in analyses conducted using the final mutant viruses obtained, with TAF activity reduced 6.5-fold from wild type for both selected viruses and TFV activity reduced 5.5- and 5.1-fold from wild-type virus for the TAF- and TFV-selected viruses, respectively (Table 97). These minimal differences between TAF and TFV in fold change from wild-type virus for each of the selected viruses were not statistically significant (Student t-test, p-values of 0.17 and 0.25 for TAF- and TFV-selected viruses, respectively). Reduced FTC susceptibility was also observed at similar levels between the 2 selected viruses (8.5- and 6.7-fold from wild-type virus), while susceptibility to the control drugs EFV (NNRTI) and EVG (INSTI) was near wild-type levels, with fold changes of < 2-fold of the wild-type control.

Overall, TAF showed a nearly identical resistance profile to TFV in these experiments, with no development of high-level resistance after extended culture.

Table 97. Characteristics and Drug Susceptibilities of Selected Viruses

Selected Viruses				EC_{50} FC From WT Control ($HIV\text{-}1_{IIIB}$)[a]				
Drug	Concentration (FC over EC_{50})	Time Point	Genotype	TAF	TFV	FTC	EFV	EVG
TAF	224 nM (16×)	Day 148	K65R	6.5[b]	5.5[b]	8.5[b]	1.4	1.7
TFV	56 µM (16×)	Day 154	K65R S68S/N/R/K	6.5[b]	5.1[b]	6.7[b]	1.5	1.4

a EC_{50} values against $HIV\text{-}1_{IIIB}$ in MT-2 standard assay were 10 nM, 2.9 µM, 1.2 nM, 0.77 µM, and 1.5 nM for TAF, TFV, EVG, FTC, and EFV, respectively. Fold changes of the average EC_{50} were obtained from 5 independent experiments.
b Student t-test p-value < 0.05 as compared with WT control.
Source: PC-120-2011

4.1.1.1.3.3. TAF In Vitro Resistance Selections with TDF-resistant HIV-1 Isolates

Resistance selection experiments using HIV-1 isolates with preexisting TFV-resistance (K65R, 3 thymidine analog-associated mutations [3TAMs], and Q151M complex) were carried out with TAF, TFV, and the INSTI comparator RAL to investigate the potential for additional resistance development in the presence of TAF or TFV (PC-120-2012). Lymphoid (MT-2) cells infected with wild-type ($HIV\text{-}1_{LAI}$) and TFV-resistant ($HIV\text{-}1_{LAI\ -K65R}$, $HIV\text{-}1_{LAI\text{-}3TAM}$, and $HIV\text{-}1_{LAI\text{-}Q151M}$) viral isolates were incubated with escalating doses of TAF, TFV, or RAL, with a starting concentration of twice the EC_{50} for each drug (Table 98). Final viral supernatants were sequenced (population sequencing) and phenotyped in a 5-day multicycle antiviral assay in MT-2 cells with TAF, TFV, RAL, ZDV, or EFV.

Table 98. Initial Drug Concentrations Used in Selection Experiments

	Starting Concentration (2 × EC_{50})		
Viral Isolate	TAF (nM)	TFV (µM)	RAL (nM)
$HIV\text{-}1_{LAI}$	30	7	20
$HIV\text{-}1_{LAI\text{-}K65R}$	90	21	20
$HIV\text{-}1_{LAI\text{-}3TAM}$	90	21	20
$HIV\text{-}1_{LAI\text{-}Q151M}$	390	91	20

Source: PC-120-2012

After 6 months of selection with the wild-type isolate HIV-1_{LAI}, the maximum viable TAF or TFV concentration supporting virus growth was 4 times the starting concentration for each drug. The selected viruses acquired the K65R mutation with TAF and the K65R+S68N mutation with TFV (Table 99). Phenotypic analyses of the resulting mutant viruses showed 3.5- and 3.7-fold decreased susceptibility to TAF and TFV, respectively, for the TAF-selected K65R virus, and 5.2- to 5.4-fold decreased susceptibility to TAF and TFV, respectively, for the TFV-selected K65R+S68N virus.

With the mutant isolate HIV-$1_{LAI-K65R}$, the maximum viable TAF or TFV concentration supporting virus growth was 3 times the starting concentration for TAF and 2 times the starting concentration for TFV (18- and 12-fold increase based on wild-type EC_{50}, respectively). The selected viruses acquired the S68N mutation. Phenotypic analyses of the 3 resulting mutant viruses showed 5.9- to 6.8-fold decreased susceptibility to TAF and similarly reduced susceptibility to TFV (5.9- to 6.3-fold above wild type). These phenotypic fold changes for viruses with K65R+S68N are consistent with the fold changes observed in the wild-type selections.

The maximum viable TAF or TFV concentration supporting virus growth when starting with the mutant isolate HIV-$1_{LAI-3TAM}$ (M41L, L210W, T215Y) was 3 times the starting concentration for either drug (18-fold increase based on wild-type EC_{50}). The selected viruses acquired the RT mutation L429I, which is located in the RT connection domain {29243}. This mutation has not been previously seen or characterized, as it lies beyond the range of standard genotypic assays (residues 1-400). Phenotypic characterization was obtained for only 3 of the 4 viruses selected with TAF or TFV, due to very weak infectivity of 1 viral isolate. A modest, approximately 2-to 3-fold change increase for both TAF and TFV was observed for all 3 selected viruses compared with the HIV-$1_{LAI-3TAM}$ starting material.

For the heavily mutated HIV-$1_{LAI-Q151M}$ isolate (A62V, K65R, S68G, V75I, F77L, F116Y, and Q151M), the maximum TAF or TFV concentration supporting virus growth was 1.5 times the starting concentration for either drug (39-fold increase based on wild-type EC_{50}). The selected viruses acquired the uncharacterized RT mutation T69I. Phenotypic susceptibilities to TAF and TFV for the 2 selected viruses were very similar for the 2 drugs, ranging from 22.1- to 34.5-fold above wild-type virus, and were within 2-fold of the value for the starting material that was determined concurrently. This suggests a very limited impact on resistance, if any, for the emerging T69I mutation in that isolate.

In contrast to TAF and TFV, growth of wild-type and TFV-resistant virus isolates was sustained at much higher concentrations of the control compound RAL (64 times wild-type EC_{50} for each isolate), where the viruses acquired INSTI-resistance mutations with > 13-fold (wild-type isolate) or > 200-fold (TFV-resistant isolates) decreases in RAL susceptibility. This result demonstrates that high levels of resistance can be achieved in this experimental model and, when compared with the relatively low maximal dose for TAF and TFV, suggests a lack of alternative resistance/survival pathways for these viruses under TAF- or TFV-selective pressure. Notably, the K65R mutation reverted to the wild-type residue in the absence of TFV selective pressure (no drug control and RAL control), consistent with the known reduced replication fitness of the K65R virus {12688}. Phenotypic susceptibilities to RAL were near wild-type levels for all

selected viruses, except those selected with RAL (noted above). Phenotypic susceptibilities of all selected viruses to EFV and ZDV were as expected, with the exception of a low fold change in susceptibility for ZDV with the K65R + S68N mutation.

Overall, the results of this study show limited viral evolution and phenotypic changes after 6 months of resistance selection with TAF or TFV in viruses harboring NRTI−resistance-associated mutation (RAMs).

Table 99. Characteristics and Drug Susceptibilities of Selected Viruses

Virus Name	Selecting Drug	Drug Concentration (FC from WT EC_{50})[a]	Genotype (RT, IN)[b]	EC_{50} and FC from WT Control ($HIV\text{-}1_{LAI}$)[c]				
				TAF	TFV	RAL	ZDV	EFV
$HIV\text{-}1_{LAI}$			RT: WT	0.014	2.6	0.003	0.17	0.002
WT-A3	TAF	120 nM (8×)	RT: **K65R**	3.5*	3.7*	1.0	0.7	0.6
WT-F3	TFV	28 µM (8×)	RT: **K65R, S68N**	5.2*	5.4*	1.6	1.2	0.6
WT-R6	RAL	640 nM (64×)	RT: WT IN: **E92Q, V151I**	0.9	1.0	13.4*	1.0	0.7
WT-ND	None	NA	RT: WT	1.0	1.1	1.9	0.7	1.0
$HIV\text{-}1_{LAI\text{-}K65R}$			RT: K65R	4.4*	4.9*	1.4	0.9	0.9
K65R-A2	TAF	180 nM (12×)	RT: K65R, **S68N**	5.9*	6.3*	1.9	2.8*	1.3
K65R-A2.5	TAF	270 nM (18×)	RT: K65R, **S68N**	6.8*	6.3*	1.5	2.3*	1.0
K65R-F2	TFV	42 µM (12×)	RT: K65R, **S68N**	6.1*	5.9*	1.2	2.2	1.4
K65R-R6	RAL	640 nM (64×)	RT: **WT** (loss of K65R) IN: **E138K, Q148R, V151I**	0.8	1.0	>200*	0.9	0.7
K65R-ND	None	NA	RT: **WT** (loss of K65R)	1.0	1.1	2.2	0.9	1.1
$HIV\text{-}1_{LAI\text{-}3TAM}$			RT: M41L, Y181C, G190A, L210W, T215Y ("3TAM") IN: WT	3.8*	3.7*	1.1	> 90*	> 54*
3TAM-A2	TAF	180 nM (12×)	RT: "3TAM" + **L429I**	8.5*	6.1*	2.2*	> 90*	> 54*
3TAM-A2.5	TAF	270 nM (18×)	RT: "3TAM" + **L429I**	8.6*	6.1*	1.9	> 90*	> 54*
3TAM-F2	TFV	42 µM (12×)	RT: "3TAM" + **L429I**	9*	6.1*	1.7	> 90*	> 54*
3TAM-F2.5	TFV	63 µM (18×)	RT: "3TAM" + **L429I**	ND	ND	ND	ND	ND
3TAM-R6	RAL	640 nM (64×)	RT: "3TAM" IN: **Q148R, D232N**	4.8*	4.9*	> 204*	> 90*	> 54*
3TAM-ND	None	NA	RT: "3TAM"	3.5*	4.2*	2.1*	> 57*	> 54*

Virus Name	Selecting Drug	Drug Concentration (FC from WT EC_{50})[a]	Genotype (RT, IN)[b]	EC_{50} and FC from WT Control ($HIV\text{-}1_{LAI}$)[c]				
				TAF	TFV	RAL	ZDV	EFV
$HIV\text{-}1_{LAI\text{-}Q151M}$			RT: A62V, K65R, S68G, V75I, F77L, F116Y, Q151M ("Q151M") IN: WT	18.6*	19*	1.7	> 90*	3.3*
Q151M-A1.5	TAF	585 nM (39×)	RT: "Q151M" + **T69I**	26.1*	22.1*	1.5	> 90*	3.4*
Q151M-F1.5	TFV	137 µM (39×)	RT: "Q151M" + **T69I**	32.5*	34.5*	2.2*	> 90*	2.7*
Q151M-R6	RAL	640 nM (64×)	RT: " Q151M" IN: **L74M, Q148R, S230R**	19.3*	15.7*	>264*	> 90*	3.0*
Q151M-ND	None	NA	RT: "Q151M"	15.3*	15.2*	2.0	> 90*	2.4*

a Concentrations based on previously defined EC_{50} values against $HIV\text{-}1_{LAI}$ in MT-2 assay of 0.015, 3.5, and 0.010 µM for TAF, TFV, and RAL, respectively.
b Boldface font indicates changes from starting material. WT IN sequences not shown.
c Fold changes calculated from EC_{50} values for $HIV\text{-}1_{LAI}$ shown in first row (shaded). Data averaged from at least 4 independent experiments.
* p-value < 0.01 (student t-test comparing mutant EC_{50} values with wild-type EC_{50} values)
Source: PC-120-2012

4.1.1.1.3.4. Molecular Mechanisms of Resistance

The molecular mechanisms of HIV resistance to TAF should reflect those of TFV since TAF, a prodrug of TFV, is predominantly hydrolyzed to TFV by CatA in target lymphoid cells {13119}, {10427}.

Reduced susceptibility to TFV associated with the K65R mutation is mediated by a decrease in the incorporation of the active metabolite of TFV, TFV-DP, relative to the natural substrate dATP. This can be enzymatically observed as an increase in K_i in steady-state kinetics experiments and as a decrease in the incorporation rate (k_{pol}) in presteady-state enzyme kinetics experiments with the K65R mutant RT {5476}, {7583}, {3852}. Similarly, presteady-state kinetics showed an approximate 5-fold decrease in incorporation (decreased k_{pol}) for both FTC-TP and 3TC 5′-triphosphate (3TC-TP) for the K65R mutant RT in accordance with the observed decreased susceptibility of the K65R mutant HIV for these drugs (TPI 15883). Significant decreases in the incorporation of natural substrates, most notably the purines dATP and dGTP, were also observed in this enzymatic analysis. The K65R mutant RT also showed decreased ATP-mediated excision of incorporated NRTIs that resulted in increased stability of the chain-termination activity of NRTIs. The combined effects of altered NRTI incorporation and excision provide explanation for the susceptibility profile of K65R, which showed low-level decreased susceptibility to all NRTIs with the exception of ZDV (which remained fully active due to the strongly decreased excision caused by the mutation) {7583}, {11304}.

The addition of the M184V mutation to a virus expressing K65R results in an increase in TFV susceptibility to near wild-type values. The mechanism by which this occurs appears to be through a reduction in the affinity of the natural substrate dATP that is associated with the M184V mutation and results in an increase in the incorporation of TFV-DP relative to dATP and, thus, improved TFV susceptibility for the double mutant virus (TPI 15883) {5476}.

The K65R mutant HIV-1 is also associated with a decrease in replication capacity for HIV-1 expressing this mutation. This has been observed previously for a site-directed mutant expressing the K65R mutation {3852} and is shown in Table 100 for a panel of clinical isolates expressing the K65R mutation that were obtained from a random set of plasma samples submitted to Monogram Biosciences for phenotypic analyses {5049} (PC-104-2004). Reduced replication capacity of K65R mutant HIV-1 was also found in macrophages {11307}. Interestingly, A62V and S68G are 2 mutations in RT that can occur with K65R and can act as partial compensatory mutations to increase the fitness of K65R-containing viruses without significantly altering the resistance to TFV {12688}. The M184V mutation is also associated with reduced replication capacity, and the combination of mutations (K65R+M184V) showed the greatest reduction in replication capacity {5476}. Decreases in natural substrate binding (M184V) and incorporation (K65R) and reduced initiation of minus strand single-stranded DNA synthesis (K65R+M184V) {10671} for these HIV mutants are likely responsible for these observed additive decreases in viral replication capacity.

Table 100. Replication Capacity of Primary HIV-1 Isolates Without Protease Inhibitor Resistance

	N	Replication Capacity			p-value[a]
		Mean	Median	SD	
No NRTI-Associated Mutations	1307	94.9	92.7	45.7	—
M184V/I Alone	291	65.4	60.8	41.5	< 0.0001
K65R Alone	17	57.6	58.7	38.6	0.0008
K65R + M184V/I Alone	12	37.7	27.5	29.3	< 0.0001

a p-value from Student's unpaired t-test.
Source: PC-104-2004

4.1.1.1.3.5. K65R and HIV-1 Subtype C

A study demonstrated a greater propensity for HIV-1 of subtype C to develop a K65R mutation under in vitro selection with TFV as compared with subtype B or other non-B subtypes {9276}. Gilead evaluated subjects with subtype C, subtype B, and other non-B HIV-1 subtypes for virologic failure and development of resistance in 2 Phase 3 clinical studies of TDF {11322}. The virologic failure rates were similar between subjects with subtype B or non-B HIV-1 subtypes (Study GS-99-903 at Week 144: 15.5% versus 19%, respectively, p = 0.75; Study GS-01-934 at Week 48: 19% versus 13%, respectively, p = 1.0). Among the 10 subjects with subtype C treated with TDF in both studies, only 1 subject was classified as a virologic failure and this subject did not develop a K65R mutation or any other resistance mutations. For Studies TMC278-TiDP6-C209 and TMC278-TiDP6-C215, there were a total of 5 subjects in the FTC+TMC278+TDF group and 2 subjects in the ATR group that had emergent K65R during the treatment period. Of those, 2 of 5 in the TMC278 group and 2 of 2 in the EFV group with the K65R mutation were HIV-1 subtype C, compared with the overall prevalence of 69.2% and 12.1%, respectively, for HIV-1 subtype B versus subtype C (PC-264-2005).

4.1.1.1.4. In Vitro Activity Against Drug-Resistant Variants of HIV-1

4.1.1.1.4.1. In Vitro Activity of TFV Against Drug-Resistant Variants of HIV-1

The activity of TFV against drug-resistant HIV-1 has been extensively studied in vitro. As shown in Table 101, TFV remains active (within 2-fold of wild type) against recombinant mutant molecular clones of HIV-1 expressing ddI resistance (L74V), ddC resistance (T69D), ZDV resistance (D67N + K70R, D67N + K70R + K219Q, or T215Y), or multinucleoside drug resistance (Q151M complex) mutations in HIV-1 RT {2078}, {2191}, {3200}, {2064}, {1793}. TFV was fully active against recombinant HIV-1 expressing the K70E mutation that was observed to develop in 2 patients treated with adefovir dipivoxil {2078}, {1648}. However, biochemical studies of the K70E mutant RT have suggested low-level reduced susceptibility of this mutant to TFV {10898}. The M184V substitution is commonly observed in HIV-1 isolates from 3TC- and FTC-treated patients and is associated with high-level resistance to FTC and 3TC and low-level resistance to ABC. TFV shows slightly increased activity against HIV-1 expressing the ABC/3TC/FTC resistance mutation M184V or the combination of the high-level ZDV resistance mutation T215Y and M184V {2078}, {1649}.

Table 101. Antiviral Susceptibilities of Molecular Clones of HIV-1 Expressing Nucleoside-Associated Resistance Mutations in Reverse Transcriptase

	EC_{50} Fold Increase Above Wild-Type (HXB2D or IIIB)						
RT Mutation	**TFV**	**ZDV**	**d4T**	**ddI**	**3TC**	**ddC**	**ABC**
D67N + K70R	0.7	5.7	ND	ND	ND	ND	1.7
D67N + K70R + K219Q	1.8	23	ND	ND	3.1	ND	1.2
T69D	2	1.7	4	ND	19	4.3	ND
K70E	1.3	0.6	1.1	1	3.8	0.7	ND
L74V	1	2	1.1	2.8	2.4	3.9	3.7
Q151M[a]	0.8	39	69	42	1.9	7.3	ND
M184V	0.2–0.9	0.7	1.5	2.8	> 50	1.8	4.9
T215Y	1.8	6.9	1.6	2.2	1.1	1.3	2.2
T215Y + M184V	0.5	0.7	1.1	2	< 50	1.7	7

a Site-directed recombinant also includes A62V, V75I, F77L, and F116Y RT mutations.
Source: {2078}, {3200}, {2064}, {1793}, {2191}

4.1.1.1.4.2. In Vitro Evaluation of TAF and TFV on Drug-Resistant Recombinant HIV-1 Clinical Isolates

TAF and TFV Antiviral Activity Against Recombinant HIV-1 Clinical Isolates

The susceptibility results with molecular clones of HIV-1 were confirmed and extended with phenotypic analyses of a panel of recombinant HIV-1 clinical isolates from ART-experienced patients (PC-120-2014). The potencies of TAF and TFV were determined for 24 patient-derived recombinant HIV-1 variants selected based on their genotypic resistance to multiple NRTIs,

spanning a wide range of NRTI resistance. The choice of the mutants present in the panel was meant to capture the diversity of fold changes observed for TFV, from hypersusceptible to highly resistant, and is not representative of their incidence in the HIV-infected population. The activity of TAF and TFV against the tested viruses was determined by Monogram Biosciences (South San Francisco, CA, USA) using the single-cycle PhenoSense® assay {2397} and expressed as the fold change in the calculated EC_{50} relative to that of the wild-type reference strain HIV-1_{NL4-3}. In the PhenoSense assay, clinical susceptibility cutoffs for TDF have been established at 1.4 (lower cutoff) and 4 (higher cutoff) {5010}. TFV fold change from wild-type < 1.4, ≥ 1.4 to ≤ 4, and > 4 indicate sensitivity, reduced sensitivity, and resistance, respectively, to TFV.

In terms of fold change compared with wild-type virus, susceptibility to TAF for this panel of HIV-1 mutants was almost identical to TFV, ranging from 0.34- to 23-fold of the EC_{50} (Table 102). Some of the variability observed between the 2 compounds was most likely stochastic, and only virus 18 was categorized differently for TAF compared with TFV, based on the TDF cutoffs. Susceptibility cutoffs for TAF have not been established. As a result, there was a strong correlation between the fold change for TFV and TAF with a coefficient of determination (R^2) value of 0.97, as shown in Figure 32, indicating that TAF and TFV show the same resistance profile against NRTI-resistant HIV-1 mutants in this assay.

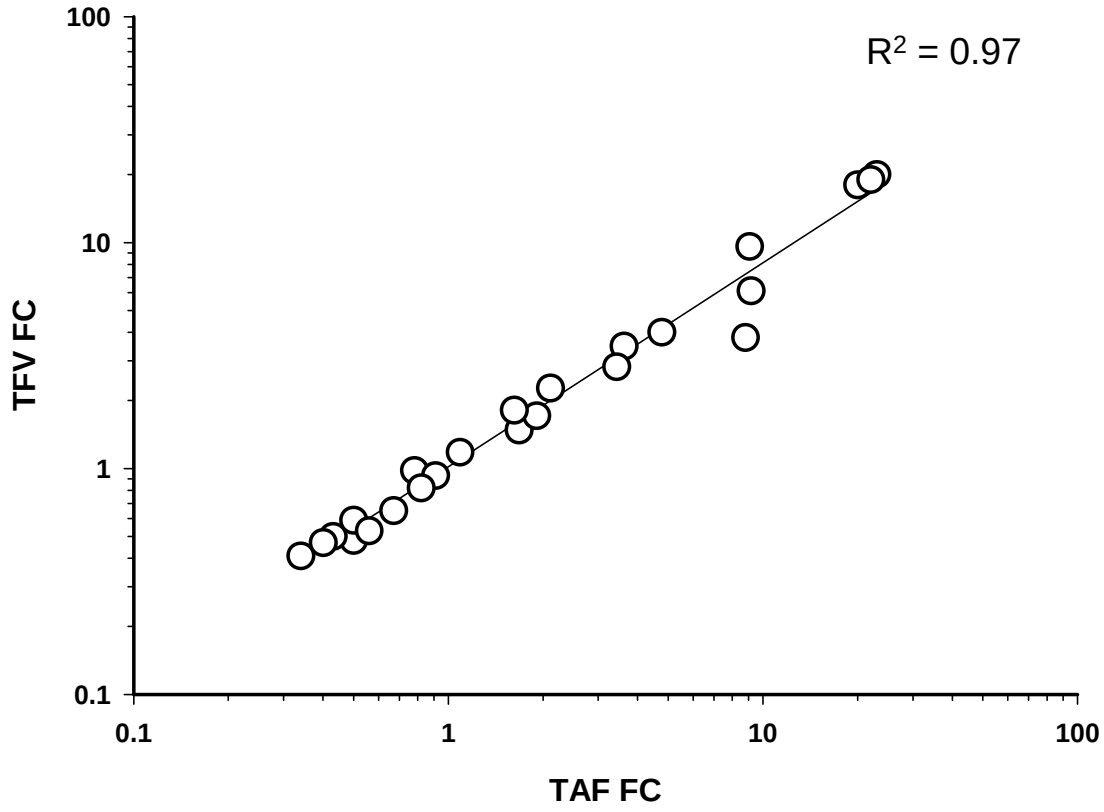
Table 102. Phenotypic Susceptibilities of 24 Recombinant HIV-1 Isolates with NRTI Mutations Against TAF and TFV

Virus ID	EC_{50} FC[a]		Mutation Category	NRTI Mutations
	TAF	TFV		
13	0.34	0.41	NRTI	L74V
16	0.40	0.47	NRTI + M184V	L74V Y115F M184V*
5	0.50	0.48	M184V	M184V
14	0.43	0.50	NRTI	L74V
22	0.56	0.53	Q151M + M184V	Q151M M184V*
15	0.50	0.59	NRTI + M184V	L74V Y115F M184V*
6	0.67	0.65	M184V	M184V*
21	0.82	0.82	Q151M + M184V	A62V V75V/I F116Y Q151M M184V*
20	0.91	0.93	Q151M	F116Y Q151M*
11	0.78	0.98	K65R + M184V	A62A/V K65R M184V*
12	1.09	1.18	K65R + M184V	K65R M184V*
9	1.68	1.48	K65R	K65R*
10	1.91	1.71	K65R	K65R*
17	1.62	1.81	3 TAMs	M41L L74V L210W T215Y
3	2.11	2.27	6 TAMs + M184V	M41L D67N K70R M184V L210W T215Y K219E
19	3.43	2.82	Q151M Complex	A62V V75I F77L Y115F F116Y Q151M*
1	3.62	3.48	6 TAMs	M41L D67N K70R L210W T215F K219Q*
18	8.80	3.80	5 TAMs	M41L D67N T69D L74V L210W T215Y K219R*
2	4.77	4.01	6 TAMs	M41L D67N K70R L210W T215Y K219E*

Virus ID	EC_{50} FC[a]		Mutation Category	NRTI Mutations
	TAF	TFV		
4	9.16	6.11	6 TAMs + M184V	M41L D67N K70R M184V L210W T215Y K219E*
24	9.07	9.60	Q151M Complex + K65R	A62V K65R K70K/R V75I F77L F116Y Q151M*
8	20.0	18.0	T69 Insertion	M41L T69ins L74V L210W T215Y*
23	22.0	19.0	T69 Insertion	M41L A62V T69ins L210W T215Y*
7	23.0	20.0	T69 Insertion	A62V T69ins V75I*

a Susceptibilities are expressed as FCs in EC_{50} from wild-type control. Wild-type EC_{50} for TAF and TFV was 10 nM and 0.6 µM, respectively.
* Indicates the presence of NNRTI RAMs (not shown).
Source: PC-120-2014

Figure 32. Resistance Profile Comparison Between TAF and TFV in the Monogram PhenoSense Assay



FCs for the panel of 24 recombinant HIV-1 isolates (Table 102) for TAF and TFV were plotted. Linear regression was calculated using SigmaPlot.
Source: PC-120-2014

The panel of recombinant mutants showed TFV fold changes from wild-type ranging from 0.41 to 20, with 11 isolates showing full sensitivity to TFV, 7 isolates showing reduced susceptibility to TFV, and 6 isolates showing full resistance to TFV (Table 102). Most isolates sensitive to TFV had the M184V mutation (8 of 11) plus few additional NRTI resistance mutations, including 2 isolates with K65R + M184V, and no TAMs (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R). Isolates with reduced susceptibility to TFV rarely had the M184V mutation (1 of 7 only) and had an increasingly complex resistance pattern, with either ≥ 3 TAMs, K65R alone, or the Q151M MDR complex. Isolates resistant to TFV had either 6 TAMs, Q151M complex + K65R, or double insertions at T69 + other NRTI mutations and/or TAMs. The highest level of resistance to TFV was observed for isolates with T69 double insertions.

TFV Antiviral Activity Against Primary HIV-1 Isolates in PBMC

The activity of TFV was also evaluated against primary PBMC-derived HIV-1 isolates directly in donor PBMCs {5044}. The 10 primary HIV-1 isolates in this study were derived from nucleoside-experienced patients, and all isolates expressed one or more nucleoside-associated RT mutations. The drug susceptibility results, as well as the resistance genotype for each isolate, are presented Table 103 in order of increasing ZDV resistance. Nine of these primary isolates demonstrated high-level 3TC resistance as a result of the M184V RT mutation. The mean fold change in TFV susceptibility of all 10 primary HIV-1 isolates was unchanged from the wild-type reference (range: 0.4 to 2.2). In contrast, these primary HIV-1 isolates showed a mean resistance to ZDV, ABC, and 3TC of 20.4-fold, 11.9-fold, and > 45-fold, respectively.

Table 103. Drug Susceptibilities of Nucleoside-Resistant Primary HIV-1 Isolates

Virus ID	Nucleoside-Associated RT Mutations[b]	Drug Susceptibility (Fold Change from Wild Type[a])			
		TFV	ZDV	ABC	3TC
1-MLS	M184V	0.5	0.3	1.7	> 50
2-JMG	M184V	0.4	0.6	1.9	> 50
3-OT	K70R M184V	0.5	0.7	1.8	> 50
4-RJN	T69N K70R	0.7	1.4	0.8	0.4
5-AB	M41L M184V T215Y	0.4	2.8	8.3	> 50
6-EDM	M41L M184V L210W T215Y	1.0	3.1	6.8	> 50
7-WK	M41L D67N M184V T215F K219Q	1.0	15	4.6	> 50
8-RON	M41L M184V T215Y	1.3	16	26	> 50
9-EMS	D67N K70R M184V T215F K219E	1.5	50	43	> 50
10-GGR	M41L D67N T69D M184V L210W T215Y	2.2	> 100	21	> 50
	Mean (n = 10):	1.0	20.4	11.9	> 45
	Range	0.4 to 2.2	0.3 to > 100	0.8 to 43	0.4 to > 50

a Wild-type HIV_{IIIB} EC_{50} values for ZDV, TFV, ABC, and 3TC were 0.012, 1.7, 0.09, and 0.27 μM, respectively, for these experiments. The fold change from these wild-type EC_{50} values was calculated as the mean of 2 to 3 independent experiments for each nucleoside-resistant primary isolate analyzed.
b NRTI RAMs are any of the following amino acid changes in RT: M41L, A62V, K65R, D67N, T69N/D, K70R, L74V/I, V75T, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F or K219Q/E.
Source: {5044}

TFV Antiviral Activity Against Recombinant HIV-1 Clinical Isolates

The distribution of TFV susceptibility in over 1000 ART-naive, HIV-infected individuals worldwide was determined using the Virco® Antivirogram® assay. In addition, phenotypic susceptibility to TFV and other RT inhibitors was determined in a panel of nearly 5000 recombinant HIV-1 clinical isolates from predominantly ART-experienced patients analyzed as a part of routine drug resistance testing.

Greater than 97.5% of isolates from ART-naive patients had TFV susceptibility < 3-fold above the wild-type controls using the Antivirogram. The clinically derived panel of 5000 samples exhibited a broad range of ARV drug susceptibilities, including 69%, 43%, and 16% having > 10-fold decreased susceptibility to at least 1, 2, and 3 ARV drug classes, respectively. Greater than 88% of these 5000 clinical isolates were within the 3-fold susceptibility range for TFV, and > 99% exhibited < 10-fold reduced susceptibility to TFV.

The results suggest that the majority of ART-naive and ART-experienced individuals are infected with HIV-1 that remains within the normal range of TFV susceptibility and may be susceptible to TDF or TAF therapy {3961}.

A retrospective analysis was undertaken to look for patterns of resistance among TFV-naive, ART-experienced patients that can result in a reduction in TFV susceptibility {5482}. In this study, 321 samples from 294 patients that had been sent to the German National Reference Centre for Retroviruses for drug resistance testing between January 1998 and July 2002 were analyzed. When the susceptibility of viruses to TFV was examined, viruses with insertion mutations (n = 6) were highly resistant. Viruses with Q151M could be divided into 2 subsets of susceptible (n = 12) and highly resistant (n = 8), where 7 of 8 viruses in the resistant set also contained K65R. A clonal analysis of viruses containing TAMs (M41L, D67N, L210W, T215F/Y, and K219Q/E/N) showed that when present as single mutations, resistance to TFV could be ranked as increasing for mutations at position 41 > 215 > 70. Additionally, viral clones with M184V or M184I exhibited slightly increased susceptibilities to TFV (0.7-fold), and almost all clones with TAM-induced resistance were resensitized when M184V was present. However, accumulation of at least 2 TAMs resulted in more than 2.0-fold reduced susceptibility to TFV, irrespective of the presence of M184V. Overall, a total of 40.4%, 34.3%, and 25.3% of the viruses had < 1.5-fold, 1.5- to 4.0-fold, and > 4.0-fold reduced susceptibilities to TFV, respectively.

Two studies have confirmed the resensitizing effect of the M184V/I mutation on TFV susceptibility with recombinant clinical isolates using the Monogram Biosciences PhenoSense assay {7279}, {12143}. The effect appears across all genotypic backgrounds, including K65R, L74V, and TAMs. For viruses with TAMs (n = 3805), the resensitization effect for viruses containing M184V/I resulted in 19% of isolates showing reduced susceptibility to TFV above the clinical cutoff of 1.4-fold versus 52% of isolates in the absence of M184V/I. The resistance mechanisms of HIV-1 RT with K65R+M184V mutations suggest that the increased susceptibility conferred by M184V to TFV is mediated by decreased incorporation of the competing natural substrate dATP relative to TFV compared with the K65R mutant {12142}, {5476}.

Using clonal sequencing analyses of viral populations, recent studies demonstrated that K65R can be found on the same genome as L74V or T215Y, although they do not often occur together {10318}. A set of studies describe that K65R and TAMs were antagonistic both for their prevalence in database searches of patient isolates, as well as for their resistance profiles and mechanisms of resistance {8925}, {9037}, {9494}, {11306}. Genotypic and molecular antagonism was also found between the RT mutations K65R and K70E using clonal sequencing of virus from patients, which was primarily explained by the dramatically reduced replication capacity of the constructed double mutant {11303}.

4.1.1.1.4.3. In Vitro Activity Against Clinical HIV-2 Isolates

The antiviral activity of TAF was assessed in fresh human PBMC against 3 wild-type HIV-2 clinical isolates (PC-120-2004). Virus and activated PBMCs were mixed in the presence of TAF and incubated for 7 days before antiviral effect (ie, inhibition of RT activity) and cytotoxicity were assessed. In this in vitro experiment, PBMC viability remains high throughout the incubation period; thus, virus-infected cells were used for the assessment of both antiviral activity and cytotoxicity. ZDV was included as a positive control drug.

Overall, TAF showed potent antiviral activity against the 3 HIV-2 isolates evaluated (Table 104). TAF EC_{50} values ranged from 0.91 to 2.63 nM. No significant differences were observed between the TAF EC_{50} values for any of the isolates evaluated. No cytotoxicity was observed with TAF or ZDV at the concentrations evaluated (CC_{50} > 500 and > 1000 nM, respectively).

Table 104. TAF Antiviral Activity Against Primary HIV-2 Isolates

Primary HIV-2 Isolates				EC_{50} (nM)	
Type	**Group**	**Subtype**	**Isolate**	**TAF**	**ZDV**
HIV-2	NA	NA	CDC310319	2.63	15.6
			CDC310342	1.96	1.39
			CBL-20	0.91	2.18

Source: PC-120-2004

In a previous analysis, a panel of HIV-2 clinical isolates with pre- and post-Q151M mutation development and laboratory strain HIV-2_{ROD} was evaluated for drug susceptibilities in a PBMC-based assay {9389}. The specific components of the ART used that led to the development of Q151M were not described. Prior to the development of the Q151M mutation, the EC_{50} value for TFV for HIV-2_{ROD} was 0.3 µM, and the clinical isolates had EC_{50} values that ranged from 0.14 to 0.52 µM (n = 4). Of the HIV-2 isolates that showed development of the Q151M mutation in their RT, 2 of 4 patients showed no change in susceptibility to TFV, while the remaining 2 showed 8.6- and 29-fold reductions in TFV susceptibility as compared with pre-Q151M HIV-2. The patients with phenotypic changes also developed either a V111I or a K65R mutation in addition to Q151M. For comparison, all 4 patients had developed reductions in susceptibility to d4T and ABC associated solely with Q151M.

4.1.1.1.5. In Vitro Evaluation of TAF Resistance Barrier

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 HIV-1 isolates (Sections 4.1.1.1.3.2 and 4.1.1.1.3.3). However, 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 (GS-US-120-0104 [Section 2.3.2.1]). Therefore, viral breakthrough experiments were conducted using previously defined TDF-resistant HIV-1 isolates (Table 105) in MT-2 cells to model the impact on antiviral efficacy of the 5-to 7-times higher TFV-DP concentration observed in vivo with TAF treatment compared with TDF treatment (PC-120-2013). These experiments were conducted at a higher multiplicity of infection (MOI) than in the typical EC_{50} assays; the EC_{50} values for TAF and TFV were 0.02 and 5 µM, respectively. The cells were incubated in the presence of TAF or TFV followed by HIV-1 infection. TAF and TFV concentrations were equivalent to the EC_{95} (estimated at 10 × EC_{50}) for each drug, with a 5-fold increase for TAF to take into account the 5-times increase in TFV-DP concentration in vivo. After 4 or 5 days of incubation, cultures were scored for viral breakthrough (ie, presence of virus-induced cytopathic effect). The procedure was repeated every 4 to 5 days for up to 4 weeks.

Table 105. Genotypic and Phenotypic Characteristics of the Viral Isolates

Isolate ID	Mutant Category[a]	RT Sequence[b]	FC (EC_{50} Fold Change from WT Control)		
			MT-2 Assay[c]		Monogram Assay[d]
			TAF	TFV	TFV
PD9	3TAMs	D67N K70R M184V K219Q	4.3	3.7	1.9
PD6	3TAMs	M41L L210W T215Y	3.0	3.1	1.8
PD20	3TAMs	M41L L210W T215Y	10.3	7.2	2.9
K65R	K65R	K65R	3.3	3.3	NA
PD11	K65R	K65R M184V	3.3	3.1	2
PD15	Q151M/ K65R	M41L A62V K65R T69I K70T L74V V75I Y115F F116Y Q151M M184V	5.9	4.1	2.4
PD25	4TAMs	D67N K70R T215F K219Q	6.1	5.1	3.3
PD30	T69ins	D67E T69SSG	10.1	10.1	4.5
PD31	5TAMs	M41L D67N T69D L210W T215Y K219R	25.5	21.9	4.5
PD34	5TAMs	M41L D67N L210W T215Y K219R	14.8	14.7	5.8

a TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/N/Q/R.
b NAMs at positions: 41, 62, 65, 67, 69, 70, 74, 75, 77, 115, 116, 151, 184, 210, 215, and 219.
c Wild-type (LAI) EC_{50} in the MT-2 assay was 0.014, and 3.4 µM for TAF and TFV, respectively.
d Wild-type EC_{50} in the Monogram PhenoSense GT assay was 1 µM for TFV.
Source: PC-120-2013 and PC-120-2015

The results of this experiment (Table 106) showed that physiologically relevant concentrations of TAF inhibited viral breakthrough for the duration of the experiment for 9 to 11 viruses, including viruses with 3 TAMs, K65R, Q151M complex, 4 TAMs, or T69 insertion. In contrast, viral breakthrough was only inhibited for 2 of 11 viruses in the presence of TFV. For viruses with the highest resistance (5 TAMs, fold change > 14), neither TAF nor TFV could achieve inhibition of viral breakthrough. These results are in agreement with the higher activity of TAF compared with TDF observed in vivo and suggest that treatment with TAF may lead to antiviral efficacy against previously defined TDF-resistant viruses.

Table 106. Time to Viral Breakthrough

Isolate ID	Mutant Category[a]	Time to Viral Breakthrough (days)	
		TAF[b]	TFV[b]
LAI	WT	> 28	> 28
PD9	3TAMs	> 28	> 28
PD6	3TAMs	> 28	13
PD20	3TAMs	> 28	4
K65R	K65R	> 28	18
PD11	K65R	> 28	4
PD15	Q151M/K65R	> 28	8
PD25	4TAMs	> 28	8
PD30	T69ins	> 28	4
PD31	5TAMs	8	4
PD34	5TAMs	8	4

a TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/N/Q/R
b Drug concentrations were 1× the EC_{95}.
Source: PC-120-2013

4.1.1.1.6. TAF Activity on HIV-1 with NNRTI, PI, and INSTI Resistance Associated Mutations

The antiviral activity of TAF was assessed against a panel of 7 drug-resistant HIV-1 clinical isolates, including NRTI-R, NNRTI-R, PI-R, and INSTI-R viruses (PC-120-2004). Five of the 7 isolates were single class resistant mutants, including 1 NNRTI-R mutant, 2 PI-R mutants, and 2 INSTI-R mutants. The 2 remaining isolates had either NRTI-R + NNRTI-R or NRTI-R + NNRTI-R + PI-R mutants (Table 107).

Virus and activated human PBMCs were mixed in the presence of TAF and incubated for 7 days before antiviral effect (ie, inhibition of RT activity) and cytotoxicity were assessed. In this in vitro experiment, PBMC viability remains high throughout the incubation period; thus, virus-infected cells were used for the assessment of both antiviral activity and cytotoxicity. Various other ARV drugs were included as positive controls, depending on the drug-resistance isolate tested: ZDV for all isolates, NVP and enfuvirtide (T-20) for NRTI-R and NNRTI-R isolates, indinavir and T-20 for PI-R isolates, and RAL and EVG for INSTI-R isolates.

Overall, TAF showed potent antiviral activity against HIV-1 isolates resistant to other ARV drug classes (Table 107). TAF demonstrated antiviral activity against the NNRTI-R, PI-R, and INSTI-R mutants. For the 2 viruses that contained NRTI-R mutations, TAF showed a 2.1- and 5.4-fold reduced susceptibility associated with the presence of the following resistance mutations: 3 TAMs + M184V (D67N, K70R, M184V, and K219E) in the first isolate (5705-72), and MDR Q151M mutation complex (A62V, V75I, F116Y, Q151M) + K65R + TAMs (M41L,

K65R, D67N, L210W, and T215Y) in the second isolate (MDR 769). No cytotoxicity was observed with TAF or the other drugs at the concentrations evaluated.

Table 107. TAF Antiviral Activity Against Drug-Resistant Primary HIV-1 Isolates

Isolate ID	Resistance Class	Resistance Mutations	EC_{50} FC From Wild-Type Virus[a]						
			TAF	ZDV	NVP	IDV	T-20	RAL	EVG
A-17	NNRTI-R	RT: K103N Y181C	1.7	0.7	> 380		0.2	—	—
1064-52	PI-R	RT: D67N PR: I54V V82F L90M	0.5	1.0	—	39.3	0.4	—	—
52-52	PI-R	PR: M46I I54V V82T	0.4	0.4	—	15.2	0.2	—	—
8070_1	INSTI-R	IN: G140S Y143H Q148H	0.2	0.2	—	—	—	250	222
4736_4	INSTI-R	IN: E92Q N155H	0.1	0.2	—	—	—	18.9	101
5705-72	NRTI-R, NNRTI-R	RT: D67N K70R K103N M184V K219E	2.1	33.1	279	—	0.6	—	—
MDR 769	NRTI-R, NNRTI-R, PI-R	RT: M41L A62V K65R D67N V75I F116Y Q151M L210W T215Y Y181I PR: M46L I54V V82A I84V L90M	5.4	> 89	—	210	0.7	—	—

— = not tested
a Fold change calculated from the average EC_{50} across wild-type isolates: 3.4 nM (TAF), 11.2 nM (ZDV), 25.1 nM (NVP), 12.0 nM (IDV), 39.4 nM (T-20), 3.1 nM (RAL), 1.0 nM (EVG)
Source: PC-120-2004

4.1.1.1.7. TAF Selectivity Index

TAF, TFV, and TDF were evaluated in vitro for antiviral activity against HIV-1 (EC_{50}) and cytotoxicity (CC_{50}) in MT-2 cells, MT-4 cells, and PBMCs (PC-120-2004, PC-120-2007, and PC-120-2009). Other ARV drugs, including NRTI, NNRTI, INSTI, and PI classes, were also evaluated in MT-2 and MT-4 cells (PC-120-2007). Quiescent and PHA-activated PBMCs, MT-2, and MT-4 cells were incubated with serially diluted drug concentrations for 5 days and then evaluated for cytotoxicity (PC-120-2007 and PC-120-2009). The maximum concentrations of drugs used were 100, 50, and 2000 µM, for TAF, TDF, and TFV, respectively. MT-2 and MT-4 cells were also infected with the $HIV\text{-}1_{IIIB}$ strain, incubated with serially diluted drug concentrations for 5 days, and then evaluated for antiviral activity (reduction of viral cytopathic effect) (PC-120-2007). The antiviral activity of TAF was evaluated against a panel of HIV-1 clinical isolates in PHA-activated PBMCs, as described in Section 4.1.1.1.2.1.

Based on the results of these experiments, the selectivity index ($SI = CC_{50}/EC_{50}$) for TAF was 1997 and > 3607 in the T-lymphoblastoid cell lines and 1889 in dividing PBMCs (Table 108). Due to its increased cellular permeability, the anti-HIV activity of TAF was increased by 228- and 1232-fold over TFV in MT-2 and MT-4 cells, respectively; in comparison, the anti-HIV activity of TDF was increased over TFV by 55- and 729-fold (Table 108; PC-120-2007). The SIs

for TAF were also higher compared with TFV and TDF in all cell types tested (Table 108; PC-120-2007 and PC-120-2009). In the MT-2 and MT-4 lymphoblastoid cell lines, TAF ranked first in SI among all the NRTIs tested, followed by TDF and TFV. Among all ARV drugs tested, TAF ranked fourth in SIs, following an NNRTI (EFV), an INSTI (RAL), and a PI (ATV). The SI values in the MT-2 cells in the current study (PC-120-2007) were within 1.7- to 2.2-fold agreement with previously reported values for TAF (8000), TFV (1250), and TDF (1000) {7415}; the differences may reflect minor differences in kinetic cell loading.

The ARV activity of TAF and TFV was also assessed in monocyte-derived macrophages (MDMs) obtained from a demographically diverse group of donors. The MDMs were infected with the HIV-1_{BaL} strain, incubated with serially diluted drug concentrations for 14 days, and then evaluated for virus production (PC-120-2017). ZDV and EFV were included as positive controls. The relative range of TAF antiviral activity across all tested donors was higher than that for TFV and comparable with that of the other HIV-1 RT inhibitors tested, with a mean EC_{50} value of 9.7 nM compared with 799, 15.3, and 0.9 nM for TFV, ZDV, and EFV, respectively (Table 108; PC-120-2017).

Table 108. Anti-HIV Activity (EC_{50}) and Cytotoxicity (CC_{50}) of TAF, TFV, and TDF

	Cells/Virus									
	MT-2/HIV-1_{IIIB}			MT-4/HIV-1_{IIIB}			PBMC[b]/HIV-1_{IIIB}[c]			Macrophage-Monocytes/ HIV-1_{BaL}
Drug	EC_{50} (µM)	CC_{50} (µM)	SI[a]	EC_{50} (µM)	CC_{50} (µM)	SI[a]	EC_{50} (µM)	CC_{50} (µM)	SI[a]	EC_{50} (µM)
TAF	0.0147	> 53.0	> 3607	0.0116	23.2	1997	0.0036	6.8	1889	0.0097
TFV	3.3565	7605	2265	14.292	6264	438	1.9	2150	> 1100	0.799
TDF	0.0614	37.1	604	0.0196	22.9	1167	0.015	19.6	> 1300	ND

CC_{50} = concentration that resulted in 50% cytotoxicity; EC_{50} = concentration inhibiting viral replication by 50%; ND = not determined; PBMC = peripheral blood mononuclear cell; SI = selectivity index; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

a Ratio of CC_{50} to EC_{50}.

b Data is shown for dividing PBMCs.

c EC_{50} for TAF is mean of EC_{50} values for 26 primary HIV-1 isolates.

Source: PC-120-2004, PC-120-2007, PC-120-2009, and PC-120-2017

TFV was investigated in a novel antiviral persistence assay to assess the ability of the intracellular drug to maintain antiviral suppression over extended periods of time {9497}. TFV demonstrated long-term antiviral persistence through 24 hours in primary CD4 T cells (58.7% persistence at 24 hours), whereas ABC was much less persistent (< 0.5% persistence at 4 hours) in comparison. Consistent with the sustained antiviral persistence of TFV, the calculated in vitro $t_{1/2}$ of TFV-DP in primary CD4 T cells was ~21 hours compared with ~5 hours for the active metabolite of ABC, CBV-TP.

4.1.1.1.8. Removal of TFV by HIV-1 Reverse Transcriptase

The removal of NRTIs by HIV-1 RT using a pyrophosphate acceptor molecule or a similar mechanism using ATP as an acceptor has been proposed as mechanisms of NRTI resistance {2043}. Removal of the inhibitors by these mechanisms frees the HIV-1 RT to incorporate the natural nucleotide substrate and resume/rescue HIV-1 replication. The excision of TFV from TFV chain-terminated primers was originally not detected {2252}. However, newer methodology has demonstrated that TFV can be efficiently excised by pyrophosphorolysis and ATP-mediated excision mechanisms {11304}, {7583}, {8925}. The excision of NRTIs occurs only when the nucleotide exists in its pretranslocational state. The binding of the next complementary nucleotide causes the formation of a stable dead-end complex in the posttranslocational state, which blocks the excision reaction. The excision of TFV was highly sensitive to dead-end complex formation, allowing greater chain termination stability. Thus, the rate of excision of TFV is partially neutralized by the facile switch to the posttranslocational state and by dead-end complex formation {11304}.

Drug-resistant HIV-1 RT with mutations that are known to cause high-level NRTI excision, such as TAMs either with or without a T69S Ins mutation, also excise TFV at high rates to contribute to resistance {11304}, {5479}. These mutants also show greater phenotypic changes to TFV in vitro. The greater levels of resistance associated with the M41L-L210W-T215Y pattern of TAM resistance have also been shown to be clinically significant in terms of reduced responses to TDF therapy {5010}.

4.1.1.1.9. Antiviral Activity and Cytotoxicity of TAF Metabolites

Two TAF metabolites, M18 and M28, were identified as intermediates during intracellular conversion of TAF to TFV and were also identified as degradation products of TAF during drug product manufacturing. The antiviral activity and cytotoxicity of these metabolites was evaluated in 2 T-lymphoblastoid cell lines (MT-2 and MT-4) following 5 days of compound exposure (PC-120-2021). Both metabolites showed weak inhibition of HIV-1 replication; relative to TAF, the inhibitory potency of M18 was 121- to 130-fold lower (EC_{50} values of 0.56 to 0.97 μM) and the inhibitory potency of M28 was 1723- to 2630-fold lower (EC_{50} values of 7.41 to 21.04 μM). Both metabolites had no cytotoxicity up to the highest tested concentration (57 μM).

4.1.1.2. TAF: In Vivo Pharmacodynamics

No primary PD studies in animals were conducted.

4.1.1.3. FTC: In Vitro Pharmacodynamics

4.1.1.3.1. Mechanism of Action

4.1.1.3.1.1. Cellular Uptake

Transport studies were conducted in confluent cultures of HepG2 cells to determine the route(s) of cellular uptake of FTC {4527}. Assays were performed at 20°C using a modified rapid, cold buffer stop method. The influx of FTC into the cells did not depend on the concentration of FTC

or the presence of a Na^+ gradient, and was only partially inhibited by competing nucleosides and nucleoside transport inhibitors. This observation along with the negligible impact of the protein modification agents N-ethylmaleimide, 4,4′-diisothiocyanato-2, 2′-stilbenedisulfonic acid, and 4-aceamido-4′-isothiocynatostilbene-2, 2′-disulfonic acid on FTC uptake suggests that a component of FTC entry into HepG2 cells was not transporter-mediated.

4.1.1.3.1.2. Intracellular Metabolism

In Vitro

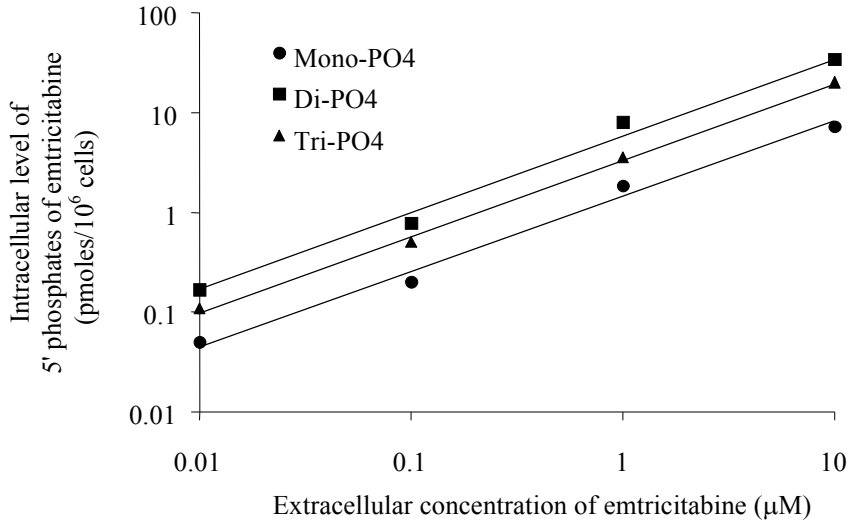
FTC is efficiently phosphorylated in HepG2 cells to the corresponding 5′-monophosphate, 5′-diphosphate, and 5′-triphosphate. A time course showed that the nucleotides of FTC were formed rapidly and reached a steady-state intracellular concentration by 3 to 6 hours {4527}. The intracellular concentrations of the 5′-phosphorylated forms produced as a function of the extracellular concentration are presented in Figure 33. The concentrations of these derivatives increase in a linear manner indicating that the anabolic pathway is not saturated over the concentration range tested. The concentration of FTC 5′-diphosphate was somewhat higher than those of the 5′-monophosphate and 5′-triphosphate derivatives {4535}, {4527}.

In studies to determine which enzymes were responsible for phosphorylating FTC to the 5′-triphosphate, 2′-deoxycytidine kinase was identified as the enzyme that catalyzes the phosphorylation of FTC to the corresponding 5′-monophosphate. An apparent Michaelis-Menton constant (K_m) value of 11.8 µM and an apparent relative maximum velocity (V_{max}) of 9.3 $nmol \cdot mL^{-1} \cdot h^{-1}$ was determined when uridine triphosphate (UTP) was the phosphate donor. When ATP was the phosphate donor, an apparent K_m value of 7.4 µM and an apparent relative V_{max} of 3.8 $nmol \cdot mL^{-1} \cdot h^{-1}$ was obtained {4544}. Using calf thymus 2′-deoxycytidine kinase, the relative rate of phosphorylation was 3.4% of that measured for 2′-deoxyguanosine and 40% of that observed for 2′-deoxycytidine (TESF/91/0014 and TESF/92/0002). Phosphorylation of the 5′-monophosphate was catalyzed by 2′-deoxycytidine monophosphate kinase {4535}, {4250}. The efficiency with which the enzyme purified from calf thymus phosphorylated the 5′-monophosphate of FTC was approximately 32% of that observed when using the natural substrate, 2′-deoxycytidine 5′-monophosphate (TEIT/92/0005). FTC 5′-monophosphate can also be phosphorylated by nucleoside monophosphate kinase purified from beef liver. However, the phosphorylation catalyzed by this enzyme is relatively inefficient. The formation of the 5′-triphosphate of FTC from the 5′-diphosphate has been proposed to be catalyzed by nucleoside diphosphate kinase {4535}, a cytosolic enzyme with a broad specificity for nucleoside 5′-diphosphates (TGZZ/93/0025). However, Cheng and colleagues have suggested that L-nucleoside 5′-diphosphates cannot be utilized as substrates by nucleoside diphosphate kinases and are selectively phosphorylated by 3-phosphoglyceride kinase {6289}.

The metabolism of FTC was studied in HepG2.2.2.15 human hepatocellular carcinoma cells (TEZA/92/0062) and CEM human T-lymphoblasts (TEZA/92/0103). Both cell lines anabolize FTC to FTC-TP, the intracellular form of the compound having antiviral activity. The intracellular $t_{1/2}$ of the triphosphate in these cells ranged from 2 to 5 hours.

The anabolism of FTC was evaluated as a function of time and drug concentration in HepG2.2.2.15 and CEM cells. The concentrations of the monophosphate, diphosphate, and triphosphate of FTC increased in a concentration-dependent manner and reached their maximum intracellular concentration by 4 hours postdose (TEZA/92/0062). Two other metabolites were observed, although at much lower concentrations than the monophosphate, diphosphate, and triphosphate. A study was performed to determine the intracellular metabolism of FTC in normal HepG2 cells and to compare it to that in HBV-infected HepG2.2.2.15 and P5A cells (TEZA/92/0111). The metabolites were identified as FTC-diphosphoethanolamine and FTC-diphosphocholine.

Figure 33. Intracellular Levels of FTC-TP as a Function of Extracellular FTC Concentration



FTC-TP = emtricitabine 5′-triphosphate; PO_4 = phosphate
Source: {4527}

In Vivo

The $t_{1/2}$ for FTC-TP has been determined directly in PBMCs, taken from healthy subjects dosed orally with 200 mg of FTC once daily. This in vivo value was found to be approximately 39 hours (Study FTC-106). The long intracellular $t_{1/2}$ supports once daily dosing.

4.1.1.3.2. Inhibition of Viral and Human DNA Polymerases

4.1.1.3.2.1. HIV-1 Reverse Transcriptase

FTC-TP serves as an alternative substrate inhibitor of HIV-1 RT and is incorporated into nascent chain viral DNA. Incorporation results in the termination of DNA synthesis due to the lack of a hydroxyl group in the 3′-position of the sugar moiety of FTC, which in turn inhibits viral replication. The K_i values for FTC-TP inhibition of HIV RT-catalyzed RNA-dependent DNA synthesis and DNA-dependent DNA synthesis were calculated to be 0.6 μM and 0.43 μM, respectively {4537}. In comparison, the K_i values for 3TC-TP inhibition of HIV RT-catalyzed

RNA-dependent and DNA-dependent DNA synthesis were comparable at 0.97 μM and 0.7 μM, respectively. In separate experiments in which calf thymus DNA was used as the template primer, a K_i value of 0.17 μM was obtained for FTC-TP against HIV-1 RT {4541}.

Using rapid quench techniques, Feng and colleagues compared the presteady-state kinetics of single nucleotide incorporation of deoxycytidine triphosphate (dCTP), 3TC-TP, and FTC-TP opposite a template guanosine in RNA-dependent DNA synthesis catalyzed by HIV-1 RT {4545}. The results are presented in Table 109. The overall k_{pol} of the oxathiolane nucleoside analogues is significantly slower than that observed for the natural substrate dCTP, as evidenced by the values of k_{pol}. However the equilibrium binding or affinity constant (K_d) values reveal that the oxathiolane substrates bind much tighter to the active site of the enzyme-DNA complex than the natural substrate, with the K_d values of the analogues being approximately 6- to 30-fold lower than those of the natural substrate. The K_d and k_{pol} values both indicate that FTC-TP is a better overall substrate for the enzyme than 3TC-TP. This efficiency advantage can account in part for the higher activity seen for FTC compared with 3TC in cell culture.

Table 109. Kinetic Constants for the Incorporation of dCTP, FTC-TP, and 3TC-TP into an RNA/DNA Template/Primer

Compound	Template/Primer	k_{pol} (s^{-1})	K_d (μM)	k_{pol}/K_d ($\mu M^{-1}s^{-1}$)
dCTP	r44/d23	9 ± 2	16 ± 5	—
	R45/D23	22.9 ± 0.7	30 ± 4	0.76
FTC-TP	r44/d23	0.240 ± 0.02	1.7 ± 0.3	—
	R45/D23	0.082 ± 0.005	1.4 ± 0.4	0.06
3TC-TP	R45/D23	0.033 ± 0.002	5.0 ± 0.8	0.0067

3TC-TP = lamivudine 5′-triphosphate; dCTP = deoxycytidine triphosphate; FTC-TP = emtricitabine 5′-triphosphate; k_{pol} = incorporation rate; K_d = equilibrium binding or affinity constant
Source: {4545}

4.1.1.3.2.2. Cellular DNA Polymerases

The inhibition of human HeLa cell DNA polymerases α, β, γ, and ε by FTC-TP was examined under steady-state conditions (TEZZ/93/0007) {4541}. Activated calf thymus DNA was used as the template for analysis of each enzyme. Under these conditions, FTC-TP was a weak inhibitor of each of the human DNA polymerases when compared with HIV-1 RT. Apparent K_i values were 6.0 μM for polymerase α; 17 μM for polymerase β; 6.0 μM for polymerase γ; and 150 μM for polymerase ε.

Inhibition of human DNA polymerase γ is one of the proposed mechanisms for nucleoside analogue-derived toxicity. Therefore the potential for FTC-TP and 3TC-TP serve as substrates for polymerase γ was investigated using presteady-state kinetics (TPI 9501). For dCTP (the natural substrate), FTC-TP, and 3TC-TP, the order of incorporation efficiency is dCTP (k_{pol}/K_d = 40 $\mu M^{-1}s^{-1}$) > 3TC-TP (k_{pol}/K_d = 0.014 $\mu M^{-1}s^{-1}$) > FTC-TP

(k_{pol}/K_d = 0.0006 $\mu M^{-1}s^{-1}$). The low rate of incorporation and poor binding affinity of FTC-TP makes it the least favorable substrate for polymerase γ in this analysis.

4.1.1.3.3. In Vitro Evaluation of Antiretroviral Activity

4.1.1.3.3.1. Anti-HIV Activity

The ability of FTC to inhibit replication of HIV-1 and HIV-2 in cell culture has been studied extensively using various human T-lymphoid cell lines (MT-2, MT-4, CEM, and HT4-6C) and PBMCs infected with laboratory-adapted strains of HIV-1 (IIIB, LAI, or LAV) and HIV-2 (ZY, ROD2). The results are summarized in Table 110. Several investigators have compared directly the anti-HIV activity of FTC with that of 3TC in the same assay. The results are summarized in Table 111. Although different laboratory strains of virus, different cell types, and different assay methods were used, FTC consistently showed greater activity than 3TC with the activity advantage ranging from 3- to 11-fold.

Table 110. Inhibitory Effect of FTC on the Replication of Laboratory Strains of HIV-1 and HIV-2

Virus	Cell Type	Assay	EC_{50} (μM)
$HIV\text{-}1_{IIIB}$	CEM	RT	0.1[a,b]
	MT-4	cytoprotection	0.5[a,b]
	PBMC	RT	0.01[b]
$HIV\text{-}1_{LAV}$	CEM	RT	0.009[a]
	HT4-6C	RT	0.02[a]
	PBMC	p24	0.009[b]
	PBMC	RT	0.001[d]
$HIV\text{-}1_{LAI}$	CEM	cytoprotection	0.04[c]
	MT-2	cytoprotection	0.62[c]
	PBMC	p24	0.03[c]
	PBMC	p24	0.0014[e]
$HIV\text{-}2_{ZY}$	MT-4	RT	1.5[a]
	CEM	RT	0.1[a]
$HIV\text{-}2_{ROD2}$	PBMC	p24	0.007[b]

EC_{50} = concentration inhibiting viral replication by 50%; PBMC = peripheral blood mononuclear cell; RT = reverse transcriptase
a Source: {4534}
b Source: {4541}
c Source: TPI 462 v2
d Source: {4526}
e Source: TPI 10498 v2

Table 111. Comparison of the Antiviral Activities of FTC and 3TC Against Various Laboratory Strains of HIV-1

HIV-1 Strain	Cell Line	EC_{50} (μM)		Sensitivity Ratio[d]
		FTC	3TC	
LAI[a]	PBMC	0.018	0.19	11
IIIB[b]	PBMC	0.01	0.07	7
IIIB[b]	MT-4	0.5	3.2	6
LAI[a]	MT-2	0.3	1.6	5
HXB2[b]	MT-4	0.09	0.24	3
LAI[c]	CD4+ HeLa	0.06	0.18	4

a Source: TPI 10498 v2
b Source: {4534}
c Source: {1794}
d Ratio of 3TC to FTC EC_{50} values

Schinazi and colleagues tested 2 low passage HIV-1 clinical isolates, J6 and 2:DR2, in PHA-stimulated PBMCs isolated from uninfected donors for FTC activity {4534}. The EC_{50} values were similar to those calculated using laboratory strains of virus in PBMCs (Table 112). The sensitivities to FTC reported for 2 additional wild-type clinical isolates, WT-pre-ZDV and WT-MKC09-day 29, were similar to those determined against J6 and 2:DR2 (TPI 462 v2). In the single experiment in which a direct comparison was made between the activity of FTC and 3TC, FTC demonstrated the same 5-fold potency advantage observed using laboratory strains of virus.

Table 112. Inhibition of HIV-1 Clinical Isolates by FTC

Virus	EC_{50} (μM)	
	FTC	3TC
J6[a]	0.002	0.01
2:DR2[a]	0.002	ND
WT – pre-ZDV[b]	0.008	ND
WT – MKC09-day 29[b]	0.02	ND

a Source: {4534}
b Source: TPI 462 v2

The potency of FTC has also been determined using a coculture assay {4248} and compared directly to the potencies of 3TC, ddC, ddI, ZDV, and the NNRTI tetrahydro-imidazo-benzodiazepine-one (TIBO) compound R82913. At the end of the coculture period, viral replication was estimated by HIV-1 p24 enzyme-linked immunosorbent assay (ELISA). Results from this study expressed as mean EC_{50}, EC_{90}, and EC_{99} values are given in Table 113. A potency ranking (based on EC_{90} values) showed FTC to be the most potent compound. The low potency ranking for ZDV compared with that observed in laboratory strains may be the result of inclusion of PBMCs from ZDV-experienced patients in the coculture.

Table 113. Comparative Potency of RT Inhibitors in HIV-1 Infected PBMCs Using a Coculture Method

Inhibitor	EC_{50} (μM)	EC_{90} (μM)	EC_{99} (μM)
FTC	0.0085	0.055	0.43
3TC	0.11	0.3	0.85
ddC	0.011	0.074	0.6
ddI	0.76	6.4	65.8
ZDV	0.055	0.53	6.4
TIBO R82913	0.17	0.67	2.95

Source: {4248}

4.1.1.3.3.2. Activity Against HIV-1 Subtypes

The activity of FTC on non-B subtypes of HIV-1 clinical isolates (group M subtypes A, C, D, E, F, and G, and O group) was evaluated. The EC_{50} values were determined in MAGI-CCR5 cells and PBMCs. Within each model, EC_{50} values were comparable for all subtypes of HIV-1. Results are presented in Table 114. FTC was more active than 3TC and ddI, and had activity comparable with that of ZDV for all subtypes of HIV-1 tested. Overall, the EC_{50} values of HIV-1 subtypes were 2- to 5-fold higher in MAGI-CCR5 cells than in PBMCs (TPI 10498 v2 and TPI 11419 v2).

Table 114. EC_{50} Values of NRTIs Against HIV-1 Group M and Group O Isolates in PBMCs and MAGI-CCR5 Cells

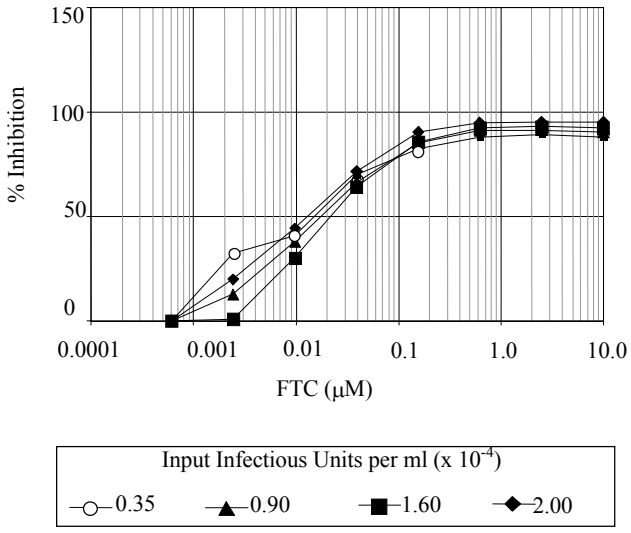
Isolate	Subtype	Host Cell	ZDV (μM)	3TC (μM)	ddI (μM)	FTC (μM)
Group M						
RW/92/008	A	PBMCs[a]	0.008	0.054	0.26	0.012
		MAGI-CCR5[b]	0.085	0.20	3.0	0.055
BR/92/025	C	PBMCs[a]	0.035	0.027	0.49	0.017
		MAGI-CCR5[b]	0.033	0.17	0.95	0.032
UG/92/024	D	PBMCs[a]	0.003	0.026	0.21	0.007
		MAGI-CCR5[b]	0.035	0.11	1.70	0.030
Tha/92/019	E	PBMCs[a]	0.039	0.069	0.5	0.028
		MAGI-CCR5[b]	0.080	0.15	1.50	0.065
Br/930/20	F	PBMCs[a]	0.003	0.022	0.34	0.009
		MAGI-CCR5[b]	0.045	0.15	1.50	0.050
RU570	G	PBMCs[a]	0.008	0.090	0.34	0.030
		MAGI-CCR5[b]	0.150	0.18	2.50	0.075
Group O						
BCF03 O		MAGI-CCR5[b]	0.09	0.20	2.20	0.065
		PBMCs[a]	0.028	2.5	4.75	0.14

a Source: TPI 10498 v2
b Source: TPI 11419 v2

4.1.1.3.3.3. Effect of Multiplicity of Infection

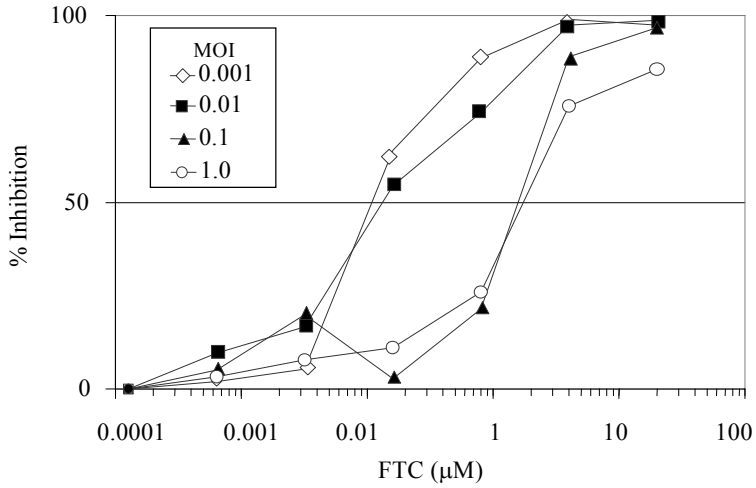
The effect of MOI on the antiviral activity of FTC was assessed in 2 cell lines using 2 different assay methods and was found to be minimal. In MAGI-CCR5 cells (Figure 34), an increase of 5.7-fold in infectious titer resulted in no change in EC_{50} (10518 v2). In PBMCs (Figure 35), using p24 ELISA, increasing the MOI from 0.01 to 0.1 caused approximately a 10-fold shift in apparent EC_{50} (11773). Increasing the MOI above 0.1 produced no further change in apparent EC_{50}.

Figure 34. Effect of Multiplicity of Infection on the EC_{50} of FTC in MAGI-CCR5 Cells



Source: 10518 v2

Figure 35. Effect of Multiplicity of Infection on the EC_{50} of FTC in PBMCs

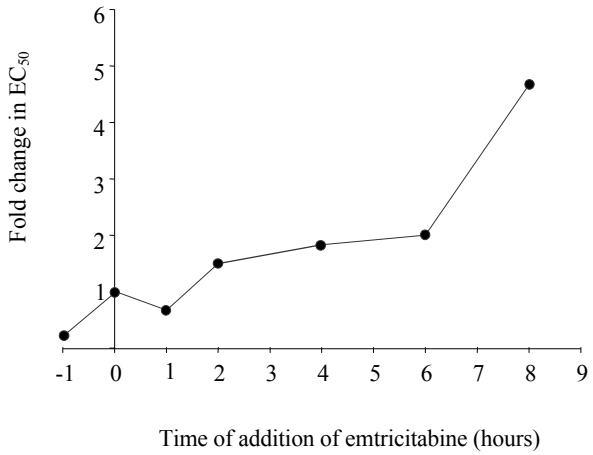


Source: 11773

4.1.1.3.3.4. Effect of Time of Addition

Various concentrations of FTC were added to MAGI-CCR5 cells infected with HIV-1_{LAI} (10247), and EC_{50} values were determined at −1, 0, +1, +2, +4, +6, and +8 hours postinfection. Results of the study are presented in Figure 36 as fold change in EC_{50} over time of addition. FTC maintained maximal antiviral activity when added as late as 6 hours postinfection. However, adding FTC 8 hours postinfection resulted in a decrease in antiviral activity consistent with the mechanism of action of an NRTI.

Figure 36. Fold Change in FTC EC_{50} as a Function of Time of Addition



Source: 10247

4.1.1.3.3.5. Effect of Serum Proteins and α_1-Acid Glycoprotein

The potential effect of protein binding on the antiviral activity of FTC was evaluated in CEM cells. Cells were infected with HIV-1_{LAI} and maintained in culture in the presence of various concentrations of FTC in standard 10% fetal bovine serum-containing media, or in modified media where fetal bovine serum was replaced with 25% human serum albumin (HSA) or 25% HSA plus 1-mg/mL α_1-acid glycoprotein. Neither the medium containing 25% HSA alone or in combination with 1-mg/mL α_1-acid glycoprotein affected the antiviral activity of FTC (463), indicating that FTC activity is not affected by binding to serum proteins.

4.1.1.3.4. In Vitro HIV-1 Resistance

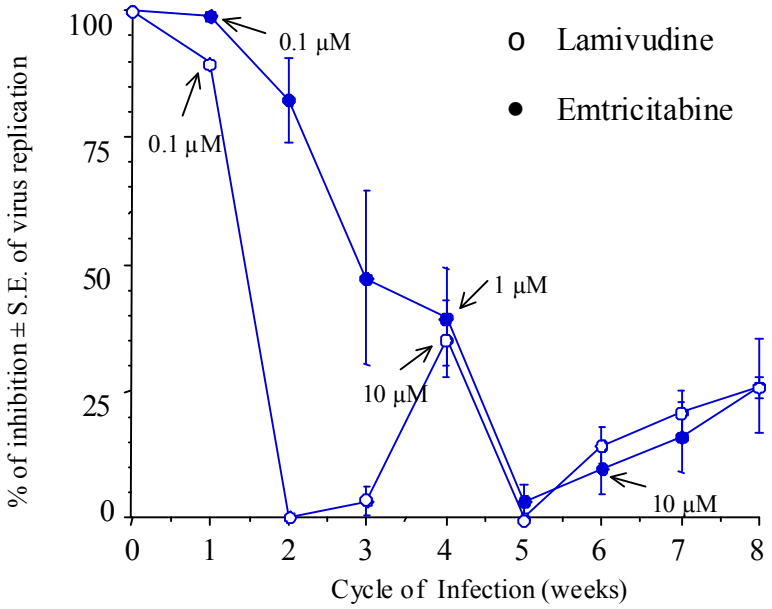
The development of resistance to FTC was examined by passaging virus in vitro in the presence of drug. In a study reported by Tisdale and colleagues, the wild-type virus HIV-1_{HXB2} or the ZDV-resistant mutant virus HIV-1_{RTMC} (containing D67N, K70R, T215Y, and K219Q RT mutations) was passaged in MT-4 cells in the presence of increasing concentrations of FTC or 3TC {1794}. Rapid emergence of resistance occurred with both compounds. By the fourth passage of HIV-1_{HXB2} and the second passage of HIV-1_{RTMC}, EC_{50} values exceeded 50 µM and by passage 6, EC_{50} values were in excess of 250 µM. These FTC-induced variants were highly cross-resistant to 3TC but showed no cross-resistance to ZDV, ddI, or NVP. DNA sequence analysis showed a change in RT of M184V. Passaging virus in the presence of increasing

concentrations of FTC and 50 µM ZDV was able to delay appreciably, but not prevent, the emergence of FTC-resistant virus.

In experiments performed by Schinazi and colleagues, the relative potential for HIV-1 to develop resistance to 3TC and FTC was evaluated by serial passage of the virus in human PBMCs in the presence of increasing drug concentrations {1777}. Results presented in Figure 37 show that after 2 weeks of infection, 0.1 µM 3TC was no longer able to inhibit virus replication and drug-resistant variants dominated the replicating virus population. In contrast, FTC remained highly active under identical conditions, reducing virus replication by 80%. FTC was still able to inhibit virus replication by 50% at Week 3. At Week 5, the concentration of 3TC was increased 100-fold to 10 µM and the concentration of FTC was increased 10-fold to 1 µM to produce the same level of inhibition. FTC retained up to a 10-fold potency advantage over 3TC after 5 weeks of passaging. These data suggest that, due to greater potency, FTC may delay the breakthrough of M184V resistant viruses longer than 3TC.

DNA sequence analysis of the RT gene amplified from resistant viruses generated in these passaging experiments consistently identified mutations at M184V/I. Resistant variants were cross-resistant to both FTC and 3TC, but remained sensitive to ddC, ddI, ZDV, phosphonoformic acid, 3′-fluoro-3′-deoxythymidine, and 2 NNRTIs, the TIBO compound R82150, and the bis(heteroaryl) piperazine (BHAP) derivative U-87201E {1777}.

Figure 37. HIV-1 Breakthrough in the Presence of FTC and 3TC



Source: {1777}

4.1.1.3.4.1. Mechanisms of Resistance

Biochemical studies were performed to quantify the change in susceptibility of HIV-1 RT derived from virus resistant to FTC-TP, 3TC-TP, and ddC 5′-triphosphate {1777}. Virus particle-derived RT was obtained from the supernatant of human PBMCs that were infected with M184V mutant virus. The mutated enzyme was 15-fold less sensitive to inhibition by FTC-TP or 3TC-TP than was wild-type (LAI) HIV-1 RT. However, only a 3-fold decrease in susceptibility was noted for ddC 5′-triphosphate. Similar results were reported using a highly purified cloned RT containing the M184V mutation for which the K_i values of FTC-TP and 3TC-TP were increased 320- and 80-fold, respectively, compared with wild-type HIV-1 RT {4545}. Using steady-state and presteady-state kinetic analysis, Wilson and colleagues examined the effect of the M184V mutation on HIV-1 RT catalytic function {4249}. These kinetic studies showed that the M184V mutation did not alter either the K_m or the enzyme catalytic constant (k_{cat}) values for the natural substrates, but did cause a 300-fold increase in the K_i for FTC-TP.

The M184V mutant HIV-1 is also associated with a decrease in replication capacity of HIV-1 expressing this mutation. This has been observed previously for a site-directed mutant expressing the M184V mutation {3852}, and is shown in Table 116 for a panel of clinical isolates expressing the M184V mutation that were obtained from a random set of plasma samples submitted to Monogram Biosciences for phenotypic analyses {5049} (PC-104-2004). The combination of K65R with M184V showed the greatest reduction in replication capacity {5476}. Decreases in natural substrate binding (M184V), incorporation (K65R), and reduced initiation of minus-strand single-stranded DNA synthesis (K65R+M184V) {10671} are likely responsible for these observed additive decreases in viral replication capacity.

4.1.1.3.4.2. Activity Against Drug-Resistant Variants of HIV-1

FTC activity has been evaluated extensively against a panel of clinical isolates (Table 115 and Table 116). The panel consists of a series of recombinant wild-type clinical isolates and recombinant isolates containing anywhere from 1 to 12 mutations. Consistent with earlier passaging experiments, a high level of resistance is imparted by introduction of the M184V mutation onto any mutation background. Moderate resistance to FTC is seen for the highly mutated isolate (M41L, E44D, D67N, T69D, L74I, K101E, V108I, V118I, Y181C, G190A, L210W, T215Y), which contains 2 mutations associated with moderate resistance to 3TC (E44D, V118I) {2359}. In addition, moderate resistance was observed for both FTC and 3TC, with isolates harboring the K65R mutation or a multidrug resistance genotype containing the T69S(SS) insertion as previously described for 3TC {2359}, {1003}, {4536}. The antiviral activity of FTC against HIV-1 containing K65R, Q151M, and K65R+Q151M showed reduced susceptibility (8.4-, 2.3-, and > 20-fold, respectively) in cell culture. Evaluation of the mutant RT enzymes suggested that resistance was mainly due to a significant decrease in the rate of incorporation of FTC using presteady-state kinetics studies in vitro. Similar levels of virus resistance and incorporation defects were measured for FTC and 3TC in this study {8887}.

Table 115. Phenotypic Analysis of a Panel of Recombinant Viruses

Genotype	EC_{50} (μM)		
	FTC	3TC	ZDV
Wild-Type (HIV-1_{HXB2})[a]	0.058	0.3235	0.0305
K65R, F116Y, Q151M, V106I[a]	2.607	3.327	0.696
M41L, D67N, K70R, A98S, Y181C, M184V[a], G190A, L219W, T215Y[a]	> 5	> 31.25	0.47
V75I, M184V[a]	> 125	> 31.25	0.028
A62V, T69S(SS), K70R, T215Y[a]	0.893	2.566	0.965
K103N, V108I/V, P225H[a]	0.123	0.618	0.0358
G190A, K238T[a]	< 0.122	0.541	< 0.05
V106A, G190A[a]	0.292	2.16	> 125
HIV-1_{IIIB}[b]	0.01	0.02	0.01
V106A[b]	0.03	0.03	0.014
V106A, F227L[b]	0.003	0.007	0.003
V106A, F227L, K101I, Y181C[b]	0.01	0.03	0.01

a Source: TPI 11148
b Source: {4538}

Table 116. Phenotypic Analysis of Recombinant Viruses Generated from Clinical Isolates

Genotype	EC_{50} (μM)[a]		
	FTC	3TC	ZDV
Wild-Type (LAI)	0.619[b]	2.567[b]	0.487[b]
Wild-Type (n = 16)	0.64[c]	2.998[c]	0.917[c]
L100I (A)	0.176	2.125	0.037
L100I (B)	0.595	2.350	0.160
G190A	0.220	0.900	0.205
G333E	1.350	1.265	0.260
M184V	> 20	> 50	0.140
K103T	0.330	1.100	0.140
V108I	0.205	0.650	0.135
K103N (A)	0.825	3.150	0.595
K103N (B)	0.680	4.000	0.250
K103N, M184V (A)	> 20	> 50	0.185
K103N, M184V (B)	> 20	> 20	3.02
E138K, M184V (A)	> 20	> 50	0.145
E138K, M184V (B)	> 20	> 50	0.130
E13Q, M184V	> 20	> 50	0.890
A98S, M184V	> 20	> 50	0.120
L74V, K103N	2.34	> 2.26	1.87
K101Q, E138K	1.38	1.94	0.54
K103R, Y188C	1.13	1.16	0.72
K103N, Y181C	0.55	1.17	0.29
K70R, L74V, M184V	> 20	> 20	0.90
K103T, V106I, M184V	> 20	> 20	0.36
K101Q, E138K, K103N	0.55	0.48	0.67
K103N, V108I, M184V	> 20	> 20	0.31
T215Y, K103N, L210W	0.73	1.05	> 2
M41L, K101R, M184V, T215Y	> 20	> 20	> 2
A98S, F116Y, Q151M, T215Y	1.45	0.55	> 2
T69N, K70R, M184V, K219Q	> 20	> 20	1.23
D67N, K70R, M184V, G190A	> 20	> 50	0.35

Genotype	EC_{50} (μM)[a]		
	FTC	3TC	ZDV
D67N, T69D, K103R, T219Q	2.58	2.92	5.75
A62V, A98S, K101D, K102Q, M184V	> 20	> 50	0.35
M41L, D67N, M184V, L210W, T215Y	> 20	> 20	> 2
D67N, K70R, E138A, M184V, T215Y, K219E	> 20	> 20	> 2
M41L, D67N, Y181C, M184V, L210W, T215Y	> 25	> 20	> 2
M41L, D67N, T69D, V108I, M184V, T215Y	> 20	> 20	> 2
A62V, V75M, K103N, F116Y, Q151M, M184V	> 20	> 20	> 2
D67N, T69D, K70R, K103N, M184V, T215Y, K219Q	> 20	> 20	> 2
M41L, D67N, A98G, K101E, K103N, M184V, G190A, L210W, T215Y, G333E	> 20	> 20	> 2
M41L, E44D, D67N, T69D, L74I, K101E, V108I, V118I, Y181C, G190A, L210W, T215Y	7.27	6.63	1.85

a EC_{50} values are expressed as the median value of at least 3 replicates unless otherwise noted.
b EC_{50} is the average value of at least 10 replicates.
c EC_{50} values are the average of replicates from 16 different recombinants displaying a wild-type genotype.

4.1.1.4. FTC: In Vivo Efficacy Against Animal Retroviruses

The anti-HIV activity of FTC has been tested in SCID mice. Mice were reconstituted with human PBMCs and, after 2 weeks, infected with HIV-1_{A018} {4525} (TPI 11985). Drug therapy was initiated 1 day before infection. Test compounds were administered intraperitoneally at 30 mg/kg twice daily. Viral inhibition was measured by quantitative cocultures for infectious HIV-1, and quantitative RNA viral load was measured on peritoneal wash cells, lymph nodes, spleen cells, and plasma. At the concentration used in this study, FTC completely inhibited viral infection.

Black and Furman evaluated the anti–HIV-1 activity of orally administered FTC and 3TC side-by-side in the HuPBMC-SCID mouse model (TPI 11985). Groups of 12 or 15 female C.B-17 SCID mice were reconstituted by the intraperitoneal injection of 1.3×10^8 human PBMCs. Two weeks later, the mice were infected intraperitoneally with 2000 tissue culture infectious doses of HIV-1_{A018}. Drugs were then administered in drinking water, which contained 0.3 mg/mL of FTC or 3TC. Seven days after infection, viral load in plasma was measured using a real-time reverse transcription polymerase chain reaction (RT-PCR). Both FTC and 3TC were well tolerated during the 7 days of the study with no evident toxicity. The average daily doses of the 2 drugs were similar, about 60 mg/kg. In the control group, the geometric mean viral load was 2.5×10^4 copies/mL. FTC reduced plasma viral loads to below 50 copies/mL in all 12 treated mice, and 3TC reduced plasma viral loads to below the limit of detection in 11 of the 12 treated mice. The reductions in viral loads in both treatment groups were statistically significant ($p < 10^{-5}$) compared with control, but did not differ significantly from each other.

4.1.1.5. FTC/TDF

4.1.1.5.1. In Vitro Phosphorylation of TFV and FTC

The intracellular phosphorylation of TFV and FTC to their active metabolites, TFV-DP and FTC-TP, respectively, was investigated for potential antagonism (PC-164-2001). All forms of TFV, the free drug, the monophosphorylated form, and diphosphorylated form (ie, TFV, TFV-MP, and TFV-DP, respectively) were quantified in this analysis. The activated form of FTC (FTC-TP) was also measured. When 10 μM TFV was incubated alone in CEM cells, conversion to the active form, TFV-DP, was readily observed over the 24-hour time course (Table 117). Similarly, FTC-TP was also readily observed to form over the same time period when incubated alone (Table 118).

When TFV and FTC were incubated together (10 μM each), slightly higher levels of each respective active metabolite (TFV-DP and FTC-TP) were observed at 2 and 24 hours as compared with the NRTIs incubated alone in CEM cells (Figure 38, Table 117, and Table 118). The slightly higher concentrations of active metabolites observed in the combination experiment may suggest slight enhancement of metabolism of both TFV and FTC; however, no difference in metabolite production was observed in cultured PBMCs {8998}.

Table 117. Metabolism of 10 μM TFV Either Alone or in Combination with 10 μM FTC

Time	TFV Alone (pmol/million cells)[a]			TFV+FTC (pmol/million cells)[a]		
(h)	TFV	TFV-MP	TFV-DP	TFV	TFV-MP	TFV-DP
2	0.74 ± 0.31	0.02 ± 0.01	0.06 ± 0.01	0.50 ± 0.10	0.04 ± 0.01	0.09 ± 0.01
24	1.32 ± 0.48	0.54 ± 0.06	1.64 ± 0.08	0.97 ± 0.78	0.34 ± 0.03	2.24 ± 0.07

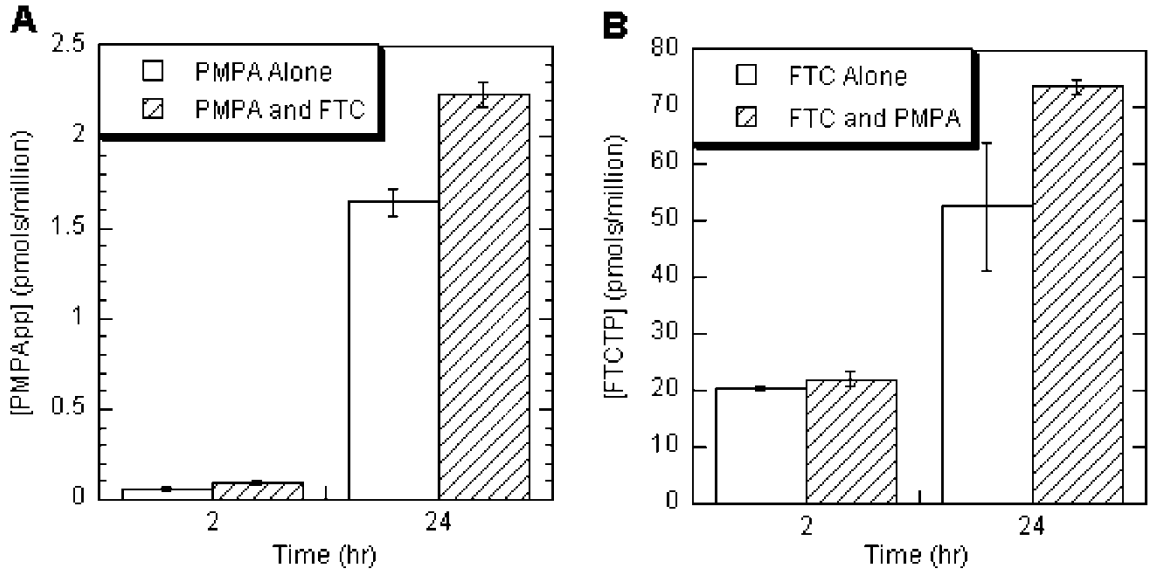
a Values determined by LC/MS/MS.
Source: PC-164-2001

Table 118. Metabolism of 10 μM FTC Either Alone or in Combination with 10 μM TFV

Time	FTC Alone (pmol/million cells)[a]	TFV+FTC (pmol/million cells)[a]
(h)	FTC-TP	FTC-TP
2	20.4 ± 0.5	22.0 ± 1.3
24	52.5 ± 11.3	71.6 ± 1.4

a Values determined by LC/MS/MS.
Source: PC-164-2001

Figure 38. Formation of the Active Metabolites of TFV and FTC



Concentrations of the active metabolites of TFV (A) and FTC (B), (TFV-DP and FTC-TP, respectively) formed after incubation of CEM-CCRF cells with 10 μM concentrations of NRTIs either alone or in combination.
Source: PC-164-2001

Experiments were also carried out using a prodrug of TFV (TAF), which more efficiently delivers TFV, TFV-MP, and TFV-DP to cells, to determine if higher levels of TFV metabolites could affect the metabolism of FTC to FTC-TP (PC-164-2001). At these higher concentrations of TFV metabolites, no significant effect on the metabolism of FTC was observed with the combination as compared with the NRTI given alone. Additionally, no effects were seen on TAF metabolism with and without FTC.

These results demonstrate that the intracellular phosphorylation of both TFV and FTC to their respective activated metabolites (TFV-DP and FTC-TP) is not negatively affected by the simultaneous presence of the other NRTI. These results were observed using concentrations of drugs that are in excess of the plasma concentrations obtained in patients treated with these drugs (C_{max} values of 1 and 7 μM for TFV and FTC, respectively). A similar lack of an intracellular phosphorylation interaction has been described for TFV and ddI, 2 adenosine analogs that are known to have a higher degree of similarity in their phosphorylation pathways {5468}. Taken together, these results show that, even at super physiological concentrations, there is little potential for a negative metabolic drug interaction at the level of phosphorylation between TFV and FTC and evidence for increased production of metabolites was detected in some cell lines.

4.1.1.5.2. In Vitro Anti-HIV Activity of TFV and FTC

Both TFV and FTC have been tested in parallel for their anti-HIV activity (PC-164-2002). Two HIV-1 isolates were used in these analyses, the laboratory-adapted LAI strain and a recombinant HIV-1 strain containing a wild-type patient-derived RT and protease sequence (MM-317). The infections were carried out at 2 different MOIs (0.03 and 0.1), and the results

were calculated as EC_{50} and EC_{90} values for each drug (Table 119). Overall, there was some effect of MOI observed, with increased EC_{50} and EC_{90} values noted for FTC with both viruses and increased values for TFV with the MM-317 virus. The drug susceptibility values derived from the laboratory strain and the patient recombinant virus were similar for both drugs. The EC_{90} values were approximately 3-fold greater than the EC_{50} values. The combined effects of TFV and FTC together on HIV-1 replication are described in the PD drug interactions section (Section 4.1.2.3).

Table 119. Mean EC_{50} and EC_{90} Values for TFV and FTC Against HIV-1_{LAI} and HIV-1_{MM-317} Strains

Viral Isolate	MOI	TFV EC_{50} (μM)	TFV EC_{90} (μM)	FTC EC_{50} (nM)	FTC EC_{90} (nM)
LAI	0.03	5.1 ± 1.8	19.1 ± 5.8	132.3 ± 38.5	439.7 ± 127.9
LAI	0.1	5.1 ± 0.9	17.0 ± 6.0	220.6 ± 65.4	720.8 ± 127.5
LAI	Mean	5.1	18	176	580
MM-317	0.03	6.2 ± 1.4	20.5 ± 4.8	126.6 ± 25.2	420.7 ± 83.7
MM-317	0.1	11.2 ± 0.9	37.0 ± 3.3	216.9 ± 38.4	720.8 ± 127.5
MM-317	Mean	8.7	29	172	571

Source: PC-164-2002

4.1.1.5.3. In Vitro Selection of Resistant HIV-1 with TFV and FTC

In vitro resistance selection experiments were performed with the wild-type HIV-1_{IIIB} in the immortalized MT-2 cell line with the combination of TFV and FTC (PC-164-2005). In parallel, resistance selections were performed with each drug separately. The concentrations of drugs used to initiate the selection experiments were at the EC_{50} values for each individual drug for the 1-drug selections and one-half the EC_{50} values for the 2-drug selections to allow for adequate virus replication. As summarized in Table 120, FTC-resistant virus was selected in both cultures containing FTC when the concentration of FTC had reached 1.6 μM or 2-fold the EC_{50} value. The genotype of this virus showed an M184I mutation in RT as the dominant mutation, with some evidence of M184V but no other genotypic changes in the first 250 amino acids of RT. Resistant virus continued to grow in the FTC-alone culture at an FTC concentration of 230 μM (> 200-fold resistance to FTC), with further evolution to dominance of the M184V mutation. Previous resistance selection experiments have also resulted in the M184I mutation, which later converted to an M184V mutation upon further in vitro passage {1777}.

Table 120. In Vitro Selection of TFV and FTC Resistant HIV-1

Selecting Drugs	Starting Drug Concentration	Ending Conditions		Days in Culture	HIV RT Genotype
		Drug Concentration	Fold Above EC_{50}		
TFV	3.5 μM	112 μM	32	99	K65R (at 56 μM TFV; Day 56)
FTC	0.8 μM	230 μM	287	48	M184I/V (at 1.6 μM FTC; Day 17) M184V/I (at 230 μM FTC; Day 44)
FTC+TFV	0.4 μM FTC	19.2 μM	24	155	M184I L214F (at 1.6 μM FTC, 7 μM TFV; Day 24)
	1.8 μM TFV	84 μM	24		K65R (at 12.8 μM FTC, 56 μM TFV; Day 114)

Source: PC-164-2005

In the TFV-alone culture, resistance to TFV was observed with the K65R mutation in RT at Day 56 at a TFV concentration of 56 μM, 16-fold above the TFV EC_{50} value. In the FTC-alone culture, resistance to FTC was observed with the M184V/I mutations in RT at Day 17 at an FTC concentration of 1.6 μM. In the combination culture, an M184I mutation was detected at Day 24 in culture and at an FTC concentration of 1.6 μM, and a K65R mutation was observed later at Day 114 at a TFV concentration of 56 μM. The M184I mutation was not observed at this time point; however, the M184V mutation was observed upon subsequent increases in the FTC concentration to 25.6 μM. Attempts to increase the TFV concentration have resulted in a loss of HIV-1 growth in both cultures. The results obtained show that resistance development to FTC occurs much more readily and quickly than resistance development to TFV in vitro. These in vitro results suggest that under conditions of continued viral replication in vivo, the combination of TFV and FTC would initially select for the M184V/I mutation, and then potentially for TFV resistance in the form of the K65R mutation. Clinical study data using the combination of TDF with FTC support this conclusion as the M184V mutation was observed to develop in the absence of K65R in patients with virologic failure.

In Vivo Antiviral Activity of the Combination of TFV and FTC in Simian Immunodeficiency Virus-Infected Macaque Monkeys

In a published study, the simian immunodeficiency virus (SIV) latent cell reservoir in SIV-infected pig-tailed macaques on a regimen of TFV and FTC was analyzed {5477}. Macaques were infected with SIV and showed primary viremia of 10^5 to 10^7 copies/mL at 2 weeks postinoculation (n = 4). At 50 days postinoculation, viral loads dropped to 10^3 to 10^5 copies/mL, and animals were either treated subcutaneously with TFV (20 mg/kg) and FTC (50 mg/kg) (n = 2) or were not given any drugs (n = 2). The treated macaques achieved SIV levels that were below the limit of detection (ie, < 100 copies/mL of viral RNA), whereas only 1 of the nontreated macaques showed a decrease in SIV RNA. Except for an isolated "blip" of detectable viremia, all treated animals remained close to or below the limit of detection for up to 6 months, suggesting that this regimen was effective against SIV in this macaque model. Given

that viral load remained controlled in the treated animals, there was no evidence of resistance development through 6 months of dual therapy with TFV and FTC in this study.

A study was presented that explored preexposure chemoprophylaxis with ARVs as a strategy to prevent the transmission of HIV {11074}. All animals were subjected to 14 weekly rectal exposures with a low dose of SHIV (SIV/HIV chimeric virus). Three groups of 6 rhesus macaques were injected subcutaneously with TFV/FTC daily, at 2 hours before and 24 hours after the first virus exposure, or at 2 hours before first virus exposure only. Twenty-one control animals did not receive any ARV treatment. Twenty of the 21 control animals became infected after a median of 2.5 challenges. In contrast, all 6 animals treated with TFV/FTC daily or before and 24 hours after the first challenge were fully protected after 14 challenges. In the single-dose group, 1 of 6 animals was infected (data from 10 challenges were analyzed). In this animal model, the multiple-dose TFV/FTC combination provided a high level of protection against repeated virus challenges, whereas the single dose was highly effective, but not sufficient to fully protect against rectal transmission.

4.1.2. Secondary Pharmacodynamics

4.1.2.1. TAF: Cellular DNA Polymerases

The in vitro specificity of TFV-DP for viral polymerases relative to its interaction with mammalian DNA polymerases was determined.

Table 121 summarizes the inhibitory effects of TFV-DP on DNA synthesis catalyzed by the mammalian DNA polymerases α, β, and γ, and by the rat DNA polymerases δ and ε {1131}, {2516}. The K_m for the natural substrate dATP is also shown. TFV-DP showed specificity for HIV-1 RT with K_i/K_m ratios of 5- to 200-fold higher for mammalian DNA polymerases compared with HIV-1 RT. The K_i/K_m ratio was particularly high (85.3) for mitochondrial polymerase γ, suggesting a low potential of TFV to interfere with the synthesis of mitochondrial DNA {1131}. Additional studies have shown that 1 mM TFV-DP exhibited little effect on the in vitro replication of SV40 DNA, indicating a significant specificity of TFV-DP toward the viral RT in comparison to the host DNA replication complex {2517}. Similar conclusions of strong specificity of TFV-DP toward HIV-1 RT have been made using presteady-state enzyme kinetic experiments {2518}.

Table 121. Kinetic Inhibition Constants of TFV-DP Against DNA Polymerases α, β, γ, δ, and ε

Enzyme	K_i (μM)	K_m dATP (μM)	K_i/K_m
Human DNA Pol α	5.2	2.7	1.92
Human DNA Pol β	81.7	5.6	14.6
Human DNA Pol γ	59.5	0.7	85.3
Rat DNA Pol δ/PCNA	7.1	0.7	10.2
Rat DNA Pol ε	95.2	6.1	15.6

Source: {1131}, {2516}

In order to evaluate TFV-DP as a potential substrate for host polymerases, its incorporation efficiency into a DNA primer/template by human DNA polymerases α, β, and γ relative to the natural dNTPs has been determined and compared with that of the triphosphates of other NRTIs {2005}. TFV-DP showed similar or lower incorporation by DNA polymerases α and β compared with dideoxyadenosine triphosphate (ddATP; the active metabolite of ddI), dideoxycytidine triphosphate (ddCTP), 3TC-TP, and d4T triphosphate (d4T-TP) (Table 122). Importantly, polymerase γ incorporates TFV-DP into a DNA primer/template with a very low efficiency (0.06%) relative to the natural substrate. This observation confirms the conclusions from the inhibition studies above.

Table 122. Relative Efficiencies of Incorporation into DNA of TFV-DP and NRTI Triphosphates by Human DNA Polymerases α, β, and γ

	Relative Efficiency of Incorporation (%)[a]		
dNTP Analog	**Pol α**	**Pol β**	**Pol γ**
TFV-DP	1.4	1.3	0.06
ddATP	0.25	80	20
ddCTP	0.1	125	25
3TC-TP	0.05	9.0	0.13
d4T-TP	6.3	142	8.0

a f inc (%) = 100 × $[V_{max}(\text{dNTP analog})/K_m(\text{dNTP analog})]/[V_{max}(\text{dNTP})/K_m(\text{dNTP})]$.
Source: {2005}

4.1.2.2. TAF Activity Against Human Viruses

4.1.2.2.1. Antiviral Activity Against Hepatitis B Virus

TFV is a potent and selective inhibitor of HBV. TFV inhibits HBV production in HepG2 2.2.15 and HB611 cells with EC_{50} values of 1.1 and 2.5 μM, respectively, and corresponding CC_{50} values of > 100 and 260 μM, respectively (P4331-00038) {21}. As observed with anti-HIV activity, TDF showed increased in vitro potency against HBV in comparison with TFV (EC_{50} = 0.018 μM in HEPG2 2.2.15 cells). TFV activity against 4 laboratory strains of HBV with up to three 3TC-associated HBV polymerase mutations was shown to be within 2.2-fold of the wild-type EC_{50} {8381}. A range of 0.7- to 3.3-fold reductions in TFV susceptibility was observed for 3TC-resistant HBV clinical isolates with multiple mutations in HBV polymerase {10426}, {10916}, {7060}. In contrast, 3TC demonstrated > 200-fold reduced activity against these HBV mutants. The rtA194T HBV mutant, either alone or in the presence of two 3TC-resistance mutations, showed < 2.4-fold change in TFV susceptibility (PC-104-2012). Laboratory strains of HBV expressing adefovir dipivoxil-associated HBV mutations (rtN236T, rtA181V/T) showed reductions in TFV susceptibility ranging from 1.5- to 10-fold as compared with wild type {10926}. A panel of entecavir-associated HBV mutations showed reductions in TFV susceptibility ranging from 0.6- to 6.9-fold as compared with wild type (PC-174-2003). TFV has also been shown to inhibit the replication of duck HBV in primary duck hepatocytes with an EC_{50} of 0.11 μM {10}.

In addition to assessing the use of TAF in HIV infection for the currently proposed indication, Gilead is conducting clinical studies to evaluate the use of TAF in subjects infected with HBV.

4.1.2.2.2. TAF: Antiviral Activity Against Animal Viruses

The antiviral activity of TAF and TFV was assessed against a panel of 18 animal viruses, including ≥ 1 isolates of adenovirus, dengue type 2, influenza A, parainfluenza 3, respiratory syncytial virus (RSV), coxsackie B virus, rhinovirus, herpes simplex virus (HSV) type 1 (HSV-1), HSV type 2 (HSV-2), human cytomegalovirus (HCMV), varicella zoster virus (VZV), vaccinia virus, HCV, HIV-1, and SIV (PC-120-2003). Virus and cells were mixed in the presence of the test compound (TAF or TFV) and incubated for 2 to 7 days, depending on the virus and assay type, before antiviral effect (ie, cytoprotection) and cytotoxicity were assessed. Each virus was pretitered such that control wells exhibited 85% to 95% loss of cell viability due to virus replication. Therefore, antiviral effect was observed when compounds prevented virus replication.

As expected, both HIV-1 and SIV isolates were potently inhibited by TAF and TFV (Table 123). No antiviral activity was observed against 12 of the 14 remaining human viruses evaluated. TFV weakly inhibited the HSV-2 strain KW with an EC_{50} value of 146 µM, which is consistent with data previously published {19333}. Similarly, TAF had an EC_{50} value of 424 nM for this viral isolate in MAGI R5 cells. Of note, initial experiments with HSV-2 strain KW in MRC-5 cells did not yield an EC_{50} value, probably due to a lack of TAF conversion to TFV in this cell type (data not shown). Overall, TAF and TFV activity against HSV-2 KW was 150- to 200-fold weaker than against HIV; weak activity was also observed for the HSV-2 strain MS strain (lab isolate). Finally, TAF had an EC_{50} of 843 nM against human parainfluenza. While the EC_{50} values against human parainfluenza indicate, at best, minimal TAF activity, cell growth inhibition was observed at the 1000 nM, indicating that the observed effect was likely due to cell inhibition. Neither TAF nor TFV exhibited cytotoxicity up to the high test concentrations of 1000 µM (TFV) or 1000 nM (TAF) used for these evaluations. Overall, the results indicate that TAF is a potent inhibitor of immunodeficiency retroviruses such as HIV and SIV and is a weak inhibitor of HSV-2. These results indicate that TAF is a highly specific antiviral agent with no relevant in vitro activity against the other tested human viral pathogens.

Table 123. TAF and TFV Antiviral Activity Against Human Viruses and SIV

Viruses	TAF (nM)		TFV (μM)		Positive Control
	EC_{50}	CC_{50}	EC_{50}	CC_{50}	
HIV-1_{NL4-3}	5.89	> 1000	2.30	> 100	ZDV
HIV-1_{BaL}	2.04	> 1000	1.05	> 100	ZDV
SIV_{mac239}	1.21	> 1000	0.73	> 1000	ZDV
SIV_{mac251}	0.51	> 1000	0.35	> 1000	ZDV
Adenovirus	> 1000	> 1000	> 1000	> 1000	RBV
Dengue Virus	> 1000	> 1000	> 1000	> 1000	RBV
HCV	> 1000	> 1000	> 1000	> 1000	rIFN-α
Coxsackie B Virus	> 1000	> 1000	> 1000	> 1000	enviroxime
Rhinovirus	> 1000	> 1000	> 1000	> 1000	enviroxime
Vaccinia	> 1000	> 1000	> 1000	> 1000	cidofovir
Influenza A	> 1000	> 1000	> 1000	> 1000	zanamivir, RBV
Human parainfluenza	843	> 1000[a]	> 1000[b]	> 1000[a]	enviroxime
RSV	> 1000	> 1000	> 1000	> 1000	RBV
VZV	> 1000	> 1000	> 1000	> 1000	acyclovir
HCMV	> 1000	> 1000	> 1000	> 1000	ganciclovir
HSV-1	> 1000	> 1000	> 1000[b]	> 1000	acyclovir
HSV-2_{KW}	424	> 1000	146	> 1000	acyclovir
HSV-2_{MS}	697	> 1000	278	> 1000	acyclovir

a Cell growth inhibition observed at the highest concentration.
b Viral inhibition observed at the highest concentration.
Source: PC-120-2003

4.1.2.3. FTC: Anti-Hepatitis B Virus Activity

4.1.2.3.1. In Vitro

HepG2 2.2.15

The in vitro anti-HBV activity of FTC has been studied extensively using the stably HBV-transfected cell line HepG2 2.2.15. In this system, FTC decreased levels of extracellular and intracellular HBV DNA in a dose-dependent manner. The EC_{50} values determined by various investigators using extracellular HBV DNA levels ranged from 0.01 to 0.04 μM. The FTC EC_{50} value based on intracellular DNA was somewhat higher, 0.16 μM, than the EC_{50}

values based on extracellular DNA (Table 124) {4535}. In contrast to the situation with HIV, the EC_{50} values for FTC and 3TC are comparable against HBV.

Primary Hepatocytes

Condreay and colleagues examined the effect of FTC on HBV replication in primary human hepatocytes {4532}. Although EC_{50} values were not calculated, FTC at 2 μM completely inhibited the production of intracellular HBV DNA, even when added 24 hours after infection. The EC_{50} value calculated from inhibition of extracellular virus production is < 0.02 μM, a value that is comparable with that determined in HepG2 2.2.15 cells (Table 124).

Table 124. Anti-HBV Activity in HepG2 2.2.15 Cells of Compounds Approved and Under Development for HBV Infection

Compound	EC_{50} Values
FTC	0.01 ± 0.005 μM[a], 0.04 ± 0.006 μM[b]
β-L-Fd4C	< 0.1 μM[d]
Adefovir	0.03 ± 0.01 μg/mL[c]
Amdoxovir	13 ± 2.1 μg/mL[c]
Clevudine	0.1 ± 0.06 μg/mL[c]
Entecavir	0.004 μM[e]
L-dT	0.19 ± 0.09 μM[d]
L-dC	0.24 ± 0.08 μM[d]
3TC	0.008 ± 0.003 μM[a], 0.0016 ± 0.0005 μg/mL[c]
Lobucavir	0.1 ± 0.1 μg/mL[c]
Penciclovir	3.5 ± 0.2 μg/mL[c], 2.5 μM[d]
TFV	0.04 ± 0.02 μg/mL[c]

a Source: {4535}
b Source: {4533}
c Source: {6287}
d Source: {6288}
e Source: {6295}

Inhibition of HBV DNA Polymerase

The replication cycle of hepadnavirus includes the reverse transcription of an RNA template. This process is carried out by a polymerase that shares significant sequence homology with the RT of retroviruses, including HIV. Since all attempts to date to purify the human HBV DNA polymerase have been unsuccessful, examination of the effect of FTC-TP on HBV DNA polymerase was carried out using an endogenous polymerase assay. In this assay, intact virus particles are treated with 1% Nonidet-P40, a nonionic detergent that partially disrupts the virus particles and allows nucleotide 5′-triphosphate substrates to enter the virus particle so that DNA synthesis can occur. Davis and colleagues, using the endogenous polymerase assay, demonstrated that the HBV DNA polymerase could incorporate [α-^{32}P]FTC-TP into minus-strand DNA {4539}. Endogenous polymerase assays using HBV particles isolated from

cell cultures treated with FTC-TP showed either reduced or no polymerase activity depending on the concentration of FTC-TP used. Furthermore, the particles produced in FTC-TP treated cells did not contain any detectable HBV plus strand DNA, which is consistent with the chain-terminating activity of incorporated FTC 5′-monophosphate. Taken together, the results demonstrate that FTC-TP serves as an alternative substrate inhibitor of the HBV DNA polymerase.

HBV Resistance

Treatment of HBV-infected patients with 3TC has been shown to be effective in suppressing virus replication and in reducing inflammatory activity. However, resistance to this agent has been documented to be associated with mutations in the YMDD motif (amino acids 203 to 206) in domain C of the viral DNA polymerase, analogous to changes seen in the YMDD motif of HIV-1 RT. Inhibition assays performed using the hepatoma derived cell lines AD38 and AD79 {6293}, which replicate wild-type and the M204V mutant HBV, respectively, confirmed that the HBV M204V mutation conferred resistance to FTC as well as to 3TC.

4.1.2.3.2. In Vivo

The in vivo anti-hepatitis activity of FTC was first tested in a chimeric mouse model {4530}. NIH bg-nu-xid mice were subcutaneously injected with suspensions of 10^7 HepG2 2.2.15 cells. Subcutaneous injection of these cells in mice resulted in the development of HBV-producing tumors in all animals. Hepatitis B virus could be detected in serum samples from the tumor-bearing mice using an immunoaffinity system linked to quantitative PCR. Beginning 1 week after injection, mice were orally dosed with 0.9, 3.5, 18.4, and 88.8 mg/kg/day FTC for 21 days. Comparison of tumor progression and human α-fetoprotein levels in control versus drug-dosed mice indicated that FTC did not have antitumor activity. However, FTC at the 18.4 and 88.8 mg/kg/day doses did significantly reduce circulating levels of HBV DNA. Examination of tumor extracts in these 2 dose groups revealed a marked reduction in intracellular levels of replicative HBV DNA intermediates, including double-stranded linear DNA.

Transgenic SCID Mice

Anti-HBV activity has also been reported for FTC in HBV transgenic SCID mice {6290}. A group of 5 mice were treated with FTC at 100 mg/kg/day intraperitoneally for 6 days, and observed for an additional 6 days posttreatment. By Day 3 of treatment, 2 mice had undetectable HBV surface antigen (HBsAg), and an additional 2 mice cleared HBsAg on Day 5. The remaining mouse cleared HBsAg on Day 8. Hepatitis B virus DNA levels in blood were determined by semiquantitative PCR at Days 3, 5, 8, and 12. By Day 3 of treatment, PCR signals had dropped 10-fold in all of the mice. By Day 8, none of the mice had detectable HBV DNA levels by PCR. In contrast to 3TC, there were no signs of rebound in the levels of HBV DNA during the course of treatment.

Woodchuck Hepatitis Virus

The Woodchuck hepatitis virus (WHV) in its natural host, the eastern woodchuck Marmata monax, is the most frequently used model of HBV infection. In an oral dosing study, 5 groups of chronically infected woodchucks were given FTC once daily at 1 of 5 doses (0.3, 1.0, 3.0, 10, or 30 mg/kg) for 4 weeks {6292}. At doses of 3.0 mg/kg and greater, FTC induced a statistically significant reduction in both serum viremia and replicative intermediates. The largest reduction in viremia, approximately 4.9 $\log_{10}$, and in replicative intermediates, approximately 80-fold, was seen at the 30-mg/kg dose. No significant effect on the levels of intrahepatic RNA, serum levels of WHV surface antigen (WHsAg), or the appearance of antibodies to WHsAg or WHV core antigen in the serum were observed. Viremia returned to pretreatment levels within 1 to 2 weeks following the cessation of treatment at all doses. This rapid rebound is consistent with a lack of significant impact on levels of WHV closed-circular cDNA.

Cullen and colleagues have studied the effect of FTC on WHV in naturally infected, wild-caught woodchucks {6293}. Animals were dosed intraperitoneally at either 20 or 30 mg/kg twice daily for 4 weeks. Administration of the 20-mg/kg dose suppressed WHV DNA levels from 6- to 49-fold (average of 27-fold in the 6 animal groups). Serum DNA polymerase activity measured by the incorporation of [^{32}P]dCTP into WHV DNA was reduced in a similar fashion. A more profound effect was seen at the 30-mg/kg dose. Serum WHV DNA levels were reduced from 20- to 150-fold (average of 56-fold) in the 6 animal groups. Serum DNA polymerase activity was similarly reduced. Woodchuck hepatitis virus DNA levels in the liver (determined in biopsy specimens) were also reduced in all 6 of the animals in the 30-mg/kg treatment group. Reductions ranged from 68% to 98% of the pretreatment levels. The authors stated that while the level of replicative intermediates remained close to those seen pretreatment, the WHV genome was being shifted toward shorter fragments.

4.1.3. Pharmacodynamic Drug Interactions

4.1.3.1. TAF: Pharmacodynamic Drug Interactions

The anti-HIV-1 activity of TAF in combination with a broad panel of representatives from the major classes of approved anti-HIV agents (N[t]RTIs, NNRTIs, INSTIs, and PIs) was evaluated in HIV-1_{IIIB} infected MT-2 cells (PC-120-2002). This study was analyzed using the Prichard and Shipman MacSynergy II model for statistical evaluation of combination anti-HIV assays {2893}, {8437}. Viral growth/inhibition was evaluated by measuring virus-induced cytopathic effects at the experimental endpoint. Combinations of ddI + ribavirin (RBV), d4T+RBV, and TAF single agent were used as controls for synergy, antagonism, and additivity, respectively.

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 (synergy volumes from 41 to 131 $\mu M^2\%$) when combined with any of the N(t)RTIs or NNRTIs (Table 125). The combination of TAF with INSTIs resulted in the highest level of synergy (synergy volumes of 271, 205, and 179 $\mu M^2\%$ for EVG, RAL, and DTG, respectively). The combination of TAF with PIs resulted in moderate synergy (synergy volumes of 96 and 56 $\mu M^2\%$ for ATV and DRV, respectively). As expected, the combination of TAF with COBI, a PK enhancer coformulated with TAF in E/C/F/TAF and devoid of antiviral activity, resulted in an additive effect.

The synergy values observed for TAF with all the drugs tested were comparable with those of TFV performed in parallel (data not shown) and to values previously reported for TFV {1469}. Importantly, none of the drug combinations containing TAF exhibited antagonistic antiviral effects.

Table 125. TAF Anti-HIV-1 Activity in Combination with Selected ARVs

Drug combination	Class	Volume ($\mu M^2\%$)		Net Effect
		Synergy[a]	Antagonism[a]	
TAF+TFV	NRTI	24	−14	Additive
TAF+FTC	NRTI	131	−9	Strong synergy
TAF+EFV	NNRTI	100	−7	Strong synergy
TAF+NVP	NNRTI	41	−14	Minor synergy
TAF+EVG	INSTI	271	−9	Strong synergy
TAF+RAL	INSTI	205	−10	Strong synergy
TAF+DTG	INSTI	179	−10	Strong synergy
TAF+ATV	PI	96	−10	Moderate synergy
TAF+DRV	PI	56	−12	Moderate synergy
TAF+COBI	PK enhancer	17	−22	Additive
TAF+TAF	Control	20	−17	Additive
ddI+RBV	Control	302	−20	Strong synergy
d4T+RBV	Control	20	−340	Strong antagonism

a Data shown represent the mean from >3 independent experiments performed in triplicate. As defined by Prichard and colleagues {42}, volumes of ≥ -25 to < 25 $\mu M^2\%$ indicate an additive effect; ≥ 25 to < 50 $\mu M^2\%$ indicate minor synergy; ≥ 50 to < 100 $\mu M^2\%$ indicate moderate synergy; ≥ 100 $\mu M^2\%$ indicates strong synergy, ≥ −50 to < −25 indicate minor antagonism, ≥ −100 to < −50 indicate moderate antagonism, and < −100 indicates strong antagonism.

Source: PC-120-2002

4.1.3.2. FTC: Pharmacodynamic Drug Interactions

The effect of combining FTC with other anti-HIV agents in the NRTI, NNRTI, and PI classes has been studied extensively using isobologram analysis. Results of 2-drug combination assays are presented in Table 126.

In all cases, in vitro combination studies with FTC and other anti-HIV agents resulted in additive to synergistic anti-HIV activity. No antagonism was observed under any of the reported conditions.

FTC has also been tested with the INSTI EVG (PC-183-2004). The results showed strong antiviral synergy of these 2 drugs paired together with a synergy volume of 167.45 $nM^2\%$.

Table 126. Synergistic Activity of FTC with Other Antiretroviral Agents

Compounds	Class	Cell line	HIV Strain	Results
DLV	NNRTI	MT-2	LAI	Additive to Synergistic
EFV	NNRTI	MT-2	LAI	Additive to Synergistic
Emivirine	NNRTI	MT-2	LAI	Additive to Synergistic
NVP	NNRTI	MT-2	LAI	Additive to Synergistic
ABC	NRTI	MT-2	LAI	Additive to Synergistic
Adefovir	NRTI	MT-2	LAI	Additive to Synergistic
Amdoxovir	NRTI	MT-2	LAI	Additive to Synergistic
ddI	NRTI	MT-4	IIIB	Strongly Synergistic
ddI	NRTI	MT-2	IIIB	Additive
ddI	NRTI	MT-2	LAI	Additive to Synergistic
EVG	INSTI	MT-2	IIIB	Synergistic
3TC	NRTI	MT-2	LAI	Additive to Synergistic
RPV	NNRTI	MT-2	IIIB	Strongly Synergistic
d4T	NRTI	MT-2	IIIB	Additive
d4T	NRTI	MT-2	LAI	Additive to Synergistic
ddC	NRTI	MT-4	IIIB	Strongly Synergistic
ddC	NRTI	MT-2	IIIB	Additive
ZDV	NRTI	MT-4	IIIB	Strongly Synergistic
ZDV	NRTI	MT-2	IIIB	Additive
ZDV	NRTI	MT-2	LAI	Additive to Synergistic
APV	PI	MT-2	LAI	Additive to Synergistic
IDV	PI	MT-2	LAI	Additive to Synergistic
NFV	PI	MT-2	LAI	Additive to Synergistic
RTV	PI	MT-2	LAI	Additive to Synergistic

Source: Studies 470, 10804, PC-183-2004, and PC-264-2001, {4541}, and {4543}

4.1.4. Discussion and Conclusions

4.1.4.1. TAF

TAF is a prodrug of TFV that is predominantly hydrolyzed to TFV by CatA in target lymphoid cells {13119}, {10427}; thus, the antiviral molecular mechanism of action of TAF reflects that of TFV, as well as the other TFV prodrug, TDF. TFV has potent ARV activity against wild-type or drug-resistant strains of HIV-1 in vitro and in vivo. TFV is a nucleotide analog (ie, a nucleoside monophosphate analog) and, therefore, is not dependent on an intracellular nucleoside kinase activity, which can be cell-cycle dependent, for the first step in the conversion to the active metabolite, TFV-DP. This difference in intracellular metabolism suggests that TFV may be a more effective inhibitor of HIV in macrophages and other nondividing cells as compared with some other nucleoside analogs. The cellular enzymes responsible for TFV metabolism to the phosphorylated forms are AK {13} and nucleotide diphosphate kinase, which are highly active

and ubiquitous. TFV-DP efficiently inhibits both RNA- and DNA-directed HIV-1 RT DNA polymerization. It competes with dATP for incorporation into DNA and, since it lacks a 3′-hydroxyl group, causes premature termination of DNA synthesis upon its incorporation into the nascent DNA chain. 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, ABC, ddI, or 3TC, has no effect on either the intracellular dNTP or rNTP pool concentrations. The removal of incorporated TFV can occur by wild-type RT and RT with mutations that enhance excision (notably T215F/Y or T69SSS) by both pyrophosphorolysis and ATP-mediated excision mechanisms; however, TFV-terminated primers are efficiently translocated, which can result in partial protection from the excision process {7583}, {11304}.

The levels of CatA and intracellular TAF metabolites differed minimally in CD4s and MDMs across demographically diverse donors. Consequently, the relative range of TAF ARV activity across all tested donors was comparable with that of other HIV-1 reverse transcriptase inhibitors. These results indicate consistent intracellular metabolism and ARV potency of TAF in relevant target cells of HIV-1 infection across demographically diverse donors.

In resting human PBMCs, 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 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 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).

A retrospective analysis of resistance patterns among TFV-naive, ART-experienced patients found that viruses with insertion mutations were highly resistant to TFV. Viruses with Q151M could be divided into 2 subsets of susceptible and highly resistant, where most of the viruses in the resistant set also contained K65R. A clonal analysis of viruses containing TAMs (M41L, D67N, L210W, T215F/Y, and K219Q/E/N) showed that, when present as single mutations, resistance to TFV could be ranked as increasing for mutations at position 41 > 215 > 70. Additionally, viral clones with M184V or M184I exhibited slightly increased susceptibilities to TFV (0.7-fold), and almost all clones with TAM-induced resistance were resensitized when M184V was present. However, accumulation of at least 2 TAMs resulted in more than 2.0-fold reduced susceptibility to TFV, irrespective of the presence of M184V. The resensitizing effect of the M184V/I mutation has been confirmed in 2 studies with recombinant clinical isolates {7279}, {12143}.

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 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 (GS-US-120-0104 [Section 2.3.2.1]). 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 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.

TAF exhibits potent antiviral activity and limited cytotoxicity in target cell lines and PBMCs, with an SI of 1997 and > 3607 in T-lymphoblastoid cell lines and 1889 in dividing PBMCs. Due to its increased cellular permeability, the anti-HIV activity of TAF was increased by 228- and 1232-fold over TFV in MT-2 and MT-4 cells, respectively; in comparison, the anti-HIV activity of TDF was increased over TFV by 55- and 729-fold. The SI for TAF was also higher compared with TFV and TDF in all cell types tested. In T-lymphoblastoid cell lines, TAF ranked first in SI among all the NRTIs tested, followed by TDF and TFV. Among all ARV drugs tested, TAF ranked fourth in SIs, following an NNRTI (EFV), an INSTI (RAL), and a PI (ATV).

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. In addition, results of in vitro assays showed that TAF is a highly specific antiviral agent for immunodeficiency viruses (ie, HIV-1,

HIV-2, and SIV) with no relevant in vitro activity against other tested human viral pathogens including adenovirus, dengue type 2, influenza A, human parainfluenza, RSV, coxsackie B virus, rhinovirus, HSV-1, HSV-2, HCMV, VZV, vaccinia virus, and HCV.

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 PK enhancer coformulated with TAF in E/C/F/TAF and devoid of antiviral activity, resulted in an additive effect.

4.1.4.2. FTC

FTC has antiviral activity against HIV-1, HIV-2, and HBV. FTC has demonstrated additive to synergistic activity with a variety of other ARV drugs. Antiretroviral resistance is associated with an M184V or I mutation that shows cross-resistance with 3TC.

4.1.4.3. FTC/TDF

TFV and FTC are analogues of 2 different nucleosides, adenosine and cytosine, respectively, and do not share a common intracellular metabolism pathway. When both drugs are incubated together (in vitro) at concentrations higher than achieved in the plasma (10 μM each), complete conversion to the fully activated forms of each drug, TFV-DP and FTC-TP, was observed. As TFV-DP and FTC-TP are alternative substrates for different natural substrates, dATP and dCTP, respectively, there should be no competition for incorporation by HIV RT and subsequent chain termination. In support of this, the antiviral activity of the combination of TFV and FTC was found to be synergistic in multiple in vitro assay systems.

In vitro resistance selection experiments with the combination of TFV and FTC have demonstrated the initial development of the M184V/I mutation with high-level resistance to FTC followed by development of the K65R mutation with low-level resistance to TFV. These results are in agreement with the results obtained from resistance selection with the individual components, ie, quick selection of M184V/I by FTC and a delayed selection of resistance by TFV. These results suggest that the in vivo combination of TFV and FTC would select for the M184V/I mutation first and then would potentially be TFV resistant in a stepwise fashion. Clinical study data using the combination of TDF with FTC support this conclusion since the M184V mutation was observed to develop in the absence of K65R in patients with virologic failure.

The antiviral activity of the combination of TFV and FTC was demonstrated in SIV-infected macaques. Daily subcutaneous administration of TFV (20 mg/kg) and FTC (50 mg/kg) resulted in complete suppression (< 100 copies/mL) of SIV for the duration of the 32-week study. There was no development of detectable resistance to either drug over the period of study. A prophylaxis study also demonstrated the efficacy of the combination of TFV and FTC for protection against rectal exposure of macaques to an SHIV chimeric virus. These results in a

model system of HIV-1 infection provide support for the potency of the combination of TFV and FTC for the control of a retroviral infection.

The combination of TFV and FTC was studied for cytotoxicity in MT-2 cells. No cytotoxicity was observed at concentrations up to 50 μM TFV and 5 μM FTC. Additive mitochondrial toxicity was not observed in HepG2 cells.

4.2. Clinical Virology

Analyses were performed for HIV-infected subjects with clinical virology data from 6 E/C/F/TAF Phase 2 and Phase 3 studies (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), and 1 D/C/F/TAF Phase 2 study (GS-US-299-0102). An integrated virology analysis was performed for HIV-infected subjects with clinical virology data from 1 E/C/F/TAF Phase 2 study (GS-US-292-0102) and 2 E/C/F/TAF Phase 3 studies (GS-US-292-0104 and GS-US-292-0111). A summary of the main findings from these analyses are provided in Sections 4.2.1 and 4.2.2, respectively.

Genotyping of the protease (PR)/RT genes and the IN gene was performed at screening for all subjects enrolled in Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0112 (Cohort 2 only), and GS-US-292-0106. Genotyping of PR/RT only was performed at screening for all subjects enrolled in Studies GS-US-292-0102 and GS-US-299-0102. For all subjects in Study GS-US-292-0109 and select subjects in Study GS-US-292-0112 Cohort 1, historical PR/RT genotypes were used as genotyping was not performed at screening, since subjects entered the study with suppressed HIV-1 RNA (< 50 copies/mL).

Drug resistance mutations are defined in Table 127.

Table 127. Resistance Mutations by Antiretroviral Class

Drug Class	Codon Mutations	
NRTIs and N(t)RTIs	M41L, E44D, A62V, K65R, D67N, T69 insertion, T69D/N, K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R	
TAMs	M41L, D67N, K70R, L210W, T215Y/F[a], K219Q/N/E/R	
NAMs	TAMs plus E44D[b], K65R, T69D/N[b], K70E, L74V/I, Y115F, V118I[b], M184V/I	
Multi-NRTI RAMs	Q151M Complex: A62V, V75I, F77L, F116Y, Q151M	
Multi-NRTI RAMs	T69 Insertion Complex: T69S-SS, -SA, -SG, or others	
NNRTIs	V90I, A98G, L100I, K101E/H/P, K103N/S, V106M/A/I, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I	
PIs	**Primary**	**Secondary**
	D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M	L10I/F/R/V/C, V11I, I13V, G16E, K20I/M/R/T/V, L24I, L33I/V, E34Q, E35G, M36I/L/V, K43T, F53L/Y, I54A/S/T/V, D60E, I62V, L63P, I64L/M/V, H69K, A71V/T/I/L, G73A/C/S/T, V77I, V82I, N83D, I85V, N88D, L89V, I93L/M

Drug Class	Codon Mutations	
Entry Inhibitors	—	G36D/S, I37V, V38A/E/M, Q39R, Q40H, N42T, N43D
INSTIs[d]	**Primary**	**Secondary**
	T66I/A/K, E92Q/G, T97A, Y143R/H/C, S147G, Q148H/K/R, N155H/S	M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C/Y, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, R263K

a Reversion mutations at RT codon T215, including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either FTC or TDF.
b E44D, T69D/N, and V118I mutations can be natural polymorphisms in RT and have not been shown to be associated with reduced response to either FTC or TDF.
c Primary and secondary IN mutations observed in clinical studies of INSTIs.
Adapted from the current International Antiviral Society-USA (IAS-USA) Guidelines lists with some modifications.

Resistance testing was performed for any subject meeting the criteria of the Resistance Analysis Population (RAP).

- The RAP included any subject who received at least 1 dose of study drug, maintained their study drug regimen, and had confirmed virologic failure through Week 48 or at the time of early study drug discontinuation (ESDD).

- The Final RAP did not include subjects who remained on study medication and later suppressed HIV-1 RNA to < 50 copies/mL

A summary of the results from these analyses are provided in Section 4.2.1.

A full description of the resistance analysis methodologies is provided in the virology analysis plan (PC-120-2010). Full details of the RAP, Final RAP, and the clinical virology resistance analyses from the E/C/F/TAF Phase 2 and Phase 3 studies and the integrated analysis may be found in the Virology Study Report (PC-120-2020). A summary of the main findings is described below.

4.2.1. Virology Resistance Analyses at Baseline and in the Resistance Analysis Population from Phase 2 and 3 Studies

4.2.1.1. E/C/F/TAF Studies

4.2.1.1.1. Study GS-US-292-0104

Study Design, Baseline Characteristics, and Viral Response

Study GS-US-292-0104 (m2.7.3, Section 2) is an ongoing Phase 3, randomized, double-blinded, multicenter, active-controlled study to assess the efficacy and safety of E/C/F/TAF compared with STB in HIV-infected, ART-naive adults.

Baseline Virology Data

HIV-1 genotyping of the PR/RT and IN genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all 867 subjects who entered Study GS-US-292-0104. Consistent with enrollment criteria, no RAMs were observed to EVG, FTC, and TFV at baseline (Table 128). The distribution of baseline NRTI, NNRTI, and PI RAMs was similar between treatment groups.

The HIV-1 subtype was determined for each subject using the screening genotype. The genotype distribution was comparable between treatment groups, with subtype B predominant in both groups.

Table 128. E/C/F/TAF Study GS-US-292-0104: Summary of Pretreatment HIV-1 Subtype and PR, RT, and IN Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Subjects n (%)		
	E/C/F/TAF[b] (N = 435)	STB[c] (N = 432)	All (N = 867)
Subtype B	340 (78.3)	345 (79.9)	685 (79.1)
Non-B Subtype	94 (21.7)	87 (20.1)	181 (20.9)
NRTI-Associated	39 (9)	22 (5.1)	61 (7)
INSTI-Associated (Primary)	0	0	0
INSTI-Associated (Secondary)	205 (47.5)	194 (45.1)	399 (46.3)
NNRTI-Associated	85 (19.6)	76 (17.6)	161 (18.6)
PI-Associated (Primary)	13 (3)	13 (3)	26 (3)

a Drug resistance mutations are defined in Table 127.
b In the E/C/F/TAF group, 3 subjects (Subjects *AD , *AE , and *AF) were IN assay failures. One subject (Subject *AE) was a PR/RT assay failure.
c In the STB group, 2 subjects (Subjects *AG and *AH) were IN assay failures.
Source: PC-120-2020: GS-US-292-0104 Virology Listings 1 and 2

Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 867 randomized and treated subjects in Study GS-US-292-0104, 12 (1.4%) met the criteria for inclusion in the RAP. The distribution of the RAP was comparable between the 2 treatment groups, with 5 of 435 subjects (1.1%) in the E/C/F/TAF group and 7 of 432 subjects (1.6%) in the STB group analyzed (Figure 39, Table 129; results for individual subjects are presented in Table 130).

All 5 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48. Subject *AI achieved HIV-1 RNA resuppression to < 50 copies/mL with further E/C/F/TAF treatment and was therefore not included in the Final RAP.

All 7 subjects in the STB group were evaluated for the development of resistance at Week 48. Two subjects (Subjects *AJ and *AK) had no emergent resistance to TFV, FTC, or EVG, achieved HIV-1 RNA resuppression to < 50 copies/mL with further STB treatment, and were therefore not included in the Final RAP.

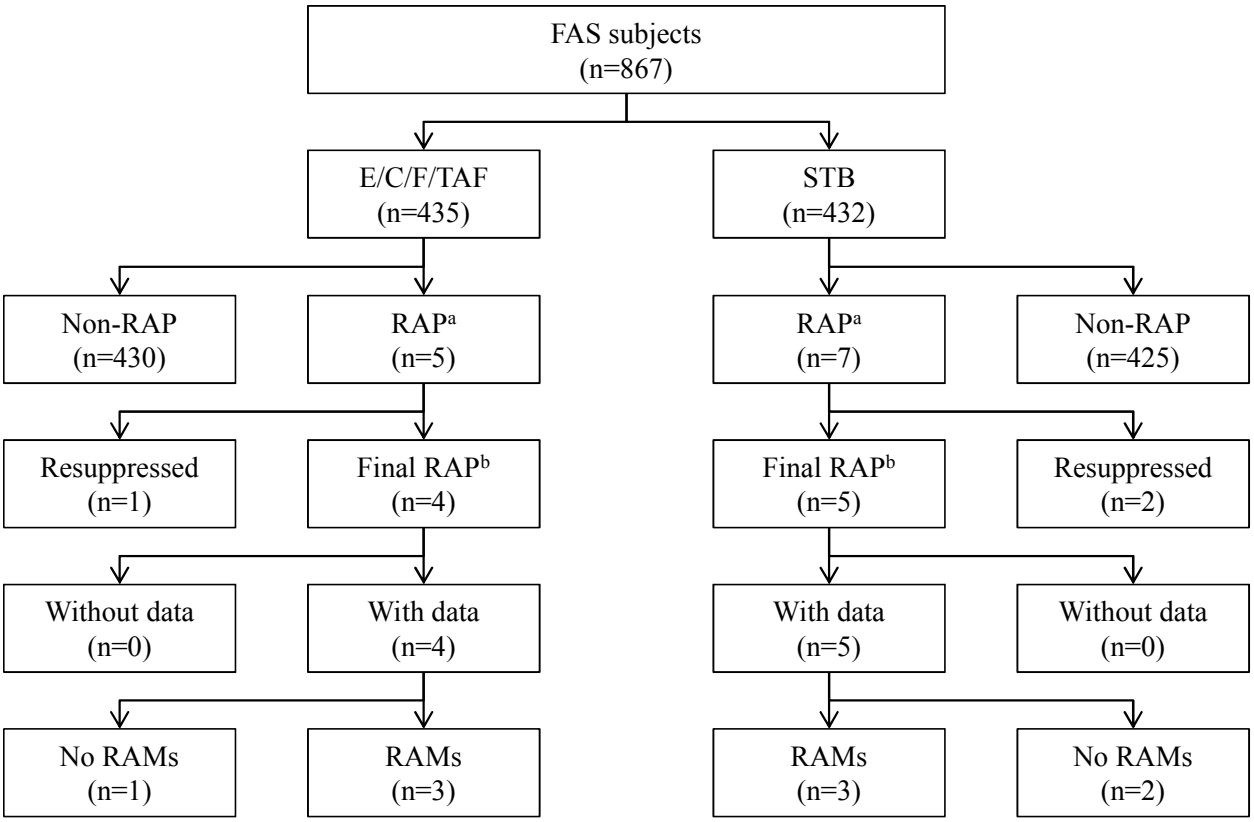
Final Resistance Analysis Population

The Final RAP comprised 4 subjects (0.9%) in the E/C/F/TAF group and 5 subjects (1.2%) in the STB group.

In the E/C/F/TAF group, of the 4 subjects with available data included in the Final RAP, 3 had resistance mutations emerge while on E/C/F/TAF and 1 had no emergent resistance. Subject *AL developed genotypic and phenotypic resistance to both FTC (M184V; FTC fold change [FC] > 70) and EVG (E92Q; EVG FC = 56) at Week 48 and Subject *AM developed genotypic resistance to FTC (M184V), EVG (N155H), and TFV (K65R) at Week 48. Phenotypic resistance was observed to both FTC (FC > 63) and EVG (FC = 60); however, no phenotypic resistance was observed to TFV (FC = 1.0). Subject *AN developed genotypic resistance to FTC (M184M/V); however, minimal phenotypic resistance was observed likely due to the mixture with wild type (FC = 2.0). Subject *AO did not have emergent resistance to any study drug at Week 48.

In the STB group, of the 5 subjects with available data included in the Final RAP, 3 had resistance mutations emerge while on STB and 1 had no emergent resistance. Subject *AP developed genotypic resistance to all 3 drugs (K65R, M184V in RT, and E92Q in IN). Phenotypic data was only obtained for EVG, which demonstrated resistance (EVG FC = 21). Subject *AQ developed genotypic and phenotypic resistance to FTC (M184V; FTC FC > 71) and EVG (E92E/Q, E138E/K, Q148R; EVG FC > 156). Subject *AR developed genotypic resistance to FTC (M184M/V); however, phenotypic resistance was not observed (FTC FC = 1.5). Subject *AR also developed the NRTI-R mutation E44E/D in RT; this mutation has limited clinical relevance. Subject *AS developed 2 secondary resistance mutations to EVG (E138K and E157K) in the absence of primary resistance; phenotypic data was not obtained for IN. Subject *AT had no genotypic or phenotypic resistance to FTC and TFV; and IN assay failure.

Figure 39. E/C/F/TAF Study GS-US-292-0104: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



a RAP criteria are summarized in PC-120-2020.
b The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0104 Virology Listings 3 and 4; GS-US-292-0104, Appendix 16.2, Listing 16.1

Table 129. E/C/F/TAF Study GS-US-292-0104: Summary of HIV-1 Genotypic Resistance Observed Through Week 48

Resistance Category[a]	Number of Subjects n (%)		
	E/C/F/TAF (N = 435)	STB (N = 432)	p-value[b]
RAP	5 (1.1)	7 (1.6)	0.58
Subjects with Data	4 (0.9)	7 (1.6)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	1 (0.2)	2 (0.5)	
Final RAP[c]	4 (0.9)	5 (1.2)	0.75
Subjects with Data	4 (0.9)	5 (1.2)	
Developed Resistance Mutations to Study Drugs	3 (0.7)	3 (0.7)	1.0
No Resistance Mutations Observed	1 (0.2)	2 (0.5)	
Developed Any NRTI-R	3 (0.7)	3 (0.7)	
E44D	0	1 (0.2)	
K65R	1 (0.2)	1 (0.2)	
M184V	3 (0.7)	3 (0.7)	
Developed Any INSTI-R	2 (0.5)	3 (0.7)	
Primary INSTI-R	2 (0.5)	2 (0.5)	
T66I/A	0	0	
E92Q	1 (0.2)	2 (0.5)	
S147G	0	0	
Q148R	0	1 (0.2)	
N155H	1 (0.2)	0	
Secondary INSTI-R	0	2 (0.5)	
E138K	0	2 (0.5)	
E157K	0	1 (0.2)	
Developed Any NNRTI-R	0	0	
Developed Any Primary PI-R	0	1 (0.2)	
V32I	0	1 (0.2)	

a Drug resistance mutations are defined in Table 127.
b Fisher exact test comparing the percentages in each group using the whole population as the denominator.
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0104 Virology Listings 3 and 4; GS-US-292-0104, Appendix 16.2, Listing 16.1

Table 130. E/C/F/TAF Study GS-US-292-0104: Details of Subjects in the Resistance Analysis Population

Subject	Treatment Group	BL HIV-1 RNA (copies/mL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (FC from WT)[b]		
					RT	IN	TFV[c]	FTC	EVG
*AO	E/C/F/TAF	14000	B	Week 48	I178I/M	AF	0.59	1.0	AF
*AM	E/C/F/TAF	385000	B	Week 48	M41M/K, **K65R**, **M184V**	G70G/R,**N155H**, V201V/I, Q216Q/R, D232D/N	1.0	> 63	60
*AL	E/C/F/TAF	367000	B	Week 48	**M184V**, T286T/I	**E92Q**	0.65	> 70	56
*AI [d]	E/C/F/TAF	67100	B	Week 16	AF	AF	AF	AF	AF
*AN	E/C/F/TAF	138000	B	ESDD	**M184M/V**	A129A/S	0.68	2.0	1.1
*AS	STB	62800	B	ESDD	None	D6N, E35K, E69K, R107K, E138K, E152K, M154I, E157K	0.88	1.1	AF
*AP	STB	127000	B	Week 16	V60I, **K65R**, **M184V**	**E92Q**, T124S, K264K/*	AF	AF	21
*AR	STB	21800	B	ESDD	E36E/Q, **E44E/D**, K49K/Q, **M184M/V**	I204I/V, V259V/I	0.85	1.5	1.2
*AJ [d]	STB	2830	B	Week 12	R78R/K, D86D/N, E224E/K	N222T	0.60	1.2	1.2
*AQ	STB	486000	B	ESDD	**M184V**	P90P/S, **E92E/Q**,H114H/Y, E138E/K, **Q148R**	0.43	> 71	> 156
*AK [d]	STB	17200	B	Week 16	None	S24N	0.66	0.98	2.0
*AT	STB	647000	AG	Week 36	None	AF	0.95	1.1	AF

a Compared with screening/baseline genotype. Primary IN- or RT-associated resistance mutations are shown in **bold**.
b Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical cutoffs were as follows: TFV = 1.4 to 4, FTC = 3.5, and EVG = 2.5.
c The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF and TDF.
d Subject resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
* indicates a stop codon
Source: PC-120-2020: GS-US-292-0104 Virology Listings 3 and 4; GS-US-292-0104, Appendix 16.2, Listing 16.1

Resistance Conclusions

For Study GS-US-292-0104, the RAP comprised 12 subjects: 5 subjects were from the E/C/F/TAF group (5 of 435 subjects, 1.1%) and 7 subjects were from the STB group (7 of 432 subjects, 1.6%). One subject from the E/C/F/TAF group and 2 subjects from the STB group resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs and were not included in the Final RAP.

The Final RAP comprised 9 subjects: 4 subjects (0.9%) in the E/C/F/TAF group and 5 subjects (1.2%) in the STB group. Three subjects (0.7%) from the E/C/F/TAF group showed emergence of resistance to study drugs while 4 subjects (0.9%) from the STB group showed emergence of resistance to study drugs. Six of 7 subjects with emergent resistance developed M184V in RT, 4 subjects (2 from each group) developed primary INSTI-R, and 2 subjects (1 from each group) developed K65R in RT. Resistance mutation development was similar between treatment groups.

4.2.1.1.2. Study GS-US-292-0111

Study Design, Baseline Characteristics, and Viral Response

Study GS-US-292-0111 (m2.7.3, Section 2) is an ongoing Phase 3, randomized, double-blinded, multicenter, active-controlled study to assess the efficacy and safety of E/C/F/TAF compared with STB in HIV-infected, ART-naive adults.

Baseline Virology Data

HIV-1 genotyping of the PR/RT and IN genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all 866 subjects who entered Study GS-US-292-0111. Consistent with enrollment criteria, no RAMs were observed to EVG, FTC, and TFV at baseline for all subjects except 1 who had T97A detected in IN (Table 131). The distribution of baseline NRTI, NNRTI, and PI RAMs was similar between treatment groups.

The HIV-1 subtype was determined for each subject using the screening genotype. The genotype distribution was comparable between treatment groups, with subtype B predominant in both groups (Table 131).

Table 131. E/C/F/TAF Study GS-US-292-0111: Summary of Pretreatment HIV-1 Subtype and PR, RT, and IN Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Subjects n (%)		
	E/C/F/TAF (N = 431)	STB (N = 435)	All (N = 866)
Subtype B	403 (93.5)	404 (92.9)	807 (93.2)
Non-B Subtype	28 (6.5)	31 (7.1)	59 (6.8)
NRTI-Associated	34 (7.9)	34 (7.8)	68 (7.9)
INSTI-Associated (Primary)	0	1 (0.2)	1 (0.1)
INSTI-Associated (Secondary)	216 (50.1)	207 (47.6)	423 (48.8)
NNRTI-Associated	70 (16.2)	83 (19.1)	153 (17.7)
PI-Associated (Primary)	16 (3.7)	15 (3.4)	31 (3.6)

a Drug resistance mutations are defined in Table 127.
Source: PC-120-2020: GS-US-292-0111 Virology Listings 1 and 2

Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 866 randomized and treated subjects in Study GS-US-292-0111, 23 (2.7%) met the criteria for inclusion in the RAP. The distribution of the RAP was comparable between the 2 treatment groups, with 11 of 431 subjects (2.6%) in the E/C/F/TAF group and 12 of 435 subjects (2.8%) in the STB group analyzed (Figure 40, Table 132; results for individual subjects are presented Table 133).

All 11 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48. Subject *AU had both PR/RT and IN assay failure, achieved HIV-1 RNA resuppression to < 50 copies/mL with further E/C/F/TAF treatment, and was therefore not included in the Final RAP.

All 12 subjects in the STB group were evaluated for the development of resistance at Week 48. Three subjects (Subjects *AV , *AW , and *AX) achieved HIV-1 RNA resuppression to < 50 copies/mL with further STB treatment and were therefore not included in the Final RAP. Two of these subjects (Subjects *AV and *AX) had no genotypic or phenotypic resistance to any study drug, and 1 subject (Subject *AW) had PR/RT and IN assay failure.

Final Resistance Analysis Population

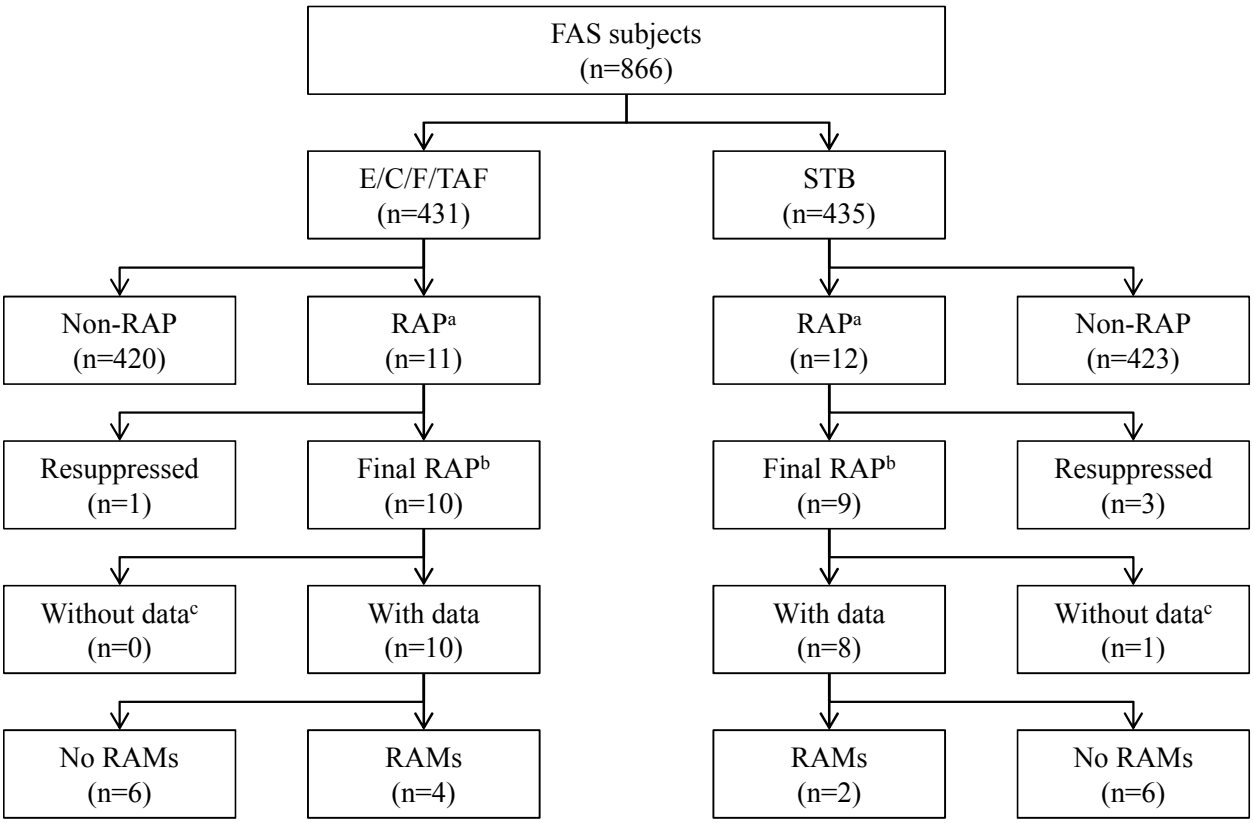
The Final RAP comprised 10 subjects (2.3%) in the E/C/F/TAF group and 9 subjects (2.1%) in the STB group.

In the E/C/F/TAF group, of the 10 subjects with available data included in the Final RAP, 4 subjects had resistance mutations emerge while on E/C/F/TAF. Subject *AY developed

genotypic and phenotypic resistance to FTC (M184M/I/V; FTC FC > 68). Subject *AZ developed genotypic resistance to FTC (M184V) and EVG (E92Q), with phenotypic resistance observed for FTC (FC > 84), while phenotypic data was not obtained for IN. Subject *BA developed genotypic and phenotypic resistance to both FTC (M184V; FTC FC > 81) and EVG (T66T/I/A/V, E138E/K, Q148Q/R; EVG FC = 10.9). Subject *BB developed genotypic and phenotypic resistance to both FTC (M184V; FTC FC > 89) and EVG (T66A; EVG FC = 12.3). For the remaining 6 subjects with data in the Final RAP, no genotypic or phenotypic resistance to any study drug was observed.

In the STB group, of the 8 subjects with available data included in the Final RAP, 2 subjects had resistance mutations emerge on STB and 5 had no genotypic or phenotypic resistance. Subject *BC developed genotypic and phenotypic resistance to FTC (M184V; FTC FC > 82) and EVG (Q148R; EVG FC > 95). In addition, this subject developed genotypic resistance to TFV (K65R); however, phenotypic resistance was not observed (TFV FC = 1.3). Subject *BD developed genotypic and phenotypic resistance to FTC (M184V; FTC FC > 64). For the remaining 6 subjects, no genotypic or phenotypic resistance to any study drug was observed.

Figure 40. E/C/F/TAF Study GS-US-292-0111: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



a RAP criteria are summarized in PC-120-2020.
b The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
c Subjects without data due to assay failure.
Source: PC-120-2020: GS-US-292-0111 Virology Listings 3 and 4; GS-US-292-0111, Appendix 16.2, Listing 16.1

Table 132. E/C/F/TAF Study GS-US-292-0111: Summary of HIV-1 Genotypic Resistance Observed Through Week 48

Resistance Category[a]	Number of Subjects n (%)		
	E/C/F/TAF (N = 431)	STB (N = 435)	p-value[b]
RAP	11 (2.6)	12 (2.8)	1.0
Subjects with Data	10 (2.3)	10 (2.3)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	1 (0.2)	3 (0.7)	
Final RAP[c]	10 (2.3)	9 (2.1)	0.82
Subjects with Data	10 (2.3)	8 (1.8)	
Developed Resistance Mutations to Study Drugs	4 (0.9)	2 (0.5)	0.45
No Resistance Mutations Observed	6 (1.4)	6 (1.4)	
Developed Any NRTI-R	4 (0.9)	2 (0.5)	
K65R	0	1 (0.2)	
M184V	4 (0.9)	2 (0.5)	
Developed Any INSTI-R	3 (0.7)	1 (0.2)	
Primary INSTI-R	3 (0.7)	1 (0.2)	
T66I/A	2 (0.5)	0	
E92Q	1 (0.2)	0	
Q148R	1 (0.2)	1 (0.2)	
Secondary INSTI-R	2 (0.5)	1 (0.2)	
L68V	1 (0.2)	0	
E138K	1 (0.2)	1 (0.2)	
Developed Any NNRTI-R	0	0	
Developed Any Primary PI-R	0	0	

a Drug resistance mutations are defined in Table 127.
b Fisher exact test comparing the percentages in each group using the whole population as the denominator.
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0111 Virology Listings 3 and 4; GS-US-292-0111, Appendix 16.2, Listing 16.1

Table 133. E/C/F/TAF Study GS-US-292-0111: Details of Subjects in the Resistance Analysis Population

Subject	Treatment Group	BL HIV-1 RNA (copies/mL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (Fold Change from WT)[b]		
					RT	IN	TFV[c]	FTC	EVG
*AY	E/C/F/TAF	115000	B	Week 16	D121H/Y, **M184M/I/V**, Q207Q/H	A265A/V	0.65	> 68	0.97
*AZ	E/C/F/TAF	384000	B	Week 24	P170P/L, V179V/I, **M184V**	L68V, **E92Q**	0.49	> 84	AF
*BA	E/C/F/TAF	1610000	B	Week 12	**M184V**	**T66T/I/A/V**, E138E/K, **Q148Q/R**, D232D/N	0.54	> 81	10.9
*BE	E/C/F/TAF	150000	B	Week 36	W71P, T139T/A, E204E/K	AF	0.98	1.3	AF
*BB	E/C/F/TAF	463000	B	Week 16	**M184V**, H208Y, E248K	**T66A**	0.48	> 89	12.3
*BF	E/C/F/TAF	8120	B	Week 48	V276V/I	A21A/T	0.96	0.95	1.6
*BG	E/C/F/TAF	36800	B	Week 36	None	I208I/L	0.79	0.99	1.1
*AU [d]	E/C/F/TAF	31700	B	Week 16	AF	AF	AF	AF	AF
*BH	E/C/F/TAF	9470	B	Week 24	K64K/R	None	0.82	1.1	1.0
*BI	E/C/F/TAF	327000	B	Week 48	T200T/A, Q207Q/R	None	0.81	1.1	1.3
*BJ	E/C/F/TAF	31100	B	Week 36	K122Q, D177E, Q207E, V245V/E, G273G/E, R277K, V292I, E297A	AF	0.87	1.1	AF
*AV [d]	STB	192000	B	Week 36	None	G59G/E	0.65	1.1	2.2
*BK	STB	1080	B	Week 16	E297E/G	AF	0.9	1.1	AF
*BC	STB	239000	B	Week 36	**K65R**, I135M, **M184V**	E138K, **Q148R**	1.3	> 82	> 95
*BD	STB	88300	B	Week 48	**M184V**	None	0.42	> 64	1.9

＊新薬承認情報提供時に置換えた

Subject	Treatment Group	BL HIV-1 RNA (copies/mL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (Fold Change from WT)[b]		
					RT	IN	TFV[c]	FTC	EVG
*BL	STB	51000	B	Week 48	None	V249I/V	0.92	1.0	AF
*BM	STB	130000	B	Retest	None	ND	0.95	1.2	ND
*BN	STB	8420	B	Week 36	AF	AF	AF	AF	AF
*BO	STB	87800	B	Week 48	None	S17S/N, V31V/I, L101L/I, K127K/R, L172L/F, I208I/L, K211K/R, T218T/S, S230S/N	0.91	1.1	1.1
*AW [d]	STB	1650000	B	Week 36	AF	AF	AF	AF	AF
*BP	STB	94100	B	Week 24	None	None	0.81	1.1	1.7
*BQ	STB	42100	B	Week 48	None	None	0.89	0.98	AF
*AX [d]	STB	1910	B	Week 36	K238K/R	T112T/I	0.85	1.1	1.0

a Compared with screening/baseline genotype. Primary IN- or RT-associated resistance mutations are shown in **bold**.
b Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical cutoffs were as follows: TFV = 1.4 to 4, FTC = 3.5, and EVG = 2.5.
c The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF and TDF.
d Subject resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0111 Virology Listings 3 and 4; GS-US-292-0111, Appendix 16.2, Listing 16.1

Resistance Conclusions

For Study GS-US-292-0111, the RAP comprised 23 subjects: 11 subjects were from the E/C/F/TAF group (2.6%, 11 of 431 subjects) and 12 subjects were from the STB group (2.8%, 12 of 435 subjects). One subject from the E/C/F/TAF group and 3 subjects from the STB group resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs and were therefore not included in the Final RAP.

The Final RAP included 19 subjects, 10 subjects (2.3%) from the E/C/F/TAF group and 9 subjects (2.1%) from the STB group. Four subjects (0.9%) from the E/C/F/TAF group showed emergence of resistance to study drugs while 2 subjects (0.5%) from the STB group showed emergence of resistance to study drugs. All subjects with emergent resistance developed M184V in RT and 4 of 6 subjects (3 in the E/C/F/TAF group and 1 in the STB group) developed primary INSTI-R. K65R in RT was observed in 1 subject from the STB group, but was not observed in any subject from the E/C/F/TAF group. Resistance mutation development was similar between treatment groups.

4.2.1.1.3. Study GS-US-292-0102

Study Design, Baseline Characteristics, and Viral Response

Study GS-US-292-0102 (m2.7.3, Section 2) was a Phase 2, randomized, double-blinded, multicenter, active-controlled study to assess the efficacy and safety of E/C/F/TAF compared with STB in HIV-infected, ART-naive adult subjects.

Baseline Virology Data

HIV-1 genotyping of the PR/RT genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all 170 subjects who entered Study GS-US-292-0102. No IN genotyping was conducted at screening in this study. Consistent with enrollment criteria, all enrolled subjects demonstrated full sensitivity to FTC and TFV (delivered as TDF or TAF) (Table 134).

The HIV-1 subtype was determined for each subject using the screening genotype. The genotype distribution was comparable between treatment groups, with subtype B predominant in both groups (Table 134).

Table 134. E/C/F/TAF Study GS-US-292-0102: Summary of Pretreatment HIV-1 Subtype and PR and RT Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Subjects n (%)		
	E/C/F/TAF (N = 112)	STB (N = 58)	All (N = 170)
Subtype B	107 (95.5)	56 (96.6)	163 (95.9)
Non-B Subtype	5 (4.5)	2 (3.4)	7 (4.1)
NRTI-Associated	8 (7.1)	6 (10.3)	14 (8.2)
NNRTI-Associated	22 (19.6)	10 (17.2)	32 (18.8)
PI-Associated (Primary)	6 (5.4)	1 (1.7)	7 (4.1)

a Drug resistance mutations are defined in Table 127.
Source: PC-120-2020: GS-US-292-0102 Virology Listing 1

Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 170 randomized and treated subjects in Study GS-US-292-0102, 6 (3.5%) met the criteria for inclusion in the RAP. The RAP comprised 3 subjects (2.7%) in the E/C/F/TAF group and 3 subjects (5.2%) in the STB group (Figure 41, Table 135; results for individual subjects are presented in Table 136).

All 3 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48. All 3 subjects achieved HIV-1 RNA resuppression to < 50 copies/mL with further E/C/F/TAF treatment and were therefore not included in the Final RAP. None of the 3 subjects

had resistance mutations emerge with E/C/F/TAF (Table 135). Prior to resuppression, these subjects showed genotypic changes in IN and/or RT at polymorphic sites only; none of these changes were associated with a phenotypic change to EVG, FTC, or TFV (Table 136).

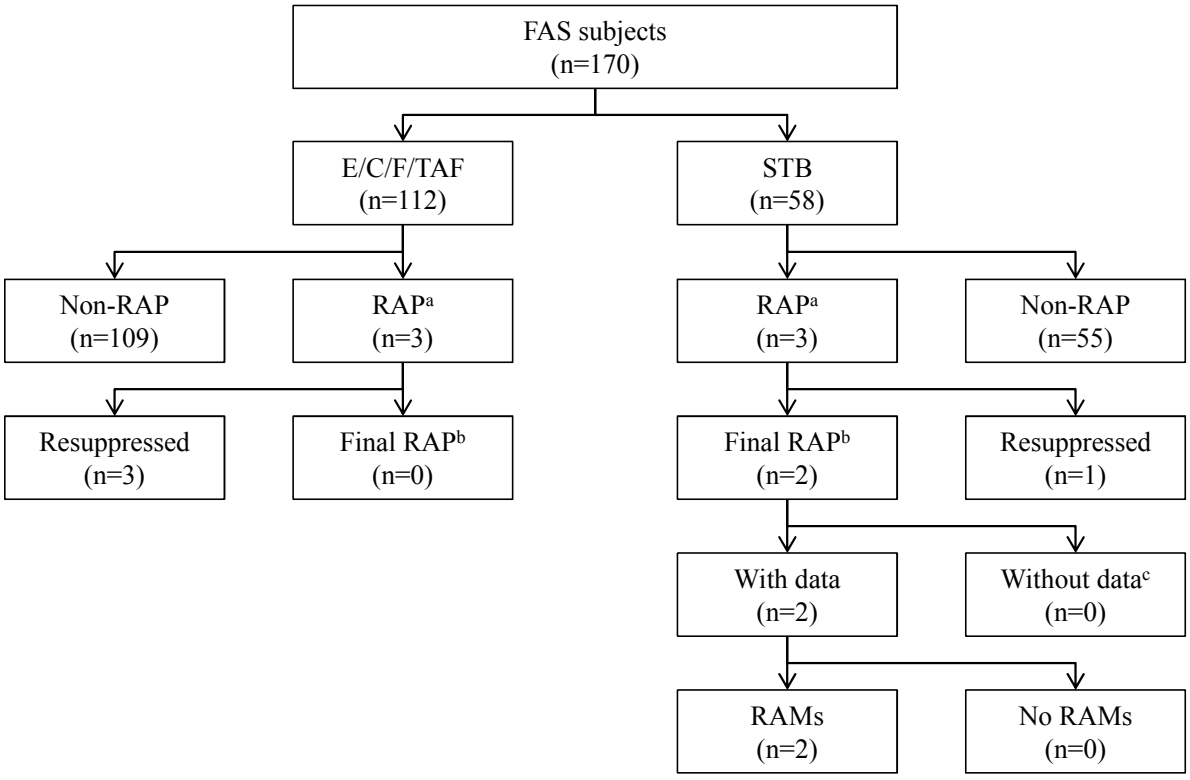
All 3 subjects in the STB group were evaluated for the development of resistance at Week 48. Subject *BR , who did not have emergent resistance, had HIV-1 RNA subsequently resuppress to < 50 copies/mL upon further treatment with STB, which was maintained with open-label E/C/F/TAF, and was therefore not included in the Final RAP.

Final Resistance Analysis Population

The Final RAP comprised 0 subjects in the E/C/F/TAF group and 2 subjects (3.4%, 2 of 58) in the STB group.

The 2 STB subjects included in the Final RAP had emergent resistance mutations (Table 135). Subject *BS developed genotypic and phenotypic resistance to both EVG (E92Q; FC = 12.8) and FTC (M184M/I/V; FTC FC > 73), and Subject *BT developed genotypic resistance to FTC (M184M/V) and TFV (K70K/E) (Table 136). Intermediate-level phenotypic resistance was observed to FTC (FC = 6.1) in the latter subject, but the subject remained sensitive to TFV (FC = 0.50).

Figure 41. E/C/F/TAF Study GS-US-292-0102: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



a RAP criteria are summarized in PC-120-2020.
b The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
c Subjects without data either due to assay failure or ongoing analysis.
Source: PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3; GS-US-292-0102, Appendix 16.2, Listing 17.1

Table 135. E/C/F/TAF Study GS-US-292-0102: Summary of HIV-1 Genotypic Resistance Observed Through Week 48

Resistance Category[a]	Number of Subjects n (%)		
	E/C/F/TAF (N = 112)	STB (N = 58)	p-value[b]
RAP	3 (2.7)	3 (5.2)	0.41
Subjects with Data	3 (2.7)	3 (5.2)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	3 (2.7)	1 (1.7)	
Final RAP[c]	0	2 (3.4)	0.12
Subjects with Data	0	2 (3.4)	
Developed Resistance Mutations to Study Drugs	0	2 (3.4)	0.12
Developed Any NRTI-R	0	2 (3.4)	
K70K/E	0	1 (1.7)	
M184V/I	0	2 (3.4)	
Developed Any INSTI-R	0	1 (1.7)	
Primary INSTI-R	0	1 (1.7)	
E92Q	0	1 (1.7)	
Secondary INSTI-R	0	0	
Developed Any NNRTI-R	0	0	
Developed Any Primary PI-R	0	0	

a Drug resistance mutations are defined in Table 127.
b Fisher exact test comparing the percentages in each group using the whole population as the denominator.
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3; GS-US-292-0102, Appendix 16.2, Listing 17.1

Table 136. E/C/F/TAF Study GS-US-292-0102: Details of Subjects in the Resistance Analysis Population

Subject	Treatment Group	BL HIV-1 RNA (copies/mL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (Fold Change from WT)[b]		
					RT	IN	TFV[c]	FTC	EVG
*BU [d]	E/C/F/TAF	34700	B	Week 24	Q207D, K259K/N	None	0.83	0.89	1.4
*BV [d]	E/C/F/TAF	15200	B	Week 40	K11K/R	None	0.83	1.0	1.1
*BW [d]	E/C/F/TAF	25600	B	Week 48	K122K/E, I135A/V, V292M	V31M, I203I/M	1.1	1.2	1.7
*BR [d]	STB	22500	B	Week 24	None	None	1.1	0.95	1.0
*BS	STB	38700	B	Week 32	K32K/E, I63I/M, Q174Q/K, **M184M/I/V**	**E92Q**	0.57	> 73	12.8
*BT	STB	22500	B	Week 24	K66K/R, **K70K/E**, Q102R, **M184M/V**, R211R/K, D250D/E, G273G/E	None	0.50	6.1	1.4

a Compared with screening/baseline genotype. Primary IN- or RT-associated resistance mutations are shown in **bold**.
b Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical cutoffs were as follows: TFV = 1.4 to 4, FTC = 3.5, and EVG = 2.5.
c The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF and TDF.
d Subject resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3; GS-US-292-0102, Appendix 16.2, Listing 17.1

Resistance Conclusions

For Study GS-US-292-0102, the RAP comprised 6 subjects: 3 subjects were from the E/C/F/TAF group (2.7%, 3 of 112 subjects) and 3 subjects were from the STB group (5.2%, 3 of 58 subjects). No subjects qualified for the RAP between Weeks 48 through 96. Three subjects from the E/C/F/TAF group and 1 subject from the STB group resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs and were therefore not included in the Final RAP.

The Final RAP included 2 subjects, none from the E/C/F/TAF group and 2 (3.4%) from the STB group. Both subjects from the STB group had emergence of resistance mutations to study drugs.

4.2.1.1.4. Study GS-US-292-0109

Study Design, Baseline Characteristics, and Viral Response

Study GS-US-292-0109 (m2.7.3, Section 2) is an ongoing, Phase 3, randomized, open-label, multicenter, active-controlled study to evaluate the efficacy and safety in virologically suppressed subjects who switched from an FTC/TDF regimen to E/C/F/TAF (Treatment Group 1) or maintained their preexisting regimen (Treatment Group 2, FTC/TDF+3rd Agent). All subjects were HIV-infected adults with virologic suppression on STB, EFV/FTC/TDF, ATV+COBI+FTC/TDF, or ATV+RTV+FTC/TDF.

Baseline Virology Data

HIV-1 genotyping was not conducted at screening since all subjects who entered Study GS-US-292-0109 had HIV RNA < 50 copies/mL at screening. Historical genotyping results for the PR/RT genes were available for all subjects since they were previously enrolled in Gilead studies, all of which enrolled ART-naive subjects. Consistent with the enrollment criteria for these studies, all enrolled subjects demonstrated full sensitivity to FTC and TFV (delivered as TDF or TAF) (Table 137).

The HIV-1 subtype was determined for each subject using the historical genotyping results. The genotype distribution was comparable between treatment groups, with subtype B predominant in both groups (Table 137).

Table 137. E/C/F/TAF Study GS-US-292-0109: Summary of Pretreatment HIV-1 Subtype and PR and RT Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Subjects n (%)		
	Group 1 (Switch to E/C/F/TAF) (N = 799)	Group 2 (Stay on FTC/TDF + 3rd Agent) (N = 397)	All (N = 1196)
Subtype B	752 (94.1)	367 (92.4)	1119 (93.6)
Non-B Subtype	47 (5.9)	30 (7.6)	77 (6.4)
NRTI-Associated	61 (7.6)	47 (11.8)	108 (9)
NNRTI-Associated	116 (14.5)	58 (14.6)	174 (14.5)
PI-Associated (Primary)	20 (2.5)	11 (2.8)	31 (2.6)

a Drug resistance mutations are defined in Table 127.
Source: PC-120-2020: GS-US-292-0109 Virology Listing 1

Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 1196 subjects comprising the Week 48 Full Analysis Set (FAS) in Study GS-US-292-0109, 5 (0.4%) met the criteria for inclusion in the RAP. The distribution of the RAP was comparable between the 2 treatment groups; with 4 of 799 subjects (0.5%) in the E/C/F/TAF group and 1 of 397 subjects (0.3%) in the FTC/TDF+3rd Agent regimen group analyzed (Figure 42, Table 138; results for individual subjects are presented in Table 139).

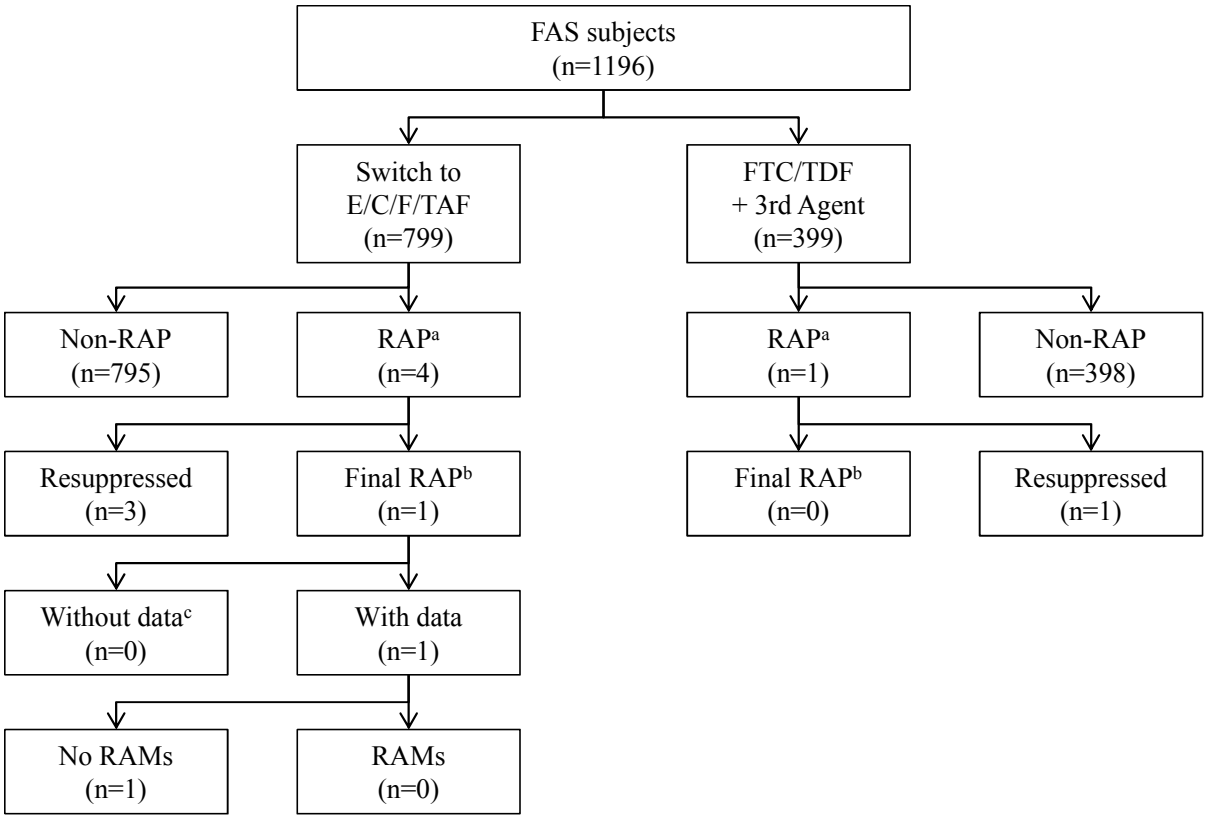
All 4 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48. Three subjects (Subjects *BX , *BY , and *BZ) achieved HIV-1 RNA resuppression to < 50 copies/mL with further E/C/F/TAF treatment and were therefore not included in the Final RAP. Subject *BX demonstrated genotypic phenotypic resistance to FTC (M184M/I; FTC FC = 3.8) at Week 8 and the HIV-1 RNA level resuppressed to < 50 copies/mL by ESDD when the subject switched to a new drug regimen. Subjects *BY and *BZ did not have resistance to study drugs detected.

One subject in the FTC/TDF+3rd Agent group was evaluated for the development of resistance at Week 48. Subject *CA experienced both PR/RT and IN assay failure at Week 12; however, this subject achieved HIV-1 RNA resuppression to < 50 copies/mL with further STB treatment. Therefore, no subject from the FTC/TDF+3rd Agent group was included in the Final RAP.

Final Resistance Analysis Population

The Final RAP comprised 1 subject (0.1%) in the E/C/F/TAF group and no subjects in the FTC/TDF+3rd Agent regimen group. The 1 subject (Subject *CB) in the E/C/F/TAF group that was included in the Final RAP had no detectable resistance to any study drug.

Figure 42. E/C/F/TAF Study GS-US-292-0109: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



a RAP criteria are summarized in PC-120-2020.
b The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
c Subjects without data either due to assay failure or ongoing analysis.
Source: PC-120-2020: GS-US-292-0109 Virology Listings 2 and 3; GS-US-292-0109, Appendix 16.2, Listing 14.1

Table 138. E/C/F/TAF Study GS-US-292-0109: Summary of HIV-1 Genotypic Resistance Observed Through Week 48

Resistance Category[a]	Number of Subjects n (%)		
	Group 1 (Switch to E/C/F/TAF) (N = 799)	Group 2 (Stay on FTC/TDF+3rd Agent) (N = 397)	p-value[b]
RAP	4 (0.5)	1 (0.3)	1.0
Subjects with Data	4 (0.5)	0	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL[c]	3 (0.4)	1 (0.3)	
Final RAP[d]	1 (0.1)	0	1.0
Subjects with Data	1 (0.1)	0	1.0
Developed Resistance Mutations to Study Drugs	0	0	
No Resistance Mutations Observed	1 (0.1)	0	

a Drug resistance mutations are defined in Table 127.
b Fisher exact test comparing the percentages in each group using the whole population as the denominator.
c Subject *BX had M184M/I detected prior to HIV-1 RNA resuppression (Table 139).
d Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0109 Virology Listings 2 and 3; GS-US-292-0109, Appendix 16.2, Listing 14.1

Table 139. E/C/F/TAF Study GS-US-292-0109: Details of Subjects in the Resistance Analysis Population

Subject	Treatment Group	BL HIV-1 RNA (copies/mL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (Fold Change from WT)[b]		
					RT	IN	TFV[c]	FTC	EVG
*BY [d]	E/C/F/TAF	< 50	B	Week 12	Q179Q/R, E224E/D, V292V/I	AF	1.2	1.0	AF
*BZ [d]	E/C/F/TAF	< 50	B	Week 2	None	None	0.98	0.86	AF
				Week 4	None	AF	0.89	1.1	AF
*BX [d]	E/C/F/TAF	< 50	B	Week 8	**M184M/I**	None	0.77	3.8	1.1
*CB	E/C/F/TAF	< 50	B	Week 24	None	None	0.84	0.91	0.97
*CA [d]	FTC/TDF+3rd Agent (STB)	< 50	B	Week 12	AF	AF	AF	AF	AF

a Compared with screening/baseline genotype for PR/RT. For IN, since no pretreatment sequences were available, only primary or secondary INSTI-R are listed. Primary IN- or RT-associated resistance mutations are shown in **bold**.
b Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical cutoffs were as follows: TFV = 1.4 to 4, FTC = 3.5, and EVG = 2.5.

c The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF and TDF.
d Subject resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0109 Virology Listings 2 and 3; GS-US-292-0109, Appendix 16.2, Listing 14.1

Resistance Conclusions

For Study GS-US-292-0109, the RAP comprised 5 subjects: 4 subjects were from the E/C/F/TAF group (0.5%, 4 of 799) and 1 subject was from the FTC/TDF+3rd Agent group (0.3%, 1 of 397).

Three subjects from the E/C/F/TAF group (including 1 subject with M184M/I detected) and the 1 subject from the FTC/TDF+3rd Agent group resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs and were therefore not included in the Final RAP.

The Final RAP included 1 subject (0.1%) from the E/C/F/TAF group and no subjects from the FTC/TDF+3rd Agent group. The subject from the E/C/F/TAF group did not have resistance detected to any study drug.

4.2.1.1.5. Study GS-US-292-0112

Study Design, Baseline Characteristics, and Viral Response

Study GS-US-292-0112 (m2.7.4, Section 1) is an ongoing, Phase 3, open-label, multicenter, multiple-cohort study to evaluate the efficacy, safety, and tolerability of E/C/F/TAF in HIV-infected adult subjects with stable, mild to moderate renal impairment (subjects with $eGFR_{CG}$ 30 to 69 mL/min, inclusive).

Baseline Virology Data

HIV-1 genotyping of the PR/RT and IN genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all Cohort 2 ART-naive subjects who entered Study GS-US-292-0112. Consistent with enrollment criteria, all enrolled Cohort 2 ART-naive subjects demonstrated full sensitivity to EVG, FTC, and TFV (delivered as TDF or TAF) (Table 140).

The HIV-1 subtype was determined for each subject in Cohort 2 (ART-naive) using the screening genotype. The predominant subtype among Cohort 2 ART-naive subjects was B (Table 140).

Table 140. E/C/F/TAF Study GS-US-292-0112: Summary of Pretreatment HIV-1 Subtype and PR, RT, and IN Resistance Mutations Detected

	Number of Subjects n (%)	
Mutation Class[a]	**Cohort 1[b]: Switch (N = 242)**	**Cohort 2: ART-Naive (N = 6)**
Subtype B	ND	5 (83.3)
Non-B Subtype	ND	1 (16.7)

Mutation Class[a]	Number of Subjects n (%)	
	Cohort 1[b]: Switch (N = 242)	Cohort 2: ART-Naive (N = 6)
NRTI-Associated	ND	0
INSTI-Associated (Primary)	ND	0
INSTI-Associated (Secondary)	ND	2 (40)[c]
NNRTI-Associated	ND	2 (33.3)
PI-Associated (Primary)	ND	0

a Drug resistance mutations are defined in Table 127.
b Subjects in Cohort 1 were HIV-1 suppressed at study enrollment.
c Subject *CC was an IN assay failure.
Source: PC-120-2020: GS-US-292-0112 Virology Listing 1 and Listing 2

Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 248 randomized and treated subjects in Study GS-US-292-0112, 4 subjects were classified as virologic failures using the FDA snapshot algorithm in the Week 24 analysis window (3 Cohort 1 switch subjects [1.2%] and 1 Cohort 2 ART-naive subject [16.6%], all with baseline $eGFR_{CG} \geq 50$ mL/min); however, only 2 subjects (0.8%) met the criteria for inclusion in the RAP. The RAP comprised 2 subjects (0.8%) in the Cohort 1 switch subjects and 0 subjects in the Cohort 2 ART-naive subjects (Figure 43, Table 141; results for individual subjects are presented in Table 142).

All 2 subjects in the Cohort 1 switch group were evaluated for the development of resistance at Week 24. Subject *CD was included in the RAP but later resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs and was therefore not included in the Final RAP.

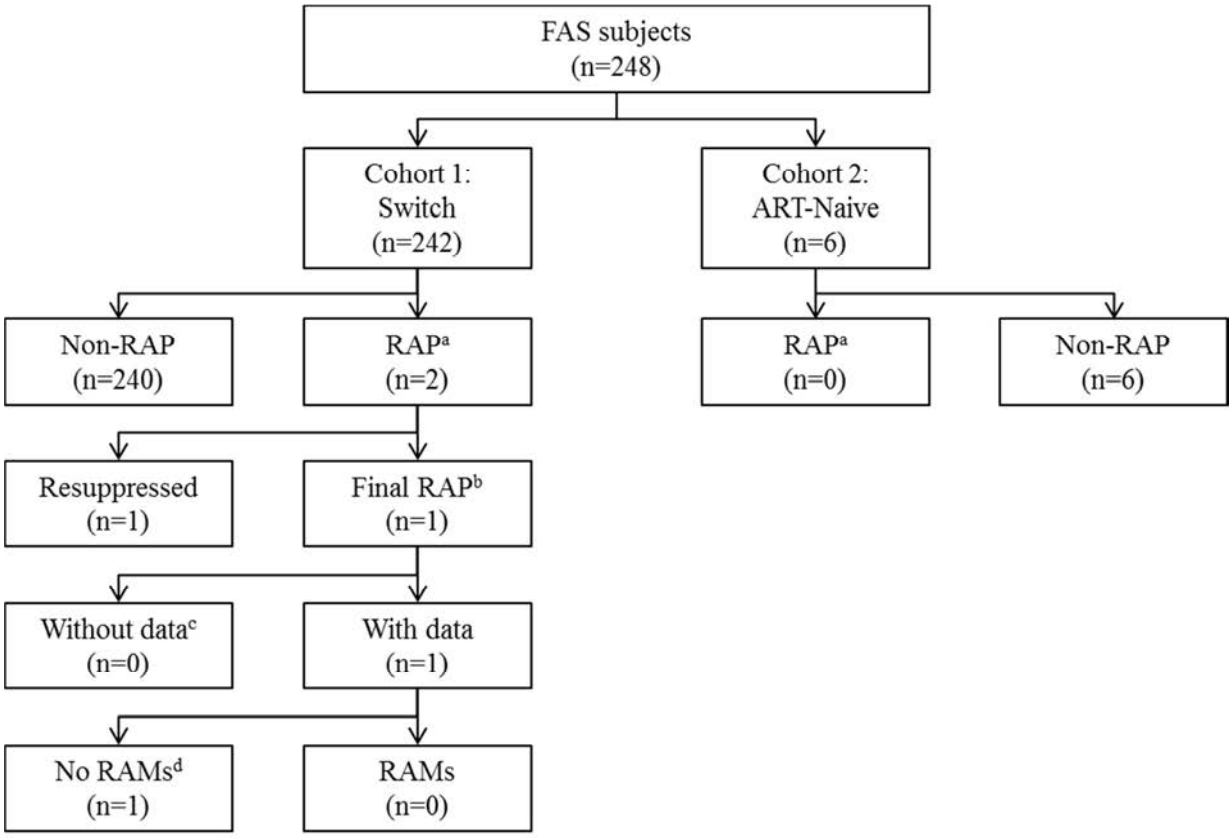
Resistance testing results for Subject *CD are presented in Table 142 and a detailed narrative is provided in the Virology Study Report (PC-120-2020). Briefly, this subject had an ARV history that included LPV/r+FTC/TDF, LPV/r+ABC/3TC, and RAL+ABC/3TC. Following switch to E/C/F/TAF, the subject remained HIV-1 RNA undetectable until Week 24, when HIV-1 RNA was 71 copies/mL. Upon repeat testing at Week 24, HIV-1 RNA was 524 copies/mL and viral rebound was confirmed. Limited data available revealed genotypic mutations to multiple drugs. Another Week 24 retest provided sufficient sample for phenotypic testing in the absence of HIV-1 RNA testing. Analysis of samples from both Week 24 retest visits revealed genotypic and phenotypic resistance to multiple drugs. Although no historical genotype was available, this subject met the inclusion criterion of no history of known resistance to EVG, TDF, or FTC while on past treatment regimens. Documented unprotected sex while on study may explain the sudden appearance of resistance due to possible reinfection. Study drug was discontinued due to lack of efficacy; however, at the ESDD visit, HIV-1 RNA was < 20 copies/mL prior to switching to a new regimen.

Final Resistance Analysis Population

The Final RAP comprised 1 subject (0.4%) in the Cohort 1 switch group and 0 subjects in the Cohort 2 ART-naive group.

Subject *CE from Cohort 1 (switch) had a confirmed rebound of HIV-1 RNA ≥ 50 copies/mL and was included in the Final RAP. Resistance testing results for this subject are presented in Table 142 and a detailed narrative is provided in the Virology Study Report (PC-120-2020). Briefly, this subject had an ARV history that included nelfinavir (NFV)+ABC+ZDV, ATV+ABC/3TC, and ATV+RTV+ABC/3TC. Following switch to E/C/F/TAF, the subject's HIV-1 RNA remained undetectable until Week 8, when the HIV-1 RNA rebounded to 55 copies/mL and was confirmed at Week 12 when HIV-1 RNA was 58 copies/mL. At Week 16, HIV-1 RNA was 329 copies/mL and analysis of this sample revealed multiple NRTI-associated resistance mutations with partial phenotypic resistance to TFV. No genotypic or phenotypic resistance to FTC or EVG was detected. All primary RAMs detected at Week 16 were confirmed to preexist upon retrospective analysis of a historical genotype taken after a previous treatment regimen of NFV+ABC+ZDV. The subject remained on E/C/F/TAF and showed low-level viremia through Week 48. At Week 36, HIV-1 RNA was 309 copies/mL and analysis of this sample revealed the same genotypic resistance profile as at Week 16. At Week 48 retest, the HIV-1 RNA was 514 copies/mL and analysis of this sample is currently pending.

Figure 43. E/C/F/TAF Study GS-US-292-0112: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 24



a RAP criteria are summarized in PC-120-2020.
b The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
c Subjects without data either due to assay failure or ongoing analysis.
d Subject *CE had RAMs detected on treatment; however, all were present prior to initiating E/C/F/TAF.
Source: PC-120-2020: GS-US-292-0112 Virology Listings 3 and 4; GS-US-292-0112, Appendix 16.2, Listing 18

Table 141. E/C/F/TAF Study GS-US-292-0112: Summary of HIV-1 Genotypic Resistance Observed Through Week 24

Resistance Category[a]	Number of Subjects n (%)	
	Cohort 1 Switch (N = 242)	Cohort 2 ART-Naive (N = 6)
RAP	2 (0.8)	0
Subjects with Data	2 (0.8)	0
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL[b]	1 (0.4)	0
Final RAP[c]	1 (0.4)	0
Subjects with Data	1 (0.4)	0
Developed Resistance Mutations to Study Drugs[d]	0	0

a Drug resistance mutations are defined in Table 127.
b Subject *CD had both NRTI-R and INSTI-R detected prior to HIV-1 RNA resuppression (Table 142).
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
d Subject *CE had RAMs detected on treatment; however, all were present prior to initiating E/C/F/TAF.
Source: PC-120-2020: GS-US-292-0112 Virology Listings 3 and 4; GS-US-292-0112, Appendix 16.2, Listing 18

Table 142. E/C/F/TAF Study GS-US-292-0112: Details of Subjects with Resistance Testing at Week 24

Subject	Treatment Group	BL HIV-1 RNA (copies/mL)	Subtype	Failure Time Point	Mutations Detected[a]			Drug Susceptibility (Fold Change from WT)[b]		
					PR	RT	IN	TFV[c]	FTC	EVG
*CD [d]	Cohort 1: Switch	< 50	B	Historical	ND	ND	ND	ND	ND	ND
				Week 24 Retest #1 (29 Jan 2014)	E35D, M36I	**M41L**, **T69SVS**, V75A, V90I, **F116Y**, V179I, **Y181I**, **M184V**, **L210W**, **T215Y**	**T66I**, S119P, E170E/K	R	R	R
				Week 24 Retest #2 (13 Feb 2014)	E35D, M36I	**M41L**, **T69SVS**, V75A, V90I, **F116Y**, V179I, **Y181I**, **M184V**, **L210W**, **T215Y**	**T66I**, S119P	10.0	> 87	11.9
*CE	Cohort 1: Switch	< 50	B	Historical (07 Nov 2005	L63P, I64V, V77I, **L90M**	**D67N**, **T69N**, **K70R**, **K103S**, **G190A**, F214L, **K219Q**	None	ND	ND	ND
				Week 16	L63P, I64V, V77I, **L90M**	**D67N**, **K70R**, K103R, **K219Q**	None	2.5	2.9	1.0
				Week 36	L63P, I64V, V77I, **L90M**	**D67N**, **K70R**, K103R, **K219Q**	None	1.9	2.6	1.2
				Week 48 Retest #2 (08 Sept 2014)	Data pending					

a Compared with reference genotype. Primary IN- or RT-associated resistance mutations are shown in **bold**.
b Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical cutoffs were as follows: TFV = 1.4 to 4, FTC = 3.5, and EVG = 2.5. PRIme assay results are reported as sensitive (S) or resistant (R) base on the proprietary algorithm from Monogram Biosciences.
c The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF and TDF.
d Subject resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0112 Virology Listings 3 and 4; GS-US-292-0112, Appendix 16.2, Listing 18

Resistance Conclusions

In Cohort 1 (switch), 2 subjects (0.8%, 2 of 242) were analyzed and showed resistance to multiple drug classes. One subject had detectable resistance to all study drugs as well as nonstudy drugs, possibly due to reinfection, but achieved HIV-1 RNA resuppression to < 20 copies/mL with continued E/C/F/TAF treatment prior to switching to a new regimen. The other subject showed persistent low-level viremia and drug resistance mutations to NRTI and PIs that were documented in a historical genotype prior to initiating E/C/F/TAF treatment. In Cohort 2 (ART-naive), no subject met the criteria for resistance analysis (0%, 0 of 6).

4.2.1.1.6. Study GS-US-292-0106

Study Design, Baseline Characteristics, and Viral Response

Study GS-US-292-0106 (m2.7.4, Section 1) is an ongoing Phase 2/3, open-label, multicenter, 2-part, single-group study of the PK, safety, tolerability, and antiviral activity of E/C/F/TAF in HIV-infected, ART-naive adolescents.

Baseline Virology Data

HIV-1 genotyping of the PR/RT and IN genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for subjects who entered Study GS-US-292-0106. Consistent with enrollment criteria, all enrolled subjects demonstrated full sensitivity to EVG, FTC, and TFV (delivered as TDF or TAF) (Table 143).

The HIV-1 subtype was determined for each subject using the screening genotype. Overall, non-B HIV-1 subtypes were predominant (Table 143).

Table 143. E/C/F/TAF Study GS-US-292-0106: Summary of Pretreatment HIV-1 Subtype, and PR, RT, and IN Resistance Mutations

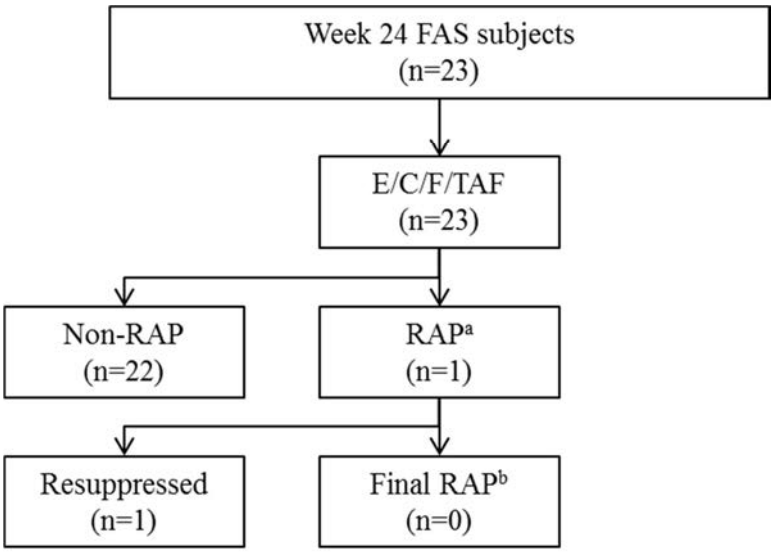
HIV-1 Subtype[a] and Mutation Class[b]	Number of Subjects n (%) E/C/F/TAF (N = 23)
Subtype B	4 (17.4)
Non-B Subtype	19 (82.6)
NRTI-Associated	4 (17.4)
INSTI-Associated (Primary)	0
INSTI-Associated (Secondary)	5 (21.7)
NNRTI-Associated	2 (8.7)
PI-Associated (Primary)	0

a HIV-1 subtypes reported as Complex by the Monogram assay were resolved using the REGA subtyping tool whenever possible {30531}.
b Drug resistance mutations are defined in Table 127.
Source: PC-120-2020: GS-US-292-0106 Virology Listings 1 and 2

Virology Analyses in Subjects in the Resistance Analysis Population

Of the 23 subjects in the Week 24 FAS for Study GS-US-292-0106, 1 subject of 23 (4.3%) was included in the RAP (Figure 44, Table 144). Subject *CF was suppressed (HIV-1 RNA < 50 copies/mL) at Weeks 12 and 16 and had unconfirmed virologic rebound to HIV-1 RNA of 1010 copies/mL at Week 24. This subject resuppressed HIV-1 RNA to < 50 copies/mL at the next study visit upon continued treatment with E/C/F/TAF. Therefore, this subject's virus was not analyzed for resistance development and no subjects were included in the Final RAP (which did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs).

Figure 44. E/C/F/TAF Study GS-US-292-0106: Resistance Analysis Population Inclusion Criteria Through Week 24



a RAP criteria are summarized in PC-120-2020.
b The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: GS-US-292-0106, Appendix 16.2, Listing 15.1

Table 144. E/C/F/TAF Study GS-US-292-0106: Summary of HIV-1 Genotypic Resistance Observed Through Week 24

Resistance Category[a]	Number of Subjects n (%) E/C/F/TAF (N = 23)
RAP	1 (4.3)
Subjects with Data	0
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	1 (4.3)
Final RAP[b]	0

a Drug resistance mutations are defined in Table 127.
b Does not include subjects who resuppressed HIV-1 RNA < 50 copies/mL while continuing study drugs.
Source: GS-US-292-0106, Appendix 16.2, Listing 15.1

Resistance Conclusions

Of the 23 subjects in the Week 24 FAS for Study GS-US-292-0106, no subjects (0 of 23) met the criteria for inclusion in the Final RAP.

4.2.1.2. D/C/F/TAF Study

4.2.1.2.1. Study GS-US-299-0102

Study Design, Baseline Characteristics, and Viral Response

Study GS-US-299-0102 (m2.7.3, Section 2) was a Phase 2, randomized, double-blinded, multicenter, active-controlled study to assess the efficacy and safety of D/C/F/TAF compared with the DRV+COBI+FTC/TDF in HIV-infected, ART-naive adult subjects.

Baseline Virology Data

A PR/RT genotyping report was obtained at screening for all subjects enrolled in the study in order to confirm genotypic sensitivity to DRV, TDF, and FTC.

The majority of subjects (97.4 %, 149 of 153) had HIV-1 subtype B, with only 4 subjects carrying HIV-1 with a non-B subtype (Table 145). Darunavir resistance has been associated with the presence of 3 or more of the following mutations in protease: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V {16104}. Six subjects had HIV-1 each containing 1 DRV-specific RAM at screening (Table 145), which did not adversely influence treatment response.

Table 145. D/C/F/TAF Study GS-US-299-0102: Summary of HIV-1 Subtype, and PR and RT Resistance Mutations Detected Pretreatment

HIV-1 Subtype and Mutation Class[a]	Number of Subjects n (%)		
	D/C/F/TAF (N = 103)	DRV+COBI+ FTC/TDF (N = 50)	All (N = 153)
Subtype B	99 (96.1)	49 (98)	149 (97.4)
Non-B Subtype	4 (3.9)	0	4 (2.6)
PI-Associated (Primary)	5 (4.9)	3 (6)	8 (5.2)
DRV RAMs[b]	3 (2.9)	3 (6)	6 (4)
PI-Associated (Secondary)	101 (98.1)	48 (96)	149 (97.4)
NNRTI-Associated	20 (19.4)	10 (20)	30 (19.6)
NAMs[c]	14 (13.6)	1 (2)	15 (9.8)

a Drug resistance mutations are defined in Table 127.
b DRV RAMs are V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V in protease.
c NAMs are M41L, E44D, A62V, K65R, D67N, T69D/N, T69 insertion, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184I/V, L210W, T215F/Y, and K219E/N/Q/R in RT.
Source: m5.3.5.1, GS-US-299-0102, Appendix 16.2, Virology Listing 1

Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 153 randomized and treated subjects in Study GS-US-299-0102, 8 (5.2%) met the criteria for inclusion in the RAP. Six (5.8%) subjects from the D/C/F/TAF group and 2 (4.0%) subjects from the DRV+COBI+FTC/TDF group comprised the RAP (Figure 45, Table 146; results for individual subjects are presented in Table 147). Seven of these subjects experienced virologic rebound and 1 had unconfirmed virologic rebound at the last study visit. Several subjects (Subjects *CG , *CH , and *CI) were analyzed on multiple occasions.

All 6 subjects in the D/C/F/TAF group were evaluated for the development of resistance. Subject *CJ achieved HIV-1 RNA resuppression to < 50 copies/mL with further D/C/F/TAF treatment and was therefore not included in the Final RAP.

The 2 subjects in the DRV+COBI+FTC/TDF group were evaluated for the development of resistance. Subject *CK achieved HIV-1 RNA resuppression to < 50 copies/mL with further DRV+COBI+FTC/TDF treatment and was therefore not included in the Final RAP.

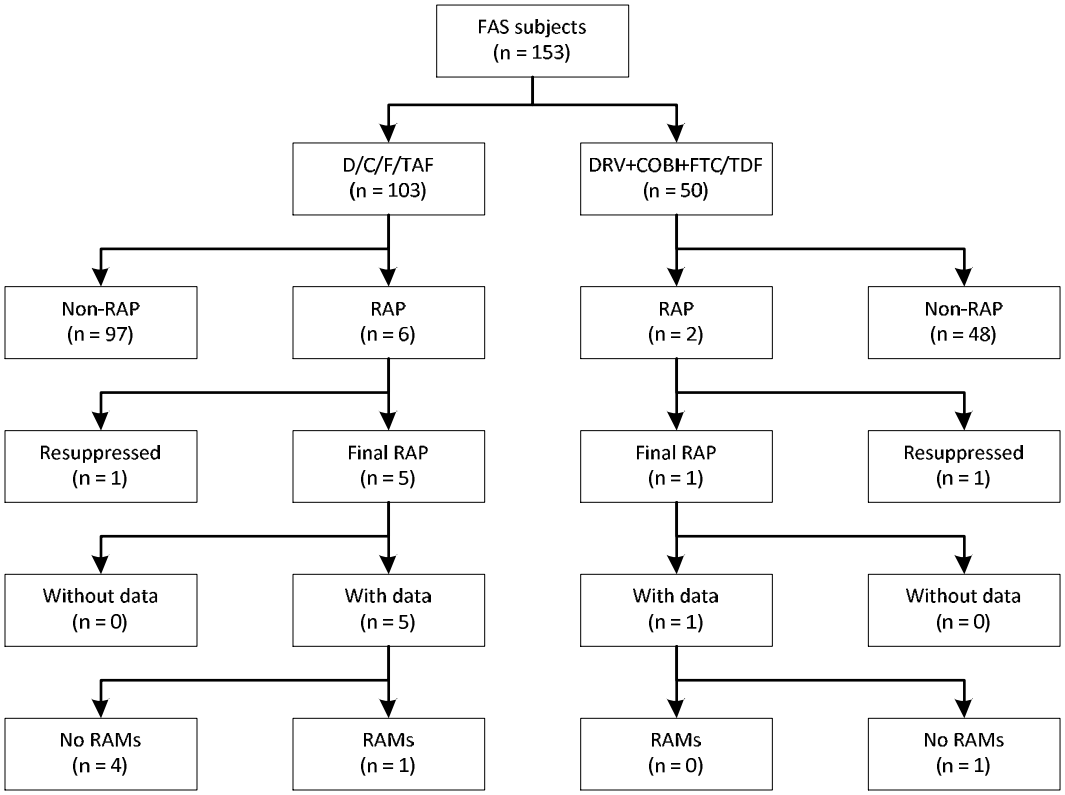
Final Resistance Analysis Population

None of the 8 subjects included in the RAP developed any primary protease resistance mutations at the time of confirmed or unconfirmed rebound (Table 147), and DRV phenotypic susceptibility was in the sensitive range (0.31- to 1.7-fold from wild type) for all isolates analyzed.

One subject in the D/C/F/TAF group had NRTI-resistance mutation emerging at the unblinding visit after Week 48 (Subject *CL) with the emergence of a mutant/wild-type mixture at position K65 (K65K/R) and a mutant/wild-type mixture at position M184 (M184M/I) (Table 147). These mutations are associated with resistance to TDF/TAF and FTC, respectively. However, phenotypic susceptibilities to both FTC and TDF were in the sensitive range despite the presence of those mutations. That subject had a prior episode of virologic failure at Week 40 followed by resuppression of HIV-1 RNA <50 copies/mL, suggesting a history of improper treatment compliance. Of note, the subject has had undetectable HIV-1 RNA for > 6 months while receiving E/C/F/TAF upon enrollment in the open-label phase of Study GS-US-292-0102, suggesting activity of the F/TAF-containing regimen against HIV with those mutations in this subject.

Out of the 7 remaining subjects in the RAP with no resistance emerging, 2 subjects had HIV-1 RNA resuppressed <50 copies/mL after resistance analysis (Subjects *CJ , and *CK), 2 subjects were discontinued for noncompliance (Subjects *CG and *CH), 2 subjects were lost to follow-up (Subjects *CM and *CN), and 1 subject with evidence of transmitted drug resistant HIV-1 at baseline (mutations I50L and V82M in protease, and K103N, L210W, and T215C in RT) completed the study with a virologic profile suggesting treatment noncompliance (Subject *CI).

Figure 45. D/C/F/TAF Study GS-US-299-0102: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



RAP criteria are summarized in m5.3.5.1, GS-US-299-0102, Section 7.5.2.5. The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: m5.3.5.1, GS-US-299-0102, Appendix 16.2, Virology Listings 1 and 2

Table 146. D/C/F/TAF Study GS-US-299-0102: Summary of HIV-1 Genotypic Resistance Observed Through Week 48

Resistance Category[a]	Number of Subjects n (%)	
	D/C/F/TAF (N = 103)	DRV+COBI+FTC/TDF (N = 50)
RAP	6 (5.8)	2 (4.0)
Subjects with Data	6 (5.8)	2 (4.0)
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	1 (1.0)	1 (2.0)
Final RAP[b]	5 (4.8)	1 (2.0)
Subjects with Data	5 (4.8)	1 (2.0)
Developed Resistance Mutations to Study Drugs	2 (1.9)	0
No Resistance Mutations Observed	3 (2.9)	0
Developed Any NRTI-R	1 (1.0)	0
K65R	1 (1.0)	0
M184I/V	1 (1.0)	0
Developed Any NNRTI-R	0	0
Developed Any Primary PI-R	0	0

a Drug resistance mutations are defined in Table 127.
b Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: m5.3.5.1, GS-US-299-0102, Appendix 16.2, Virology Listing 2

Table 147. D/C/F/TAF Study GS-US-299-0102: Details of Subjects in the Resistance Analysis Population

Subject	Treatment Group	BL HIV-1 RNA (copies/mL)	Subtype	Visit	Emergent Mutations[a]		Drug Susceptibility (FC from WT)[b]		
					PR	RT	TFV[c]	FTC	DRV
*CG	D/C/F/TAF	26800	B	ESDD	None	E224E/K	0.61	0.83	0.35
*CL	D/C/F/TAF	211000	B	Unblinding	None	I63I/V **K65K/R** D67D/G **M184M/I**[d]	0.73	2.5	0.39
*CM	D/C/F/TAF	8590	B	Week 16	K14K/R	D123D/E/K/N D177D/E	0.75	0.98	0.90
*CJ	D/C/F/TAF	22100	B	Week 60	F99F/L	F214F/L K220K/I K249K/Q	0.86	1.0	0.68
*CH	D/C/F/TAF	35400	B	ESDD	M36M/I	None	0.55	1.1	0.68
*CI	D/C/F/TAF	56500	B	Week 48	None	None	0.92	1.2	1.7
*CK	DRV+COBI +FTC/TDF	51000	B	Week 48	I15I/V	K64K/R I202I/V[d]	0.73	1.0	0.44
*CN	DRV+COBI +FTC/TDF	45400	B	Week 48	None	None	0.65	1.0	0.96

a Compared to screening genotype. Primary PR- or RT-associated resistance mutations are shown in **bold**.
b Replication capacity expressed as percentage of wild-type control. Drug phenotypic data expressed as EC_{50} fold change from wild-type control.
c Monogram Biosciences PhenoSenseGT Assay was performed with TFV, the parent compound of TAF and TDF.
d Subjects have had undetectable HIV-1 RNA subsequently for > 6 months (Subject *CL) and > 3 months (Subject *CK) while receiving E/C/F/TAF in the rollover open-label phase of study GS-US-292-0102.
Source: m5.3.5.1, GS-US-299-0102, Appendix 16.2, Virology Listing 2

Resistance Conclusions

For Study GS-US-299-0102, 8 subjects comprised the RAP: 6 subjects were from the D/C/F/TAF group (5.8%, 6 of 103) and 2 subjects were from the DRV+COBI+FTC/TDF group (4.0%, 2 of 50).

No subjects developed primary PR resistance mutations through the initial Week 48 primary endpoint timepoint. One subject in the D/C/F/TAF group had NRTI-R mutation emerging at the unblinding visit after Week 48 with the emergence of a mutant/wild-type mixture at position K65 (K65K/R) and a mutant/wild-type mixture at position M184 (M184M/I). These mutations are associated with resistance to TDF/TAF and FTC, respectively. However, phenotypic susceptibilities to both FTC and TDF were in the sensitive range despite the presence of those mutations. That subject had a prior episode of virologic failure at Week 40 followed by resuppression of HIV-1 RNA <50 copies/mL, suggesting a history of improper treatment compliance. Of note, the subject had successful HIV-1 RNA suppression for > 6 months in a subsequent E/C/F/TAF rollover study (Study GS-US-292-0102), suggesting activity of the F/TAF-containing regimen against HIV with those mutations in this subject.

4.2.2. Integrated Virology Analyses at Baseline and in Subjects Experiencing Virologic Failure

Integrated virology analyses were performed for Phase 2 Study GS-US-292-0102 and Phase 3 Studies GS-US-292-0104 and GS-US-292-0111.The resistance analyses from the Phase 2 study have been conducted through 96 weeks. The resistance analyses from the 2 separate Phase 3 studies were based on at least 48 weeks of treatment in the majority of subjects. To allow integration with the Phase 3 studies, the Phase 2 data through 48 weeks were included.

Resistance analyses were performed on plasma samples for all subjects who were included in the RAP. All of the integrated analyses were performed using the Final RAP, which did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs. None of the subjects who were not included in the Final RAP showed emergence of resistance mutations.

4.2.2.1. Baseline Resistance Analyses

Genotyping of the PR/RT genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all subjects who entered Studies GS-US-292-0102 (170 subjects), GS-US-292-0104 (867 subjects), and GS-US-292-0111 (866 subjects). As defined in all 3 protocols, subjects had genotypic sensitivity to FTC and TDF. Genotyping of the IN gene was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all subjects who entered Studies GS-US-292-0104 and GS-US-292-0111. As defined in both protocols, subjects also had genotypic sensitivity to EVG.

Consistent with enrollment criteria, no RAMs were observed to EVG, FTC, and TFV at baseline for all subjects except one who had T97A detected in IN. Resistance mutations observed pretreatment for PR and RT, and IN are presented in Table 148. The distribution of baseline RAMs was comparable between treatment groups.

Table 148. E/C/F/TAF Integrated Analysis: Summary of PR and RT Resistance Mutations Detected Pretreatment

	Number of Subjects n (%)		
Drug Class[a]	**E/C/F/TAF (N = 978)**	**STB (N = 925)**	**All (N = 1903)**
NRTI-Associated	81 (8.3)[b]	62 (6.7)	143 (7.5)
NNRTI-Associated	177 (18.1)[b]	169 (18.3)	346 (18.2)
PI-Associated (Primary)	35 (3.6)[b]	29 (3.1)	64 (3.4)
	E/C/F/TAF[c] (N = 866)	**STB[d] (N = 867)**	**All (N = 1733)**
INSTI-Associated (Primary)	0	1 (0.1)	1 (0.1)
T97A	0	1 (0.1)	1 (0.1)
INSTI-Associated (Secondary)	421 (48.8)	401 (46.4)	822 (47.6)

a Drug resistance mutations are defined in Table 127.
b Subject *AE had PR/RT assay failure
c Subjects *AD , *AE , and *AF were IN assay failures.
d Subjects *AG and *AH were IN assay failures.
Source: PC-120-2020: Appendix Table 1, Appendix Table 2, and Appendix Table 3

The HIV-1 subtype was determined for each subject using the screening genotype. The genotype distribution was comparable between treatment groups, with subtype B predominant in both groups (87% overall) followed by subtype AE (6.7%) (Table 149). The majority of subjects with subtype AE are from Study GS-US-292-0104, which enrolled subjects from South East Asia, where subtype AE is the predominant HIV-1 strain {16847}.

Table 149. E/C/F/TAF Integrated Analyses: Summary of HIV-1 Subtypes

HIV-1 Subtype	Number of Subjects n (%)		
	E/C/F/TAF[a] (N = 978)	STB (N = 925)	All (N = 1903)
Subtype B	850 (87)	805 (87)	1655 (87)
Non-B Subtype	127 (13)	120 (13)	247 (13)
Subtype A	2 (0.2)	0	2 (0.1)
Subtype A1	5 (0.5)	6 (0.6)	11 (0.6)
Subtype A2	0	1 (0.1)	1 (0.1)
Subtype AE	66 (6.8)	62 (6.7)	128 (6.7)
Subtype AG	12 (1.2)	15 (1.6)	27 (1.4)
Subtype B/C	1 (0.1)	0	1 (0.1)
Subtype BC	0	1 (0.1)	1 (0.1)
Subtype BF	0	1 (0.1)	1 (0.1)
Subtype C	14 (1.4)	12 (1.3)	26 (1.4)
Subtype D	1 (0.1)	3 (0.3)	4 (0.2)
Subtype F	1 (0.1)	0	1 (0.1)
Subtype F1	6 (0.6)	3 (0.3)	9 (0.5)
Subtype G	1 (0.1)	3 (0.3)	4 (0.2)
Complex	18 (1.8)	11 (1.2)	29 (1.5)
Unknown	0	2 (0.2)	2 (0.1)

a Subject *AE had no subtype information available due to assay failure.
Source: PC-120-2020: Appendix Table 4

4.2.2.2. Impact of Baseline Resistance Mutations and Subtype on Treatment Outcomes

The impact of baseline RAMs as well as subtype on treatment outcomes was assessed for all subjects. For the baseline RAM analysis, the presence or absence of PI-R, NNRTI-R, NRTI-R, TAMs, and K103N/S were evaluated. For the subtype analysis, subtype B versus non-B subtype

was evaluated. No impact of baseline RAMs or subtype was observed on treatment outcomes ($p > 0.05$) (Table 150).

Table 150. E/C/F/TAF Integrated Analyses: Percentage of Subjects With Treatment Success at Week 48 by Baseline Virologic Category

Category	Number of Subjects with Treatment Success[a] n (%)	
	E/C/F/TAF[b] (N = 978)	STB (N = 925)
All Subjects	898/977 (91.9)	835/925 (90.3)
HIV-1 Subtype B	782/850 (92.0)	725/805 (90.1)
HIV-1 Subtype Non-B	116/127 (91.3)	110/120 (91.7)
p-value[c]	0.73	0.74
Primary PI-R[d]	29/35 (82.9)	27/29 (93.1)
No Primary PI-R	869/942 (92.3)	808/896 (90.2)
p-value[c]	0.056	1.0
NNRTI-R[d]	158/177 (89.3)	155/169 (91.7)
No NNRTI-R	740/800 (92.5)	680/756 (89.9)
p-value[c]	0.17	0.57
K103N/S	49/56 (87.5)	49/52 (94.2)
No K103N/S	849/921 (92.2)	786/873 (90.0)
p-value[c]	0.21	0.47
NRTI-R[d]	72/81 (88.9)	55/62 (88.7)
No NRTI-R	826/896 (92.2)	780/863 (90.4)
p-value[c]	0.29	0.66
TAMs[d]	24/26 (92.3)	14/17 (82.4)
No TAMs	874/951 (91.9)	821/908 (90.4)
p-value[c]	1.0	0.23

a Percentage of subjects in the FDA snapshot algorithm category "Virologic Success at Week 48" are shown.
b Subject *AE had no subtype or PR/RT information available due to assay failure.
c Fisher exact test comparing treatment response rates among subjects with and without a particular virologic category.
d Drug resistance mutations are defined in Table 127.
Source: PC-120-2020: Appendix Table 5

4.2.2.2.1. Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 1903 randomized and treated subjects in Studies GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111, 41 subjects (2.2%) met the criteria for inclusion in the RAP. The RAP

comprised 1.9% of subjects (19 of 978) in the E/C/F/TAF group and 2.4% of subjects (22 of 925) in the STB group (Figure 46, Table 151).

Final Resistance Analysis Population

The Final RAP comprised 14 subjects (1.4%) in the E/C/F/TAF group and 16 subjects (1.7%) in the STB group. Integrated analyses are presented for subjects with available data (Table 152).

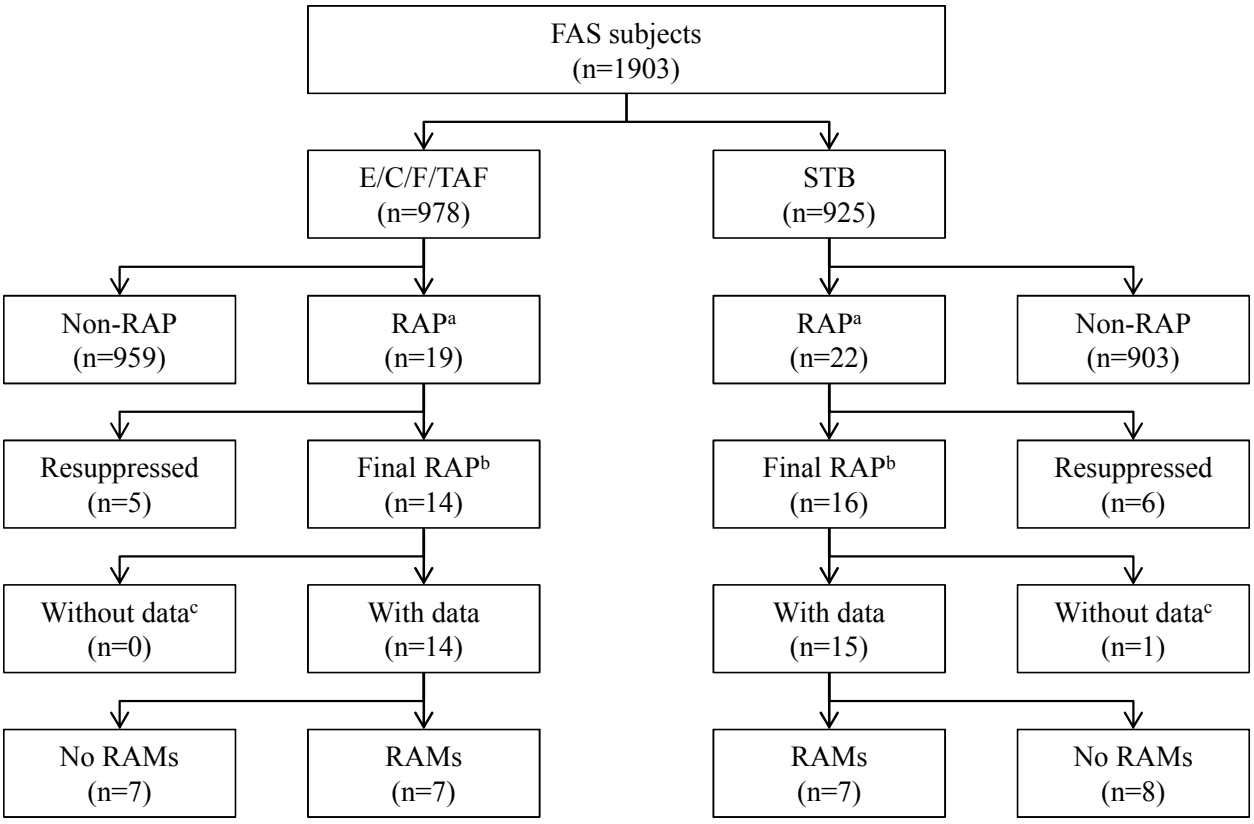
All 14 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48. Of the 14 subjects with available data included in the Final RAP, 7 subjects (0.7%, 7 of 978 subjects in the E/C/F/TAF group) had resistance mutations emerge while on E/C/F/TAF and 7 subjects (0.7%) had no emergent resistance. All 7 subjects with emergent resistance mutations (Subjects *AM , *AL , *AN , *AY , *AZ , *BA , and *BB) had M184V detected, which was associated with phenotypic resistance to FTC in 6 of 7 subjects (FC ≥ 63 to > 89). In addition, 5 subjects had emergent primary INSTI-R, with 2 subjects (Subjects *AL and *AZ) harboring E92Q, 1 subject each harboring N155H (Subject *AM) and T66A (Subject *BB), and 1 subject (Subject *BA) harboring T66T/I/A/V and Q148Q/R, along with the secondary INSTI-R E138E/K. Phenotypic resistance to EVG was observed in 4 subjects (FC = 10.9 to 60), with Subject *AZ having assay failure. One subject (Subject *AM) developed K65R; however, no phenotypic resistance to TFV was observed (FC = 1.0).

For the remaining 7 subjects in the E/C/F/TAF group, no genotypic or phenotypic resistance to any study drug was observed.

All 16 subjects in the STB group were evaluated for the development of resistance at Week 48, with 1 subject having assay failure. Of the 16 subjects with available data included in the Final RAP, 7 subjects (0.8%, 7 of 925 subjects in the STB group) had resistance mutations emerge while on STB and 8 subjects (0.9%) had no emergent resistance. All 7 subjects with emergent resistance (Subjects *BS , *BT , *AP , *AR , *AQ , *BC , and *BD) had M184V/I detected, with phenotypic resistance to FTC observed in 5 subjects. Four subjects had emergent primary INSTI-R, with 2 subjects (Subjects *BS and *AP) harboring E92Q, 1 subject (Subject *BC) harboring Q148R, and 1 subject (Subject *AQ) harboring E92E/Q and Q148R. Phenotypic resistance to EVG was observed in all subjects with genotypic resistance (FC = 12.8 to > 156). Four subjects had additional NRTI-R detected, with 2 subjects (Subjects *AP and *BC) harboring K65R, 1 subject (Subject *BT) harboring K70K/E, and 1 subject (Subject *AR) harboring E44E/D. All subjects with additional NRTI-R remained sensitive to TFV (FC = 0.5 to 1.3) except Subject *AP , who was not determined due to assay failure.

For the remaining 8 subjects in the STB group, no genotypic or phenotypic resistance to any study drug was observed.

Figure 46. E/C/F/TAF Integrated Analysis: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



a RAP criteria are summarized in PC-120-2020.
b The Final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
c Subjects without data due to assay failure.
Source: PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3; GS-US-292-0104 Virology Listings 3 and 4; GS-US-292-0111 Virology Listings 3 and 4

Table 151. E/C/F/TAF Integrated Analyses: Summary of HIV-1 Genotypic Resistance Through Week 48

Resistance Category[a]	Number of Subjects n (%)		
	E/C/F/TAF (N = 978)	STB (N = 925)	p-value[b]
RAP	19 (1.9)	22 (2.4)	0.53
Subjects with Data	17 (1.7)	18 (1.9)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	5 (0.5)	6 (0.7)	
Final RAP[c]	14 (1.4)	16 (1.7)	0.71
Subjects with Data	14 (1.4)	15 (1.6)	
Developed Resistance Mutations to Study Drugs	7 (0.7)	7 (0.8)	1.0
No Resistance Mutations Observed	7 (0.7)	8 (0.9)	
Developed Any NRTI-R	7 (0.7)	7 (0.8)	
E44E/D	0	1 (0.1)	
K65R	1 (0.1)	2 (0.2)	
K70K/E	0	1 (0.1)	
M184V/I	7 (0.7)	7 (0.8)	
Developed Any INSTI-R	5 (0.5)	5 (0.5)	
Primary INSTI-R	5 (0.5)	4 (0.4)	
T66A	2 (0.2)	0	
E92Q	2 (0.2)	3 (0.3)	
Q148R	1 (0.1)	2 (0.2)	
N155H	1 (0.1)	0	
Secondary INSTI-R	1 (0.1)	2 (0.2)	
L68V	1 (0.1)	0	
E138K	1 (0.1)	2 (0.2)	
E157K	0	1 (0.1)	
Developed Any NNRTI-R	0	0	
Developed Any Primary PI-R	0	0	

a Drug resistance mutations are defined in Table 127.
b Fisher exact test comparing the percentages in each group using the whole population as the denominator.
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3, GS-US-292-0104 Virology Listings 3 and 4, GS-US-292-0111 Virology Listings 3 and 4

Table 152. E/C/F/TAF Integrated Analysis: Details of Subjects With Available Data in the Final Resistance Analysis Population

Subject	Study	Treatment Group	BL HIV-1 RNA (copies/mL)	BL CD4 (cells/µL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (Fold Change from WT)[b]		
							RT	IN	TFV[c]	FTC	EVG
*AO	GS-US-292-0104	E/C/F/TAF	14000	300	B	Week 48	I178I/M	AF	0.59	1.0	AF
*AM	GS-US-292-0104	E/C/F/TAF	385000	11	B	Week 48	M41M/K, **K65R**, **M184V**	G70G/R, **N155H**, V201V/I, Q216Q/R, D232D/N	1.0	> 63	60
*AL	GS-US-292-0104	E/C/F/TAF	367000	1	B	Week 48	**M184V**, T286T/I	**E92Q**	0.65	> 70	56
*AN	GS-US-292-0104	E/C/F/TAF	138000	264	B	ESDD	**M184M/V**	A129A/S	0.68	2.0	1.1
*AY	GS-US-292-0111	E/C/F/TAF	115000	80	B	Week 16	D121H/Y, **M184M/I/V**, Q207Q/H	A265A/V	0.65	> 68	0.97
*AZ	GS-US-292-0111	E/C/F/TAF	384000	137	B	Week 24	P170P/L, V179V/I, **M184V**	L68V, **E92Q**	0.49	> 84	AF
*BA	GS-US-292-0111	E/C/F/TAF	1610000	17	B	Week 12	**M184V**	**T66T/I/A/V**, E138E/K, **Q148Q/R**, D232D/N	0.54	> 81	10.9
*BE	GS-US-292-0111	E/C/F/TAF	150000	283	B	Week 36	W71P, T139T/A, E204E/K	AF	0.98	1.3	AF
*BB	GS-US-292-0111	E/C/F/TAF	463000	21	B	Week 16	**M184V**, H208Y, E248K	**T66A**	0.48	> 89	12.3
*BF	GS-US-292-0111	E/C/F/TAF	8120	468	B	Week 48	V276V/I	A21A/T	0.96	0.95	1.6
*BG	GS-US-292-0111	E/C/F/TAF	36800	244	B	Week 36	None	I208I/L	0.79	0.99	1.1
*BH	GS-US-292-0111	E/C/F/TAF	9470	592	B	Week 24	K64K/R	None	0.82	1.1	1.0
*BI	GS-US-292-0111	E/C/F/TAF	327000	153	B	Week 48	T200T/A, Q207Q/R	None	0.81	1.1	1.3

Subject	Study	Treatment Group	BL HIV-1 RNA (copies/mL)	BL CD4 (cells/µL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (Fold Change from WT)[b]		
							RT	IN	TFV[c]	FTC	EVG
*BJ	GS-US-292-0111	E/C/F/TAF	31100	395	B	Week 36	K122Q, D177E, Q207E, V245V/E, G273G/E, R277K, V292I, E297A	AF	0.87	1.1	AF
*BS	GS-US-292-0102	STB	38700	252	B	Week 32	K32K/E, I63I/M, Q174Q/K, **M184M/I/V**	**E92Q**	0.57	>73	12.8
*BT	GS-US-292-0102	STB	22500	397	B	Week 24	K66K/R, **K70K/E**, Q102R, **M184M/V**, R211R/K, D250D/E, G273G/E	None	0.5	6.1	1.4
*AS	GS-US-292-0104	STB	62800	554	B	ESDD	None	D6N, E35K, E69K, R107K, E138K, E152K, M154I, E157K	0.88	1.1	AF
*AP	GS-US-292-0104	STB	127000	20	B	Week 16	V60I, **K65R**, **M184V**	**E92Q**, T124S, K264K/*	AF	AF	21
*AR	GS-US-292-0104	STB	21800	384	B	ESDD	E36E/Q, **E44E/D**, K49K/Q, **M184M/V**	I204I/V, V259V/I	0.85	1.5	1.2
*AQ	GS-US-292-0104	STB	486000	24	B	ESDD	**M184V**	P90P/S, **E92E/Q**, H114H/Y, E138E/K, **Q148R**	0.43	> 71	> 156
*AT	GS-US-292-0104	STB	647000	58	AG	Week 36	None	AF	0.95	1.1	AF
*BK	GS-US-292-0111	STB	1080	291	B	Week 16	E297E/G	AF	0.9	1.1	AF
*BC	GS-US-292-0111	STB	239000	2	B	Week 36	**K65R**, I135M, **M184V**	E138K, **Q148R**	1.3	> 82	> 95

Subject	Study	Treatment Group	BL HIV-1 RNA (copies/mL)	BL CD4 (cells/µL)	Subtype	Failure Time Point	Emergent Mutations[a]		Drug Susceptibility (Fold Change from WT)[b]		
							RT	IN	TFV[c]	FTC	EVG
*BD	GS-US-292-0111	STB	88300	348	B	Week 48	**M184V**	None	0.42	> 64	1.9
*BL	GS-US-292-0111	STB	51000	271	B	Week 48	None	V249I/V	0.92	1.0	AF
*BM	GS-US-292-0111	STB	130000	395	B	Retest	None	ND	0.95	1.2	ND
*BO	GS-US-292-0111	STB	87800	513	B	Week 48	None	S17S/N, V31V/I, L101L/I, K127K/R, L172L/F, I208I/L, K211K/R, T218T/S, S230S/N	0.91	1.1	1.1
*BP	GS-US-292-0111	STB	94100	750	B	Week 24	None	None	0.81	1.1	1.7
*BQ	GS-US-292-0111	STB	42100	287	B	Week 48	None	None	0.89	0.98	AF

a Compared with screening/baseline genotype. Primary IN- or RT-associated resistance mutations are shown in **bold**.
b Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical cutoffs were as follows: TFV = 1.4 to 4, FTC = 3.5, and EVG = 2.5.
c The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF and TDF.
* indicates a stop codon
Source: PC-120-2020: GS-US-292-0102 Virology Listings 1, 2, and 3, GS-US-292-0104 Virology Listings 3 and 4, GS-US-292-0111 Virology Listings 3 and 4; GS-US-292-0102, Appendix 16.2, Listing 17.1; GS-US-292-0104, Appendix 16.2, Listing 16.1; GS-US-292-0111, Appendix 16.2, Listing 16.1

4.2.2.3. Analysis of Treatment Emergent Substitutions in Virologic Failure Subjects

An analysis was conducted to determine if any unique amino acid substitutions (full mutations) in the RT and IN genes not previously demonstrated to be associated with resistance to TAF, EVG, or FTC were observed in more than 1 subject with virologic failure in the E/C/F/TAF or STB groups. No such additional substitutions in the RT or IN genes were observed in more than 1 subject with virologic failure in the E/C/F/TAF or STB groups.

4.2.2.4. Cross-Resistance Profiles for Virologic Failure Subjects

Subjects with virologic failure were assessed for phenotypic resistance to all commercially available NRTIs, NNRTIs, PIs, and INSTIs in addition to study drugs to assess for potential cross-resistance. Overall, the cross-resistance profiles for the subjects with virologic failure who had emergent resistance to EVG, FTC, and TFV were consistent with historical data. The 12 subjects with virologic failure who had emergent M184V/I and phenotypic resistance to FTC also had cross-resistance to lamivudine, with FC values of 5 to > 128. Five subjects with virologic failure harbored additional NRTI-R, with 3 subjects harboring K65R, 1 subject harboring K70K/E, and 1 subject harboring E44E/D, with none demonstrating phenotypic resistance to TFV (1 subject had assay failure). The 2 subjects harboring K65R who were successfully phenotyped had cross-resistance to ABC (FC = 6.3 and 6.4), but were sensitive to ZDV. The subjects harboring K70K/E and E44E/D remained sensitive to both ABC and ZDV.

Of the 8 virologic failure subjects with emergent primary INSTI-R and phenotypic resistance to EVG, 6 also had cross-resistance to raltegravir (FC = 2.9 to 75). One subject was not cross-resistant to raltegravir; however, the subject had emergent T66A at virologic failure, which is an EVG-specific resistance mutation. Another subject (Subject *BA) was not cross resistant to raltegravir; however, this subject also had emergent T66A and a Q148Q/R mixture at VF. Four of the 8 subjects with virologic failure and emergent INSTI-R were assessed for cross-resistance to DTG. Consistent with their IN genotype at virologic failure and the established cross-resistance profile for DTG, all 4 remained sensitive to DTG, with FC values < 4.

4.2.2.5. Integrated Virology Analysis Conclusions

Across the 3 randomized and controlled studies comparing E/C/F/TAF with STB in HIV-infected, ART-naive subjects, the baseline RAMs and HIV-1 subtype were comparable across the E/C/F/TAF and STB treatment groups. In addition, baseline RAMs and HIV-1 subtype had no impact on treatment outcomes.

After 48 weeks of treatment across the E/C/F/TAF and STB groups, the emergence of resistance mutations was rare. There were 14 subjects who developed any treatment-emergent genotypic resistance, 7 of 978 subjects (0.7%) in the E/C/F/TAF group and 7 of 925 subjects (0.8%) in the STB group.

In the E/C/F/TAF group, M184V was observed in conjunction with primary INSTI-R mutations in 5 of 7 subjects (2 with T66T/A/I/V, 2 with E92Q, 1 with Q148Q/R, and 1 with N155H), with 1 subject also developing K65R. All 7 subjects had baseline HIV-1 RNA levels of

≥ 115,000 copies/mL and 4 of 7 subjects had baseline CD4 counts < 100 cells/μL. No other unique substitutions in the RT or IN genes were observed in more than 1 subject with virologic failure in the E/C/F/TAF group.

In the STB group, M184V was observed in all 7 subjects with emergent resistance. In addition, primary INSTI-R mutations were observed in 4 subjects (0.4%) (3 with E92Q and 2 with Q148R), and K65R was observed in 2 subjects.

The patterns of emergent resistance in the E/C/F/TAF group (0.7%) were similar with the STB group (0.8%). No other unique substitutions in the RT or IN genes were observed in more than 1 subject with virologic failure in the STB group.

Overall, the cross-resistance profiles for the subjects with virologic failure who had emergent resistance to EVG, FTC, and TFV were consistent with historical data.

4.2.3. Conclusions

An integrated virology analysis was conducted for Phase 2 Study GS-US-292-0102 and Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 in ART-naive, HIV-infected subjects who received either E/C/F/TAF or STB. In these 3 studies, the emergence of resistance mutations was rare across the E/C/F/TAF and STB groups. The emergence of resistance was similar for the E/C/F/TAF group (0.7%) compared with the STB group (0.8%).

The results observed in the additional 3 studies analyzed (Studies GS-US-292-0106, GS-US-292-0112, and GS-US-292-0109) were consistent with the results observed in the integrated analysis. Overall, the 6 analyzed studies demonstrated that the emergence of resistance mutations in subjects receiving E/C/F/TAF was rare. The genotypic changes detected in the E/C/F/TAF group were comparable with the genotypic changes detected in the STB group. No novel TAF resistance mutations were observed to develop in any of the E/C/F/TAF virologic failure subjects.

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6. APPENDIX

Appendix Number	Appendix Title
6.1	Tabular Summary of Clinical Pharmacology Studies
6.2	Pharmacokinetic/Pharmacodynamic (or Ad Hoc) Analyses
6.3	Tabular Summary of Applicable Nonclinical Studies
6.4	Analyses for Study GS-US-311-1089

6.1. Tabular Summary of Clinical Pharmacology Studies

6.1.1. F/TAF Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-311-1088 (synopsis)	Evaluate the bioequivalence between F/TAF FDC and FTC + TAF coadministered as individual agents	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/25 mg FDC PO (A) • FTC 200 mg + TAF 25 mg PO (B)	2 days (Single doses on Days 1 and 15)	Enrolled: 56 Completed: 54 Safety Analysis Set: A: 56 B: 55	Healthy adult subjects	Study completed; m5.3.1.2 Final CSR
Comparative BA/BE	GS-US-311-1472 (synopsis)	Evaluate the bioequivalence of FTC and TAF administered as F/TAF FDC + EVG + COBI, or as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/10 mg FDC + EVG 150 mg + COBI 150 mg PO (A) • E/C/F/TAF (150/150/200/10 mg) FDC PO (B)	2 days (Single doses on Days 1 and 7)	Enrolled: 100 Completed: 99 Safety Analysis Set: A: 99 B: 100	Healthy adult subjects	Study completed; m5.3.1.2 Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-311-1473 (synopsis)	Evaluate the bioequivalence of FTC and TAF administered as F/TAF FDC, or as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/25 mg FDC PO (A) • E/C/F/TAF (150/150/200/10 mg) FDC PO (B)	2 days (Single doses on Days 1 and 7)	Enrolled: 116 Completed: 116 Safety Analysis Set: A: 116 B: 116	Healthy adult subjects	Study completed; m5.3.1.2 Final CSR
Extrinsic Factor PK	GS-US-311-0101 (synopsis)	Cohort 1: Evaluate the PK of TAF, TFV, and FTC following once-daily coadministration of F/TAF FDC and EFV relative to the administration of F/TAF FDC alone Cohorts 2 and 3: Evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF FDC and DRV+COBI relative to the administration of these agents alone Cohort 4: Evaluate the PK of TAF, TFV, and COBI following once-daily	Phase 1, nonrandomized, open-label, crossover, multicohort, multiple-dose study	Cohort 1: • F/TAF (200/40 mg) QD PO (Days 1-12, fasted) (A) • F/TAF (200/40 mg) + EFV 600 mg QD PO (Days 13-26, fasted) (B) Cohort 2: • F/TAF (200/25 mg) QD PO (Days 1-12, fed) (C) • F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 13-22, fed) (D) Cohort 3: • DRV 2 × 400 mg + COBI 150 mg QD PO (Days 1-10, fed)	Cohort 1: 26 days Cohorts 2-4: 22 days	Enrolled:50 Completed: 48 Safety Analysis Set: A: 12 B: 12 C: 12 D: 25[a] E: 14 F: n/a G: 12 H: 12 [a] Includes 11 subjects who received Treatment D and 14 subjects who received Treatment F	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
		coadministration of TAF+COBI relative to the administration of TAF alone		(E) • F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 11-22, fed) (F) <u>Cohort 4:</u> • TAF 8 mg QD PO (Days 1-12, fed) (G) • TAF 8 mg + COBI 150 mg QD PO (Days 13-22, fed) (H)				
Extrinsic Factor PK	GS-US-311-1386 (synopsis)	Determine the effect of food on the PK of TAF and FTC when administered as F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-period, crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/25 mg FDC PO fasted (A) • F/TAF 200.25 mg FDC PO fed (B)	2 days (Single doses on Days 1 and 8)	Enrolled: 40 Completed: 38 Safety Analysis Set: A: 40 B: 38	Healthy adult subjects	Study completed; m5.3.3.4 Final CSR

6.1.2. TAF Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Tolerability	GS-US-120-0109 (synopsis)	Determine the mass balance of TAF following administration of a single, oral dose of radiolabeled [^{14}C]TAF	Phase 1, open-label, mass-balance study	• TAF 25 mg (mixture of unlabeled TAF and [^{14}C]TAF) PO	Single dose	Enrolled: 8 Completed: 8 Safety Analysis Set: 8	Healthy adult male subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0108 (synopsis)	Evaluate the PK of TAF and its metabolite TFV following administration of TAF in subjects with and without severe renal impairment	Phase 1, open-label, parallel-design, single-dose, PK study	• TAF 25 mg PO	Single dose	Enrolled: 27 Completed: 27 Safety Analysis Set: Subjects with severe renal impairment: 14 Age and sex matched controls: 13	Adult subjects with severe renal impairment ($eGFR_{CG}$ of 15 to ≤ 29 mL/min) or healthy matched control subjects ($eGFR_{CG}$ of ≥ 90 mL/min)	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0114 (synopsis)	Evaluate the PK of TAF in subjects with normal and impaired hepatic function	Phase 1, open-label, 2-cohort, parallel-group, single-dose, multicenter study	• TAF 25 mg PO	Single dose	Enrolled: 40 Completed: 40 Safety Analysis Set: Cohort 1: Subjects with mild hepatic impairment: 10 Matched controls: 10	Cohort 1: Adult subjects with mild hepatic impairment (CPT Class A) and healthy matched control subjects Cohort 2: Adult subjects with moderate hepatic	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
						Cohort 2: Subjects with moderate hepatic impairment: 10 Matched controls: 10	impairment (CPT Class B) and healthy matched control subjects	
Extrinsic Factor PK	GS-US-120-0117 (synopsis)	Evaluate the PK of RPV and TAF following single-dose administration of RPV and TAF alone and in combination in healthy subjects	Phase 1, open-label, single-center, single-dose, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments: Cohort 1: • TAF 25 mg QD PO (A) • TAF 25 mg + RPV 25 mg QD PO (B) Cohort 2: • TAF 25 mg + RPV 25 mg QD PO (B) • RPV 25 mg QD PO (C)	2 days (Days 1 and 12)	Randomized: 36 Completed: 36 Safety Analysis Set: Cohort 1: 18 Cohort 2: 18	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-120-0118 (synopsis)	Evaluate the effect of common boosted PIs ATV+RTV; DRV+RTV; LPV/r, or the INSTI DTG on the PK of TAF, and evaluate the PK of ATV, DRV, LPV,	Phase 1, open-label, DDI study	Cohort 1: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • ATV 300 mg + RTV 100 mg QD PO (Days 2-14) (B)	15 days	Enrolled: 40 Completed: 39 Safety Analysis Set: Cohort 1: 10 Cohort 2: 10	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
		and DTG alone and in combination with FTC and TAF		• A + B (Day 15) Cohort 2: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • DRV 800 mg + RTV 100 mg QD PO (Days 2-14) (C) • A + C (Day 15) Cohort 3: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • LPV/r (4 × 200/50 mg) QD PO (Days 2-14) (D) • A + D (Day 15) Cohort 4: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (F) • DTG 50 mg QD PO (Days 2-14) (E) • F + E (Day 15)		Cohort 3: 10 Cohort 4: 10 (1 subject excluded from the FTC+TAF+ DTG safety analysis)		
Extrinsic Factor PK	GS-US-120-1538 (synopsis)	Evaluate the PK and drug interaction potential between TAF and MDZ (Oral and IV)	Phase 1, open-label, multiple-dose, single-center study	Subjects received the following treatments in a fixed sequence under fed conditions in the morning: • Day 1: MDZ_{oral} 2.5 mg syrup (A)	18 days (Day 1, washout on Day 2, and doses on Days 3-18)	Enrolled: 18 Completed: 18 Safety Analysis Set: A: 18 B: 18 C: 18	Healthy adult subjects	Study completed; m5.3.3.4 Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				• Day 3: MDZ_{IV} 1 mg solution (B) • Days 4-15 and 17: TAF 25 mg PO (C) • Day 16: TAF 25 mg PO + MDZ_{oral} 2.5 mg syrup coadministered (D) • Day 18: TAF 25 mg PO + MDZ_{IV} 1 mg solution administered within 5 min of each other (E)		D: 18 E: 18 F: 18		
Extrinsic Factor PK	GS-US-120-1554 (synopsis)	Evaluate the PK and drug interaction potential between TAF and RPV	Phase 1, open-label, randomized, fixed-sequence, 2-cohort, 2-period, multiple-dose study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments under fed conditions: Cohort 1: • TAF 25 mg QD PO (Days 1-14) (A) • TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C) Cohort 2: • RPV 25 mg QD PO (Days 1-14) (B) • TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C)	28 days	Randomized: 34 Completed: 32 Safety Analysis Set: Cohort 1: 17 Cohort 2: 17	Healthy adult subjects	Study completed; m5.3.3.4 Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subjects PK and PK/PD	GS-US-120-0107 (synopsis)	Evaluate the effects of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, randomized, partially-blinded, placebo- and positive-controlled, 4-period, single-dose crossover study	Subjects were randomized to 1 of 8 treatment sequences and received the following treatments: • TAF 25 mg + 4 × placebo-to-match TAF QD PO (A) • TAF 125 mg (5 × 25 mg) QD PO (B) • Placebo-to-match TAF (C) • Moxifloxacin 400 mg PO, administered open-label (D)	37 days (4 single-dose treatment days separated by 11 days of washout between doses)	Randomized: 59 Completed: 58 Safety Analysis Set: A: 58 B: 58 C: 59 D: 58	Healthy adult subjects	Study completed; Final CSR
Patient PD and PK/PD	GS-US-120-0104 (synopsis)	Evaluate the short-term antiviral potency of TAF 8 mg, 25 mg, and 40 mg compared to placebo-to-match TAF or TDF 300 mg	Phase 1, randomized, partially-blinded, active- and placebo-controlled study	• TAF 8 mg QD PO (A) • TAF 25 mg QD PO (B) • TAF 40 mg QD PO (C) • TDF 300 mg QD PO (D) • Placebo-to-match TAF QD PO (E)	10 days	Randomized: 40 Completed: 37 Safety Analysis Set: A: 9 B: 8 C: 8 D: 6 E: 7	HIV-infected adult subjects, who had not received ART within 90 days of screening	Study completed; Final CSR

6.1.3. E/C/F/TAF Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-292-0103 (synopsis)	Evaluate the PK and relative bioavailability of EVG, COBI, FTC, TAF, and TFV administered as E/C/F/TAF FDC relative to the administration of the individual components	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort, 2-period, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments: Cohort 1: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • EVG 150 mg + COBI 150 mg QD PO (B) Cohort 2: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • FTC 200 mg + TAF 25 mg QD PO (C)	24 days (12 days for each treatment period within a sequence)	Randomized: 34 Completed: 33 Safety Analysis Set: Cohort 1: 14 Cohort 2: 20	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-292-0101 (synopsis)	Evaluate the relative bioavailability of EVG, COBI, FTC, and TFV when administered as 1 of 2 formulations of E/C/F/TAF FDC vs STB STR and TAF alone	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort study	Within each cohort, subjects were randomized to 1 of 4 treatment sequences and received the following treatments: Cohort 1: • Formulation 1 E/C/F/TAF (150/150/200/25 mg) QD PO (A)	54 days (4 12-day treatment sequences with a 2-day washout period between each sequence)	Randomized: 40 Completed: 36 Safety Analysis Set: Cohort 1: 20 Cohort 2: 20	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				• Formulation 1 E/C/F/TAF (150/150/200/40 mg) QD PO (B) • STB STR (150/150/200/ 300 mg) QD PO (C) • TAF 25 mg QD PO (D) Cohort 2: • Formulation 2 E/C/F/TAF (150/150/200/25 mg) QD PO (E) • Formulation 2 E/C/F/TAF (150/150/200/40 mg) QD PO (F) • STB STR (150/150/200/ 300 mg) QD PO (C) • TAF 25 mg QD PO (D)				
Healthy Subject PK and Tolerability	GS-US-292-0108 (synopsis)	Investigate the PK of EVG, COBI, FTC, TAF, and TFV when administered as E/C/F/TAF FDC in healthy Japanese and Caucasian subjects	Phase 1, open-label, sequential single- and multiple-dose study	• E/C/F/TAF (150/150/200/10 mg) QD PO	13 days (1 single dose on Day 1, followed by a washout and then once-daily doses of study treatment on	Enrolled: 20 Completed: 17 Safety Analysis Set: Single-dose phase: 20 (10 Japanese; 10 Caucasian)	Healthy adult Japanese (first generation Japanese descent) or Caucasian (not of Japanese or Asian descent) subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
					Days 8 to 19	Multiple-dose phase: 18 (10 Japanese; 8 Caucasian)		
Extrinsic Factor PK	GS-US-292-0110 (synopsis)	Evaluate the effect of food (high-calorie/high-fat meal or light/low-fat meal) on the PK of TAF when administered as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-center, 3-period, 6-sequence, crossover, food-effect study	Subjects were randomized to 1 of 6 treatment sequences and received E/C/F/TAF (150/150/200/10 mg) QD PO administered under the following meal conditions: • Fasted (A) • Light/low-fat meal (B) • High-calorie/high-fat meal (C)	15 days (study drug was administered on Days 1, 8, and 15)	Randomized: 43 Completed: 42 Safety Analysis Set: 43	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-292-1316 (synopsis)	Evaluate the PK of EVG, TAF, and SER following the coadministration of E/C/F/TAF FDC and SER relative to the administration of E/C/F/TAF or SER alone	Phase 1, open-label, 3-period, fixed-sequence, single-center study	• SER 50 mg QD PO (Day 1) (A) • E/C/F/TAF (150/150/200/10 mg) QD PO (Days 2-13) (B) • SER 50 mg + E/C/F/TAF (150/150/200/10 mg) QD PO (Day 14) (C)	14 days	Enrolled: 20 Completed: 19 Safety Analysis Set: 20	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-342-1167 (synopsis)	Evaluate the PK of SOF and metabolites GS-566500 and GS-331007, and	Phase 1, open-label, multiple-dose, 4-cohort study	Cohorts 1-3: Subjects were randomized to treatments that did not	Cohort 4: 24 days	Randomized to Cohort 4: 24 Completed: 23 Safety Analysis	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
		GS-5816 upon administration of SOF/GS-5816 FDC with ATR STR, CPA STR, DTG, or E/C/F/TAF, and evaluate the PK of COBI, DTG, EFV, EVG, FTC, RPV, TAF and/or TFV upon administration of ATR, CPA, DTG, or E/C/F/TAF with SOF/GS-5816 FDC		include E/C/F/TAF. Cohort 4: Subjects were randomized to 1 of 6 treatment sequences and received the following treatments with a moderate fat meal: • SOF/GS-5816 (400/100 mg) QD PO (8 days) (J) • E/C/F/TAF (150/150/200/10 mg) QD PO (8 days) (K) • SOF/GS-5816 (400/100 mg) + E/C/F/TAF (150/150/200/10 mg) QD PO (8 days) (L)		Set: 24		
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0102 (synopsis)	Evaluate the efficacy of a regimen containing E/C/F/TAF FDC versus STB STR	Phase 2, randomized, double-blind and open-label, multicenter, active-controlled study	Randomized Phase: • E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/ 300 mg) + placebo-to-match E/C/F/TAF QD PO (B) Open-Label Extension Phase:	Randomized Phase: 48 weeks until unblinding Open-Label Extension Phase: Until E/C/F/TAF is commercially available or development is terminated	Randomized: 171 Completed: 158 Safety Analysis Set: A: 112 B: 58 Entered Open-Label Extension: A: 105 B: 53	Randomized Phase: HIV-infected, ART-naive adult subjects Open-Label Extension Phase: Additional HIV-infected adult subjects had received a DRV+COBI containing regimen in Study	Study ongoing; Week 96 Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				• E/C/F/TAF (150/150/200/10 mg) QD PO (C)		299-0102: 108 Continuing study drug at Week 96: A: 104 B: 53 299-0102: 107	GS-US-299-0102 and were ART-naive at the time of entry into that study.	
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0104 (synopsis)	Evaluate the efficacy of E/C/F/TAF FDC versus STB STR	Phase 3, randomized, double-blind, active-controlled, multicenter study	• E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/ 300 mg) + placebo-to-match E/C/F/TAF QD PO (B)	96 weeks Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 872 Safety Analysis Set: A: 435 B: 432 Continuing study drug at Week 48: A: 413 B: 400	HIV-infected, ART-naive adult subjects	Study ongoing; Week 48 Interim CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0109 (synopsis)	Evaluate the noninferiority of switching to a TAF-containing FDC relative to maintaining TDF-containing regimens in virologically suppressed, HIV-infected subjects	Phase 3, randomized, open-label, active-controlled, multicenter study	• Switch to E/C/F/TAF (150/150/200/10 mg) QD PO from a predefined FTC/TDF regimen (A) • Stay on pre-existing FTC/TDF+3rd Agent regimen (B): STB STR (150/150/200/ 300 mg) QD PO; ATR STR	96 weeks Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 1443 Safety Analysis Set: A: 959 B: 477 Continuing study drug at Week 48: A: 939 B: 447	HIV-infected adult subjects from a predefined set of Gilead clinical studies receiving ARV regimens for at least 6 consecutive months, and who had maintained plasma HIV-1 RNA levels at undetectable	Study ongoing; Week 48 Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				(600/200/300 mg) QD PO; ATV 300 mg + COBI 150 mg + FTC/TDF (200/300 mg) QD PO; or ATV 300 mg + RTV 100 mg + FTC/TDF (200/300 mg) QD PO			levels for ≥ 6 consecutive months prior to screening	
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0111 (synopsis)	Evaluate the efficacy of E/C/F/TAF FDC versus STB STR	Phase 3, randomized, double-blind, active-controlled, multicenter study	• E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/300 mg) + placebo-to-match E/C/F/TAF QD PO (B)	96 weeks Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 872 Safety Analysis Set: A: 431 B: 435 Continuing study drug at Week 48: A: 408 B: 396	HIV-infected, ART-naive adult subjects	Study ongoing; Week 48 Interim CSR
Uncontrolled Clinical Studies	GS-US-292-0106 (synopsis)	Part A: Evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC Part B: Evaluate the safety and tolerability of the E/C/F/TAF FDC	Phase 2/3, open-label, multicenter, 2-part, single-group study	• E/C/F/TAF (150/150/200/10 mg) QD PO	48 weeks Extension Phase: Subjects have option to continue study drug until subject turns 18 and	Enrolled: 48 Part A: 24 Part B: 24 Safety Analysis Set: 48 Continuing study drug at Week 24: Main study:	HIV-infected, ART-naive adolescents (12 to < 18 years of age)	Study ongoing; Week 24 Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
					E/C/F/TAF is commercially available for adults in country of enrollment, E/C/F/TAF becomes commercially available for adolescents in country of enrollment, or E/C/F/TAF development is terminated in country of enrollment	47 Extension: 1		
Uncontrolled Clinical Studies	GS-US-292-0112 (synopsis)	Evaluate the effect of the E/C/F/TAF FDC on renal parameters	Phase 3, open-label, multicenter, multi-cohort study	• E/C/F/TAF (150/150/200/10 mg) QD PO	96 weeks Extension Phase: Subjects have option to continue study drug until E/C/F/TAF is commercially available or development is terminated	Enrolled: 252 Safety Analysis Set: Cohort 1: 242 Cohort 2: 6 Continuing study drug at Week 24 Cohort 1: 226 Cohort 2: 6	HIV-infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min Cohort 1: ART-experienced Cohort 2: ART-naive	Study ongoing; Week 24 Interim CSR

6.1.4. D/C/F/TAF Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-299-0101 (synopsis)	Evaluate the bioavailability of 3 formulations of D/C/F/GS-7340 STR relative to the administration of individual components DRV/co, FTC, and GS-7340	Phase 1, randomized, open-label, multiple-dose, 3-part, multiple-cohort, single-center study	**Part 1:** Subjects were randomized (1:1:1) to 1 of 3 treatments: • DRV/COBI/FTC/ GS-7340 STR Formulation 1 monolayer (800/150/200/25) (A) • DRV/COBI/FTC/ GS-7340 STR Formulation 2 bilayer (800/150/200/25) (B) • DRV/COBI/FTC/ GS-7340 STR Formulation 3 monolayer (800/150/200/10) (C) **Part 2:** Subjects were randomized (1:1) to treatment sequences within Cohort 1 or Cohort 2: Cohort 1 treatments: • DRV 800 mg + COBI 150 mg +	**Part 1:** 21 days **Part 2:** 20 days (10 days/ treatment) **Part 3:** 24 days (12 days/ treatment)	**Part 1:** Randomized: 30 Safety Analysis Set: A: 10 B: 10 C: 10 **Part 2, Cohort 1:** Randomized: 20 Safety Analysis Set: DE: 10 ED: 10 **Part 2, Cohort 2:** Randomized: 16 Safety Analysis Set: DF: 8 FD: 8 **Part 3, Cohort 1:** Randomized: 20 Safety	Healthy adult subjects	Study completed; m5.3.5.2 Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				TVD (FTC 200 mg/TDF 300 mg) (D) • DRV 800 mg + COBI 150 mg (E) Cohort 2 treatments: • DRV 800 mg + COBI 150 mg + TVD (FTC 200 mg/TDF 300 mg) (D) • TVD (FTC 200 mg/TDF 300 mg) (F) **Part 3:** Subjects were randomized (1:1) to treatment sequences within Cohort 1 or Cohort 2: Cohort 1 treatments: • DRV/COBI/FTC/ GS-7340 STR Formulation 3 monolayer (800/150/200/10) (C) • DRV 800 mg + COBI 150 mg (E) Cohort 2 treatments: • DRV/COBI/FTC/ GS-7340 STR Formulation 3		Analysis Set: CE: 10 EC: 9 **Part 3, Cohort 2:** Randomized: 16 Safety Analysis Set: CG: 8 GC: 8		

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				monolayer (800/150/200/10) (C) • FTC 200 mg + GS-7340 25 mg (G)				
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-299-0102 (synopsis)	Evaluate the efficacy of D/C/F/TAF FDC versus DRV+COBI+TVD	Phase 2, randomized, double-blind, active-controlled, multicenter, study	Subjects were randomized in a 2:1 ratio to 1 of 2 treatment groups as follows: • D/C/F/TAF (800/150/200/10 mg) + placebo-to-match DRV+COBI+FTC/TDF QD PO (A) • DRV (800 mg) + COBI (150 mg) + FTC/TDF (200/300 mg) + placebo-to-match D/C/F/TAF QD PO (B)	48 weeks Extension Phase: Subjects continued to receive blinded drug until unblinding and then were given option to participate in Study GS-US-292-0102 and receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 153 Safety Analysis Set: A: 103 B: 50	HIV-infected, ART-naive adult subjects	Study completed; m5.3.5.1 Final CSR

6.1.5. FTC Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
BA	FTC-110 (synopsis)	Evaluate relative and absolute BA of FTC	Phase 1, open-label, randomized, 3-way crossover, single 200-mg doses administered as IV solution, oral solution, or oral capsule	• FTC 1 × 200-mg capsule, PO, fasted (A) • 20 mL of FTC 10 mg/mL solution, PO, fasted (B) • 20 mL of FTC 10 mg/mL solution, IV infused over 1 hour, fasted (C)	3 single doses	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Comparative BA/BE	FTC-109 (synopsis)	Pilot study to evaluate the BE/BA of FTC between the 100-and 200-mg capsules	Phase 1, open-label, randomized, 2-way crossover, single 200-mg dose study	• FTC 2 × 100-mg capsules, PO, single dose (Formulation C) (A) • FTC 1 × 200-mg capsule, PO, single dose (Formulation B) (B)	2 single doses	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Comparative BA/BE	FTC-111 (synopsis)	Determine the BA/BE of 100- and 200-mg capsules, and the effect of food on the BA of FTC administered as a 200-mg capsule	Phase 1, open-label, randomized, 3-way crossover, single 200-mg dose, food-effect study	• FTC 2 × 100 mg capsules, PO, single dose (fasted state) (Formulation C) (A) • FTC 1 × 200 mg capsule, PO single dose	3 single doses	Enrolled: 24 Completed: 24 Safety Analysis Set: 24	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				(fasted state) (Formulation B) (B) • FTC 1 × 200 mg capsule, PO, single dose (fed state) (Formulation B) (C)				
Healthy Subject PK and Tolerability	FTC-106 (synopsis)	Evaluate ADME of [^{14}C]FTC, mass balance by urinary and fecal recovery, plasma and PBMCs (FTC-triphosphate)	Phase 1, open-label, single-dose and 8-day repeated doses of FTC (with a single [^{14}C]FTC dose) in healthy adult volunteers	• Day 1: 200 mg single dose PO (N = 6) • Days 3−11: 200 mg QD PO for 8 days, single 250 µCi [^{14}C]FTC dose PO on the last day (N = 5)	11 days	Enrolled: 6 Completed: 5 Safety Analysis Set: 6	Healthy male subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	Burroughs Wellcome 143-001 (synopsis)	Assess the safety, PK, and effect of food on the BA of FTC	Phase 1, randomized, single-blind, single-dose, placebo-controlled, escalating doses (100 to 1200 mg)	• Single escalating oral doses of FTC administered as capsules: 100, 200, 400 (± food), 800, and 1200 mg, PO • Placebo, PO	6 total doses, each given 1 week apart	Enrolled: 18 Active: 12 Placebo: 6 Completed: 17	HIV-infected adult subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	FTC-101 (synopsis)	Evaluate the safety, tolerance, PK, and antiviral activity of repeat doses of FTC	Phase 1, open-label, dose-ranging study with 14 days of repeated doses of monotherapy	Multiple escalating oral doses of FTC administered as capsules for: 25 mg BID (N=9) 100 mg BID (N=8)	14 days	Enrolled: 41 Completed: 41	HIV-infected, therapy-naive adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				200 mg BID (N=8) 100 mg QD (N=8) 200 mg QD (N=8)				
Patient PK and Initial Tolerability	FTC-102 (synopsis)	Safety, antiviral activity, dose-defining, comparison with 3TC	Phase 1/2, randomized, open-label, 3TC-controlled, 3 doses of FTC, 10-day repeated doses of monotherapy in adult HIV infected, ART-naive patients	• FTC 25 mg QD PO (N = 20) (A) • FTC 100 mg QD PO (N = 21) (B) • FTC 200 mg QD PO (N = 19) (C) • 3TC 150 mg BID PO (N = 21) (D)	10 days	As treated: 81 Completed: 81 Safety Analysis Set: 81	HIV-infected adult subjects	Study completed; Final CSR
Intrinsic Factor PK	FTC-107 (synopsis)	Assess the PK profiles in subjects with various degrees of renal insufficiency (for potential dosage adjustment) and effect of hemodialysis	Phase 1, open-label, single-dose study of FTC in adult volunteers with varying degrees of renal insufficiency without and with hemodialysis	One single dose of FTC 200 mg administered PO in capsule formulation to: • Group 1 (normal renal function, CL_{cr} > 80 mL/min, N=6) • Group 2 (mild renal impairment, CL_{cr} = 50−80 mL/min, N=6) • Group 3 (moderate renal impairment, CL_{cr} = 30−49 mL/min, N=6) • Group 4 (severe renal impairment,	1−2 single doses	Enrolled: 29 Completed: 29	Adult subjects with varying degrees of renal insufficiency with and without hemodialysis	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				CL_{cr} < 30 mL/min, N=5) • Group 5 (end-stage renal disease, requiring hemodialysis, N=6) For Group 5 subjects, a second FTC 200 mg dose PO was administered ~1.5 hour before the start of a 3-hour hemodialysis				
Intrinsic Factor PK	FTCB-101 (synopsis)	Assess the safety, tolerance, antiviral activity, and PK of FTC	Phase 1, open-label, dose-escalation, multiple repeat doses, 8 week study	• FTC 25 mg QD PO • FTC 50 mg QD PO • FTC 100 mg QD PO • FTC 200 mg QD PO • FTC 300 mg QD PO	56 days with 28 day follow up	Enrolled: 49 Completed: 45 Safety Analysis Set: 49	HBV-infected adult subjects	Study completed; Final CSR
Extrinsic Factor PK	FTC-103 (synopsis)	Evaluate PK interactions of FTC, ZDV, and d4T	Phase 1, randomized, open-label, single-dose, 3-period crossover study	Subjects were assigned to 1 of 2 treatment cohorts, then randomized into 1 of 3 single oral dosing sequences per cohort in a 3-period crossover design	3 single doses (Days 1, 3, and 5)	Enrolled: 13 Completed: 12 Safety Analysis Set: Cohort 1: 6 Cohort 2: 7	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				using treatments as follows: Cohort 1: • FTC 200 mg • ZDV 300 mg • Combination of FTC 200 mg and ZDV 300 mg Cohort 2: • FTC 200 mg • d4T 40 mg • Combination of FTC 200 mg and d4T 40 mg				
Extrinsic Factor PK	FTC-108 (synopsis)	Assess potential PK interactions with concomitant antiviral drug (ie, famciclovir) with extensive renal excretion	Phase 1, randomized, open-label, single-dose, 3-way crossover study	3 single crossover doses (all PO) of: • FTC 200 mg alone • FCV 500 mg alone • FTC 200 mg + FCV 500 mg 1-week washout interval between doses	Single dose	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	FTC-114 (synopsis)	Evaluate the steady-state PK interaction of FTC and TDF when administered alone and in combination	Single-center, open-label, randomized, 3-way crossover study	Subjects received each of the following 3 treatments: • FTC 200 mg QD (A) • TDF 300 mg	21 days (7 days/treatment)	Enrolled: 19 Completed: 17 Safety Analysis Set: 19	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				QD (B) • FTC 200 mg + TDF 300 mg QD (C)				
Extrinsic Factor PK	GS-US-174-0105 (synopsis)	Evaluate the PK interactions between FTC/TDF FDC and TCL when administered alone and together	Single-center, open-label, randomized, 3-way crossover study	Subjects received each of the following treatments: • FTC/TDF (200/300 mg) QD PO • TCL 0.1 mg/kg/day in 2 divided doses BID PO	21 days (7 days FTC/TDF FDC, 7 days TCL, 7 days FTC/TDF FDC + TCL)	Enrolled: 31 Completed: 21 Safety Analysis Set: 31	Healthy adult subjects	Study completed; Final CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-303 (synopsis)	Compare FTC to 3TC in HIV-infected subjects with copies/mL (HIV-1 RNA ≤ 400) on a stable (≥ 12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI	Phase 3, randomized (2:1) open-label, multi-center equivalence study	• Subjects switch from 3TC to FTC PO while continuing on current background therapy (A) • Subjects continue on current 3TC-containing regimen (B)	48 weeks	Randomized: 459 ITT: 440 A: 294 B: 146	HIV-infected, 3TC-experienced, adult subjects with stable HIV-1 RNA	Study completed; Final CSR and Addendum
Uncontrolled Clinical Studies	FTC 203 (synopsis)	Obtain long-term safety, PK, and antiviral activity of FTC in pediatric subjects	Phase 2, multicenter, open-label study in ART-naive and ART-experienced male or female	ART-naive (triple-drug ART regimen): • FTC (6 mg/kg QD; up to 200 mg	96 weeks	Enrolled: 117 ITT: 116 ART-naive: 71 ART-experienced: 45	Pediatric subjects (3 mo-17 y) with HIV infection, $CD4^+$ > 200 cells/mm^3	Study completed; Final Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
			pediatric patients. ART-naive patients had no or very limited prior ART exposure.	capsule or 240 mg oral solution QD) • d4T (mg/kg BID dosage based on weight): 1 mg/kg (< 30 kg); 30 mg/kg (30-59 kg); 40 mg/kg (≥ 60 kg) • LPV/r (mg/kg BID dosage based on weight): 12/3 mg/kg (7- < 15 kg); 10/2.5 mg/kg (15-40 kg); 400/100 mg/kg (> 40 kg) ART-experienced: • FTC (same dosage as above) plus background ART medications (no 3TC) No control regimen		Age groups: 3–24 mo: 16 25 mo–6 y: 68 7–12 y: 29 13–17 y: 3	ART-naive: Plasma copies/mL (HIV-1 RNA 5,000-600,000) ART-experienced: Copies/mL (HIV-1 RNA ≤ 400), stable on 3TC regimen for ≥ 3 mo	

6.2. Pharmacokinetic, Pharmacokinetic/Pharmacodynamic and Ad Hoc Analyses

The following outputs present data from E/C/F/TAF PK/PD analyses.

E/C/F/TAF PK/PD Table 1.1	Plasma TAF PK Parameters from Population PK Modeling by Subject with Summary Statistics for Each Parameter, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 1.2	Plasma TFV PK Parameters from Population PK Modeling by Subject with Summary Statistics for Each Parameter, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 2.1	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Algorithm) by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 3.1.1	Summary for TAF AUCtau by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 3.1.2	Summary for TAF Cmax by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 3.2.1	Summary for TFV AUCtau by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 3.2.2	Summary for TFV Cmax by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 4.1.1	Summary of TAF PK Parameters by Selected Adverse Event, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 4.1.2	Percentage of Subjects with Selected Adverse Events by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 4.2.1	Summary of TFV PK Parameters by Selected Adverse Event, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 4.2.2	Percentage of Subjects with Selected Adverse Events by TFV AUCtau and Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 5.1	Summary of Maximum Increase from Baseline in Serum Creatinine by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 5.2	Summary of Maximum Increase from Baseline in Serum Creatinine by TFV AUCtau and Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 6.1.1	Summary of Change from Baseline at Week 48 in Fasting Total Cholesterol by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Table 6.1.2	Summary of Change from Baseline at Week 48 in Fasting LDL by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 6.1.3	Summary of Change from Baseline at Week 48 in Fasting HDL by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 6.2.1	Summary of Change from Baseline at Week 48 in Fasting Total Cholesterol by TFV AUCtau and Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 6.2.2	Summary of Change from Baseline at Week 48 in Fasting LDL by TFV AUCtau and Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 6.2.3	Summary of Change from Baseline at Week 48 in Fasting HDL by TFV AUCtau and Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 7.1.1	Summary of Percentage Change from Baseline at Week 48 in Hip BMD by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 7.1.2	Summary of Percentage Change from Baseline at Week 48 in Spine BMD by TAF AUCtau and Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Table 7.2.1	Summary of Percentage Change from Baseline at Week 48 in Hip BMD by TFV AUCtau and Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Table 7.2.2	Summary of Percentage Change from Baseline at Week 48 in Spine BMD by TFV AUCtau and Cmax Quartile Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Figure 1.1.1	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Algorithm) by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Figure 1.1.2	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Algorithm) by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Figure 2.1.1	Box Plot of TAF AUCtau by Selected Adverse Events Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Figure 2.1.2	Box Plot of TAF Cmax by Selected Adverse Events Subgroup, TAF PK/PD Analysis Set
E/C/F/TAF PK/PD Figure 2.2.1	Box Plot of TFV AUCtau by Selected Adverse Events Subgroup, TFV PK/PD Analysis Set
E/C/F/TAF PK/PD Figure 2.2.2	Box Plot of TFV Cmax by Selected Adverse Events Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.1.1 Percentage of Subjects with Diarrhoea by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.1.2 Percentage of Subjects with Nausea by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.1.3 Percentage of Subjects with Vomiting by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.1.4 Percentage of Subjects with GI/Abdominal Pain by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.2.1 Percentage of Subjects with Diarrhoea by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.2.2 Percentage of Subjects with Nausea by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.2.3 Percentage of Subjects with Vomiting by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.1.2.4 Percentage of Subjects with GI/Abdominal Pain by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.1.1 Percentage of Subjects with Diarrhoea by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.1.2 Percentage of Subjects with Nausea by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.1.3 Percentage of Subjects with Vomiting by TFV AUCtau Quartile Subgroup, TFV, PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.1.4 Percentage of Subjects with GI/Abdominal Pain by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.2.1 Percentage of Subjects with Diarrhoea by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.2.2 Percentage of Subjects with Nausea by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.2.3 Percentage of Subjects with Vomiting by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 3.2.2.4 Percentage of Subjects with GI/Abdominal Pain by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 4.1.1 Box Plot of Maximum Increase from Baseline in Serum Creatinine by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 4.1.2 Box Plot of Maximum Increase from Baseline in Serum Creatinine by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 4.2.1 Box Plot of Maximum Increase from Baseline in Serum Creatinine by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 4.2.2 Box Plot of Maximum Increase from Baseline in Serum Creatinine by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.1.1.1 Box Plot of Change from Baseline at Week 48 in Fasting Total Cholesterol by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.1.1.2 Box Plot of Change from Baseline at Week 48 in Fasting LDL by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.1.1.3 Box Plot of Change from Baseline at Week 48 in Fasting HDL by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.1.2.1 Box Plot of Change from Baseline at Week 48 in Fasting Total Cholesterol by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.1.2.2 Box Plot of Change from Baseline at Week 48 in Fasting LDL by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.1.2.3 Box Plot of Change from Baseline at Week 48 in Fasting HDL by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.2.1.1 Box Plot of Change from Baseline at Week 48 in Fasting Total Cholesterol by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.2.1.2 Box Plot of Change from Baseline at Week 48 in Fasting LDL by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.2.1.3 Box Plot of Change from Baseline at Week 48 in Fasting HDL by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.2.2.1 Box Plot of Change from Baseline at Week 48 in Fasting Total Cholesterol by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.2.2.2 Box Plot of Change from Baseline at Week 48 in Fasting LDL by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 5.2.2.3 Box Plot of Change from Baseline at Week 48 in Fasting HDL by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.1.1.1 Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.1.1.2 Box Plot of Percent Change from Baseline at Week 48 in Spine BMD by TAF AUCtau Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.1.2.1 Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.1.2.2 Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TAF Cmax Quartile Subgroup, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.2.1.1 Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.2.1.2 Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TFV AUCtau Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.2.2.1 Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Figure 6.2.2.2 Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TFV Cmax Quartile Subgroup, TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Listing 1 TAF PK Parameters and Selected Efficacy Endpoints at Week 48, TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Listing 2.1.1 TAF PK Parameters and Selected Safety Endpoints (Part 1), TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Listing 2.1.2 TAF PK Parameters and Selected Safety Endpoints (Part 2), TAF PK/PD Analysis Set

E/C/F/TAF PK/PD Listing 2.2.1 TFV PK Parameters and Selected Safety Endpoints (Part 1), TFV PK/PD Analysis Set

E/C/F/TAF PK/PD Listing 2.2.2 TFV PK Parameters and Selected Safety Endpoints (Part 2), TFV PK/PD Analysis Set

The following outputs present data from ad hoc analyses.

Pooled Data from E/C/F/TAF Studies GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111

Ad Hoc Table 6875.1	Plasma TFV Pharmacokinetic Parameters by Subject and Treatment with Summary Statistics for Each Parameter, PK Substudy Analysis Set
Ad Hoc Table 6875.2	PBMC TFV-DP Pharmacokinetic Parameters by Subject and Treatment with Summary Statistics for Each Parameter, PBMC PK Analysis Set
Ad Hoc Table 6875.3	Statistical Comparisons of Pharmacokinetic Parameter Estimates Between Test and Reference Treatments, All Substudy PK Analysis Set
Ad Hoc Figure 6875.1	Mean (+/- 1 SD) Plasma TFV Concentrations: Linear and Semi-Log Scales, PK Substudy Analysis Set
Ad Hoc Figure 6875.2	Mean (+/- 1 SD) PBMC TFV-DP Concentrations (ng/million cells): Linear and Semi-Log Scales, PBMC PK Analysis Set
Ad Hoc Figure 6875.3	Median (Q1, Q3) Plasma TFV Concentrations: Linear and Semi-Log Scales, PK Substudy Analysis Set
Ad Hoc Figure 6875.4	Median (Q1, Q3) PBMC TFV-DP Concentrations (ng/million cells): Linear and Semi-Log Scales, PBMC PK Analysis Set

Pooled Data from E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111

Ad Hoc Table 6905.1	Plasma TFV Pharmacokinetic Parameters by Subject and Treatment with Summary Statistics for Each Parameter, PK Substudy Analysis Set
Ad Hoc Table 6905.2	PBMC TFV-DP Pharmacokinetic Parameters by Subject and Treatment with Summary Statistics for Each Parameter, PBMC PK Analysis Set
Ad Hoc Table 6905.3	Statistical Comparisons of Pharmacokinetic Parameter Estimates Between Test and Reference Treatments, All Substudy PK Analysis Set
Ad Hoc Figure 6905.1	Mean (+/- 1 SD) Plasma TFV Concentrations: Linear and Semi-Log Scales, PK Substudy Analysis Set
Ad Hoc Figure 6905.2	Mean (+/- 1 SD) PBMC TFV-DP Concentrations (ng/million cells): Linear and Semi-Log Scales, PBMC PK Analysis Set
Ad Hoc Figure 6905.3	Median (Q1, Q3) Plasma TFV Concentrations: Linear and Semi-Log Scales, PK Substudy Analysis Set
Ad Hoc Figure 6905.4	Median (Q1, Q3) PBMC TFV-DP Concentrations (ng/million cells): Linear and Semi-Log Scales, PBMC PK Analysis Set

PK/PD Analyses from E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111

Ad Hoc Table 6918.1.1.1	Logistic Regression of Nausea (Present/Absent) by TAF AUCtau, TAF PK/PD Analysis Set
Ad Hoc Table 6918.1.1.2	Logistic Regression of Nausea (Present/Absent) by TAF Cmax, TAF PK/PD Analysis Set
Ad Hoc Table 6918.1.2.1	Logistic Regression of Vomiting (Present/Absent) by TAF AUCtau, TAF PK/PD Analysis Set
Ad Hoc Table 6918.1.2.2	Logistic Regression of Vomiting (Present/Absent) by TAF Cmax, TAF PK/PD Analysis Set
Ad Hoc Table 6918.2.1.1	Logistic Regression of Nausea Severity by TAF AUCtau in Subjects who Experienced Nausea, TAF PK/PD Analysis Set
Ad Hoc Table 6918.2.1.2	Logistic Regression of Nausea Severity by TAF Cmax in Subjects who Experienced Nausea, TAF PK/PD Analysis Set
Ad Hoc Table 6918.2.2.1	Logistic Regression of Vomiting Severity by TAF AUCtau in Subjects who Experienced Vomiting, TAF PK/PD Analysis Set
Ad Hoc Table 6918.2.2.2	Logistic Regression of Vomiting Severity by TAF Cmax in Subjects who Experienced Vomiting, TAF PK/PD Analysis Set
Ad Hoc Table 6921.1	CART Analysis Determining Cutoffs for Nausea and Vomiting for TAF AUCtau and Cmax using JMP, TAF PK/PD Analysis Set

TAF Population PK Analyses

Ad Hoc Table 6919.1.1	TAF PK Parameters After Once Daily Administration of E/C/F/TAF in HIV Infected Subjects by Renal Function, TAF Population PK
Ad Hoc Table 6919.1.2	TFV PK Parameters After Once Daily Administration of E/C/F/TAF in HIV Infected Subjects by Renal Function TFV Population PK
Ad Hoc Table 6919.2	Baseline Weight and Age, TFV Population PK

Integrated Ad Hoc Pharmacokinetic Analysis

Table 1.1	Summary Statistics for TAF Pharmacokinetic Parameters by Study, TAF PK Analysis Set
Table In-text1	Single- and Multiple-Dose PK of TAF Following Administration of Unboosted TAF 25 mg or Boosted TAF 10 mg, TAF PK Analysis Set
Table In-text2	Single- and Multiple-Dose PK of TFV Following Administration of Unboosted TAF 25 mg or Boosted TAF 10 mg, TFV PK Analysis Set
Table In-text3	Means (%CV) of TAF Exposure by Covariate Following Administration of Unboosted TAF 10 mg, TAF PK Analysis Set

The following outputs present data from STB PK/PD analyses.

STB PK/PD Table 2.3	Plasma FTC PK Parameters from PK Substudies by Subject with Summary Statistics for Each Parameter, Subjects in PK Substudies
STB PK/PD Figure 4.1	Box Plot of FTC AUCtau (ng*h/mL) by Selected Adverse Events Subgroup, FTC PK/PD Analysis Set
STB PK/PD Figure 4.2	Box Plot of FTC Cmax (ng/mL) by Selected Adverse Events Subgroup, FTC PK/PD Analysis Set
STB PK/PD Figure 8.1	Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by FTC AUCtau (ng*h/mL) Quartile Subgroup, FTC PK/PD Analysis Set
STB PK/PD Figure 8.3	Box Plot of Maximum Decrease from Baseline in eGFR(CG) (mL/min) by FTC AUCtau (ng*h/mL) Quartile Subgroup, FTC PK/PD Analysis Set

6.3. Tabular Summary of Applicable Nonclinical Virology Studies

6.3.1. TAF Studies

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Primary Pharmacodynamics					
Drug Combination Studies with TAF	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2002
Antiviral Activity of TAF and TFV Against a Panel of Animal Viruses	No	In Vitro	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2003
Profiling of TAF Antiviral Activity Against HIV-1 and HIV-2 Clinical Isolates in Primary Cells	No	Primary Cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2004
Cytotoxicity Assay with TAF	No	MT-2, MT-4, and HepG2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2007
Cytotoxic Effect of TAF on PBMCs	No	PBMCs	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2009
TAF In Vitro Resistance Selection Studies with Wild-Type HIV-1 Isolates	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2011
TAF In Vitro Resistance Selection Studies with TDF-Resistant HIV-1 Isolates	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2012
In Vitro Evaluation of TAF Resistance Barrier	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2013
In Vitro Resistance Profile of TAF Against Patient-Derived Recombinant HIV-1 Isolates	No	Recombinant HIV-1 Clinical Isolates	In Vitro	[redacted] USA	PC-120-2014
Comparison of TAF Resistance Profile in Multiple In Vitro Assays	No	In Vitro	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2015
Effect of TAF on CatA Hydrolase Activity and TAF Antiretroviral Activity	No	Purified CatA, primary CD4+, T-lymphocytes, MDMs	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2017

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Antiviral Activity and Cytotoxicity of TAF Metabolites	No	MT-2 and MT-4 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2021

a An entry of "Yes" indicates that the study includes a Good Laboratory Practice (GLP) compliance statement.

6.3.2. TDF Studies

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
TDF Primary Pharmacodynamics				
Mechanism of action (activation of tenofovir via phosphorylation)	Human T lymphoid cells (CEMss, CEMss^{r-1})	In vitro	[redacted], USA	Antimicrob Agents Chemother 1995 Oct;39(10):2304–8 {4887}
Antiviral activity of vs wild-type HIV_{IIIB} and evaluation of cytotoxicity	Human resting/activated PBMCs and T lymphocyte (MT-2) cells	In vitro	[redacted], USA	Antimicrob Agents Chemother 1998 Mar;42(3):612–7 {1574}
Mechanism of action (intracellular metabolism): In vitro phosphorylation of tenofovir and abacavir	CEM-CCRF cells	In vitro	Gilead Sciences, Inc., USA	PC-104-2008
Mechanism of action (intracellular metabolism): Role of purine nucleoside phosphorylase in drug interactions between 2′,3′-dideoxyinosine and allopurinol, ganciclovir, or tenofovir	CEM-CCRF cells and activated PBMCs	In vitro	Gilead Sciences, Inc., USA	Antimicrob Agents Chemother 2004;48(4):1089–95 {6054}
Mechanism of action (intracellular metabolism): Effect of tenofovir in combination with other anti-HIV nucleoside reverse transcriptase inhibitors (NRTIs) on intracellular nucleotide pools	CEM-CRFF cells	In vitro	Gilead Sciences, Inc., USA	45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Poster H-1901 {8573}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
Mechanism of action (intracellular metabolism in vitro following in vivo dosing)	PBMCs Macaque monkeys	In vitro In vivo, subcutaneous (SC)	[redacted], USA	P2001025
Inhibitory effects of tenofovir & TDF on human HIV_{IIIB} RT and human DNA polymerases	HIV_{IIIB} RT, human DNA polymerase (α, β, γ)	In vitro	Gilead Sciences, Inc., USA	Antiviral Chemistry and Chemotherapy 1995;6(4):217–21 {1131}
Structural features of acyclic nucleotide analogs conferring inhibitory effects on cellular replicative DNA polymerases	In vitro	In vitro	Gilead Sciences Inc., USA	Institute of Organic Chemistry and Biochemistry, Academy of Sciences of Czech Republic 1996;1:188–91 {2516}
Incorporation into DNA by DNA polymerase	Primer template DNA, DNA polymerases (α, β, γ)	In vitro	Gilead Sciences, Inc., USA	Antiviral Chemistry and Chemother 1997 May;8(3):187–95 {2005}
Antiviral activity of tenofovir vs HIV-1 non-B subtypes (A, C, D, E, F, G, O) and HIV-1 isolates with nucleoside-associated resistance	PBMCs	In vitro	Gilead Sciences, Inc., USA and [redacted], USA	AIDS Res Hum Retroviruses 2001;17:1167–73 {5044}.
Antiviral activity and resistance properties vs wild type HIV_{IIIB}	MT-2 cells	In vitro	[redacted], Canada	Antiviral Therapy 1999;4(2):87–94 {2078}
Selection of resistant virus with subtype C HIV-1	Cord blood mononuclear cells	In vitro	[redacted]	AIDS 2006;20(9):F9–F13 {9276}
Antiviral activity vs HIV-1 expressing the K70E mutation	Clinical isolates from AIDS patients treated with adefovir dipivoxil long-term therapy	In vitro	Gilead Sciences, Inc., USA	Antimicrob Agents Chemother 1998 Jul;42(7):1620–8 {1648}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
Molecular mechanism by which the K70E mutation in HIV-1 reverse transcriptase confers resistance to NRTIs	In vitro	In vitro	[redacted], USA	Antimicrob Agents Chemother 2007;51:48–53 {10898}
HIV-1: resistance to nucleoside analogues and replication capacity in primary human macrophages	Primary human macrophages	In vitro	[redacted], France	J. Virol 2007;81:4540–4550 {11307}
A combination of decreased NRTI incorporation and decreased excision determines the resistance profile of HIV-1 K65R RT	MT-2 cells, RT enzyme assay	In vitro	Gilead Sciences Inc., USA	AIDS 2005;19:1751–1760 {7583}
Effects of the translocation status of HIV-1 reverse transcriptase on the efficiency of excision of tenofovir	RT enzyme assay	In vitro	[redacted], Canada and Gilead Sciences Inc., USA	Antimicrob Agents Chemother 2007;51:2911–2919 {11304}
The K65R reverse transcriptase mutation in HIV-1 reverses the excision phenotype of ZDV resistance mutations	MT-2 cells, RT enzyme assay	In vitro	Gilead Sciences Inc., USA	Antiviral Ther 2006;11:155–163 {8925}
Antagonism between the HIV-1 reverse transcriptase mutation K65R and TAMs at the genomic level	In vitro	In vitro	[redacted], USA	J Infec Dis 2006,194:651–660 {9494}
Molecular mechanisms of bidirectional antagonism between K65R and TAMs in HIV-1 RT	In vitro	In vitro	[redacted], USA	AIDS 2007;21:1405–1414 {11306}
The K65R mutation in HIV-1 reverse transcriptase exhibits bidirectional phenotypic antagonism with TAMs	In vitro	In vitro	[redacted], USA	J Virol 2006,80:4971–4977 {9037}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
Coexistence of the K65R/L74V and/or K65R/T215Y mutations on the same HIV-1 genome	In vitro	In vitro	[redacted], France	J Clin Virol 2006;37:227–230 {10318}
The A62V and S68G mutations in HIV-1 reverse transcriptase partially restore the replication defect associated with the K65R mutation	MT-2 cells, RT enzyme assay	In vitro	Gilead Sciences Inc., USA	J Acquir Immune Defic Syndr 2008;48:428–436 {12688}
Diminished efficiency of HIV-1 reverse transcriptase containing the K65R and M184V drug resistance mutations	In vitro	In vitro	[redacted], Canada	AIDS 2007;21:665–675 {10671}
The balance between NRTI discrimination and excision drives the susceptibility of HIV-1 RT mutant K65R, M184V, and K65R+M184V	MT-2 cells, RT enzyme assay	In vitro	Gilead Sciences Inc., USA	Antivir Chem Chemother 2008;18:307–316 {12142}
Molecular basis of antagonism between K70E and K65R tenofovir-associated mutations in HIV-1 reverse transcriptase	In vitro	In vitro	[redacted], USA; [redacted] USA; [redacted], USA; and [redacted], USA	Antivir Res 2007;75:210–218 {11303}
Mechanistic basis for reduced viral and enzymatic fitness of HIV-1 reverse transcriptase containing both K65R and M184V mutations	In vitro	In vitro	[redacted], France and Gilead Sciences Inc., USA	J Biol Chem 2004;279:509–516 {5476}
Antiviral activity vs drug resistant HIV variants	Clinical isolates of drug resistant HIV-1 variants, MT-2 cells	In vitro	[redacted], USA	Antimicrob Agents. Chemother 1998;42:1484–7 {2191}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
Patterns of HIV resistance of clinical isolates from Study GS-96-408	MT-2 cells	In vitro	Gilead Sciences, Inc., USA	JAIDS 2001;27:450–8 {3200}
Antiviral activity vs HIV-1 variants from clinical isolates	MOLT-4 cells, PBMCS, and H9 cells	In vitro	[redacted], USA	Proc Natl Acad Sci USA 1995;92:2398–2402 {2064}
Unblocking of chain-terminated primer by HIV-1 reverse transcriptase	In vitro	In vitro	[redacted], USA	Proc Natl Acad Sci 1998 Nov;95(23):13471–6 {2043}
Unblocking of chain-terminated primer by HIV-1 reverse transcriptase	In vitro	In vitro	Gilead Sciences, Inc., USA	XIV International Roundtable on Nucleosides, Nucleotides and their Biological Applications; 2000; San Francisco, CA {2252}
Antiviral activity and replication capability vs HIV-1 expressing the 3TC-associated M184V mutation	MT-2 cells and PBMCs	In vitro	Gilead Sciences, Inc., USA	J Infect Dis 1999 Jan;179(1):92–100 {1649}
Effects of K65R mutation on HIV-1 replication capacity	293T cells	In vitro	[redacted], USA	PC-104-2004
Antiviral activity vs wild-type and drug-resistant HIV-1	MT-4 cells	In vitro	[redacted], Belgium and Gilead Sciences, Inc., USA	Antimicrob Agents Chemother 2002 Apr;46(4):1067–72. {3961}
Protein binding of cidofovir, cyclic HPMPC, PMEA, and PMPA in human plasma and serum	In vitro	In vitro	Gilead Sciences, Inc., USA	P0504-00039.1

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
TDF Secondary Pharmacodynamics				
Antiviral activity vs human HBV	Human hepatoblastoma cell line (HB611)	In vitro	[redacted], Japan	Antiviral Chemistry and Chemother 1994;5(2):57–63. {21}
Antiviral activity vs human HBV and duck HBV	Human hepatoma cell line HepG2, primary duck hepatocytes	In vitro	[redacted], Holland, Belgium	Antimicrob Agents Chemother 1994 Sep;38(9):2180–2 {10}
Antiviral activity vs 3TC-resistant human HBV	HepG2 cells	In vitro	Gilead Sciences, Inc., USA	Antiviral Therapy 2005;10:625–33 {8381}
Antiviral activity vs wild type and 3TC-resistant human HBV	HepG2, HepAD38, and HepAD79 cells	In vitro	Gilead Sciences, Inc., USA	P4331-00038
Antiviral activity against HBV with the rtA194T mutation	HepG2 cells	In vitro	Gilead Sciences, Inc., USA	PC-104-2012
Antiviral activity against HBV with entecavir-associated resistance mutations	HepG2 cells	In vitro	[redacted]	PC-174-2003
TDF Pharmacodynamic Drug Interactions				
Antiviral activity in combination with other antiretroviral drugs	MT-2 cells	In vitro	Gilead Sciences, Inc., USA	PC-183-2004

6.3.3. FTC/TDF Studies

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
FTC/TDF Primary Pharmacodynamics				
Phosphorylation of tenofovir and FTC	CEM CRFF cells	In vitro	Gilead Sciences, Inc., USA	PC-164-2001
Selection of resistant HIV-1 with combinations of tenofovir and FTC	MT-2 cells	In vitro	Gilead Sciences, Inc., USA	PC-164-2005
Antiviral activity of the combination of tenofovir and FTC	SIV-infected rhesus monkeys	SC	[redacted], USA	Journal of Virology 2003;77:4938–4949 {5477}
Intermittent antiretroviral prophylaxis with tenofovir and FTC protects macaques against repeated rectal SHIV exposures	SHIV-challenged rhesus monkeys	SC	[redacted], USA; [redacted], USA	16th International HIV Resistance Workshop, 2007, Barbados, Abstract 85 {11074}
FTC/TDF Pharmacodynamic Drug Interactions				
Antiviral activity in combination with other antiretroviral drugs	MT-2 cells	In vitro	Gilead Sciences, Inc., USA	PC-164-2002
Antiviral HIV-1 dual drug combination study of FTC, RPV, and TFV	MT-2 cells	In Vitro	Gilead Sciences, Inc., USA	PC-264-2001

6.3.4. FTC Studies

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
FTC Primary Pharmacodynamics				
Phosphorylation of FTC	Calf thymus deoxycytidine kinase	In vitro	[redacted] USA	TESF/91/0014
Phosphorylation of FTC	Calf thymus deoxycytidine kinase	In vitro	[redacted] USA	TESF/92/0002
Phosphorylation of FTC	dCMP kinase and nucleoside monophosphate kinase	In vitro	[redacted] USA	TEIT/92/0005
Phosphorylation of FTC	Nucleoside monophosphate kinase and nuclear diphosphate kinase	In vitro	[redacted] USA	TGZZ/93/0025
Inhibition of HIV-1 reverse transcriptase	Endogenous RT assay Chain-termination substrate assays Purified HIV-1 reverse transcriptase enzyme assay	In vitro	[redacted]	Antimicrob Agents Chemother 1993;37:1270–2 {4249}
Inhibition of HIV-1 reverse transcriptase	Pre–steady-state kinetic analysis of HIV-1 reverse transcriptase	In vitro	Gilead Sciences, Inc., USA	FASEB J 1999;13:1511-7 {4545}
Antiviral activity vs HIV-1 and HIV-2	Human PBMCs and various T cell lines	In vitro	[redacted]	Antimicrob Agents Chemother 1992;36:2423–31 {4534}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
Antiviral activity vs HIV-1	Human PBMCs, human T-cell lines MT-2 and CEM	In vitro	Gilead Sciences, Inc., USA	TPI 462 v2
Antiviral activity against various subtypes of HIV-1	Human PBMCs	In vitro	Gilead Sciences, Inc., USA	TPI 10498 v2
Antiviral activity against various subtypes of HIV-1	HeLa cells	In vitro	Gilead Sciences, Inc., USA	TPI 11419 v2
MAGI-LU assay validation 1: Inhibitory effect of FTC on HIV-1 xxLAI viral infection is independent of MOI of the infecting virus	MAGI cells	In vitro	Gilead Sciences, Inc., USA	10518 v2
Effect of MOI on inhibition of HIV-1 replication by FTC	Human PBMCs	In vitro	Gilead Sciences, Inc., USA	11773
DXG, FTC, and ZDV: Time of addition	MAGI cells	In vitro	Gilead Sciences, Inc., USA	10247
Effect of human serum on the antiviral activity of FTC assessed in CEM cells infected with the LAI strain of HIV-1	CEM cells	In vitro	Gilead Sciences, Inc., USA	463
Selection of FTC resistant virus	Human T-cell lines, MT-4 cells	In vitro	[redacted] USA	Proc Natl Acad Sci USA 1993;90:5653–5656 {1794}
Selection of FTC resistant virus	Human PBMCs	In vitro	[redacted], USA	Antimicrob Agents Chemother 1993;37:875–881 {1777}
Antiviral activity vs nucleoside reverse transcriptase inhibitor-resistant recombinant HIV-1 clinical isolates	MT-4 cells	In vitro	[redacted], Belgium	TPI 11148
Activity against drug-resistant HIV-1 with K65R mutation	Recombinant mutant enzymes and viruses in MT-2 cells	In vitro	Gilead Sciences, Inc., USA	TPI 15883

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
Virologic and enzymatic studies revealing the mechanism of K65R- and Q151M-associated HIV-1 drug resistance towards FTC and lamivudine (3TC)	MT-2 cells and in vitro	In vitro	Gilead Sciences, Inc., USA	Nucleosides, Nucleotides, and Nucleic Acids 2006;25:89–107 {8887}
Metabolism of FTC	$HepG_2$ 2.2.15 (P5A) cells	In vitro	[redacted] USA	TEZA/92/0062
Metabolism of FTC	CEM T-lymphoblast cells	In vitro	[redacted] USA	TEZA/92/0103
Metabolism of FTC in hepatitis B infected cells	HepG2 (human hepatocellular carcinoma) cells	In vitro	[redacted] USA	TEZA/92/0111
Effect of FTC on human DNA polymerase	HeLa S3 cells and purified human polymerases α, β, γ, and ε	In vitro	[redacted] USA	TEZZ/93/0007
Effect of FTC on human polymerase γ	Human polymerase γ	In vitro	Gilead Sciences, Inc., USA	TPI 9501
Effect of orally administered FTC and lamivudine in the HuPBMC-SCID mouse model of HIV-1 infection	HuPBMC-SCID mouse model of HIV-1 infection	Oral	Gilead Sciences, Inc., USA	TPI 11985
Antiviral activity of FTC in vivo	HuPBMC-SCID mouse model of HIV-1 infection	Intraperitoneal (IP)	[redacted], USA	2nd International Workshop on HIV Drug Resistance and Treatment Strategies, 1998, Lake Maggiore, Italy, Abstract 9 {4525}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
FTC Secondary Pharmacodynamics				
Antiviral activity vs human hepatitis B virus (HBV), Cytotoxicity	Human hepatoma cell line HepG2.2.15	In vitro	[redacted], USA	Antimicrob Agents Chemother 1994;38:2172–2174 {4533}
Antiviral activity vs human hepatitis B virus (HBV)	Human hepatoma cell line HepG2.2.15	In vitro	[redacted], USA	{6287}
Antiviral activity vs human hepatitis B virus (HBV)	Human hepatoma cell line HepG2.2.15	In vitro	[redacted], Australia	{6288}
Antiviral activity vs human hepatitis B virus (HBV)	Primary human hepatocytes	In vitro	[redacted] USA	{4532}
Antiviral activity vs human HBV, Cytotoxicity	Human hepatoma cell line HepG2.2.15	In vitro	[redacted] USA	Antimicrob Agents Chemother 1992;36:2686–2692 {4535}
Effect on HBV replication in vivo	Mouse	Oral	[redacted] USA	Antimicrob Agents Chemother 1994;38:616–619 {4530}
Effect on HBV replication in vivo	In vitro	In vitro	[redacted], USA	{4539}
Effect on HBV replication in vivo	SCID mouse	IP	[redacted], USA	Frontiers in Viral Hepatitis 2002. Elsevier Science, Printed in the Netherlands {6290}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
Effect on HBV replication in vivo	Woodchuck	Oral	[redacted], USA	Antimicrob Agents Chemother 2000;44:1757–1760 {6290}
Effect on HBV replication in vivo	Woodchuck	IP	[redacted], USA	Antimicrob Agents Chemother 1997;41:2076–2082 {6293}
Cytotoxicity assay	Molt-4 cells	In vitro	[redacted], USA	J Biol Chem 264:11934–7 {4249}
FTC Pharmacodynamic Drug Interactions				
Antiviral activity in combination with other antiretroviral drugs	MT 2 cells	In vitro	Gilead Sciences, Inc., USA	470
In vitro synergy studies with FTC and other anti-HIV compounds.	MT 2 cells	In vitro	Gilead Sciences, Inc., USA	10804

6.4. Analyses for Study GS-US-311-1089

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Gilead Sciences, Inc.
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Table 3: Subject Disposition
All Screened Subjects

	F/TAF	FTC/TDF	Total
Subjects Screened			780
Screen Failure Subjects Who Were Not Randomized			79
Subjects Met All Eligibility Criteria and Not Randomized*			33
Subjects Randomized	334	334	668
Subjects Randomized and Never Treated	1	4	5
Subjects in Safety Analysis Set	333	330	663
Subjects in Full (FAS) Analysis Set	333	330	663
Subjects still on Study Treatment up to the Data Cut Date	312 (93.7%)	309 (93.6%)	621 (93.7%)
Subjects Prematurely Discontinuing Study Treatment prior to the Data Cut Date	21 (6.3%)	21 (6.4%)	42 (6.3%)
Reasons for Prematurely Discontinuing Study Treatment			
Adverse Event	7 (2.1%)	3 (0.9%)	10 (1.5%)
Death	0	0	0
Pregnancy	1 (0.3%)	0	1 (0.2%)
Lack of Efficacy	0	0	0
Investigator's Discretion	1 (0.3%)	1 (0.3%)	2 (0.3%)
Non-Compliance with Study Drug	1 (0.3%)	2 (0.6%)	3 (0.5%)
Protocol Violation	0	4 (1.2%)	4 (0.6%)
Withdrew Consent	10 (3.0%)	10 (3.0%)	20 (3.0%)

The denominator for percentages is based on the number of subjects in the safety analysis set.
The number of screen failures is counted by unique subject based on the date of birth, race, ethnicity, sex, country, and initials.
CRF data collected up to [redacted] (except for 9 subjects, [redacted]) and lab data collected up to [redacted] are included in the Week 48 analysis data cut, including data collected after the Week 48 visit.
* Among subjects who met all eligibility criteria and not randomized, 18 were due to withdrawal of consent, 5 due to outside of visit window, 6 due to lost to follow-up, and 4 due to other reasons.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-disposit.sas v9.2 [redacted]:11:05 Page 1 of 2

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 3: Subject Disposition
All Screened Subjects

	F/TAF	FTC/TDF	Total
Lost to Follow-Up	1 (0.3%)	1 (0.3%)	2 (0.3%)
Study Terminated by Sponsor	0	0	0
Subjects still in Study up to the Data Cut Date	315 (94.6%)	316 (95.8%)	631 (95.2%)
Subjects Prematurely Discontinuing from Study prior to the Data Cut Date	18 (5.4%)	14 (4.2%)	32 (4.8%)
Reasons for Prematurely Discontinuing from Study			
Adverse Event	4 (1.2%)	0	4 (0.6%)
Death	0	0	0
Pregnancy	0	0	0
Lack of Efficacy	0	0	0
Investigator's Discretion	1 (0.3%)	0	1 (0.2%)
Non-Compliance with Study Drug	1 (0.3%)	1 (0.3%)	2 (0.3%)
Protocol Violation	0	2 (0.6%)	2 (0.3%)
Withdrew Consent	10 (3.0%)	10 (3.0%)	20 (3.0%)
Lost to Follow-Up	2 (0.6%)	1 (0.3%)	3 (0.5%)
Study Terminated by Sponsor	0	0	0

The denominator for percentages is based on the number of subjects in the safety analysis set.
The number of screen failures is counted by unique subject based on the date of birth, race, ethnicity, sex, country, and initials.
CRF data collected up to [redacted] (except for 9 subjects, [redacted]) and lab data collected up to [redacted] are included in the Week 48 analysis data cut, including data collected after the Week 48 visit.
* Among subjects who met all eligibility criteria and not randomized, 18 were due to withdrawal of consent, 5 due to outside of visit window, 6 due to lost to follow-up, and 4 due to other reasons.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-disposit.sas v9.2 [redacted]:11:05 Page 2 of 2

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Table 5: Demographics and Baseline Characteristics
Safety Analysis Set

	F/TAF (N=333)	FTC/TDF (N=330)	Total (N=663)	F/TAF vs. FTC/TDF p-value
Age (Years)				
N	333	330	663	0.83
Mean (SD)	47 (9.9)	48 (9.7)	48 (9.8)	
Median	48	49	49	
Q1, Q3	42, 54	42, 54	42, 54	
Min, Max	22, 78	22, 79	22, 79	
Sex				
Male	285 (85.6%)	276 (83.6%)	561 (84.6%)	0.49
Female	48 (14.4%)	54 (16.4%)	102 (15.4%)	
Race				
American Indian or Alaska Native	2 (0.6%)	1 (0.3%)	3 (0.5%)	0.21
Asian	6 (1.8%)	0	6 (0.9%)	
Black	69 (20.7%)	67 (20.3%)	136 (20.5%)	
Native Hawaiian or Pacific Islander	2 (0.6%)	1 (0.3%)	3 (0.5%)	
White	244 (73.3%)	253 (76.7%)	497 (75.0%)	
Not Permitted	1 (0.3%)	1 (0.3%)	2 (0.3%)	
Other	9 (2.7%)	7 (2.1%)	16 (2.4%)	
Ethnicity				
Hispanic or Latino	48 (14.4%)	78 (23.6%)	126 (19.0%)	0.003
Not Hispanic or Latino	285 (85.6%)	252 (76.4%)	537 (81.0%)	

The denominator for percentages is based on the number of subjects in the safety analysis set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
For subjects *CO and *CP , race was not permitted. These 2 subjects were excluded from the CMH test.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-demog.sas v9.2 [redacted]:11:03 Page 1 of 2

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 5: Demographics and Baseline Characteristics
Safety Analysis Set

	F/TAF (N=333)	FTC/TDF (N=330)	Total (N=663)	F/TAF vs. FTC/TDF p-value
Baseline Weight (kg)				
N	333	330	663	0.57
Mean (SD)	83.3 (17.06)	83.7 (17.29)	83.5 (17.16)	
Median	80.4	81.6	80.7	
Q1, Q3	72.4, 91.2	72.1, 93.9	72.3, 92.5	
Min, Max	42.0, 167.8	46.3, 147.8	42.0, 167.8	
Baseline Height (cm)				
N	333	330	663	0.48
Mean (SD)	174.9 (8.72)	174.2 (9.69)	174.6 (9.21)	
Median	175.3	175.2	175.3	
Q1, Q3	170.2, 180.3	168.0, 180.3	170.0, 180.3	
Min, Max	142.2, 200.7	134.6, 203.2	134.6, 203.2	
Baseline Body Mass Index (kg/m^2)				
N	333	330	663	0.34
Mean (SD)	27.3 (5.54)	27.6 (5.76)	27.4 (5.65)	
Median	26.1	26.4	26.3	
Q1, Q3	23.6, 29.3	23.8, 30.1	23.7, 29.7	
Min, Max	17.3, 58.5	17.9, 63.6	17.3, 63.6	

The denominator for percentages is based on the number of subjects in the safety analysis set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
For subjects *CO and *CP , race was not permitted. These 2 subjects were excluded from the CMH test.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-demog.sas v9.2 [redacted]:11:03 Page 2 of 2

Gilead Sciences, Inc.
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Table 54.1: Summary of PBMC TFV-DP Concentrations (pg/million cells) by Treatment
PBMC PK Analysis Set

	F/TAF (N=308)	FTC/TDF (N=271)
N	304	265
Mean	192.370	44.261
SD	219.4379	61.5146
% CV	114.1	139.0
Median	121.000	28.200
Min	2.510	1.100
Max	1980.000	564.000
Q1	54.900	14.500
Q3	265.500	52.900
N (LN-scale)	304	265
Geom. Mean	114.001	27.781
95% CI(L)	100.899	24.799
95% CI(U)	128.804	31.122
Mean of LN	4.736	3.324
SD of LN	1.0817	0.9389

Geom. Mean = Geometric Mean. LN = Natural Log. L = Lower, U = Upper.
For each subject, a trough blood sample was collected at Week 4, 8 or 12.
Subject *CQ , whose third agent was RAL, was incorrectly enrolled into the stratum of F/TAF 10mg and received the randomized study drug.
This subject was excluded in this summary.
Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie. sample age >= 61).

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-pkconc-trt.sas v9.2 Output file: t-pkconc-tfvdp-pg.out [redacted]:11:48 Page 1 of 1

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 56.1.1: Summary of PBMC TFV-DP Concentrations (pg/million cells) by Third Agent, F/TAF 10mg, Boosted PIs
PBMC PK Analysis Set

	F/TAF + ATV/r (N=50)	F/TAF + DRV/r (N=82)	F/TAF + LPV/r (N=17)	Total (N=149)
N	50	82	16	148
Mean	187.214	123.681	121.913	144.954
SD	175.0200	143.7532	91.3834	152.8637
% CV	93.5	116.2	75.0	105.5
Median	133.000	71.850	86.650	92.450
Min	12.700	7.100	35.900	7.100
Max	875.000	1020.000	336.000	1020.000
Q1	67.600	39.000	58.750	47.350
Q3	227.000	157.000	182.500	186.500
N (LN-scale)	50	82	16	148
Geom. Mean	126.292	78.879	96.052	94.465
95% CI(L)	96.649	64.028	66.029	81.047
95% CI(U)	165.027	97.175	139.725	110.103
Mean of LN	4.839	4.368	4.565	4.548
SD of LN	0.9413	0.9494	0.7033	0.9430

Geom. Mean = Geometric Mean. LN = Natural Log. L = Lower, U = Upper.
For each subject, a trough blood sample was collected at Week 4, 8 or 12.
Subject *CQ , whose third agent was RAL, was incorrectly enrolled into the stratum of F/TAF 10mg and received the randomized study drug.
This subject was excluded in this summary.
Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie. sample age >= 61).

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-pkconc.sas v9.2 Output file: t-pkconc-tfvdp-pg1.out [redacted]:11:37 Page 1 of 1

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 56.1.2: Summary of PBMC TFV-DP Concentrations (pg/million cells) by Third Agent, F/TAF 25mg, Other Protocol Allowed Third Agents
PBMC PK Analysis Set

	F/TAF + DTG (N=24)	F/TAF + EFV (N=8)	F/TAF + MVC (N=1)	F/TAF + NVP (N=67)	F/TAF + RAL (N=56)	F/TAF + RPV (N=3)	Total (N=159)
N	24	8	1	65	55	3	156
Mean	154.921	99.900	268.000	227.936	295.804	385.633	237.354
SD	125.0298	122.1428		207.7833	342.2145	436.4895	260.3587
% CV	80.7	122.3		91.2	115.7	113.2	109.7
Median	104.000	50.900	268.000	157.000	159.000	271.000	154.500
Min	7.210	12.000	268.000	2.510	11.600	17.900	2.510
Max	432.000	352.000	268.000	951.000	1980.000	868.000	1980.000
Q1	64.650	23.000	268.000	87.100	75.900	17.900	65.550
Q3	215.000	143.700	268.000	335.000	462.000	868.000	349.000
N (LN-scale)	24	8	1	65	55	3	156
Geom. Mean	106.571	54.224	268.000	137.937	167.293	161.478	136.257
95% CI(L)	70.145	20.281		102.738	122.471	1.146	113.167
95% CI(U)	161.913	144.976		185.196	228.519	22750.113	164.058
Mean of LN	4.669	3.993	5.591	4.927	5.120	5.084	4.915
SD of LN	0.9905	1.1763		1.1890	1.1536	1.9918	1.1740

Geom. Mean = Geometric Mean. LN = Natural Log. L = Lower, U = Upper.
For each subject, a trough blood sample was collected at Week 4, 8 or 12.
Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie. sample age >= 61).

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-pkconc.sas v9.2 Output file: t-pkconc-tfvdp-pg2.out [redacted]:11:37 Page 1 of 1

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 56.1.3: Summary of PBMC TFV-DP Concentrations (pg/million cells) by Third Agent, FTC/TDF, Boosted PIs
PBMC PK Analysis Set

	FTC/TDF + ATV/r (N=35)	FTC/TDF + DRV/r (N=70)	FTC/TDF + LPV/r (N=14)	Total (N=119)
N	34	69	14	117
Mean	33.054	35.778	79.861	40.261
SD	28.8392	45.4635	143.8662	63.1209
% CV	87.2	127.1	180.1	156.8
Median	23.050	21.000	37.650	23.000
Min	2.990	4.350	1.100	1.100
Max	117.000	317.000	564.000	564.000
Q1	12.100	12.800	13.200	12.800
Q3	40.200	37.800	93.800	41.600
N (LN-scale)	34	69	14	117
Geom. Mean	23.208	23.317	31.070	24.099
95% CI(L)	17.062	18.927	13.040	20.207
95% CI(U)	31.569	28.725	74.029	28.741
Mean of LN	3.145	3.149	3.436	3.182
SD of LN	0.8817	0.8683	1.5037	0.9620

Geom. Mean = Geometric Mean. LN = Natural Log. L = Lower, U = Upper.
For each subject, a trough blood sample was collected at Week 4, 8 or 12.
Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie. sample age >= 61).

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-pkconc.sas v9.2 Output file: t-pkconc-tfvdp-pg3.out [redacted]:11:37 Page 1 of 1

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 56.1.4: Summary of PBMC TFV-DP Concentrations (pg/million cells) by Third Agent, FTC/TDF, Other Protocol Allowed Third Agents
PBMC PK Analysis Set

	FTC/TDF + DTG (N=19)	FTC/TDF + EFV (N=6)	FTC/TDF + MVC (N=6)	FTC/TDF + NVP (N=57)	FTC/TDF + RAL (N=58)	FTC/TDF + RPV (N=6)	Total (N=152)
N	19	6	5	56	57	5	148
Mean	53.583	44.050	34.220	43.924	50.355	47.020	47.423
SD	81.7154	43.5248	23.5722	43.4502	71.8507	38.0891	60.2413
% CV	152.5	98.8	68.9	98.9	142.7	81.0	127.0
Median	34.900	31.200	28.200	32.650	31.700	21.800	32.650
Min	7.320	10.500	10.700	4.430	1.250	20.700	1.250
Max	380.000	130.000	72.500	282.000	484.000	106.000	484.000
Q1	15.400	19.600	21.800	18.650	15.500	21.300	18.300
Q3	58.600	41.800	37.900	55.750	59.900	65.300	56.500
N (LN-scale)	19	6	5	56	57	5	148
Geom. Mean	32.724	32.002	28.276	31.464	29.920	36.695	31.087
95% CI(L)	20.960	13.222	11.792	25.240	22.720	14.161	26.825
95% CI(U)	51.091	77.459	67.799	39.223	39.403	95.089	36.026
Mean of LN	3.488	3.466	3.342	3.449	3.399	3.603	3.437
SD of LN	0.9243	0.8423	0.7043	0.8231	1.0376	0.7669	0.9078

Geom. Mean = Geometric Mean. LN = Natural Log. L = Lower, U = Upper.
For each subject, a trough blood sample was collected at Week 4, 8 or 12.
Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie. sample age >= 61).

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-pkconc.sas v9.2 Output file: t-pkconc-tfvdp-pg4.out [redacted]:11:37 Page 1 of 1

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 57.1: Statistical Comparisons of PBMC TFV-DP Concentrations (pg/million cells) between F/TAF and FTC/TDF Groups
PBMC PK Analysis Set

	Treatment				Statistical Comparison				
	Test		Reference		Ratio		90% Confidence Interval	Model	
	n	GLS Mean	n	GLS Mean	Test/Reference	(%)	(%)	rMSE	rInter
TFV-DP	304	113.541	265	27.287	TAF/TDF	416.100	(362.390,477.771)	0.7286	0.7800

For each subject, a trough blood sample was collected at Week 4, 8 or 12.
GLS Mean = Geometric Least Squares Mean.
rMSE = Square Root of Mean Square Error. rInter = Square Root of Intersubject Variance.
Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie. sample age >= 61).

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-pkstat.sas v9.2 Output file: t-pkstat-tfvdp-pg.out [redacted]:11:49 Page 1 of 1

Gilead Sciences, Inc.
Protocol GS-US-311-1089 (Week 48 Analysis)

Table 58.1: Statistical Comparisons of PBMC TFV-DP Concentrations (pg/million cells) between F/TAF and FTC/TDF Groups by Third Agent
PBMC PK Analysis Set

	Treatment				Statistical Comparison				
	Test		Reference		Ratio		90% Confidence Interval	Model	
	n	GLS Mean	n	GLS Mean	Test/Reference	(%)	(%)	rMSE	rInter
Overall	304	113.541	265	27.287	TAF/TDF	416.100	(362.390,477.771)	0.7286	0.7800
ATV/r	50	126.292	34	23.208	TAF/TDF	544.164	(389.197,760.833)	0.6789	0.6520
DRV/r	82	78.879	69	23.317	TAF/TDF	338.294	(264.774,432.228)	0.6824	0.6600
LPV/r	16	96.052	14	31.070	TAF/TDF	309.144	(146.581,651.992)	0.7033	1.3291
DTG	24	106.571	19	32.724	TAF/TDF	325.664	(198.902,533.213)	0.6971	0.7037
EFV	8	54.224	6	32.002	TAF/TDF	169.441	(64.761,443.327)	0.8337	0.8299
MVC	1	268.000	5	28.276	TAF/TDF	947.810	(233.900,3840.727)	0.5758	0.4056
NVP	65	137.937	56	31.464	TAF/TDF	438.402	(323.162,594.737)	0.8231	0.8580
RAL	55	167.293	57	29.920	TAF/TDF	559.127	(396.255,788.945)	0.7494	0.8771
RPV	3	161.478	5	36.695	TAF/TDF	440.057	(42.736,4531.321)	0.7669	1.8383

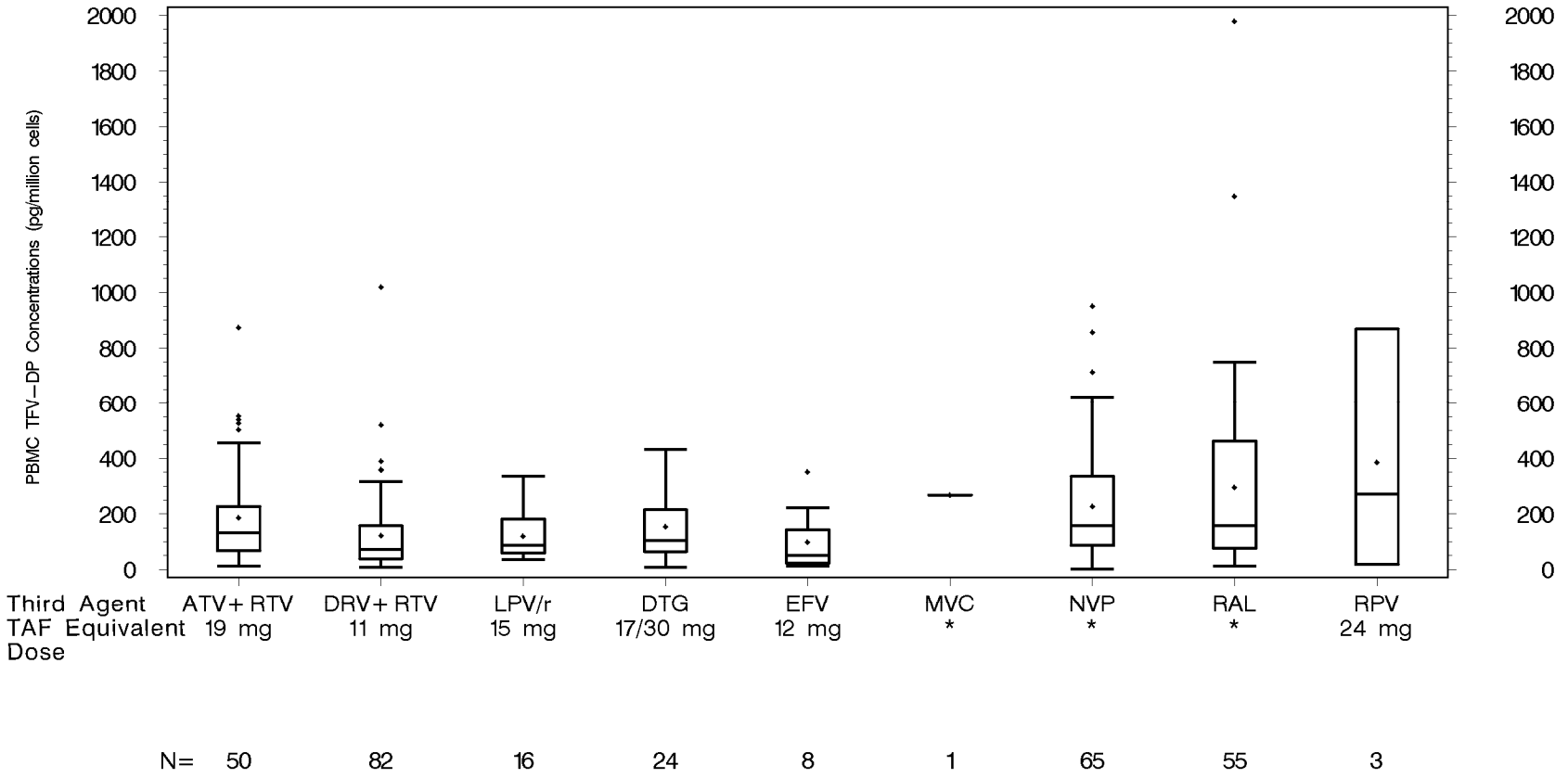
For each subject, a trough blood sample was collected at Week 4, 8 or 12.
GLS Mean = Geometric Least Squares Mean.
rMSE = Square Root of Mean Square Error. rInter = Square Root of Intersubject Variance.
Four and six subjects in the F/TAF and FTC/TDF group, respectively, were excluded from PBMC analysis because the PBMC samples were out of the 61 days window of stability (ie. sample age >= 61).

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../s3111089/wk_48/version3/prog/t-pkstat-arv.sas v9.2 Output file: t-pkstat-tfvdp-pg-arv.out [redacted]:11:49 Page 1 of 1

Gilead Sciences, Inc.

Protocol GS-US-311-1089 (Week 48 Analysis)

Figure req7762.1: Box Plot of Intracellular TFV-DP Concentration for Subjects Who Received F/TAF by Third Agent
PBMC PK Analyis Set



Data Extracted: CRF Data: [redacted] 20[redacted] Lab Data: [redacted] 20[redacted] DXA Data: [redacted] 20[redacted] PK Data: [redacted] 20[redacted]
Source: .../adhoc/req7762/prog/r-req7762-pbmc-tfvdp.sas v9.2 [redacted] 20[redacted] 15:21

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY

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

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV	atazanavir
BHIVA	British HIV Association
BMD	bone mineral density
BMI	body mass index
CD4	cluster determinant 4
CG	Cockcroft-Gault
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula for calculating glomerular filtration rate
CMH	Cochran-Mantel-Haenszel
COBI, C	cobicistat (Tybost®)
CSR	clinical study report
C-telopeptide	type 1 collagen C-telopeptide
CV	coefficient of variation
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
DDI	drug-drug interaction
DHHS	Department of Health and Human Services
DRV, D	darunavir
DTG	dolutegravir
EACS	European AIDS Clinical Society
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
$eGFR_{CKD\text{-}EPI,\ Creatinine}$	estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration serum creatinine equation
EQ VAS	EQ visual analogue scale
EVG, E	elvitegravir (Vitekta®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
$FEPO_4$	fractional excretion of phosphate
FEUA	fractional excretion of uric acid
FTC, F	emtricitabine (Emtriva®)

GFR	glomerular filtration rate
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HDL	high-density lipoprotein
HIV, HIV-1	human immunodeficiency virus, type 1
INSTI	integrase strand-transfer inhibitor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	intravenous
LDL	low-density lipoprotein
LOCF	last observation carried forward
LPV/r	ritonavir-boosted lopinavir
LSM	least-squares mean
m	Module
M = E	missing = excluded
M = F	missing = failure
M = LOCF	missing = last observation carried forward
MH	Mantel-Haenszel
MVC	maraviroc
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
NC	not calculated
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NNRTI	nonnucleoside reverse transcriptase inhibitor
NVP	nevirapine
OATP	organic anion transporting polypeptide
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PEP	postexposure prophylaxis
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PO	orally
PP	per protocol
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PT	preferred term
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QD	once daily

RAL	raltegravir
RBP	retinol binding protein
RNA	ribonucleic acid
ROW	Rest of World
RPV	rilpivirine
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36	Short Form-36
SOC	system organ class
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TmP/GFR	renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
UACR	urine albumin to creatinine ratio
UPCR	urine protein to creatinine ratio
US	United States
vs	versus

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

AUC	area under the plasma/PBMC concentration versus time curve
AUC_{inf}	area under the plasma/PBMC concentration versus time curve extrapolated to infinite time
AUC_{last}	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma/PBMC concentration versus time curve over the dosing interval
C_{max}	maximum observed plasma concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
$t_{1/2}$	estimate of the terminal elimination half-life of the drug
T_{max}	time (observed time point) of C_{max}

1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

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.

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

For ART-naive HIV-infected patients, treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI). Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {32519}, {27621}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an oral prodrug of TFV. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs {26885}, {34210}.

TDF in combination with emtricitabine (FTC; F) forms a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients that can be combined with different third agents. The combination of FTC and TDF is used within several once-daily fixed-dose combinations (FDCs) (Truvada® [TVD; FTC/TDF], Atripla® [ATR; efavirenz (EFV)/FTC/TDF], Complera®/Eviplera® [FTC/rilpivirine/TDF], and Stribild® [STB; elvitegravir (EVG; E)/cobicistat (COBI; C)/FTC/TDF]). Availability of a stand-alone NRTI backbone is important when there is a medical need to use a third agent that is not part of an FDC (eg, ritonavir [RTV]-boosted PIs), and particularly to provide a range of treatment options in patients with virologic resistance to their third agent but not to the backbone.

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

Gilead Sciences (Gilead) has coformulated TAF (as TAF fumarate) with FTC into an FDC tablet available in 2 dosage strengths, F/TAF (200/25 mg) and F/TAF (200/10 mg). Because, TAF is a substrate of intestinal efflux transporters (ie, P-glycoprotein [P-gp]) and hepatic transporters (ie, organic anion transporting polypeptide [OATP]1B1 and OATP1B3), TAF exposure may be

increased upon coadministration with inhibitors of these transporters, with the effect apparently driven predominantly by P-gp inhibition (ie, by RTV or COBI; m2.7.2, Sections 3.1.3.4 and 3.2.3.2.2). Therefore, the recommended F/TAF dose (200/25 mg or 200/10 mg based on third agent) is generally based on whether or not the coadministered agent has any clinically relevant effect on TAF exposure (eg, via inhibition of intestinal P-gp). Specifically, F/TAF 200/25 mg is recommended to be used with unboosted third agents, and F/TAF 200/10 mg with boosted third agents.

This submission for the N(t)RTI backbone F/TAF is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1472 and GS-US-311-1473) that pharmacokinetically bridge each F/TAF FDC tablet strength (200/25 mg and 200/10 mg) to Gilead's FDC tablet containing the HIV-1 INSTI EVG, the pharmacoenhancer COBI, FTC, and TAF (E/C/F/TAF 150/150/200/10 mg), for which clinical safety and efficacy have been established in a broad range of patient populations.

The PK and pharmacodynamic data from clinical studies conducted with F/TAF and E/C/F/TAF are supported with data from clinical studies conducted with TAF and FTC, and with data from nonclinical studies. Data from studies conducted with the darunavir (DRV; D)/C/F/TAF FDC support dosing recommendations.

Across 6 studies, a total of 2394 subjects were enrolled or randomized and received at least 1 dose of E/C/F/TAF in the United States (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). In a D/C/F/TAF study, a total of 103 subjects were randomized and received at least 1 dose of D/C/F/TAF in the US (m5.3.5.1, GS-US-299-0102, Section 15.1, Tables 1 and 3). The studies relevant to the proposed indication are summarized by study drug and subject population in Table 2.

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

	US	Europe	ROW	Total Enrolled
Phase 3 Studies[a]	1360	311	450	2121
Phase 2 Study[b]	273	0	0	273
TOTAL	**1633**	**311**	**450**	**2394**

ROW = Rest of World

a Phase 3 studies: 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: GS-US-292-0104 Week 48 CSR, Section 15.1, Table 1; GS-US-292-0111 Week 48 CSR, Section 15.1, Table 1; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 1.1 and 1.2; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 1; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 1; GS-US-292-0106 Interim CSR, Section 15.1, Table 1

Table 2. Studies Supporting Clinical Efficacy for the F/TAF Fixed-Dose Combination Marketing Application

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	CSR Reference and Narrative Locations
E/C/F/TAF Studies				
HIV-Infected, ART-Naive Adult Subjects				
GS-US-292-0104	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 435) STB + placebo-to-match E/C/F/TAF FDC (N = 432)	Week 48 efficacy, PK, and safety	**CSR:** GS-US-292-0104 Interim Week 48 CSR **Narrative:** Section 2.1.1.1
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:** GS-US-292-0111 Interim Week 48 CSR **Narrative:** Section 2.1.1.2
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:** GS-US-292-0102 Interim Week 96 CSR **Narrative:** Section 2.1.1.3
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 TVD+3rd Agent (N = 477)	Week 48 efficacy and safety	**CSR:** GS-US-292-0109 Interim Week 48 CSR **Narrative:** Section 2.1.2
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:** GS-US-292-0112 Interim Week 24 CSR **Narrative:** m2.7.4, Section 1.1.4.1.1

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	CSR Reference and Narrative Locations
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:** GS-US-292-0106 Interim Week 24 CSR **Narrative:** m2.7.4, Section 1.1.4.1.2
D/C/F/TAF Study				
HIV-Infected, ART-Naive Adult Subjects				
GS-US-299-0102	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+TVD	D/C/F/TAF FDC (N = 103) DRV+COBI+TVD (N = 50)	Week 48 efficacy, PK, and safety	**CSR:** m5.3.5.1, GS-US-299-0102 Final CSR **Narrative:** Section 2.2.1

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).
b The randomized phase of Study GS-US-292-0102 was 48 weeks; most subjects in the open-label extension completed 96 weeks of treatment.

1.1. Overview of Clinical Efficacy

1.1.1. E/C/F/TAF Studies

ART-Naive Subjects: Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102

The efficacy of F/TAF for the treatment of HIV-1 infection in ART-naive subjects is supported by data from the randomized, double-blind, active-controlled E/C/F/TAF Phase 3 Studies GS-US-292-0104, GS-US-292-0111, and the E/C/F/TAF Phase 2 Study GS-US-292-0102 (randomized phase). The Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 were identical in their study design and objectives (with the exception of the geographic regions in which they were conducted), and used STB as the comparator. Eligible subjects were ART-naive, HIV-infected adults with plasma HIV-1 RNA ≥ 1000 copies/mL, and a screening genotype showing sensitivity to EVG, FTC, and TDF. Subjects must have had an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault (CG) equation ($eGFR_{CG}$) of ≥ 50 mL/min at screening, except in France and Sweden where subjects must have had an $eGFR_{CG}$ of ≥ 70 mL/min at screening. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL), CD4 cell count (< 50 cells/µL, 50 to 199 cells/µL, or ≥ 200 cells/µL), and region (US versus ex-US) at screening.

Study GS-US-292-0102, a Phase 2, randomized, double-blind, active-controlled study in ART-naive subjects also used STB as the comparator. For the randomized phase of Study GS-US-292-0102, subjects were HIV-infected adults with plasma HIV-1 RNA levels ≥ 5000 copies/mL, no prior use of any anti-HIV drug for any length of time, and an $eGFR_{CG}$ of ≥ 70 mL/min at screening. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

STB was chosen as the comparator in these studies because it allowed for a direct and exclusive comparison between TAF and TDF (as the other components of the regimens are identical). STB is a recommended standard of care regimen for initial therapy in the US Department of Health and Human Services (DHHS) guidelines, the European AIDS Clinical Society (EACS) guidelines, International Antiviral Society-USA Panel HIV recommendations, and the British HIV Association (BHIVA) guidelines {32519}, {32690}, {29697}, {27621}.

Virologically Suppressed Subjects: Studies GS-US-292-0109 and GS-US-292-0102

The efficacy of F/TAF in virologically suppressed adult subjects is supported by data from E/C/F/TAF Phase 3 Study GS-US-292-0109 and the extension phase of E/C/F/TAF Phase 2 Study GS-US-292-0102. For the Phase 3, randomized, open-label Study GS-US-292-0109, all subjects were drawn from a predefined set of Gilead clinical studies. Eligible subjects were HIV-infected adults receiving ART regimens consisting of STB, ATR, COBI-boosted atazanavir (ATV+COBI)+ TVD, or RTV-boosted atazanavir (ATV+RTV)+TVD for at least 6 consecutive months. Subjects were randomized in a 2:1 ratio to switch to open-label E/C/F/TAF or remain on their prior regimen consisting of FTC/TDF+3rd Agent. Randomization was stratified by prior treatment regimen (ie, STB, ATR, ATV/boosted+TVD) at screening. This design allowed for a direct comparison between TAF and TDF after switching from an

approved, standard-of-care regimen. All subjects were required to have maintained plasma HIV-1 RNA levels at undetectable levels for at least 6 consecutive months prior to the screening visit, HIV-1 RNA < 50 copies/mL at the screening visit, and an $eGFR_{CG} \geq 50$ mL/min at screening.

The switch subjects in the Phase 2, open-label, extension phase of Study GS-US-292-0102 consisted of virologically suppressed subjects continuing on study after the 48-week randomized phase who switched from STB to E/C/F/TAF, and virologically suppressed subjects (HIV-1 RNA < 50 copies/mL at the last study visit) who received a DRV+COBI-containing regimen in Study GS-US-299-0102 who switched to E/C/F/TAF. All of these subjects were required to have an $eGFR_{CG}$ of > 50 mL/min at study entry.

Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

The efficacy of F/TAF in adult subjects with mild to moderate renal impairment is supported by data from E/C/F/TAF Study GS-US-292-0112, a Phase 3, open-label, single-arm study that enrolled both ART-experienced and ART-naive subjects. For the ART-experienced cohort, eligible subjects were HIV-infected adults with plasma HIV-1 RNA concentrations at undetectable levels for at least 6 months and at < 50 copies/mL at screening, CD4 cell count ≥ 50 cells/μL, no history of known resistance to EVG, FTC, or TDF, and $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening; subjects may have been previously enrolled in Gilead studies. For the ART-naive cohort (Cohort 2), eligible subjects were HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell count ≥ 50 cells/μL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and stable $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening.

ART-Naive Adolescent Subjects: Study GS-US-292-0106

Data from the Phase 2/3, open-label E/C/F/TAF Study GS-US-292-0106 support the efficacy of F/TAF in adolescent subjects. Eligible subjects were HIV-infected, ART-naive adolescents, 12 to < 18 years of age, weighing ≥ 35 kg, with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell count > 100 cells/μL, and an eGFR ≥ 90 mL/min/1.73 m^2 (as calculated using the Schwartz formula) at screening, with no prior use of any anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission) and sensitivity to TFV, EVG, and FTC as demonstrated by HIV-1 genotyping at screening.

1.1.2. D/C/F/TAF Study

ART-Naive Subjects: Study GS-US-299-0102

The efficacy of F/TAF for the treatment of HIV-1 infection in ART-naive subjects is further supported by data from a Phase 2, randomized, double-blind, active-controlled D/C/F/TAF Study GS-US-299-0102. This study in ART-naive subjects used DRV+COBI+TVD as the comparator. Eligible subjects were HIV-infected adults with plasma HIV-1 RNA levels ≥ 5000 copies/mL; no prior use of any anti-HIV drug for any length of time; a screening genotype showing sensitivity to DRV, FTC, and TDF; and an $eGFR_{CG}$ of ≥ 70 mL/min at screening.

1.2. Efficacy Endpoints of Studies

The primary efficacy endpoint for the pivotal Phase 3 studies in ART-naive (Studies GS-US-292-0104 and GS-US-292-0111) and virologically suppressed subjects (Study GS-US-292-0109) was the proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 48 as defined by the Food and Drug Administration (FDA) snapshot algorithm {18738}, {28155}; this endpoint is also presented for the E/C/F/TAF and D/C/F/TAF Phase 2 studies in ART-naive subjects (Studies GS-US-292-0102 and GS-US-299-0102, respectively), and for subjects with mild to moderate renal impairment (Study GS-US-292-0112).

The proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 24 as defined by the FDA snapshot algorithm is presented for adolescents (Study GS-US-292-0106), subjects with mild to moderate renal impairment (Study GS-US-292-0112), and switch subjects in Study GS-US-292-0102.

Additional endpoints presented in this summary are outlined in Table 3.

Table 3. Efficacy Endpoints Included in this Summary by Study

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects	Renally Impaired Subjects	ART-Naive Adolescent Subjects
	GS-US-292-0104/ GS-US-292-0111[a]	GS-US-292-0102[b]	GS-US-299-0102	GS-US-292-0109	GS-US-292-0112	GS-US-292-0106
HIV-1 RNA < 50 copies/mL Using FDA Snapshot Algorithm	Week 48	Week 48	Week 48	Week 48	Weeks 24 & 48	Week 24
HIV-1 RNA < 20 copies/mL Using FDA Snapshot Algorithm	Week 48	Week 48	—	Week 48	—	—
HIV-1 RNA < 50 copies/mL Using M = E	Week 48	Week 48	Week 48	Week 48	Weeks 24 & 48	Week 24
HIV-1 RNA < 50 copies/mL Using M = F	Week 48	Week 48	Week 48	Week 48	Week 24	Week 24
Change from Baseline in HIV-1 RNA	Week 48	Week 48	Week 48	—	—	—
Change from Baseline in CD4 Cell Count	Week 48	Week 48	Week 48	Week 48	Weeks 24 & 48	Week 24

M = E = missing = excluded; M = F = missing = failure

a All endpoints presented for Studies GS-US-292-0104 and GS-US-292-0111 individually and pooled, except change from baseline in CD4% (pooled analysis not performed).

b Only presented for the randomized phase of Study GS-US-292-0102, with the exception that for the extension phase of Study GS-US-292-0102, the following are presented: HIV-1 RNA < 50 copies/mL using FDA snapshot algorithm at Week 24 (of the extension phase) and change from baseline (defined as switching to E/C/F/TAF) in CD4 cell count at Week 24 (of the extension phase).

Because of the identical study design, which selected a study population based on identical eligibility criteria, integrated analyses were conducted on pooled data from Studies GS-US-292-0104 and GS-US-292-0111. The pooling of data was prespecified in the protocol for each of these studies. Data from the other Phase 3 E/C/F/TAF studies and the D/C/F/TAF study were not pooled due to differences in treatment regimens, treatment durations, and the subject populations evaluated.

For the integrated analyses, data were pooled by treatment group (E/C/F/TAF versus STB) according to the randomized treatment from Study GS-US-292-0104 or GS-US-292-0111. Pooled analyses are labeled as such in this summary document, with data from individual studies presented in side-by-side comparisons or stand-alone tables.

Resistance analyses for all 6 E/C/F/TAF studies and for the D/C/F/TAF study are presented in m2.7.2, Section 4.2.

Statistical methods are presented in the statistical analysis plans (SAPs) for the individual studies and in the Integrated Summary of Efficacy (ISE) SAP for the pooled studies. A tabular summary of study designs for Studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0109, GS-US-292-0111, and GS-US-299-0102 is provided in Appendix 7.1.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. E/C/F/TAF Studies

2.1.1. ART-Naive Subjects

2.1.1.1. Study GS-US-292-0104 (Phase 3)

A complete study description and results for Study GS-US-292-0104 are available in the clinical study report (CSR) (GS-US-292-0104 Week 48) and a brief narrative of this study is presented below.

Title

A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide versus Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naive Adults

Objectives

The primary objective of this study was as follows:

- To evaluate the efficacy of an FDC tablet containing E/C/F/TAF versus STB in HIV-infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives of this study were as follows:

- To determine the safety of the 2 treatment regimens as determined by the percentage change from baseline in hip and spine BMD at Week 48
- To determine the safety of the 2 treatment regimens as determined by the change from baseline in serum creatinine at Week 48
- To evaluate the safety and tolerability of the 2 treatment regimens through Week 48
- To evaluate the efficacy, durability, safety and tolerability of the 2 treatment regimens through Week 96

Diagnosis and Main Criteria for Inclusion

Eligible subjects were ART-naive (excluding pre-exposure prophylaxis [PrEP] or postexposure prophylaxis [PEP] up to 6 months prior to screening), HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and had an $eGFR_{CG}$ ≥ 50 mL/min, except in France and Sweden where subjects must have had an $eGFR_{CG}$ of ≥ 70 mL/min at screening.

SUMMARY OF RESULTS

Subject Disposition

In this study, 1105 subjects were screened, 872 subjects were randomized, and 867 subjects received at least 1 dose of study drug (E/C/F/TAF 435 subjects; STB 432 subjects); 3 subjects randomized to E/C/F/TAF and 2 subjects randomized to STB did not receive study drug.

A total of 813 subjects (E/C/F/TAF 94.9%, 413 subjects; STB 92.6%, 400 subjects) were continuing study drugs as of the Week 48 data cut date. Of the 867 subjects randomized and treated, 54 subjects (6.2%) discontinued study drugs (E/C/F/TAF 5.1%, 22 subjects; STB 7.4%, 32 subjects) and 48 subjects (5.5%) discontinued from the study prior to the Week 48 data cut date (E/C/F/TAF 4.8%, 21 subjects; STB 6.3%, 27 subjects). The reasons for premature discontinuation of study drugs were generally comparable between study groups. The most common reasons for discontinuation of study drugs were withdrawal of consent (E/C/F/TAF 1.8%, 8 subjects; STB 1.6%, 7 subjects), lost to follow-up (E/C/F/TAF 1.1%, 5 subjects; STB 2.1%, 9 subjects), and adverse events (AEs; E/C/F/TAF 0.9%, 4 subjects; STB 1.4%, 6 subjects).

Subject Demographics and Baseline Disease Characteristics

Demographic and general baseline characteristics were similar between the 2 treatment groups. The majority of subjects were male (85.4% overall). The median age was 33 years (range: 18 to 74) in the E/C/F/TAF group and 35 years (range: 18 to 76) in the STB group ($p = 0.014$). The most common races were white (58.2%), black (20.2%), and Asian (17.6%), and most subjects were not Hispanic or Latino (85.0%). The median (first quartile [Q1], third quartile [Q3]) value for body mass index (BMI) at baseline was 24.3 (21.7, 27.7) kg/m^2.

Baseline disease characteristics were generally similar between the 2 treatment groups. Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.61 (4.16, 4.97) log_{10} copies/mL. At baseline, 76.9% of subjects had HIV-1 RNA $\leq$ 100,000 copies/mL, 17.4% had > 100,000 to $\leq$ 400,000 copies/mL, and 5.7% had > 400,000 copies/mL. Overall, median (Q1, Q3) baseline CD4 count was 404 (289, 554) cells/μL. At baseline, 2.5% (22 subjects) had a CD4 cell count < 50 cells/μL and 10.3% (89 subjects) had 50 to < 200 cells/μL. The most common HIV risk factor category was homosexual sex (74.7% of subjects); 23.9% of subjects reported heterosexual sex as the mode of infection. The majority of subjects (93.4%) had asymptomatic HIV-1 infection; 4.4% had symptomatic HIV-1 infection, and 2.2% were diagnosed with AIDS.

At baseline, the median (Q1, Q3) $eGFR_{CG}$ value was slightly higher in the E/C/F/TAF group (118.5 [101.6, 135.7] mL/min) compared with the STB group (112.8 [97.8, 134.2] mL/min) ($p = 0.031$). Similar results were obtained for eGFR using the Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD-EPI) serum creatinine method ($eGFR_{CKD\text{-}EPI,\ Creatinine}$). Seventy-nine subjects (9.1%) had proteinuria (Grade 1, 2, or 3 by dipstick) on urinalysis.

Overall, 14.6% of subjects had a medical history of hypertension, 10.6% had a medical history of hyperlipidemia, 3.2% had a medical history of diabetes, and 2.0% had a medical history of cardiovascular disease.

Efficacy Results

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm. Virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the Full Analysis Set (FAS). Virologic success rates were high in both treatment groups, as follows: E/C/F/TAF 93.1%; STB 92.4%; difference in percentages: 1.0%, 95.002% CI: −2.6% to 4.5%. Because the lower bound of the 2-sided 95.002% CI of the difference in the response (E/C/F/TAF – STB) rate was greater than the prespecified −12% margin, E/C/F/TAF was determined to be noninferior to STB. Virologic success rates for the Week 48 Per Protocol (PP) Analysis Set were consistent with those for the FAS and were as follows: E/C/F/TAF 97.8%, 395 of 404 subjects; STB 98.0%, 389 of 397 subjects; difference in percentages: −0.1% (95.002% CI: −2.2% to 2.1%).

Virologic outcomes at Week 48 were similar between the 2 treatment groups when assessed using the FDA snapshot algorithm, defined as HIV-1 RNA < 20 copies/mL, based on the FAS. Virologic success rates were as follows: E/C/F/TAF 86.4%; STB 87.3%; difference in percentages: −0.6% (95% CI: −5.1% to 3.8%).

High and similar rates of virologic suppression were achieved in the 2 treatment groups, as assessed using the missing = failure (M = F) and missing = excluded (M = E) methods at Week 48 based on the FAS. The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 were as follows: M = F: E/C/F/TAF 93.6%; STB 93.8%; difference in percentages: 0%, 95% CI: −3.3% to 3.3%); M = E: E/C/F/TAF 97.8%; STB 98.5%; difference in percentages: −0.6% (95% CI: −2.6% to 1.4%). Results for the Week 48 PP Analysis Set were consistent with those for the FAS.

HIV-1 RNA levels decreased rapidly in the first 2 weeks following initiation of study drug. After Week 8, the decreases were stable and similar between the 2 groups through Week 48; mean (SD) decreases at Week 48 were as follows: E/C/F/TAF 3.24 (0.684) $\log_{10}$ copies/mL; STB 3.27 (0.663) $\log_{10}$ copies/mL; difference in least-squares mean (LSM): 0.04 $\log_{10}$ copies/mL, 95% CI: −0.03 to 0.11 $\log_{10}$ copies/mL.

The mean (SD) increases from baseline in CD4 cell counts were similar for each treatment group through Week 48 (observed data) using the FAS and were as follows: E/C/F/TAF 235 (183.1) cells/μL; STB 222 (178.0) cells/μL; difference in LSM: 12 cells/μL, 95% CI: −13 to 37 cells/μL. A similar trend was observed using the missing = last observation carried forward (M = LOCF) method. Results for the Week 48 PP Analysis Set were consistent with the results for the FAS.

At Week 48, the rates of virologic success by the FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) for subgroups according to age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, region, or study drug adherence rate were similar for the E/C/F/TAF and STB groups. The 95% CIs for differences in virologic success between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments.

Pharmacokinetics Results

The steady-state plasma pharmacokinetic (PK) parameters of TAF following administration of E/C/F/TAF for subjects who participated in the intensive PK substudy are shown in Table 4.

Table 4. E/C/F/TAF Study GS-US-292-0104: Summary of TAF Pharmacokinetic Parameters (PK Substudy Analysis Set)

Treatment E/C/F/TAF (N = 15)	AUC_{last} (ng*h/mL) Mean (%CV)	C_{max} (ng/mL) Mean (%CV)	T_{max} (h) Median (Q1, Q3)	$t_{1/2}$ (h) Median (Q1, Q3)
TAF	229.8 (33.7)	259.2 (43.8)	0.75 (0.50, 1.50)	0.42 (0.36, 0.57)

CV = coefficient of variation
Source: GS-US-292-0104 Week 48 CSR, Section 15.1, Table 61.1

The steady-state plasma PK parameters and statistical comparisons for TFV following administration of E/C/F/TAF or STB for subjects who participated in the intensive PK substudy are shown in Table 5.

Table 5. E/C/F/TAF Study GS-US-292-0104: Summary of TFV Pharmacokinetic Parameters (PK Substudy Analysis Set)

	Mean (%CV) by Treatment	
Parameter[a]	E/C/F/TAF (Test) (N = 15)	STB (Reference) (N = 15)
AUC_{tau} (ng*h/mL)	311.8 (17.1)	3021.6 (23.0)[b]
C_{max} (ng/mL)	17.3 (16.0)	370.3 (25.8)[b]
C_{tau} (ng/mL)	10.5 (18.7)[b]	60.3 (31.0)
T_{max} (h)	2.00 (1.50, 3.00)	2.00 (0.75, 2.02)[b]
$t_{1/2}$ (h)	34.95 (28.57, 48.50)	12.71 (10.84, 14.27)[b]

a Values are listed as mean (%CV) except T_{max} and $t_{1/2}$, which are listed as median (Q1, Q3).
b N = 14
Source: GS-US-292-0104 Week 48 CSR, Section 15.1, Table 61.2

The statistical comparisons for TFV following administration of E/C/F/TAF or STB for subjects who participated in the intensive PK substudy are shown in Table 6.

Table 6. E/C/F/TAF Study GS-US-292-0104: Statistical Comparisons of TFV Pharmacokinetic Parameter Estimates Between Test and Reference Treatments (PK Substudy Analysis Set)

TFV PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 15)	STB (N = 15)		
AUC_{tau} (ng*h/mL)	307.17	2948.64[a]	10.42	(9.13, 11.89)
C_{max} (ng/mL)	17.05	357.14[a]	4.77	(4.10, 5.56)
C_{tau} (ng/mL)	10.27[a]	57.62	17.83	(15.07, 21.08)

GLSM = geometric least-squares mean
a N = 14
Source: GS-US-292-0104 Week 48 CSR, Section 15.1, Table 63

The statistical comparison of TFV-DP AUC_{tau} following administration of E/C/F/TAF or STB for subjects who participated in the intensive PK substudy is shown in Table 7.

Table 7. E/C/F/TAF Study GS-US-292-0104: Statistical Comparisons of TFV-DP AUC_{tau} Between Test and Reference Treatments (PBMC PK Substudy Analysis Set)

TFV-DP PK Parameter	Mean (%CV) by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 10)	STB (N = 10)		
AUC_{tau} (h*µmol/L)	9.4 (56.8)	3.4 (122.2)	338.22	(163.78, 698.45)

Source: GS-US-292-0104 Week 48 CSR, Section 15.1, Tables 62 and 63

Overall, the steady-state plasma exposures of TAF and TFV, and intracellular exposure of TFV-DP, were in the range of historical data and concurrent study data from the ongoing Phase 3 program. Plasma exposures of TAF and TFV were consistent with exposures observed following administration of E/C/F/TAF in HIV-infected subjects in Phase 2 and Phase 3 studies (Studies GS-US-292-0102 and GS-US-292-0111) and following administration of E/C/F/TAF or TAF 25-mg single-agent in healthy subjects (Study GS-US-292-0103). Plasma TFV exposure (AUC_{tau}) following administration of E/C/F/TAF was 89.58% lower than TFV exposure achieved with administration of STB. The TFV PK parameters in subjects receiving STB were consistent with historical data (STB prescribing information). The TFV exposure following E/C/F/TAF was also lower than the exposure seen after coadministration of TDF with or without boosted PIs.

The peripheral blood mononuclear cell (PBMC) TFV-DP AUC_{tau} was higher in subjects receiving E/C/F/TAF compared with subjects receiving STB, and in the range of concurrent and historical study data on TFV-DP exposure observed following administration of E/C/F/TAF (Studies GS-US-292-0102 and GS-US-292-0111) as well as administration of TAF 25-mg single-agent (Study GS-US-120-0104).

Safety Results

E/C/F/TAF and STB were well tolerated in this study through a median duration of study drugs exposure of 60.0 and 59.4 weeks, respectively.

Adverse Events

Similar percentages of subjects in each group had any AE (E/C/F/TAF 91.0%, 396 subjects; STB 90.7%, 392 subjects). Two subjects died during the study, 1 in each treatment group. The subject in the E/C/F/TAF group died as a result of embolic stroke in the setting of atrial fibrillation that transformed into hemorrhagic stroke. The subject in the STB group died as a result of cardiac arrest that occurred following cholesteatoma removal (reported as vagally-mediated bradycardic/asystole).

Serious adverse events (SAEs) were reported for similar percentages of subjects in both treatment groups (E/C/F/TAF 8.5%, 37 subjects; STB 6.7%, 29 subjects). The incidence of SAEs considered related to study drugs by the investigator was low and similar in both treatment groups (E/C/F/TAF 0.7%, 3 subjects; STB 0.2%, 1 subject). Similar percentages of subjects in both treatment groups had any AE considered related to study drugs by the investigator (E/C/F/TAF 41.8%, 182 subjects; STB 45.4%, 196 subjects); or any Grade 3 or 4 AE considered related to study drugs (E/C/F/TAF 2.1%, 9 subjects; STB 0.5%, 2 subjects).

Similar percentages of subjects in both treatment groups had an AE leading to discontinuation of study drugs (E/C/F/TAF 0.9%, 4 subjects; STB 1.4%, 6 subjects). All AEs leading to discontinuation of study drugs, except for those reported for the 2 subjects who died, were considered related to study drugs by the investigator. One subject in the STB group had a confirmed pregnancy during the study, and subsequently delivered a healthy baby. The AEs by preferred term (PT) reported for ≥ 10% of subjects in either treatment group were as follows:

- E/C/F/TAF group — diarrhea (17.9%, 78 subjects), nausea (14.3%, 62 subjects), and headache and upper respiratory tract infection (11.5%, 50 subjects for each)

- STB group — diarrhea (18.8%, 81 subjects), nausea (17.4%, 75 subjects), upper respiratory tract infection (14.8%, 64 subjects), and headache (11.8%, 51 subjects)

Overall, the rates and types of AEs observed in this study were similar in the 2 groups, and consistent with the study population.

Bone Safety

The incidence of fracture events was low (E/C/F/TAF 1.6%, 7 subjects; STB 2.5%, 11 subjects). All reported fracture AEs were nonserious, considered by the investigator as unrelated to the study drugs, and none resulted in discontinuation of study drugs.

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for this study, respectively. Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which were

dependent on the results from preceding tests. Mean percentage decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48). Mean (SD) percentage decreases from baseline at Week 48 in BMD were as follows: at the hip: E/C/F/TAF 0.883% (3.2882%), STB 3.288% (3.6213%); at the spine: E/C/F/TAF 1.322% (3.1546%), STB 2.964% (3.4717%). Differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were also statistically significant ($p < 0.001$ at Weeks 24 and 48). At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a > 3% decrease from baseline in hip (E/C/F/TAF 19.0%; STB 54.7%) or spine BMD (E/C/F/TAF 25.1%; STB 45.4%).

Mean percentage increases from baseline in the bone turnover biomarkers type 1 collagen C-telopeptide (C-telopeptide) (bone resorption) and procollagen type 1 N-terminal propeptide (P1NP) (bone formation), as well as parathyroid hormone (PTH), a hormone involved in bone metabolism, were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows: C-telopeptide: E/C/F/TAF 10.7% (−6.9%, 33.3%), STB 23.3% (3.9%, 47.8%); P1NP: E/C/F/TAF 27.46% (3.72%, 66.99%), STB 75.20% (42.84%, 118.60%); PTH: E/C/F/TAF 17.3% (−9.9%, 50.9%), STB 33.6% (3.7%, 75.8%).

Renal Safety

Two subjects, 1 in each treatment group, had an SAE related to renal function, neither of which resulted in discontinuation of study drugs nor was considered related to study drugs by the investigator: Grade 2 nephrotic syndrome (E/C/F/TAF) and Grade 2 acute renal failure (reported as acute kidney injury; STB). Three subjects, all in the STB group, had renal AEs that resulted in discontinuation of study drugs (nephropathy, renal failure, and decreased glomerular filtration rate [GFR]); the events were nonserious and considered related to study drugs by the investigator. There were no reports of proximal renal tubulopathy (PRT; including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy.

Change from baseline in serum creatinine at Week 48 was the third key alpha-protected safety endpoint for this study. Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which were dependent on the results from preceding tests. Increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. Increases were observed by Week 2 for each treatment group, and remained stable through Week 48 (mean changes [SD] from baseline at Week 48: E/C/F/TAF 0.08 [0.110] mg/dL, STB 0.11 [0.117] mg/dL). The difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48 ($p < 0.001$ at Week 48).

Decreases from baseline in median $eGFR_{CG}$ values were smaller in the E/C/F/TAF group compared with the STB group. Decreases were observed by Week 2 for each treatment group and remained stable through Week 48 (median [Q1, Q3] changes from baseline at Week 48: E/C/F/TAF −6.8 [−16.6, 1.2] mL/min, STB −10.4 [−21.0, −2.4] mL/min). The difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48 ($p < 0.001$ at Week 48). A smaller percentage of subjects had a decrease from baseline in

$eGFR_{CG}$ of ≥ 25% in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 12.4%, 54 of 434 subjects; STB 26.9%, 116 of 431 subjects; $p < 0.001$).

Treatment-emergent proteinuria by urinalysis (dipstick) through the Week 48 data cut date was the fourth key alpha-protected safety endpoint for this study. Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which were dependent on the results from preceding tests. Fewer subjects in the E/C/F/TAF group than in the STB group had treatment-emergent proteinuria (E/C/F/TAF 30.4% [132 of 434 subjects]; STB 37.4% [161 of 431 subjects]; $p = 0.034$). Most of the proteinuria was Grade 1. There were decreases from baseline in median urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR) values for the E/C/F/TAF group at Week 48 compared with increases from baseline for the STB group, the differences of which were statistically significant (median [Q1, Q3] percentage change from baseline at Week 48: UPCR: E/C/F/TAF −1.5% [−33.4%, 38.9%], STB 18.7% [−24.4%, 75.1%], $p < 0.001$; UACR: E/C/F/TAF −4.4% [−31.7%, 41.3%], STB 6.4% [−29.6%, 72.4%], $p = 0.031$). A summary of UACR to UPCR ratios from baseline to Week 48 showed no change in the median percentage change from baseline for the E/C/F/TAF group compared with a decrease in the STB group at Week 48; the difference was statistically significant between treatment groups at Week 48 ($p = 0.022$). Urine creatinine was similar for both treatment groups at each measured time point.

There were statistically significant differences between treatment groups in urine retinol binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, and fractional excretion of uric acid (FEUA) using adjusted serum creatinine at all time points through Week 48 ($p < 0.001$ for the differences between the 2 groups in percentage changes from baseline at Week 48 for all parameters). There were no differences in fractional excretion of phosphate ($FEPO_4$) or the renal tubular maximum reabsorption rate of phosphate to the GFR (TmP/GFR) ratio using adjusted serum creatinine values at Week 48.

Ocular Safety

The incidence of AEs in the eye disorders system organ class (SOC) was similar for both treatment groups (E/C/F/TAF 5.3%, 23 subjects; STB 6.3%, 27 subjects). Five subjects (1.1%) in the E/C/F/TAF group and 2 subjects (0.5%) in the STB group had AEs in the eye disorders SOC considered related to study drugs by the investigator. One subject in the E/C/F/TAF group had an SAE in the eye disorders SOC (retinal detachment). No eye disorder AEs resulted in discontinuation of study drugs. There were no AEs of uveitis during the study.

Laboratory Abnormalities

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.

The majority of subjects had at least 1 laboratory abnormality (E/C/F/TAF 93.1%, 404 subjects; STB 90.5%, 390 subjects). The majority of reported abnormalities were Grade 1 or 2.

Metabolic Laboratory Parameters

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and glucose at Weeks 24 and 48. The median (Q1, Q3) increase from baseline was greater in the E/C/F/TAF group compared with the STB group at Week 48, as follows: total cholesterol: E/C/F/TAF 30 (13, 48) mg/dL; STB 12 (−8, 28) mg/dL ($p < 0.001$); direct LDL: E/C/F/TAF 15 (2, 30) mg/dL; STB 2 (−13, 17) mg/dL ($p < 0.001$); HDL: E/C/F/TAF 7 (2, 13) mg/dL; STB 3 (−2, 9) mg/dL ($p < 0.001$); triglycerides: E/C/F/TAF 18 (−9, 49) mg/dL; STB 8 (−20, 39) mg/dL ($p = 0.003$); glucose: E/C/F/TAF 3 (−4, 9) mg/dL; STB 1 (−6, 8) mg/dL ($p = 0.032$). For total cholesterol to HDL ratio, there was an increase from baseline at Week 48 in the E/C/F/TAF group, and no change at Week 48 in the STB group (median [Q1, Q3] change from baseline at Week 48: E/C/F/TAF 0.1 [−0.3, 0.6], STB 0.0 [−0.5, 0.5]; $p = 0.016$ for the difference between treatment groups).

In general, AEs and graded laboratory abnormalities related to lipid parameters were more common in the E/C/F/TAF group compared with the STB group. However, none of the AEs were serious or resulted in discontinuation of study drugs. The majority of laboratory abnormalities were Grade 1 or 2; Grade 3 or 4 abnormalities were infrequent, and reported for similar percentages of subjects in each treatment group.

Patient Reported Outcomes

Health Utilization Assessment

Healthcare utilization up to Week 48 was comparable in both treatment groups as assessed by the numbers of hospitalizations, unplanned visits for a healthcare issue, and unplanned specialty care provider visits.

EQ-5D-3L

For each of the 5 dimensions of the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), response profiles were similar between the 2 treatment groups at baseline and remained similar through Week 48. There were no significant differences between treatment groups in the changes from baseline in the EQ-5D-3L index score (median change from baseline was 0.000 in both groups) and the EQ visual analogue scale (EQ VAS) (median change from baseline was 3.0 in the E/C/F/TAF group and 2.0 in the STB group), or in the responder analysis for the EQ-5D-3L index score at Week 48.

Conclusions

The Week 48 conclusions from this study are as follows:

- E/C/F/TAF once daily was noninferior to STB once daily when administered for 48 weeks to HIV-infected, ART-naive adults, as assessed using the FDA snapshot algorithm with HIV-1 RNA < 50 copies/mL. Virologic success rates at Week 48 were as follows: E/C/F/TAF 93.1%; STB 92.4%; difference in percentages: 1.0%, 95.002% CI: −2.6% to 4.5%. Both

groups had increases from baseline in mean CD4 cell counts (Week 48: E/C/F/TAF 235 cells/μL; STB 222 cells/μL).

- Administration of E/C/F/TAF resulted in TAF exposure associated with efficacy and consistent with historical and concurrent study data for E/C/F/TAF in Phase 2 and Phase 3 studies in HIV-infected subjects.

- Administration of E/C/F/TAF resulted in 89.58% lower plasma TFV relative to STB. Conversely, administration of E/C/F/TAF resulted in higher intracellular TFV-DP concentrations relative to STB.

- Both E/C/F/TAF and STB were well tolerated, with comparably low rates of SAEs considered related to study drugs and AE-related drug discontinuations in both treatment groups.

- There were statistically significant differences favoring E/C/F/TAF over STB at Week 48 for all 4 key (alpha-protected) secondary safety endpoints: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), and change from baseline in treatment-emergent proteinuria ($p = 0.034$).

- E/C/F/TAF showed an improved renal and bone safety profile compared with STB, as evidenced by significantly less of the following in subjects who received E/C/F/TAF:

  — Decline in hip and spine BMD

  — Increase in serum creatinine

  — Reduction in $eGFR_{CG}$

  — Proteinuria

- Increases from baseline in fasting lipid parameters were higher in the E/C/F/TAF group than the STB group.

2.1.1.2. Study GS-US-292-0111 (Phase 3)

A complete study description and results for Study GS-US-292-0111 are available in the CSR (GS-US-292-0111 Week 48) and a brief narrative of this study is presented below.

Title

A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naive Adults

Objectives

The primary objective of this study was as follows:

- To evaluate the efficacy of an FDC tablet containing E/C/F/TAF versus STB in HIV-infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives of this study were as follows:

- To determine the safety of the 2 treatment regimens as determined by the percentage change from baseline in hip and spine BMD at Week 48
- To determine the safety of the 2 treatment regimens as determined by the change from baseline in serum creatinine at Week 48
- To evaluate the safety and tolerability of the 2 treatment regimens through Week 48
- To evaluate the efficacy, durability, safety and tolerability of the 2 treatment regimens through Week 96

Diagnosis and Main Criteria for Inclusion

Eligible subjects were ART-naive (excluding PrEP or PEP up to 6 months prior to screening), HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and had an $eGFR_{CG} \geq 50$ mL/min, except in France and Sweden where subjects must have had an $eGFR_{CG}$ of ≥ 70 mL/min at screening.

SUMMARY OF RESULTS

Subject Disposition

In this study, 1070 subjects were screened, 872 subjects were randomized, and 866 subjects received at least 1 dose of study drug (E/C/F/TAF 431 subjects; STB 435 subjects); 4 subjects randomized to E/C/F/TAF and 2 subjects randomized to STB did not receive study drug.

A total of 804 subjects (E/C/F/TAF 94.7%, 408 subjects; STB 91.0%, 396 subjects) were continuing study drugs as of the Week 48 data cut date. Of the 866 subjects randomized and treated, 62 subjects (7.2%) discontinued study drugs (E/C/F/TAF 5.3%, 23 subjects; STB 9.0%, 39 subjects) and 46 subjects (5.3%) discontinued from the study prior to the Week 48 data cut date (E/C/F/TAF 4.2%, 18 subjects; STB 6.4%, 28 subjects). The reasons for premature discontinuation of study drugs were generally balanced between study groups. The most common reasons for discontinuation of study drugs were lost to follow-up (E/C/F/TAF 2.3%, 10 subjects; STB 2.1%, 9 subjects), withdrawal of consent (E/C/F/TAF 0.9%, 4 subjects; STB 2.1%, 9 subjects), and AE (E/C/F/TAF 0.9%, 4 subjects; STB 1.4%, 6 subjects).

Subject Demographics and Baseline Disease Characteristics

Demographic and general baseline characteristics were similar between the 2 treatment groups. The majority of subjects were male (84.6% overall). The median age was 33 years (range: 18 to 66 years) in the E/C/F/TAF group and 34 years (range: 18 to 71 years) in the STB group ($p = 0.049$). The most common races were white (55.2%), black (30.1%), and other (10.5%), and most subjects were not Hispanic or Latino (76.2%). The median (Q1, Q3) value for BMI at baseline was 24.7 (22.1, 28.2) kg/m^2.

Baseline disease characteristics were generally similar between the 2 treatment groups. Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.55 (4.12, 4.94) log_{10} copies/mL. At baseline, 77.9% of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL, 17.3% had > 100,000 to ≤ 400,000 copies/mL, and 4.7% had > 400,000 copies/mL. Overall, the median (Q1, Q3) CD4 count was 406 (284, 536) cells/μL. Overall, 3.4% (29 subjects) had a baseline CD4 cell count < 50 cells/μL and 10.3% (89 subjects) had 50 to < 200 cells/μL. The most common HIV risk factor category was homosexual sex (74.9% of subjects); 25.6% of subjects reported heterosexual sex as the mode of infection. The majority of subjects (89.9%) had asymptomatic HIV-1 infection; 5.8% had symptomatic HIV-1 infection, and 4.3% were diagnosed with AIDS.

At baseline, the median (Q1, Q3) $eGFR_{CG}$ value was similar in the E/C/F/TAF group (115.9 [98.4, 135.6] mL/min) compared with the STB group (114.7 [99.6, 133.4] mL/min). Similar results were obtained using the $eGFR_{CKD\text{-}EPI,\ Creatinine}$ and eGFR by CKD-EPI cystatin C formulas. Ninety-five subjects (11.0%) had proteinuria (Grade 1 or 2 by dipstick) on urinalysis.

Overall, 15.8% of subjects had a medical history of hypertension, 11.5% had a medical history of hyperlipidemia, 4.3% had a medical history of diabetes, and 0.9% had a medical history of cardiovascular disease.

Efficacy Results

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm. Virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the FAS. Virologic success rates were as follows: E/C/F/TAF 91.6%, STB 88.5%; difference in percentages: 3.1%, 95.002% CI: −1.0% to 7.1%. Because the lower bound of the 2-sided 95.002% CI of the difference in the response (E/C/F/TAF – STB) rate was greater than the prespecified −12% margin, E/C/F/TAF was determined to be noninferior to STB. Virologic success rates for the Week 48 PP Analysis Set were consistent with those for the FAS and were as follows: E/C/F/TAF 97.2%, 386 of 397 subjects; STB 95.4%, 374 of 392 subjects; difference in percentages: 1.6%, 95.002% CI: −1.1% to 4.4%).

Virologic outcomes at Week 48 were similar between the 2 treatment groups when assessed using the FDA snapshot algorithm, defined as HIV-1 RNA < 20 copies/mL, based on the FAS. Virologic success rates were as follows: E/C/F/TAF 82.4%, STB 80.7%; difference in percentages: 1.4%, 95% CI: −3.7% to 6.5%.

High and similar rates of virologic suppression were achieved in the 2 treatment groups, as assessed using the M = F and M = E methods at Week 48 based on the FAS. The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 were as follows: M = F: E/C/F/TAF 92.3%; STB 90.8% (difference: 1.5%, 95% CI: −2.3% to 5.3%); M = E: E/C/F/TAF 97.1%; STB 95.4% (difference: 1.5%, 95% CI: −1.2% to 4.3%). Results for the Week 48 PP Analysis Set were consistent with those for the FAS.

HIV-1 RNA levels decreased rapidly in the first 2 weeks following initiation of study drug. After Week 8, the decreases were stable and similar between the 2 groups; mean (SD) decreases at Week 48 were as follows: E/C/F/TAF 3.19 (0.705) $\log_{10}$ copies/mL; STB 3.14 (0.745) $\log_{10}$ copies/mL; difference in LSM of −0.06 $\log_{10}$ copies/mL, 95% CI: −0.15 to 0.02 $\log_{10}$ copies/mL.

The mean (SD) increase from baseline in CD4 cell count at Week 48 (observed data) based on the FAS was greater for the E/C/F/TAF group compared with the those in the STB group, as follows: E/C/F/TAF 225 (171.2) cells/μL; STB 200 (162.5) cells/μL; difference in LSM 27 cells/μL (95% CI: 4 to 50 cells/μL, p = 0.019). A similar trend was observed using the M = LOCF method. Results for the Week 48 PP were consistent with the results for the FAS.

At Week 48, the rates of virologic success by FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) for subgroups according to age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, region, or study drug adherence rate were similar for the E/C/F/TAF and STB groups. The 95% CIs for differences in virologic success between treatment groups included zero for most subgroups evaluated, suggesting no differences between the treatments. For 4 subgroups (female subjects, subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL, subjects with baseline CD4 count ≥ 200 cell/μL, and subjects with an adherence rate ≥ 95%), the differences in virologic success favored E/C/F/TAF over STB, as the lower bound of the 95% CI was > 0.

Pharmacokinetics Results

The steady-state plasma PK parameters of TAF following administration of E/C/F/TAF for subjects who participated in the intensive PK substudy are shown in Table 8.

Table 8. E/C/F/TAF Study GS-US-292-0111: Summary of TAF Pharmacokinetic Parameters (PK Substudy Analysis Set)

Treatment E/C/F/TAF	AUC_{last} (ng*h/mL) Mean (%CV) (N = 20)[a]	C_{max} (ng/mL) Mean (%CV) (N = 20)[a]	T_{max} (h) Median (Q1, Q3) (N = 21)	$t_{1/2}$ (h) Median (Q1, Q3) (N = 19)[b]
TAF	259.0 (71.6)	201.6 (72.6)	1.00 (0.50, 2.05)	0.48 (0.39, 0.68)

a For Subject *CR , $AUC_{0\text{-}last}$ and C_{max} could not be estimated.
b For Subjects *CR and *CS , $t_{1/2}$ could not be estimated.
Source: GS-US-292-0111 Week 48 CSR, Section 15.1, Table 61.1

The steady-state plasma PK parameters for TFV following administration of E/C/F/TAF or STB for subjects who participated in the intensive PK substudy are shown in Table 9.

Table 9. E/C/F/TAF Study GS-US-292-0111: Summary of TFV Pharmacokinetic Parameters (PK Substudy Analysis Set)

TFV PK Parameter[a]	Mean (%CV) by Treatment	
	E/C/F/TAF (Test) (N = 21)	STB (Reference) (N = 15)
AUC_{tau} (ng*h/mL)	286.2 (22.5)	3772.1 (22.2)
C_{max} (ng/mL)	16.7 (26.2)	457.7 (27.7)
C_{tau} (ng/mL)	9.6 (25.0)	77.9 (28.0)
T_{max} (h)	3.00 (1.00, 4.00)	1.03 (0.78, 1.55)
$t_{1/2}$ (h)	35.77 (26.69, 65.29)	12.68 (12.39, 15.34)

a Values are listed as mean (%CV) except T_{max} and $t_{1/2}$, which are listed as median (Q1, Q3).
Source: GS-US-292-0111 Week 48 CSR, Section 15.1, Table 61.2

The statistical comparisons for TFV following administration of E/C/F/TAF or STB for subjects who participated in the intensive PK substudy are shown in Table 10.

Table 10. E/C/F/TAF Study GS-US-292-0111: Statistical Comparisons of TFV Pharmacokinetic Parameter Estimates Between Test and Reference Treatments (PK Substudy Analysis Set)

TFV PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 21)	STB (N = 15)		
AUC_{tau} (ng*h/mL)	278.73	3682.91	7.57	(6.62, 8.65)
C_{max} (ng/mL)	16.14	442.74	3.65	(3.12, 4.26)
C_{tau} (ng/mL)	9.34	74.69	12.51	(10.59, 14.78)

Source: GS-US-292-0111 Week 48 CSR, Section 15.1, Table 63

The statistical comparison of TFV-DP AUC_{tau} following administration of E/C/F/TAF or STB for subjects who participated in the intensive PK substudy is shown in Table 11.

Table 11. E/C/F/TAF Study GS-US-292-0111: Statistical Comparisons of TFV-DP AUC_{tau} Between Test and Reference Treatments (PBMC PK Substudy Analysis Set)

TFV-DP PK Parameter	Mean (%CV) by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 11)	STB (N = 4)		
AUC_{tau} (µmol*h/L)	22.6 (41.2)	8.6 (53.6)	270.90	(164.29, 446.71)

Source: GS-US-292-0111 Week 48 CSR, Section 15.1, Tables 62 and 63

Overall, the steady-state plasma exposures of TAF and TFV, and intracellular exposure of TFV-DP, were in the range of historical data and concurrent study data from the ongoing Phase 3 program. Plasma exposures of TAF and TFV were consistent with exposures observed following administration of E/C/F/TAF in HIV-infected subjects in Phase 2 and Phase 3 studies (Studies GS-US-292-0102 and GS-US-292-0104) and following administration of E/C/F/TAF or TAF 25-mg single-agent in healthy subjects (Study GS-US-292-0103). Plasma TFV exposure (AUC_{tau}) following administration of E/C/F/TAF was 92.43% lower than TFV exposure achieved with administration of STB. The TFV PK parameters in subjects receiving STB were consistent with historical data {30848}, {34198}. The TFV exposure following E/C/F/TAF was also lower than the exposure seen after coadministration of TDF with or without boosted PIs.

The PBMC TFV-DP AUC_{tau} was higher in subjects receiving E/C/F/TAF compared with subjects receiving STB, and in the range of concurrent and historical study data on TFV-DP exposure observed following administration of E/C/F/TAF (Studies GS-US-292-0102 and GS-US-292-0104) as well as administration of TAF 25-mg single-agent (Study GS-US-120-0104).

Safety Results

E/C/F/TAF and STB were well tolerated in this study through a median duration of study drugs exposure of 48.1 and 48.3 weeks, respectively.

Adverse Events

Similar percentages of subjects in each group had any AE (E/C/F/TAF 88.6%, 382 subjects; STB 89.7%, 390 subjects). Three subjects died during the study, 1 in the E/C/F/TAF group and 2 in the STB group. The subject in the E/C/F/TAF group died as a result of alcohol intoxication. One subject in the STB group died as a result of acute myocardial infarction, 2 days after the onset of meningococcal meningitis. The second subject in the STB group died as a result of acute ethanol and multiple drug toxicity (reported as an SAE of recreational drug and alcohol overdose).

SAEs were reported for similar percentages of subjects in both treatment groups (E/C/F/TAF 7.7%, 33 subjects; STB 6.9%, 30 subjects). The incidence of SAEs considered related to study drugs by the investigator was low in both treatment groups (E/C/F/TAF 0 subjects; STB 0.2%, 1 subject). Similar percentages of subjects in both treatment groups had any AE considered related to study drugs by the investigator (E/C/F/TAF 37.1%, 160 subjects; STB 38.6%, 168 subjects); or any Grade 3 AE considered related to study drugs (E/C/F/TAF 0.7%, 3 subjects; STB 1.6%, 7 subjects). There were no Grade 4 AEs related to study drugs.

Similar percentages of subjects in both treatment groups had an AE leading to discontinuation of study drugs (E/C/F/TAF 0.9%, 4 subjects; STB 1.6%, 7 subjects). All AEs leading to discontinuation of study drugs, except for those reported in 2 subjects in the STB group (SAE of iridocyclitis in 1 subject, and nonserious AE of arthropod bite in 1 subject), were considered related to study drugs by the investigator. Four subjects, all in the STB group, had a confirmed pregnancy during the study; delivery was pending for the 3 of the subjects at the time of this

report, and a male infant was delivered with no reported complications during or after birth in the fourth subject.

The AEs by PT reported for ≥ 10% of subjects in either treatment group were as follows:

- E/C/F/TAF group — headache (17.2%, 74 subjects), nausea (16.2%, 70 subjects), diarrhea (16.0%, 69 subjects), upper respiratory tract infection (11.4%, 49 subjects), and nasopharyngitis (10.0%, 43 subjects)

- STB group — diarrhea (19.1%, 83 subjects), nausea (17.5%, 76 subjects), headache (13.1%, 57 subjects), nasopharyngitis (11.3%, 49 subjects), and upper respiratory tract infection (10.3%, 45 subjects)

Overall, the rates and types of AEs observed in this study were similar in the 2 groups, and consistent with the study population.

Bone Safety

The incidence of fracture events was low (0.9%, 4 subjects for each treatment group). Two fracture events were also reported as SAEs: ankle fracture (E/C/F/TAF) and thoracic vertebral fracture (STB). All reported fracture AEs were considered by the investigator as unrelated to the study drugs, and none resulted in discontinuation of study drugs. All fracture events were the result of trauma, and none were reported as fragility fractures.

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for this study, respectively. Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which were dependent on the results from preceding tests.

Mean percentage decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups Weeks 24 and 48). Mean (SD) percentage decreases from baseline at Week 48 in BMD were as follows: at the hip: E/C/F/TAF 0.420 % (3.2268%), STB 2.603% (3.1482%); at the spine: E/C/F/TAF 1.278% (3.0098%), STB 2.759% (3.0024%). Differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were also statistically significant ($p < 0.001$ at Weeks 24 and 48). At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a > 3% decrease from baseline in hip (E/C/F/TAF 14.5%, STB 45.4%) or spine BMD (E/C/F/TAF 28.0%, STB 46.2%).

Mean percentage increases from baseline in the bone turnover biomarkers C-telopeptide (bone resorption) and P1NP (bone formation), as well as PTH, a hormone involved in bone metabolism, were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups at both Weeks 24 and 48 for all parameters except PTH at Week 24 [$p = 0.003$]). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows: C-telopeptide E/C/F/TAF 7.9% (−10.8%, 30.8%), STB 18.6% (0.0%, 42.3%); P1NP E/C/F/TAF 25.51% (2.45%, 55.46%), STB 69.48% (39.65%, 122.90%); PTH E/C/F/TAF 27.8% (0.3%, 69.0%), STB 50.5% (14.4%, 94.1%).

Renal Safety

One subject, in the STB group, had a renal AE that resulted in discontinuation of study drugs: nonserious, Grade 3 renal failure (reported as renal insufficiency) with associated AEs of hypertensive crises and cerebrovascular accident. The renal failure was considered related to study drugs by the investigator. Only 1 renal SAE (ureteric calculus) was reported for 1 subject in the E/C/F/TAF group, and the event was not considered related to study drugs. There were no reports of PRT (including Fanconi Syndrome).

Change from baseline in serum creatinine at Week 48 was the third key alpha-protected safety endpoint for this study. Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which were dependent on the results from preceding tests. Increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. Increases were observed by Week 2 for each treatment group, and remained stable through Week 48 (mean changes [SD] from baseline at Week 48: E/C/F/TAF 0.08 (0.136) mg/dL, STB 0.12 (0.283) mg/dL. The difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48 ($p = 0.008$ at Week 48).

Decreases from baseline in median $eGFR_{CG}$ values were smaller in the E/C/F/TAF group compared with the STB group. Decreases were observed by Week 2 for each treatment group and remained stable through Week 48 (median [Q1, Q3] changes from baseline at Week 48: E/C/F/TAF −5.7 [−14.3, 3.0] mL/min, STB −11.9 [−19.8, −2.1] mL/min). The difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48 ($p < 0.001$ at Week 48). A smaller percentage of subjects had a decrease from baseline in $eGFR_{CG}$ of $\geq 25\%$ in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 12.4%, 53 of 428 subjects; STB 24.4%, 106 of 434 subjects; $p < 0.001$).

Treatment-emergent proteinuria by urinalysis (dipstick) through the Week 48 data cut was the fourth key alpha-protected safety endpoint for this study. Fewer subjects in the E/C/F/TAF group than in the STB group had at least 1 recorded, graded proteinuria by dipstick during the study (E/C/F/TAF 32.0% [137 of 428 subjects]; STB 36.2% [157 of 434 subjects]; $p = 0.25$). Most of the proteinuria was Grade 1. There were decreases from baseline in median UPCR and UACR values for the E/C/F/TAF group at Week 48 compared with increases from baseline for the STB group, the differences of which were statistically significant (median [Q1, Q3] change from baseline at Week 48: UPCR: E/C/F/TAF −8.4% [−34.5%, 46.8%], STB: 20.2% [−21.0%, 79.5%], $p < 0.001$; UACR: E/C/F/TAF −4.7% [−34.3%, 31.9%], STB 7.4% [−25.7%, 57.5%], $p = 0.014$). Urine creatinine was similar for both treatment groups at each measured time point.

There were statistically significant differences between treatment groups in urine RBP to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, and FEUA using adjusted serum creatinine at all time points through Week 48 ($p < 0.001$ for the differences between the 2 groups in percentage changes from baseline at Week 48 for all parameters). In addition, there were statistically significant differences between treatment groups in $FEPO_4$ using adjusted serum creatinine at all time points except Week 24 ($p = 0.012$ at Week 48). There were no differences in TmP/GFR ratio using adjusted serum creatinine values at Week 48.

Ocular Safety

The incidence of AEs in the eye disorders SOC was similar for both treatment groups (E/C/F/TAF 8.8%, 38 subjects; STB 8.3%, 36 subjects). Eleven subjects (2.6%) in the E/C/F/TAF group and 7 subjects (1.6%) in the STB group had AEs in the eye disorders SOC considered related to study drugs by the investigator. One subject in each treatment group had AEs in the eye disorders SOC resulted in discontinuation of study drugs. One subject in the STB group had an anterior uveitis event, reported as an SAE of iridocyclitis, which resulted in discontinuation of study drugs, and was considered unrelated to study drugs by the investigator.

Laboratory Abnormalities

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.

The majority of subjects had at least 1 laboratory abnormality (E/C/F/TAF 94.2%, 403 subjects; STB 89.6%, 389 subjects). The majority of reported abnormalities were Grade 1 or 2.

Metabolic Laboratory Parameters

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct LDL, HDL, triglycerides, and glucose at Weeks 24 and 48. The median (Q1, Q3) increase from baseline was greater in the E/C/F/TAF group compared with the STB group at Week 48, as follows: total cholesterol: E/C/F/TAF 27 (12, 48) mg/dL; STB 14 (−3, 34) mg/dL ($p < 0.001$); direct LDL: E/C/F/TAF 11 (−3, 29) mg/dL; STB 2 (−11, 17) mg/dL ($p < 0.001$); fasting HDL: E/C/F/TAF 7 (1, 13) mg/dL; STB 4 (−1, 10) mg/dL ($p < 0.001$); triglycerides: E/C/F/TAF 18 (−9, 55) mg/dL; STB 4 (−21, 34) mg/dL ($p < 0.001$); fasting glucose: E/C/F/TAF 2 (−3, 9) mg/dL; STB 2 (−5, 8) mg/dL ($p = 0.13$). For total cholesterol to HDL ratio, there was an increase from baseline at Week 48 in the E/C/F/TAF group, and no change at Week 48 in the STB group (median [Q1, Q3] change from baseline at Week 48: E/C/F/TAF 0.1 [−0.3, 0.5], STB 0.0 [−0.4, 0.4]; $p = 0.016$ for the difference between treatment groups).

In general, AEs and graded laboratory abnormalities related to lipid parameters were more common in the E/C/F/TAF group compared with the STB group. Except for 1 subject, none of the AEs were serious or resulted in discontinuation of study drugs. One subject in the E/C/F/TAF group had Grade 4 elevated triglycerides that resulted in discontinuation of study drugs.
The majority of laboratory abnormalities were Grade 1 or 2; Grade 3 or 4 abnormalities were infrequent, and reported for similar percentages of subjects in each treatment group.

Patient Reported Outcomes

Health Utilization Assessment

Healthcare utilization up to Week 48 was comparable in both treatment groups as assessed by the numbers of hospitalizations, unplanned visits for a healthcare issue, and unplanned specialty care provider visits.

EQ-5D-3L

For each of the 5 dimensions of the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), response profiles were similar between the 2 treatment groups at baseline and remained similar through Week 48. There were no significant differences between treatment groups in the changes from baseline in the EQ-5D-3L Index Score (median change from baseline was 0.000 in both groups) and the EQ VAS (median change from baseline was 2.0 in the E/C/F/TAF group and 1.0 in the STB group), or in the responder analysis for the EQ-5D-3L Index Score at Week 48.

Conclusions

The Week 48 conclusions from this study are as follows:

- E/C/F/TAF once daily was noninferior to STB once daily when administered for 48 weeks to HIV-infected, ART-naive adults, as assessed using the FDA snapshot algorithm with HIV-1 RNA < 50 copies/mL. Virologic success rates at Week 48 were as follows: E/C/F/TAF 91.6%; STB 88.5%; difference in percentages: 3.1%, 95.002% CI: −1.0% to 7.1%.
  Both groups had increases from baseline in mean CD4 cell counts, which were greater for the E/C/F/TAF group compared with the STB group (Week 48: E/C/F/TAF 225 cells/μL; STB 200 cells/μL; difference in LSM: 27 cells/μL, 95% CI: 4 to 50 cells/μL; p = 0.019).

- Administration of E/C/F/TAF resulted in TAF exposure associated with efficacy and consistent with historical and concurrent study data for E/C/F/TAF in Phase 2 and 3 studies in HIV-infected subjects.

- Administration of E/C/F/TAF resulted in 92.43% lower plasma TFV relative to STB. Conversely, administration of E/C/F/TAF resulted in higher intracellular TFV-DP concentrations relative to STB.

- Both E/C/F/TAF and STB were well tolerated, with comparably low rates of SAEs considered related to study drugs and AE-related drug discontinuations in both treatment groups.

- There were statistically significant differences favoring E/C/F/TAF over STB at Week 48 for 3 key (alpha-protected) safety endpoints: mean percentage changes from baseline in hip BMD (p < 0.001) and spine BMD (p < 0.001), and mean change from baseline in serum creatinine (p = 0.008).

- E/C/F/TAF showed an improved renal and bone safety profile compared with those who received STB, as evidenced by significantly less of the following in subjects who received E/C/F/TAF:

  — Decline in hip and spine BMD

  — Increase in serum creatinine

  — Reduction in $eGFR_{CG}$

- Increases from baseline in fasting lipid parameters were higher in the E/C/F/TAF group than the STB group.

2.1.1.3. Study GS-US-292-0102 (Phase 2)

A complete study description and results for Study GS-US-292-0102 are available in the CSR (GS-US-292-0102 Week 96) and a brief narrative of this study is presented below.

Title

A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide Single Tablet Regimen Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen in HIV-1 Infected, Antiretroviral Treatment-Naive Adults

Objectives

The primary objective of this study was as follows:

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

The secondary objectives of this study were as follows:

- To evaluate the efficacy of a regimen containing E/C/F/TAF versus STB in HIV-infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48.

- To evaluate the safety and tolerability of the 2 treatment regimens through 48 weeks of treatment.

- To evaluate the safety and efficacy of switching subjects suppressed on a regimen containing DRV+COBI to E/C/F/TAF.

Diagnosis and Main Criteria for Inclusion

Subjects enrolled in the randomized phase of the study were HIV-infected adults with plasma HIV-1 RNA levels ≥ 5000 copies/mL, no prior use of any approved or experimental anti-HIV drug for any length of time, and had an $eGFR_{CG}$ ≥ 70 mL/min at screening.

Additional subjects enrolled into the open-label extension phase had received a DRV+COBI-containing regimen in Study GS-US-299-0102, were treatment naive at the time of entry into that study, had reached at least the Week 48 visit (protocol-defined secondary endpoint), and were virologically suppressed (HIV-1 RNA < 50 copies/mL at the last study visit). These subjects were required to have an $eGFR_{CG}$ > 50 mL/min at entry into this study.

All subjects had documented sensitivity to TDF and FTC and CD4 cell count > 50 cells/μL.

SUMMARY OF RESULTS

Subject Disposition

A total of 171 subjects were randomized and 170 randomized subjects received at least 1 dose of study drug (E/C/F/TAF 112 subjects; STB 58 subjects); 1 subject randomized to E/C/F/TAF did not receive study drug.

Of the 170 subjects treated during the randomized phase, 7.1% (12 subjects) discontinued study drug treatment (E/C/F/TAF 6.3%, 7 subjects; STB 8.6%, 5 subjects) and 5.9% (10 subjects) discontinued from the study (E/C/F/TAF 4.5%, 5 subjects; STB 8.6%, 5 subjects). The most common reasons for discontinuation of study drug during the randomized phase were AE (E/C/F/TAF 3.6%, 4 subjects; STB 0%), lost to follow-up (E/C/F/TAF 1.8%, 2 subjects; STB 3.4%, 2 subjects), and subject noncompliance (E/C/F/TAF 0.9%, 1 subject; STB 1.7%, 1 subject).

A total of 266 subjects entered the extension phase and received E/C/F/TAF, including 158 subjects from this study who completed the 48-week randomized phase and 108 subjects who rolled over from Study GS-US-299-0102.

Of the 266 subjects who entered the extension phase, 264 are continuing treatment; 2 subjects (1 each in the E/C/F/TAF group and D/C/F/TAF to E/C/F/TAF group) discontinued treatment with study drug and discontinued from the study (lost to follow-up) during the extension phase.

Subject Demographics and Baseline Disease Characteristics

ART-Naive Subjects

Demographic and general baseline characteristics were similar between the 2 treatment groups in the randomized phase (Safety Analysis Set). The majority of subjects were male (97.1%), with a median age of 34 years (range: 18 to 71 years); most were either white (67.1%) or black (30.0%) and not Hispanic/Latino (78.8%). The median (Q1, Q3) value for BMI at baseline was 25.4. (22.9, 27.8) kg/m^2.

Baseline disease characteristics were similar between the 2 treatment groups in the randomized phase. The median (Q1, Q3) baseline HIV-1 RNA value was 4.55 (4.32, 4.91) $\log_{10}$ copies/mL, and CD4 count was 391 (259, 530) cells/μL. Overall, 79.4% of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL, 15.9% had > 100,000 to ≤ 400,000 copies/mL, and 4.7% had > 400,000 copies/mL. The most common HIV risk factor category was homosexual sex (88.8% of subjects). The majority of subjects (88.8%) had asymptomatic HIV infection; 8.2% of subjects had symptomatic HIV infection, and 2.9% of subjects were diagnosed with AIDS. Most subjects (91.8%) had no proteinuria (Grade 0 by dipstick) on urinalysis. The median (Q1, Q3) $eGFR_{CG}$ values were similar in the 2 treatment groups: E/C/F/TAF 115.2 (100.8, 131.7) mL/min, STB 113.3 (97.7, 129.4) mL/min. Less than 5% of subjects had medical histories of diabetes (3.5%) or cardiovascular disease (2.9%); 11.8% of subjects had a medical history of hypertension and 12.4% of subjects had a medical history of hyperlipidemia.

Virologically Suppressed Subjects who Switched Treatment

Most subjects in the switch groups had baseline HIV-1 RNA values < 50 copies/mL (all TDF to TAF: 93.4%; D/C/F/TAF to E/C/F/TAF: 97.1%).

Efficacy Results

ART-Naive Subjects

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 of the randomized phase using the FDA snapshot algorithm. Virologic outcomes at Week 24 were similar between the 2 treatment groups for the primary endpoint analysis using the FAS. Virologic success rates were as follows: E/C/F/TAF 88.4%, STB 89.7%; difference in percentages: −2.9%, 95% CI −13.5% to 7.7%.

Similar rates of virologic success in the 2 treatment groups were achieved through Week 48 when assessed using the FDA snapshot algorithm using the FAS, as follows: E/C/F/TAF 88.4%, STB 87.9%; difference in percentages: −1.0%, 95% CI: −12.1% to 10.0%.

High and similar rates of virologic suppression were achieved and maintained in the 2 treatment groups, as assessed using the M = F and M = E methods at Weeks 24 and 48. The percentages of subjects with virologic suppression (HIV-1 RNA < 50 copies/mL) at Week 48 were as follows: M = F: E/C/F/TAF 90.2%, STB 89.7% (difference: −1.2%, 95% CI: −11.6% to 9.2%); M = E: E/C/F/TAF 94.4%, STB 92.9% (difference: −0.1%, 95% CI: −9.0% to 8.9%).

High rates of virologic suppression (HIV-1 RNA levels < 50 copies/mL) were achieved and maintained through Week 96 for the E/C/F/TAF group in the extension phase (M = F at Week 96: 87.5%; M = E at Week 96: 96.1%).

The mean (SD) increases from baseline in CD4 cell count were similar for each treatment group through Week 48 (observed data), as follows: E/C/F/TAF 177 [144.1] cells/μL; STB 204 [120.4] cells/μL; difference in LSM: −19 cells/μL, 95% CI: −63 to 26 cells/μL.

CD4 cell counts continued to increase for the E/C/F/TAF group through the extension phase. The mean (SD) change from baseline at Week 96 was 284 (191.5) cells/μL.

At Week 24, the rate of virologic success by FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) for subgroups according to age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, or study drug adherence rate was similar for the E/C/F/TAF and STB groups. The 95% CIs for differences in virologic success between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments. Data for Week 48 were consistent with results for Week 24.

The resistance analysis population comprised 6 subjects who all experienced confirmed virological rebound during the randomized phase: E/C/F/TAF 2.7%, 3 of 112 subjects; STB 5.2%, 3 of 58 subjects. No subjects experienced virologic rebound from Week 48 of the randomized phase to Week 96 in the extension phase. None of the 3 subjects from the E/C/F/TAF group analyzed for resistance demonstrated emergence of resistance to study drugs, and all 3 subjects showed HIV-1 RNA resuppression to < 50 copies/mL upon continued treatment with E/C/F/TAF. In contrast, 2 of the 3 subjects from the STB group analyzed for resistance had emergent resistance to study drugs.

Virologically Suppressed Subjects who Switched Treatment

Virologic suppression was maintained and CD4 cell count increased in subjects who switched treatment to E/C/F/TAF in the extension phase. At Week 24 of the extension phase, 98.9% of subjects in the all TDF to TAF group had HIV-1 RNA levels < 50 copies/mL (M = E), and mean (SD) change from open-label baseline in CD4 cell count was 61 (159.1) cells/μL.

Pharmacokinetics Results

Steady-state plasma PK parameters were determined following administration of E/C/F/TAF for subjects who participated in the intensive PK substudy (n = 19).

For TAF, the median (Q1, Q3) plasma half-life was 0.47 (0.37 to 0.87) hours, no drug was detectable 8 hours after administration, and the mean (%CV) AUC_{last} was 227.5 (47.3) ng*h/mL, consistent with historical data for subjects administered E/C/F/TAF or TAF 25-mg single-agent (Study GS-US-292-0103).

Administration of E/C/F/TAF led to lower (> 90%) mean (%CV) systemic TFV AUC_{tau} (326.2 [14.8] ng*h/mL) versus administration of STB (3795.2 [21.9] ng*h/mL) and versus coadministration of TDF with boosted PIs.

The PBMC TFV-DP AUC_{tau} (E/C/F/TAF 10 subjects; STB 5 subjects) was markedly higher in subjects receiving E/C/F/TAF compared with subjects receiving STB. The TFV-DP AUC_{tau} geometric least-squares mean (GLSM) ratio of 531.83% was consistent with the approximate 5- to 7-fold increase in TFV-DP exposure observed following administration of TAF 25 mg versus TDF 300 mg (Study GS-US-120-0104).

The plasma exposures (mean [%CV] systemic AUC_{tau}) of EVG (22,797.0 [34.7 ng*h/mL), COBI (9459.1 [33.9] ng*h/mL), and FTC (11,714.1 [16.6] ng*h/mL were consistent with historical data for these agents

Safety Results

ART-Naive Subjects

E/C/F/TAF and STB were well tolerated during the randomized phase of this study through a median duration of study drugs exposure of 61.1 weeks prior to unblinding. Cumulatively, E/C/F/TAF was well tolerated through a median duration of study drug exposure of 105.3 weeks for the E/C/F/TAF group.

Adverse Events

Similar percentages of subjects in each group had any AE. An overall summary of AEs during the randomized phase is shown in Table 12:

Table 12. E/C/F/TAF Study GS-US-292-0102: Overall Summary of Adverse Events (Safety Analysis Set)

	E/C/F/TAF (N = 112)	STB (N = 58)
Adverse Event	107 (95.5%)	57 (98.3%)
Grade 2, 3, or 4 Adverse Event	72 (64.3%)	29 (50.0%)
Grade 3 or 4 Adverse Event	13 (11.6%)	3 (5.2%)
Study Drug-Related Adverse Event	43 (38.4%)	19 (32.8%)
Grade 2, 3, or 4 Study Drug-Related Adverse Event	9 (8.0%)	1 (1.7%)
Grade 3 or 4 Study Drug-Related Adverse Event	1 (0.9%)	0
Serious Adverse Event	12 (10.7%)	3 (5.2%)
Adverse Event Leading to Premature Study Drug Discontinuation	4 (3.6%)	0

Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 20.1

No SAEs were considered related to study drug by the investigator. Four subjects (3.6%) in the E/C/F/TAF group had any AE leading to premature study drug discontinuation. One subject in the E/C/F/TAF group had 2 AEs (flushing and photosensitivity reaction) resulting in discontinuation of study drugs that were considered related to study drugs by the investigator. No subject died. One subject in each treatment group had a confirmed pregnancy, 1 of which was reported as an SAE for (E/C/F/TAF). The AEs by PT reported for at least 10% of subjects in either treatment group were as follows:

- E/C/F/TAF group — nausea (22.3%, 25 subjects); diarrhea (17.0%, 19 subjects); upper respiratory tract infection and fatigue (both 16.1%, 18 subjects); and depression (10.7%, 12 subjects)

- STB group — upper respiratory tract infection (20.7%, 12 subjects); diarrhea (15.5%, 9 subjects); back pain and headache (both 13.8%, 8 subjects); nausea (12.1%, 7 subjects); and cough (10.3%, 6 subjects)

Nausea was reported for a higher percentage of subjects in the E/C/F/TAF group than in the STB group (E/C/F/TAF 22.3%, 25 subjects; STB 12.1%, 7 subjects), and was the most common AE considered related to the study drugs by the investigator (E/C/F/TAF 12.5%, 14 subjects, STB 8.6%, 5 subjects). Study drug-related nausea typically occurred in the first few days of therapy and lasted 1 to 2 days. All study drug-related AEs of nausea were Grade 1 and the majority resolved without treatment. No subject in either group discontinued study drugs due to nausea.

The overall AE profile for the E/C/F/TAF group through a median exposure of 105.3 weeks was consistent with that in the randomized phase.

Bone Safety

The incidence of fracture events was low (E/C/F/TAF 1 subject, STB 2 subjects). All fracture AEs were the result of trauma, considered by the investigator as unrelated to the study drugs, and none resulted in discontinuation of study drug.

Decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between groups in the mean percentage changes from baseline in hip or spine BMD at Weeks 24 and 48).

Mean (SD) percentage decreases from baseline in hip BMD were as follows:

- At Week 24: E/C/F/TAF 0.42% (1.678), STB 2.02% (2.664)
- At Week 48: E/C/F/TAF 0.67% (2.180), STB 3.12% (3.367)

Mean (SD) percentage decreases from baseline in spine BMD were as follows:

- At Week 24: E/C/F/TAF 0.93% (2.965), STB 2.55% (2.507)
- At Week 48: E/C/F/TAF 1.02% (3.447), STB 3.24% (3.219)

In the E/C/F/TAF group at Week 96, mean (SD) percentage decreases from baseline in hip or spine BMD were consistent with results at Week 48.

Increases from baseline in the bone biomarkers C-telopeptide and P1NP were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups in median percent changes from baseline at Weeks 24 and 48).

Median percent changes from baseline in C-telopeptide were as follows:

- At Week 24: E/C/F/TAF 22.08%, STB 62.19%
- At Week 48: E/C/F/TAF 19.29%, STB 78.25%

Median percent changes from baseline in P1NP were as follows:

- At Week 24 : E/C/F/TAF 3.66%, STB 45.12%
- At Week 48: E/C/F/TAF 8.77%, STB 69.39%

In the E/C/F/TAF group at Week 96, median percent changes from baseline in P1NP and C-telopeptide were consistent with results at Week 48.

Renal Safety

There were no cases of PRT reported in either treatment group, and no subjects discontinued study drugs due to a renal AE. Two subjects in the E/C/F/TAF group had events of renal failure considered unrelated to study drugs by the investigator. Neither event result in discontinuation of study drugs. No cases of renal failure were reported for subjects in the STB group.

Increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. Increases were observed at Week 2 for each treatment group, and remained stable through Week 48. Mean (SD) increases from baseline at Week 48 were as follows: E/C/F/TAF 0.08 (0.112) mg/dL, STB 0.12 (0.144) mg/dL (p = 0.011). In the E/C/F/TAF group at Week 96, increases from baseline in mean values for serum creatinine were consistent with results at Week 48.

Decreases from baseline in median $eGFR_{CG}$ were smaller in the E/C/F/TAF group compared with the STB group. Decreases were observed at Week 2 for each treatment group, and remained stable through Week 48. Median decreases from baseline at Week 48 were as follows: E/C/F/TAF 5.5 mL/min, STB 10.1 mL/min; p = 0.041.In the E/C/F/TAF group at Week 96, changes from baseline in $eGFR_{CG}$ were consistent with results at Week 48.

Proteinuria was reported in each treatment group (E/C/F/TAF 26.1% of subjects; STB 34.5% of subjects). Most proteinuria by dipstick was Grade 1 (E/C/F/TAF 23 subjects; STB 19 subjects).

No statistically significant differences were observed between the 2 treatment groups in median percentage change from baseline in UPCR or UACR (at Week 48, median percent changes from baseline for UPCR: E/C/F/TAF −7.2%, STB 13.5%; p = 0.092, for UACR: E/C/F/TAF −6.9%, STB 8.1%; p = 0.089). In the E/C/F/TAF group at Week 96, median percentage change from baseline in UPCR and UACR were consistent with results at Week 48.

There was no change from baseline at Week 48 in RBP to creatinine ratio for the E/C/F/TAF group, but an increase from baseline was seen for the STB group (E/C/F/TAF −0.1%, STB 36.2%; p = 0.002 for the difference between groups). The median percent change from baseline

in urine beta-2-microglobulin to creatinine ratio decreased for the E/C/F/TAF group compared with no change for the STB group through Week 48 (change from baseline at Week 48: E/C/F/TAF −40%, STB −1%; p = 0.007 for the difference between groups). At Week 96, there was a transient increase in median RBP to creatinine ratio for the E/C/F/TAF group (change from baseline at Week 96 was 20.6%). The median decrease from baseline in beta-2-microglobulin to creatinine ratio at Week 96 was consistent with that at Week 48.

Ocular Safety

Adverse events in the eye disorders SOC were reported for 7.1% of subjects in the E/C/F/TAF group. No AE in the eye disorders SOC was reported in the STB group. One nonserious AE of photophobia (reported as "intermittent sensitivity to light") in the E/C/F/TAF group was considered related to study drugs by the investigator. All other eye disorders were considered by the investigator as not related to study drugs. All eye disorder PTs resolved without treatment and none resulted in discontinuation of study drugs. No cases of anterior or posterior uveitis were reported. In the SOC of infections and infestations, conjunctivitis was reported for 8.0% of subjects in the E/C/F/TAF group and no subjects in the STB group. All AEs of conjunctivitis were Grade 1 or Grade 2, were nonserious, and resolved without interruption to, or discontinuation of, study drugs. No AE of conjunctivitis was considered related to study drugs.

Laboratory Abnormalities

The majority of subjects had at least 1 laboratory abnormality reported during the randomized phase of the study (E/C/F/TAF 95.5%, 106 subjects; STB 94.8%, 55 subjects).

The majority of reported abnormalities were Grade 1 or Grade 2. More subjects in the E/C/F/TAF group compared with the STB group had Grade 3 or 4 abnormalities (E/C/F/TAF 27.9%, 31 subjects; STB 19.0%, 11 subjects). The most commonly reported Grade 3 or 4 laboratory abnormality was fasting LDL (E/C/F/TAF 9.1%, 10 subjects; STB 5.2%, 3 subjects).

Metabolic Laboratory Parameters

Increases from baseline were observed for fasting total cholesterol, fasting direct LDL cholesterol, and fasting HDL cholesterol at Weeks 24 and 48 for each treatment group. The median increase from baseline was greater in the E/C/F/TAF group compared with the STB group at both Week 24 and Week 48. Statistically significant differences between the 2 groups in change from baseline were seen for all 3 lipid parameters at Week 24, and for fasting total cholesterol and fasting HDL cholesterol at Week 48.

Median increases from baseline in fasting total cholesterol were as follows:

- At Week 24: E/C/F/TAF 30 mg/dL, STB 13 mg/dL; p < 0.001
- At Week 48: E/C/F/TAF 30 mg/dL, STB 17 mg/dL; p = 0.007

Median increases from baseline in fasting direct LDL cholesterol were as follows:

- At Week 24: E/C/F/TAF 16 mg/dL, STB 3 mg/dL; $p < 0.001$
- At Week 48: E/C/F/TAF 17 mg/dL, STB 11 mg/dL; $p = 0.11$

Median increases from baseline in fasting HDL cholesterol were as follows:

- At Week 24: E/C/F/TAF 6 mg/dL, STB 2 mg/dL; $p = 0.010$
- At Week 48: E/C/F/TAF 7 mg/dL, STB 3 mg/dL; $p = 0.023$

There were no changes from baseline or statistically significant differences between treatment groups for median fasting total cholesterol to HDL ratio, fasting triglycerides, or fasting glucose for either treatment group.

Graded fasting hypercholesterolemia was more commonly reported in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 56.4%, 62 subjects; STB 29.3%, 17 subjects). The majority of the hypercholesterolemia abnormalities were Grade 1 (E/C/F/TAF 44 subjects; STB 8 subjects). More subjects in the E/C/F/TAF group compared with the STB group had graded abnormalities in fasting LDL (E/C/F/TAF 50.9%, 56 subjects; STB 36.2%, 21 subjects). The majority of these abnormalities were Grade 1 (E/C/F/TAF 32 subjects; STB 10 subjects). Grade 2 fasting LDL was reported for 12.7% of subjects (n = 14) in the E/C/F/TAF groups and 13.8% of subjects (n = 2) in the STB group. Grade 3 fasting LDL was reported for 9.1% of subjects (n = 10) in the E/C/F/TAF group and 5.2% of subjects (n = 3) in the STB group. No Grade 4 fasting LDL abnormalities were reported in either group.

Virologically Suppressed Subjects who Switched Treatment

During the extension phase, E/C/F/TAF was generally well tolerated with a median (Q1, Q3) of 36.0 (24.1, 42.4) weeks of exposure in the all TDF to TAF group and 24.1 (23.7, 24.3) weeks in the D/C/F/TAF to E/C/F/TAF group, as evidenced by the absence of discontinuations due to AEs and study drug-related SAEs.

The percentages of subjects in the switch groups who had any AE were as follows: all TDF to TAF 69.2%, 63 of 91 of subjects and D/C/F/TAF to E/C/F/TAF 52.9%, 37 of 70 subjects.

At Week 24 of the extension phase, BMD increased from baseline for the all TDF to TAF switch group (mean percentage changes from baseline: hip 0.58%; spine 1.18%). In the D/C/F/TAF to E/C/F/TAF group, the mean percentage changes from baseline in BMD at Week 24 of the extension phase were 0.22% at the hip and 0.71% at the spine.

In the all TDF to TAF group, decreases from baseline in mean values for serum creatinine were observed as early as Week 2 (−0.06 mg/dL) during the extension phase and were maintained through Week 24 (−0.04 mg/dL). In this switch group, corresponding increases from baseline in median values for $eGFR_{CG}$ were observed at as early as Week 2 (5.8 mL/min) during the extension phase and were maintained through Week 24 (5.5 mL/min).

In the D/C/F/TAF to E/C/F/TAF group, a decrease from baseline in serum creatinine was observed (−0.03 mg/dL) and a corresponding increase in the median value for $eGFR_{CG}$ was observed (3.8 mL/min) at Week 24 of the extension phase.

During the extension phase, the incidence of graded laboratory abnormalities in the switch groups was as follows: all TDF to TAF 84.6%, 77 subjects; D/C/F/TAF to E/C/F/TAF 77.1%, 55 subjects. The types of graded laboratory abnormalities in the switch groups were generally consistent with those in the ART-naive groups.

In the all TDF to TAF switch group, increases from baseline at Week 24 of the extension phase were observed in fasting values of total cholesterol (24 mg/dL), direct LDL cholesterol (16 mg/dL), HDL cholesterol (5 mg/dL), and triglycerides (10 mg/dL). In the D/C/F/TAF to E/C/F/TAF group, decreases from baseline at Week 24 were observed in fasting direct LDL cholesterol (−10 mg/dL) and fasting triglycerides (−12 mg/dL).

Conclusions

- HIV-infected, ART-naive subjects who received E/C/F/TAF or STB achieved and maintained virologic success through 24 and 48 weeks of treatment by the FDA snapshot algorithm with HIV-1 RNA cutoff at 50 copies/mL (Week 24: E/C/F/TAF 88.4%, STB 89.7%; Week 48: E/C/F/TAF 88.4%, STB 87.9%). Both groups had increases from baseline in mean CD4 cell counts (Week 24: E/C/F/TAF 169 cells/μL, STB 179 cells/μL; Week 48: E/C/F/TAF 177 cells/μL; STB 204 cells/μL).

- Subjects who received E/C/F/TAF for 96 weeks maintained virologic control, and had increased CD4 cell counts.

- Virologic resistance to study drugs was noted in 0 of the 3 subjects from the E/C/F/TAF group and 2 of 3 subjects from the STB group.

- HIV-infected, virologically suppressed subjects who switched to E/C/F/TAF from STB or a DRV+COBI-containing regimen, maintained high rates of virologic control, and had increases in CD4 count through 24 weeks of treatment following the switch.

- Subjects who received E/C/F/TAF had intracellular TFV-DP concentrations 5.3-fold higher than subjects who received STB. Conversely, subjects who received E/C/F/TAF had plasma TFV levels 91% lower than those who received STB.

- Both E/C/F/TAF and STB were well tolerated, with comparably low rates of SAEs and AE-related drug discontinuation in both treatment groups. E/C/F/TAF showed a preferential renal and bone safety profile compared with those who received STB, as evidenced by significantly less of each the following:

  — Increase in serum creatinine

  — Reduction in $eGFR_{CG}$

  — Tubular proteinuria

— Decline in hip and spine BMD

— Changes in markers of bone turnover

- Small but significant increases from baseline in fasting total cholesterol, fasting LDL cholesterol and fasting HDL cholesterol were noted in the E/C/F/TAF group. Similar increases were noted in the all TDF to TAF switch population.

- In HIV-infected, virologically suppressed subjects who switched to E/C/F/TAF from STB or a DRV+COBI-containing regimen, E/C/F/TAF was well tolerated, with low rates of SAEs and AE-related drug discontinuation.

- HIV-infected subjects who switched to E/C/F/TAF from a TDF containing regimen showed signs of improved bone and renal safety parameters through 24 weeks of treatment following the switch.

2.1.2. Virologically Suppressed Subjects

2.1.2.1. Study GS-US-292-0109

A complete study description and results for Study GS-US-292-0109 are available in the CSR (GS-US-292-0109 Week 48) and a brief narrative of this study is presented below.

Title

A Phase 3, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects

Objectives

The primary objective of this study was as follows:

- To evaluate the noninferiority of switching to a TAF-containing FDC relative to maintaining TDF-containing regimens in virologically suppressed, HIV-infected subjects as determined by having HIV-1 RNA < 50 copies/mL at Week 48 FDA snapshot algorithm

The secondary objectives of this study are as follows:

- To determine the safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine BMD at Week 48

- To determine the safety of the 2 treatment groups as determined by the change from baseline in serum creatinine at Week 48

- To evaluate the safety and tolerability of the 2 treatment groups through Week 48

- To evaluate the durability of the efficacy, safety, and tolerability of the 2 treatment groups through Week 96

The current report describes the 48-week results through a data cutoff that includes a sufficient number of subjects (1196 subjects) who had reached the primary time point of interest (Week 48) in order to assess both efficacy and safety of E/C/F/TAF in the virologically suppressed population.

Diagnosis and Main Criteria for Inclusion

Subjects enrolled in this study were HIV-infected adults receiving ART regimens consisting of STB, ATR, ATV+RTV+TVD, or ATV+COBI+TVD for at least 6 consecutive months preceding the final visit in their earlier study, and who had maintained plasma HIV-1 RNA levels at undetectable levels for at least 6 consecutive months prior to the screening visit; had HIV-1 RNA < 50 copies/mL at the screening visit; and had an $eGFR_{CG} \geq 50$ mL/min at screening.

SUMMARY OF RESULTS

Subject Disposition

In this study, 1559 subjects were screened, 1443 subjects were randomized, and 1436 subjects received at least 1 dose of study drug (E/C/F/TAF 959 subjects; FTC/TDF+3rd Agent 477 subjects); 7 randomized subjects did not receive study drug (E/C/F/TAF 4 subjects; FTC/TDF+3rd Agent 3 subjects). The distributions of prior treatment regimens were comparable between the 2 treatment groups (STB: E/C/F/TAF 31.9%, 306 subjects; FTC/TDF+3rd Agent 32.1%, 153 subjects; ATR: E/C/F/TAF 26.2%, 251 subjects; FTC/TDF+3rd Agent 26.2%, 125 subjects; ATV/boosted+TVD: E/C/F/TAF 41.9%, 402 subjects; FTC/TDF+3rd Agent 41.7%, 199 subjects).

Through the data cutoff date, 1386 subjects are continuing study drug treatment (E/C/F/TAF 97.9%, 939 subjects; FTC/TDF+3rd Agent 93.7%, 447 subjects), and 1397 subjects are continuing on study (E/C/F/TAF 98.2%, 942 subjects; FTC/TDF+3rd Agent 95.4%, 455 subjects). Fifty subjects (3.5%) discontinued study drug (E/C/F/TAF 2.1%, 20 subjects; FTC/TDF+3rd Agent 6.3%, 30 subjects), and 39 subjects (2.7%) discontinued from the study (E/C/F/TAF 1.8%, 17 subjects; FTC/TDF+3rd Agent 4.6%, 22 subjects) prior to the data cutoff date. The reasons for premature discontinuation of study drug were generally balanced between treatment groups, although a lower percentage of subjects discontinued E/C/F/TAF (0.4%, 4 subjects) compared with FTC/TDF+3rd Agent (2.5%, 12 subjects) due to withdrawal of consent, which is possibly a reflection of the open-label study design. Two subjects (0.2%) in the E/C/F/TAF group discontinued study drug due to death; both deaths were considered by the investigator to be unrelated to study drug. Adverse events led to discontinuation of study drug in 16 subjects (E/C/F/TAF 0.9%, 9 subjects; FTC/TDF+3rd Agent group 1.5%, 7 subjects).

Subject Demographics and Baseline Disease Characteristics

Demographic and general baseline characteristics were similar between the 2 treatment groups with the exception of ethnicity; a higher proportion of subjects in the E/C/F/TAF group (25.9%, 248 subjects) compared with the FTC/TDF+3rd Agent group (17.2%, 82 subjects) were of Hispanic or Latino ethnicity ($p < 0.001$). Most subjects in the Safety Analysis Set were male (89.3%), with a median age of 41 years (range: 21 to 77); most were either white (67.2%) or

black (18.9%), and most were not Hispanic/Latino (76.7%). The median (Q1, Q3) value for BMI at baseline was 25.9 (23.1, 29.2) kg/m^2.

Most subjects (98.1%, 1409 subjects) had baseline HIV-1 RNA < 50 copies/mL, which reflects that the study design targeted a virologically suppressed, HIV-infected population. The median (Q1, Q3) baseline CD4 count was 669 (522, 831) cells/μL. The most common HIV risk factor category was homosexual sex (78.6%); 22.1% of subjects reported heterosexual sex as the mode of infection.

Most subjects (90.8%) had no proteinuria (Grade 0 by dipstick) on urinalysis. Values for eGFR (as measured by CG or by either of the CKD-EPI methods) were similar between the 2 treatment groups. Treatment groups were similar with respect to the 10-year probability of hip or major osteoporotic fracture by FRAX estimation. For subjects in the Safety Analysis Set, regardless of age (where subjects < 40 years of age were treated as having an age of 40 years), the baseline median (Q1, Q3) 10-year probability of hip fracture by FRAX estimate was 0.16% (0.05, 0.45) and of major osteoporotic fracture was 1.92% (1.20, 3.14).

Efficacy Results

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm. Virologic success rates at Week 48 were high in both groups using the Week 48 FAS (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 92.9%; difference in percentages: 2.7%, 95.01% CI: −0.3% to 5.6%). Because the lower bound of the 2-sided 95.01% CI of the difference in response rate was greater than the prespecified −12% margin, switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent at Week 48.

Virologic success rates also were similar between treatment groups using the Week 48 PP Analysis Set (E/C/F/TAF 99.1%, 748 of 755 subjects; FTC/TDF+3rd Agent 98.9%, 363 of 367 subjects; difference in percentages: 0.2%, 95.01% CI: −1.3% to 1.6%), confirming that switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent at Week 48.

Virologic success rates using the Week 48 FAS were balanced in both treatment groups for predefined age, sex, race, geographic regions, prior treatment regimen, and study drug adherence subgroups.

A high percentage of subjects in both treatment groups had virologic success defined as HIV-1 RNA < 20 copies/mL at Week 48 using the FDA snapshot algorithm for the Week 48 FAS (E/C/F/TAF 92.2%; FTC/TDF+3rd Agent 90.4%; difference in percentages: 1.8%, 95% CI: −1.7% to 5.3%) or Week 48 PP Analysis Set (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 96.2%; difference in percentages: −0.6%, 95% CI: −3.1% to 2.0%).

The rates of virologic success as assessed in the M = F and M = E analyses for the percentages of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48, were high and similar in both treatment groups (M = F: E/C/F/TAF 96.4%, FTC/TDF+3rd Agent 94.7%; M = E: E/C/F/TAF 99.1%, FTC/TDF+3rd Agent 98.7%; stratum weighted difference in response rate between treatment groups at Week 48: M = F: 1.7%, 95% CI: −1.0% to 4.3%; M = E: 0.4%, 95% CI:

−1.1% to 1.9%). Rates of virologic success also were high (approximately 90% or greater) in both treatment groups when assessed in the M = F and M = E analyses for the percentage of subjects with HIV-1 RNA levels < 20 copies/mL at Week 48.

The proportions of subjects who were pure virologic responders at Week 48 were high and similar in both treatment groups (E/C/F/TAF 97.1%, 776 of 799 subjects; FTC/TDF+3rd Agent 98.0%, 389 of 397 subjects).

The mean (SD) changes in CD4 cell counts were similar between groups through Week 48, with both groups having slight increases from baseline. Using observed data (ie, M = E), the mean (SD) changes from baseline at Week 48 in CD4 cell counts were 33 (166.6) cells/μL in the E/C/F/TAF group and 27 (160.2) cells/μL in the FTC/TDF+3rd Agent group (difference in LSM: 6 cells/μL, 95% CI: −14 to 26 cells/μL). The changes from baseline in CD4 counts at Week 48 (observed data) were consistent when analyzed by prior treatment regimen (STB, ATR, or ATV/boosted+TVD), and results for the Week 48 PP (observed data) were consistent with those for the Week 48 FAS.

Pharmacokinetics Results

The plasma concentrations of TAF and TFV were assessed in a randomly selected subset that included 200 subjects. Results are presented by individual subject in the listings in the CSR.

Safety Results

In subjects switching from their baseline regimen, E/C/F/TAF was generally well tolerated through a median of 48.0 weeks of exposure, as evidenced by the infrequent discontinuations due to AEs and the absence of study drug-related SAEs. In subjects who stayed on their baseline regimen, study drugs were generally well tolerated through a median of 48.0 weeks of exposure.

Adverse Events

Similar percentages of subjects in each group had any AE. Subjects who switched to E/C/F/TAF had a higher incidence of any AE considered by the investigator as related to study drug (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects). An overall summary of treatment-emergent AEs is shown in Table 13:

Table 13. E/C/F/TAF Study GS-US-292-0109: Treatment-Emergent Adverse Events- Overall Summary (Safety Analysis Set)

	E/C/F/TAF (N = 959)	FTC/TDF+3rd Agent (N = 477)
Adverse Event	764 (79.7%)	368 (77.1%)
Grade 3 or 4 Adverse Event	61 (6.4%)	32 (6.7%)
Study Drug-Related Adverse Event	185 (19.3%)	61 (12.8%)
Grade 3 or 4 Study Drug-Related Adverse Event	3 (0.3%)	6 (1.3%)
Serious Adverse Event	42 (4.4%)	21 (4.4%)
Subjects Experiencing Any Study Drug-Related Serious Adverse Event	0	1 (0.2%)
Adverse Event Leading to Premature Study Drug Discontinuation	9 (0.9%)	7 (1.5%)
Treatment-Emergent Death	2 (0.2%)	0

Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 21

Two subjects in the E/C/F/TAF group died during the study (1 subject due to septic shock and the other due to stage 4 adenocarcinoma); these events were considered by the investigator as not related to study drug. One subject in the FTC/TDF+3rd Agent group taking ATR had an SAE of acute renal failure that was considered by the investigator as related to study drugs. No AE by PT that led to study drug discontinuation was reported for more than 1 subject in the E/C/F/TAF group. In the FTC/TDF+3rd Agent group, 3 subjects (all taking ATV/boosted+TVD) had jaundice that led to study drug discontinuation. Most of the AEs leading to discontinuation were nonserious and considered by the investigator as related to study drug. One subject in the E/C/F/TAF group had a confirmed pregnancy.

The most common AEs (ie, occurred in ≥ 5% of subjects) by treatment group were as follows:

- E/C/F/TAF: Upper respiratory tract infection (12.1%, 116 of 959 subjects), diarrhea (8.0%, 77 subjects), nasopharyngitis (6.7%, 64 subjects), headache (6.0%, 58 subjects), and cough (5.1%, 49 subjects)

- FTC/TDF+3rd Agent: Upper respiratory tract infection (7.5%, 36 of 477 subjects), diarrhea (7.5%, 36 subjects), and nasopharyngitis (5.5%, 26 subjects)

Overall, the AE profile for E/C/F/TAF was similar across the subgroups of age, sex, race, region, and prior treatment regimen.

Bone Safety

Similar percentages of subjects in each group had a fracture event (E/C/F/TAF 1.5%, FTC/TDF+3rd Agent 0.6%; p = 0.20). All reported fracture AEs were the result of trauma, considered by the investigator as unrelated to the study drugs, and none resulted in permanent discontinuation of study drugs. There were no reported fragility fractures.

There were increases from baseline in mean (SD) BMD at the hip and at the spine in the E/C/F/TAF group as compared with minimal changes from baseline in both parameters in the FTC/TDF+3rd Agent group ($p < 0.001$ for the differences between groups at Weeks 24 and 48).

Mean (SD) percentage changes from baseline in BMD at Week 48 were as follows:

- Hip: E/C/F/TAF 1.949% (2.9956); FTC/TDF+3rd Agent −0.136% (2.9890)
- Spine: E/C/F/TAF 1.861% (3.0889); FTC/TDF+3rd Agent −0.110% (3.7415)

Among subjects aged 40 years or older, the changes from baseline in the 10-year probability of hip fracture and of major osteoporotic fracture, by FRAX analysis, were lower in the E/C/F/TAF group than in the FTC/TDF+3rd Agent group at Week 48. The mean percentage changes from baseline in the 10-year probability of hip fracture were as follows: E/C/F/TAF 0.00%; FTC/TDF+3rd Agent group 0.10% ($p < 0.001$ for the difference between groups), and in the 10-year probability of major osteoporotic fracture were as follows: E/C/F/TAF 0.10%; FTC/TDF+3rd Agent 0.23% ($p = 0.002$ for the difference between groups).

There were decreases from baseline in serum levels of the bone formation biomarker P1NP and also in PTH, a hormone involved in bone formation and resorption, in the E/C/F/TAF group as compared with increases from baseline in both parameters in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). There was no change from baseline in serum levels of the bone resorption biomarker C-telopeptide in the E/C/F/TAF group as compared with an increase from baseline in the FTC/TDF+3rd Agent at Week 48 ($p = 0.007$ for the difference between groups).

Median (Q1, Q3) percentage changes from baseline in P1NP, C-telopeptide, and PTH at Week 48 were as follows:

- P1NP: E/C/F/TAF −26.89% (−41.41, −10.63); FTC/TDF+3rd Agent 4.48% (−12.54, 25.36)
- C-telopeptide: E/C/F/TAF 0.0% (−16.0, 18.2); FTC/TDF+3rd Agent 2.9% (−10.0, 22.6)
- PTH: E/C/F/TAF −3.3% (−24.6, 21.7); FTC/TDF+3rd Agent 7.1% (−12.6, 39.4)

Renal Safety

One subject in the FTC/TDF+3rd Agent group had a study drug-related SAE of acute renal failure that did not result in discontinuation of study drugs. In the E/C/F/TAF group, 2 subjects had nonserious renal AEs (tubulointerstitial nephritis [subject had recurrent hematuria on and off treatment and was diagnosed with Hodgkin's disease after treatment discontinuation] and acute renal failure [event was prerenal, linked to Hodgkin's disease and generalized worsening]) that resulted in discontinuation of the study drug; both events were considered by the investigator as not related to study drugs.

There were no AEs of PRT (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy reported in the E/C/F/TAF group. One subject in the FTC/TDF+3rd

Agent group (taking ATV/boosted+TVD) had a study drug-related, nonserious AE of acquired Fanconi syndrome that resulted in discontinuation of study drugs.

There were decreases or no changes from baseline in mean serum creatinine values in the E/C/F/TAF group as compared with increases or no changes from baseline in the FTC/TDF+3rd Agent group after excluding subjects switching from ATR ($p \leq 0.014$ for the differences between treatment groups at Weeks 2 through 48). At Week 48, the mean (SD) changes from baseline in serum creatinine were as follows: E/C/F/TAF −0.01 (0.117) mg/dL; FTC/TDF+3rd Agent 0.04 (0.123) mg/dL ($p < 0.001$ for the difference between groups).

For changes in serum creatinine analyzed by prior treatment regimen, decreases from baseline were observed among subjects who switched to E/C/F/TAF from STB, and either increases or no changes from baseline at most time points among the subjects who switched to E/C/F/TAF from ATV/boosted regimens. In contrast, among subjects who switched to E/C/F/TAF from ATR, increases in serum creatinine were observed at Week 2 (consistent with the established COBI effect on serum creatinine), and through Week 48.

There were increases from baseline in $eGFR_{CG}$ values in the E/C/F/TAF group compared with decreases from baseline in the FTC/TDF+3rd Agent group at Weeks 2 through 48 after excluding subjects switching from ATR. Median changes from baseline at Week 48 were as follows: E/C/F/TAF 1.8 mL/min, FTC/TDF+3rd Agent −3.7 mL/min ($p < 0.001$ for the difference between groups). The changes from baseline in $eGFR_{CG}$ corresponded with those observed for serum creatinine at most time points in both treatment groups among subjects with STB or ATR as their prior regimen and among subjects who remained on ATV/boosted+TVD regimens.

Based on results for subjects with available data at Week 48, a higher percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had improvements from baseline in proteinuria (E/C/F/TAF 7.1%, 55 of 772 subjects; FTC/TDF+3rd Agent 5.6%, 21 of 374 subjects) and a lower percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had worsening proteinuria (E/C/F/TAF 4.3%, 33 of 772 subjects; FTC/TDF+3rd Agent 7.0%, 26 of 374 subjects).

Proteinuria was reported as an AE for a similar percentage of subjects in each treatment group (E/C/F/TAF 1.4%; FTC/TDF+3rd Agent 1.3%); all AEs of proteinuria were Grade 1 or 2 in severity and none resulted in discontinuation of study drugs.

There were decreases from baseline in UPCR, UACR, and in urine RBP to creatinine and beta-2-microglobulin to creatinine ratios in the E/C/F/TAF group as compared with increases from baseline in the FTC/TDF+3rd Agent group in all of these parameters at Week 48 ($p < 0.001$ for the differences between groups). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows:

- UPCR: E/C/F/TAF −18.5% (−45.5, 18.1); FTC/TDF+3rd Agent 9.4% (−16.9, 51.8)
- UACR: E/C/F/TAF −18.4% (−45.1, 21.0); FTC/TDF+3rd Agent 5.3% (−25.5, 58.5)

- Urine RBP to creatinine ratio: E/C/F/TAF −32.9% (−63.9, 0.0); FTC/TDF+3rd Agent 15.7% (−22.9, 75.1)

- Beta-2-microglobulin to creatinine ratio: E/C/F/TAF −49.2% (−80.0, −4.9); FTC/TDF+3rd Agent 14.4% (−33.6, 92.9)

Decreases from baseline in UPCR, UACR, and in urine RBP to creatinine and beta-2-microglobulin to creatinine ratios were observed in the E/C/F/TAF group regardless of prior treatment regimen.

Ocular Safety

Adverse events in the SOC of eye disorders were reported for similar percentages of subjects in the 2 groups (E/C/F/TAF 5.5%; FTC/TDF+3rd Agent 4.6%). One subject in the E/C/F/TAF group had an SAE of retinal detachment during the study; the event resolved with treatment and was considered by the investigator as unrelated to the study drug. Nonserious AEs reported for 2 subjects in the E/C/F/TAF group (visual acuity reduced and vision blurred) and for 5 subjects in the FTC/TDF+3rd Agent group (ocular icterus, all subjects taking ATV/boosted+TVD) were considered by the investigator as related to study drugs. All other eye disorder AEs were considered by the investigator as not related to study drugs. Most eye disorder SOC AEs resolved and none resulted in discontinuation of study drugs.

There were no cases of uveitis, and no subjects in the ophthalmic substudy had fundoscopic findings consistent with uveitis.

Efavirenz-Related Symptom Assessment

The decrease (ie, improvement) from baseline in the EFV-related symptom composite score was greater for subjects who switched to E/C/F/TAF from ATR compared with subjects who stayed on ATR (median [mean] changes from baseline at Week 48, as follows: E/C/F/TAF 0.0 [−1.6]; FTC/TDF+3rd Agent 0.0 [−0.1]; $p < 0.001$ for the difference between groups).

For subjects who switched to E/C/F/TAF from ATR, there was a significant increase from baseline in the percentage of subjects who reported having no symptoms (ie, score of 0) of dizziness (baseline: 76.2%; Week 48: 94.3%), trouble sleeping (baseline: 73.2%; Week 48: 82.4%), impaired concentration (baseline: 76.6%; Week 48: 84.3%), sleepiness (baseline: 69.9%; Week 48: 80.5%), and abnormal or vivid dreams (baseline: 56.1%; Week 48: 90.0%).
In contrast, for subjects who continued to take ATR, there were no significant changes from baseline in the percentages of subjects reporting no symptom or any level of symptom for any of the 5 EFV-related symptoms at Week 48.

Laboratory Abnormalities

The majority of subjects had at least 1 graded laboratory abnormality reported during the study (E/C/F/TAF 90.5%, 868 subjects; FTC/TDF+3rd Agent 88.3%, 421 subjects). The incidence of laboratory abnormalities of any grade was balanced in both treatment groups for most chemistry, hematology, and urinalysis parameters. 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%; FTC/TDF+3rd Agent 14.3%). Almost all cases (66 of 68) of Grade 3 or 4 hyperbilirubinemia in the FTC/TDF+3rd Agent group occurred in subjects taking ATV.

Metabolic Laboratory Parameters

There were increases from baseline in fasting values of total cholesterol, LDL cholesterol, and triglycerides in the E/C/F/TAF group, while these parameters remained unchanged or were changed to a relatively smaller extent in the FTC/TDF+3rd Agent group at both Week 24 and Week 48 ($p < 0.001$ for the differences between groups).

Median (Q1, Q3) changes from baseline at Week 48 in fasting total cholesterol, fasting LDL cholesterol, and fasting triglycerides were as follows:

- Total cholesterol: E/C/F/TAF 20 (1, 41) mg/dL; FTC/TDF+3rd Agent 6 (−9, 19) mg/dL
- LDL cholesterol: E/C/F/TAF 9 (−9, 25) mg/dL; FTC/TDF+3rd Agent 0 (−13, 11) mg/dL
- Triglycerides: E/C/F/TAF 10 (−18, 48) mg/dL; FTC/TDF+3rd Agent 0 (−28, 27) mg/dL

Consistent with these results, of subjects with available data at Week 48, higher percentages in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had the following categorical shifts from baseline based on National Cholesterol Education Program Adult Treatment Panel III classifications: total cholesterol (< 200 mg/dL to ≥ 200 mg/dL: E/C/F/TAF 34.0%, 168 of 494 subjects; FTC/TDF+3rd Agent 20.2%, 53 of 262 subjects); LDL cholesterol (< 130 mg/dL to ≥ 130 mg/dL: E/C/F/TAF 23.6%, 114 of 483 subjects; FTC/TDF+3rd Agent 13.6%, 34 of 250 subjects); and triglycerides (< 200 mg/dL to ≥ 200 mg/dL: E/C/F/TAF 13.0%, 81 of 621 subjects; FTC/TDF+3rd Agent 8.2%, 25 of 305 subjects).

There were increases in HDL cholesterol in both treatment groups at Week 48 (median [Q1, Q3] changes from baseline: E/C/F/TAF 2 [−4, 8] mg/dL; FTC/TDF+3rd Agent 1 [−4, 5] mg/dL; $p = 0.025$ for the difference between groups); the increases were not considered clinically relevant. There were no clinically relevant changes from baseline in the median fasting values for the total cholesterol to HDL ratio or glucose for either treatment group.

In general, AEs and laboratory abnormalities related to lipids were more commonly reported in the E/C/F/TAF group than the FTC/TDF+3rd Agent group. All of the AEs were nonserious, and none led to discontinuation of study drugs.

Patient-Reported Outcomes

Health Utilization Assessment

Healthcare utilization up to Week 48 was comparable in the 2 treatment groups as assessed by hospitalizations, unplanned visits for a healthcare issue, and unplanned specialty care provider visits.

EQ-5D-3L

For each of the 5 dimensions of the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), response profiles in the 2 treatment groups were comparable at baseline and remained comparable through Week 48. There were no significant differences between treatment groups in the changes from baseline in the EQ-5D-3L Index Score (median changes from baseline were 0.000 in both groups) and the EQ VAS (median changes from baseline were 0.0 in both groups), or in the responder analysis for the EQ-5D-3L Index Score at Weeks 24 and 48.

Medical Outcome Study Short Form-36 (SF-36)

For each of the SF-36 subcomponents of physical and mental function (General Health, Physical Functioning, Role Functioning [Physical], Bodily Pain, Vitality, Role Functioning [Emotional], Mental Health, and Social Functioning), median scores were comparable between the 2 groups at baseline and there were no changes from baseline in the individual scores in either treatment group at Week 24 or 48 (median change from baseline for each component was 0.0 in both groups).

Conclusions

The interim Week 48 conclusions from this study are as follows:

- In virologically suppressed, HIV-infected subjects, switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent (STB, ATR, ATV/boosted+TVD) as assessed using the FDA snapshot algorithm (Week 48 FAS) with HIV-1 RNA cutoff at 50 copies/mL (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 92.9%; difference in percentages: 2.7%, 95.01% CI: −0.3% to 5.6%). Virologic success rates were balanced in both treatment groups for predefined age, sex, race, geographic regions, prior treatment regimen, and study drug adherence subgroups.

- In both treatment groups, CD4 cell counts were similar and continued to improve through Week 48, with both groups having slight increases from baseline (E/C/F/TAF 33 cells/μL; FTC/TDF+3rd Agent 27 cells/μL).

- In subjects who switched to E/C/F/TAF and subjects who stayed on FTC/TDF+3rd Agent regimens, study drugs were well tolerated, with low rates of SAEs and AE-related drug discontinuations in both treatment groups.

- There were statistically significant differences favoring E/C/F/TAF over FTC/TDF+3rd Agent at Week 48 for all 4 key safety endpoints: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), and change from baseline in EFV-related symptom assessment composite score ($p < 0.001$).

- An improved renal and bone safety profile was observed in subjects who switched to E/C/F/TAF compared with those who stayed on FTC/TDF+3rd Agent, as evidenced by the following seen in the E/C/F/TAF group:

  — Increases in hip and spine BMD

  — Decreases in bone turnover and decreases in PTH

  — Decreases or minimal changes in serum creatinine

  — Increases in $eGFR_{CG}$

  — Decreases in proteinuria and albuminuria

  — Decreases in several markers of PRT function (RBP to creatinine ratio, beta-2-microglobulin to creatinine ratio, and FEUA)

  — Minimal changes in measures of renal phosphate handling ($FEPO_4$, TmP/GFR)

- There were no differences in ocular findings between subjects who switched to E/C/F/TAF compared with those who stayed on FTC/TDF+3rd Agent.

- Increases from baseline in fasting total cholesterol, fasting LDL cholesterol, and fasting triglycerides were noted in the E/C/F/TAF group.

2.2. D/C/F/TAF Study

2.2.1. ART-Naive Subjects

2.2.1.1. Study GS-US-299-0102 (Phase 2)

A complete study description and results for Study GS-US-299-0102 are available in the CSR (m5.3.5.1, GS-US-299-0102) and a brief narrative of this study is presented below.

Title

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

Objectives

The primary objective of this study was as follows:

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

The secondary objectives of this study were as follows:

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

- To evaluate the safety and tolerability of the 2 treatment regimens through 48 weeks of treatment.

Diagnosis and Main Criteria for Inclusion

HIV-infected subjects who met the following criteria were eligible for study participation: plasma HIV-1 RNA levels ≥ 5000 copies/mL at screening; CD4+ cell count > 50 cells/μL at screening; adequate renal function, defined as $eGFR_{CG} \geq 70$ mL/min; no prior use of any approved or experimental anti-HIV drug for any length of time; and DRV-, TDF-, and FTC-sensitive according to the screening genotype report.

SUMMARY OF RESULTS

Subject Disposition

A total of 153 were randomized into the study and received at least 1 dose of study drug (D/C/F/TAF 103 subjects; DRV+COBI+TVD 50 subjects).

Of the 153 subjects treated, 17.6% (27 subjects) discontinued study drug treatment (D/C/F/TAF 18.4%, 19 subjects; DRV+COBI+TVD 16.0%, 8 subjects) and 18.3% (28 subjects) discontinued from the study (D/C/F/TAF 19.4%, 20 subjects; DRV+COBI+TVD 16.0%, 8 subjects). The most common reasons for premature discontinuation of study drug were lost to follow-up (D/C/F/TAF 9.7%, 10 subjects; DRV+COBI+TVD 8.0%, 4 subjects), withdrawal of consent (D/C/F/TAF 3.9%, 4 subjects; DRV+COBI+TVD 4.0%, 2 subjects), and AE (D/C/F/TAF 1.0%, 1 subject; DRV+COBI+TVD 4.0%, 2 subjects).

A total of 126 subjects completed study drug treatment in the current study and were given the option to enroll in the extension phase of Study GS-US-292-0102 to receive open-label treatment with E/C/F/TAF.

Subject Demographics and Baseline Disease Characteristics

Demographic and general baseline characteristics were similar between the 2 treatment groups (Safety Analysis Set). The majority of subjects were male (92.8%), with a mean age of 35 years (range: 18 to 68 years); most were either white (60.1%) or black (34.6%) and not Hispanic/Latino (79.1%). The mean (SD) value for BMI at baseline was 26.2 (4.81) kg/m^2.

Baseline disease characteristics were similar between the 2 treatment groups. The mean (SD) baseline HIV-1 RNA value was 4.68 (0.515) log_{10} copies/mL, and CD4 count was 417 (205.7) cells/μL. Overall, 80.4% of the subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL, 14.4% had > 100,000 to ≤ 400,000 copies/mL, and 5.2% had > 400,000 copies/mL. The most common HIV risk factor category was homosexual sex (84.3% of subjects). The majority of subjects (89.5%) had asymptomatic HIV infection; 7.2% of subjects had symptomatic HIV infection, and 3.3% of subjects were diagnosed with AIDS. The median $eGFR_{CG}$ values were similar in the 2 treatment groups: D/C/F/TAF 116.0 mL/min, DRV+COBI+TVD 109.6 mL/min.

Efficacy Results

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm. Virologic outcomes at Week 24 were similar between the 2 treatment groups for the primary endpoint analysis using the FAS. Virologic success rates were as follows: D/C/F/TAF 74.8%, DRV+COBI+TVD 74.0%; difference in percentages: 3.3% (95% CI: −11.4% to 18.1%). Because the lower bound of the 2-sided 95% CI of the difference in the response rate (D/C/F/TAF – DRV+COBI+TVD) was greater than the prespecified –12% noninferiority margin, D/C/F/TAF was determined to be noninferior to DRV+COBI+TVD. Virologic success rates for the Week 24 PP Analysis Set were supportive of those for the FAS, as follows: D/C/F/TAF 84.6%, 77 of 91 subjects; DRV+COBI+TVD 78.7%, 37 of 47 subjects; difference in percentages: 8.3%, 95% CI: −5.3% to 22.0%.

The rates of virologic success through Week 48 when assessed using the FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) using the FAS were as follows: D/C/F/TAF 76.7%, DRV+COBI+TVD 84.0%; difference in percentages: −6.2%, 95% CI: −19.9% to 7.4%. The difference in rates of virologic success between treatment arms was primarily due to a difference in the numbers of subjects who discontinued study drug due to other reasons and had the last available HIV-1 RNA ≥ 50 copies/mL (D/C/F/TAF: 8.7%, 9 subjects; DRV+COBI+TVD: 4.0%, 2 subjects). Virologic success rates for the Week 48 PP Analysis Set were similar between the 2 treatment groups, as follows: D/C/F/TAF 92.9%, 79 of 85 subjects, DRV+COBI+TVD 91.3%, 42 of 46 subjects; difference in percentages: 2.4%, 95% CI: −8.8% to 13.7%.

The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) using the M = F and M = E methods at Week 48 using the FAS were as follows: M = F: D/C/F/TAF 77.7%, DRV+COBI+TVD 86.0% (difference: −7.2%, 95% CI: −20.3% to 6.0%); M = E: D/C/F/TAF 89.9%, DRV+COBI+TVD 91.5% (difference: −0.5%, 95% CI: −11.9% to 10.9%).

The mean (SD) increases from baseline in CD4 cell count were similar for each treatment group through Week 48 (observed data), as follows: D/C/F/TAF 231 (141.9) cells/μL; DRV+COBI+TVD 212 (151.5) cells/μL; difference in LSM: 18 cells/μL (95% CI: −35 to 72 cells/μL).

At Week 24, the rate of virologic success by FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) for subgroups according to age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, or study drug adherence rate was similar for the D/C/F/TAF and DRV+COBI+TVD groups. The 95% CIs for differences in virologic success between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments. Data for Week 48 were consistent with results for Week 24.

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

Pharmacokinetics Results

Steady-state plasma PK parameters were determined following administration of D/C/F/TAF for subjects who participated in the intensive PK substudy (n = 21).

For TAF, the median (Q1, Q3) plasma half-life was 0.45 (0.38, 0.66) hours, no drug was detectable 8 hours after administration, and the mean (%CV) AUC_{last} was 130.5 (34.1) ng*h/mL, consistent with historical data for subjects receiving D/C/F/TAF or TAF 25-mg single-agent (Studies GS-US-120-0104 and GS-US-299-0102).

Administration of D/C/F/TAF led to substantially lower (> 90%) mean (%CV) systemic TFV AUC_{tau} (339.0 [37.1] ng*h/mL) versus administration of DRV+COBI+TVD (3737.0 [26.8] ng*h/mL) and versus coadministration of TDF with boosted PIs.

The PBMC TFV-DP AUC_{tau} (D/C/F/TAF 14 subjects; DRV+COBI+TVD 8 subjects) was markedly higher in subjects receiving D/C/F/TAF compared with subjects receiving DRV+COBI+TVD. The TFV-DP AUC_{tau} GLSM ratio of 652.09% was consistent with the approximate 5- to 7-fold increase in TFV-DP exposure observed following administration of TAF 25 mg versus TDF 300 mg (Study GS-US-120-0104).

The plasma exposures (mean [%CV] systemic AUC_{tau}) of DRV (99,301.8 [45.3 ng*h/mL]), COBI (8744.5 [43.9] ng*h/mL), and FTC (11,918.0 [35.9] ng*h/mL were consistent with historical data for these agents.

Safety Results

D/C/F/TAF and DRV+COBI+TVD were generally well tolerated in this study through a median duration of study drug exposure of 68.0 weeks in the D/C/F/TAF group and 69.1 weeks in the DRV+COBI+TVD group.

Adverse Events

Similar percentages of subjects in each group experienced an AE. An overall summary of AEs is shown in Table 14:

Table 14. D/C/F/TAF Study GS-US-299-0102: Overall Summary of Adverse Events (Safety Analysis Set)

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

Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 21.1

One subject (1.0%) in the D/C/F/TAF group had an SAE (hypersensitivity) that was considered by the investigator to be related to study drug; no subjects in the DRV+COBI+TVD group had a treatment-related SAE. Two subjects (1.9%) had 3 AEs resulting in discontinuation of study drug in the D/C/F/TAF group (hypersensitivity and rash; substance abuse), and 2 subjects (4.0%) had 2 AEs resulting in discontinuation of study drug in the DRV+COBI+TVD group (diarrhea; renal tubular disorder). No subject died. No pregnancies were reported.

The AEs by PT reported for at least 10% of subjects in either treatment group were as follows:

- D/C/F/TAF group — diarrhea (21.4%, 22 subjects); upper respiratory tract infection (15.5%, 16 subjects); fatigue (13.6%, 14 subjects); nausea (12.6%, 13 subjects); and rash (11.7%, 12 subjects)

- DRV+COBI+TVD group — diarrhea (26.0%, 13 subjects); fatigue (18.0%, 9 subjects); upper respiratory tract infection (14.0%, 7 subjects); flatulence (12.0%, 6 subjects); and nausea, pain in extremity, vitamin D deficiency, and vomiting (each in 10.0%, 5 subjects)

Bone Safety

No fracture events were reported during the study in either treatment group.

Decreases from baseline in BMD at the hip or spine were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group.

The mean (SD) baseline hip BMD values were 1.02 (0.142) g/cm^2 for the D/C/F/TAF group and 1.09 (0.145) g/cm^2 for the DRV+COBI+TVD group (p = 0.011). Mean (SD) percentage changes from baseline in hip BMD were as follows:

- At Week 24: D/C/F/TAF −0.53% (2.410), DRV+COBI+TVD −2.09% (2.283) (p < 0.001)
- At Week 48: D/C/F/TAF −0.84% (2.582), DRV+COBI+TVD −3.82% (2.651) (p < 0.001)

The mean (SD) baseline spine BMD values were 1.12 (0.155) g/cm^2 for the D/C/F/TAF group and 1.18 (0.172) g/cm^2 for the DRV+COBI+TVD group (p = 0.059). Mean (SD) percentage changes from baseline in spine BMD were as follows:

- At Week 24: D/C/F/TAF −1.09% (2.972), DRV+COBI+TVD −3.82% (3.633) (p < 0.001)
- At Week 48: D/C/F/TAF −1.57% (3.920), DRV+COBI+TVD −3.62% (3.128) (p = 0.003)

Increases from baseline in the bone biomarkers C-telopeptide and P1NP were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group (p < 0.001 for the differences between the 2 groups in median percent changes from baseline at Weeks 24 and 48). Median (Q1, Q3) percent changes from baseline in C-telopeptide were as follows:

- At Week 24: D/C/F/TAF 33.0% (0.3, 68.0), DRV+COBI+TVD 79.2% (33.7, 149.8)
- At Week 48: D/C/F/TAF 23.2% (−12.2, 77.2), DRV+COBI+TVD 74.4% (34.9, 154.7)

Median (Q1, Q3) percent changes from baseline in P1NP were as follows:

- At Week 24 : D/C/F/TAF 10.95% (−14.93, 34.18), DRV+COBI+TVD 49.19% (24.68, 75.06)
- At Week 48: D/C/F/TAF 4.73% (−18.68, 27.12), DRV+COBI+TVD 52.47% (20.57, 92.04)

Renal Safety

One subject in the DRV+COBI+TVD group had an SAE of Grade 2 renal tubular disorder (reported as PRT) that resulted in discontinuation of study drug. The PRT resolved and was not considered by the investigator to be related to study drug. Two subjects in D/C/F/TAF group had AEs of increased serum creatinine (related to study drug in 1 subject), and 1 subject in the DRV+COBI+TVD group experienced an AE of proteinuria.

Increases from baseline in mean values for serum creatinine were smaller in the D/C/F/TAF group compared with those in the DRV+COBI+TVD group. Increases were observed at Week 2 for each treatment group, and remained stable through Week 48 (mean [SD] increases from baseline at Week 48 were as follows: D/C/F/TAF 0.06 [0.101] mg/dL, DRV+COBI+TVD 0.09 [0.161] mg/dL [p = 0.053]).

Decreases from baseline in median $eGFR_{CG}$ were smaller in the D/C/F/TAF group compared with those in the DRV+COBI+TVD group. Decreases were observed at Week 2 for each treatment group, and remained stable through Week 48. Median (Q1, Q3) changes from baseline at Week 48 were as follows: D/C/F/TAF −2.9 (−11.8, 6.2) mL/min, DRV+COBI+TVD −10.6 (−22.4, −0.5) mL/min; p = 0.017.

Treatment-emergent proteinuria was reported in each treatment group (D/C/F/TAF 32.4%, 33 subjects, DRV+COBI+TVD 34.0%, 17 subjects). Most proteinuria by dipstick was Grade 1 or 2, with only 1 subject in the DRV+COBI+TVD group with Grade 3 proteinuria.

No statistically significant differences were observed between the 2 treatment groups in median percentage change from baseline in UPCR or UACR (at Week 48, median [Q1, Q3] percent changes from baseline for UPCR: D/C/F/TAF −8.22% [−35.10%, 21.31%], DRV+COBI+TVD −27.52% [−48.28%, 29.36%]; p = 0.19; for UACR: D/C/F/TAF −13.1% [−39.7%, 28.2%], DRV+COBI+TVD −22.6% [−58.8%, 25.9%]; p = 0.17).

The increase from baseline to Week 48 in urine RBP to creatinine ratio was smaller for the D/C/F/TAF group compared with that for the DRV+COBI+TVD group (median [Q1, Q3] percent change: D/C/F/TAF 9% [−22%, 51%], DRV+COBI+TVD 54% [5%, 152%]; p = 0.003 for the difference between groups). The median (Q1, Q3) percent change from baseline at Week 48 in urine beta-2-microglobulin to creatinine ratio was −42.0% (−66.4%, −11.0%) for the D/C/F/TAF group and 2.3% (−53.5%, 100.3%) for the DRV+COBI+TVD group (p = 0.002 for the difference between groups).

Ocular Safety

Adverse events in the eye disorders SOC were reported for 5.8% of subjects in the D/C/F/TAF group. No AE in the eye disorders SOC was reported in the DRV+COBI+TVD group. One nonserious AE of photophobia in the D/C/F/TAF group was considered by the investigator to be related to study drug. All other eye disorders were not considered by the investigator to be related to study drug. No eye disorder resulted in discontinuation of study drugs. There were no AEs of uveitis during the study.

Laboratory Abnormalities

The majority of subjects had at least 1 laboratory abnormality reported (D/C/F/TAF 96.1%, 98 subjects; DRV+COBI+TVD 94.0%, 47 subjects).The majority of laboratory abnormalities were Grade 1 or Grade 2. Similar percentages of subjects in both treatment groups had treatment-emergent Grade 3 or 4 abnormalities (D/C/F/TAF 27.5%, 28 subjects; DRV+COBI+TVD 28.0%, 14 subjects). The most commonly reported Grade 3 or 4 laboratory abnormality was creatine kinase (D/C/F/TAF 8.8%, 9 subjects; DRV+COBI+TVD 12.0%,

6 subjects). Grade 3 or 4 abnormalities in neutrophils, gamma-glutamyl transferase, platelets, alanine aminotransferase, hyperglycemia, hypernatremia, fasting total cholesterol, and fasting triglycerides were reported in more subjects in the D/C/F/TAF group compared with the DRV+COBI+TVD group.

Metabolic Laboratory Parameters

Increases from baseline were observed for fasting total cholesterol, fasting direct LDL cholesterol, fasting HDL cholesterol, and fasting triglycerides at Weeks 24 and 48 for each treatment group, with the exception of a decrease in fasting triglycerides at Week 48 for the DRV+COBI+TVD group. The median increase from baseline was greater in the D/C/F/TAF group compared with the DRV+COBI+TVD group at both Week 24 and Week 48. Statistically significant differences between the 2 groups in change from baseline were seen for fasting total cholesterol and fasting LDL cholesterol at Week 24, and for all 4 lipid parameters at Week 48.

Median increases from baseline in fasting total cholesterol were as follows:

- At Week 24: D/C/F/TAF 31 mg/dL, DRV+COBI+TVD 14 mg/dL; $p = 0.014$
- At Week 48: D/C/F/TAF 40 mg/dL, DRV+COBI+TVD 5 mg/dL; $p < 0.001$

Median increases from baseline in fasting direct LDL cholesterol were as follows:

- At Week 24: D/C/F/TAF 22 mg/dL, DRV+COBI+TVD 7 mg/dL; $p = 0.004$
- At Week 48: D/C/F/TAF 26 mg/dL, DRV+COBI+TVD 4 mg/dL; $p < 0.001$

Median increases from baseline in fasting HDL cholesterol were as follows:

- At Week 24: D/C/F/TAF 3 mg/dL, DRV+COBI+TVD 2 mg/dL; $p = 0.35$
- At Week 48: D/C/F/TAF 7 mg/dL, DRV+COBI+TVD 3 mg/dL; $p = 0.009$

Median changes from baseline in fasting triglycerides were as follows:

- At Week 24: D/C/F/TAF 24 mg/dL, DRV+COBI+TVD 10 mg/dL; $p = 0.13$
- At Week 48: D/C/F/TAF 29 mg/dL, DRV+COBI+TVD −5 mg/dL; $p = 0.007$

There were no clinically relevant changes from baseline for either treatment group or statistically significant differences in changes from baseline between treatment groups for median fasting total cholesterol to HDL ratio or fasting glucose.

Graded fasting hypercholesterolemia was more commonly reported in the D/C/F/TAF group compared with the DRV+COBI+TVD group (D/C/F/TAF 57.6%, 57 of 99 subjects, DRV+COBI+TVD 36.7%, 18 of 49 subjects). The majority of the hypercholesterolemia abnormalities were Grade 1. More subjects in the D/C/F/TAF group compared with the

DRV+COBI+TVD group had graded abnormalities in fasting LDL (D/C/F/TAF 53.5%, 53 subjects; DRV+COBI+TVD 34.7%, 17 subjects). The majority of these abnormalities were Grade 1.

Conclusions

- D/C/F/TAF once daily was noninferior to DRV+COBI+TVD once daily when administered for 24 weeks to HIV-infected, ART-naive subjects as assessed using the FDA snapshot algorithm with HIV-1 RNA cutoff at 50 copies/mL, in accordance with the primary objective of this study. Virologic success rates at Week 24 were as follows: D/C/F/TAF 74.8%, DRV+COBI+TVD 74.0%; difference in percentages: 3.3%, 95% CI −11.4% to 18.1%. Both groups had increases from baseline in mean CD4 cell counts (Week 24: D/C/F/TAF 186 cells/μL, DRV+COBI+TVD 139 cells/μL; Week 48: D/C/F/TAF 231 cells/μL, DRV+COBI+TVD 212 cells/μL).

- Through 48 weeks of treatment, no subjects developed primary protease resistance mutations, and 1 subject in the D/C/F/TAF treatment group had evidence of NRTI-resistance emergence.

- Subjects who received D/C/F/TAF had intracellular TFV-DP concentrations 6.5-fold higher than subjects who received DRV+COBI+TVD. Conversely, subjects who received D/C/F/TAF had plasma TFV levels 91% lower than those who received DRV+COBI+TVD.

- Both D/C/F/TAF and DRV+COBI+TVD were well tolerated, with comparably low rates of SAEs and AE-related drug discontinuation in both treatment groups. D/C/F/TAF showed a preferential renal and bone safety profile compared with those who received DRV+COBI+TVD, as evidenced by significantly less of each of the following:

  — Reduction in $eGFR_{CG}$

  — Tubular proteinuria

  — Decline in hip and spine BMD

  — Changes in markers of bone turnover

- Increases from baseline in fasting total cholesterol, fasting LDL cholesterol, fasting HDL cholesterol, and fasting triglycerides were noted in the D/C/F/TAF group.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Study Populations

3.1.1. Subject Disposition

3.1.1.1. E/C/F/TAF Studies

Across the 6 E/C/F/TAF studies summarized in this document, 2394 subjects were randomized or enrolled and received at least 1 dose of E/C/F/TAF (Table 15). 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. The percentages of subjects who discontinued study drug prematurely were comparable across studies; and were comparable between treatment groups in randomized studies. Across all 6 studies, 88 subjects (3.7%) prematurely discontinued E/C/F/TAF. The reasons for premature discontinuation of study drug were generally comparable across studies and between treatment groups in randomized studies. The most common reasons (across all 6 studies) for discontinuation of E/C/F/TAF were AE (1.2%, 29 subjects), lost to follow-up (0.9%, 22 subjects), and withdrawal of consent (0.8%, 19 subjects).

A further breakdown of the 2394 subjects that received E/C/F/TAF is as follows.

A total of 1032 ART-naive subjects across 5 E/C/F/TAF studies were randomized or enrolled and received at least 1 dose of E/C/F/TAF as follows: 866 adult subjects in the pivotal Phase 3 studies (GS-US-292-0104 and GS-US-292-0111); 112 adult subjects in the Phase 2 study (GS-US-292-0102); 6 adult subjects with mild to moderate renal impairment in a Phase 3 study (GS-US-292-0112); and 48 adolescent subjects in the Phase 2/3 study (GS-US-292-0106).

A total of 1362 virologically suppressed, ART-experienced adult subjects across 3 studies were randomized or enrolled and received at least 1 dose of E/C/F/TAF as follows: 959 subjects in Phase 3 Study GS-US-292-0109, 161 subjects who switched to E/C/F/TAF (from D/C/F/TAF, DRV+COBI+TVD, or STB) in the extension phase of Phase 2 Study GS-US-292-0102, and 242 subjects with mild to moderate renal impairment in Phase 3 Study GS-US-292-0112.

Table 15. E/C/F/TAF Studies 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: Subject Disposition (Safety Analysis Set)

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		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	
	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)	ART-Experienced E/C/F/TAF (N = 242)	ART-Naive E/C/F/TAF (N = 6)	E/C/F/TAF (N = 48)	Total E/C/F/TAF[b] (N = 2394)
Subjects in Safety Analysis Set	866	867	112	58	959	477	242	6	48	2394
Subjects in FAS	866 (100%)	867 (100%)	112 (100%)	58 (100%)	799 (83.3%)	397 (83.2%)	242 (100%)	6 (100%)	48 (100%)	2234 (93.3%)
Subjects still on study treatment up to the data cut date	821 (94.8%)	796 (91.8%)	105 (93.8%)	53 (91.4%)	939 (97.9%)	447 (93.7%)	226 (93.4%)	6 (100%)	48 (100%)	2306 (96.3%)
Subjects prematurely discontinuing study treatment prior to the data cut date	45 (5.2%)	71 (8.2%)	7 (6.3%)	5 (8.6%)	20 (2.1%)	30 (6.3%)	16 (6.6%)	0	0	88 (3.7%)
Reasons for prematurely discontinuing study treatment										
Adverse event	8 (0.9%)	13 (1.5%)	4 (3.6%)	0	9 (0.9%)	7 (1.5%)	8 (3.3%)	0	0	29 (1.2%)
Death	1 (0.1%)	2 (0.2%)	0	0	2 (0.2%)	0	0	0	0	3 (0.1%)
Pregnancy	0	5 (0.6%)	0	0	0	0	0	0	0	0
Lack of efficacy	2 (0.2%)	3 (0.3%)	0	1 (1.7%)	1 (0.1%)	0	1 (0.4%)	0	0	4 (0.2%)
Investigator's discretion	0	7 (0.8%)	0	0	1 (0.1%)	4 (0.8%)	1 (0.4%)	0	0	2 (0.1%)
Non-compliance with study drug	2 (0.2%)	1 (0.1%)	1 (0.9%)	1 (1.7%)	0	2 (0.4%)	0	0	0	3 (0.1%)
Protocol violation	5 (0.6%)	6 (0.7%)	0	0	0	0	1 (0.4%)	0	0	6 (0.3%)
Withdrew consent	12 (1.4%)	16 (1.8%)	0	1 (1.7%)	4 (0.4%)	12 (2.5%)	3 (1.2%)	0	0	19 (0.8%)
Lost to follow-up	15 (1.7%)	18 (2.1%)	2 (1.8%)	2 (3.4%)	3 (0.3%)	5 (1.0%)	2 (0.8%)	0	0	23 (1.0%)
Subjects still in study up to the data cut date	827 (95.5%)	812 (93.7%)	105 (93.8%)	53 (91.4%)	942 (98.2%)	455 (95.4%)	232 (95.9%)	6 (100%)	48 (100%)	2320 (96.9%)
Subjects prematurely discontinuing from study prior to the data cut date	39 (4.5%)	55 (6.3%)	5 (4.5%)[c]	5 (8.6%)	17 (1.8%)	22 (4.6%)	10 (4.1%)	0	0	72 (3.0%)

a Includes subjects in the randomized phase of Study GS-US-292-0102. Subject disposition for switch subjects in the open-label extension are summarized in GS-US-292-0102, Section 8.1.

b Includes the 161 subjects who switched to E/C/F/TAF in the extension phase of Study GS-US-292-0102 (Table 2).

c Two subjects from Study GS-US-292-0102 are not counted as still in study or as prematurely discontinuing from study. These subjects completed the study in the double-blind phase and did not enter the open-label extension phase.

The denominator for percentages was based on the number of subjects in the Safety Analysis Set.

Source: E/C/F/TAF, ISS, Table 1 and Figure 1; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 3.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 3; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 2; GS-US-292-0106 Interim CSR, Section 15.1, Table 2

3.1.1.2. D/C/F/TAF Study

In the D/C/F/TAF Phase 2 Study GS-US-299-0102, 103 ART-naive subjects received at least 1 dose of D/C/F/TAF (Table 16). For the D/C/F/TAF group, 84 subjects (81.6%) completed randomized treatment and 19 subjects (18.4%) prematurely discontinued study drug.
The percentages of subjects who discontinued study drug prematurely were comparable between the 2 treatment groups. The most common reasons for discontinuation of D/C/F/TAF were lost to follow-up (9.7%, 10 subjects), withdrawal of consent (3.9%, 4 subjects), and investigator's discretion and subject noncompliance (each 1.9%, 2 subjects).

Table 16. D/C/F/TAF Study GS-US-299-0102: Subject Disposition (All Screened Subjects)

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)
Subjects in Safety Analysis Set	103	50	153
Subjects in FAS	103 (100%)	50 (100%)	153 (100%)
Completed study treatment	84 (81.6%)	42 (84.0%)	126 (82.4%)
Prematurely discontinued study treatment	19 (18.4%)	8 (16.0%)	27 (17.6%)
Adverse event	1 (1.0%)	2 (4.0%)	3 (2.0%)
Death	0	0	0
Pregnancy	0	0	0
Lack of efficacy	0	0	0
Investigator's discretion	2 (1.9%)	0	2 (1.3%)
Non-compliance with study drug	2 (1.9%)	0	2 (1.3%)
Protocol violation	0	0	0
Withdrew consent	4 (3.9%)	2 (4.0%)	6 (3.9%)
Lost to follow-up	10 (9.7%)	4 (8.0%)	14 (9.2%)
Completed study	83 (80.6%)	42 (84.0%)	125 (81.7%)
Prematurely discontinued study[a]	20 (19.4%)	8 (16.0%)	28 (18.3%)

a Subjects prematurely discontinuing study drug could still be in the study (ie, not prematurely discontinued from the study).
The denominator for percentages was based on the number of subjects in the Safety Analysis Set.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 3

3.1.2. Demographic and Other Baseline Characteristics

3.1.2.1. Demographic and General Baseline Characteristics

3.1.2.1.1. E/C/F/TAF Studies

Demographic and general baseline characteristics were generally similar between treatment groups within each randomized study (Table 17). The median ages of subjects who were ART-naive (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102) or virologically suppressed (Study GS-US-292-0109) ranged from 33 to 41 years. Renally impaired subjects in Study GS-US-292-0112 were older, with a median age of 58 years in the ART-experienced cohort (range: 24 to 82) and with a median age of 54 years in the ART-naive cohort (range: 46 to 65). Across studies, a total of 97 subjects were ≥ 65 years of age. The median age of adolescent subjects in Study GS-US-292-0106 was 15 years (range: 12 to 17).

Women comprised approximately 15% of the ART-naive population in the E/C/F/TAF pivotal studies (Studies GS-US-292-0104 and GS-US-292-0111), approximately 11% of the virologically suppressed population in Study GS-US-292-0109, and approximately 20% of the population with mild to moderate renal impairment in Study GS-US-292-0112. The adolescent study (Study GS-US-292-0106) included 28 female subjects (58.3%). Across the E/C/F/TAF Phase 2 and 3 studies of adult subjects, the most common races were white (range: 56.0% to 69.0%) and black (range: 17.6% to 31.3%), and approximately 15% to 25% subjects were Hispanic or Latino. Of the adolescent subjects (Study GS-US-292-0106), 87.5% were black and 12.5% were Asian, and none were Hispanic or Latino. The median BMI was generally similar across all studies (approximately 25 kg/m^2), except for adolescent subjects in Study GS-US-292-0106 (median [Q1, Q3] BMI 20.0 [18.1, 23.2] kg/m^2).

Table 17. E/C/F/TAF Studies 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: Demographic and Baseline Characteristics (Safety Analysis Set)

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Age (Years)									
N	866	867	112	58	959	477	242	6	48
Mean (SD)	35 (10.4)	36 (10.7)	35 (11.3)	37 (10.6)	41 (10.1)	41 (10.1)	58 (9.9)	55 (7.1)	15 (1.9)
Median	33	35	34	38	41	40	58	54	15
Q1, Q3	26, 42	28, 44	26, 43	26, 46	33, 48	33, 48	52, 65	49, 59	13, 17
Min, Max	18, 74	18, 76	18, 71	20, 55	21, 77	22, 69	24, 82	46, 65	12, 17
Sex									
Male	733 (84.6%)	740 (85.4%)	108 (96.4%)	57 (98.3%)	856 (89.3%)	427 (89.5%)	192 (79.3%)	6 (100%)	20 (41.7%)
Female	133 (15.4%)	127 (14.6%)	4 (3.6%)	1 (1.7%)	103 (10.7%)	50 (10.5%)	50 (20.7%)	0	28 (58.3%)
Race									
American Indian or Alaska Native	5 (0.6%)	8 (0.9%)	0	1 (1.7%)	5 (0.5%)	2 (0.4%)	1 (0.4%)	0	0
Asian	91 (10.5%)	89 (10.3%)	3 (2.7%)	1 (1.7%)	59 (6.2%)	35 (7.3%)	34 (14.0%)	1 (16.7%)	6 (12.5%)
Black	223 (25.8%)	213 (24.6%)	35 (31.3%)	16 (27.6%)	169 (17.6%)	102 (21.4%)	44 (18.2%)	3 (50.0%)	42 (87.5%)
Native Hawaiian or Pacific Islander	5 (0.6%)	4 (0.5%)	0	0	6 (0.6%)	1 (0.2%)	2 (0.8%)	0	0
White	485 (56.0%)	498 (57.4%)	74 (66.1%)	40 (69.0%)	651 (67.9%)	314 (65.8%)	152 (62.8%)	2 (33.3%)	0
Not Permitted	–	–	0	0	2 (0.2%)	1 (0.2%)	2 (0.8%)	0	0
Other	57 (6.6%)	55 (6.3%)	0	0	67 (7.0%)	22 (4.6%)	7 (2.9%)	0	0

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Ethnicity									
Hispanic or Latino	167 (19.3%)	167 (19.3%)	25 (22.3%)	11 (19.0%)	248 (25.9%)	82 (17.2%)	31 (12.8%)	1 (16.7%)	0
Not Hispanic or Latino	698 (80.6%)	698 (80.6%)	87 (77.7%)	47 (81.0%)	709 (73.9%)	392 (82.2%)	209 (86.4%)	5 (83.3%)	48 (100.0%)
Not Permitted	1 (0.1%)	1 (0.1%)	0	0	2 (0.2%)	3 (0.6%)	2 (0.8%)	0	0
Missing	0	1	0	0	0	0	0	0	0
Region									
US	532 (61.4%)	532 (61.4%)	112 (100%)	58 (100%)	648 (67.6%)	316 (66.2%)	166 (68.6%)	5 (83.3%)	9 (18.8%)
ex-US	334 (38.6%)	335 (38.6%)	0	0	311 (32.4%)	161 (33.8%)	76 (31.4%)	1 (16.7%)	39 (81.3%)
Baseline Body Mass Index (kg/m^2)									
N	866	867	112	58	957	476	242	6	48
Mean (SD)	25.5 (5.23)	25.5 (5.12)	26.0 (4.31)	25.5 (4.41)	26.6 (5.29)	26.9 (5.34)	24.4 (4.12)	23.9 (4.03)	20.8 (3.24)
Median	24.4	24.5	25.6	25.1	25.8	26.1	24.1	23.6	20.0
Q1, Q3	22.0, 28.0	21.7, 28.0	23.1, 28.0	22.6, 27.5	23.1, 29.1	23.1, 29.4	21.4, 26.9	21.4, 25.7	18.1, 23.2
Min, Max	16.6, 71.0	16.6, 54.3	17.8, 46.0	18.2, 46.9	13.4, 65.4	16.2, 51.1	15.7, 39.8	18.6, 30.5	16.2, 31.8

a Includes subjects in the randomized phase of Study GS-US-292-0102. Demographics and other baseline characteristics for switch subjects in the open-label extension are summarized in GS-US-292-0102, Section 8.3.1.

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.

Source: E/C/F/TAF ISS Table 2; GS-US-292-0102 Week 96 CSR, Section 15.1, Tables 1.1 and 5.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 1 and 5.1; GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 1 and 4.1; GS-US-292-0106 Interim CSR, Section 15.1, Tables 1, 4.1, and 5

3.1.2.1.2. D/C/F/TAF Study

Demographic and general baseline characteristics were similar between the 2 treatment groups in the D/C/F/TAF Phase 2 Study GS-US-299-0102 (Table 18). The majority of subjects were male (92.8%), and the median age was 33 years (range: 18 to 68). The most common races were white (60.1%) or black (34.6%), and the most common ethnicity was not Hispanic or Latino (79.1%).

Table 18. D/C/F/TAF Study GS-US-299-0102: Demographic and Baseline Characteristics (Safety Analysis Set)

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

The denominator for percentages is based on the number of subjects in the safety analysis set.
For categorical data, p-value was from the Cochran-Mantel-Haenszal (CMH) test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 5

3.1.2.2. Baseline Disease Characteristics

3.1.2.2.1. E/C/F/TAF Studies

In the Phase 2 and Phase 3 E/C/F/TAF studies, baseline disease characteristics were generally similar between treatment groups within each E/C/F/TAF randomized study (Table 19).
The median baseline HIV-1 RNA value in ART-naive subjects (across all 5 E/C/F/TAF studies) was approximately 4.5 $\log_{10}$ copies/mL, and approximately 25% had baseline HIV-1 RNA > 100,000 copies/mL. Of virologically suppressed subjects in Studies GS-US-292-0109 and

GS-US-292-0112, approximately 98% had baseline HIV-1 RNA < 50 copies/mL, and most subjects in the switch groups of Study GS-US-292-0102 also had baseline HIV-1 RNA values < 50 copies/mL (all TDF to TAF: 93.4%; D/C/F/TAF to E/C/F/TAF: 97.1%). Median baseline CD4 cell count was approximately 400 cells/μL in ART-naive subjects (across all 5 E/C/F/TAF studies) and approximately 650 cells/μL in virologically suppressed subjects (Studies GS-US-292-0109 and GS-US-292-0112). The most common HIV risk factor was homosexual sex (approximately 75% to 90%) across subjects who were ART-naive (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102) or virologically suppressed (Study GS-US-292-0109). Heterosexual sex and homosexual sex were approximately equal risk factors (approximately 50% each) for subjects with mild to moderate renal impairment (Study GS-US-292-0112), and vertical transmission was the most common HIV risk factor (66.7%) for adolescent subjects (Study GS-US-292-0106). Most subjects in each study had asymptomatic HIV-1 infection (approximately 75% to 90%; status was not collected at baseline in Study GS-US-292-0109).

The median baseline $eGFR_{CG}$ value was generally similar across adult subjects who were ART-naive (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102) or virologically suppressed (Study GS-US-292-0109) (ranged from 105.7 to 117.0 mL/min), and proteinuria by urinalysis (dipstick) of any grade was observed in approximately 10% or less of these subjects.

The median (Q1, Q3) baseline $eGFR_{CG}$ value in Study GS-US-292-0112 was 55.6 mL/min (45.7, 62.4) among subjects who were ART-experienced and 60.2 mL/min (45.0, 63.2) among subjects who were ART-naive. Overall, 33.1% of ART-experienced subjects (80 of 242 subjects) had $eGFR_{CG}$ < 50 mL/min, 42.3% (101 of 239 subjects) had clinically significant proteinuria (UPCR > 200 mg/g), and 48.9% (115 of 235 subjects) had clinically significant albuminuria (UACR ≥ 30 mg/g). At baseline, 9.5% of ART-experienced subjects had Grade 2 proteinuria by urinalysis (dipstick) and 23.1% had Grade 1 proteinuria. Most subjects (ART-experienced or ART-naive) were in CKD Stage 3 ($eGFR_{CG}$ 30 to 59 mL/min; 63.3% [157 of 248 subjects]) at baseline.

The median (Q1, Q3) baseline eGFR (calculated using the modified Schwartz formula) value of adolescent subjects (Study GS-US-292-0106) was 110.9 (95.8, 118.8) mL/min/1.73 m^2, and proteinuria by urinalysis (dipstick) of any grade was observed in 4.2% of these subjects.

Table 19. E/C/F/TAF Studies 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: Baseline Disease Characteristics (Safety Analysis Set)

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
HIV-1 RNA (log_{10} copies/mL)									
N	866	867	112	58	NC	NC	242	6	48
Mean (SD)	4.54 (0.665)	4.53 (0.682)	4.63 (0.572)	4.69 (0.577)	NC	NC	1.32 (0.318)	4.66 (0.675)	4.62 (0.593)
Median	4.58	4.58	4.55	4.58	NC	NC	1.28	4.72	4.65
Q1, Q3	4.14, 4.95	4.15, 4.96	4.30, 4.89	4.35, 5.08	NC	NC	1.28, 1.28	4.01, 5.35	4.24, 4.94
Min, Max	2.57, 6.89	1.28, 6.98	3.11, 6.94	3.50, 6.44	NC	NC	1.28, 4.88	3.76, 5.39	3.25, 6.50
HIV-1 RNA categories (copies/mL)									
< 50	—	—	—	—	943 (98.3%)	466 (97.7%)	236 (97.5%)	0	—
≤ 100,000	670 (77.4%)	672 (77.5%)	93 (83.0%)	42 (72.4%)	959 (100%)	477 (100%)	242 (100%)	4 (66.7%)	38 (79.2%)
> 100,000 to ≤ 400,000	147 (17.0%)	154 (17.8%)	14 (12.5%)	13 (22.4%)	—	—	0	2 (33.3%)	10 (20.8%)[b]
> 400,000	49 (5.7%)	41 (4.7%)	5 (4.5%)	3 (5.2%)	—	—	0	0	NC
CD4 cell count (cells/µL)									
N	865	867	112	58	959	477	242	6	48
Mean (SD)	426 (215.6)	429 (219.6)	404 (181.6)	394 (209.6)	701 (261.8)	689 (248.0)	664 (286.4)	412 (244.0)	468 (215.4)
Median	404	406	385	397	675	662	632	397	452
Q1, Q3	283, 550	291, 542	283, 528	232, 535	520, 833	525, 831	456, 811	184, 673	326, 563
Min, Max	0, 1311	1, 1360	30, 897	2, 866	89, 1951	79, 1739	126, 1813	115, 708	95, 1110
CD4 cell count categories (cells/µL)									
< 50	24 (2.8%)	27 (3.1%)	2 (1.8%)	1 (1.7%)	0	0	0	0	NC
≥ 50 to < 200	88 (10.2%)	90 (10.4%)	12 (10.7%)	10 (17.2%)	5 (0.5%)	4 (0.8%)	5 (2.1%)	2 (33.3%)	4 (8.3%)[c]
≥ 200 to < 350	218 (25.2%)	200 (23.1%)	32 (28.6%)	14 (24.1%)	54 (5.6%)	25 (5.2%)	19 (7.9%)	0	9 (18.8%)
≥ 350 to < 500	256 (29.6%)	284 (32.8%)	33 (29.5%)	17 (29.3%)	151 (15.7%)	70 (14.7%)	53 (21.9%)	2 (33.3%)	18 (37.5%)
≥ 500	279 (32.3%)	266 (30.7%)	33 (29.5%)	16 (27.6%)	749 (78.1%)	378 (79.2%)	165 (68.2%)	2 (33.3%)	17 (35.4%)

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Missing	1	0	0	0	0	0	0	0	0
Mode of infection (HIV risk factors)[d]									
Heterosexual sex	210 (24.2%)	219 (25.3%)	16 (14.3%)	7 (12.1%)	216 (22.5%)	101 (21.2%)	99 (40.9%)	3 (50.0%)	10 (20.8%)
Homosexual sex	652 (75.3%)	645 (74.4%)	100 (89.3%)	51 (87.9%)	753 (78.5%)	375 (78.6%)	126 (52.1%)	3 (50.0%)	6 (12.5%)
IV drug use	5 (0.6%)	6 (0.7%)	0	1 (1.7%)	9 (0.9%)	5 (1.0%)	2 (0.8%)	0	1 (2.1%)
Transfusion	2 (0.2%)	6 (0.7%)	0	0	2 (0.2%)	2 (0.4%)	5 (2.1%)	0	0
Vertical transmission	2 (0.2%)	0	0	0	0	0	0	0	32 (66.7%)
Unknown	18 (2.1%)	27 (3.1%)	0	1 (1.7%)	17 (1.8%)	12 (2.5%)	13 (5.4%)	0	2 (4.2%)
Other	18 (2.1%)	9 (1.0%)	1 (0.9%)	0	8 (0.8%)	7 (1.5%)	2 (0.8%)	0	0
HIV disease status									
Asymptomatic	780 (90.4%)	802 (92.9%)	99 (88.4%)	52 (89.7%)	—[e]	—[e]	180 (74.4%)	5 (83.3%)	40 (83.3%)
Symptomatic HIV infection	53 (6.1%)	35 (4.1%)	9 (8.0%)	5 (8.6%)	—[e]	—[e]	28 (11.6%)	1 (16.7%)	8 (16.7%)
AIDS	30 (3.5%)	26 (3.0%)	4 (3.6%)	1 (1.7%)	—[e]	—[e]	34 (14.0%)	0	0
Unknown	3	4	0	0	—[e]	—[e]	0	0	0
$eGFR_{CG}$ (mL/min)									
N	866	867	112	58	959	477	242	6	47
Mean (SD)	120.8 (30.87)	118.7 (30.73)	120.4 (30.77)	114.8 (23.72)	111.9 (33.39)	112.1 (32.70)	54.8 (11.64)	55.1 (11.73)	109.1 (17.18)[f]
Median	117.0	113.9	115.2	113.3	105.7	107.7	55.6	60.2	110.9[f]
Q1, Q3	99.6, 135.6	99.0, 133.6	100.8, 131.7	97.7, 129.4	89.4, 126.0	88.7, 128.2	45.7, 62.4	45.0, 63.2	95.8, 118.8[f]
Min, Max	33.7, 287.2	55.3, 320.2	72.6, 239.5	73.5, 176.8	48.0, 344.1	53.7, 304.8	26.2, 89.7	36.3, 65.5	77.5, 146.1[f]
Proteinuria by urinalysis									
Grade 1	80 (9.2%)	67 (7.7%)	10 (8.9%)	2 (3.4%)	81 (8.5%)	44 (9.2%)	56 (23.1%)	0	1 (2.1%)
Grade 2	8 (0.9%)	18 (2.1%)	1 (0.9%)	1 (1.7%)	4 (0.4%)	3 (0.6%)	23 (9.5%)	1 (16.7%)	1 (2.1%)
Grade 3	0	1 (0.1%)	0	0	0	0	0	0	0
Missing	0	1	0	0	1	0	0	0	0

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Diabetes mellitus[g]									
Yes	25 (2.9%)	40 (4.6%)	5 (4.5%)	1 (1.7%)	—[e]	—[e]	33 (13.6%)	0	NA[h]
Hypertension[g]									
Yes	118 (13.6%)	146 (16.8%)	14 (12.5%)	6 (10.3%)	—[e]	—[e]	95 (39.3%)	3 (50%)	NA[h]
Cardiovascular disease[g]									
Yes	11 (1.3%)	14 (1.6%)	4 (3.6%)	1 (1.7%)	—[e]	—[e]	—	—	NA[h]
Hyperlipidemia[g]									
Yes	92 (10.6%)	100 (11.5%)	15 (13.4%)	6 (10.3%)	—[e]	—[e]	—	—	NA[h]

NA = not applicable; NC = not calculated
a Includes subjects in the randomized phase of Study GS-US-292-0102. Baseline disease characteristics for switch subjects in the open-label extension are summarized in GS-US-292-0102, Section 8.3.2.
b HIV-1 RNA >100,000 copies/mL for GS-US-292-0106
c < 200/µL for GS-US-292-0106
d A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
e Medical history data were presented in the original studies from which subjects were rolled over and were not summarized for Study GS-US-292-0109.
f eGFR calculated using modified Schwartz formula (mL/min/1.73 m^2) for Study GS-US-292-0106
g Medical history characteristics (diabetes mellitus, hypertension, cardiovascular disease and hyperlipidemia) were determined by past medical history.
h Patients with diabetes, uncontrolled cardiac illness, and uncontrolled illness were excluded from Study GS-US-292-0106.
The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
Source: E/C/F/TAF ISS, Table 3; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 6.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 6.1 and Appendix 16.2, Listing 7; GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 5.1, 20.2, 21.2, and Ad Hoc Table req6756.14; GS-US-292-0106 Interim CSR, Section 15.1, Tables 4.1 and 5

3.1.2.2.2. D/C/F/TAF Study

Baseline disease characteristics were similar between the 2 treatment groups of ART-naive subjects in the D/C/F/TAF Phase 2 Study GS-US-299-0102 (Table 20). The median baseline HIV-1 RNA value across both groups was 4.66 log10 copies/mL, and approximately 20% of subjects had baseline HIV-1 RNA > 100,000 copies/mL. Median CD4 count was 384 cells/μL. The most common HIV risk factor category was homosexual sex (84.3% of subjects). The majority of subjects (89.5%) had asymptomatic HIV-1 infection; 7.2% of subjects had symptomatic HIV-1 infection, and 3.3% of subjects were diagnosed with AIDS.

Values for $eGFR_{CG}$ were similar between the 2 treatment groups. Across both groups the median $eGFR_{CG}$ was 114.6 mL/min. Most subjects (90.2%) had no or trace proteinuria (Grade 0 by dipstick) on urinalysis.

Table 20. D/C/F/TAF Study GS-US-299-0102: Baseline Disease Characteristics (Safety Analysis Set)

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)
HIV-1 RNA (log_{10} copies/mL)			
N	103	50	153
Mean (SD)	4.70 (0.516)	4.65 (0.514)	4.68 (0.515)
Median	4.67	4.58	4.66
Q1, Q3	4.43, 4.93	4.28, 4.91	4.37, 4.91
Min, Max	3.27, 6.12	3.59, 6.29	3.27, 6.29
HIV-1 RNA Category (copies/mL)			
<= 100,000	80 (77.7%)	43 (86.0%)	123 (80.4%)
> 100,000 to <= 400,000	17 (16.5%)	5 (10.0%)	22 (14.4%)
> 400,000	6 (5.8%)	2 (4.0%)	8 (5.2%)
CD4 Cell Count (/uL)			
N	103	50	153
Mean (SD)	395 (169.3)	464 (261.6)	417 (205.7)
Median	368	433	384
Q1, Q3	270, 515	320, 606	283, 532
Min, Max	7, 909	49, 1463	7, 1463
CD4 Cell Count Category (/uL)			
< 50	1 (1.0%)	1 (2.0%)	2 (1.3%)
>=50 and <200	10 (9.7%)	9 (18.0%)	19 (12.4%)
>=200 and <350	37 (35.9%)	8 (16.0%)	45 (29.4%)
>=350 and <500	27 (26.2%)	12 (24.0%)	39 (25.5%)
>= 500	28 (27.2%)	20 (40.0%)	48 (31.4%)
CD4 Percentage (%)			
N	103	50	153
Mean (SD)	22.9 (8.14)	25.3 (9.95)	23.7 (8.81)
Median	22.1	25.3	23.6
Q1, Q3	17.4, 29.1	18.5, 31.1	17.6, 29.6
Min, Max	1.0, 42.8	6.9, 49.7	1.0, 49.7

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)
HIV Risk Factors			
Heterosexual Sex	19 (18.4%)	8 (16.0%)	27 (17.6%)
Homosexual Sex	86 (83.5%)	43 (86.0%)	129 (84.3%)
IV Drug Use	0	2 (4.0%)	2 (1.3%)
Unknown	3 (2.9%)	0	3 (2.0%)
Other	2 (1.9%)	2 (4.0%)	4 (2.6%)
HIV Disease Status			
Asymptomatic	93 (90.3%)	44 (88.0%)	137 (89.5%)
Symptomatic HIV Infections	8 (7.8%)	3 (6.0%)	11 (7.2%)
AIDS	2 (1.9%)	3 (6.0%)	5 (3.3%)
$eGFR_{CG}$ (mL/min)			
N	103	50	153
Mean (SD)	119.6 (26.89)	115.7 (31.41)	118.3 (28.40)
Median	116.0	109.6	114.6
Q1, Q3	97.0, 137.6	92.5, 131.4	96.5, 132.3
Min, Max	77.3, 223.0	73.7, 259.2	73.7, 259.2
Proteinuria by Urinalysis (dipstick)			
Negative	69 (67.0%)	39 (78.0%)	108 (70.6%)
Trace	22 (21.4%)	8 (16.0%)	30 (19.6%)
+1	9 (8.7%)	2 (4.0%)	11 (7.2%)
+2	2 (1.9%)	0	2 (1.3%)
+3	1 (1.0%)	1 (2.0%)	2 (1.3%)

The denominator for percentages is based on the number of subjects in the safety analysis set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistics was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 6

3.1.3. Analysis Populations

3.1.3.1. E/C/F/TAF Studies

For E/C/F/TAF studies in ART-naive subjects (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), efficacy results are presented primarily using the FAS, which included all subjects who were randomized and received at least 1 dose of study drug (Table 21).
For virologically suppressed subjects in Study GS-US-292-0109, efficacy results are presented primarily using the Week 48 FAS, which included all subjects who were randomized by [redacted] 20[redacted] and received at least 1 dose of study drug. For these studies (GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, and GS-US-292-0109), some endpoints are supported with analyses using the Week 48 PP Analysis Set, which included all subjects who were randomized, received at least 1 dose of study drug, had on-treatment HIV-1 RNA in the Week 48 window (unless the missing data was due to discontinuation of study drug due to lack of efficacy), and had no major protocol violation, including the violation of key entry criteria; subjects were also excluded from the Week 48 PP Analysis Set for nonadherence to study drug (ie, an adherence rate for study drug up to the Week 48 visit below the 2.5th percentile).

For subjects with mild to moderate renal impairment (Study GS-US-292-0112), efficacy results are presented using the Week 48 FAS, which included all subjects who were enrolled on or prior to [redacted] 20[redacted] and received at least 1 dose of study drug. For adolescent subjects (Study GS-US-292-0106), efficacy results are presented primarily using the Week 24 FAS, which included all subjects who were enrolled by [redacted] 20[redacted] and received at least 1 dose of study drug, with supportive analyses using the FAS, which included all subjects who were enrolled in the study and received at least 1 dose of study drug.

The rationale for defining the analysis sets of Studies GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106 by the specified dates was to include the most current data from these subject populations in the initial marketing applications for E/C/F/TAF.

Table 21. E/C/F/TAF Studies 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: Analysis Sets

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		ART-Naive Adolescent Subjects
	GS-US-292-0104/ GS-US-292-0111[a]		GS-US-292-0102[a,b]		GS-US-292-0109[a]		GS-US-292-0112[c]		GS-US-292-0106[d]
	E/C/F/TAF	STB	E/C/F/TAF	STB	E/C/F/TAF	FTC/TDF + 3rd Agent	ART-Experienced E/C/F/TAF	ART-Naive E/C/F/TAF	E/C/F/TAF
Subjects randomized/enrolled	873	871	113	58	963	480	246	6	48
Subjects in FAS	866 (99.2%)	867 (99.5%)	112 (99.1%)	58 (100%)	—	—	242 (100%)	6 (100%)	48 (100%)
Subjects in the Week 48 PP Analysis Set	801 (91.8%)	789 (90.6%)	101 (89.4%)	54 (93.1%)	755 (78.4%)	367 (76.5%)	—	—	—
Reason for exclusion from Week 48 PP Analysis Set[e]									
Did not have on-treatment HIV-1 RNA in Week 48 window unless due to discontinuation of study drug due to lack of efficacy	43	56	7	2	26	23	—	—	—
Screening genotype did not show sensitivity to EVG, FTC, and TDF	0	5	—	—	—	—	—	—	—
Took prohibited medications	3	4	1	1	0	0	—	—	—
Adherence rate for study drug up to Week 48 Visit below the 2.5th percentile	24	18	3	1	20	9	—	—	—
Subjects in Week 48 FAS	—	—	—	—	799 (83.0%)	397 (82.7%)	175 (72.3%)	2 (33.3%)	—
Subjects in Week 24 FAS	—	—	—	—	—	—	—	—	23 (47.9%)

a The denominator for percentages is based on the number of subjects in the Randomized Analysis Set
b Includes subjects in the randomized phase of Study GS-US-292-0102. A total of 266 subjects entered the extension phase of Study GS-US-292-0102 and received E/C/F/TAF, including 158 subjects from this study after completing the 48-week randomized phase (105 of whom continued on E/C/F/TAF and 53 of whom switched from STB to E/C/F/TAF) and 108 virologically suppressed subjects who rolled over from Study US-GS-299-0102.
c The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
d The denominator for percentages was the number of subjects in the All Enrolled Analyses Set.

e Exclusion criteria from the Week 48 PP Analysis Sets are only applicable to FAS (or Week 48 FAS for Study GS-US-292-0109) subjects. A subject may fit more than 1 exclusion criterion.

Source: GS-US-292-0104 Week 48 CSR, Section 15.1, Table 4; GS-US-292-0111 Week 48 CSR, Section 15.1, Table 4; GS-US-292-0102 Week 96 CSR, Section 15.1, Tables 4.1 and 4.2; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 4; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 3; GS-US-292-0106 Interim CSR, Section 15.1, Table 3

3.1.3.2. D/C/F/TAF Study

For ART-naive subjects in the D/C/F/TAF Phase 2 Study GS-US-299-0102, efficacy results are presented primarily using the FAS, which included all subjects who were randomized and received at least 1 dose of study drug (Table 22). Some endpoints are supported with analyses using the Week 24 and Week 48 PP Analysis Sets, both of which included all subjects who were randomized into the study, received at least 1 dose of study drug, and had no major protocol violation, including the violation of key entry criteria.

Table 22. D/C/F/TAF Study GS-US-299-0102: Analysis Sets

	D/C/F/TAF	DRV+COBI+TVD	Total
Subjects Randomized	103	50	153
Subjects in Full Analysis Set	103 (100.0%)	50 (100.0%)	153 (100.0%)
Subjects in Week 24 PP Analysis Set	91 (88.3%)	47 (94.0%)	138 (90.2%)
Reasons for Exclusion from Week 24 PP Analysis Set			
Discontinued Study Drug for Reason Other than Lack of Efficacy with No Week 24 HIV-1 RNA Data	12	2	14
Adherence Rate for Active Study Drug up to Week 24 Visit Below the 2.5th Percentile	2	1	3
Subjects in Week 48 PP Analysis Set	85 (82.5%)	46 (92.0%)	131 (85.6%)
Reasons for Exclusion from Week 48 PP Analysis Set			
Discontinued Study Drug for Reason Other than Lack of Efficacy with No Week 48 HIV-1 RNA Data	17	4	21
Adherence Rate for Active Study Drug up to Week 48 Visit Below the 2.5th Percentile	3	0	3

PP = per protocol
The denominator for percentages is based on the number of subjects in the randomized analysis set.
Exclusion criteria from the PP analysis sets are only applicable to the FAS subjects. A subject may fit more than 1 exclusion criterion from the PP sets.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 4

3.2. Comparison of Efficacy Results

3.2.1. E/C/F/TAF Studies

3.2.1.1. ART-Naive Subjects in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102

A summary of efficacy of E/C/F/TAF from Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102 is presented below. Detailed efficacy results are presented in the individual

CSRs (GS-US-292-0104 Week 48, Section 9; GS-US-292-0111 Week 48, Section 9; GS-US-292-0102 Week 96, Section 9).

3.2.1.1.1. Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using FDA Snapshot Algorithm

Study GS-US-292-0104

In Study GS-US-292-0104, virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the FAS (Table 23). Virologic success rates were high in both groups, as follows: E/C/F/TAF 93.1%; STB 92.4%; difference in percentages: 1.0%, 95.002% CI: −2.6% to 4.5%. Because the lower bound of the 2-sided 95.002% CI of the difference in the response (E/C/F/TAF – STB) rate was greater than the prespecified −12% margin, E/C/F/TAF was determined to be noninferior to STB.

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 3.0%; STB 2.5%).

Virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the Week 48 PP Analysis Set. Virologic success rates were high in both groups, as follows: E/C/F/TAF 97.8%, 395 of 404 subjects; STB 98.0%, 389 of 397 subjects; difference in percentages: −0.1%, 95.002% CI: −2.2% to 2.1%. Because the lower bound of the 2-sided 95.002% CI of the difference in the response (E/C/F/TAF – STB) rate was greater than the prespecified −12% margin, E/C/F/TAF was confirmed to be noninferior to STB.

Study GS-US-292-0111

In Study GS-US-292-0111, virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the FAS (Table 23). Virologic success rates were high in both groups, as follows: E/C/F/TAF 91.6%, STB 88.5%; difference in percentages: 3.1%, 95.002% CI −1.0% to 7.1%. Because the lower bound of the 2-sided 95.002% CI of the difference in the response (E/C/F/TAF – STB) rate was greater than the prespecified −12% margin, E/C/F/TAF was determined to be noninferior to STB.

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 4.2%; STB 5.5%).

Virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the PP Analysis Set. Virologic success rates were high in both groups, as follows: E/C/F/TAF 97.2%, 386 of 397 subjects; STB 95.4%, 374 of 392 subjects; difference in percentages: 1.6%, 95.002% CI: −1.1% to 4.4%. Because the lower bound of the 2-sided 95.002% CI of the difference in the response (E/C/F/TAF – STB) rate was greater than the prespecified −12% margin, E/C/F/TAF was confirmed to be noninferior to STB.

Table 23. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA <50 copies/mL – Individual Studies (FAS)

	292-0104		292-0111	
	E/C/F/TAF (N=435)	STB (N=432)	E/C/F/TAF (N=431)	STB (N=435)
Virologic success at Week 48[a]				
HIV-1 RNA < 50 copies/mL	405 (93.1%)	399 (92.4%)	395 (91.6%)	385 (88.5%)
Difference in percentages (95.002% CI)[b]	1.0% (−2.6% to 4.5%)		3.1% (−1.0% to 7.1%)	
p-value[c]	0.58		0.13	
Virologic failure at Week 48 [a]	13 (3.0%)	11 (2.5%)	18 (4.2%)	24 (5.5%)
HIV-1 RNA >= 50 copies/mL	9 (2.1%)	6 (1.4%)	11 (2.6%)	17 (3.9%)
Discontinued study drug due to lack of efficacy	0	2 (0.5%)	2 (0.5%)	1 (0.2%)
Discontinued study drug due to other reasons and last available HIV-1 RNA >= 50 copies/mL[d]	3 (0.7%)	3 (0.7%)	5 (1.2%)	5 (1.1%)
Added new ARV	1 (0.2%)	0	0	1 (0.2%)
No virologic data in Week 48 window [a]	17 (3.9%)	22 (5.1%)	18 (4.2%)	26 (6.0%)
Discontinued study drug due to AE/death	4 (0.9%)	5 (1.2%)	4 (0.9%)	9 (2.1%)
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d]	11 (2.5%)	15 (3.5%)	10 (2.3%)	16 (3.7%)
Missing data during window but on study drug	2 (0.5%)	2 (0.5%)	4 (0.9%)	1 (0.2%)

a Week 48 window is between Day 294 and 377 (inclusive).
b Difference in percentages of virologic success between treatment groups and its 95.002% CI were calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline HIV-1 RNA and region stratum.
c P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and region stratum. Baseline HIV-1 RNA stratum: <= 100,000 or > 100,000 copies/mL; region stratum: US or ex-US.
d Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Programming Details: .../version1/prog/t-snapshot.sas v9.2 Output file: t-snapshot-50-wk48.out [redacted]20[redacted]:15:51
Source: E/C/F/TAF ISE, Table 1

Pooled Data from Studies GS-US-292-0104 and GS-US-292-0111

Based on the pooled data from Studies GS-US-292-0104 and GS-US-292-0111, virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the FAS (Table 24). Virologic success rates were high in both groups, as follows: E/C/F/TAF 92.4%; STB 90.4%; difference in percentages: 2.0%, 95% CI: −0.7% to

4.7%. Because the lower bound of the 2-sided 95% CI of the difference in the response (E/C/F/TAF – STB) rate was greater than the prespecified −12% margin, E/C/F/TAF was determined to be noninferior to STB.

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 3.6%; STB 4.0%).

Table 24. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Pooled Data (FAS)

			E/C/F/TAF vs. STB	
	E/C/F/TAF (N=866)	**STB (N=867)**	**p-value[a]**	**Difference in Percentages (95% CI)[b]**
Virologic success at Week 48[c]				
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[c]	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[d]	8 (0.9%)	8 (0.9%)		
Added New ARV	1 (0.1%)	1 (0.1%)		
No virologic data in Week 48 window[c]	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[d]	21 (2.4%)	31 (3.6%)		
Missing data during window but on study drug	6 (0.7%)	3 (0.3%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA, region and study stratum. Baseline HIV-1 RNA stratum: <= 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.

b Difference in percentages of virologic success between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA, region, and study stratum.

c Week 48 window is between Day 294 and 377 (inclusive).

d Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Programming Details: .../version1/prog/t-snapshot-pooled.sas v9.2 Output file: t-snapshot-50-wk48-pooled.out [redacted]20[redacted]:15:51

Source: E/C/F/TAF ISE, Table 2

Study GS-US-292-0102

In Study GS-US-292-0102, virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the FAS (Table 25). Virologic success rates

were as follows: E/C/F/TAF 88.4%, STB 87.9%; difference in percentages: −1.0%, 95% CI −12.1% to 10.0%.

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 6.3%; STB 10.3%).

Virologic outcomes at Week 48 were similar between the 2 treatment groups using the Week 48 PP Analysis Set. Virologic success rates were high in both groups, as follows: E/C/F/TAF 95.0%, 96 of 101 subjects; STB 90.7%, 49 of 54 subjects; difference in percentages: 2.8%, 95% CI: −7.1% to 12.7%.

Table 25. E/C/F/TAF Study GS-US-292-0102: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	E/C/F/TAF (N=112)	STB (N=58)	E/C/F/TAF vs. STB	
			p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 48[c]				
HIV-1 RNA < 50 copies/mL	99 (88.4%)	51 (87.9%)	0.84	−1.0% (−12.1% to 10.0%)
Virologic Failure at Week 48[c]	7 (6.3%)	6 (10.3%)		
HIV-1 RNA ≥ 50 copies/mL	6 (5.4%)	4 (6.9%)		
Discontinued Study Drug Due to Lack of Efficacy	0	1 (1.7%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[d]	1 (0.9%)	1 (1.7%)		
No Virologic Data in Week 48 Window[c]	6 (5.4%)	1 (1.7%)		
Discontinued Study Drug Due to AE	4 (3.6%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	2 (1.8%)	1 (1.7%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 48 window was between Day 308 and 377 (inclusive).
d Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

Programming Details: .../version1/prog/t-snapshot.sas v9.2 Output file: t-snapshot-50-wk48.out [redacted]20[redacted]:20:52
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 10.3

3.2.1.1.2. Percentage of Subjects with HIV-1 RNA < 20 copies/mL at Week 48 Using FDA Snapshot Algorithm

Study GS-US-292-0104

In Study GS-US-292-0104, virologic outcomes at Week 48 were similar between the 2 treatment groups when assessed using the FDA snapshot algorithm (HIV-1 RNA < 20 copies/mL) based on the FAS. Virologic success rates were high in both groups, as follows: E/C/F/TAF 86.4%; STB 87.3%; difference in percentages: −0.6%, 95% CI: −5.1% to 3.8%.

Percentages of subjects with virologic failure (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 9.9%; STB 7.9%).

Virologic success rates at Week 48 were similar using the PP Analysis Set, as follows: E/C/F/TAF 91.1 %, 368 of 404 subjects; STB 92.4%, 367 of 397 subjects; difference in percentages: −1.4%, 95% CI: −5.2% to 2.4%.

Study GS-US-292-0111

In Study GS-US-292-0111, virologic outcomes at Week 48 were similar between the 2 treatment groups when assessed using the FDA snapshot algorithm (HIV-1 RNA < 20 copies/mL) based on the FAS. Virologic success rates were high in both groups, as follows: E/C/F/TAF 82.4%; STB 80.7%; difference in percentages: 1.4%, 95% CI: −3.7% to 6.5%.

Percentages of subjects with virologic failure (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 13.9%; STB 13.8%).

Virologic success rates at Week 48 were similar using the PP Analysis Set, as follows: E/C/F/TAF 87.7 %, 348 of 397 subjects; STB 87.2%, 342 of 392 subjects; difference in percentages: −0.2%, 95% CI: −4.7% to 4.3%.

Pooled Data from Studies GS-US-292-0104 and GS-US-292-0111

Based on the pooled data from Studies GS-US-292-0104 and GS-US-292-0111, virologic outcomes at Week 48 were similar between the 2 treatment groups when assessed using the FDA snapshot algorithm (HIV-1 RNA < 20 copies/mL) based on the FAS (Ad Hoc Table Req6769.1). Virologic success rates were high in both groups, as follows: E/C/F/TAF 84.4%; STB 84.0%; difference in percentages: 0.4%, 95% CI: −3.0% to 3.8%.

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 11.9%; STB 10.8%).

Study GS-US-292-0102

In Study GS-US-292-0102, virologic outcomes at Week 48 were similar between the 2 treatment groups when assessed using the FDA snapshot algorithm (HIV-1 RNA < 20 copies/mL) based

on the FAS. Virologic success rates were high in both groups, as follows: E/C/F/TAF 77.7%; STB 72.4%; difference in percentages: 2.0%, 95% CI: −11.8% to 15.9%.

3.2.1.1.3. Percentage of Subjects with HIV-1 RNA < 50 copies/mL Using Missing Data Imputation Methods

Study GS-US-292-0104

In Study GS-US-292-0104, high and similar rates of virologic suppression were achieved in the 2 treatment group, as assessed using the M = F and M = E methods at Week 48 for the FAS. The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 were as follows: M = F: E/C/F/TAF 93.6%, STB 93.8%; difference in percentages: 0%, 95% CI: −3.3% to 3.3%; M = E: E/C/F/TAF 97.8%, STB 98.5%; difference in percentages: −0.6%, 95% CI: −2.6% to 1.4%).

High and similar rates of virologic suppression were achieved in the 2 treatment groups at Week 48 based on the PP Analysis Set. The percentages of subjects with virologic suppression at Week 48 were as follows: M = F: E/C/F/TAF 98.0%, 396 of 404 subjects; STB 98.0%, 389 of 397 subjects; M = E: E/C/F/TAF 98.0%, 396 of 404 subjects; STB 98.5%, 389 of 395 subjects.

Study GS-US-292-0111

In Study GS-US-292-0111, high and similar rates of virologic suppression were achieved in the 2 treatment group, as assessed using the M = F and M = E methods at Week 48 for the FAS. The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 were as follows: M = F: E/C/F/TAF 92.3%, STB 90.8%; difference in percentages: 1.5%, 95% CI: −2.3% to 5.3%; M = E: E/C/F/TAF 97.1%, STB 94.5%; difference in percentages: 1.5%, 95% CI: −1.2% to 4.3%.

High and similar rates of virologic suppression were achieved in the 2 treatment groups at Week 48 based on the PP Analysis Set. The percentages of subjects with virologic suppression at Week 48 were as follows: M = F: E/C/F/TAF 97.2%, 386 of 397 subjects; STB 95.7%, 375 of 392 subjects; M = E: E/C/F/TAF 97.7%, 386 of 395 subjects; STB 95.9%, 375 of 391 subjects.

Pooled Data from Studies GS-US-292-0104 and GS-US-292-0111

Based on the pooled data from Studies GS-US-292-0104 and GS-US-292-0111, high and similar rates of virologic suppression at Week 48 were achieved in the 2 treatment groups, as assessed using the M = F and M = E methods for the FAS. The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 were as follows: M = F: E/C/F/TAF 93.0%, STB 92.3%; difference in percentages: 0.8%, 95% CI: −1.8% to 3.3% (Ad Hoc Table Req6769.3); M = E: E/C/F/TAF 97.5%, STB 97.0%; difference in percentages: 0.5%, 95% CI: −1.2% to 2.1% (Ad Hoc Table Req6769.4).

Study GS-US-292-0102

In Study GS-US-292-0102, high and similar rates of virologic suppression were achieved in the 2 treatment groups, as assessed using the M = F and M = E methods at Weeks 24 and 48 for the FAS. The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 were as follows: M = F: E/C/F/TAF 90.2%, STB 89.7%; difference in percentages: −1.2%, 95% CI: −11.6% to 9.2%; M = E: E/C/F/TAF 94.4%, STB 92.9%; difference in percentages: −0.1%, 95% CI: −9.0% to 8.9%.

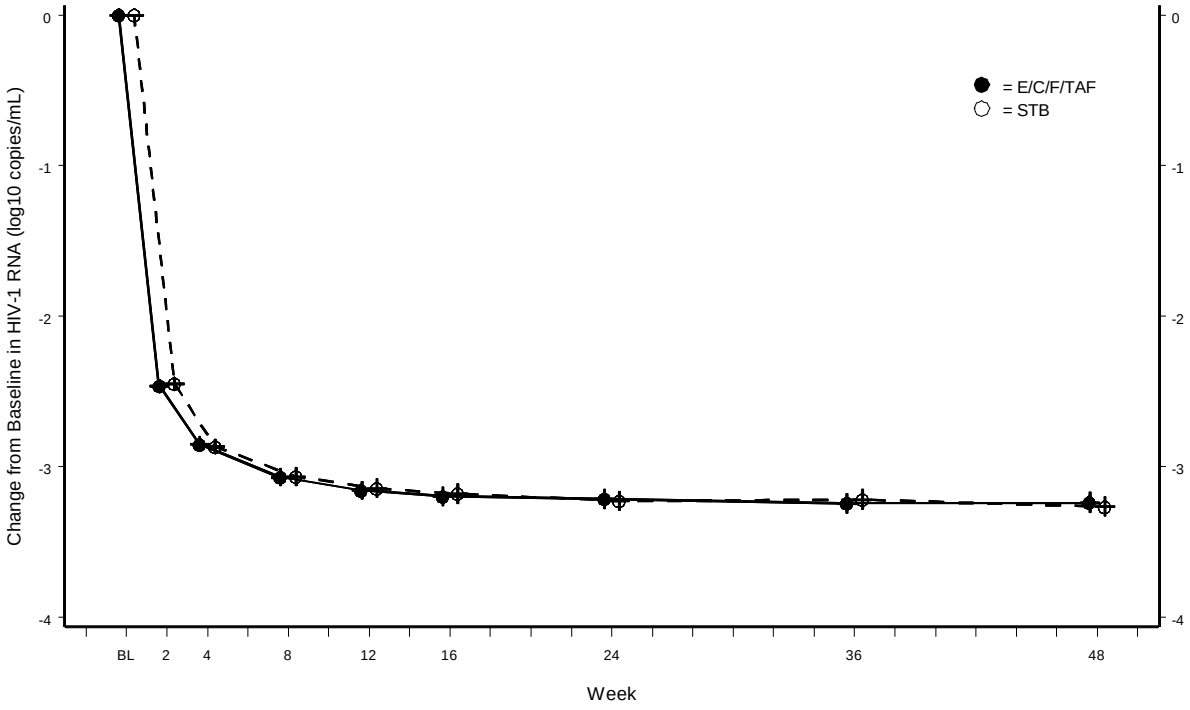
High and similar rates of virologic suppression were achieved in the 2 treatment groups at Weeks 24 and 48 using the Week 48 PP Analysis Set. The percentages of subjects with virologic suppression at Week 48 were as follows: M = F: E/C/F/TAF 95.0%, 96 of 101 subjects; STB 90.7%, 49 of 54 subjects; M = E: E/C/F/TAF 95.0%, 96 of 101 subjects; STB 92.5%, 49 of 53 subjects.

3.2.1.1.4. Change from Baseline in Plasma HIV-1 RNA

Study GS-US-292-0104

In Study GS-US-292-0104, mean (SD) baseline HIV-1 RNA levels were as follows: E/C/F/TAF 4.55 (0.682) $\log_{10}$ copies/mL; STB 4.55 (0.674) $\log_{10}$ copies/mL. HIV-1 RNA levels decreased rapidly in the first 2 weeks following initiation of study drugs for both treatment groups. After Week 8, the decreases were stable and similar between the 2 groups through Week 48 (Figure 1); mean (SD) decreases at Week 48 were as follows: E/C/F/TAF 3.24 (0.684) $\log_{10}$ copies/mL; STB 3.27 (0.663) $\log_{10}$ copies/mL; difference in LSM: 0.04 $\log_{10}$ copies/mL, 95% CI: −0.03 to 0.11 $\log_{10}$ copies/mL.

Figure 1. E/C/F/TAF Study GS-US-292-0104: Mean and 95% CIs of Change from Baseline by Visit in HIV-1 RNA (log_{10} copies/mL) (FAS)



E/C/F/TAF (n=):	435	415	427	429	422	423	420	417	416
STB (n=):	432	419	425	427	422	425	423	416	411

BL = Baseline.
< 20 copies/mL HIV-1 RNA in the Taqman assay was imputed as 19 copies/mL for analysis purpose.

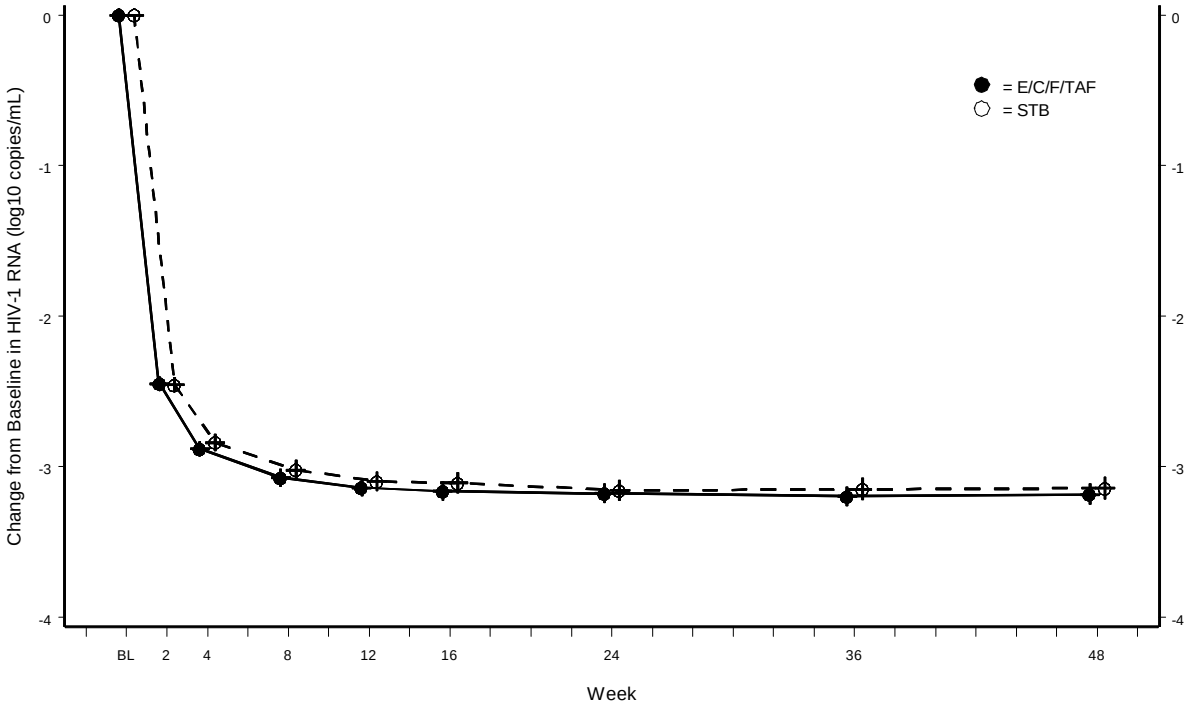
Data Extracted: CRF Data: [redacted]20[redacted], Lab Data: [redacted]20[redacted], DXA Data: [redacted]20[redacted], PK Data: [redacted]20[redacted]
Source: .../version1/prog/t-effchg.sas v9.2 Output file: g-effchg-rna.out [redacted]20[redacted]:10:17

Source: GS-US-292-0104 Week 48 CSR, Section 15.1, Figure 6

Study GS-US-292-0111

In Study GS-US-292-0111, mean (SD) baseline HIV-1 RNA levels were as follows: E/C/F/TAF 4.53 (0.647) log_{10} copies/mL; STB 4.50 (0.690) log_{10} copies/mL. HIV-1 RNA levels decreased rapidly in the first 2 weeks following initiation of study drugs for both treatment groups. After Week 8, the decreases were stable and similar between the 2 groups through Week 48 (Figure 2); mean (SD) decreases at Week 48 were as follows: E/C/F/TAF 3.19 (0.705) log_{10} copies/mL; STB 3.14 (0.745) log_{10} copies/mL; difference in LSM of −0.06 log_{10} copies/mL, 95% CI: −0.15 to 0.02 log_{10} copies/mL.

Figure 2. E/C/F/TAF Study GS-US-292-0111: Mean and 95% CIs of Change from Baseline by Visit in HIV-1 RNA (log_{10} copies/mL) (FAS)



E/C/F/TAF (n=):	431	408	428	421	422	424	419	419	410
STB (n=):	435	421	429	429	424	424	421	416	414

BL = Baseline.
"< 20 cp/mL HIV-1 RNA Detected" or "No HIV-1 RNA Detected" in the Taqman assay were imputed as 19 copies/mL for analysis purpose.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../version1/prog/t-effchg.sas v9.2 Output file: g-effchg-rna.out [redacted]

Source: GS-US-292-0111 Week 48 CSR, Section 15.1, Figure 6

Pooled Data from Studies GS-US-292-0104 and GS-US-292-0111

For the pooled data from Studies GS-US-292-0104 and GS-US-292-0111, mean (SD) baseline HIV-1 RNA levels were as follows: E/C/F/TAF 4.54 (0.665) log_{10} copies/mL; STB 4.53 (0.682) log_{10} copies/mL. HIV-1 RNA levels decreased rapidly in the first 2 weeks following initiation of study drugs for both treatment groups. After Week 8, the decreases were stable and similar between the 2 groups through Week 48; mean (SD) decreases at Week 48 were as follows: E/C/F/TAF 3.21 (0.695) log_{10} copies/mL; STB 3.20 (0.708) log_{10} copies/mL; difference in LSM: −0.01 log_{10} copies/mL, 95% CI: −0.07 to 0.04 log_{10} copies/mL (Ad Hoc Table Req6769.2).

Study GS-US-292-0102

In Study GS-US-292-0102, mean (SD) baseline HIV-1 RNA levels were as follows: E/C/F/TAF 4.63 (0.572) log_{10} copies/mL; STB 4.69 (0.577) log_{10} copies/mL. HIV-1 RNA levels decreased following initiation of study drugs for both treatment groups. The mean (SD) decreases from

baseline were similar for the 2 groups through Week 48, as follows: E/C/F/TAF 3.22 (0.606) log_{10} copies/mL; STB 3.33 (0.572) log_{10} copies/mL; difference in LSM: −0.02 log_{10} copies/mL, 95% CI: −0.18 to 0.13 log_{10} copies/mL.

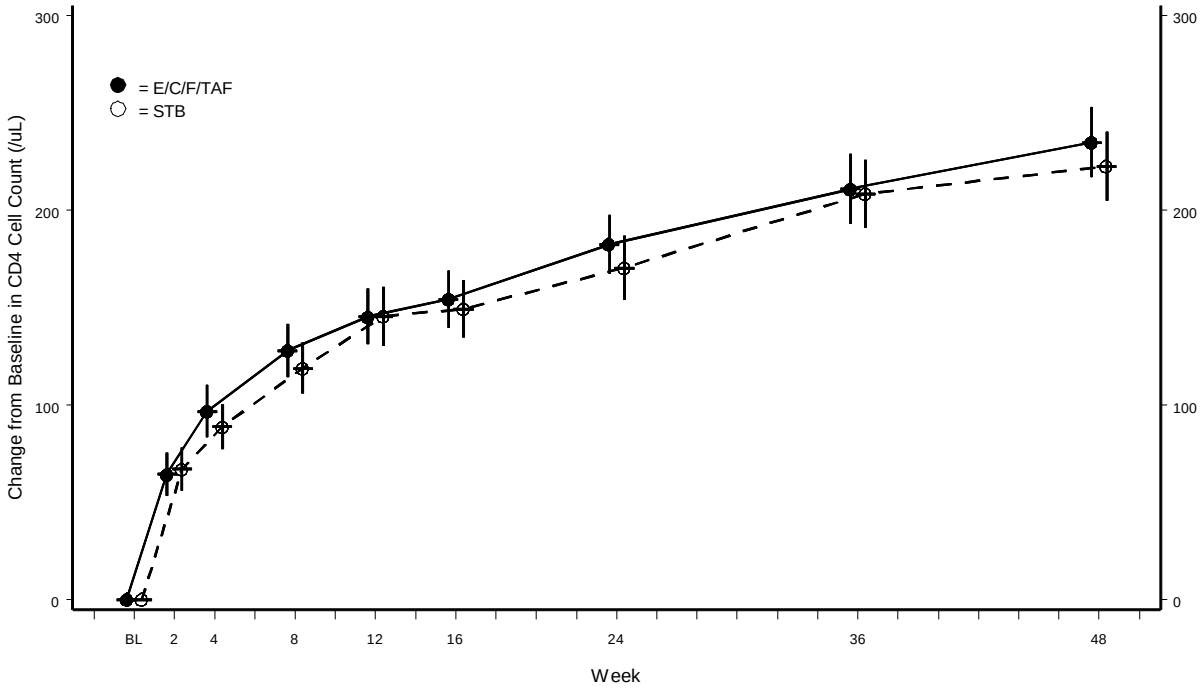
3.2.1.1.5. Change from Baseline in CD4 Cell Counts

Study GS-US-292-0104

In Study GS–US-292-0104, following initiation of study drug, CD4 cell counts increased for each treatment group in the FAS, based on observed data (ie, M = E) (Figure 3). Mean (SD) baseline CD4 cell counts were as follows: E/C/F/TAF 437 (223.7) cells/μL; STB 426 (212.3) cells/μL. The mean (SD) increases were similar for each treatment group through Week 48 (observed data) based on the FAS, as follows: E/C/F/TAF 235 (183.1) cells/μL; STB 222 (178.0) cells/μL; difference in LSM: 12 cells/μL, 95% CI: −13 to 37 cells/μL. Results at Week 48 for the PP Analysis Set were consistent with the results for the FAS.

The change from baseline in CD4 cell counts using last observation carried forward (LOCF) to impute missing values showed similar trends compared with the observed data. Mean (SD) increases from baseline at Week 48 were as follows: E/C/F/TAF 231 (183.1) cells/μL; STB 220 (177.0) cells/μL; difference in LSM: 11 cells/μL, 95% CI: −13 to 35 cells/μL.

Figure 3. E/C/F/TAF Study GS-US-292-0104: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS)



E/C/F/TAF (n=):	435	412	425	425	419	418	418	409	413
STB (n=):	432	417	421	420	415	419	415	407	402

BL = Baseline.
On-treatment values include data after the first dose date up to the database finalization date for ongoing subjects or up to the last dose date + 1 day for subjects who prematurely discontinued study drug.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../version1/prog/t-effchg.sas V9.2 Output file: g-effchg-cd4.out [redacted]

Source: GS-US-292-0104 Week 48 CSR, Section 15.1, Figure 7.1

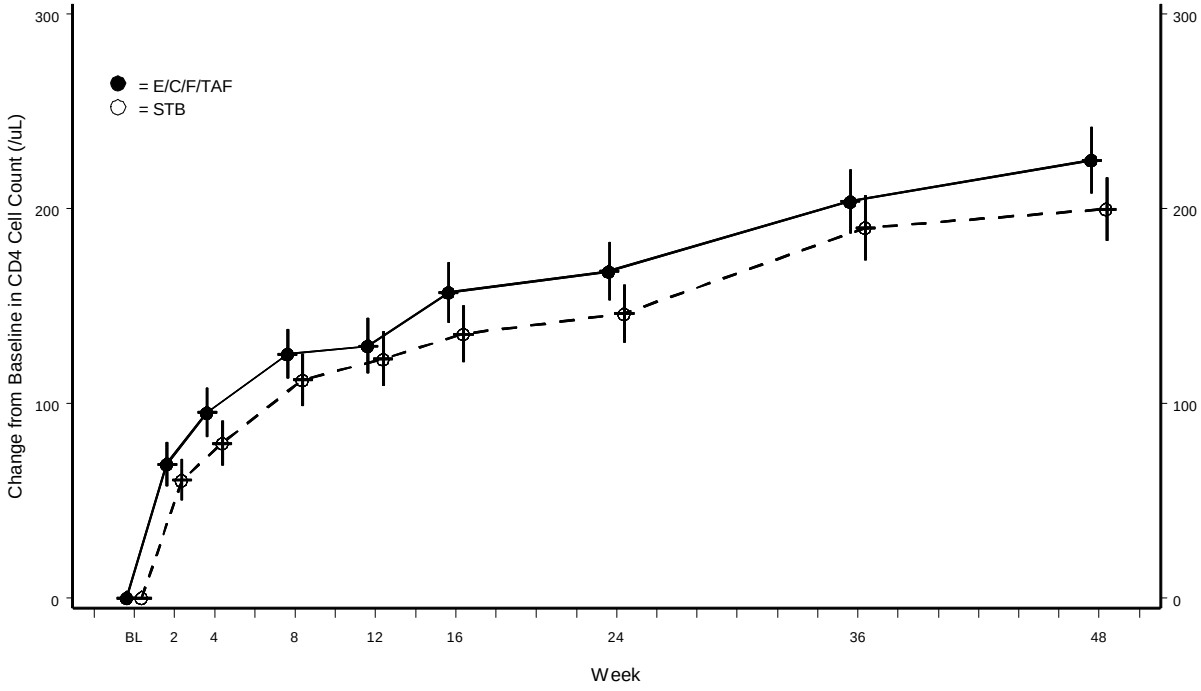
Study GS-US-292-0111

In Study GS-US-292-0111, following initiation of study drug, CD4 cell counts increased for each treatment group in the FAS, based on observed data (ie, M = E) (Figure 4). Mean (SD) baseline CD4 cell counts were as follows: E/C/F/TAF 414 (206.8) cells/μL; STB 431 (226.8) cells/μL. The mean (SD) increases from baseline at Week 48 (observed data) based on the FAS were greater for the E/C/F/TAF group compared with the STB group, as follows: E/C/F/TAF 225 (171.2) cells/μL; STB 200 (162.5) cells/μL; difference in LSM 27 cells/μL, 95% CI: 4 to 50 cells/μL; p = 0.019. Results at Week 48 for the PP Analysis Set were consistent with the results for the FAS.

The change from baseline in CD4 cell counts using LOCF to impute missing values showed similar trends compared with the observed data. Mean (SD) increase from baseline at Week 48 (LOCF) was greater for the E/C/F/TAF group compared with the STB group, as follows:

E/C/F/TAF 224 (174.7) cells/μL; STB 195 (165.0) cells/μL; difference in LSM 30 cells/μL, 95% CI: 7 to 53 cells/μL; p = 0.009.

Figure 4. E/C/F/TAF Study GS-US-292-0111: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS)



E/C/F/TAF (n=):	430	406	424	415	413	420	415	413	404
STB (n=):	435	419	427	421	413	417	413	405	400

BL = Baseline.
On-treatment values include data after the first dose date up to the database finalization date for ongoing subjects or up to the last dose date + 1 day for subjects who prematurely discontinued study drug.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], DXA Data: [redacted], PK Data: [redacted]
Source: .../version1/prog/t-effchg.sas v9.2 Output file: g-effchg-cd4.out [redacted]

Source: GS-US-292-0111 Week 48 CSR, Section 15.1, Figure 7.1

Pooled Data from Studies GS-US-292-0104 and GS-US-292-0111

For the pooled data from Studies GS-US-292-0104 and GS-US-292-0111, following initiation of study drug, CD4 cell counts increased for each treatment group in the FAS, based on observed data (ie, M = E). Mean (SD) baseline CD4 cell counts were as follows: E/C/F/TAF 426 (215.6) cells/μL; STB 429 (219.6) cells/μL. The mean (SD) increases were similar for each treatment group through Week 48 (observed data) based on the FAS, as follows: E/C/F/TAF 230 (177.3) cells/μL; STB 211 (170.7) cells/μL; difference in LSM: 19 cells/μL, 95% CI: 3 to 36 cells/μL (Ad Hoc Table Req6854.2).

The change from baseline in CD4 cell counts using LOCF to impute missing values showed similar trends compared with the observed data. Mean (SD) increases from baseline at Week 48

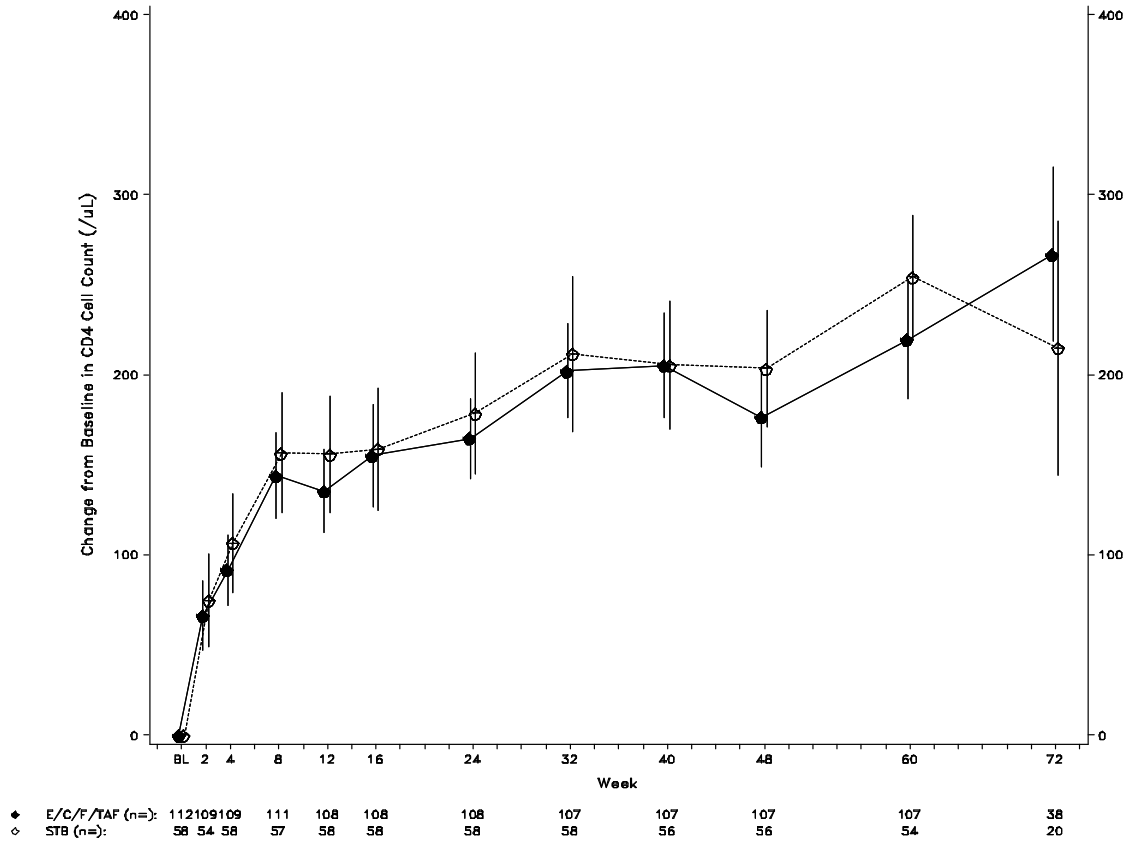
were as follows: E/C/F/TAF 228 (178.9) cells/μL; STB 207 (171.5) cells/μL; difference in LSM: 20 cells/μL, 95% CI: 4 to 37 cells/μL (Ad Hoc Table Req6854.1).

Study GS-US-292-0102

In Study GS-US-292-0102, following initiation of study drug, CD4 cell counts increased for each treatment group (Figure 5). Mean (SD) baseline CD4 cell counts were as follows: E/C/F/TAF 404 (181.6) cells/μL; STB 394 (209.6) cells/μL. The mean (SD) increases were similar for each treatment group through Week 48 (observed data) using the FAS, as follows: E/C/F/TAF 177 [144.1] cells/μL; STB 204 [120.4] cells/μL; difference in LSM −19 cells/μL, 95% CI: −63 to 26 cells/μL. Results for the Week 48 PP Analysis Set were consistent with the results for the FAS.

The change from baseline in CD4 cell counts using LOCF to impute missing values showed similar trends compared with the observed data. Mean (SD) increases from baseline at Week 48 were as follows: E/C/F/TAF 173 (143.4) cells/μL; STB 200 (119.2) cells/μL; difference in LSM: −20 cells/μL, 95% CI: −64 to 23 cells/μL.

Figure 5. E/C/F/TAF Study GS-US-292-0102: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS)



Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Figure 4.1

3.2.1.2. Virologically Suppressed Subjects in Studies GS-US-292-0109 and GS-US-292-0102

A summary of efficacy of E/C/F/TAF from Study GS-US-292-0109 and the extension phase of Study GS-US-292-0102 is presented below.

3.2.1.2.1. Study GS-US-292-0109

Detailed efficacy results are presented in the CSR (GS-US-292-0109 Week 48, Section 9).

Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using FDA Snapshot Algorithm

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm. The rates of maintained virologic suppression in Study GS-US-292-0109 at Week 48 were high in both groups using the Week 48 FAS (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 92.9%; difference in percentages: 2.7%, 95.01% CI: −0.3% to 5.6%) (Table 26). Because the lower bound of the 2-sided 95.01% CI of the difference in response rate was greater than the prespecified −12% margin, switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent at Week 48.

The rates of maintained virologic suppression were also similar between treatment groups using the Week 48 PP Analysis Set (E/C/F/TAF 99.1%, 748 of 755 subjects; FTC/TDF+3rd Agent 98.9%, 363 of 367 subjects; difference in percentages: 0.2%, 95.01% CI: −1.3% to 1.6%), confirming that switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent at Week 48.

Table 26. E/C/F/TAF Study GS-US-292-0109: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (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[c]				
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[c]	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[c]	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[d]	5 (0.6%)	15 (3.8%)		
Missing data during window but on study drug	13 (1.6%)	5 (1.3%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by the prior treatment regimen (STB, ATR, ATV/boosted+TVD).
b Difference in percentages of virologic success and its 95.01% CI were calculated based on the MH proportion adjusted by the prior treatment regimen.
c Week 48 window is between Day 294 and 377 (inclusive). The Week 48 FAS is defined as subjects randomized by [redacted]20[redacted] and received at least 1 dose of study drug.
d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

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 Week 48 CSR, Section 15.1, Table 10.1

Percentage of Subjects with Plasma HIV-1 RNA < 20 copies/mL at Week 48 Using FDA Snapshot Algorithm

A high percentage of subjects in both treatment groups had virologic success defined as HIV-1 RNA < 20 copies/mL at Week 48 using the FDA snapshot algorithm for the Week 48 FAS (E/C/F/TAF 92.2%; FTC/TDF+3rd Agent 90.4%; difference in percentages: 1.8%, 95% CI: −1.7% to 5.3%) or Week 48 PP Analysis Set (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 96.2%; difference in percentages: −0.6%, 95% CI: −3.1% to 2.0%).

Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using M = F and M = E Methods

In virologically suppressed subjects in Study GS-US-292-0109, the rates of virologic success as assessed in the M = F and M = E analyses for the percentages of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 were high and similar in both treatment groups, as follows:

- For the M = F analysis, rates of virologic suppression at Week 48 were 96.4% (770 of 799 subjects) for the E/C/F/TAF group and 94.7% (376 of 397 subjects) for the FTC/TDF+3rd Agent group.

- For the M = E analysis, rates of virologic suppression at Week 48 were 99.1% (770 of 777 subjects) for the E/C/F/TAF group and 98.7% (376 of 381 subjects) for the FTC/TDF+3rd Agent group.

- The 95% CI was constructed using Mantel-Haenszel (MH) proportion stratified by prior treatment regimen (STB, ATR, or ATV/boosted+TVD). The stratum-weighted differences in response rate between treatment groups at Week 48 were as follows: M = F: 1.7%, 95% CI: −1.0% to 4.3%; M = E: 0.4%, 95% CI: −1.1% to 1.9%.

Change from Baseline in CD4 Cell Count at Week 48

As expected in virologically suppressed subjects in Study GS-US-292-0109, only slight changes from baseline in mean CD4 cell counts were observed in each group. Using observed data (ie, M = E), the mean (SD) changes from baseline at Week 48 in CD4 cell counts were 33 (166.6) cells/μL in the E/C/F/TAF group and 27 (160.2) cells/μL in the FTC/TDF+3rd Agent group (difference in LSM: 6 cells/μL, 95% CI: −14 to 26 cells/μL). The changes from baseline in CD4 counts at Week 48 (observed data) were consistent when analyzed by prior treatment regimen (STB, ATR, or ATV/boosted+TVD), and results for the Week 48 PP (observed data) were consistent with those for the Week 48 FAS.

3.2.1.2.2. Study GS-US-292-0102 Open-Label Extension

Detailed efficacy results are presented in the CSR (GS-US-292-0102 Week 96, Section 9).

Virologic suppression was maintained and CD4 cell count increased in subjects who switched from a TDF-containing regimen to E/C/F/TAF in the extension phase of Study GS-US-292-0102. At Week 24 of the extension phase, 98.9% of subjects (87 of 88) in the all TDF to TAF group had HIV-1 RNA levels < 50 copies/mL (M = E), and the mean (SD) change from baseline (defined as start of E/C/F/TAF treatment) in CD4 cell count was 61 (159.1) cells/μL.

3.2.1.3. Subjects with Mild to Moderate Renal Impairment in Study GS-US-292-0112

Detailed efficacy results are presented in the CSR (GS-US-292-0112 Week 24, Section 9).

3.2.1.3.1. Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 24 Using FDA Snapshot Algorithm

The primary efficacy endpoint was the percentage of subjects with HIV 1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm (Table 27). The virologic success rate among virologically suppressed subjects with mild to moderate renal impairment who switched treatment to E/C/F/TAF in Study GS-US-292-0112 was 95.0% (baseline $eGFR_{CG}$ < 50 mL/min 95.0%; baseline $eGFR_{CG}$ ≥ 50 mL/min 95.1%). Three subjects (1.2%) were classified as virologic failures at Week 24. Of those 3 subjects, 2 had HIV-1 RNA ≥ 50 copies/mL at Week 24, and 1 added a new ARV.

Table 27. E/C/F/TAF Study GS-US-292-0112: Virologic Outcome at Week 24 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	Cohort 1: Switch			Cohort 2: ART-Naive
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)	Total (N = 6)
Virologic success at Week 24[a]				
HIV-1 RNA < 50 copies/mL	76 (95.0%)	154 (95.1%)	230 (95.0%)	5 (83.3%)
95% CI[b]	87.7% to 98.6%	90.5% to 97.8%	91.5% to 97.4%	35.9% to 99.6%
Virologic failure at Week 24[a]	0	3 (1.9%)	3 (1.2%)	1 (16.7%)
HIV-1 RNA ≥ 50 copies/mL	0	2 (1.2%)	2 (0.8%)	1 (16.7%)
Added new ARV	0	1 (0.6%)	1 (0.4%)	0
No virologic data in Week 24 window[a]	4 (5.0%)	5 (3.1%)	9 (3.7%)	0
Discontinued study drug due to AE/death	4 (5.0%)	2 (1.2%)	6 (2.5%)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[c]	0	3 (1.9%)	3 (1.2%)	0
Missing data during window but on study drug	0	0	0	0

a Week 24 window was between Days 140 and 209 (inclusive).
b The 95% CIs for virologic success rate in each cohort and baseline $eGFR_{CG}$ category were obtained using the exact method.
c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinuation by sponsor.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Table 26.1

3.2.1.3.2. Percentage of Subjects with Plasma HIV-1 RNA < 20 copies/mL at Week 24 Using FDA Snapshot Algorithm

At Week 24, the virologic success rate by HIV-1 RNA < 20 copies/mL was 93.0% using the FDA snapshot algorithm.

3.2.1.3.3. Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using FDA Snapshot Algorithm

At Week 48, the virologic success rate among virologically suppressed subjects with mild to moderate renal impairment who switched treatment to E/C/F/TAF in Study GS-US-292-0112 was 93.7% (164 of 175 subjects; HIV-1 RNA < 50 copies/mL) using the FDA snapshot algorithm (Table 28). Three subjects (1.7%; all in the baseline $eGFR_{CG} \geq 50$ mL/min group) were classified as virologic failures at Week 48. Of those 3 subjects, 1 had HIV-1 RNA ≥ 50 copies/mL at Week 48, 1 discontinued due to lack of efficacy, and 1 added a new ARV.

Table 28. E/C/F/TAF Study GS-US-292-0112: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	Cohort 1: Switch			Cohort 2: ART-Naive
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 44)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 131)	Total (N = 175)	Total (N = 2)
Virologic success at Week 48[a]				
HIV-1 RNA < 50 copies/mL	43 (97.7%)	121 (92.4%)	164 (93.7%)	2 (100.0%)
95% CI[b]	88.0% to 99.9%	86.4% to 96.3%	89.0% to 96.8%	15.8% to 100.0%
Virologic failure at Week 48[a]	0	3 (2.3%)	3 (1.7%)	0
HIV-1 RNA ≥ 50 copies/mL	0	1 (0.8%)	1 (0.6%)	0
Discontinued study drug due to lack of efficacy	0	1 (0.8%)	1 (0.6%)	0
Added new ARV	0	1 (0.8%)	1 (0.6%)	0
No virologic data in Week 48 window[a]	1 (2.3%)	7 (5.3%)	8 (4.6%)	0
Discontinued study drug due to AE/death	1 (2.3%)	2 (1.5%)	3 (1.7%)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[c]	0	4 (3.1%)	4 (2.3%)	0
Missing data during window but on study drug	0	1 (0.8%)	1 (0.6%)	0

a Week 48 window was between Day 294 and 377 (inclusive).
b The 95% CIs for virologic success rate in each cohort and baseline $eGFR_{CG}$ category were obtained using the exact method.
c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinuation by sponsor.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Table 26.2

3.2.1.3.4. Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL Using M = F and M = E Methods

High rates of virologic suppression were maintained, as assessed using the M = F (at Week 24) and M = E (at Weeks 24 and 48) methods using the FAS. Among virologically suppressed subjects with mild to moderate renal impairment who switched treatment to E/C/F/TAF in

Study GS-US-292-0112, the percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 24 were 97.5% and 99.2% for M = F and M = E, respectively. The percentage of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 was 99.4% (M = E).

3.2.1.3.5. Change from Baseline in CD4 Cell Count

Among virologically suppressed subjects with mild to moderate renal impairment who switched treatment to E/C/F/TAF in Study GS-US-292-0112, CD4 cell counts remained stable during treatment with E/C/F/TAF. The mean (SD) baseline CD4 cell count was 664 (286.4) cells/μL. The mean (SD) change from baseline in CD4 cell counts at Week 24 (observed data) using the FAS was −7 (159.2) cells/μL. The mean (SD) change from baseline in CD4 cell counts through Week 48 (observed data) using the FAS was 16 (158.0) cells/μL.

3.2.1.4. ART-Naive Adolescent Subjects in Study GS-US-292-0106

Detailed efficacy results are presented in the CSR (GS-US-292-0106 Interim, Section 9).

3.2.1.4.1. Percentage of Subjects with Plasma HIV 1 RNA < 50 copies/mL at Week 24 Using FDA Snapshot Algorithm

In Study GS-US-292-0106, the virologic success rate at Week 24 was 91.3% (21 of 23 subjects) for HIV-infected, ART-naive adolescents receiving E/C/F/TAF (assessed using the FDA snapshot algorithm with a cutoff of HIV-1 RNA < 50 copies/mL; Table 29). Two subjects (8.7%) who had virologic failure achieved virologic suppression (HIV-1 RNA < 50 copies/mL) prior to the Week 24 analysis window, remained on study drug, and had HIV-1 RNA < 50 copies/mL at later study visits.

Table 29. E/C/F/TAF Study GS-US-292-0106: Virologic Outcome at Week 24 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

HIV-1 RNA Category[a]	E/C/F/TAF (N = 23)
Virologic Success at Week 24[b]	
HIV-1 RNA < 50 copies/mL	21 (91.3%)
Virologic Failure at Week 24[b]	2 (8.7%)
HIV-1 RNA >= 50 copies/mL	2 (8.7%)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[c]	0
Added New ARV	0
No Virologic Data in Week 24 Window[b]	0
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	0
Missing Data during Window but on Study Drug	0

a The Week 24 FAS included subjects in the FAS who were enrolled by [redacted] 20[redacted].
b The Week 24 window was between Days 140 and 195 (inclusive).
c Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

Programming Details: .../s2920106/wk_24/version1/prog/t-snapshot.sas v9.2 Output file: t-snapshot-50-wk24.out [redacted]20[redacted]:11:44
Source: GS-US-292-0106 Interim CSR, Section 15.1, Table 9.1

3.2.1.4.2. Percentage of Subjects with Plasma HIV 1 RNA < 50 copies/mL at Week 24 Using M = F and M = E Methods

In Study GS-US-292-0106, in both the M = F (Week 24 FAS) and M = E (FAS) analyses, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 was 91.3% (21 of 23 subjects).

3.2.1.4.3. Change from Baseline in Plasma HIV-1 RNA

In Study GS-US-292-0106, mean (SD) baseline HIV-1 RNA levels were 4.62 (0.593) $\log_{10}$ copies/mL for the FAS. HIV-1 RNA levels decreased following initiation of E/C/F/TAF, with a mean (SD) decrease of 3.16 (0.511) $\log_{10}$ copies/mL by Week 8. At Week 24, the mean (SD) decrease from baseline in HIV-1 RNA was 3.34 (0.679) $\log_{10}$ copies/mL.

3.2.1.4.4. Change from Baseline in CD4 Cell Count at Week 24

In Study GS-US-292-0106, CD4 cell count increased following initiation of study drug, and continued to increase with increased duration of exposure to study drug. Mean (SD) baseline CD4 cell count (FAS; based on observed data) was 468 (215.4) cells/μL, and at Week 24, the mean (SD) increase from baseline in CD4 cell count was 212 (144.3) cells/μL.

3.2.2. D/C/F/TAF Study

3.2.2.1. ART-Naive Subjects in Study GS-US-299-0102

Detailed efficacy results are presented in the CSR (m5.3.5.1, GS-US-299-0102, Section 9).

3.2.2.1.1. Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using FDA Snapshot Algorithm

The rates of virologic success through Week 48 when assessed using the FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) using the FAS were as follows: D/C/F/TAF 76.7%, DRV+COBI+TVD 84.0%; difference in percentages: −6.2%, 95% CI: −19.9% to 7.4% (Table 30). The difference in rates of virologic success between treatment arms was primarily due to a difference in the numbers of subjects who discontinued study drug due to other reasons and had the last available HIV-1 RNA ≥ 50 copies/mL (D/C/F/TAF: 8.7%, 9 subjects; DRV+COBI+TVD: 4.0%, 2 subjects) or < 50 copies/mL (D/C/F/TAF: 6.8%, 7 subjects; DRV+COBI+TVD: 2.0%, 1 subject).

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treament groups (D/C/F/TAF 15.5%, DRV+COBI+TVD 12.0%).

Virologic success rates at Week 48 were similar between the 2 treatment groups using the Week 48 PP analysis set, as follows: D/C/F/TAF 92.9%, 79 of 85 subjects, DRV+COBI+TVD 91.3%, 42 of 46 subjects; difference in percentages: 2.4%, 95% CI: −8.8% to 13.7%.

Table 30. D/C/F/TAF Study GS-US-299-0102: Virologic Outcome at Week 48 using Snapshot Analysis Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

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

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and race strata.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 48 window was between Day 308 and 337 (inclusive).
d Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 11.1

3.2.2.1.2. Percentage of Subjects with HIV-1 RNA < 50 copies/mL Using Missing Data Imputation Methods

The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) using the M = F and M = E method at Week 48 using the FAS were as follows:
M = F: D/C/F/TAF 77.7%, DRV+COBI+TVD 86.0% (difference: −7.2%, 95% CI: −20.3% to 6.0%); M = E: D/C/F/TAF 89.9%, DRV+COBI+TVD 91.5% (difference: −0.5%, 95% CI: −11.9% to 10.9%).

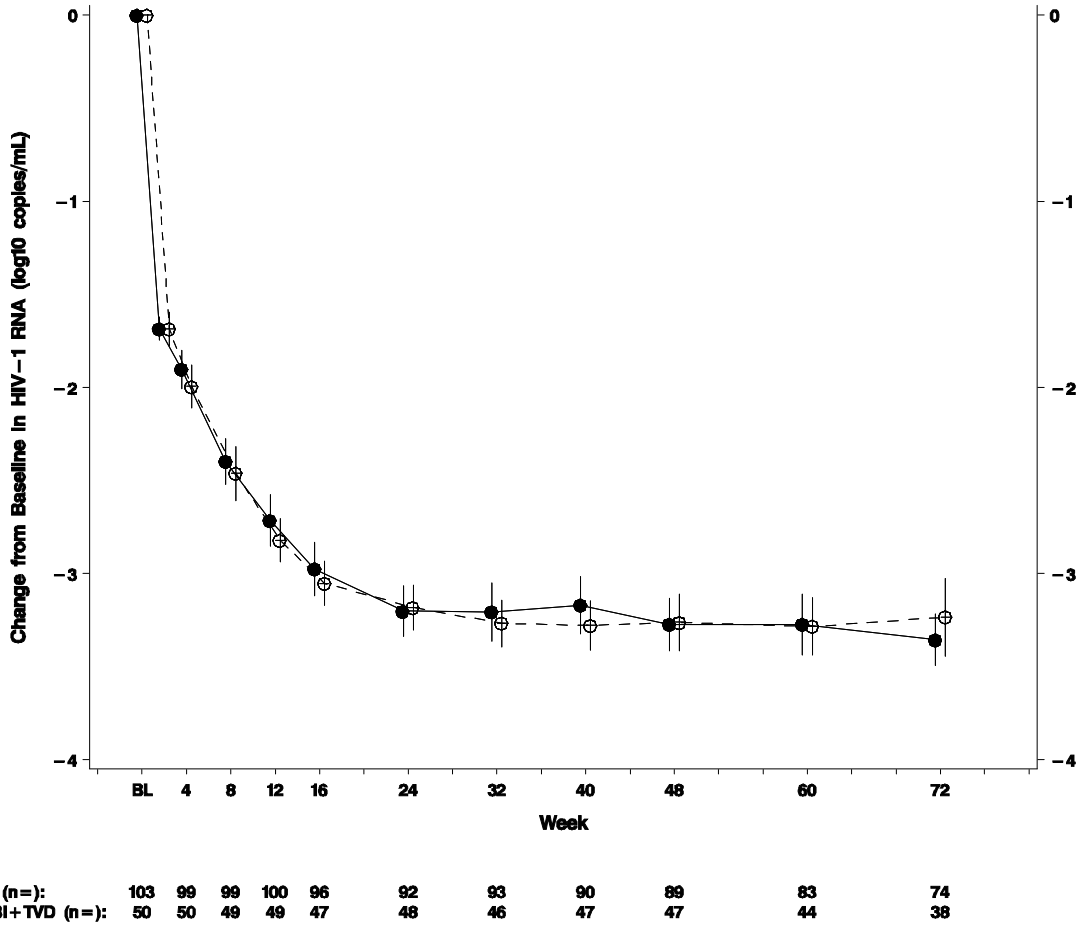
Similar rates of virologic suppression were achieved in the 2 treatment groups at Weeks 24 and 48 using the Week 48 PP analysis set. The percentages of subjects with virologic suppression at Week 48 were as follows: M = F: D/C/F/TAF 92.9%, 79 of 85 subjects; DRV+COBI+TVD

91.3%, 42 of 46 subjects; M = E: D/C/F/TAF 92.9%, 79 of 85 subjects; DRV+COBI+TVD 91.3%, 42 of 46 subjects.

3.2.2.1.3. Change from Baseline in Plasma HIV-1 RNA

HIV-1 RNA levels decreased following initiation of study drug (Figure 6). Mean (SD) baseline HIV-1 RNA levels were as follows: D/C/F/TAF 4.70 (0.516) log_{10} copies/mL, DRV+COBI+TVD 4.65 (0.514) log_{10} copies/mL. The mean decreases were similar for the 2 groups through Week 48, as follows: D/C/F/TAF −3.27 (0.668) log_{10} copies/mL; DRV+COBI+TVD −3.26 (0.521) log_{10} copies/mL; difference in LSM: 0.06 log_{10} copies/mL, 95% CI: −0.11 to 0.23 log_{10} copies/mL.

Figure 6. D/C/F/TAF Study GS-US-299-0102: Mean and 95% CIs of Change from Baseline by Visit in HIV-1 RNA (log_{10} copies/mL) by Visit (FAS)



Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Figure 7

3.2.2.1.4. Change from Baseline in CD4 Cell Counts

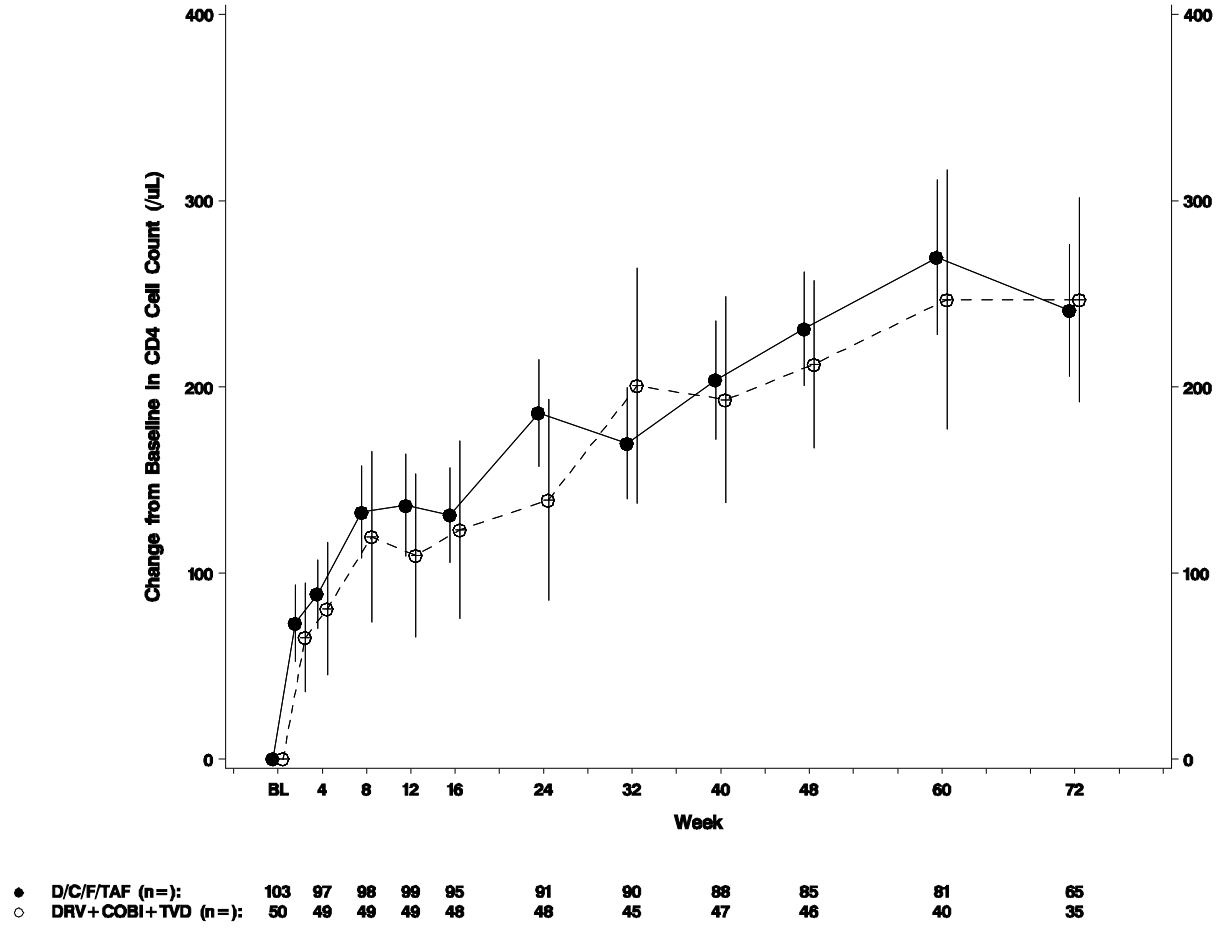
Following initiation of study drug, CD4 cell counts increased for each treatment group (Figure 7). Mean (SD) baseline CD4 cell counts were as follows: D/C/F/TAF

395 (169.3) cells/μL, DRV+COBI+TVD 464 (261.6) cells/μL. The mean (SD) increases were similar for each treatment group through Week 48 (observed data) using the FAS, as follows: D/C/F/TAF 231 (141.9) cells/μL; DRV+COBI+TVD 212 (151.5) cells/μL; difference in LSM: 18 cells/μL, 95% CI: −35 to 72 cells/μL.

The change from baseline in CD4 cell counts using the LOCF imputation method (FAS) showed similar trends compared with the observed data. Mean (SD) increases from baseline at Week 48 were as follows: D/C/F/TAF 207 (153.7) cells/μL; DRV+COBI+TVD 195 (161.9) cells/μL; difference in LSM: 8 cells/μL, 95% CI: −45 to 62 cells/μL.

Results for the Week 48 PP analysis set were similar to results for the FAS.

Figure 7. D/C/F/TAF Study GS-US-299-0102: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS)



Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Figure 8.1

3.3. Comparison of Results in Subpopulations

Subgroups Analyzed

In ART-naive subjects from E/C/F/TAF pivotal studies (GS-US-292-0104 and GS-US-292-0111), the primary analysis of virologic success (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) was analyzed for each of the following subgroups:

- Age (years): < 50 and ≥ 50
- Sex: male and female
- Race: black and nonblack
- Baseline CD4 count (cells/μL): < 200 and ≥ 200
- Baseline HIV-1 RNA level (copies/mL): ≤ 100,000 and > 100,000
- Region: US and ex-US
- Study drug adherence (%): < 95 and ≥ 95

In ART-naive subjects from the E/C/F/TAF Study GS-US-292-0102 (Phase 2), virologic success (percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using the FDA snapshot algorithm) was analyzed for age (< 40 and ≥ 40 years), sex (male and female), race (black and nonblack), baseline CD4 count (< 200 and ≥ 200 cells/μL), baseline HIV-1 RNA level (≤ 100,000 and > 100,000 copies/mL), and study drug adherence (< 95% and ≥ 95%) subgroups.

In virologically suppressed subjects from the E/C/F/TAF Study GS-US-292-0109, virologic success (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) was analyzed for age (< 50 and ≥ 50 years), sex (male and female), race (black and nonblack), region (US and ex-US), prior treatment regimen (ie, STB, ATR, and ATV/boosted+TVD), and study drug adherence (< 95% and ≥ 95%) subgroups. The change from baseline in CD4 cell count was also assessed by prior treatment regimen (STB, ATR, and ATV/boosted+TVD) as a predefined subgroup analysis.

In subjects with mild to moderate renal impairment who switched treatment to E/C/F/TAF in Study GS-US-292-0112, virologic success (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm) was analyzed for age (< 50 and ≥ 50 years), sex (male and female), race (black and nonblack), region (US and ex-US), and study drug adherence (< 95% and ≥ 95%) subgroups.

In ART-naive adolescent subjects, from the E/C/F/TAF Study GS-US-292-0106, no subgroup analyses were performed.

Demographic factors (age, sex, and race) were analyzed in accordance with International Conference on Harmonization M4E guidance. CD4 cell counts and baseline HIV-1 RNA level are widely accepted surrogate markers of HIV disease severity. The 200 cells/μL cutoff for baseline CD4 count was determined to be a clinically relevant value and near the median baseline CD4 counts observed in each treatment group. The 100,000 copies/mL cutoff for baseline HIV-1 RNA was chosen because levels > 100,000 copies/mL are associated with a high HIV-1 viral burden. Region was chosen (US versus ex-US) due to differences in genetic make-up of populations as well as differences in HIV-1 subtypes circulating there. Study drug adherence was chosen to account for the effect that adherence has on the efficacy of any medication and to be able to assess the true efficacy of study drug if taken as directed.

In ART-naive subjects from the D/C/F/TAF Phase 2 Study GS-US-299-0102, virologic success was analyzed as per the methods for the E/C/F/TAF Phase 2 Study GS-US-292-0102.

Methods

Subgroup analysis was performed using the FAS. For each subgroup factor, the percentage differences between treatment groups and 95% CIs were computed based on the MH proportions adjusted for baseline HIV-1 RNA and region stratum (if it was not the factor defining the subgroups) and study (for pooled analysis). A forest plot was used to present the overall and within subgroup treatment differences with the corresponding 95% CIs.

Additionally, for Studies GS-US-292-0104 and GS-US-292-0111, and pooled data from these studies, a logistic regression model was performed including the baseline HIV-1 RNA stratum, region stratum, study, subgroup factor, treatment, and treatment by subgroup factor. The odds ratio and the associated 95% CI were estimated within each subgroup. The homogeneity of the treatment effects between subgroups was evaluated based on the Wald test of the interaction between treatment and subgroup factor.

3.3.1. E/C/F/TAF Studies

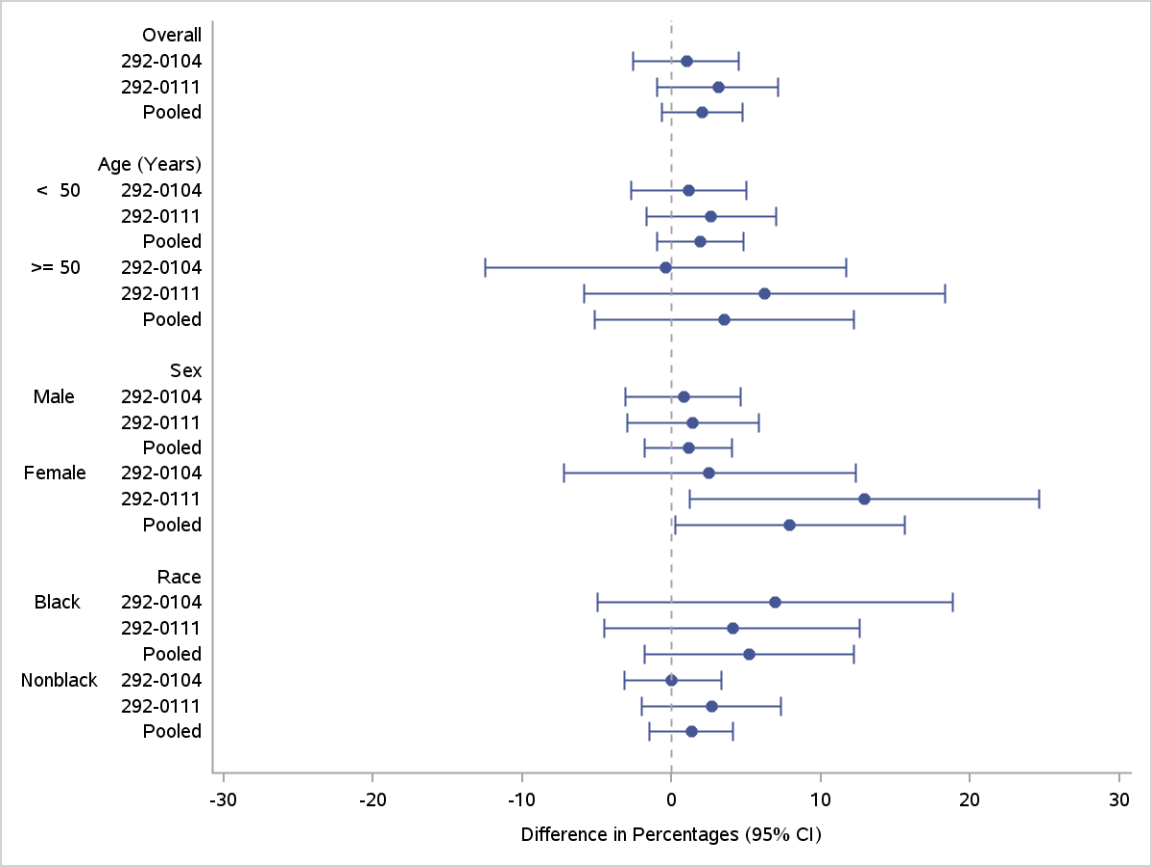
3.3.1.1. ART-Naive Subjects in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102

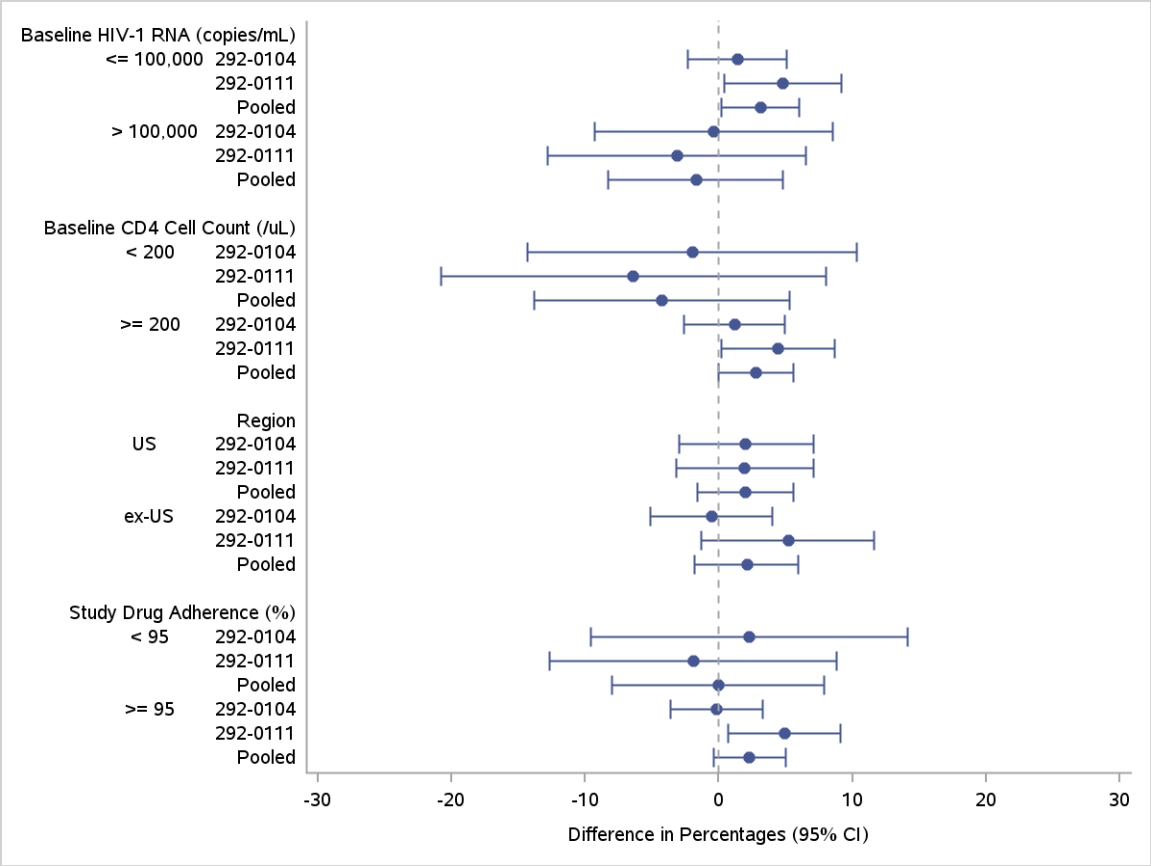
Pooled Data from Studies GS-US-292-0104 and GS-US-292-0111

In the pooled analyses for studies GS-US-292-0104 and GS-US-292-0111, the rates of virologic success at Week 48 by FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) for subgroups according to 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. The 95% CIs for differences in virologic success between treatment groups included zero for most subgroups evaluated suggesting no differences between the treatments. In 2 subgroups (female subject 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, (Figure 8 and Table 31).

Homogeneity tests of the treatment effects between subgroups were performed for individual and pooled study data for virologic success at Week 48 using FAS. The tests did not show a significant difference in treatment effects between subgroups (Table 32).

Figure 8. **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)**





Difference in response rates and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA and region (if not the subgroup factor), and study (for pooled analysis) stratum.
Relative to the vertical line at 0, differences on the right favor the E/C/F/TAF group and differences on the left favor the STB group.
Baseline HIV-1 RNA stratum: <= 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.

Data Extracted: s292-0104: CRF,DXA Data: [redacted], Lab Data: [redacted], s292-0111: CRF,DXA Data: [redacted], Lab Data: [redacted]
Source: .../version1/prog/t-snapshot-trtdiff.sas v9.2 Output file: g-snapshot-forest-wk48.out [redacted]:15:52
Source: E/C/F/TAF ISE, Figure 1

Table 31. E/C/F/TAF Studies GS-US 292-0104 and GS-US-292-0111: Treatment Difference in Virologic Success by Subgroup at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Individual Studies and Pooled Data (FAS)

				E/C/F/TAF vs. STB
		E/C/F/TAF (N=866)	STB (N=867)	Difference in Percentages (95% CI)[a]
Overall				
	292-0104	405/435 (93.1%)	399/432 (92.4%)	1.0% (−2.6% to 4.5%)
	292-0111	395/431 (91.6%)	385/435 (88.5%)	3.1% (−1.0% to 7.1%)
	Pooled	800/866 (92.4%)	784/867 (90.4%)	2.0% (−0.7% to 4.7%)
Age (Years)				
< 50	292-0104	368/397 (92.7%)	353/385 (91.7%)	1.1% (−2.7% to 5.0%)
	292-0111	348/380 (91.6%)	327/368 (88.9%)	2.6% (−1.7% to 7.0%)
	Pooled	716/777 (92.1%)	680/753 (90.3%)	1.9% (−1.0% to 4.8%)
>= 50	292-0104	37/38 (97.4%)	46/47 (97.9%)	−0.4% (−12.5% to 11.7%)
	292-0111	47/51 (92.2%)	58/67 (86.6%)	6.2% (−5.9% to 18.3%)
	Pooled	84/89 (94.4%)	104/114 (91.2%)	3.5% (−5.2% to 12.2%)
Sex				
Male	292-0104	338/364 (92.9%)	347/376 (92.3%)	0.8% (−3.1% to 4.6%)
	292-0111	336/369 (91.1%)	326/364 (89.6%)	1.4% (−3.0% to 5.8%)
	Pooled	674/733 (92.0%)	673/740 (90.9%)	1.1% (−1.8% to 4.0%)
Female	292-0104	67/71 (94.4%)	52/56 (92.9%)	2.5% (−7.2% to 12.3%)
	292-0111	59/62 (95.2%)	59/71 (83.1%)	12.9% (1.2% to 24.6%)
	Pooled	126/133 (94.7%)	111/127 (87.4%)	7.9% (0.2% to 15.6%)
Race				
Black	292-0104	81/94 (86.2%)	64/81 (79.0%)	6.9% (−5.0% to 18.8%)
	292-0111	116/129 (89.9%)	113/132 (85.6%)	4.1% (−4.5% to 12.6%)
	Pooled	197/223 (88.3%)	177/213 (83.1%)	5.2% (−1.8% to 12.2%)
Nonblack	292-0104	324/341 (95.0%)	335/351 (95.4%)	0.0% (−3.2% to 3.3%)
	292-0111	279/302 (92.4%)	272/303 (89.8%)	2.7% (−2.0% to 7.3%)
	Pooled	603/643 (93.8%)	607/654 (92.8%)	1.3% (−1.5% to 4.1%)
Baseline HIV-1 RNA (copies/mL)[b]				
<= 100,000	292-0104	313/331 (94.6%)	313/336 (93.2%)	1.4% (−2.3% to 5.1%)
	292-0111	316/339 (93.2%)	297/336 (88.4%)	4.8% (0.4% to 9.2%)
	Pooled	629/670 (93.9%)	610/672 (90.8%)	3.1% (0.2% to 6.0%)

				E/C/F/TAF vs. STB
		E/C/F/TAF (N=866)	**STB (N=867)**	**Difference in Percentages (95% CI)[a]**
> 100,000	292-0104	92/104 (88.5%)	86/96 (89.6%)	−0.4% (−9.3% to 8.5%)
	292-0111	79/92 (85.9%)	88/99 (88.9%)	−3.1% (−12.8% to 6.5%)
	Pooled	171/196 (87.2%)	174/195 (89.2%)	−1.7% (−8.3% to 4.8%)
Baseline CD4 Cell Count (/μL)				
< 200	292-0104	52/58 (89.7%)	48/53 (90.6%)	−2.0% (−14.3% to 10.3%)
	292-0111	44/54 (81.5%)	56/64 (87.5%)	−6.4% (−20.8% to 8.0%)
	Pooled	96/112 (85.7%)	104/117 (88.9%)	−4.3% (−13.8% to 5.3%)
>= 200	292-0104	353/377 (93.6%)	351/379 (92.6%)	1.2% (−2.6% to 4.9%)
	292-0111	350/376 (93.1%)	329/371 (88.7%)	4.4% (0.2% to 8.7%)
	Pooled	703/753 (93.4%)	680/750 (90.7%)	2.8% (−0.0% to 5.6%)
Region[b]				
US	292-0104	231/252 (91.7%)	225/250 (90.0%)	2.0% (−3.0% to 7.1%)
	292-0111	253/280 (90.4%)	249/282 (88.3%)	1.9% (−3.2% to 7.1%)
	Pooled	484/532 (91.0%)	474/532 (89.1%)	2.0% (−1.6% to 5.6%)
ex-US	292-0104	174/183 (95.1%)	174/182 (95.6%)	−0.5% (−5.1% to 4.0%)
	292-0111	142/151 (94.0%)	136/153 (88.9%)	5.2% (−1.3% to 11.6%)
	Pooled	316/334 (94.6%)	310/335 (92.5%)	2.1% (−1.8% to 5.9%)
Study Drug Adherence (%)[c]				
< 95	292-0104	58/67 (86.6%)	70/82 (85.4%)	2.3% (−9.6% to 14.1%)
	292-0111	78/92 (84.8%)	73/83 (88.0%)	−1.9% (−12.7% to 8.8%)
	Pooled	136/159 (85.5%)	143/165 (86.7%)	−0.0% (−8.0% to 7.9%)
>= 95	292-0104	347/367 (94.6%)	329/347 (94.8%)	−0.2% (−3.6% to 3.3%)
	292-0111	317/336 (94.3%)	312/349 (89.4%)	4.9% (0.7% to 9.1%)
	Pooled	664/703 (94.5%)	641/696 (92.1%)	2.3% (−0.4% to 5.0%)

Note: Week 48 window is between Day 294 and 377 (inclusive).

a Difference in response rates and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA and region (if not the subgroup factor), and study (for pooled analysis) stratum.

b Baseline HIV-1 RNA stratum: <= 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.

c Study drug adherence subgroups are based on the adherence up to Week 48 visit for active study drug.

Programming Details: .../version1/prog/t-snapshot-trtdiff.sas v9.2 [redacted]20[redacted]:15:52

Source: E/C/F/TAF ISE, Table 3

Table 32. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Homogeneity Test of Treatment Effect Between Subgroups in Virologic Success at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Individual Studies and Pooled Data (FAS)

				E/C/F/TAF vs. STB	
		E/C/F/TAF (N=866)	STB (N=867)	p-value[a]	Odds Ratio (95% CI)[b]
Age (Years)					
292-0104	< 50	368/397 (92.7%)	353/385 (91.7%)	0.87	1.16 (0.69 to 1.97)
	>= 50	37/38 (97.4%)	46/47 (97.9%)		0.91 (0.05 to 15.29)
292-0111	< 50	348/380 (91.6%)	327/368 (88.9%)	0.66	1.36 (0.83 to 2.21)
	>= 50	47/51 (92.2%)	58/67 (86.6%)		1.84 (0.53 to 6.37)
Pooled	< 50	716/777 (92.1%)	680/753 (90.3%)	0.64	1.26 (0.88 to 1.80)
	>= 50	84/89 (94.4%)	104/114 (91.2%)		1.67 (0.54 to 5.09)
Sex					
292-0104	Male	338/364 (92.9%)	347/376 (92.3%)	0.79	1.11 (0.64 to 1.94)
	Female	67/71 (94.4%)	52/56 (92.9%)		1.38 (0.32 to 5.83)
292-0111	Male	336/369 (91.1%)	326/364 (89.6%)	0.094	1.18 (0.72 to 1.93)
	Female	59/62 (95.2%)	59/71 (83.1%)		3.93 (1.05 to 14.67)
Pooled	Male	674/733 (92.0%)	673/740 (90.9%)	0.12	1.15 (0.79 to 1.66)
	Female	126/133 (94.7%)	111/127 (87.4%)		2.52 (0.99 to 6.38)
Race					
292-0104	Black	81/94 (86.2%)	64/81 (79.0%)	0.31	1.62 (0.73 to 3.60)
	Nonblack	324/341 (95.0%)	335/351 (95.4%)		0.93 (0.46 to 1.88)
292-0111	Black	116/129 (89.9%)	113/132 (85.6%)	0.93	1.45 (0.68 to 3.09)
	Nonblack	279/302 (92.4%)	272/303 (89.8%)		1.39 (0.79 to 2.45)
Pooled	Black	197/223 (88.3%)	177/213 (83.1%)	0.54	1.47 (0.85 to 2.55)
	Nonblack	603/643 (93.8%)	607/654 (92.8%)		1.19 (0.77 to 1.84)
Baseline HIV-1 RNA (copies/mL)[c]					
292-0104	<= 100,000	313/331 (94.6%)	313/336 (93.2%)	0.59	1.26 (0.67 to 2.39)
	> 100,000	92/104 (88.5%)	86/96 (89.6%)		0.93 (0.38 to 2.28)
292-0111	<= 100,000	316/339 (93.2%)	297/336 (88.4%)	0.092	1.81 (1.05 to 3.10)
	> 100,000	79/92 (85.9%)	88/99 (88.9%)		0.76 (0.32 to 1.79)
Pooled	<= 100,000	629/670 (93.9%)	610/672 (90.8%)	0.089	1.56 (1.04 to 2.36)

				E/C/F/TAF vs. STB	
		E/C/F/TAF (N=866)	STB (N=867)	p-value[a]	Odds Ratio (95% CI)[b]
	> 100,000	171/196 (87.2%)	174/195 (89.2%)		0.82 (0.44 to 1.53)
Baseline CD4 Cell Count (/μL)					
292-0104	< 200	52/58 (89.7%)	48/53 (90.6%)	0.66	0.88 (0.25 to 3.12)
	>= 200	353/377 (93.6%)	351/379 (92.6%)		1.20 (0.68 to 2.12)
292-0111	< 200	44/54 (81.5%)	56/64 (87.5%)	0.079	0.62 (0.23 to 1.71)
	>= 200	350/376 (93.1%)	329/371 (88.7%)		1.72 (1.03 to 2.87)
Pooled	< 200	96/112 (85.7%)	104/117 (88.9%)	0.11	0.72 (0.33 to 1.58)
	>= 200	703/753 (93.4%)	680/750 (90.7%)		1.46 (1.00 to 2.14)
Region[c]					
292-0104	US	231/252 (91.7%)	225/250 (90.0%)	0.53	1.26 (0.69 to 2.33)
	ex-US	174/183 (95.1%)	174/182 (95.6%)		0.88 (0.33 to 2.33)
292-0111	US	253/280 (90.4%)	249/282 (88.3%)	0.36	1.23 (0.72 to 2.11)
	ex-US	142/151 (94.0%)	136/153 (88.9%)		1.97 (0.85 to 4.58)
Pooled	US	484/532 (91.0%)	474/532 (89.1%)	0.74	1.24 (0.83 to 1.85)
	ex-US	316/334 (94.6%)	310/335 (92.5%)		1.41 (0.75 to 2.64)
Study Drug Adherence (%)[d]					
292-0104	< 95	58/67 (86.6%)	70/82 (85.4%)	0.66	1.23 (0.48 to 3.17)
	>= 95	347/367 (94.6%)	329/347 (94.8%)		0.95 (0.49 to 1.83)
292-0111	< 95	78/92 (84.8%)	73/83 (88.0%)	0.087	0.78 (0.33 to 1.88)
	>= 95	317/336 (94.3%)	312/349 (89.4%)		1.95 (1.10 to 3.47)
Pooled	< 95	136/159 (85.5%)	143/165 (86.7%)	0.33	0.98 (0.52 to 1.85)
	>= 95	664/703 (94.5%)	641/696 (92.1%)		1.44 (0.94 to 2.20)

Note: Week 48 window is between Day 294 and 377 (inclusive).
a P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup.
b Odds ratio and its 95% CI for each subgroup were estimated from the logistic regression model including the following: baseline HIV-1 RNA and region stratum (if not the subgroup factor), study (for pooled analysis), subgroup, treatment, and the interaction between treatment and subgroup.
c Baseline HIV-1 RNA stratum: <= 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.
d Study drug adherence subgroups are based on the adherence up to Week 48 visit for active study drug.
Programming Details: .../version1/prog/t-snapshot-homog.sas v9.2 [redacted]20[redacted]:15:51
Source: E/C/F/TAF ISE, Table 4

Study GS-US-292-0102

In Study GS-US-292-0102, the rate of virologic success rate at Week 24 was similar between the 2 treatment groups when assessed using the FDA snapshot algorithm (HIV-1 RNA

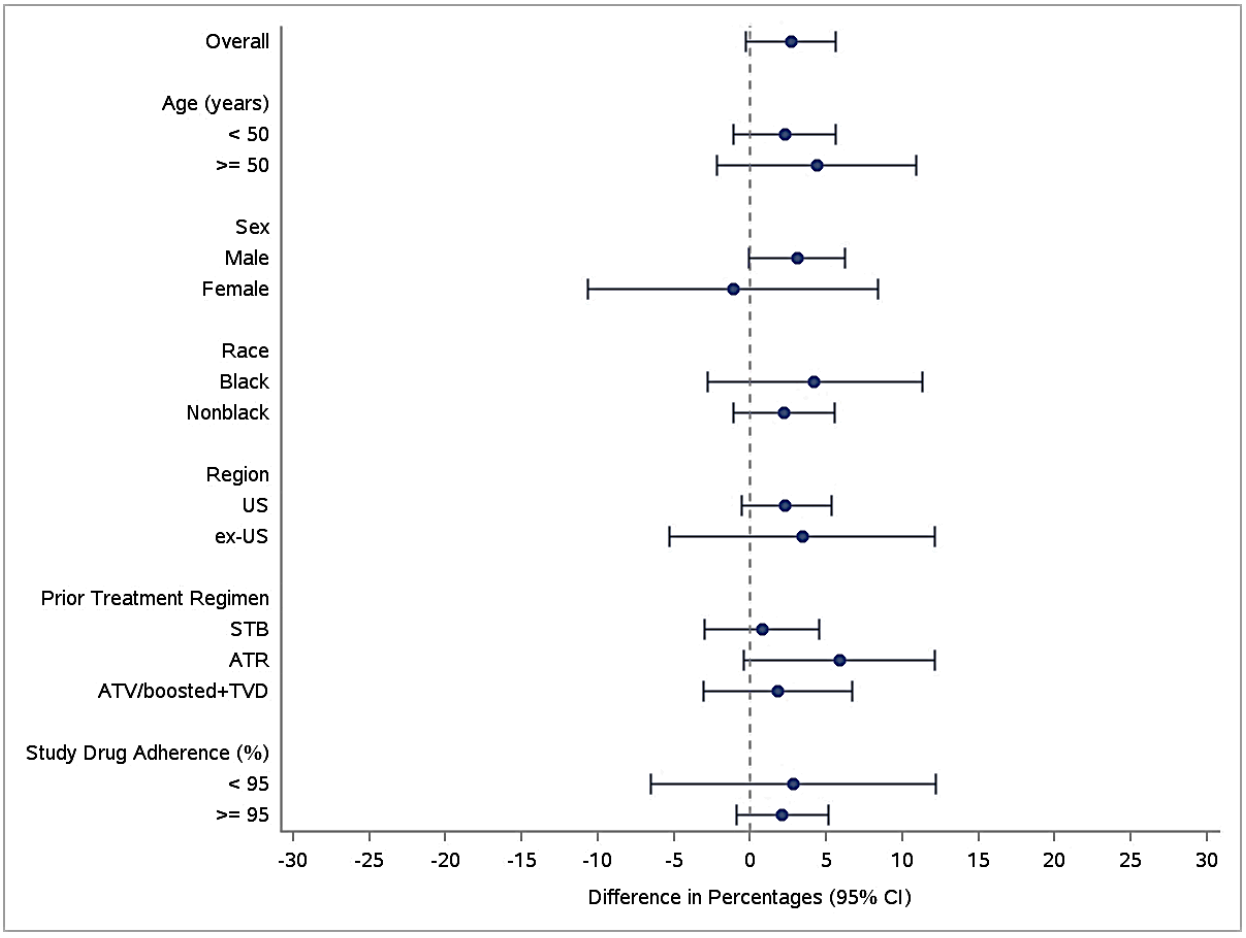
< 50 copies/mL) for all prespecified subgroups. The 95% CIs for differences in virologic success between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments. Data for Week 48 were consistent with results for Week 24 (GS-US-292-0102, Section 9.3).

3.3.1.2. Virologically Suppressed Subjects in Study GS-US-292-0109

The primary efficacy endpoint (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) was evaluated by several predefined subgroups in Study GS-US-292-0109. Virologic success rates at Week 48 were generally higher for the E/C/F/TAF-treated subgroups compared with the FTC/TDF+3rd Agent-treated subgroups using the Week 48 FAS; however, the 95% CIs for the differences in response rates included zero for all subgroups (Figure 9 and Table 33) (GS-US-292-0109, Section 9.3).

The change from baseline in CD4 counts at Week 48 were consistent when analyzed by prior treatment regimen (STB, ATR, or ATV/boosted+TVD [Week 48 FAS, observed data]; GS-US-292-0109, Section 15.1, Tables 19.2.1, 19.2.2, and 19.2.3, respectively). Further, overall results for the Week 48 PP (observed data) were consistent with those for the Week 48 FAS (GS-US-292-0109, Section 15.1, Table 19.3).

Figure 9. **E/C/F/TAF Study GS-US-292-0109: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)**



Difference in response rate and its 95% CI were calculated based on the MH proportion and normal approximation adjusted by the prior treatment regimen (except for prior treatment regimen subgroup).
For prior treatment regimen subgroup, difference in response rate and its 95% CIs were from normal approximation.
Relative to the vertical line at 0, differences on the right favor the E/C/F/TAF group and differences on the left favor the FTC/TDF+3rd Agent group.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Figure 3

Table 33. E/C/F/TAF Study GS-US-292-0109: Treatment Difference in Virologic Success by Subgroup at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

			E/C/F/TAF vs. FTC/TDF+3rd Agent
	E/C/F/TAF (N=799)	FTC/TDF+3rd Agent (N=397)	Difference in Percentages (95% CI)[a]
Overall	764 (95.6%)	369 (92.9%)	2.7% (−0.3% to 5.6%)
Age (Years)			
< 50	605/636 (95.1%)	288/310 (92.9%)	2.3% (−1.1% to 5.6%)
>= 50	159/163 (97.5%)	81/87 (93.1%)	4.4% (−2.2% to 10.9%)
Sex			
Male	689/721 (95.6%)	333/360 (92.5%)	3.1% (−0.1% to 6.2%)
Female	75/78 (96.2%)	36/37 (97.3%)	−1.1% (−10.7% to 8.4%)
Race			
Black	151/158 (95.6%)	86/94 (91.5%)	4.2% (−2.8% to 11.3%)
Nonblack	613/641 (95.6%)	283/303 (93.4%)	2.2% (−1.1% to 5.5%)
Region			
US	615/635 (96.9%)	294/311 (94.5%)	2.3% (−0.6% to 5.3%)
ex-US	149/164 (90.9%)	75/86 (87.2%)	3.4% (−5.3% to 12.1%)
Prior Treatment Regimen[b]			
STB	264/272 (97.1%)	130/135 (96.3%)	0.8% (−3.0% to 4.5%)
ATR	226/238 (95.0%)	106/119 (89.1%)	5.9% (−0.4% to 12.1%)
ATV/boosted+TVD	274/289 (94.8%)	133/143 (93.0%)	1.8% (−3.1% to 6.7%)
Study Drug Adherence (%)[c]			
< 95	118/126 (93.7%)	55/61 (90.2%)	2.8% (−6.5% to 12.2%)
>= 95	646/672 (96.1%)	313/333 (94.0%)	2.1% (−0.9% to 5.1%)

Note: Week 48 window is between Day 294 and 377 (inclusive).
a Difference in response rates and its 95% CI were calculated based on the MH proportion and normal approximation adjusted by the prior treatment regimen (except for prior treatment regimen subgroup).
b For prior treatment regimen subgroup, difference in response rate and its 95% CI were from normal approximation.
c Study drug adherence subgroup analysis is based on the adherence up to the Week 48 Visit.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 12.1

3.3.1.3. Subjects with Mild to Moderate Renal Impairment in Study GS-US-292-0112

Among virologically suppressed subjects with mild to moderate renal impairment who switched treatment to E/C/F/TAF in Study GS-US-292-0112, there were no clinically significant differences in virologic success at Week 24 (FDA snapshot algorithm, HIV-1 RNA

< 50 copies/mL) between subgroups (age, sex, race, region, or study drug adherence rate) (GS-US-292-0112, Section 9.3).

3.3.1.4. Results of Ad Hoc Analyses in Subjects of Age ≥ 65 years who Received E/C/F/TAF

In addition to the discussed prespecified analyses in Section 3.2.2, ad hoc analysis of the primary analysis of virologic success (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm) was performed in subjects ≥ 65 years of age using the FAS. Overall, among subjects ≥ 65 years of age who received E/C/F/TAF (n = 78), the virologic success rates were similar to those for the FAS in the respective studies.

In the pooled data from ART-naive subjects from Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102, the virologic success rate at Week 48 using the FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) based on the ≥ 65 years age group of the FAS was 100% (4 of 4 subjects) in the E/C/F/TAF group (Ad Hoc Table Req6744.1).

Among virologically suppressed subjects in Study GS-US-292-0109, the virologic success rate at Week 48 using the FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) based on the ≥ 65 years age group of the FAS was 100% (10 of 10 subjects) in the E/C/F/TAF group (Ad Hoc Table 6758.2.1).

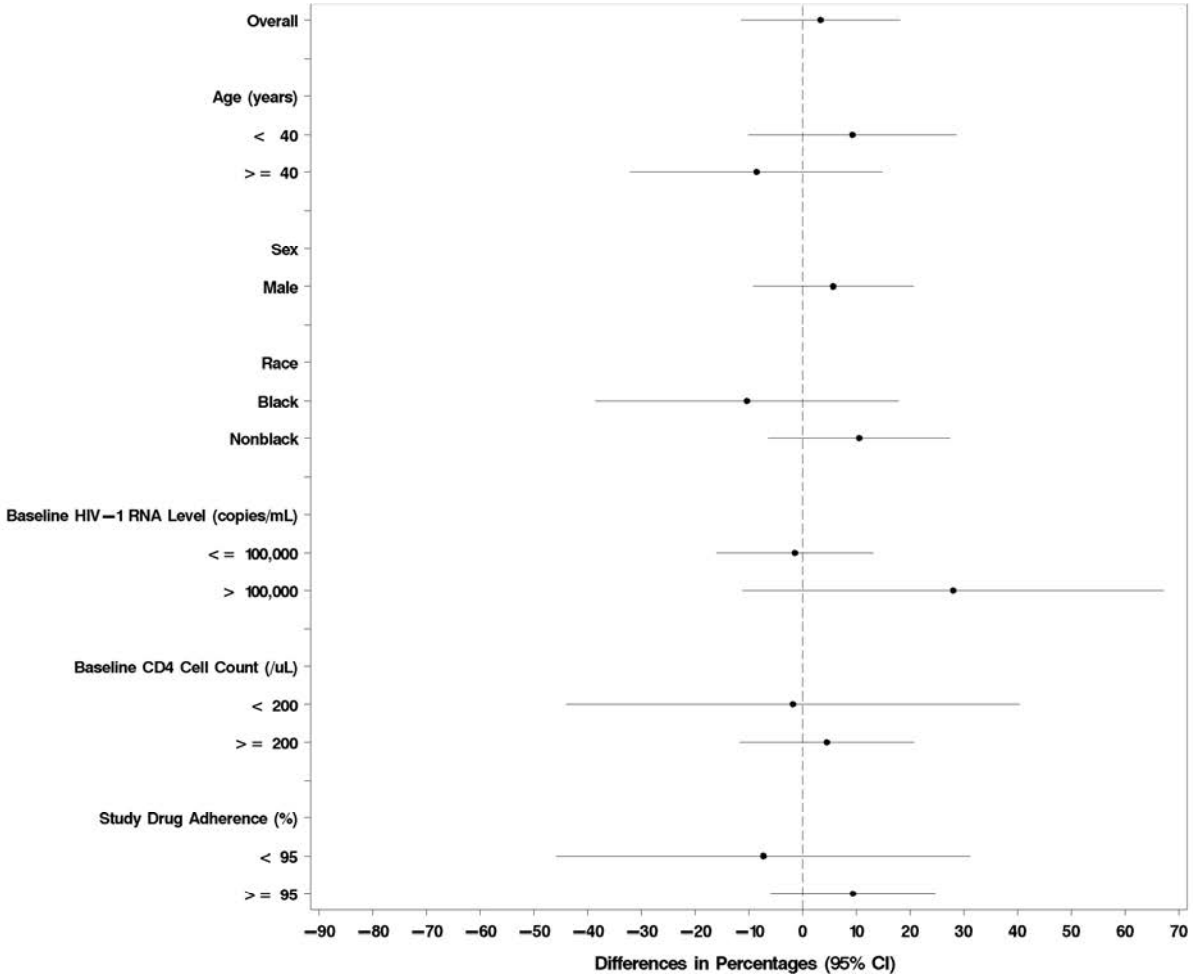
Among subjects with mild to moderate renal impairment in Study GS-US-292-0112, the virologic success rate at Week 24 using the FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) based on the ≥ 65 years age group of the FAS was 92.1% for virologically suppressed subjects (58 of 63 subjects), and the only ART-naive subject ≥ 65 years of age also achieved virologic success (Ad Hoc Table Req6756.9).

3.3.2. D/C/F/TAF Study

3.3.2.1. ART-Naive Subjects in Study GS-US-299-0102

At Week 24, the rate of virologic success by FDA snapshot algorithm (HIV-1 RNA < 50 copies/mL) for subgroups according to age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, or study drug adherence rate was similar for the D/C/F/TAF and DRV+COBI+TVD groups. The 95% CIs for differences in virologic success between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments (Figure 10). Data for Week 48 were consistent with results for Week 24 (m5.3.5.1, GS-US-299-0102, Section 9.3).

Figure 10. D/C/F/TAF Study GS-US-299-0102: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 24 using Snapshot Analysis Algorithm and HIV-1 RNA < 50 copies/mL (FAS)



Difference in response rate and its 95% CI were from baseline HIV-1 RNA stratum-adjusted MH proportion and normal approximation (except for baseline HIV-1 RNA subgroup).
For baseline HIV-1 RNA subgroup, difference in response rate and its 95% CI were from normal approximation.
Relative to the vertical line at 0, differences on the right favor the D/C/F/TAF group and differences on the left favor the DRV+COBI+TVD group.
Point estimate of the treatment difference and 95% CI were not calculable for female subgroup.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Figure 3

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

4.1. Choice of Dose

The recommended dose of F/TAF per the third ARV agent is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered as E/C/F/TAF, for which an extensive safety and efficacy database exists. The different TAF dose (25 or 10 mg) is generally based on whether or not the coadministered third agent has any clinically relevant effect on TAF exposure (eg, via inhibition of intestinal P-gp; m2.7.2, Section 3.2.3.2.3). Given the wide range of safe and efficacious TAF exposure established in the single-agent, proof-of-concept study (GS-US-120-0104), in Phase 2 and Phase 3 studies of E/C/F/TAF (m2.7.2, Sections 3.2.1.2.1, 3.3.1.1, and 3.3.2.1), and the Phase 2 study of D/C/F/TAF (Study GS-US-299-0102), the variability in TAF-equivalent dose by third agent is considered acceptable.

Specifically, F/TAF 200/25 mg is recommended with third agents that do not have a clinically relevant effect on TAF exposure (eg, EFV, rilpivirine, dolutegravir), and F/TAF 200/10 mg is recommended with third agents that substantially increase TAF exposure (eg, ATV+RTV, RTV-boosted lopinavir, EVG+COBI). Although coadministration with boosted DRV (DRV+RTV or DRV+COBI) did not result in increased TAF absorption, clinical data from Study GS-US-299-0102 demonstrated that D/C/F/TAF was noninferior to DRV+COBI+TVD when administered for 24 weeks using the USA FDA snapshot algorithm with HIV-1 RNA cutoff at 50 copies/mL, the primary endpoint of this study. These data support the use of F/TAF 200/10 mg with boosted DRV (either DRV+RTV or DRV+COBI). Although clinical studies were not conducted to evaluate the drug interaction potentials between TAF and raltegravir, maraviroc, nevirapine, buprenorphine, methadone, naloxone, norbuprenorphine, or norgestimate/ethinyl estradiol, none is expected based on nonclinical information (m2.7.2, Sections 3.1.3 and 3.2.3.2.1).

The dosing recommendations for F/TAF, outlined in Table 34, were developed based on the totality of TAF plasma PK data from drug-drug interaction studies, the wide range of safe and efficacious TAF exposure established in the single-agent, proof-of-concept study (GS-US-120-0104), a number of Phase 2 and 3 studies of E/C/F/TAF, and a Phase 2 study of D/C/F/TAF (Study GS-US-299-0102), and intracellular TFV-DP levels observed in combination with various third agents.

Table 34. Dose Recommendations for F/TAF with Potential Concomitant Antiretroviral Drugs

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

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

4.2. Food Effect on Dose of F/TAF FDC

TAF

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

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

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

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

FTC

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

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

In Phase 2 E/C/F/TAF Study GS-US-292-0102, subjects had the option to continue E/C/F/TAF in an open-label extension phase after unblinding at the end of randomized phase. Subjects from the D/C/F/TAF Phase 2 Study GS-US-299-0102 also had the opportunity to rollover to Study GS-US-292-0102 and switch to E/C/F/TAF.

Of a total of 112 subjects treated with E/C/F/TAF during the randomized phase of Study GS-US-292-0102, 105 subjects entered the extension phase and received E/C/F/TAF. Of the subjects who entered the extension phase, 104 are currently continuing treatment; 1 subject (E/C/F/TAF group) discontinued treatment with study drug and discontinued from the study (lost to follow-up) during the extension phase (GS-US-292-0102, Section 8.1).

High rates of virologic suppression were maintained through Week 96 for the E/C/F/TAF group in the extension phase (M = F at Week 96: 87.5%, 98 of 112 subjects; M = E at Week 96: 96.1%, 98 of 102 subjects). The CD4 cell counts continued to increase for the E/C/F/TAF group through the extension phase. The mean (SD) change from double-blind baseline at Week 96 was 284 (191.5) cells/μL. No subjects had virologic rebound from Weeks 48 to 96 (GS-US-292-0102, Section 9).

Of a total of 70 subjects treated with D/C/F/TAF that rolled over from Study GS-US-299-0102 to the extension phase of Study GS-US-292-0102, 69 are currently continuing E/C/F/TAF treatment; 1 subject (D/C/F/TAF to E/C/F/TAF group) was lost to follow-up.

All Phase 3 E/C/F/TAF studies are ongoing and longer-term data will be presented in future CSRs.

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7. APPENDIX

Appendix Number	Appendix Title
7.1	Tabular Summary of Studies Relevant to Efficacy
7.2	Additional Efficacy Analysis

7.1. Tabular Summary of Studies Relevant for Efficacy

7.1.1. E/C/F/TAF Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0102 (synopsis)	Evaluate the efficacy of a regimen containing E/C/F/TAF FDC versus STB STR	Phase 2, randomized, double-blind and open-label, multicenter, active-controlled study	Randomized Phase: E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) STB STR (150/150/200/300 mg) + placebo-to-match E/C/F/TAF QD PO (B) Open-Label Extension Phase: E/C/F/TAF (150/150/200/10 mg) QD PO (C)	Randomized Phase: 48 weeks until unblinding Open-Label Extension Phase: Until E/C/F/TAF is commercially available or development is terminated	Randomized: 171 Completed: 158 Safety Analysis Set: A: 112 B: 58 Entered Open-Label Extension: A: 105 B: 53 299-0102: 108 Continuing study drug at Week 96: A: 104 B: 53 299-0102: 107	Randomized Phase: HIV-infected, ART-naive adult subjects Open-Label Extension Phase: Additional HIV-infected adult subjects had received a DRV+COBI containing regimen in Study GS-US-299-0102 and were ART-naive at the time of entry into that study.	Study ongoing; Week 96 Interim CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0104 (synopsis)	Evaluate the efficacy of E/C/F/TAF FDC versus STB STR	Phase 3, randomized, double-blind, multicenter, active-controlled study	• E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/300 mg) + placebo-to-match E/C/F/TAF QD PO (B)	96 weeks Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 872 Safety Analysis Set: A: 435 B: 432 Continuing study drug at Week 48: A: 413 B: 400	HIV-infected, ART-naive adult subjects	Study ongoing; Week 48 Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0109 (synopsis)	Evaluate the noninferiority of switching to a TAF-containing FDC relative to maintaining TDF-containing regimens in virologically suppressed, HIV-infected subjects	Phase 3, randomized, open-label, multicenter, active-controlled, multicenter study	• Switch to E/C/F/TAF (150/150/200/10 mg) QD PO from a predefined FTC/TDF regimen (A) • Stay on pre-existing FTC/TDF+3rd Agent regimen (B): STB STR (150/150/200/300 mg) QD PO; ATR STR (600/200/300 mg) QD PO; ATV 300 mg + COBI 150 mg + FTC/TDF (200/300 mg) QD PO; or ATV 300 mg + RTV 100 mg + FTC/TDF (200/300 mg) QD PO	96 weeks Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 1443 Safety Analysis Set: A: 959 B: 477 Continuing study drug at Week 48: A: 939 B: 447	HIV-infected adult subjects from a predefined set of Gilead clinical studies receiving ARV regimens for at least 6 consecutive months, and who had maintained plasma HIV-1 RNA levels at undetectable levels for ≥ 6 consecutive months prior to screening	Study ongoing; Week 48 Interim CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0111 (synopsis)	Evaluate the efficacy of E/C/F/TAF FDC versus STB STR	Phase 3, randomized, double-blind, active-controlled, multicenter study	• E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/300 mg) + placebo-to-match E/C/F/TAF QD PO (B)	96 weeks Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 872 Safety Analysis Set: A: 431 B: 435 Continuing study drug at Week 48: A: 408 B: 396	HIV-infected, ART-naive adult subjects	Study ongoing; Week 48 Interim CSR

PO = orally; QD = once daily

7.1.2. D/C/F/TAF Study

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-299-0102 (synopsis)	Evaluate the efficacy of D/C/F/TAF FDC versus DRV+COBI+ TVD	Phase 2, randomized, double-blind, active controlled, multicenter study	Subjects were randomized in a 2:1 ratio to 1 of 2 treatment groups as follows: • D/C/F/TAF (800/150/200/10 mg) + placebo-to-match DRV+COBI+FTC/TDF QD PO (A) • DRV (800 mg) + COBI (150 mg) + FTC/TDF (200/300 mg) + placebo-to-match D/C/F/TAF QD PO (B)	48 weeks Extension Phase: Subjects continued to receive blinded drug until unblinding and then were given option to participate in Study GS-US-292-0102 and receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 153 Safety Analysis Set: A: 103 B: 50	HIV-infected, ART-naive adult subjects	Complete, m5.3.5.1, Final CSR

PO = orally; QD = once daily

7.2. Additional Efficacy Analysis

The following outputs for Studies GS-US-292-0104 and GS-US-292-0111 are described in the ISE SAP:

Table 1	Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm) - Individual Studies, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Table 2	Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm) - Pooled Data, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Table 3	Treatment Difference in Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Algorithm) by Subgroup, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Table 4	Homogeneity Test of Treatment Effect Between Subgroups in Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Algorithm) Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Figure 1	Forest Plot of Treatment Difference in Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Algorithm) by Subgroup, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set

The following tables were not prespecified in the ISE SAP:

Ad Hoc Table Req6744.1	Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm) (Age >= 65 Years) Studies GS-US-292-0102, GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Ad Hoc Table Req6756.9	Virologic Outcome at Week 24 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis), Full Analysis Set Subjects with Age >= 65 Years Only
Ad Hoc Table 6758.2.1	Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis) Subjects with Age >= 65 Years Only, Week 48 Full Analysis Set
Ad Hoc Table Req6769.1	Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 20 copies/mL, Snapshot Algorithm) Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Ad Hoc Table Req6769.2	Change from Baseline in HIV-1 RNA (Log10 copies/mL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set

Ad Hoc Table Req6769.3	Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Visit: Missing = Failure, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Ad Hoc Table Req6769.4	Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Visit: Missing = Excluded, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Ad Hoc Table Req6854.1	Change from Baseline in CD4 Cell Count (/µL, LOCF Imputation) by Visit While On Treatment, Full Analysis Set, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set
Ad Hoc Table Req6854.2	Change from Baseline in CD4 Cell Count (/µL) by Visit While On Treatment, Full Analysis Set, Studies GS-US-292-0104 and GS-US-292-0111, Full Analysis Set

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

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

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
aGFR	actual glomerular filtration rate
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
AST	aspartate aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV	atazanavir
BCRP	breast cancer resistance protein
BE	bioequivalence
BID	twice daily
BL	baseline
BMD	bone mineral density
BMI	body mass index
CD4	cluster determinant 4
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula for calculating glomerular filtration rate
$CL_{iohexol}$	iohexol clearance
CMH	Cochran-Mantel-Haenszel
COBI, C	cobicistat (Tybost®)
CPT	Child-Pugh-Turcotte
CSR	clinical study report
C-telopeptide, CTx	type I collagen C-telopeptide
CV	coefficient of variation
CYP	cytochrome P450 enzyme
d4T	stavudine
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
ddI	didanosine
DDI	drug-drug interaction
DRV, D	darunavir
DTG	dolutegravir
DXA	dual-energy x-ray absorptiometry

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
ECG	electrocardiogram
eCRF	electronic case report form
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
$eGFR_{CKD\text{-}EPI,creatinine}$	estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation
$eGFR_{CKD\text{-}EPI,\ cysC}$	estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation
EVG, E	elvitegravir (Vitekta®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEPO4	fractional excretion of phosphate
FEUA	fractional excretion of uric acid
FTC, F	emtricitabine (Emtriva®)
GGT	gamma-glutamyltransferase
GI	gastrointestinal
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV, HIV-1	human immunodeficiency virus, type 1
HLGT	high-level group term
HLT	high-level term
IC_{xx}	concentration that results in xx% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INSTI	integrase strand-transfer inhibitor
ISS	Integrated Summary of Safety
ITT	intent-to-treat
IV	intravenous
LDL	low-density lipoprotein
LLT	lower-level term
LOCF	last observation carried forward
LPV	lopinavir
LPV/r	ritonavir boosted lopinavir
LSM	least-squares mean

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

m	Module
MACDP	Metropolitan Atlanta Congenital Defects Program
M = E	missing = excluded
M = F	missing = failure
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
NCEP	National Cholesterol Education Program
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OATP	organic anion transporting polypeptide
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PO	orally
PRT	proximal renal tubulopathy
PT	preferred term
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QD	once daily
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
ΔQTcF	time-matched, baseline-adjusted QTcF.
ΔΔQTcF	time-matched, baseline-adjusted, placebo-corrected QTcF
QTcF	QT interval corrected for heart rate using the Fridericia formula
RBC	red blood cell
RBP	retinol binding protein
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
SAE	serious adverse event

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOF	sofosbuvir (Solvaldi®)
ST segment	period when the ventricles are depolarized
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
tQT	thorough QT
TAF	tenofovir alafenamide
TBDR	Texas Birth Defects Registry
TBLH	total body less head
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TmP/GFR	renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
TVD	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
vs	versus
ZDV	zidovudine

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

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

INTRODUCTION

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 (ARV) therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression.

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

For ART-naive HIV-infected patients, treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI). Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {27621}, {32519}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an oral prodrug of TFV. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs {26885}, {34210}.

TDF in combination with emtricitabine (FTC; F) forms a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients that can be combined with different third agents. The combination of FTC and TDF is used within several once-daily fixed-dose combinations (FDCs) (Truvada® [TVD; FTC/TDF], Atripla® [ATR; efavirenz (EFV)/FTC/TDF], Complera/Eviplera® [FTC/rilpivirine (RPV)/TDF], and Stribild® [elvitegravir (EVG; E)/cobicistat (COBI; C)/FTC/TDF]). Availability of a stand-alone NRTI backbone is important when there is a medical need to use a third agent that is not part of an FDC (eg, ritonavir [RTV]-boosted PIs), and particularly to provide a range of treatment options in patients with virologic resistance to their third agent but not to the backbone.

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

Gilead Sciences (Gilead) has coformulated TAF (as TAF fumarate) with FTC into an FDC tablet available in 2 doses, F/TAF 200/25 mg and F/TAF 200/10 mg. Because TAF is a substrate of intestinal efflux transporters (eg, P-glycoprotein [P-gp]) and hepatic transporters (ie, organic anion transporting polypeptide [OATP]1B1 and OATP1B3), TAF exposure may be increased

upon coadministration with inhibitors of these transporters with the effect apparently driven predominantly by P-gp inhibition (m2.7.2, Sections 3.2.3.2.2). Therefore, the recommended F/TAF dose (200/25 mg or 200/10 mg based on third agent) is generally based on whether or not the coadministered agent has any clinically relevant effect on TAF exposure (eg, via inhibition of intestinal P-gp). Accordingly, F/TAF 200/25 mg is recommended to be used with unboosted third agents, and F/TAF 200/10 mg with boosted third agents.

This submission for the N(t)RTI backbone F/TAF is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1472 and GS-US-311-1473) that pharmacokinetically bridge each F/TAF FDC tablet strength (200/25 mg or 200/10 mg) to Gilead's FDC tablet containing the HIV-1 INSTI EVG, the pharmacoenhancer COBI, FTC, and TAF (E/C/F/TAF 150/150/200/10 mg), for which clinical safety and efficacy have been established in a broad range of patient populations.

To support a direct comparison of TAF versus TDF, 2 identical Phase 3 E/C/F/TAF studies differing only in geographic regions were conducted with STB as the comparator. Accordingly, the safety of E/C/F/TAF has been established by these 2 pivotal studies in ART-naive subjects. In addition, 1 Phase 3 study in virologically suppressed subjects, 1 Phase 3 study in subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min), and 1 Phase 3 study in ART-naive adolescent subjects assessed the safety profile of E/C/F/TAF in these populations. Additional safety information is provided by 1 E/C/F/TAF Phase 2 study that enrolled ART-naive subjects who received E/C/F/TAF for more than 96 weeks; this study also provides data for subjects who switched to E/C/F/TAF from STB or darunavir (DRV; D)/C/F/TAF during the open-label extension phase. Lastly, safety information is provided by 1 D/C/F/TAF (800/150/200/10 mg) Phase 2 study that enrolled ART-naive subjects. Supportive safety data are also provided by Phase 1 studies of TAF (E/C/F/TAF, D/C/F/TAF, F/TAF, and TAF) as well as Phase 2 and Phase 3 studies of FTC.

EXECUTIVE SUMMARY

Exposure to Drug

Across the E/C/F/TAF Phase 2 and Phase 3 studies, a total of 2394 subjects have received E/C/F/TAF with a median (first quartile [Q1], third quartile [Q3]) exposure of 48.1 weeks (42.3, 60.0). In the D/C/F/TAF Phase 2 study, a total of 103 subjects received D/C/F/TAF, with a median (first quartile [Q1], third quartile [Q3]) exposure of 68.0 weeks (65.4, 72.7). In the Phase 1 TAF Safety Population, a total of 911 subjects received at least 1 dose of TAF as single agent or part of an FDC (F/TAF, E/C/F/TAF, or D/C/F/TAF).

Demographic and Other Characteristics of the Study Population

Demographic and general baseline characteristics were generally similar between treatment groups within each E/C/F/TAF Phase 2 and 3 study. The median ages of adult subjects with normal renal function who were ART-naive or virologically suppressed were generally similar, ranging from 33 to 41 years. Subjects with mild to moderate renal impairment were older, with a median age of 58 years in Cohort 1 (ART-experienced subjects who switched to E/C/F/TAF; range: 24 to 82). Across studies, a total of 97 subjects were ≥ 65 years of age. The median age of adolescent subjects in Study GS-US-292-0106 was 15 years (range: 12 to 17). In the D/C/F/TAF Phase 2 study, the median age was 33 years (range: 18 to 68).

Approximately 15% of subjects in the E/C/F/TAF pivotal ART-naive studies were women. With the exception of Study GS-US-292-0106, most subjects across studies were white or black. Subjects in Study GS-US-292-0106 were black (87.5%) or Asian (12.5%). The median body mass index (BMI) was generally similar across all studies (approximately 25 kg/m^2), except for adolescent subjects in Study GS-US-292-0106 (median [Q1, Q3] BMI 20.0 [18.1, 23.2] kg/m^2).

Baseline disease characteristics were generally similar between treatment groups within each E/C/F/TAF study. The median baseline estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) value was generally similar across ART-naive and virologically suppressed adult subjects, ranging from 105.7 to 117.0 mL/min. In subjects with mild to moderate renal impairment, the median (Q1, Q3) $eGFR_{CG}$ value was 55.6 (45.7, 62.4) mL/min among subjects who were virologically suppressed at baseline. In ART-naive adolescent subjects, the median (Q1, Q3) eGFR calculated using the modified Schwartz formula was 110.9 (95.8, 118.8) mL/min/1.73 m^2. The demographics and baseline characteristics of the subjects in the D/C/F/TAF Phase 2 study were consistent with those from the E/C/F/TAF studies in ART-naive subjects.

Across the Phase 3 E/C/F/TAF studies in adults with normal renal function, most subjects (>89%) had no graded proteinuria at baseline. In subjects with mild to moderate renal impairment, 9.5% of virologically suppressed subjects had Grade 2 proteinuria at baseline, and 23.1% of subjects had Grade 1 proteinuria at baseline. Among adolescent subjects, < 5% had proteinuria at baseline. Results from the D/C/F/TAF Phase 2 study in adults with normal renal function were consistent with those from the E/C/F/TAF studies in ART-naive subjects.

Adverse Events

The frequency and type of reported adverse events (AEs) were generally similar in ART-naive adults, virologically suppressed adults, adults with mild to moderate renal impairment, and ART-naive adolescents across all studies. The percentage of subjects reporting any AE was generally similar across studies, with somewhat lower percentages among virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109 and ART-naive adolescent subjects in E/C/F/TAF Study GS-US-292-0106. The overall incidence of AEs was similar between treatment groups within each randomized study.

Serious AEs (SAEs) were reported for a similar percentage of subjects in both treatment groups in the comparative E/C/F/TAF studies (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109) and were < 10% in the E/C/F/TAF group in each study. Results from the D/C/F/TAF Phase 2 study were consistent with those from the E/C/F/TAF studies in ART-naive subjects. Across all studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study.

Analysis of AEs by Organ System or Syndrome

Because TAF is associated with >90% lower systemic TFV exposure relative to that associated with TDF, less off-target TFV-associated toxicity was anticipated in subjects receiving E/C/F/TAF in the Phase 2 and Phase 3 randomized studies, including less impact on the nephrotoxicity and reduced BMD. Results from the Phase 2 Studies GS-US-292-0102 (E/C/F/TAF) and GS-US-299-0102 (D/C/F/TAF) supported this, demonstrating that subjects receiving E/C/F/TAF relative to STB or D/C/F/TAF relative to DRV+COBI+TVD had less impact on BMD, bone turnover markers, serum creatinine, and tubular proteins (urine retinol binding protein [RBP] to creatinine ratio and beta-2-microglobulin to creatinine ratio). After the primary hypothesis of noninferior efficacy of E/C/F/TAF relative to STB was achieved in the E/C/F/TAF Phase 3 comparative studies, multiplicity adjustments were made for 4 safety endpoints with a fallback procedure in sequential order with prespecified 2-sided alpha levels: hip BMD, spine BMD, serum creatinine, and treatment-emergent proteinuria. Statistically significant differences favoring E/C/F/TAF over STB at Week 48 for all key secondary safety endpoints in ART-naive adults and virologically suppressed subjects were observed: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), 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; $p < 0.001$).

Bone Safety

Fractures

Across all studies, fractures were uncommon, balanced between treatment groups, the result of trauma, and considered by the investigator as unrelated to the study drugs; none resulted in permanent discontinuation of study drugs.

Bone Mineral Density

Across all E/C/F/TAF studies in ART-naive subjects, subjects receiving E/C/F/TAF experienced significantly less BMD reduction than those receiving STB. Results in the Phase 2 D/C/F/TAF study were consistent with those from the E/C/F/TAF studies in ART-naive subjects.

In the Phase 3 E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, statistical analysis using the fallback procedure confirmed significance using adjusted alphas. At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a clinically significant (> 3%) decrease from baseline in hip BMD (E/C/F/TAF 16.8%, STB 50.1%) and in spine BMD (E/C/F/TAF 26.5%, STB 45.8%).

Across studies in virologically suppressed subjects, improvements in BMD were observed in subjects who switched from a TDF-based regimen. In subjects with renal impairment (Study GS-US-292-0112), hip and spine BMD increased for Cohort 1 subjects after switching to E/C/F/TAF. In ART-naive adolescent subjects (Study GS-US-292-0106), mean changes from baseline of approximately 1.7% and 0.8% in spine and total body less head (TBLH) BMD, respectively, were observed at Week 24. Both spine and TBLH median (Q1, Q3) height-age adjusted BMD Z-scores were within the expected range for age.

Fracture Probability

For ART-naive subjects aged ≥ 40 years in Studies GS-US-292-0104 and GS-US-292-0111, baseline fracture risk was low, but subjects experienced less increase in fracture risk in the E/C/F/TAF group by FRAX analysis than subjects in the STB group.

For virologically suppressed subjects aged ≥ 40 years in Study GS-US-292-0109, baseline fracture risk was low, but subjects experienced less increase in fracture risk by FRAX analysis after switching to E/C/F/TAF than subjects who retained their TDF-based regimen. For subjects with renal impairment aged ≥ 40 years in Study GS-US-292-0112, fracture risk was higher, but subjects experienced less increase in fracture risk by FRAX analysis after switching to E/C/F/TAF.

Bone Laboratory Parameters

Across ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111, increases from baseline in the bone turnover biomarkers type I collagen C-telopeptide (C-telopeptide; bone resorption biomarker) and procollagen type 1 N-terminal propeptide (P1NP; bone formation biomarker), as well as parathyroid hormone (PTH; a hormone involved in bone metabolism) were smaller in the E/C/F/TAF group compared with the STB group at both Weeks 24 and 48 ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows: C-telopeptide: E/C/F/TAF 9.1% (−9.4%, 32.7%), STB 21.1% (0.0%, 44.6%); P1NP: E/C/F/TAF 26.86% (3.42%, 60.18%), STB 72.85% (41.28%, 120.58%); PTH: E/C/F/TAF 23.0% (−4.5%, 58.7%), STB 41.9% (8.9%, 88.0%). Results from virologically suppressed subjects in Studies GS-US-292-0109, GS-US-292-0112, and GS-US-292-0102 (open-label extension phase) supported the results in E/C/F/TAF studies of ART-naive subjects. Subjects who switched to

E/C/F/TAF experienced a decrease from baseline in serum levels of the P1NP and PTH. Results from the D/C/F/TAF Phase 2 Study GS-US-299-0102 were also consistent with the results in E/C/F/TAF studies of ART-naive subjects.

Renal Safety

Renal Events

There were no cases of proximal renal tubulopathy (PRT) reported (including Fanconi syndrome) in HIV-infected subjects receiving E/C/F/TAF or D/C/F/TAF. In Study GS-US-292-0109 in virologically suppressed subjects, 1 subject in the FTC/TDF+3rd Agent group (taking COBI-boosted atazanavir [ATV+COBI]+TVD) had a renal AE of Fanconi syndrome which resulted in discontinuation of study drug. In the D/C/F/TAF Phase 2 study, 1 subject receiving DRV+COBI+TVD had an SAE of renal tubular disorder (reported as PRT), which also resulted in discontinuation of study drug.

Renal Laboratory Parameters

Across all E/C/F/TAF ART-naive studies, increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. A consistent effect on serum creatinine was observed in ART-naive adults and adolescents receiving E/C/F/TAF (mean SD increase from baseline: ART-naive adults 0.08 [0.124] mg/dL at Week 48; ART-naive adolescents 0.10 [0.083] mg/dL at Week 24). Increases were observed by Week 2 and remained stable. Across all studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, minimal changes in serum creatinine were observed in subjects receiving E/C/F/TAF. At Week 48 in Study GS-US-292-0109, the mean (SD) changes from baseline in serum creatinine were as follows: E/C/F/TAF −0.01 (0.117) mg/dL; FTC/TDF+3rd Agent 0.04 (0.123) mg/dL ($p < 0.001$ for the difference between groups). In subjects with mild to moderate renal impairment (GS-US-292-0112) who switched from a non-TDF containing regimen, the mean (SD) increase in serum creatinine was 0.05 (0.28) mg/dL. Results from the D/C/F/TAF Phase 2 study were consistent with those of the E/C/F/TAF studies in ART-naive subjects.

Across all E/C/F/TAF ART-naive studies, fewer subjects receiving E/C/F/TAF developed treatment-emergent proteinuria than subjects receiving STB. Across all studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, statistically significant decreases in proteinuria were observed. In the ART-naive Phase 3 studies, significantly less proteinuria, quantified by urine protein to creatinine ratio (UPCR), and a decrease from baseline in albuminuria, quantified by urine albumin to creatinine ratio (UACR), in the E/C/F/TAF group were observed at Week 2 and persisted through Week 48. In contrast, there was an increase from baseline in UPCR and UACR in the STB group. Across studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, decreases in proteinuria, quantified by UPCR, and decreases in albuminuria, quantified by UACR, were observed as early as Week 1 and persisted through Week 48. The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42% to 21% and 49% to 27%, respectively, through Week 24. In subjects with mild to moderate renal impairment (GS-US-292-0112) who switched from a non-TDF containing regimen, median percentage changes from baseline in UPCR and UACR were 0.1% and −19.5%, respectively. In the D/C/F/TAF Phase 2 study, no

statistically significant differences were observed between the 2 treatment groups in median percentage change from baseline in UPCR or UACR at Week 48.

Across the E/C/F/TAF ART-naive studies, there was minimal change from baseline in RBP to creatinine ratio for the E/C/F/TAF group and a progressive increase from baseline to Week 48 for the STB group. Across studies in which subjects switched from a TDF-based regimen to E/C/F/TAF, decreases from baseline in urine RBP to creatinine and beta-2-microglobulin to creatinine ratios were observed as early as Week 1 and persisted through Week 48. Each of these differences between treatment groups was statistically significant favoring E/C/F/TAF. In subjects with mild to moderate renal impairment (GS-US-292-0112) who switched from a non-TDF containing regimen, decreases from baseline in RBP to creatinine and beta-2-microglobulin to creatinine ratios were observed at Week 24. In the D/C/F/TAF Phase 2 study, there were statistically significant differences between the treatment groups, favoring D/C/F/TAF, in change from baseline in RBP to creatinine and beta-2-microglobulin to creatinine ratios.

In the E/C/F/TAF ART-naive Phase 3 studies, there was no change from baseline in median (Q1, Q3) fractional excretion of uric acid (FEUA; marker of proximal renal tubular function) using adjusted serum creatinine at Week 48 in the E/C/F/TAF group, compared with an increase in the STB group (E/C/F/TAF 0.0% [−1.3%, 1.1%]; STB 0.4% [−0.8%, 2.0%]).

In Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109, subclinical renal tubulopathy was defined as confirmed abnormalities in any 2 out of 4 renal parameters (serum creatinine and 3 markers of tubular dysfunction). There were no cases identified with confirmed increases in serum creatinine plus confirmed increases in 2 of the 3 markers of tubular dysfunction for clinical review in either treatment group in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102 (randomized phase and open-label extension) or in subjects with renal impairment in Study GS-US-292-0112. In Study GS-US-292-0109 in virologically suppressed subjects, no subjects in the E/C/F/TAF group had subclinical renal tubulopathy, while 1 subject in the FTC/TDF+3rd Agent group (taking ATV+COBI+TVD) had all 4 confirmed renal laboratory abnormalities as well as a renal AE of Fanconi syndrome.

Ocular Safety

Across all E/C/F/TAF studies, eye disorders were uncommon, balanced between treatment groups, and considered by the investigator as unrelated to the study drugs. For subjects who received E/C/F/TAF, no AEs in the eye disorders system organ class (SOC) were indicative of posterior uveitis, and only 1 subject discontinued study drugs due to 3 eye disorder AEs, all of which were considered related to study drugs by the investigator. One subject in Study GS-US-292-0106 had an AE of intermediate uveitis that was considered related to study drug by the investigator but was resolving while the subject continued on study drug without interruption. No subjects in the ophthalmic substudy of Study GS-US-292-0109 had fundoscopic findings consistent with uveitis.

In the D/C/F/TAF Phase 2 study, 6 subjects (5.8%) receiving D/C/F/TAF had nonserious AEs in the eye disorders SOC compared with none of the subjects in the DRV+COBI+TVD group.

There were no AEs of uveitis during the study. No eye disorder resulted in discontinuation of study drugs.

Clinical Laboratory Evaluations

Laboratory Abnormalities

In the E/C/F/TAF ART-naive Phase 3 studies, 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; all median values were within normal ranges.

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 low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol to HDL ratio, and triglycerides were observed in subjects treated with E/C/F/TAF compared with those treated with a TDF comparator at both Weeks 24 and 48. Consistent with these results, greater percentages of subjects treated with E/C/F/TAF than those treated with a TDF comparator had categorical changes in the National Cholesterol Education Program (NCEP) ATP III lipid classifications from baseline. These small lipid categorical changes were consistent with data from other studies of abacavir, stavudine (d4T), and other non-TDF-based NRTIs in ART-naive patients {11417}. In the E/C/F/TAF studies, the majority of lipid abnormalities were Grade 1 or 2, and the percentage of subjects who received concomitant lipid modifying agents during the study was comparable between treatment groups. Similarly, in the single-group Study GS-US-292-0112, median changes from baseline in metabolic laboratory parameters at Weeks 24 and 48 demonstrated a trend toward increase in all parameters for subjects who received TDF at baseline and, notably, a trend toward decrease in most parameters for subjects who did not receive TDF at baseline.

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

The differences in metabolic laboratory parameters observed between treatment with E/C/F/TAF or D/C/F/TAF compared with TDF-containing regimens (including STB) may be associated with the previously reported lipid lowering effect of TFV {27870}, {16173} and the markedly lower plasma concentrations of TFV associated with TAF relative to TDF.

Safety in Special Groups and Situations

The safety of F/TAF as assessed by reported AEs and laboratory test abnormalities associated with treatment with E/C/F/TAF were not affected by sex, age, race, HIV-1 RNA level, CD4 count, prior treatment regimen, or region. Subgroup analyses of safety were based on the Phase 3 E/C/F/TAF studies only. Sex, age, race, did not have a clinically relevant effect on TAF (25 mg or 10 mg) or FTC exposures.

Safety in Subjects with Renal Impairment

Pharmacokinetic (PK) and relevant safety data support administration of F/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min). Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, baseline eGFR was not a statistically significant or clinically relevant covariate influencing TAF PK. As expected due to renal elimination, FTC PK parameters were higher in subjects with mild to moderate renal impairment compared with those having normal renal function in the Phase 2 and 3 E/C/F/TAF studies in ART naive subjects. However, the FTC PK parameters were comparable to the mean FTC PK parameters achieved in subjects with mild renal impairment not requiring dose adjustment (mean [%CV] AUC 19,900 [6.2] ng*h/mL; C_{max} 3800 [2.3] ng/mL) {23270}, {30162}. Moreover, subjects with $eGFR_{CG} < 50$ mL/min did not have a different safety profile compared with subjects with $eGFR_{CG} \geq 50$ mL/min.

No additional measures outside of standard clinical practice guidelines for routine monitoring renal safety in subjects with mild to moderate renal impairment are indicated.

Safety in Subjects with Hepatic Impairment

Pharmacokinetic and relevant safety data support administration of F/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Class A or B). The PK of F/TAF has not been studied in subjects with hepatic impairment. The efficacy and safety of F/TAF have not been established in patients with significant underlying liver disorders. The PK of TAF and its metabolite TFV have been studied in subjects with moderate hepatic impairment, and no dose adjustment is required in these patients. The PK of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so no dose adjustment is anticipated in patients with mild to moderate hepatic impairment.

1. EXPOSURE TO THE DRUG

1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

The principal sources of safety data for the F/TAF FDC are 2 pivotal Phase 3 studies in ART-naive subjects (Studies GS-US-292-0104 and GS-US-292-0111), 1 Phase 3 study in virologically suppressed subjects (Study GS-US-292-0109), 1 Phase 3 study in subjects with mild to moderate renal impairment (Study GS-US-292-0112), and 1 Phase 2/3 study in ART-naive adolescent subjects (Study GS-US-292-0106) (Table 1). Supportive safety information is provided by 2 Phase 2 studies in ART-naive subjects: E/C/F/TAF Study GS-US-292-0102 and D/C/F/TAF Study GS-US-299-0102; the E/C/F/TAF Study GS-US-292-0102 also includes safety information from the open-label extension phase in virologically suppressed subjects who switched to E/C/F/TAF (from STB or D/C/F/TAF). Supportive safety data are provided by Phase 1 studies of TAF (E/C/F/TAF, D/C/F/TAF, F/TAF, and TAF) (Table 2).

1.1.1. Primary Safety Populations for F/TAF

The primary safety populations for F/TAF consist of 6 E/C/F/TAF Phase 2 and Phase 3 clinical studies (Studies 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) and 1 D/C/F/TAF Phase 2 study (Study GS-US-299-0102).

1.1.1.1. E/C/F/TAF Studies

ART-Naive Adult Subjects

The 2 pivotal Phase 3 E/C/F/TAF studies supporting the safety of E/C/F/TAF for the treatment of HIV-1 infection in ART-naive subjects are Studies GS-US-292-0104 and GS-US-292-0111, which were randomized, double-blind studies that used STB as the comparator (m2.7.3, Sections 2.1.1 and 2.1.2 for summary information). Eligible subjects were ART-naive (excluding pre-exposure prophylaxis or postexposure prophylaxis up to 6 months prior to screening), HIV-infected adults with plasma HIV-1 RNA $\geq$ 1000 copies/mL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and an $eGFR_{CG} \geq 50$ mL/min at screening. Data are presented through a data cutoff performed when all randomized subjects had completed the Week 48 visit or had discontinued study drugs before their Week 48 visit.

The data from Studies GS-US-292-0104 and GS-US-292-0111 are supported by the Phase 2, randomized, double-blind, active-controlled Study GS-US-292-0102 (randomized phase), which evaluated E/C/F/TAF versus STB in ART-naive, HIV-infected adult subjects (m2.7.3, Section 2.1.3 for summary information). Eligible subjects for the randomized phase of the study had plasma HIV-1 RNA levels $\geq$ 5000 copies/mL, no prior use of any approved or experimental anti-HIV drug for any length of time, and an $eGFR_{CG} \geq 70$ mL/min at screening. The randomized phase of the study was 48 weeks. Data are presented through a data cutoff performed when all subjects enrolled into the randomized phase had completed 96 weeks of study drug treatment, or had discontinued study treatment before their Week 96 visit.

Using STB as a comparator in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102 allows for a direct comparison of the safety of TAF versus TDF, as the other components of the regimen and their respective doses are identical (ie, EVG 150 mg, COBI 150 mg, and FTC 200 mg).

Virologically Suppressed Adult Subjects

Data from Study GS-US-292-0109 support the safety of E/C/F/TAF in virologically suppressed subjects who switched to E/C/F/TAF from regimens containing FTC/TDF (m2.7.3, Section 2.2 for summary information). All subjects in this Phase 3 open-label study were enrolled from a predefined set of Gilead clinical studies. Eligible subjects were HIV-infected adults receiving ART regimens consisting of STB, ATR, ATV+COBI+ TVD, or RTV-boosted ATV (ATV+RTV)+TVD for at least 6 consecutive months preceding the final visit in their earlier study and who had maintained plasma HIV-1 RNA levels at undetectable levels for at least 6 consecutive months prior to the screening visit, had HIV-1 RNA < 50 copies/mL at the screening visit, and had an $eGFR_{CG} \geq 50$ mL/min at screening. Subjects must have completed between 60 and 144 weeks of treatment with another regimen in the previous study.

The choice of comparators in Study GS-US-292-0109 allows a direct comparison of the safety of TAF versus TDF in subjects switching to E/C/F/TAF or remaining on standard-of-care regimens.

The data cutoff for Study GS-US-292-0109 was designed to include a sufficient number of subjects who had reached the primary time point of interest (Week 48) in order to assess both efficacy and safety of E/C/F/TAF in the virologically suppressed population. This data cutoff was performed when all subjects randomized by [redacted] 20[redacted] had been followed through the lower limit of Week 48 analysis window (ie, Week 42) or had discontinued study treatment before this time.

Data are also available from the extension phase of Study GS-US-292-0102, in which HIV-infected subjects who had previously received STB in the randomized phase and subjects who had received D/C/F/TAF in Study GS-US-299-0102 were allowed to switch to open-label E/C/F/TAF.

Adult Subjects with Mild to Moderate Renal Impairment

The safety of E/C/F/TAF in adult subjects with mild to moderate renal impairment is supported by data from Study GS-US-292-0112, which was a Phase 3 open-label study that enrolled both ART-experienced (switch) and ART-naive subjects (summary information in Section 1.1.4.1.1). For the switch cohort (Cohort 1), eligible subjects were HIV-infected adults with plasma HIV-1 RNA concentrations at undetectable levels for at least 6 months and at < 50 copies/mL at screening, CD4 count ≥ 50 cells/μL, no history of known resistance to EVG, FTC, or TDF, and stable $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening. For the ART-naive cohort (Cohort 2), eligible subjects were HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell count ≥ 50 cells/μL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and stable $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening. The study planned to enroll a subset of at least 30 subjects (either switch or ART-naive) with screening $eGFR_{CG}$ of 30 to 49 mL/min.

The data cutoff was performed when all subjects who initiated study drugs on or prior to [redacted] 20[redacted] either completed their Week 48 study visits or prematurely discontinued study drugs before their Week 48 visits.

ART-Naive Adolescent Subjects

The safety of E/C/F/TAF in adolescent subjects is supported by data from the Phase 2/3 open-label Study GS-US-292-0106 (summary information in Section 1.1.4.1.2). Eligible subjects were HIV-infected, ART-naive adolescents of 12 to < 18 years of age weighing ≥ 35 kg, with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell count > 100 cells/μL, and eGFR ≥ 90 mL/min/1.73m^2 (as calculated using the Schwartz formula) at screening, no prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission), and sensitivity to EVG, FTC, and TFV as demonstrated by HIV-1 genotyping at screening.

The interim Week 24 analysis for Study GS-US-292-0106 was conducted when all subjects enrolled in Parts A and B by [redacted] 20[redacted] (N = 23) had completed their Week 24 visit.

1.1.1.2. D/C/F/TAF Study

ART-Naive Adult Subjects

Data from the Phase 2, randomized, double-blinded, active-controlled Study GS-US-299-0102 (m2.7.3, Section 2.2.1.1 for summary information) comparing D/C/F/TAF with DRV+COBI+TVD in HIV-infected, ART-naive adult subjects support the safety results from the E/C/F/TAF studies. Eligible subjects were HIV-infected adults with plasma HIV-1 RNA levels ≥ 5000 copies/mL; no prior use of any anti-HIV drug for any length of time; a screening genotype showing sensitivity to DRV, FTC, and TDF; and an $eGFR_{CG}$ of ≥ 70 mL/min at screening. After Week 48, subjects continued to take blinded study drug and attend visits every 12 weeks until treatment assignments were unblinded. If still receiving study drug at that point, subjects were given the option to participate in the open-label rollover extension phase of Study GS-US-292-0102 and receive E/C/F/TAF.

Data from the final analysis for Study GS-US-299-0102 are presented following the results of the primary E/C/F/TAF studies in each subsection of this summary.

Table 1. Studies Supporting Clinical Safety for the F/TAF Fixed-Dose Combination Marketing Application

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	CSR Reference & Narrative Locations
E/C/F/TAF Studies				
HIV-Infected, ART-Naive Adult Subjects				
GS-US-292-0104	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 435) STB + placebo-to-match E/C/F/TAF FDC (N = 432)	Week 48 efficacy, PK, and safety	**CSR:** GS-US-292-0104 Week 48 CSR **Narrative:** m2.7.3, Section 2.1.1.1
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:** GS-US-292-0111 Week 48 CSR **Narrative:** m2.7.3, Section 2.1.1.2
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 the D/C/F/TAF Phase 2 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 (N = 53) from D/C/F/TAF to E/C/F/TAF (N = 70) from DRV+COBI+TVD to E/C/F/TAF (N = 38)	Week 48[b] efficacy, PK, and safety	**CSR:** GS-US-292-0102 Week 96 CSR **Narrative:** m2.7.3, Section 2.1.1.3
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:** GS-US-292-0109 Week 48 CSR **Narrative:** m2.7.3, Section 2.1.2

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	CSR Reference & Narrative Locations
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:** GS-US-292-0112 Week 24 CSR **Narrative:** Section 1.1.4.1.1
HIV-Infected, ART-Naive Adolescent Subjects				
GS-US-292-0106	Phase 2/3, open-label, multicenter, 2-part, single-group study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 48) PK substudy: N = 24	Week 24 efficacy, PK, and safety	**CSR:** GS-US-292-0106 Week 24 CSR **Narrative:** Section 1.1.4.1.2
D/C/F/TAF Study				
HIV-Infected, ART-Naive Adult Subjects				
GS-US-299-0102	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+TVD	D/C/F/TAF FDC (N = 103) DRV+COBI+TVD (N = 50)	Week 48 efficacy, PK, and safety	**CSR:** m5.3.5.1, GS-US-299-0102 **Narrative:** m2.7.3, Section 2.2.1

ART = antiretroviral therapy; COBI = cobicistat; CSR = clinical study report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated); DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; STB = Stribild; TDF = tenofovir disoproxil fumarate; TVD = Truvada; vs = versus

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

b Most subjects in the randomized phase of Study GS-US-292-0102 received study drug for ≥ 60 weeks when unblinding occurred; most subjects in the open-label extension had completed ≥ 24 weeks of treatment.

1.1.2. Other Safety Populations Supportive of F/TAF

Supportive safety data are also provided by Phase 1 studies (including E/C/F/TAF, D/C/F/TAF, F/TAF, and TAF) that showed TAF was safe and generally well tolerated in healthy subjects. Deaths, SAEs, and discontinuations due to AEs are summarized for the TAF, F/TAF, D/C/F/TAF, and E/C/F/TAF Phase 1 studies. Further details on these Phase 1 studies are provided in the individual clinical study reports (CSRs) located as specified in Table 2. Studies for FTC are also included with this application as supportive safety information, listed in Table 3.

Table 2. Studies Providing Supporting Clinical Safety for the F/TAF Fixed-Dose Combination

Safety Population	Studies Included in Population	N Receiving TAF	CSR Reference
E/C/F/TAF Phase 1	GS-US-292-0101 (dose ranging)	38	GS-US-292-0101 Final CSR
	GS-US-292-0103 (BE)	34	GS-US-292-0103 Final CSR
	GS-US-292-0108 (race/ethnicity)	20	GS-US-292-0108 Final CSR
	GS-US-292-0110 (food effect)	43	GS-US-292-0110 Final CSR
	GS-US-292-1316 (DDI)	20	GS-US-292-1316 Final CSR
	GS-US-342-1167 (DDI)	24	GS-US-342-1167 Final CSR
D/C/F/TAF Phase 1	GS-US-299-0101 (BE)	65	m5.3.1.2, GS-US-299-0101 Final CSR
TAF Phase 1	GS-120-1101 (first in human)	20	GS-120-1101 Final CSR
	GS-US-120-0104 (dose ranging)	25	GS-US-120-0104 Final CSR
	GS-US-120-0107 (tQT)	58	GS-US-120-0107 Final CSR
	GS-US-120-0108 (renal impairment)	27	GS-US-120-0108 Final CSR
	GS-US-120-0109 (ADME)	8	GS-US-120-0109 Final CSR
	GS-US-120-0114 (hepatic impairment)	40	GS-US-120-0114 Final CSR
	GS-US-120-0117 (DDI)	36	GS-US-120-0117 Final CSR
	GS-US-120-0118 (DDI)	40	m5.3.3.4, GS-US-120-0118 Final CSR
	GS-US-120-1538 (DDI)	18	m5.3.3.4, GS-US-120-1538 Final CSR
	GS-US-120-1554 (DDI)	33	m5.3.3.4, GS-US-120-1554 Final CSR
F/TAF Phase 1	GS-US-311-0101 (DDI)	50	GS-US-311-0101 Final CSR
	GS-US-311-1088 (BE)	56	m5.3.1.2. GS-US-311-1088 Final CSR
	GS-US-311-1386 (food effect)	40	m5.3.3.4, GS-US-311-1386 Final CSR
	GS-US-311-1472 (BE)	100	m5.3.1.2 GS-US-311-1472 Final CSR
	GS-US-311-1473 (BE)	116	m5.3.1.2 GS-US-311-1473 Final CSR

ADME = absorption, distribution, metabolism, and excretion; BE = bioequivalence; DDI = drug-drug interaction; tQT = thorough QT

Table 3. Other FTC Studies

Safety Population	Studies Included in Population	Location
FTC Phase 2 and Phase 3	FTC-301A	Appendix 7.1.3
	FTC-302	
	FTC-303	
	FTC-203	

1.1.3. Safety Assessments

Primary safety data were pooled for the 2 pivotal Phase 3 E/C/F/TAF studies (Studies GS-US-292-0104 and GS-US-292-0111) because the study designs and populations were identical, differing only in geography. Unless otherwise stated, no other data were pooled due to differences in the subject populations studied, treatment durations, and randomization. The primary safety data consist of 4 distinct subject populations: ART-naive adults, virologically suppressed subjects, subjects with mild to moderate renal impairment, and ART-naive adolescents. The main safety endpoint analysis was at 48 weeks for all studies except E/C/F/TAF Study GS-US-292-0106 (24 weeks). The studies in ART-naive adults were double-blind, randomized studies, whereas the other studies were open-label. Data for Studies GS-US-292-0104 and GS-US-292-0111 are presented pooled or side-by-side; data for other studies are presented individually.

For all Phase 2 and Phase 3 studies described in this document, clinical and laboratory AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0, with SOC, high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) attached to the clinical databases.

In this summary, all AEs discussed were treatment emergent and are referred to as AEs. All AEs were assessed by the investigator or qualified designee and recorded on the AE electronic case report form (eCRF). The AE entry indicated whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug or to a study procedure, the action taken with the study drugs due to the AE, and the severity of the AE. The investigator was responsible for final review and confirmation of accuracy of events, relationship, and severity, confirmed by the signature on the eCRF.

Laboratory abnormalities were not usually recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that required medical or surgical intervention or led to study drug interruption or discontinuation were recorded as an AE or SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram [ECG], x-rays, vital signs) associated with signs and/or symptoms were recorded as an AE or SAE if they met the definitions. If the laboratory abnormality was part of a syndrome, the syndrome or diagnosis was recorded (eg, anemia), not the laboratory result (eg, decreased hemoglobin).

All AEs and laboratory abnormalities were recorded according to uniform guidelines and were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

To control for the overall type I error in the assessment of the primary efficacy endpoint and the key safety endpoints in the E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109; hypothesis testing was performed in sequential order. The primary hypothesis of noninferiority of E/C/F/TAF relative to the active comparator in each study, 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. The noninferiority test was performed at a 1-sided, 0.02499 alpha level for Studies GS-US-292-0104 and GS-US-292-0111 and 0.02495 for Study GS-US-292-0109. 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; 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 the E/C/F/TAF Integrated Summary of Safety statistical analysis plan (E/C/F/TAF ISS SAP) and are included in sections below when appropriate.

1.1.4. Summary of Results of Individual Studies

Narrative safety data from clinical pharmacology, and efficacy studies of E/C/F/TAF, D/C/F/TAF, F/TAF, and TAF are presented in m2.7.2, and m2.7.3.

1.1.4.1. E/C/F/TAF Studies

Narrative safety data are provided in this section for subjects with mild to moderate renal impairment receiving E/C/F/TAF (GS-US-292-0112, Section 1.1.4.1.1) and for ART-naive adolescent subjects receiving E/C/F/TAF (GS-US-292-0106, Section 1.1.4.1.2).

1.1.4.1.1. Subjects with Mild to Moderate Renal Impairment in Study GS-US-292-0112

A complete study description and results for Study GS-US-292-0112 are available in the CSR (GS-US-292-0112 Week 24 CSR), and a brief narrative of this study is presented below.

Title of Study: A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

Objectives: Study GS-US-292-0112 was conducted to evaluate safety, efficacy, and tolerability of E/C/F/TAF FDC in in HIV-infected adult subjects with stable, mild to moderate renal function (subjects with baseline $eGFR_{CG}$ 30 to 69 mL/min, inclusive).

The primary objective of this study was as follows:

- To evaluate the effect of the E/C/F/TAF FDC on renal parameters at Week 24

The secondary objectives of this study were as follows:

- To evaluate the effect of the E/C/F/TAF FDC on renal parameters at Weeks 48 and 96
- To measure the proportion of subjects achieving virologic response (HIV-1 RNA < 50 copies/mL, Food and Drug Administration [FDA] snapshot algorithm) at Weeks 24, 48, and 96
- To evaluate the safety and tolerability of the E/C/F/TAF through 96 weeks of treatment

Diagnosis and Main Criteria for Inclusion:

Cohort 1 (Switch): Eligible subjects were HIV-infected adults with plasma HIV-1 RNA concentrations at undetectable levels for at least 6 months and < 50 copies/mL at screening, CD4+ cell count ≥ 50 cells/μL, no history of known resistance to EVG, FTC, or TDF, and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening.

Cohort 2 (ART-Naive): Eligible subjects were ART naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4+ cell count ≥ 50 cells/μL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 380 subjects screened, 252 were enrolled in the study (246 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects). A total of 248 subjects received at least 1 dose of study drug (242 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects).

Of the 248 treated subjects, 6.5% (16 subjects) discontinued study drug treatment, all of whom were Cohort 1 switch subjects. The reasons for discontinuation of study drug in the Cohort 1 switch subjects (n = 242) were AE (3.3%, 8 subjects), withdrew consent (1.2%, 3 subjects), lost to follow-up (0.8%, 2 subjects), lack of efficacy (0.4%, 1 subject), protocol violation (0.4%, 1 subject), and investigator's discretion (0.4%, 1 subject).

Cohort 1: Switch Subjects

The majority of subjects were male (79.3%), and the median age was 58 years (range: 24 to 82). A total of 63 subjects (26%) were ≥ 65 years of age. The most common races were white (62.8%), black (18.2%), or Asian (14.0%), and the most common ethnicity was not Hispanic/Latino (86.4%). The median (Q1, Q3) BMI at baseline was 24.1 (21.4, 26.9) kg/m^2.

Of 242 Cohort 1 switch subjects, 39.3% had a medical history of hypertension, and 13.6% had a medical history of diabetes. A total of 65.3% of subjects were taking TDF-containing regimens prior to switching to E/C/F/TAF. The baseline median (Q1, Q3) values for CD4 count and CD4% were 632 (456, 811) cells/μL and 34.7% (26.4%, 41.1%), respectively. Overall, 97.5% of subjects had baseline HIV-1 RNA < 50 copies/mL. The most common HIV risk factor categories were homosexual sex (52.1% of subjects) and heterosexual sex (40.9% of subjects). The majority of subjects (74.4%) had asymptomatic HIV-1 infection; 11.6% had symptomatic HIV-1 infection, and 14.0% were diagnosed with AIDS.

At baseline, the median (Q1, Q3) $eGFR_{CG}$ was 55.6 (45.7, 62.4) mL/min. Overall, 33.1% of subjects (80 of 242) had $eGFR_{CG}$ < 50 mL/min, 42.3% of subjects (101 of 239) had clinically significant proteinuria (UPCR > 200 mg/g), and 48.9% of subjects (115 of 235) had clinically significant albuminuria (UACR ≥ 30 mg/g). At baseline, 9.5% of subjects had Grade 2 proteinuria by urinalysis (dipstick), 23.1% of subjects had Grade 1 proteinuria. Most subjects were in chronic kidney disease (CKD) Stage 3 ($eGFR_{CG}$ 30 to 59 mL/min; 63.6%).

Cohort 2: ART-Naive Subjects

All 6 subjects were male, and the median age was 54 years (range: 46 to 65). The races were black (3 subjects), white (2 subjects), and Asian (1 subject), and the most common ethnicity was not Hispanic/Latino (5 subjects). The median (Q1, Q3) BMI at baseline was 23.6 (21.4, 25.7) kg/m^2.

The baseline median (Q1, Q3) values for HIV-1 RNA, CD4 count, and CD4% were 4.72 (4.01, 5.35) log_{10} copies/mL, 397 (184, 673) cells/μL, and 24.6% (11.7%, 28.8%), respectively. Four subjects had baseline HIV-1 RNA ≥ 50 to ≤ 100,000 copies/mL, and 2 subjects had baseline HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL. The HIV risk factor categories were homosexual sex (3 subjects) and heterosexual sex (3 subjects). Five subjects had asymptomatic HIV-1 infection, and 1 subject had symptomatic HIV-1 infection.

The median (Q1, Q3) $eGFR_{CG}$ in Cohort 2 ART-naive subjects was 60.2 (45.0, 63.2) mL/min. One of the 6 subjects had Grade 2 proteinuria. Three subjects were in eGFR category CKD Stage 2, and 3 subjects were in eGFR category CKD Stage 3.

Efficacy Results:

Cohort 1: Switch Subjects

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm. The virologic success rate was 95.0% (baseline

$eGFR_{CG}$ < 50 mL/min 95.0%; baseline $eGFR_{CG}$ ≥ 50 mL/min 95.1%). Three subjects (1.2%) were classified as virologic failures at Week 24. Of those 3 subjects, 2 had HIV-1 RNA ≥ 50 copies/mL at Week 24, and 1 added a new ARV. At Week 24, the virologic success rate by HIV-1 RNA < 20 copies/mL was 93.0% using the FDA snapshot algorithm.

At Week 48, the virologic success rate was 93.7% (164 of 175 subjects; HIV-1 RNA < 50 copies/mL) using the FDA snapshot algorithm. Three subjects (1.7%; all in the baseline $eGFR_{CG}$ ≥ 50 mL/min group) were classified as virologic failures at Week 48. Of those 3 subjects, 1 had HIV-1 RNA ≥ 50 copies/mL at Week 48, 1 discontinued due to lack of efficacy, and 1 added a new ARV.

High rates of virologic suppression were maintained, as assessed using the missing = failure (M = F) (at Week 24) and missing = excluded (M = E) (at Weeks 24 and 48) methods using the Full Analysis Set (FAS). The percentages of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 24 were 97.5% and 99.2% for M = F and M =E, respectively. The percentage of subjects with virologic suppression (HIV-1 RNA levels < 50 copies/mL) at Week 48 was 99.4% (M = E).

CD4 cell counts remained stable during treatment with E/C/F/TAF. The mean (SD) baseline CD4 cell count was 664 (286.4) cells/μL. The mean (SD) change from baseline in CD4 cell counts at Week 24 (observed data) using the FAS was −7 (159.2) cells/μL. The mean (SD) change from baseline in CD4 cell counts through Week 48 (observed data) using the FAS was 16 (158.0) cells/μL.

There were no clinically significant differences in virologic success at Week 24 (FDA snapshot algorithm, HIV-1 RNA < 50 copies/mL) between subgroups (age, sex, race, region, or study drug adherence rate).

Cohort 2: ART Naive Subjects

At Week 24, 5 of 6 Cohort 2 ART-naive subjects had HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm. One subject was classified as a virologic failure at Week 24 but had HIV-1 RNA < 50 copies/mL at Week 48.

CD4 cell counts increased during treatment with E/C/F/TAF. Mean (SD) baseline CD4 cell count for the Cohort 2 ART-naive subjects was 412 (244.0) cells/μL. The mean (SD) change from baseline in CD4 cell count through Week 24 (observed data) using the FAS was 126 (106.3) cells/μL. The mean (SD) change from baseline in CD4 cell count through Week 48 (observed data) using the FAS was 144 (169.7) cells/μL.

Pharmacodynamics Results:

Statistical comparisons of actual glomerular filtration rate (aGFR) based on iohexol plasma clearance between postbaseline and baseline visits are summarized below using the Pharmacodynamic (PD) Substudy Analysis Set for Cohort 1 switch subjects.

Table 4. E/C/F/TAF Study GS-US-292-0112: Statistical Analysis and Comparisons of aGFR (mL/min) Between Visits (PD Substudy Analysis Set)

Comparison	aGFR (GLSM)				GLSM Ratio (%)	90% CI
	n	Test Treatment	n	Reference Treatment		
Week 2/4/8 aGFR vs Baseline aGFR (mL/min)	32	59.5 (30.4)	32	60.1 (31.7)	98.94	(93.71,104.46)
Week 24 aGFR vs Baseline aGFR (mL/min)	30	61.5 (24.9)	32	60.1 (31.7)	102.66	(97.11,108.53)

aGFR = actual glomerular filtration rate; CI = confidence interval; GLSM = geometric least-squares mean
Actual GFR (aGFR) using iohexol plasma clearance (mL/min) = Iohexol Dose/Iohexol AUC_{inf}
It was confirmed that most time points with iohexol concentrations > 2000 µg/mL had blood samples taken from the same arm as iohexol infusion; therefore, time points with iohexol concentrations > 2000 µg/mL were excluded from PK parameter (eg, AUC_{inf}) estimates.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 13.3 and 13.4

The geometric least-squares mean (GLSM) ratio and associated 90% CIs for each comparison of aGFR for (1) Week 2, 4, or 8 (ie, the intensive PK visit) versus baseline and (2) Week 24 versus baseline were within the predefined lack of alteration boundary of 80% to 125%. These data indicate that the study treatments did not alter aGFR. Additionally, there were no differences in aGFR between on-treatment versus baseline when assessed in subgroups according to baseline $eGFR_{CG}$ < 50 mL/min versus $eGFR_{CG} \geq 50$ mL/min or in subgroups according to pre-switch TDF use (with or without), as evidenced by the 90% CIs of the GLSM ratios contained within 80% to 125% in all cases.

Pharmacokinetics Results:

The plasma PK parameters of E/C/F/TAF in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min are presented in the table below for the PK Substudy Analysis Set:

Table 5. E/C/F/TAF Study GS-US-292-0112: TAF, TFV, FTC, EVG, and COBI Plasma PK Parameters (PK Analysis Sets)

	AUC[a] Mean (%CV)		C_{max} Mean (%CV)		C_{tau} Mean (%CV)	
	N	(ng*h/mL)	N	(ng/mL)	N	(ng/mL)
TAF[b]	29	254.2 (54.1)	29	265.2 (68.7)		Not applicable
TFV	29	552.7 (32.0)	30	29.3 (29.2)	25	19.2 (31.1)
FTC	29	20,968.6 (25.5)	30	2645.3 (24.7)	26	194.2 (33.8)
EVG	28	27,107.7 (32.1)	30	2394.3 (31.6)	26	356.9 (75.5)
COBI	29	9924.2 (45.2)	30	1290.9 (31.7)	25	38.3 (104.2)

CV = coefficient of variation
For each subject in PK substudy, the intensive PK analysis was conducted at Weeks 2, 4, or 8.
All subjects in the PK Substudy Analysis Set are from Cohort 1 (switch).
a AUC_{tau} was calculated for all analytes with the exception of TAF, which was AUC_{last}.
b Subject *CT (baseline $eGFR_{CG}$ < 50 mL/min) was excluded for sensitivity analysis as TAF PK parameter estimates are unreliable due to an unusual PK profile.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 63.1, 63.2, 63.3, 63.4, and 63.5

TAF PK in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min was consistent with data following administration of E/C/F/TAF in nonrenally impaired HIV-infected subjects in Phase 2 and Phase 3 studies. Specifically, the mean (%CV) TAF AUC_{last} of 254.2 (54.1) ng*h/mL in this study was comparable with TAF AUC_{last} of 227.5 (47.3), 229.8 (33.7), and 259.0 (71.6) ng*h/mL in Phase 2 Study GS-US-292-0102 and Phase 3 Studies GS-US-292-0104 and GS-US-292-0111, respectively. The TAF exposure was numerically higher in subjects with baseline $eGFR_{CG}$ < 50 versus ≥ 50 mL/min, with mean (%CV) TAF AUC_{last} of 340.5 (60.1) ng*h/mL and 226.7 (44.1) ng*h/mL, respectively, and was less than the TAF AUC_{last} of 510.6 (47.4) ng*h/mL in severely renally impaired subjects ($eGFR_{CG}$ 15 to 29 mL/min) in a previous study (Study GS-US-120-0108).

Due to TFV being primarily renally eliminated, TFV PK was higher in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min in this study versus Phase 2 and Phase 3 studies in nonrenally impaired HIV-infected subjects (mean [%CV] TFV AUC_{tau} 552.7 [32.0] ng*h/mL versus 326.2 [14.8], 311.8 [17.1], 286.2 [22.5] ng*h/mL in Phase 2 Study GS-US-292-0102 and Phase 3 Studies GS-US-292-0104 and GS-US-292-0111, respectively). However, TFV exposures were well below the TFV exposure in severely renally impaired subjects ($eGFR_{CG}$ 15-29 mL/min) in Study GS-US-120-0108 (mean AUC_{inf} 2073.8 [47.1] ng*h/mL) and were well below the TFV exposures from TDF-containing regimens in nonrenally impaired subjects ($eGFR_{CG}$ ≥ 90 mL/min).

Due to FTC being primarily renally eliminated, FTC PK was higher in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min in this study versus the Phase 2 study in nonrenally impaired HIV-infected subjects (mean [%CV] FTC AUC_{tau} 20968.6 [25.5] ng*h/mL versus 11,714.1 [16.6] ng*h/mL in Phase 2 Study GS-US-292-0102). However, the FTC exposure were comparable with the mean FTC exposure achieved in subjects with mild renal impairment not requiring dose adjustment (mean [%CV] FTC AUC 19,900 [6] ng*h/mL). The FTC PK parameters were higher in subjects with baseline $eGFR_{CG} < 50$ versus ≥ 50 mL/min, consistent with the FTC PK parameters observed in subjects with mild ($eGFR_{CG} = 50$ to 80 mL/min) or moderate renal impairment ($eGFR_{CG} = 30$ to 49 mL/min).

Mean (%CV) EVG AUC_{tau} of 27,107.7 (32.1) ng*h/mL and COBI AUC_{tau} of 9924.2 (45.2) ng*h/mL in this study were in the range of data from Phase 2 Study (Study GS-US-292-0102: mean EVG AUC_{tau} 22,797.0 [34.7] ng*h/mL, mean COBI AUC_{tau} 9459.1 [33.9] ng*h/mL). Additionally, EVG and COBI exposure were comparable across eGFR groups in this study (EVG AUC_{tau}: 28,705.8 [38.3] and 26,468.4 [29.6] ng*h/mL in subjects with baseline $eGFR_{CG} < 50$ and ≥ 50 mL/min, respectively; COBI AUC_{tau}: 11,316.8 [48.8] and 9393.7 [43.1] ng*h/mL in subjects with baseline $eGFR_{CG} < 50$ and ≥ 50 mL/min, respectively), consistent with the nonrenal elimination pathway of these agents.

Safety Results:

Cohort 1: Switch Subjects

In Cohort 1 (switch), the median (Q1, Q3) duration of exposure to study drug was 43.1 (36.1, 48.0) weeks.

Renal Safety

The aGFR was directly measured at baseline, Week 2, 4, and/or 8, and Week 24 using iohexol clearance ($CL_{iohexol}$) for subjects enrolled in the PK/PD substudy (N = 32). Median (Q1, Q3) changes from baseline in aGFR were −1.8 (−5.3, 3.7) mL/min at Week 2, 4, or 8 and 0.1 (−4.3, 4.4) at Week 24. The GLSM ratios (90% CIs) for Week 2, 4, or 8 and Week 24 versus baseline were 98.94 (93.71, 104.46) and 102.66 (97.11, 108.53), respectively, indicating aGFR was not affected by E/C/F/TAF over 24 weeks of treatment.

Median changes from baseline at each time point through Week 48 ranged from −0.01 to 0.04 mg/dL for serum creatinine, −0.06 to −0.01 mg/dL for serum cystatin C, and 0 to 0.3 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters.

The primary renal endpoints were defined as change from baseline at Week 24 in $eGFR_{CG}$, eGFR calculated using the CKD Epidemiology Collaboration (CKD-EPI) cystatin C equation ($eGFR_{CKD\text{-}EPI,\ cysC}$), and eGFR using the CKD-EPI creatinine equation ($eGFR_{CKD\text{-}EPI,\ creatinine}$). No clinically significant changes from baseline eGFR through Week 24 were observed using any of the 3 equations. The overall median (Q1, Q3) change from baseline in $eGFR_{CG}$ at Week 24 was −0.4 (−4.7, 4.5) mL/min for $eGFR_{CG}$, −1.8 (−6.1, 4.9) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.8 (−4.8, 11.2) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ cysC}$. The baseline $eGFR_{CG} < 50$ mL/min

group had median increases from baseline at Weeks 24 and 48 using any of the 3 equations. The baseline $eGFR_{CG} \geq 50$ mL/min group had an increase in eGFR as assessed by $eGFR_{CKD\text{-}EPI,\ cysC}$ and decreases as assessed by $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ at Weeks 24 and 48.

Only 2 of 242 subjects (0.8%) (both in the baseline $eGFR_{CG} < 50$ mL/min group) had an AE in the renal and urinary disorders SOC that led to study drug discontinuation (renal failure and renal failure chronic). Both discontinuations were due to declining glomerular filtration rate: 1 subject had labile hypertension and was using concomitant ramipril and valsartan, and the discontinuation for another subject was assessed as likely related to progression of CKD and not related to study drug. There were no AEs of PRT (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy.

Most subjects had either no change or an improvement (toxicity grade decreased at least 1 grade from baseline) from the baseline proteinuria toxicity grade at Week 24. For 75.0% of subjects (57 of 76) with nonmissing values, the proteinuria grade improved from baseline at Week 24; for only 5.7% of subjects (13 of 230) with nonmissing values, proteinuria grade worsened from baseline at Week 24. For 82.5% of subjects (47 of 57) with pre-switch TDF use who had nonmissing values, the proteinuria grade improved from baseline at Week 24; for only 5.3% of subjects (8 of 151) with nonmissing values, proteinuria grade worsened from baseline at Week 24. For 52.6% of subjects (10 of 19) without pre-switch TDF use and nonmissing values, the proteinuria grade improved from baseline at Week 24; for only 6.3% of subjects (5 of 79) with nonmissing values, proteinuria grade worsened from baseline at Week 24.

More than half of subjects (57.0%, 53 of 93 subjects with nonmissing values) with clinically significant proteinuria (UPCR > 200 mg/g) at baseline had no clinically significant proteinuria by Week 24. Only 8 of 133 subjects (6.0%) developed clinically significant proteinuria (UPCR > 200 mg/g) by Week 24. Nearly half of subjects (47.2%, 50 of 106) with clinically significant albuminuria (UACR ≥ 30 mg/g) at baseline had no clinically significant albuminuria (< 30 mg/g) by Week 24. Only 4 of 117 subjects (3.4%) developed clinically significant albuminuria (UACR ≥ 30 mg/g) by Week 24.

Clinically significant proteinuria was defined as UPCR > 200 mg/g, and clinically significant albuminuria was defined as UACR ≥ 30 mg/g. Decreases in UPCR from the baseline median of 160.6 mg/g were observed at Week 1 (median of 110.3 mg/g) and persisted through Week 48 (median of 80.1 mg/g). Median UPCR percentage changes from baseline for Weeks 1 to 48 ranged from −27.3% to −47.1%. For subjects with baseline $eGFR_{CG} < 50$ mL/min, median baseline UPCR was 270.0 mg/g, and medians for Weeks 1 to 48 ranged from 130.0 to 209.0 mg/g with median percentage changes from baseline ranging from −23.8% to −40.1%; for subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median baseline UPCR was 138.5 mg/g, and medians for Weeks 1 to 48 ranged from 68.9 to 88.9 mg/g with median percentage changes from baseline ranging from −28.7% to −47.7%. Similar to UPCR, decreases in UACR from the baseline median of 28.8 mg/g were observed at Week 1 (median of 16.6 mg/g) and persisted through Week 48 (median of 8.3 mg/g). Median UACR percentage changes from baseline for Weeks 1 to 48 ranged from −33.7% to −52.3%. For subjects with baseline $eGFR_{CG} < 50$ mL/min, median baseline UACR was 53.2 mg/g, and medians for Weeks 1 to 48 ranged from 25.2 to 34.9 mg/g with median percentage changes from baseline ranging from −28.2% to

−42.6% for subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median baseline UACR was 22.7 mg/g, and medians for Weeks 1 to 48 ranged from 6.5 to 11.3 mg/g with median percentage changes from baseline ranging from −33.8% to −53.2%.

Decreases in median percentage change from baseline in urine RBP to creatinine ratio (baseline of 800.5 µg/g) and beta-2-microglobulin to creatinine ratio (baseline of 1562.5 µg/g) were observed from Weeks 1 to 48: RBP to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −71.9% to −43.4%; beta-2-microglobulin to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −80.5% to −48.2%.

No clinically significant changes from baseline through Week 48 were observed for renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR), fractional excretion of phosphate ($FEPO_4$), FEUA, or urine creatinine overall or for the baseline $eGFR_{CG} < 50$ mL/min and $eGFR_{CG} \geq 50$ mL/min groups.

Adverse Events

At least 1 AE was reported in 86.4% of Cohort 1 switch subjects (n = 209: 67 [83.8%] with baseline $eGFR_{CG} < 50$ mL/min and 142 [87.7%] with baseline $eGFR_{CG} \geq 50$ mL/min). No subjects died during this study.

A total of 10.7% of subjects reported at least 1 SAE (n = 26: 9 [11.3%] with baseline $eGFR_{CG} < 50$ mL/min and 17 [10.5%] with baseline $eGFR_{CG} \geq 50$ mL/min); all SAEs were considered unrelated to study drug by the investigator. The AEs considered related to study drug by the investigator were reported in 25.6% of subjects (n = 62: 21 [26.3%] with baseline $eGFR_{CG} < 50$ mL/min and 41 [25.3%] with baseline $eGFR_{CG} \geq 50$ mL/min). At least 1 Grade 3 or 4 AE was reported in 7.4% of subjects (n = 18: 7 [8.8%] with baseline $eGFR_{CG} < 50$ mL/min and 11 [6.8%] with baseline $eGFR_{CG} \geq 50$ mL/min); of these, 3 subjects had Grade 3 or 4 AEs considered related to study drug by the investigator: blood creatine phosphokinase increased (baseline $eGFR_{CG} < 50$ mL/min group), gastroesophageal reflux disease (baseline $eGFR_{CG} \geq 50$ mL/min group), and hypercholesterolemia (baseline $eGFR_{CG} \geq 50$ mL/min group).

The AEs leading to premature study drug discontinuation were reported in 3.3% of subjects (n = 8; 6 [7.5%] with baseline $eGFR_{CG} < 50$ mL/min and 2 [1.2%] with baseline $eGFR_{CG} \geq 50$ mL/min); of these, 3 subjects (2 with baseline $eGFR_{CG} < 50$ mL/min and 1 with baseline $eGFR_{CG} \geq 50$ mL/min) had a single AE leading to premature study drug discontinuation considered related to study drug by the investigator (worsening of sleep disturbance, worsening renal insufficiency, and choking, respectively).

The most commonly reported AEs were diarrhea (8.7%, 21 subjects), arthralgia (8.3%, 20 subjects), and bronchitis and osteopenia (7.9%, 19 subjects for each AE). Of note, 16 of 19 subjects had the AE of osteopenia reported on Day 1, suggesting that these AEs were most likely reported based on the baseline (predose) dual-energy x-ray absorptiometry (DXA) scan and were not truly treatment emergent; the other 3 subjects had the AE of osteopenia reported within 12 days after the first dose of study drug. The most commonly reported AEs considered related to the study drug by the investigator were dizziness (2.9%, 7 subjects), diarrhea (2.5%,

6 subjects), and headache (2.1%, 5 subjects). Importantly, rates of AEs associated with FTC were low despite higher FTC exposure in the $eGFR_{CG} < 50$ mL/min group.

Bone Safety

A total of 5 subjects (2.1%) experienced 6 fracture events, of whom 4 were subjects with pre-switch TDF use and 1 was a subject without pre-switch TDF use. All reported fracture AEs were considered unrelated to study drug by the investigator, and none resulted in discontinuation of study drug. All fracture events were the result of trauma, and none were reported as fragility fractures.

Overall, hip and spine BMD increased for Cohort 1 subjects after switching to E/C/F/TAF: mean (SD) percentage increases from baseline were observed in hip BMD (Week 24: 0.733% [2.7674]; Week 48: 1.575% [4.5738]) and spine BMD (Week 24: 1.643% [3.6250]; Week 48: 2.368% [4.2582]). Mean percentage changes from baseline in hip and spine BMD for those with pre-switch TDF use compared with those without pre-switch TDF use were 1.151% versus −0.071% for hip BMD and 2.370% versus 0.291% for spine BMD at Week 24 and 1.843% versus 0.997% for hip BMD and 2.994% versus 1.104% for spine BMD at Week 48. There was evidence for an improvement in hip and spine BMD after switch to E/C/F/TAF when assessed using a threshold of 3% for changes from baseline; higher percentages of subjects had increases versus decreases from baseline in BMD at both hip (Week 24: 13.8% versus 7.1%; Week 48: 22.4% versus 6.2%) and spine (Week 24: 33.6% versus 8.0%; Week 48: 38.8% versus 4.4%). In addition, few changes from baseline at Weeks 24 and 48 were observed in hip and spine BMD clinical status.

Median percentage changes from baseline at Weeks 24 and 48 were observed in the bone turnover biomarkers C-telopeptide and P1NP, as well as PTH. For each of the bone biomarkers and PTH, subjects with pre-switch TDF use had median percentage decreases from baseline at Weeks 24 and 48, whereas those without pre-switch TDF use had median percentage increases from baseline at Weeks 24 and 48. Median (Q1, Q3; baseline value) percentage changes from baseline at Week 24 for subjects with and without pre-switch TDF use were as follows: C-telopeptide: with pre-switch TDF use −5.4% (−19.2%, 7.1%; 4.8 µg/L), without pre-switch TDF use 5.2% (−8.1%, 21.3%; 5.1 µg/L); PINP: with pre-switch TDF use −24.27% (−39.98%, −8.34%; 57.21 ng/mL), without pre-switch TDF use 8.94% (−15.64%, 43.64%; 45.43 ng/mL); PTH: with pre-switch TDF use −15.9% (−32.0%, 8.1%; 48.3 pg/mL), without pre-switch TDF use 14.6% (−9.3%, 65.2%; 43.4 pg/mL).

Ocular Safety

Adverse events in the eye disorders SOC were reported in 22 of 242 subjects (9.1%), 6 of 80 subjects (7.5%) with baseline $eGFR_{CG} < 50$ mL/min and 16 of 162 subjects (9.9%) with baseline $eGFR_{CG} \geq 50$ mL/min. None of the AEs in the eye disorders SOC were serious, resulted in discontinuation of study drug, or were considered representative of an actual case of clinical uveitis.

Laboratory Abnormalities

There were no clinically significant changes from baseline in median values for hematology or clinical chemistry parameters through Week 48. The majority of reported laboratory abnormalities were Grade 1 or Grade 2. The most commonly observed Grade 3 or 4 laboratory abnormalities in Cohort 1 switch subjects were LDL (fasting) (Grade 3, 14 subjects), creatine kinase (Grade 3, 8 subjects; Grade 4, 2 subjects), serum glucose (nonfasting, hyperglycemia) (Grade 3, 8 subjects; Grade 4, 2 subjects), and total cholesterol (fasting, hypercholesterolemia (Grade 3, 10 subjects). Importantly, rates of laboratory abnormalities associated with FTC were low despite higher FTC exposure in the $eGFR_{CG} < 50$ mL/min group.

Metabolic Laboratory Parameters

For subjects from each baseline $eGFR_{CG}$ group in Cohort 1, median changes from baseline to Weeks 24 or 48 were observed while fasting for total cholesterol, direct LDL cholesterol, HDL cholesterol, total cholesterol to HDL ratio, triglycerides, and glucose demonstrated a trend toward increase in most parameters evaluated. Median changes from baseline in metabolic laboratory parameters at Weeks 24 and 48 demonstrated a trend toward increase in all parameters for subjects with pre-switch TDF use and a decrease in most parameters for subjects without pre switch TDF use.

Cohort 2: ART Naive Subjects

In Cohort 2 (ART naive), the median (Q1, Q3) duration of exposure to study drug was 42.8 (36.1, 48.1) weeks. The majority of the subjects (83.3%, 5 subjects) received study drug for ≥ 36 weeks. Only 6 Cohort 2 ART-naive subjects were enrolled; therefore, limited summaries are provided for these subjects, and interpretation of their data should be made with caution.

Renal Safety

Median changes from baseline in serum creatinine at each time point through Week 48 ranged from −0.01 to 0.13 mg/dL, indicating no clinically significant changes in serum creatinine in these subjects. Graded serum creatinine laboratory abnormalities (Grade 1 only) were reported for 1 subject. Median changes from baseline at each time point through Week 48 ranged from −0.13 to 0.19 mg/dL for serum cystatin C and −0.6 to 0.2 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters.

The median (Q1, Q3) change from baseline in eGFR at Week 24 (primary endpoint) was −0.3 (−3.6, 1.3) mL/min for $eGFR_{CG}$, −2.6 (−11.1, −0.9) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.9 (−3.3, 13.2) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ cysC}$.

No renal SAEs or AEs in the renal and urinary disorders SOC that led to study drug discontinuation were reported. There were no AEs of PRT (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy.

No changes from the baseline proteinuria toxicity grade were observed. Changes from baseline in median UPCR and UACR were observed, but no subject developed new clinically significant

proteinuria (UPCR > 200 mg/g) or clinically significant albuminuria (UACR > 30 mg/g). Changes in UPCR from the baseline median of 45.9 mg/g were observed from Weeks 1 to 48, with medians of 50.8, 48.8, 48.7, 48.4, 55.0, 43.2, 58.2, 48.9, and 59.9 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively. Changes in UACR from the baseline median of 12.3 mg/g were observed from Weeks 1 to 48, with medians of 5.3, 7.8, 10.4, 8.1, 8.9, 7.2, 12.4, 7.1, and 8.6 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively.

Changes in urine RBP to creatinine ratio were observed from Weeks 1 to 48, with median percentage changes from baseline of 12.1%, −20.8%, −5.0%, −9.6%, 68.8%, and 69.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively. Changes in beta-2-microglobulin to creatinine ratio were observed from Weeks 1 to 48, with median percentage changes from baseline of −15.2%, 43.4%, −47.1%, −10.2%, −19.5%, and 34.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively.

No clinically significant changes from baseline through Week 48 were observed for TmP/GFR, $FEPO_4$, or FEUA.

Adverse Events

At least 1 AE was reported for 5 Cohort 2 ART-naive subjects, any Grade 2, 3, or 4 AE was reported in 3 subjects, and a Grade 2 AE considered related to study drug by the investigator was reported in 1 subject. No SAEs, Grade 3 or 4 AEs, or AEs leading to study drug discontinuation were reported for this cohort, and no individual AE occurred in > 1 subject. No subjects died during this study.

Bone Safety

No fracture events occurred in Cohort 2 ART-naive subjects. Mean (SD) percentage changes from baseline were observed in hip BMD (Week 24: 0.022% [1.6853]; Week 48: −0.222% [2.3207]) and spine BMD (Week 24: −2.686 [4.5755]; Week 48: −4.538 [6.8917]) for subjects after switching to E/C/F/TAF. Change from baseline for hip and spine BMD was < 3% in Cohort 2 (ART naive). Overall, few subjects had changes from baseline in hip and spine BMD clinical status.

Ocular Safety

No Cohort 2 ART-naive subjects had an AE reported in the SOC of eye disorders.

Laboratory Abnormalities

There were no clinically significant changes from baseline in median values for hematology or clinical chemistry parameters through Week 48. The majority of reported laboratory abnormalities were Grade 1 or Grade 2. One Grade 3 (amylase) and 1 Grade 4 (creatine kinase) laboratory abnormality was observed in a single Cohort 2 ART naive subject, neither of which was reported as an AE.

Metabolic Laboratory Parameters

Among the 6 ART-naive subjects in Cohort 2, no Grade 3 to 4 fasting total cholesterol, triglycerides, or LDL abnormalities were reported. Four subjects had Grade 1 and 2 subjects had Grade 2 hypercholesterolemia. No subjects had graded triglyceride values. Two subjects had Grade 1 and 3 subjects had Grade 2 increased fasting LDL. One subject had Grade 2 fasting hyperglycemia and 1 subject had Grade 1 fasting hypoglycemia). One subject had an AE of hyperlipidemia considered related to study drug by the investigator.

Other Outcome Measures:

Most subjects did not require hospitalization, unplanned visits for a healthcare issue, or unplanned specialty care provider visits. No clinically meaningful trends or changes at any assessment time point were observed.

CONCLUSIONS:

The interim Week 24 conclusions from this study are as follows:

- Cohort 1 subjects who switched treatment to E/C/F/TAF maintained virologic suppression and had increases in CD4 counts.
- The PK of the individual components of E/C/F/TAF in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min was consistent with historical and concurrent data on these agents.
- While TFV PK was higher in subjects with mild and moderate renal impairment, TFV exposures were well below those in patients with severe renal impairment and were well below the TFV exposures from TDF-containing regimens.
- Despite higher FTC PK in this study, once daily administration of E/C/F/TAF without dose adjustment in subjects with baseline $eGFR_{CG} < 50$ mL/min did not have a different safety profile compared with subjects with baseline $eGFR_{CG} < 50$ mL/min and despite Emtriva® dose recommendations, E/C/F/TAF does not require dose adjustment in patients with $eGFR_{CG} \geq 30$ to < 50 mL/min.
- Cohort 1 switch subjects had no change in aGFR through 24 weeks, regardless of baseline $eGFR_{CG}$ or pre-switch TDF use.
- E/C/F/TAF was generally well tolerated, with no on-study deaths and low rates of SAEs, discontinuations of study drug due to AEs, and AEs considered related to study drug by the investigator.
- No notable changes from baseline in median values for hematology, clinical chemistry, or liver related laboratory parameters were observed in either cohort through Week 48, and the majority of reported laboratory abnormalities were Grade 1 or 2.

- Median changes from baseline in metabolic laboratory parameters at Weeks 24 and 48 demonstrated a trend toward increase in all parameters for subjects who received TDF at baseline and a trend toward decrease in most parameters for subjects who did not receive TDF at baseline.
- The rate of study drug discontinuation due to renal AEs was low, and no AEs of PRT (including Fanconi Syndrome) were reported.
- No clinically significant effects of E/C/F/TAF on serum creatinine or cystatin C estimates of glomerular function in Cohort 1 switch and Cohort 2 ART-naive subjects were observed.
- Multiple assessments of renal function 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, including significant improvements in proteinuria, albuminuria, tubular proteinuria, and FEUA. No notable trends in changes from baseline through Week 48 were observed for TmP/GFR, $FEPO_4$, urine FEUA, or urine creatinine.
- There were decreases in clinically significant proteinuria (UPCR > 200 mg/g) or albuminuria (UACR ≥ 30 mg/g) through Week 48 in a notable proportion of subjects.
- These improvements in renal function observed after switch to E/C/F/TAF may be of substantial clinical significance for HIV-infected patients taking lifelong ARV therapy and accumulating age-related comorbidities.
- Switch to E/C/F/TAF generally resulted in improvements in BMD over 24 and/or 48 weeks. No fragility fractures were reported.
- E/C/F/TAF may be administered once daily without dose adjustment in patients with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min), and after switching to E/C/F/TAF, rapid, clinically significant improvements in renal and bone safety occur.

1.1.4.1.2. ART-Naive Adolescent Subjects in Study GS-US-292-0106

A complete study description and results for Study GS-US-292-0106 are available in the CSR (GS-US-292-0106 Interim CSR), and a brief narrative of this study is presented below.

Title of Study: A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents

Objectives: Study GS-US-292-0106 is being conducted to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF in HIV-infected, ART-naive adolescents.

The primary objectives of this ongoing study are as follows:

Part A:

- To evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC in HIV-infected, ART-naive adolescents

Part B:

- To evaluate the safety and tolerability of the E/C/F/TAF FDC through Week 24 in HIV-infected, ART-naive adolescents

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of the E/C/F/TAF FDC through Week 48 in HIV-infected, ART-naive adolescents

- To evaluate the antiviral activity of the E/C/F/TAF FDC through Week 48 in HIV-infected, ART-naive adolescents

The current report (interim Week 24 analysis) describes the results of the study through the date when all subjects enrolled by [redacted] 20[redacted] had completed their Week 24 visit.

Acceptability and palatability assessments are also being conducted as a part of the study; those results will be presented in a future CSR.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were HIV-infected, ART-naive adolescents, 12 to < 18 years of age, weight ≥ 35 kg, with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell counts > 100 cells/μL, and eGFR ≥ 90 mL/min/1.73 m^2 (as calculated using the Schwartz formula) at screening, with no prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother to child transmission) and sensitivity to TFV, EVG, and FTC as demonstrated by HIV-1 genotyping at screening.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of 63 screened subjects, 48 were enrolled into the study (24 in Part A and 24 in Part B) and received at least 1 dose of E/C/F/TAF.

At the time of the interim Week 24 analysis, 2.1% (1 subject) had completed the main phase of the study (ie, 48 weeks), and 97.9% (47 subjects) were still on study. The subject who completed the main phase of the study entered into the extension phase and was receiving study drug.

In the Safety Analysis Set, 58.3% of subjects were female. The median age of subjects was 15 years (range: 12 to 17); all of the subjects were either black (87.5%), or Asian (12.5%), and none were Hispanic or Latino.

The median (Q1, Q3) body weight of subjects at baseline was 52.0 (40.5, 60.5) kg; and the median (Q1, Q3) baseline Z-score for weight was −0.37 (−1.12, 0.47). The median (Q1, Q3) baseline height was 157.3 (147.2, 166.7) cm; and the median (Q1, Q3) baseline Z-score for height was −0.81 (−1.81, 0.05). The median (Q1, Q3) value for BMI at baseline was 20.0 (18.1, 23.2) kg/m^2, and the median (Q1, Q3) baseline eGFR calculated using the Schwartz and modified Schwartz formulas was 157.5 (133.0, 187.0) mL/min/1.73 m^2 and 110.9 (95.8, 118.8) mL/min/1.73 m^2, respectively. For males, the most frequently observed stage for pubic hair and

genitalia was Tanner Stage 5 (45.0% each). For females, the most frequently observed stages for pubic hair were Tanner Stages 3 and 5 (25.0% each); and the most frequently observed Tanner stage for breasts was Stage 5 (32.1%).

The median (Q1, Q3) baseline HIV-1 RNA value was 4.65 (4.24, 4.94) $\log_{10}$ copies/mL. Overall, 20.8% of subjects had baseline HIV-1 RNA > 100,000 copies/mL. Median (Q1, Q3) baseline CD4 cell count was 452 (326, 563) cells/μL; 64.6% of subjects had CD4 cell counts < 500 copies/mL, and 27.1% had CD4 cell counts < 350 copies/mL. The median (Q1, Q3) CD4% was 23.0% (17.3, 30.3). The most common risk factor for HIV infection was vertical transmission (66.7%), followed by heterosexual sex (20.8%), and homosexual sex (12.5%). The majority of subjects (83.3%) had asymptomatic HIV-1 infection. None of the subjects were hepatitis B virus (HBV) surface antigen positive. One subject (2.1%) was hepatitis C virus (HCV) antibody positive at baseline, but had a negative confirmatory HCV polymerase chain reaction result.

Efficacy Results: At the interim Week 24 analysis, the virologic success rate was 91.3% (21 of 23 subjects in the Week 24 FAS) for HIV-infected, ART-naive adolescents receiving E/C/F/TAF (assessed using the FDA snapshot algorithm with a cutoff of HIV-1 RNA < 50 copies/mL). 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.

HIV-1 RNA outcomes were similar for the M = F (Week 24 FAS) and M = E (FAS) analyses. At Week 24, 91.3% had HIV-1 RNA < 50 copies/mL, and 95.7% had HIV-1 RNA < 400 copies/mL.

HIV-1 RNA levels decreased following initiation of E/C/F/TAF (FAS), with a mean (SD) decrease of 3.16 (0.511) $\log_{10}$ copies/mL by Week 8. At Week 24, the mean (SD) change from baseline in HIV-1 RNA was −3.34 (0.679) $\log_{10}$ copies/mL.

No subject met the protocol-specified criteria for postbaseline resistance analysis (suboptimal virologic response or virologic rebound); thus, there was no evidence of virologic resistance to E/C/F/TAF in any subject.

CD4 cell count and percentage increased following initiation of study drug, and continued to increase with increased duration of exposure to study drug (FAS). Mean (SD) baseline CD4 cell count was 468 (215.4) cells/μL, and at Week 24, the mean (SD) change from baseline in CD4 cell count was 212 (144.3) cells/μL. Mean (SD) baseline CD4% was 23.5% (8.93%), and at Week 24, the mean (SD) change from baseline in CD4% was 7.2% (4.97%).

Pharmacokinetics Results: The PK parameters for EVG, TAF, TFV, COBI, and FTC were analyzed for the 24 subjects enrolled in Part A; statistical comparisons were performed of PK data from adolescents who received E/C/F/TAF in Part A of this study and combined PK data from the adult comparator.

Table 6. E/C/F/TAF Study GS-US-292-0106: Statistical Comparisons of EVG, TAF, TFV, COBI, and FTC PK Parameter Estimates Between Adolescents and Adults (PK Analysis Sets)

PK Parameter	GLSMs		GLSM Ratio (%)	90% CI
	GS-US-292-0106 (Test) (N = 24)	GS-US-292-0102, GS-US-292-0103 (Reference) (N = 52)		
EVG				
AUC_{tau} (ng*h/mL)	23128.88	21865.51	105.78	94.66, 118.21
C_{max} (ng/mL)	2186.24	2023.29	108.05	97.87, 119.30
C_{trough} (ng/mL)	234.44	338.24	69.31	52.79, 91.01
TAF				
AUC_{last} (ng*h/mL)	159.50	225.53	70.72	56.12, 89.11
C_{max} (ng/mL)	135.19	173.97	77.71	59.88, 100.85
TFV				
AUC_{tau} (ng*h/mL)[a]	282.64	322.64	87.60	81.23, 94.47
C_{max} (ng/mL)	17.18	18.78	91.50	83.93, 99.75
C_{trough} (ng/mL)	9.73	11.20	86.94	79.73, 94.81
COBI				
AUC_{tau} (ng*h/mL)[a]	7762.56	9832.00	78.95	68.68, 90.75
C_{max} (ng/mL)	1144.60	1456.27	78.60	69.71, 88.62
C_{trough} (ng/mL)[b,c]	13.42	22.21	60.41	39.13, 93.26
FTC				
AUC_{tau} (ng*h/mL)	14,007.48	11,964.30	117.08	106.68, 128.49
C_{max} (ng/mL)	2209.14	1947.42	113.44	103.49, 124.35
C_{trough} (ng/mL)[a]	94.98	97.42	97.49	83.42, 113.94

a N = 23 for the Test group
b N = 15 for the Test group
c N = 51 for the Reference group
Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 51.1, 51.2, 51.3, 51.4 and 51.5

The 90% CIs of the GLSM ratios for EVG AUC_{tau} and C_{max} were contained within the predefined equivalence boundaries of 70% to 143%, indicating that exposure of EVG in adolescents receiving E/C/F/TAF was comparable with that in adult subjects. Additionally, EVG C_{trough} was above the protein binding-adjusted concentration that resulted in 95% inhibition (IC_{95}) (44.5 ng/mL) in all adolescent subjects. TAF AUC_{last} and C_{max} following E/C/F/TAF administration to adolescents in this study were 29.28% and 22.29% lower, respectively, than exposure in the adult comparator, which was based on available adult PK data. These differences were not considered clinically relevant, as the TAF exposure observed in adolescents was consistent with the range of exposure associated with antiviral activity in adults. Moreover, the 90% CI of the GLSM ratios for TFV AUC_{tau}, C_{max}, and C_{trough} were contained within the predefined equivalence boundaries of 70% to 143%. TFV exposure in adolescents following E/C/F/TAF administration was approximately 90% lower compared with TFV exposure in adults following STB administration and coadministration of TDF with boosted PIs. The 90% CIs of

the GLSM ratios for FTC AUC_{tau}, C_{max}, and C_{trough} were contained within the predefined equivalence boundaries of 70% to 143%. COBI AUC_{tau}, C_{max}, and C_{trough} in adolescents were 21.05%, 21.40%, and 39.59% lower, respectively, compared with the adult comparator; however, they were in the range of exposure observed in historical studies that was associated with a robust pharmacodynamic effect (boosting), which is the function of COBI in E/C/F/TAF.

Safety Results: E/C/F/TAF was well tolerated by the 48 HIV-infected, ART-naive adolescents in this study, through a median duration of exposure of 12.1 weeks. Overall, 47.9% (23 subjects) had received study drug for ≥ 24 weeks. One or more AEs were reported for most subjects (81.3%; 39 of 48 subjects), most of which were Grade 1 or 2 in severity. The most common AEs were nausea (22.9%, 11 subjects), upper respiratory tract infection (20.8%, 10 subjects), and diarrhea (16.7%, 8 subjects). Eighteen subjects (37.5%) had an AE considered related to study drug by the investigator, most of which were Grade 1 in severity. Four subjects (8.3%) had a Grade 3 or 4 AE. Study drug-related AEs that occurred in > 1 subject were either gastrointestinal, including nausea (20.8%, 10 subjects), abdominal pain (12.5%, 6 subjects), vomiting (10.4%, 5 subjects), upper abdominal pain (6.3%, 3 subjects), and diarrhea (6.3%, 3 subjects), or nervous system disorders, including somnolence (6.3%, 3 subjects), dizziness (4.2%, 2 subjects), and headache (4.2%, 2 subjects). Four subjects (8.3%) had a SAE. One subject had Grade 2 visual impairment and uveitis reported as SAEs considered related to study drug by the investigator that resolved while study drug continued. No subject had an AE that led to study drug discontinuation, and there were no deaths.

Prespecified AEs of interest were selected renal events and bone fractures. One subject had urinary retention of 6 days' duration reported as an SAE considered unrelated to study drug by the investigator; study drug dosing was not interrupted. No subject had a bone fracture.

The median (Q1, Q3) change from baseline in serum creatinine was 0.06 (0.00, 0.13) mg/dL at Week 1 (baseline median [Q1, Q3], 0.57 [0.50, 0.71] mg/dL). Creatinine subsequently stabilized without progressive changes; median (Q1, Q3) change from baseline at Week 24 was 0.08 (0.04, 0.17) mg/dL. No graded abnormalities of serum creatinine were reported.

The median (Q1, Q3) change from baseline in eGFR (calculated using the Schwartz formula) at Week 1 was −14.0 (−27.0, −1.0) mL/min/1.73 m^2 (baseline median [Q1, Q3], 157.5 [133.0, 187.0] mL/min/1.73 m^2). The median (Q1, Q3) change from baseline at Week 24 was −20.0 (−32.0, −12.0) mL/min/1.73 m^2.

No AEs of decreased eGFR or renal failure were reported.

The median (Q1, Q3) change from baseline in cystatin C at Week 24 was −0.10 (−0.16, −0.04) mg/L (baseline median [Q1, Q3], 0.74 [0.68, 0.82] mg/L.

At baseline, 4.2% (2 of 48 subjects) had Grade 1 or Grade 2 proteinuria as assessed by dipstick analysis. Postbaseline, treatment-emergent Grade 1 or Grade 2 proteinuria, generally isolated and transient, was reported for 20.8% (10 of 48 subjects). Proteinuria was not reported as an AE for any subject.

There were no clinically meaningful changes from baseline in proteinuria, as assessed by UPCR (median [Q1, Q3]: baseline, 86.14 [41.49, 139.29] mg/g; percentage change from baseline at Week 24, 9.29% [−27.59%, 47.83%]). A reduction from baseline was observed at Week 24 in the urine beta-2-microglobulin to creatinine ratio, an exploratory marker of renal tubular proteinuria (median [Q1, Q3]: baseline, 179.16 [92.31, 264.71] μg/g; percentage change from baseline at Week 24, −44.61% [−72.46%, −21.00%]). No clinically meaningful change from baseline in urine RBP to creatinine ratio, TmP/GFR, $FEPO_4$, or FEUA was observed through Week 24.

No subject had laboratory findings consistent with PRT.

Mean and median baseline values and percentage changes from baseline at Week 24 in spine and TBLH BMD are shown in the following table.

Table 7. E/C/F/TAF Study GS-US-292-0106: Baseline Value and Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD at Week 24 (Spine and TBLH DXA Analysis Sets)

	Spine (N = 23)		TBLH (N = 23)	
Time Point	**Mean (SD)**	**Median (Q1, Q3)**	**Mean (SD)**	**Median (Q1, Q3)**
Baseline (g/cm^2)	0.779 (0.2102)	0.778 (0.677, 0.838)	0.872 (0.1305)	0.856 (0.805, 0.935)
% Change at Week 24	1.726 (4.2840)	2.773 (−1.182, 4.557)	0.772 (2.5631)	0.340 (−1.228, 2.122)

Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 36.1 and 36.2

At Week 24, 2 of 23 subjects (8.7%) had a ≥ 4% decrease in spine BMD; no subject had a ≥ 4% decrease in TBLH BMD.

Baseline height-age adjusted spine and TBLH BMD Z-scores were higher than unadjusted Z-scores (consistent with the below average height of the study population). Baseline and changes from baseline in spine and TBLH height-age adjusted BMD Z-scores at Week 24 are shown in the following table.

Table 8. E/C/F/TAF Study GS-US-292-0106: Spine and Total-Body-Less-Head Height-Age Adjusted BMD Z-Scores at Baseline and Change from Baseline at Week 24 (Spine and TBLH DXA Analysis Sets)

	Spine BMD Z-Score (Height-Age Adjusted) (N = 21)		TBLH BMD Z-Score (Height-Age Adjusted) (N = 20)	
	Mean (SD)	**Median (Q1, Q3)**	**Mean (SD)**	**Median (Q1, Q3)**
Baseline	–0.84 (1.201)	–0.75 (–1.86, 0.09)	–0.44 (1.007)	–0.66 (–1.24, 0.48)
Change from Baseline at:				
Week 24	–0.08 (0.391)	–0.02 (–0.15, 0.13)	–0.10 (0.256)	–0.09 (–0.26, 0.10)

Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 37.3 and 37.4

An increase in serum PTH was observed; the median (Q1, Q3) values at baseline and Week 24 were 35.8 (28.6, 53.7) and 44.3 (35.7, 52.0) pg/mL, respectively; the median (Q1, Q3) percentage change from baseline at Week 24 was 33.4% (12.6%, 60.6%).

There were no clinically relevant changes from baseline in median values for any hematology or clinical chemistry parameter. Increases from baseline in the following fasting lipid parameters were observed at Week 24 (median [Q1, Q3] change from baseline: fasting total cholesterol, 34 [22, 41] mg/dL; fasting LDL cholesterol, 18 [5, 30] mg/dL; and fasting HDL cholesterol, 10 [4, 21] mg/dL).

Most subjects had at least 1 treatment-emergent laboratory abnormality reported during the study (81.3%, 39 of 48 subjects). The majority of abnormalities reported were Grade 1 or 2 in severity. Excluding Grade 3 hematuria detected by nonquantitative dipstick analysis, Grade 3 laboratory abnormalities were reported for 4 subjects. Grade 3 decreased neutrophils were reported for 3 subjects. One subject had transient Grade 3 hematuria following quantitative analysis. None of these laboratory abnormalities was reported as an AE.

CONCLUSIONS:

The interim Week 24 conclusions from this study are as follows:

- Based on PK analyses, the dose of E/C/F/TAF (150/150/200/10 mg) is appropriate for adolescent use. Specifically:
  - EVG exposure in adolescents administered E/C/F/TAF was similar to that in adults.
  - TAF exposure in adolescents was consistent with the range of exposure associated with antiviral activity in adults, despite being lower than that in the adult comparator.
  - TFV exposure in adolescents was similar to that in adults.
  - FTC exposure in adolescents was consistent with adult data.
  - COBI exposure in adolescents was lower compared with the adult comparator, but was consistent with the totality of historical data and in the range of exposure associated with robust pharmacoenhancement (boosting).
- Nearly all ART-naive adolescents who received E/C/F/TAF achieved virologic suppression to < 50 copies/mL at Week 24 (91.3% virologic success rate), further confirming the E/C/F/TAF 150/150/200/10 mg dose in adolescents.
- There was evidence of a robust immunological response to E/C/F/TAF in treatment-naive adolescents. Mean (SD) CD4 cell count and CD4% were 639 (254.0) cells/μL and 29.6% (9.54%), respectively, at Week 24, representing mean (SD) increases from baseline of 212 (144.3) cells/μL and 7.2% (4.97%), respectively.

- E/C/F/TAF was well tolerated, as evidenced by the low incidence of SAEs and the absence of AEs leading to discontinuation of study drug.

- The lack of notable changes from baseline in height-age adjusted spine and TBLH BMD Z-scores at Week 24 indicates that subjects mineralized bone at rates consistent with those of the reference population. Few subjects experienced a clinically relevant decrease from baseline in BMD at Week 24.

- Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration.

1.2. Overall Extent of Exposure

In the E/C/F/TAF studies, a total of 2573 subjects received at least 1 dose of E/C/F/TAF (150/150/200/10 mg), including 2121 subjects in E/C/F/TAF Phase 3 studies, 273 subjects in the E/C/F/TAF Phase 2 study (including the randomized phase and open-label extension), and 179 subjects in the E/C/F/TAF Phase 1 studies (Table 1 and Table 2).

In the D/C/F/TAF Phase 2 study, a total of 103 subjects received at least 1 dose of D/C/F/TAF (Table 1). In the D/C/F/TAF Phase 1 study a total of 65 subjects received at least 1 dose of D/C/F/TAF (Table 2).

In the TAF and F/TAF Phase 1 studies, a total of 667 subjects received at least 1 dose of TAF as a single agent or part of an FDC (F/TAF or E/C/F/TAF) (Table 2).

Disposition for subjects in the E/C/F/TAF Phase 2 and Phase 3 studies and the D/C/F/TAF Phase 2 study is described in m2.7.3, Section 3.1.1.

1.2.1. E/C/F/TAF Studies

Table 9 presents the duration of exposure to study drug in the E/C/F/TAF Phase 2 and Phase 3 studies. Across the Phase 2 and Phase 3 studies, a total of 2394 subjects have received E/C/F/TAF with a median (Q1, Q3) exposure of 48.1 weeks (42.3, 60.0). 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 (Study GS-US-292-0109), and subjects with mild to moderate renal impairment (Study GS-US-292-0112). The median (Q1, Q3) exposure was shorter in adolescent subjects in Study GS-US-292-0106 compared with the studies in adults (12.1 [4.1, 32.1] weeks); 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.

In the open-label extension phase of Study GS-US-292-0102, the median (Q1, Q3) duration of exposure for the E/C/F/TAF group in the All E/C/F/TAF analysis was 105.3 (98.0, 108.1) weeks, with the majority of subjects completing 96 weeks of treatment (92.0%, 103 subjects).

Table 9. E/C/F/TAF Studies 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: Duration of Exposure to Study Drug (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	
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)	Total E/C/F/TAF (N=2233)
Total Exposure to Study Drug (weeks)										
N	866	867	112	58	959	477	242	6	48	2394[b]
Mean (SD)	53.6 (12.54)	52.7 (13.10)	60.8 (12.94)	62.0 (9.16)	46.7 (10.46)	45.9 (11.79)	41.7 (11.03)	42.5 (5.74)	19.2 (15.14)	49.4 (17.93)[b]
Median	49.9	49.1	61.6	61.1	48.0	48.0	43.1	42.8	12.1	48.1[b]
Q1, Q3	47.6, 60.3	47.3, 60.3	60.0, 66.4	60.0, 67.4	42.3, 50.3	42.1, 50.1	36.1, 48.0	36.1, 48.1	4.1, 32.1	42.3, 60.0[b]
Min, Max	0.1, 78.7	0.1, 77.1	3.3, 76.9	25.1, 72.7	1.7, 70.4	0.3, 65.0	4.9, 71.9	35.9, 49.4	1.0, 60.0	0.1, 120.1[b]
Total Exposure to Study Drug										
>= 4 Weeks (28 days)	859 (99.2%)	857 (98.8%)	111 (99.1%)	58 (100.0%)	958 (99.9%)	472 (99.0%)	242 (100.0%)	6 (100.0%)	44 (91.7%)	2220 (99.4%)
>= 8 Weeks (56 days)	855 (98.7%)	854 (98.5%)	110 (98.2%)	58 (100.0%)	958 (99.9%)	471 (98.7%)	240 (99.2%)	6 (100.0%)	31 (64.6%)	2200 (98.5%)

	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	
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)	Total E/C/F/TAF (N=2233)
>= 12 Weeks (84 days)	853 (98.5%)	849 (97.9%)	109 (97.3%)	58 (100.0%)	955 (99.6%)	471 (98.7%)	235 (97.1%)	6 (100.0%)	26 (54.2%)	2184 (97.8%)
>= 16 Weeks (112 days)[c]	850 (98.2%)	845 (97.5%)	107 (95.5%)	58 (100.0%)	–	–	233 (96.3%)	6 (100.0%)	23 (47.9%)	1219 (95.7%)
>= 24 Weeks (168 days)	842 (97.2%)	832 (96.0%)	106 (94.6%)	58 (100.0%)	919 (95.8%)	449 (94.1%)	222 (91.7%)	6 (100.0%)	23 (47.9%)	2118 (94.8%)
>= 36 Weeks (252 days)[d]	830 (95.8%)	819 (94.5%)	106 (94.6%)	57 (98.3%)	864 (90.1%)	417 (87.4%)	189 (78.1%)	5 (83.3%)	14 (29.2%)	2008 (89.9%)
>= 48 Weeks (336 days)	620 (71.6%)	618 (71.3%)	105 (93.8%)	54 (93.1%)	502 (52.3%)	239 (50.1%)	67 (27.7%)	2 (33.3%)	1 (2.1%)	1297 (58.1%)
>= 60 Weeks (420 days)	351 (40.5%)	328 (37.8%)	95 (84.8%)	46 (79.3%)	158 (16.5%)	85 (17.8%)	19 (7.9%)	0	1 (2.1%)	624 (27.9%)
>= 72 Weeks (504 days)[e]	96 (11.1%)	91 (10.5%)	8 (7.1%)	4 (6.9%)	—	—	—	—	—	—

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.
If the last dose date was completely missing, or only the year was known, or for subjects still on study drug, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date; in case of the last study drug end date was nonmissing, then it was used to impute the last dose date.

a Includes subjects in the randomized phase of Study GS-US-292-0102; 161 subjects in the open-label extension are not presented in this column. One hundred three of 112 subjects (92.0%) in the E/C/F/TAF group completed > 96 weeks of treatment with E/C/F/TAF.
b N includes 161 subjects who received E/C/F/TAF in the open-label phase of Study GS-US-292-0102 (53 subjects who switched from STB in the randomized phase and 108 subjects who rolled over from the D/C/F/TAF Phase 2 Study GS-US-299-0102). Descriptive statistics were calculated using N = 2394 that includes these 161 subjects.
c Exposure data for >= 16 weeks were not summarized for Study GS-US-292-0109.
d At 32 weeks (224 days) for Studies GS-US-292-0102 and GS-US-292-0106
e Exposure data for ≥ 72 weeks were not available for Studies GS-US-292-0109, GS-US-292-0112 and GS-US-292-0106

Source: E/C/F/TAF ISS, Tables 4 and Req6863.5; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 7.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 7; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 7; GS-US-292-0106 Interim CSR, Section 15.1, Table 6

1.2.2. D/C/F/TAF Study

In the D/C/F/TAF Phase 2 Study GS-US-299-0102, the median (Q1, Q3) duration of exposure for the D/C/F/TAF group was 68.0 (65.4, 72.7) weeks, with the majority of subjects (>80%) completing ≥ 60 weeks of treatment (m5.3.5.1, GS-US-299-0102 Final CSR, Section 11.1).

1.3. Demographic and Other Characteristics of Study Population

1.3.1. Summary of Demographic and General Baseline Characteristics

1.3.1.1. E/C/F/TAF Studies

In the Phase 2 and Phase 3 E/C/F/TAF clinical studies, demographic and general baseline characteristics were generally similar between treatment groups within each randomized study (Table 10). The median ages of adult subjects with normal renal function who were ART-naive or virologically suppressed were generally similar (range: 33 to 41 years). Subjects with mild to moderate renal impairment in Study GS-US-292-0112 were older, with a median age of 58 years in Cohort 1 (range: 24 to 82). Across the E/C/F/TAF studies, a total of 97 subjects were ≥ 65 years of age. The median age of adolescent subjects in Study GS-US-292-0106 was 15 years (range: 12 to 17).

Women comprised approximately 15% of the ART-naive population in the E/C/F/TAF pivotal studies (Studies GS-US-292-0104 and GS-US-292-0111), approximately 11% of the virologically suppressed population in Study GS-US-292-0109, approximately 20% of the population with mild to moderate renal impairment in Study GS-US-292-0112. The adolescent study (Study GS-US-292-0106) included 28 female subjects (58.3%). Across the E/C/F/TAF Phase 2 and Phase 3 studies of adult subjects, most subjects were white (range: 56.0% to 69.0%) and black (range: 17.6% to 31.3%), and approximately 15% to 25% subjects were Hispanic or Latino. Of the adolescent subjects, 87.5% were black and 12.5% were Asian, and none were Hispanic or Latino. The median BMI was generally similar across all studies (approximately 25 kg/m^2), except for adolescent subjects in Study GS-US-292-0106 (median [Q1, Q3] BMI 20.0 [18.1, 23.2] kg/m^2).

Table 10. E/C/F/TAF Studies 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: Demographic and Baseline Characteristics (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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Age (Years)									
N	866	867	112	58	959	477	242	6	48
Mean (SD)	35 (10.4)	36 (10.7)	35 (11.3)	37 (10.6)	41 (10.1)	41 (10.1)	58 (9.9)	55 (7.1)	15 (1.9)
Median	33	35	34	38	41	40	58	54	15
Q1, Q3	26, 42	28, 44	26, 43	26, 46	33, 48	33, 48	52, 65	49, 59	13, 17
Min, Max	18, 74	18, 76	18, 71	20, 55	21, 77	22, 69	24, 82	46, 65	12, 17
Sex									
Male	733 (84.6%)	740 (85.4%)	108 (96.4%)	57 (98.3%)	856 (89.3%)	427 (89.5%)	192 (79.3%)	6 (100%)	20 (41.7%)
Female	133 (15.4%)	127 (14.6%)	4 (3.6%)	1 (1.7%)	103 (10.7%)	50 (10.5%)	50 (20.7%)	0	28 (58.3%)
Race									
American Indian or Alaska Native	5 (0.6%)	8 (0.9%)	0	1 (1.7%)	5 (0.5%)	2 (0.4%)	1 (0.4%)	0	0
Asian	91 (10.5%)	89 (10.3%)	3 (2.7%)	1 (1.7%)	59 (6.2%)	35 (7.3%)	34 (14.0%)	1 (16.7%)	6 (12.5%)
Black	223 (25.8%)	213 (24.6%)	35 (31.3%)	16 (27.6%)	169 (17.6%)	102 (21.4%)	44 (18.2%)	3 (50.0%)	42 (87.5%)

	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Native Hawaiian or Pacific Islander	5 (0.6%)	4 (0.5%)	0	0	6 (0.6%)	1 (0.2%)	2 (0.8%)	0	0
White	485 (56.0%)	498 (57.4%)	74 (66.1%)	40 (69.0%)	651 (67.9%)	314 (65.8%)	152 (62.8%)	2 (33.3%)	0
Not Permitted	–	–	0	0	2 (0.2%)	1 (0.2%)	2 (0.8%)	0	0
Other	57 (6.6%)	55 (6.3%)	0	0	67 (7.0%)	22 (4.6%)	7 (2.9%)	0	0
Ethnicity									
Hispanic or Latino	167 (19.3%)	167 (19.3%)	25 (22.3%)	11 (19.0%)	248 (25.9%)	82 (17.2%)	31 (12.8%)	1 (16.7%)	0
Not Hispanic or Latino	698 (80.6%)	698 (80.6%)	87 (77.7%)	47 (81.0%)	709 (73.9%)	392 (82.2%)	209 (86.4%)	5 (83.3%)	48 (100.0%)
Not Permitted	1 (0.1%)	1 (0.1%)	0	0	2 (0.2%)	3 (0.6%)	2 (0.8%)	0	0
Missing	0	1	0	0	0	0	0	0	0
Region									
US	532 (61.4%)	532 (61.4%)	109 (97.3%)	56 (96.6%)	648 (67.6%)	316 (66.2%)	166 (68.6%)	5 (83.3%)	9 (18.8%)
ex-US	334 (38.6%)	335 (38.6%)	3 (2.7%)	2 (3.4%)	311 (32.4%)	161 (33.8%)	76 (31.4%)	1 (16.7%)	39 (81.3%)
Baseline Weight (kg)									

	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
N	866	867	112	58	959	477	242	6	48
Mean (SD)	77.2 (17.07)	77.6 (17.09)	80.4 (13.88)	79.0 (12.60)	82.0 (17.67)	82.7 (18.07)	70.2 (13.82)	69.9 (13.22)	51.9 (13.52)
Median	75.0	75.3	78.0	79.2	79.7	80.3	69.2	70.5	52.0
Q1, Q3	65.0, 86.8	65.3, 86.6	71.2, 89.3	71.2, 86.2	70.7, 90.7	71.7, 90.7	61.2, 78.3	56.5, 83.6	40.5, 60.5
Min, Max	40.5, 176.0	41.7, 152.4	56.0, 133.3	54.4, 112.5	36.2, 218.6	43.0, 185.3	37.8, 118.4	54.0, 84.0	35.0, 88.8
Baseline Height (cm)									
N	866	867	112	58	957	476	242	6	48
Mean (SD)	173.9 (9.46)	174.2 (9.30)	175.9 (8.21)	176.3 (8.19)	175.4 (9.13)	175.3 (8.90)	169.4 (9.22)	170.8 (6.93)	157.0 (12.93)
Median	175.3	175.3	175.3	177.8	176.0	175.7	170.1	168.9	157.3
Q1, Q3	169.0, 180.3	168.0, 180.3	170.2, 182.9	172.4, 182.9	170.2, 180.3	170.0, 180.3	164.0, 175.3	166.0, 177.8	147.2, 166.7
Min, Max	130.0, 198.1	142.2, 198.1	149.9, 193.0	152.4, 193.0	138.0, 204.0	142.2, 198.1	139.0, 190.5	162.6, 180.3	122.5, 182.0
Baseline Body Mass Index (kg/m^2)									
N	866	867	112	58	957	476	242	6	48
Mean (SD)	25.5 (5.23)	25.5 (5.12)	26.0 (4.31)	25.5 (4.41)	26.6 (5.29)	26.9 (5.34)	24.4 (4.12)	23.9 (4.03)	20.8 (3.24)
Median	24.4	24.5	25.6	25.1	25.8	26.1	24.1	23.6	20.0

	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Q1, Q3	22.0, 28.0	21.7, 28.0	23.1, 28.0	22.6, 27.5	23.1, 29.1	23.1, 29.4	21.4, 26.9	21.4, 25.7	18.1, 23.2
Min, Max	16.6, 71.0	16.6, 54.3	17.8, 46.0	18.2, 46.9	13.4, 65.4	16.2, 51.1	15.7, 39.8	18.6, 30.5	16.2, 31.8

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. Demographics and baseline characteristics for subjects in the open-label extension are summarized in Study GS-US-292-0102 Week 96 CSR, Section 8.

Source: E/C/F/TAF ISS, Table 2; GS-US-292-0102 Week 96 CSR, Section 15.1, Tables 1.1 and 5.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 1 and 5.1; GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 1 and 4.1; GS-US-292-0106 Interim CSR, Section 15.1, Tables 1 and 4.1

1.3.1.2. D/C/F/TAF Study

In the D/C/F/TAF Phase 2 study in ART-naive subjects, demographic and general baseline characteristics were generally similar between treatment groups (Table 11). The majority of subjects were male (92.8%), and the mean age was 35 years (range: 18 to 68). The most common races were white (60.1%) or black (34.6%) and the most common ethnicity was not Hispanic/Latino (79.1%).

Table 11. D/C/F/TAF Study GS-US-299-0102: Demographic and Baseline Characteristics (Safety Analysis Set)

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

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
For categorical data, p-value was from the Cochran-Mantel-Haenszel (CMH) test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 5

1.3.2. Summary of Baseline Disease Characteristics

1.3.2.1. E/C/F/TAF Studies

In the Phase 2 and Phase 3 E/C/F/TAF studies, baseline disease characteristics were generally similar between treatment groups within each randomized study (Table 12). The median baseline HIV-1 RNA value in ART-naive subjects (across all 5 E/C/F/TAF studies) was approximately 4.5 $\log_{10}$ copies/mL, and approximately 25% had baseline HIV-1 RNA > 100,000 copies/mL. Of virologically suppressed subjects in Studies GS-US-292-0109 and GS-US-292-0112, approximately 98% had baseline HIV-1 RNA < 50 copies/mL, and most subjects in the switch groups of Study GS-US-292-0102 also had baseline HIV-1 RNA values < 50 copies/mL (all TDF to TAF: 93.4%; D/C/F/TAF to E/C/F/TAF: 97.1%). Median baseline CD4 cell count was approximately 400 cells/μL in ART-naive subjects (across all 5 E/C/F/TAF studies) and approximately 650 cells/μL in virologically suppressed subjects (Studies GS-US-292-0109 and GS-US-292-0112). The most common HIV risk factor was homosexual sex (approximately 75% to 90%) across subjects who were ART-naive (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102) or virologically suppressed (Study GS-US-292-0109). Heterosexual sex and homosexual sex were approximately equal risk factors (approximately 50% each) for subjects with mild to moderate renal impairment (Study GS-US-292-0112), and vertical transmission was the most common HIV risk factor (66.7%) for adolescent subjects (Study GS-US-292-0106). Most subjects in each study had asymptomatic HIV-1 infection (approximately 75% to 90%; status was not collected at baseline in Study GS-US-292-0109).

The median baseline $eGFR_{CG}$ value was generally similar across ART-naive and virologically suppressed adult subjects (range: 105.7 to 117.0 mL/min). In subjects with mild to moderate renal impairment, the median (Q1, Q3) $eGFR_{CG}$ value was 55.6 (45.7, 62.4) mL/min among subjects who were virologically suppressed at baseline and 60.2 mL/min (45.0, 63.2) among subjects who were ART-naive. In ART-naive adolescent subjects, the median (Q1, Q3) eGFR calculated using the modified Schwartz formula was 110.9 (95.8, 118.8) mL/min/1.73 m^2.

Across the Phase 3 studies in adults with normal renal function, most subjects (>89%) had no proteinuria at baseline. In subjects with mild to moderate renal impairment, 9.5% of virologically suppressed subjects had Grade 2 proteinuria at baseline, and 23.1% of subjects had Grade 1 proteinuria at baseline. Among adolescent subjects, < 5% had proteinuria at baseline.

Table 12. E/C/F/TAF Studies 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: Baseline Disease Characteristics (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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
HIV-1 RNA (log_{10} copies/mL)									
N	866	867	112	58	—	—	242	6	48
Mean (SD)	4.54 (0.665)	4.53 (0.682)	4.63 (0.572)	4.69 (0.577)	—	—	1.32 (0.318)	4.66 (0.675)	4.62 (0.593)
Median	4.58	4.58	4.55	4.58	—	—	1.28	4.72	4.65
Q1, Q3	4.14, 4.95	4.15, 4.96	4.30, 4.89	4.35, 5.08	—	—	1.28, 1.28	4.01, 5.35	4.24, 4.94
Min, Max	2.57, 6.89	1.28, 6.98	3.11, 6.94	3.50, 6.44	—	—	1.28, 4.88	3.76, 5.39	3.25, 6.50
HIV-1 RNA Categories (copies/mL)									
<= 100,000	670 (77.4%)	672 (77.5%)	93 (83.0%)	42 (72.4%)	—	—	242 (100%)	4 (66.7%)	38 (79.2%)
> 100,000 to <= 400,000	147 (17.0%)	154 (17.8%)	14 (12.5%)	13 (22.4%)	—	—	0	2 (33.3%)	10 (20.8%)[b]
> 400,000	49 (5.7%)	41 (4.7%)	5 (4.5%)	3 (5.2%)	—	—	0	0	

	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
CD4 Cell Count (/uL)									
N	865	867	112	58	959	477	242	6	48
Mean (SD)	426 (215.6)	429 (219.6)	404 (181.6)	394 (209.6)	701 (261.8)	689 (248.0)	664 (286.4)	412 (244.0)	468 (215.4)
Median	404	406	385	397	675	662	632	397	452
Q1, Q3	283, 550	291, 542	283, 528	232, 535	520, 833	525, 831	456, 811	184, 673	326, 563
Min, Max	0, 1311	1, 1360	30, 897	2, 866	89, 1951	79, 1739	126, 1813	115, 708	95, 1110
CD4 Cell Count Categories (/uL)									
< 50	24 (2.8%)	27 (3.1%)	2 (1.8%)	1 (1.7%)	0	0	0	0	—
>= 50 to < 200	88 (10.2%)	90 (10.4%)	12 (10.7%)	10 (17.2%)	5 (0.5%)	4 (0.8%)	5 (2.1%)	2 (33.3%)	4 (8.3%)[c]
>= 200 to < 350	218 (25.2%)	200 (23.1%)	32 (28.6%)	14 (24.1%)	54 (5.6%)	25 (5.2%)	19 (7.9%)	0	9 (18.8%)
>= 350 to < 500	256 (29.6%)	284 (32.8%)	33 (29.5%)	17 (29.3%)	151 (15.7%)	70 (14.7%)	53 (21.9%)	2 (33.3%)	18 (37.5%)
>= 500	279 (32.3%)	266 (30.7%)	33 (29.5%)	16 (27.6%)	749 (78.1%)	378 (79.2%)	165 (68.2%)	2 (33.3%)	17 (35.4%)
Missing	1	0	0	0	0	0	0	0	0

	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Mode of Infection (HIV Risk Factors)									
Heterosexual Sex	210 (24.2%)	219 (25.3%)	16 (14.3%)	7 (12.1%)	216 (22.5%)	101 (21.2%)	99 (40.9%)	3 (50.0%)	10 (20.8%)
Homosexual Sex	652 (75.3%)	645 (74.4%)	100 (89.3%)	51 (87.9%)	753 (78.5%)	375 (78.6%)	126 (52.1%)	3 (50.0%)	6 (12.5%)
IV Drug Use	5 (0.6%)	6 (0.7%)	0	1 (1.7%)	9 (0.9%)	5 (1.0%)	2 (0.8%)	0	1 (2.1%)
Transfusion	2 (0.2%)	6 (0.7%)	0	0	2 (0.2%)	2 (0.4%)	5 (2.1%)	0	0
Vertical Transmission	2 (0.2%)	0	0	0	0	0	0	0	32 (66.7%)
Unknown	18 (2.1%)	27 (3.1%)	0	1 (1.7%)	17 (1.8%)	12 (2.5%)	13 (5.4%)	0	2 (4.2%)
Other	18 (2.1%)	9 (1.0%)	1 (0.9%)	0	8 (0.8%)	7 (1.5%)	2 (0.8%)	0	0
HIV Disease Status[e]									
Asymptomatic	780 (90.4%)	802 (92.9%)	99 (88.4%)	52 (89.7%)	—	—	180 (74.4%)	5 (83.3%)	40 (83.3%)
Symptomatic HIV Infection	53 (6.1%)	35 (4.1%)	9 (8.0%)	5 (8.6%)	—	—	28 (11.6%)	1 (16.7%)	8 (16.7%)
AIDS	30 (3.5%)	26 (3.0%)	4 (3.6%)	1 (1.7%)	—	—	34 (14.0%)	0	0
Unknown	3	4	0	0	—	—	0	0	0

	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
$eGFR_{CG}$ (mL/min)									
N	866	867	112	58	959	477	242	6	47
Mean (SD)	120.8 (30.87)	118.7 (30.73)	120.4 (30.77)	114.8 (23.72)	111.9 (33.39)	112.1 (32.70)	54.8 (11.64)	55.1 (11.73)	109.1 (17.18)[d]
Median	117.0	113.9	115.2	113.3	105.7	107.7	55.6	60.2	110.9[d]
Q1, Q3	99.6, 135.6	99.0, 133.6	100.8, 131.7	97.7, 129.4	89.4, 126.0	88.7, 128.2	45.7, 62.4	45.0, 63.2	95.8, 118.8[d]
Min, Max	33.7, 287.2	55.3, 320.2	72.6, 239.5	73.5, 176.8	48.0, 344.1	53.7, 304.8	26.2, 89.7	36.3, 65.5	77.5, 146.1[d]
Proteinuria by Urinalysis									
Grade 0	778 (89.8%)	780 (90.1%)	101 (90.2%)	55 (94.8%)	873 (91.1%)	430 (90.1%)	163 (67.4%)	5 (83.3%)	46 (95.8%)
Grade 1	80 (9.2%)	67 (7.7%)	10 (8.9%)	2 (3.4%)	81 (8.5%)	44 (9.2%)	56 (23.1%)	0	1 (2.1%)
Grade 2	8 (0.9%)	18 (2.1%)	1 (0.9%)	1 (1.7%)	4 (0.4%)	3 (0.6%)	23 (9.5%)	1 (16.7%)	1 (2.1%)
Grade 3	0	1 (0.1%)		0	0	0	0	0	0
Missing	0	1		0	1	0	0	0	0
Diabetes Mellitus[e]									
Yes	25 (2.9%)	40 (4.6%)	5 (4.5%)	1 (1.7%)	—	—	33 (13.6%)	0	NA[f]
No	841 (97.1%)	827 (95.4%)	107 (95.5%)	57 (98.3%)	—	—	209 (86.4%)	6 (100%)	NA[f]

	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Hypertension[e]									
Yes	118 (13.6%)	146 (16.8%)	14 (12.5%)	6 (10.3%)	—	—	95 (39.3%)	3 (50%)	NA[f]
No	748 (86.4%)	721 (83.2%)	98 (87.5%)	52 (89.7%)	—	—	147 (60.7%)	3 (50%)	NA[f]
Cardiovascular Disease[e]									
Yes	11 (1.3%)	14 (1.6%)	4 (3.6%)	1 (1.7%)	—	—	—	—	NA[f]
No	855 (98.7%)	853 (98.4%)	108 (96.4%)	57 (98.3%)	—	—	—	—	NA[f]
Hyperlipidemia[e]									
Yes	92 (10.6%)	100 (11.5%)	15 (13.4%)	6 (10.3%)	—	—	—	—	NA[f]
No	774 (89.4%)	767 (88.5%)	97 (86.6%)	52 (89.7%)	—	—	—	—	NA[f]

NA = not applicable
The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
Medical history characteristics (diabetes mellitus, hypertension, cardiovascular disease and hyperlipidemia) were determined by past medical history.

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. Baseline disease characteristics for subjects in the open-label extension are summarized in Study GS-US-292-0102 Week 96 CSR, Section 8.
b HIV-1 RNA >100,000 copies/mL for Study GS-US-292-0106
c CD4 cell count category of < 200/μL for Study GS-US-292-0106
d eGFR calculated using modified Schwartz formula (mL/min/1.73 m^2 for Study GS-US-292-0106
e Medical history data were presented in the original studies from which subjects were rolled over and were not summarized for Study GS-US-292-0109.
f Patients with diabetes, uncontrolled cardiac illness, and uncontrolled illness were excluded from Study GS-US-292-0106.

Source: E/C/F/TAF ISS, Table 3; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 6.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 6.1; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 5.1; GS-US-292-0106 Interim CSR, Section 15.1, Table 5.1

1.3.2.2. D/C/F/TAF Study

Baseline disease characteristics were similar between the 2 treatment groups of ART-naive subjects in the D/C/F/TAF Phase 2 Study GS-US-299-0102 (Table 13). The median baseline HIV-1 RNA value across both groups was 4.66 $\log_{10}$ copies/mL, and approximately 20% of subjects had baseline HIV-1 RNA > 100,000 copies/mL. Median CD4 count was 384 cells/μL. The most common HIV risk factor category was homosexual sex (84.3% of subjects). The majority of subjects (89.5%) had asymptomatic HIV-1 infection; 7.2% of subjects had symptomatic HIV-1 infection, and 3.3% of subjects were diagnosed with AIDS.

Values for $eGFR_{CG}$ were similar between the 2 treatment groups. Across both groups the median $eGFR_{CG}$ was 114.6 mL/min. Most subjects (90.2%) had no or trace proteinuria (Grade 0 by dipstick) on urinalysis.

Table 13. D/C/F/TAF Study GS-US-299-0102: Baseline Disease Characteristics (Safety Analysis Set)

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)	D/C/F/TAF vs DRV+COBI+TVD (p-value)
HIV-1 RNA ($\log_{10}$ copies/mL)				
N	103	50	153	0.39
Mean (SD)	4.70 (0.516)	4.65 (0.514)	4.68 (0.515)	
Median	4.67	4.58	4.66	
Q1, Q3	4.43, 4.93	4.28, 4.91	4.37, 4.91	
Min, Max	3.27, 6.12	3.59, 6.29	3.27, 6.29	
HIV-1 RNA Category (copies/mL)				
<= 100,000	80 (77.7%)	43 (86.0%)	123 (80.4%)	0.28
> 100,000 to <= 400,000	17 (16.5%)	5 (10.0%)	22 (14.4%)	
> 400,000	6 (5.8%)	2 (4.0%)	8 (5.2%)	
CD4 Cell Count (/uL)				
N	103	50	153	0.14
Mean (SD)	395 (169.3)	464 (261.6)	417 (205.7)	
Median	368	433	384	
Q1, Q3	270, 515	320, 606	283, 532	
Min, Max	7, 909	49, 1463	7, 1463	
CD4 Cell Count Category (/uL)				
< 50	1 (1.0%)	1 (2.0%)	2 (1.3%)	0.48
>=50 and <200	10 (9.7%)	9 (18.0%)	19 (12.4%)	
>=200 and <350	37 (35.9%)	8 (16.0%)	45 (29.4%)	
>=350 and <500	27 (26.2%)	12 (24.0%)	39 (25.5%)	
>= 500	28 (27.2%)	20 (40.0%)	48 (31.4%)	
CD4 Percentage (%)				
N	103	50	153	0.16
Mean (SD)	22.9 (8.14)	25.3 (9.95)	23.7 (8.81)	
Median	22.1	25.3	23.6	
Q1, Q3	17.4, 29.1	18.5, 31.1	17.6, 29.6	
Min, Max	1.0, 42.8	6.9, 49.7	1.0, 49.7	

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)	D/C/F/TAF vs DRV+COBI+TVD (p-value)
HIV Risk Factors				
Heterosexual Sex	19 (18.4%)	8 (16.0%)	27 (17.6%)	
Homosexual Sex	86 (83.5%)	43 (86.0%)	129 (84.3%)	
IV Drug Use	0	2 (4.0%)	2 (1.3%)	
Unknown	3 (2.9%)	0	3 (2.0%)	
Other	2 (1.9%)	2 (4.0%)	4 (2.6%)	
HIV Disease Status				
Asymptomatic	93 (90.3%)	44 (88.0%)	137 (89.5%)	0.39
Symptomatic HIV Infections	8 (7.8%)	3 (6.0%)	11 (7.2%)	
AIDS	2 (1.9%)	3 (6.0%)	5 (3.3%)	
$eGFR_{CG}$ (mL/min)				
N	103	50	153	0.17
Mean (SD)	119.6 (26.89)	115.7 (31.41)	118.3 (28.40)	
Median	116.0	109.6	114.6	
Q1, Q3	97.0, 137.6	92.5, 131.4	96.5, 132.3	
Min, Max	77.3, 223.0	73.7, 259.2	73.7, 259.2	
Proteinuria by Urinalysis (dipstick)				
Negative	69 (67.0%)	39 (78.0%)	108 (70.6%)	0.23
Trace	22 (21.4%)	8 (16.0%)	30 (19.6%)	
+1	9 (8.7%)	2 (4.0%)	11 (7.2%)	
+2	2 (1.9%)	0	2 (1.3%)	
+3	1 (1.0%)	1 (2.0%)	2 (1.3%)	

The denominator for percentages is based on the number of subjects in the Safety Analysis Set.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistics was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 6

1.4. Analysis Sets

1.4.1. E/C/F/TAF Studies

Safety Analysis Set

For ART-naive subjects in the E/C/F/TAF studies (GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), the Safety Analysis Set included all subjects who were randomized and received at least 1 dose of study drug (Table 14). For virologically suppressed subjects in Study GS-US-292-0109, data are presented primarily using the Week 48 Safety Analysis Set, which included all subjects who were randomized by [redacted] 20[redacted] and received at least 1 dose of study drug. For subjects with mild to moderate renal impairment (Study GS-US-292-0112), data are presented using the Week 48 Safety Analysis Set, which included all subjects who were enrolled on or prior to [redacted] 20[redacted] and received at least 1 dose of study drug. For adolescent subjects (Study GS-US-292-0106), data are presented primarily using the Week 24 Safety Analysis Set, which included all subjects who were enrolled by [redacted] 20[redacted] and received at least 1 dose of study drug.

The rationale for defining the analysis sets of Studies GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106 by the specified dates was to include the most current data from these subject populations in the initial marketing applications for E/C/F/TAF.

Subjects were grouped according to the treatment they actually received.

DXA Analysis Sets

For studies in ART-naive subjects (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), virologically suppressed subjects (Study GS-US-292-0109), and subjects with mild to moderate renal impairment (Study GS-US-292-0112) the Hip DXA Analysis Set included all randomized subjects who received at least 1 dose of study drug and had nonmissing baseline hip BMD values. The Spine DXA Analysis Set (all Phase 2 and Phase 3 studies in adults) included all randomized subjects who received at least 1 dose of study drug and had nonmissing baseline spine BMD values.

For adolescent subjects (Study GS-US-292-0106), the Spine DXA Analysis Set included all enrolled subjects who received at least 1 dose of study drug and had nonmissing baseline and at least 1 postbaseline spine BMD values. The TBLH DXA Analysis Set (Study GS-US-292-0106 only) included all enrolled subjects who received at least 1 dose of study drug and had nonmissing baseline and at least 1 postbaseline TBLH BMD values.

For the Hip, Spine, and TBLH DXA Analysis Sets, subjects were grouped according to the treatment they actually received. All data including data collected after the last dose of study drug were used for analysis, unless specified otherwise.

Other Analysis Sets

In ART-naive subjects in Study GS-US-292-0102, the All E/C/F/TAF Analysis Set included all subjects who received at least 1 dose of double-blinded E/C/F/TAF during the randomized phase and those subjects who received at least 1 dose of open-label E/C/F/TAF during the open-label extension phase. The All E/C/F/TAF Hip DXA Analysis Set included all subjects who had received at least 1 dose of E/C/F/TAF and had nonmissing baseline value for hip BMD. The All E/C/F/TAF Spine DXA Analysis Set included all subjects who had received at least 1 dose of E/C/F/TAF and had nonmissing baseline value for spine BMD.

In virologically suppressed subjects in Study GS-US-292-0109, the EFV-Related Symptom Analysis Set included all subjects who were on ATR at the time of randomization, received at least 1 dose of study drug, and completed EFV related symptom assessments at the baseline visit and at least 1 postbaseline visit. The Ophthalmologic Substudy Analysis Set included all subjects who participated in the ophthalmologic substudy, received at least 1 dose of study drug, and had nonmissing ophthalmologic assessment results for the baseline visit and at least 1 postbaseline visit.

Table 14. E/C/F/TAF Studies 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: Analysis Sets

	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
	E/C/F/TAF	STB	E/C/F/TAF	STB	E/C/F/TAF	FTC/TDF+ 3rd Agent	ART-Experienced E/C/F/TAF	ART-Naive E/C/F/TAF	E/C/F/TAF
Subjects Randomized/Enrolled	873	871	113	58	963	480	246	6	48
Subjects in Safety Analysis Set	866 (99.2%)	867 (99.5%)	112 (99.1%)	58 (100.0%)	959 (99.6%)	477 (99.4%)	242 (100%)	6 (100%)	48 (100.0%)
Subjects in Hip DXA Analysis Set	836 (95.8%)	848 (97.4%)	103 (91.2%)	57 (98.3%)	902 (93.7%)	452 (94.2%)	236 (97.5%)	6 (100%)	—
Subjects in Spine DXA Analysis Set	845 (96.8%)	850 (97.6%)	106 (93.8%)	58 (100.0%)	912 (94.7%)	457 (95.2%)	236 (97.5%)	6 (100%)	23 (47.9%)
Subjects in TBLH DXA Analysis Set	—	—	—	—	—	—	—	—	23 (47.9%)
Subjects in Efavirenz-Related Symptom Analysis Set	—	—	—	—	239 (24.8%)	116 (24.2%)	—	—	—
Subjects in Ophthalmologic Substudy Analysis Set	—	—	—	—	32 (3.3%)	15 (3.1%)	—	—	—
Subjects in All E/C/F/TAF Analysis Set	—	—	112	53[b]	—	—	—	—	—

	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
	E/C/F/TAF	STB	E/C/F/TAF	STB	E/C/F/TAF	FTC/TDF+ 3rd Agent	ART-Experienced E/C/F/TAF	ART-Naive E/C/F/TAF	E/C/F/TAF
Subjects in All E/C/F/TAF Hip DXA Analysis Set	—	—	103 (92.0%)	52 (98.1%)[b]	—	—	—	—	—
Subjects in All E/C/F/TAF Spine DXA Analysis Set	—	—	106 (94.6%)	53 (100.0%)[b]	—	—	—	—	—

The denominator for percentages is based on the number of subjects in the Randomized Analysis Set.

a Includes subjects in the randomized phase of Study GS-US-292-0102. A total of 266 subjects entered the extension phase of Study GS-US-292-0102 and received E/C/F/TAF, including 158 subjects from this study after completing the 48-week randomized phase (105 of whom continued on E/C/F/TAF and 53 of whom switched from STB to E/C/F/TAF) and 108 virologically suppressed subjects who rolled over from Study US-GS-299-0102.

b Subjects who switched from STB to E/C/F/TAF in the open-label extension. Not presented here are All TDF to TAF, DRV+COBI+TVD to E/C/F/TAF, and D/C/F/TAF to E/C/F/TAF (GS-US-292-0102 Week 96 CSR, Section 15.1, Table 4.1)

Source: E/C/F/TAF ISS, Tables 1, 20.1.2, and 20.2.2; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 4.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 4; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 3; GS-US-292-0106 Interim CSR, Section 15.1, Table 3

1.4.2. D/C/F/TAF Study

For ART-naive subjects in the D/C/F/TAF Phase 2 Study GS-US-299-0102, data are presented primarily using the Safety Analysis Set, which included all subjects who were randomized and received at least 1 dose of study drug (Table 15). The Spine and Hip DXA Analysis Sets included all subjects who had nonmissing spine and hip BMD values, respectively, for the baseline visit and ≥ 1 postbaseline visit. For these analysis sets, subjects were grouped by actual treatment received.

Table 15. D/C/F/TAF Study GS-US-299-0102: Analysis Sets Related to Safety

	D/C/F/TAF	DRV+COBI+TVD	Total
Subjects Randomized	103	50	153
Subjects in Safety Analysis Set	103 (100.0%)	50 (100.0%)	153 (100.0%)
Subjects in Spine DXA Analysis Set	86 (83.5%)	48 (96.0%)	134 (87.6%)
Subjects in Hip DXA Analysis Set	85 (82.5%)	48 (96.0%)	133 (86.9%)

The denominator for percentages was based on the number of subjects in the Randomized Analysis Set.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 4

2. ADVERSE EVENTS

This section provides an overall summary of AEs relevant for F/TAF, with the main focus on the E/C/F/TAF Phase 2 and Phase 3 studies in ART-naive adult subjects, virologically suppressed subjects, subjects with mild to moderate renal impairment, and ART-naive adolescent subjects, as well as supportive safety data from ART-naive subjects in the D/C/F/TAF Phase 2 study. Adverse events from the Phase 1 TAF, F/TAF, E/C/F/TAF, and D/C/F/TAF studies are not described in detail in this summary; deaths, SAEs, and AEs leading to discontinuation are summarized for all Phase 1 studies.

2.1. Analysis of Adverse Events

2.1.1. E/C/F/TAF Studies

Table 16 presents an overall summary of AEs for the E/C/F/TAF Phase 2 and Phase 3 studies. The frequency and type of reported AEs were generally similar in ART-naive adults, virologically suppressed subjects, subjects with mild to moderate renal impairment, and ART-naive adolescents. 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. The overall incidence of AEs was similar between treatment groups within each randomized study.

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) in Studies GS-US-292-0104 and GS-US-292-0111. 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 the other due to Stage 4 lung adenocarcinoma). None of these events were considered by the investigator as related to study drug. No other subject died in any of the Phase 2 or 3 studies.

The incidences of Grade 3 or 4 AEs and of SAEs were low and generally similar across all studies; few of the reported events were considered related to study drugs by the investigator. Within each study, the incidences of Grade 3 or 4 AEs and of SAEs were also generally similar between treatment groups. These events were reported as not related to study drugs in all but 1 subject (Grade 3 diarrhea lasting 1 day) in the E/C/F/TAF group. The percentage of subjects with Grade 3 or 4 AEs and SAEs was similar between treatment groups in the larger Phase 3 data set of ART-naive subjects.

The percentages of subjects who had any AE considered related to study drugs by the investigator were generally similar across studies and within each study except for Study GS-US-292-0109. As expected, among virologically suppressed subjects who were stable on their prior treatment regimen before participating in Study GS-US-292-0109, subjects who switched to open-label E/C/F/TAF had a higher incidence of any AE considered by the investigator as related to study drug (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. 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.

Across all studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study.

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.

Table 16. E/C/F/TAF Studies 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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Adverse Event	778 (89.8%)	782 (90.2%)	107 (95.5%)	57 (98.3%)	764 (79.7%)	368 (77.1%)	209 (86.4%)	5 (83.3%)	39 (81.3%)
Grade 2, 3, or 4 Adverse Event	419 (48.4%)	380 (43.8%)	72 (64.3%)	29 (50.0%)	389 (40.6%)	177 (37.1%)	114 (47.1%)	3 (50.0%)	13 (27.1%)
Grade 3 or 4 Adverse Event	71 (8.2%)	75 (8.7%)	13 (11.6%)	3 (5.2%)	61 (6.4%)	32 (6.7%)	18 (7.4%)	0	4 (8.3%)
Study-Drug-Related Adverse Event	342 (39.5%)	364 (42.0%)	43 (38.4%)	19 (32.8%)	185 (19.3%)	61 (12.8%)	62 (25.6%)	1 (16.7%)	18 (37.5%)
Grade 2, 3, or 4 Study-Drug-Related Adverse Event	84 (9.7%)	75 (8.7%)	9 (8.0%)	1 (1.7%)	46 (4.8%)	20 (4.2%)	24 (9.9%)	1 (16.7%)	2 (4.2%)
Grade 3 or 4 Study-Drug-Related Adverse Event	12 (1.4%)	9 (1.0%)	1 (0.9%)	0	3 (0.3%)	6 (1.3%)	3 (1.2%)	0	1 (2.1%)
Serious Adverse Event	70 (8.1%)	59 (6.8%)	12 (10.7%)	3 (5.2%)	42 (4.4%)	21 (4.4%)	26 (10.7%)	0	4 (8.3%)
Study-Drug-Related Serious Adverse Event	3 (0.3%)	2 (0.2%)	0	0	0	1 (0.2%)	0	0	1 (2.1%)

Subjects Experiencing Any	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
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
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: E/C/F/TAF ISS, Table 6; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 20.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 21; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 32; GS-US-292-0106 Interim CSR, Section 15.1, Table 14

2.1.2. D/C/F/TAF Study

Table 17 presents an overall summary of AEs for the D/C/F/TAF Phase 2 Study GS-US-299-0102. The frequency and type of reported AEs were consistent with those for ART-naive subjects in the E/C/F/TAF studies. The percentage of subjects reporting any AE was generally as expected for the study population.

Within the study, the overall incidence of AEs was similar between treatment groups. Most subjects in the study reported at least 1 AE. No subjects died during the study. The incidences of Grade 3 or 4 AEs and of SAEs were low and similar between treatment groups; they were also consistent with those in the E/C/F/TAF studies. The percentages of subjects who had any AE considered related to study drug by the investigator was similar between treatment groups, and consistent with the rates of study drug–related AEs for the E/C/F/TAF Phase 3 studies in ART-naive subjects. Within the study, AEs leading to study drug discontinuation were uncommon, and the percentages were similar between treatment groups.

Table 17. D/C/F/TAF Study GS-US-299-0102: Overall Summary of Adverse Events (Safety Analysis Set)

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

Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 21.1

2.1.3. Common Adverse Events

2.1.3.1. Summary of Common Adverse Events

In the E/C/F/TAF Phase 2 and 3 studies and the D/C/F/TAF Phase 2 study, the frequency and type of reported AEs were generally similar in ART-naive adults, virologically suppressed subjects, subjects with mild to moderate renal impairment, and ART-naive adolescents. The percentage of subjects reporting any AE was generally similar across studies, with somewhat lower percentages among virologically suppressed subjects in Study GS-US-292-0109 and

ART-naive adolescent subjects in Study GS-US-292-0106. A similar percentage of subjects reported any AE between treatment groups within each E/C/F/TAF and D/C/F/TAF study.

2.1.3.2. E/C/F/TAF Studies

2.1.3.2.1. ART-Naive Subjects

2.1.3.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Detailed AE results for the Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 may be found in the respective CSRs (GS-US-292-0104 Week 48 CSR, Section 11.2; GS-US-292-0111 Week 48 CSR, Section 11.2). Pooled results for the 2 studies are described below; AEs that occurred in ≥ 5% of subjects in either treatment group during the studies are presented in Table 18.

The AEs by PT reported for ≥ 10% of subjects in either treatment group of Studies GS-US-292-0104 and GS-US-292-0111 were as follows:

- E/C/F/TAF group — diarrhea (17.0%, 147 subjects), nausea (15.2%, 132 subjects), headache (14.3%, 124 subjects), and upper respiratory tract infection (11.4%, 99 subjects)
- STB group — diarrhea (18.9%, 164 subjects), nausea (17.4%, 151 subjects), upper respiratory tract infection (12.6%, 109 subjects), and headache (12.5%, 108 subjects)

Table 18. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Adverse Events Reported for ≥ 5% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term	E/C/F/TAF (N=866)	STB (N=867)
Number of Subjects Experiencing Any Adverse Event	778 (89.8%)	782 (90.2%)
Gastrointestinal disorders	394 (45.5%)	425 (49.0%)
Diarrhoea	147 (17.0%)	164 (18.9%)
Nausea	132 (15.2%)	151 (17.4%)
Vomiting	62 (7.2%)	54 (6.2%)
General disorders and administration site conditions	181 (20.9%)	164 (18.9%)
Fatigue	71 (8.2%)	71 (8.2%)
Pyrexia	45 (5.2%)	41 (4.7%)
Infections and infestations	503 (58.1%)	506 (58.4%)
Upper respiratory tract infection	99 (11.4%)	109 (12.6%)
Nasopharyngitis	78 (9.0%)	80 (9.2%)
Musculoskeletal and connective tissue disorders	241 (27.8%)	213 (24.6%)
Back pain	60 (6.9%)	57 (6.6%)
Arthralgia	61 (7.0%)	39 (4.5%)
Osteopenia	32 (3.7%)	44 (5.1%)
Nervous system disorders	218 (25.2%)	197 (22.7%)
Headache	124 (14.3%)	108 (12.5%)
Dizziness	44 (5.1%)	37 (4.3%)
Psychiatric disorders	163 (18.8%)	174 (20.1%)
Insomnia	57 (6.6%)	48 (5.5%)
Respiratory, thoracic and mediastinal disorders	158 (18.2%)	165 (19.0%)
Cough	67 (7.7%)	60 (6.9%)
Oropharyngeal pain	39 (4.5%)	47 (5.4%)
Skin and subcutaneous tissue disorders	208 (24.0%)	210 (24.2%)
Rash	55 (6.4%)	46 (5.3%)

Adverse events were coded using MedDRA 17.0.
System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: E/C/F/TAF ISS, Table 7

Adverse Events by Severity

The majority of the AEs reported in Studies GS-US-292-0104 and GS-US-292-0111 were Grade 1 or 2. Similar percentages of subjects in each treatment group reported any Grade 3 or 4 AEs (E/C/F/TAF 8.2%, 71 subjects; STB 8.7%, 75 subjects) (E/C/F/TAF ISS, Tables 7 and 10).

No individual Grade 3 or 4 AEs were reported for ≥ 1% of subjects in either treatment group.

Adverse Events Considered Related to Study Drug

Similar percentages of subjects in both treatment groups had any AE considered related to study drugs by the investigator (E/C/F/TAF 39.5%, 342 subjects; STB 42.0%, 364 subjects); any Grade 2, 3, or 4 AE considered related to study drugs by the investigator (E/C/F/TAF 9.7%, 84 subjects; STB 8.7%, 75 subjects); or any Grade 3 or 4 AE considered related to study drugs by the investigator (E/C/F/TAF 1.4%, 12 subjects; STB 1.0%, 9 subjects; Table 16 and Table 19). The AEs considered related to study drugs by the investigator reported for ≥ 5% of subjects in either treatment group were as follows:

- E/C/F/TAF group — nausea (10.4%, 90 subjects), diarrhea (7.2%, 62 subjects), headache (6.0%, 52 subjects), and fatigue (5.0%, 43 subjects)

- STB group — nausea (13.0%, 113 subjects), diarrhea (8.5%, 74 subjects), and headache (5.4%, 47 subjects)

Table 19. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Adverse Events Related to Study Drug Reported in ≥ 1% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term	E/C/F/TAF (N=866)	STB (N=867)
Number of Subjects Experiencing Any Study-Drug-Related Adverse Event	342 (39.5%)	364 (42.0%)
Gastrointestinal disorders	185 (21.4%)	224 (25.8%)
Nausea	90 (10.4%)	113 (13.0%)
Diarrhoea	62 (7.2%)	74 (8.5%)
Flatulence	19 (2.2%)	25 (2.9%)
Vomiting	16 (1.8%)	27 (3.1%)
Abdominal distension	13 (1.5%)	9 (1.0%)
Abdominal pain	11 (1.3%)	11 (1.3%)
Abdominal pain upper	9 (1.0%)	11 (1.3%)
General disorders and administration site conditions	61 (7.0%)	46 (5.3%)
Fatigue	43 (5.0%)	35 (4.0%)
Metabolism and nutrition disorders	26 (3.0%)	17 (2.0%)
Decreased appetite	12 (1.4%)	9 (1.0%)
Musculoskeletal and connective tissue disorders	29 (3.3%)	39 (4.5%)
Osteopenia	8 (0.9%)	17 (2.0%)
Nervous system disorders	97 (11.2%)	82 (9.5%)
Headache	52 (6.0%)	47 (5.4%)
Dizziness	26 (3.0%)	19 (2.2%)
Somnolence	9 (1.0%)	10 (1.2%)
Psychiatric disorders	47 (5.4%)	58 (6.7%)
Abnormal dreams	13 (1.5%)	26 (3.0%)
Insomnia	17 (2.0%)	14 (1.6%)
Renal and urinary disorders	10 (1.2%)	20 (2.3%)
Proteinuria	7 (0.8%)	10 (1.2%)
Skin and subcutaneous tissue disorders	46 (5.3%)	42 (4.8%)
Rash	13 (1.5%)	11 (1.3%)

Adverse events were coded using MedDRA 17.0.
System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: E/C/F/TAF ISS, Table 11

2.1.3.2.1.2. Study GS-US-292-0102

Detailed AE results for the Phase 2 Study GS-US-292-0102 may be found in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.2).

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

- E/C/F/TAF group — nausea (22.3%, 25 subjects); diarrhea (17.0%, 19 subjects); upper respiratory tract infection and fatigue (both 16.1%, 18 subjects); and depression (10.7%, 12 subjects)

- STB group — upper respiratory tract infection (20.7%, 12 subjects); diarrhea (15.5%, 9 subjects); back pain and headache (both 13.8%, 8 subjects); nausea (12.1%, 7 subjects); and cough (10.3%, 6 subjects)

Table 20. E/C/F/TAF Study GS-US-292-0102: Treatment Emergent Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b]	E/C/F/TAF (N=112)	STB (N=58)
Number of Subjects Experiencing Any Adverse Event	107 (95.5%)	57 (98.3%)
Endocrine disorders	7 (6.3%)	0
Hypogonadism	7 (6.3%)	0
Gastrointestinal disorders	59 (52.7%)	28 (48.3%)
Nausea	25 (22.3%)	7 (12.1%)
Diarrhoea	19 (17.0%)	9 (15.5%)
Vomiting	9 (8.0%)	4 (6.9%)
Flatulence	6 (5.4%)	2 (3.4%)
Constipation	4 (3.6%)	3 (5.2%)
Dyspepsia	4 (3.6%)	3 (5.2%)
General disorders and administration site conditions	31 (27.7%)	9 (15.5%)
Fatigue	18 (16.1%)	5 (8.6%)
Immune system disorders	5 (4.5%)	3 (5.2%)
Seasonal allergy	4 (3.6%)	3 (5.2%)
Infections and infestations	83 (74.1%)	33 (56.9%)
Upper respiratory tract infection	18 (16.1%)	12 (20.7%)
Pharyngitis	10 (8.9%)	2 (3.4%)
Bronchitis	7 (6.3%)	3 (5.2%)
Sinusitis	7 (6.3%)	3 (5.2%)
Conjunctivitis	9 (8.0%)	0
Nasopharyngitis	7 (6.3%)	2 (3.4%)
Influenza	8 (7.1%)	0
Syphilis	5 (4.5%)	3 (5.2%)
Acarodermatitis	4 (3.6%)	3 (5.2%)
Musculoskeletal and connective tissue disorders	30 (26.8%)	16 (27.6%)
Back pain	3 (2.7%)	8 (13.8%)
Neck pain	3 (2.7%)	3 (5.2%)
Pain in extremity	1 (0.9%)	3 (5.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (7.1%)	8 (13.8%)
Anorectal human papilloma virus infection	6 (5.4%)	4 (6.9%)
Skin papilloma	0	3 (5.2%)

Adverse Events by System Organ Class and Preferred Term[a,b]	E/C/F/TAF (N=112)	STB (N=58)
Nervous system disorders	23 (20.5%)	14 (24.1%)
Headache	11 (9.8%)	8 (13.8%)
Paraesthesia	3 (2.7%)	4 (6.9%)
Psychiatric disorders	28 (25.0%)	13 (22.4%)
Depression	12 (10.7%)	3 (5.2%)
Insomnia	6 (5.4%)	4 (6.9%)
Abnormal dreams	8 (7.1%)	1 (1.7%)
Anxiety	4 (3.6%)	5 (8.6%)
Respiratory, thoracic and mediastinal disorders	26 (23.2%)	13 (22.4%)
Cough	11 (9.8%)	6 (10.3%)
Skin and subcutaneous tissue disorders	37 (33.0%)	15 (25.9%)
Rash	11 (9.8%)	3 (5.2%)

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 21.1

Adverse Events by Severity

The majority of the AEs reported in Study GS-US-292-0102 were Grade 1 or Grade 2.

In the randomized phase, similar percentages of subjects in each group had any Grade 3 AEs (E/C/F/TAF 11.6%, 13 subjects; STB 5.2%, 3 subjects). No Grade 4 AEs were reported in either treatment group. By individual PT, no Grade 3 AE was reported for > 1 subject in either group. One Grade 3 AE of diarrhea lasting 1 day was reported for Subject *CU in the E/C/F/TAF group and was considered related to the study drugs by the investigator.

Grade 3 AEs were reported for 17 subjects (15.2%) in the E/C/F/TAF group in the all E/C/F/TAF analysis. No Grade 4 AEs were reported. Blood creatine phosphokinase increased was the only Grade 3 AE reported for 2 subjects (Subjects *CV and *CW). Both events were nonserious and considered unrelated to the study drugs by the investigator. Neither subject discontinued study drug due to blood creatine phosphokinase increased.

Adverse Events Considered Related to Study Drug

In the randomized phase, similar percentages of subjects in each group had any AE considered related to the study drugs by the investigator (E/C/F/TAF 38.4%, 43 subjects; STB 32.8%, 19 subjects; Table 21). The most commonly reported AEs considered related to the study drugs by the investigator by PT were as follows: nausea (E/C/F/TAF 12.5%, 14 subjects, STB 8.6%, 5 subjects), diarrhea (E/C/F/TAF 6.3%, 7 subjects; STB 6.9%, 4 subjects), and fatigue (E/C/F/TAF 6.3%, 7 subjects; STB 3.4%, 2 subjects).

Table 21. E/C/F/TAF Study GS-US-292-0102: Study Drug Related, Treatment Emergent Adverse Events Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term and Highest Severity[a,b]	E/C/F/TAF (N=112)	STB (N=58)
Number of Subjects Experiencing Any Study-Drug-Related Adverse Event	43 (38.4%)	19 (32.8%)
Gastrointestinal disorders	25 (22.3%)	13 (22.4%)
Nausea	14 (12.5%)	5 (8.6%)
Diarrhoea	7 (6.3%)	4 (6.9%)
Flatulence	6 (5.4%)	2 (3.4%)
Constipation	2 (1.8%)	1 (1.7%)
Abdominal distension	1 (0.9%)	1 (1.7%)
Abdominal pain	2 (1.8%)	0
Dyspepsia	0	2 (3.4%)
Vomiting	2 (1.8%)	0
Faeces soft	0	1 (1.7%)
General disorders and administration site conditions	8 (7.1%)	2 (3.4%)
Fatigue	7 (6.3%)	2 (3.4%)
Investigations	1 (0.9%)	1 (1.7%)
Bone density decreased	0	1 (1.7%)
Metabolism and nutrition disorders	5 (4.5%)	1 (1.7%)
Hyperlipidaemia	2 (1.8%)	1 (1.7%)
Decreased appetite	2 (1.8%)	0
Musculoskeletal and connective tissue disorders	2 (1.8%)	2 (3.4%)
Osteopenia	1 (0.9%)	2 (3.4%)
Nervous system disorders	9 (8.0%)	1 (1.7%)
Headache	5 (4.5%)	0
Dysgeusia	2 (1.8%)	0
Paraesthesia	2 (1.8%)	0
Somnolence	0	1 (1.7%)
Psychiatric disorders	8 (7.1%)	1 (1.7%)
Abnormal dreams	5 (4.5%)	1 (1.7%)
Depressed mood	0	1 (1.7%)

Adverse Events by System Organ Class and Preferred Term and Highest Severity[a,b]	E/C/F/TAF (N=112)	STB (N=58)
Insomnia	0	1 (1.7%)
Skin and subcutaneous tissue disorders	4 (3.6%)	1 (1.7%)
Night sweats	2 (1.8%)	0
Onychoclasis	0	1 (1.7%)

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 25.1

2.1.3.2.2. Virologically Suppressed Subjects

2.1.3.2.2.1. Study GS-US-292-0109

Detailed AE results for the Phase 3 Study GS-US-292-0109 may be found in the CSR (GS-US-292-0109 Week 48 CSR, Section 11.2).

Adverse events that occurred in ≥ 5% of subjects in Study GS-US-292-0109 are presented in Table 22. Common AEs were consistent with those expected in the subject population, the known safety profiles of the study drugs, and with previous clinical study experience with E/C/F/TAF. The most common AEs (ie, occurred in ≥ 5% of subjects) by treatment group were as follows:

- E/C/F/TAF: Upper respiratory tract infection (12.1%, 116 of 959 subjects), diarrhea (8.0%, 77 subjects), nasopharyngitis (6.7%, 64 subjects), headache (6.0%, 58 subjects), and cough (5.1%, 49 subjects)

- FTC/TDF+3rd Agent: Upper respiratory tract infection (7.5%, 36 of 477 subjects), diarrhea (7.5%, 36 subjects), and nasopharyngitis (5.5%, 26 subjects)

No AE by PT was reported with a difference in percentages of ≥ 5% between groups.

Table 22. E/C/F/TAF Study GS-US-292-0109: Treatment Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c]	E/C/F/TAF (N=959)	FTC/TDF+3rd Agent (N=477)
Number of Subjects Experiencing Any Adverse Event	764 (79.7%)	368 (77.1%)
Gastrointestinal disorders	263 (27.4%)	102 (21.4%)
Diarrhoea	77 (8.0%)	36 (7.5%)
Infections and infestations	461 (48.1%)	215 (45.1%)
Upper respiratory tract infection	116 (12.1%)	36 (7.5%)
Nasopharyngitis	64 (6.7%)	26 (5.5%)
Nervous system disorders	159 (16.6%)	50 (10.5%)
Headache	58 (6.0%)	17 (3.6%)
Respiratory, thoracic and mediastinal disorders	149 (15.5%)	55 (11.5%)
Cough	49 (5.1%)	15 (3.1%)

a Adverse events were coded using MedDRA 17.0.
b System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 22

Adverse Events by Severity

Most AEs reported in either treatment group were Grade 1 or Grade 2 (Table 16). A similar percentage of subjects in each group had any Grade 3 or Grade 4 AE reported (E/C/F/TAF 6.4%, 61 subjects; FTC/TDF+3rd Agent 6.7%, 32 subjects); most of these events were Grade 3 (E/C/F/TAF 53 subjects; FTC/TDF+3rd Agent 29 subjects).

No Grade 3 or Grade 4 AEs were reported for ≥ 1% of subjects in either group.

Adverse Events Considered Related to Study Drug

A higher percentage of subjects in the switch group (ie, E/C/F/TAF treatment group) had any AE considered by the investigator as related to study drug (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects, Table 23).

The most common AEs by PT considered by the investigator as related to study drug, reported for ≥ 1% of subjects in either group were as follows:

- E/C/F/TAF: Diarrhea (2.5%, 24 of 959 subjects), nausea (2.2%, 21 subjects), flatulence (1.9%, 18 subjects), headache (1.8%, 17 subjects), abnormal dreams (1.3%, 12 subjects), dizziness (1.1%, 11 subjects), and insomnia (1.0%, 10 subjects)

- FTC/TDF+3rd Agent: Jaundice (1.9%, 9 of 477 subjects), osteopenia (1.3%, 6 subjects), dizziness (1.3%, 6 subjects), abnormal dreams (1.3%, 6 subjects), diarrhea (1.3%, 6 subjects), insomnia (1.3%, 6 subjects), and ocular icterus (1.0%, 5 subjects)

The incidence of common study drug-related AEs were similar for each treatment group. All reports of study drug-related jaundice and ocular icterus were for subjects taking ATV/boosted+TVD regimens.

Table 23. E/C/F/TAF Study GS-US-292-0109: Study Drug-Related Adverse Events Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c]	E/C/F/TAF (N=959)	FTC/TDF+3rd Agent (N=477)
Number of Subjects Experiencing Any Study-Drug-Related Adverse Event	185 (19.3%)	61 (12.8%)
Eye disorders	2 (0.2%)	5 (1.0%)
Ocular icterus	0	5 (1.0%)
Gastrointestinal disorders	74 (7.7%)	11 (2.3%)
Diarrhoea	24 (2.5%)	6 (1.3%)
Nausea	21 (2.2%)	2 (0.4%)
Flatulence	18 (1.9%)	1 (0.2%)
Hepatobiliary disorders	1 (0.1%)	11 (2.3%)
Jaundice	0	9 (1.9%)
Musculoskeletal and connective tissue disorders	19 (2.0%)	9 (1.9%)
Osteopenia	8 (0.8%)	6 (1.3%)
Nervous system disorders	44 (4.6%)	8 (1.7%)
Dizziness	11 (1.1%)	6 (1.3%)
Headache	17 (1.8%)	0
Psychiatric disorders	38 (4.0%)	9 (1.9%)
Abnormal dreams	12 (1.3%)	6 (1.3%)
Insomnia	10 (1.0%)	6 (1.3%)

a Adverse events were coded using MedDRA 17.0.
b System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 26

2.1.3.2.2.2. Study GS-US-292-0102 Open-Label Extension

In the open-label extension of Phase 2 Study GS-US-292-0102, common AEs among virologically suppressed subjects who switched treatment were consistent with those observed in this subject population and those seen during the randomized phase (Section 2.1.3.2.1.2).

Adverse Events by Severity

The percentages of subjects in the switch groups who had Grade 3 or Grade 4 AEs were low (all TDF to TAF 4.4%, 4 of 91 subjects; D/C/F/TAF to E/C/F/TAF 1.4%, 1 of 70 subjects); no Grade 4 AEs were reported in any switch group. By individual PT, no Grade 3 AEs were reported for > 1 subject in any switch group, and none was considered related to the study drugs by the investigator.

Adverse Events Considered Related to Study Drug

The percentages of subjects in the switch groups who had study drug related AEs were low. One subject in the all TDF to TAF group had a Grade 2 AE of dyspepsia considered related to study drug by the investigator.

2.1.3.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.3.2.3.1. Study GS-US-292-0112

Detailed AE results for the Phase 3 Study GS-US-292-0112 may be found in the CSR (GS-US-292-0112 Week 24 CSR, Section 11.3).

Adverse events that occurred in ≥ 5% of Cohort 1 switch subjects are presented in Table 24. Common AEs were consistent with those expected in the subject population and with the safety profiles seen in subjects with normal renal function. The most commonly reported AEs in Cohort 1 switch subjects were diarrhea (8.7%, 21 subjects), arthralgia (8.3%, 20 subjects), and bronchitis and osteopenia (7.9%, 19 subjects for each AE). Of note, 16 of 19 subjects had the AE of osteopenia reported on Day 1, suggesting that these AEs were most likely reported based on the baseline (predose) DXA scan and not truly treatment emergent.

In Cohort 1 switch subjects, the following AEs were reported for a lower percentage of subjects with baseline $eGFR_{CG} < 50$ mL/min than with baseline $eGFR_{CG} \geq 50$ mL/min: upper respiratory infection (1.3% versus 9.9%); headache (2.5% versus 9.3%); and back pain (2.5% versus 8.0%).

Rates of AEs in general were low despite higher FTC exposures in subjects with baseline $eGFR_{CG} < 50$ mL/min. Pruritus generalized was reported in 1 subject (1.3%), and pain was reported in 1 subject (1.3%), in Cohort 1 subjects with baseline $eGFR_{CG} < 50$ mL/min.

No individual AE occurred in > 1 subject in the Cohort 2 ART-naive subjects.

Table 24. E/C/F/TAF Study GS-US-292-0112: Adverse Events Reported for at Least 5% of Subjects in Cohort 1 (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b]	Cohort 1: Switch			Cohort 2: ART-Naive
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)	Total (N = 6)
Subjects Experiencing Any Adverse Event	67 (83.8%)	142 (87.7%)	209 (86.4%)	5 (83.3%)
Gastrointestinal Disorders				
Diarrhoea	8 (10.0%)	13 (8.0%)	21 (8.7%)	1 (16.7%)
Nausea	5 (6.3%)	12 (7.4%)	17 (7.0%)	0
General Disorders and Administration Site Conditions				
Fatigue	4 (5.0%)	10 (6.2%)	14 (5.8%)	1 (16.7%)
Infections and Infestations				
Bronchitis	7 (8.8%)	12 (7.4%)	19 (7.9%)	0
Upper Respiratory Tract Infection	1 (1.3%)	16 (9.9%)	17 (7.0%)	1 (16.7%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	6 (7.5%)	14 (8.6%)	20 (8.3%)	1 (16.7%)
Osteopenia	8 (10.0%)	11 (6.8%)	19 (7.9%)	0
Pain in Extremity	3 (3.8%)	13 (8.0%)	16 (6.6%)	1 (16.7%)
Back Pain	2 (2.5%)	13 (8.0%)	15 (6.2%)	0
Nervous System Disorders				
Headache	2 (2.5%)	15 (9.3%)	17 (7.0%)	0
Dizziness	7 (8.8%)	7 (4.3%)	14 (5.8%)	0
Renal and Urinary Disorders				
Renal Cyst	5 (6.3%)	8 (4.9%)	13 (5.4%)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	4 (5.0%)	8 (4.9%)	12 (5.0%)	0

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Table 33

Adverse Events by Severity

The majority of the AEs reported in Study GS-US-292-0112 were Grade 1 or Grade 2.

In Cohort 1 (switch), Grade 3 and 4 AEs were reported for 7.4% of subjects (n = 18): 6.6% of subjects (n = 16) had Grade 3 AEs and 0.8% of subjects (n = 2) had Grade 4 AEs. Myocardial infarction (3 subjects) was the only Grade 3 or 4 AE reported in > 1 subject; each event was serious and considered unrelated to study drug by the investigator. Three subjects had a single nonserious Grade 3 AE considered related to study drug by the investigator: blood creatine phosphokinase increased (baseline $eGFR_{CG}$ < 50 mL/min group), gastroesophageal reflux disease (baseline $eGFR_{CG} \geq$ 50 mL/min group), and hypercholesterolemia (baseline $eGFR_{CG}$ $\geq$ 50 mL/min group).

No Grade 3 or 4 AEs were reported for Cohort 2 ART-naive subjects.

Adverse Events Considered Related to Study Drug

Adverse events considered related to the study drugs by the investigator that occurred in ≥ 1% of Cohort 1 switch subjects are presented in Table 25. The most commonly reported AEs considered related to the study drugs by the investigator subjects were dizziness (2.9%, 7 subjects), diarrhea (2.5%, 6 subjects), and headache (2.1%, 5 subjects).

One AE considered related to the study drug by the investigator was reported in a Cohort 2 ART-naive subject (hyperlipidemia).

Table 25. E/C/F/TAF Study GS-US-292-0112: Study Drug Related, Treatment Emergent Adverse Events Reported for at Least 1% of Subjects in Cohort 1 (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b]	Cohort 1: Switch			Cohort 2: ART-Naive
	Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)	Total (N = 242)	Total (N = 6)
Subjects Experiencing Any Study Drug-Related Adverse Event	21 (26.3%)	41 (25.3%)	62 (25.6%)	1 (16.7%)
Gastrointestinal Disorders				
Diarrhoea	1 (1.3%)	5 (3.1%)	6 (2.5%)	0
Constipation	1 (1.3%)	3 (1.9%)	4 (1.7%)	0
Flatulence	2 (2.5%)	2 (1.2%)	4 (1.7%)	0
Nausea	1 (1.3%)	3 (1.9%)	4 (1.7%)	0
Abdominal Discomfort	2 (2.5%)	1 (0.6%)	3 (1.2%)	0
Dyspepsia	0	3 (1.9%)	3 (1.2%)	0
Metabolism and Nutrition Disorders				
Hypercholesterolemia	1 (1.3%)	2 (1.2%)	3 (1.2%)	0
Nervous System Disorders				
Dizziness	4 (5.0%)	3 (1.9%)	7 (2.9%)	0
Headache	1 (1.3%)	4 (2.5%)	5 (2.1%)	0
Psychiatric Disorders				
Insomnia	1 (1.3%)	2 (1.2%)	3 (1.2%)	0

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Table 37

2.1.3.2.4. ART-Naive Adolescent Subjects

2.1.3.2.4.1. Study GS-US-292-0106

Detailed AE results for the Phase 2/3 Study GS-US-292-0106 may be found in the CSR (GS-US-292-0106 Interim CSR, Section 11.2).

Adverse events that occurred in ≥ 5% of subjects in Study GS-US-292-0106 are summarized in Table 26. Adverse events by PT reported for at least 10% of subjects were nausea (22.9%, 11 subjects); upper respiratory tract infection (20.8%, 10 subjects); diarrhea (16.7%, 8 subjects); headache, respiratory tract infection, abdominal pain (each 14.6%, 7 subjects), vomiting (12.5%, 6 subjects), and dizziness and vitamin D deficiency (both 10.4%, 5 subjects).

Table 26. E/C/F/TAF Study GS-US-292-0106: Adverse Events Occurring in ≥ 5% of Subjects (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term[a,b]	E/C/F/TAF (N = 48)
Subjects Experiencing Any Adverse Event	39 (81.3%)
Gastrointestinal disorders	21 (43.8%)
Nausea	11 (22.9%)
Diarrhoea	8 (16.7%)
Abdominal pain	7 (14.6%)
Vomiting	6 (12.5%)
Abdominal pain upper	3 (6.3%)
Infections and infestations	19 (39.6%)
Upper respiratory tract infection	10 (20.8%)
Respiratory tract infection	7 (14.6%)
Body tinea	4 (8.3%)
Bronchopneumonia	4 (8.3%)
Urinary tract infection	3 (6.3%)
Metabolism and nutrition disorders	5 (10.4%)
Vitamin D deficiency	5 (10.4%)
Nervous system disorders	12 (25.0%)
Headache	7 (14.6%)
Dizziness	5 (10.4%)
Somnolence	3 (6.3%)
Skin and subcutaneous tissue disorders	3 (6.3%)
Rash papular	3 (6.3%)

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively. System organ class was presented alphabetically and PT was presented by descending order of the total frequencies.
Source: GS-US-292-0106 Interim CSR, Section 15.1, Table 16

Adverse Events by Severity

Most AEs reported were Grade 1 or Grade 2 in severity (Table 16). Four subjects (8.3%) had a Grade 3 or Grade 4 AE. Grade 3 neuralgia was reported for 1 subject; Grade 3 bipolar disorder, conduct disorder, mania, and substance abuse were reported for 1 subject; Grade 3 chorioretinitis was reported for 1 subject; Grade 3 drug abuse and Grade 4 suicide attempt were reported for 1 subject.

Adverse Events Considered Related to Study Drug

Adverse events related to study drug were reported for 18 subjects (37.5%) (Table 27). Study drug-related AEs that occurred in > 1 subject were either gastrointestinal, including nausea (10 subjects, 20.8%), abdominal pain (6 subjects, 12.5%), vomiting (5 subjects, 10.4%), and upper abdominal pain and diarrhea (both 3 subjects, 6.3%), or nervous system disorders, including somnolence (3 subjects, 6.3%), dizziness (4.2%, 2 subjects), and headache (4.2%, 2 subjects). With the exception of 1 event each of Grade 2 visual impairment, Grade 3 chorioretinitis, Grade 2 intermediate uveitis, (all reported for 1 subject), and Grade 2 headache (1 subject), all of the study drug-related AEs were Grade 1 in severity.

Table 27. E/C/F/TAF Study GS-US-292-0106: Study Drug-Related Adverse Event (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term[a,b]	E/C/F/TAF (N = 48)
Subjects Experiencing Any Adverse Event Related to Study Drug	18 (37.5%)
Eye disorders	1 (2.1%)
Intermediate uveitis	1 (2.1%)
Visual impairment	1 (2.1%)
Gastrointestinal disorders	17 (35.4%)
Nausea	10 (20.8%)
Abdominal pain	6 (12.5%)
Vomiting	5 (10.4%)
Abdominal pain upper	3 (6.3%)
Diarrhoea	3 (6.3%)
Dyspepsia	1 (2.1%)
Flatulence	1 (2.1%)
General disorders and administration site conditions	1 (2.1%)
Fatigue	1 (2.1%)
Infections and infestations	1 (2.1%)
Chorioretinitis	1 (2.1%)
Metabolism and nutrition disorders	2 (4.2%)
Decreased appetite	1 (2.1%)
Increased appetite	1 (2.1%)
Nervous System Disorders	7 (14.6%)
Somnolence	3 (6.3%)
Dizziness	2 (4.2%)
Headache	2 (4.2%)
Lethargy	1 (2.1%)

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively. System organ class was presented alphabetically and PT was presented by descending order of the total frequencies.
Source: GS-US-292-0106 Interim CSR, Section 15.1, Table 19

2.1.3.3. D/C/F/TAF Study

2.1.3.3.1. ART-Naive Subjects

2.1.3.3.1.1. Study GS-US-299-0102

Detailed AE results for the Phase 2 Study GS-US-299-0102 may be found in m5.3.5.1, GS-US-299-0102 Week 48 CSR, Section 11.2.

Adverse events that occurred in ≥ 5% of subjects in the D/C/F/TAF Phase 2 Study GS-US-299-0102 are presented in Table 28. Common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs. The most common AEs (ie, occurred in ≥ 10% of subjects) by treatment group were as follows:

- D/C/F/TAF group — diarrhea (21.4%, 22 subjects); upper respiratory tract infection (15.5%, 16 subjects); fatigue (13.6%, 14 subjects); nausea (12.6%, 13 subjects); and rash (11.7%, 12 subjects)

- DRV+COBI+TVD group — diarrhea (26.0%, 13 subjects); fatigue (18.0%, 9 subjects); upper respiratory tract infection (14.0%, 7 subjects); flatulence (12.0%, 6 subjects); and nausea, pain in extremity, vitamin D deficiency, and vomiting (each in 10.0%, 5 subjects)

Table 28. D/C/F/TAF Study GS-US-299-0102: Adverse Events Reported for ≥5% of Subjects in Either Treatment Group (Safety Analysis Set)

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

a Adverse events were coded using MedDRA 17.0.
b Multiple AEs were counted only once per subject for each SOC, high level term, and PT, respectively.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 22

Adverse Events by Severity

The majority of the AEs in the Phase 2 D/C/F/TAF Study GS-US-299-0102 were Grade 1 or Grade 2.

Similar percentages of subjects in each group had Grade 3 AEs (D/C/F/TAF 6.8%, 7 subjects; DRV+COBI+TVD 8.0%, 4 subjects). No Grade 4 AEs were reported in either treatment group. By individual PT, no Grade 3 AE was reported for > 1 subject in either group. One subject in each treatment group had a Grade 3 AE that was considered by the investigator to be related to study drug.

Adverse Events Considered Related to Study Drug

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

2.1.4. Deaths

Seven subjects died during the E/C/F/TAF Phase 2 and Phase 3 studies: 5 subjects in Studies GS-US-292-0104 and GS-US-292-0111, and 2 subjects in Study GS-US-292-0109 (Table 16). None of the events that resulted in death was considered related to study drug by the investigator.

There were no other deaths in any study of TAF, F/TAF, E/C/F/TAF, or D/C/F/TAF.

2.1.4.1. E/C/F/TAF Studies

2.1.4.1.1. ART-Naive Subjects

2.1.4.1.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Five 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) in Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF ISS, Listing 4). None of the SAEs that resulted in the deaths were considered related to study drugs by the investigator. Subject *CX in the E/C/F/TAF group in Study GS-US-292-0104 died as a result of embolic stroke that transformed into hemorrhagic stroke. Subject *CY in the STB group in Study GS-US-292-0104 died as a result of cardiac arrest (reported as vagally mediated bradycardic/asystole). Subject *CZ in the E/C/F/TAF group in Study GS-US-292-0111 died on Day 90 of alcohol intoxication (reported as an SAE of alcohol poisoning on Day 90). Subject *DA in the STB group in Study GS-US-292-0111 died on Day 62 of acute ethanol

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and multiple drug toxicity (reported as an SAE of recreational drug and alcohol overdose on Day 62). Subject *DB in the STB group in Study GS-US-292-0111 died on Day 110 of myocardial infarction (reported as an SAE of acute myocardial infarction on Day 110, 2 weeks after the onset of an SAE of meningococcal meningitis).

2.1.4.1.2. Virologically Suppressed Subjects

2.1.4.1.2.1. Study GS-US-292-0109

Two subjects in the E/C/F/TAF group died during Study GS-US-292-0109 (Table 16; GS-US-292-0109 Week 48 CSR, Section 11.3). Subject *DC died on Day 148 of septic shock and Subject *DD died on Day 391 as a result of Stage 4 adenocarcinoma of the lung. Both events were considered by the investigator as not related to study drug.

2.1.5. Other Serious Adverse Events

2.1.5.1. Summary of Other Serious Adverse Events

Serious AEs were reported for a similar percentage of subjects in both treatment groups in the comparative E/C/F/TAF studies (GS-US-292-0104, GS-US-292-0111, GS-US-292-0109) and < 10% in the E/C/F/TAF group in each study. No individual SAE occurred in ≥ 1% of subjects in either treatment group. Serious AEs were reported in Study GS-US-292-0112 for 10.7% of Cohort 1 switch subjects (n = 26), with similar percentages reported in subjects with baseline $eGFR_{CG} \geq 50$ mL/min (11.3%, n = 9) and $eGFR_{CG} < 50$ mL/min (10.5%, n = 17). SAEs were reported for 4 subjects (8.3%) in the adolescent study (Study GS-US-292-0106).

The incidence of Grade 3 or 4 SAEs was low and generally similar across all E/C/F/TAF studies; few of these were reported as related to study drugs

Results for the D/C/F/TAF Phase 2 study were consistent with those from the E/C/F/TAF studies in ART-naive subjects.

2.1.5.2. E/C/F/TAF Studies

2.1.5.2.1. ART-Naive Subjects

2.1.5.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

The SAEs were reported for a similar percentage of subjects in both treatment groups across Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF 8.1%, 70 subjects; STB 6.8%, 59 subjects; Table 16). Overall, the incidence of SAEs considered related to study drugs by the investigator was low and similar in both treatment groups (E/C/F/TAF 0.3%, 3 subjects; STB 0.2%, 2 subjects).

No individual SAE occurred in ≥ 1% of subjects in either treatment group. Appendicitis (E/C/F/TAF 0.5%, 4 subjects; STB 0.3%, 3 subjects) and cellulitis (E/C/F/TAF 0.1%, 1 subject;

STB 0.3%, 3 subjects) were the only SAEs reported for > 2 subjects in either treatment group (E/C/F/TAF ISS, Table 14).

The SAEs that were considered related to study drugs by the investigator were staphylococcal skin infection, erythematous rash, and hypovolemic shock (for each AE: E/C/F/TAF 0.1%, 1 subject; STB 0 subjects) and immune reconstitution inflammatory syndrome and cholelithiasis (for each AE: E/C/F/TAF 0 subjects; STB 0.1%, 1 subject; E/C/F/TAF ISS, Table 15).

Three subjects had SAEs associated with renal function (E/C/F/TAF: ureteric calculus and nephrotic syndrome; STB: acute renal failure, reported as acute kidney injury); these events are described in Section 2.1.7.3.2.1.1.1.

2.1.5.2.1.2. Study GS-US-292-0102

In the randomized phase of Study GS-US-292-0102, similar percentages of subjects in each group (E/C/F/TAF 10.7%, 12 subjects; STB 5.2%, 3 subjects) had any SAE (Table 16; GS-US-292-0102 Week 96 CSR, Section 11.4). Depression and suicidal ideation were the only SAEs reported for > 1 subject (E/C/F/TAF 0.9%, 1 subject; STB 3.4%, 2 subjects for both events). No SAEs were considered related to study drugs by the investigator.

2.1.5.2.2. Virologically Suppressed Subjects

2.1.5.2.2.1. Study GS-US-292-0109

The SAEs were reported in Study GS-US-292-0109 for similar percentages of subjects in the 2 groups (E/C/F/TAF 4.4%, 42 subjects; FTC/TDF+3rd Agent 4.4%, 21 subjects) (Table 16; GS-US-292-0109 Week 48 CSR, Section 11.5). The following SAEs were reported for > 1 subject in either treatment group: aseptic meningitis (E/C/F/TAF 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%); pneumonia (E/C/F/TAF 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%); sepsis (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); sinusitis (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); chest pain (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject); diarrhea (E/C/F/TAF 0.1%; 1 subject; FTC/TDF+3rd Agent 0.4%, 2 subjects); and abdominal pain (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%).

One subject in the FTC/TDF+3rd Agent group had an SAE of acute renal failure that was considered by the investigator as related to study drugs.

2.1.5.2.2.2. Study GS-US-292-0102 Open-Label Extension

Overall, few subjects in the switch groups in Study GS-US-292-0102 had SAEs (all TDF to TAF 3.3%, 3 of 91 subjects; D/C/F/TAF to E/C/F/TAF 2.9%, 2 of 70 subjects). By PT, no SAE was reported for more than 1 subject in any switch group. No SAEs were considered related to study drugs by the investigator.

2.1.5.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.5.2.3.1. Study GS-US-292-0112

Serious AEs were reported in Study GS-US-292-0112 for 10.7% of Cohort 1 switch subjects (n = 26), with similar percentages reported in subjects with baseline $eGFR_{CG} \geq 50$ mL/min (11.3%, n = 9) and $eGFR_{CG} < 50$ mL/min (10.5%, n = 17) (GS-US-292-0112 Week 24 CSR Section 11.5).

Myocardial infarction (3 subjects) and syncope (2 subjects) were the only SAEs reported in > 1 subject. All SAEs were considered unrelated to study drugs by the investigator.

No Grade SAEs were reported for Cohort 2 ART-naive subjects.

2.1.5.2.4. ART-Naive Adolescent Subjects

2.1.5.2.4.1. Study GS-US-292-0106

The SAEs were reported for 4 subjects (8.3%) in Study GS-US-292-0106 (Table 16; GS-US-292-0106 Interim CSR, Section 11.4). With the exception of visual impairment and intermediate uveitis in Subject *DE , no SAE was considered related to study drug by the investigator. No SAE occurred in more than 1 subject.

Visual impairment and intermediate uveitis in Subject *DE are noted as ocular events and described in more detail in Section 2.1.7.4.3.4.

2.1.5.3. D/C/F/TAF Study

2.1.5.3.1. ART-Naive Subjects

2.1.5.3.1.1. Study GS-US-299-0102

In the D/C/F/TAF Phase 2 study, similar percentages of subjects in each treatment group had SAEs (D/C/F/TAF 4.9%, 5 subjects; DRV+COBI+TVD 4.0%, 2 subjects; m5.3.5.1, GS-US-299-0102, Section 11.4). One subject (1.0%) in the D/C/F/TAF group and no subjects in the DRV+COBI+TVD group had an SAE that was considered related to study drug by the investigator (hypersensitivity). No SAEs were reported for > 1 subject.

2.1.5.4. Phase 1 TAF Safety Population

One SAE was reported in Phase 1 studies with TAF. In Study GS-US-120-0104, 1 subject (Subject *DF) experienced chest pain considered unrelated to study drug by the investigator (GS-US-120-0104, Section 11.4).

Two SAEs were reported in Phase 1 studies with F/TAF. In Study GS-US-311-1386, 1 subject (Subject *DG) had an SAE of spontaneous abortion that was considered by the investigator as related to study drug (m5.3.3.4, GS-US-311-1386, Section 11.4). In Study GS-US-311-1473, 1 subject (Subject *DH) experienced an SAE of Grade 3 peritoneal hemorrhage that was

considered unrelated to study drug by the investigator (m5.3.1.2, GS-US-311-1473, Section 11.4).

There were no SAEs reported in Phase 1 studies with E/C/F/TAF or D/C/F/TAF.

2.1.6. Other Significant Adverse Events

2.1.6.1. Summary of Other Significant Adverse Events

Adverse events that led to discontinuation of study drug are described in this section. Across all Phase 2 and Phase 3 studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study. With longer exposures for the E/C/F/TAF group through 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. Among virologically suppressed subjects in 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 (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects).

2.1.6.2. E/C/F/TAF Studies

2.1.6.2.1. ART-Naive Subjects

2.1.6.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

The AEs that led to discontinuation of study drugs were reported for a similar percentage of subjects in either treatment group across Studies GS-US-292-0104 and GS-US-292-0111 (E/C/F/TAF 0.9%, 8 subjects; STB 1.5%, 13 subjects; Table 16). Most AEs leading to discontinuation of study drugs were nonserious. No AE leading to discontinuation was reported for >1 subject in the E/C/F/TAF group. Three AEs leading to discontinuation were reported for > 1 subject in the STB group (vomiting, headache, and renal failure, all 0.2%, 2 subjects; E/C/F/TAF ISS, Table 16).

All AEs leading to discontinuation of study drugs were considered related to study drugs by the investigator, except those reported for the 2 subjects who died (cardiac arrest [1 subject, STB], cerebral infarction and hemorrhagic transformation stroke [1 subject, E/C/F/TAF]) and for 2 other subjects in the STB group (right and left sided anterior uveitis and spider bites, each 1 subject).

As described in Section 2.1.7.3.2.1.1.1, 4 subjects had renal AEs that resulted in discontinuation of study drugs.

2.1.6.2.1.2. Study GS-US-292-0102

In the randomized phase of Study GS-US-292-0102, 4 subjects (3.6%) in the E/C/F/TAF group discontinued study drug due to the following 6 AEs: neutropenia and acute promyelocytic leukemia; coxsackie viral infection; *Mycobacterium avium* complex infection; flushing and photosensitivity reaction. No subjects in the STB group discontinued study drug due to an AE.

One subject (Subject *DI) in the E/C/F/TAF group had 2 AEs resulting in discontinuation of study drug (flushing and photosensitivity reaction). Both were considered related to study drugs by the investigator.

No AEs leading to discontinuation of study drug were reported for the E/C/F/TAF group in the extension phase.

2.1.6.2.2. Virologically Suppressed Subjects

2.1.6.2.2.1. Study GS-US-292-0109

Few subjects in either group in Study GS-US-292-0109 discontinued study drug due to AEs (E/C/F/TAF 0.9%, 9 subjects; FTC/TDF+3rd Agent 1.5%, 7 subjects; Table 16). In the E/C/F/TAF group, no AE by PT that led to study drug discontinuation was reported for more than 1 subject. In the FTC/TDF+3rd Agent group, 3 subjects, all of whom were taking ATV/boosted+TVD regimens, had jaundice that led to study drug discontinuation.

Most of the AEs leading to discontinuation were nonserious and considered by the investigator as related to study drug.

2.1.6.2.2.2. Study GS-US-292-0102 Open-Label Extension

No subjects in the switch groups of Study GS-US-292-0102 discontinued treatment due to AEs during the extension phase.

2.1.6.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.6.2.3.1. Study GS-US-292-0112

In Study GS-US-292-0112, AEs leading to study drug discontinuation were reported for 3.3% of Cohort 1 switch subjects (n = 8), with a higher percentage reported in subjects with baseline $eGFR_{CG} < 50$ mL/min (7.5%, n = 6) compared with subjects with baseline $eGFR_{CG} \geq 50$ mL/min (1.2%, n = 2). No individual AE leading to study drug discontinuation was reported in > 1 subject. All AEs leading to discontinuation of study drugs were considered unrelated to the study drug by the investigator, with the exception of 3 subjects (2 with baseline $eGFR_{CG} < 50$ mL/min and 1 with baseline $eGFR_{CG} \geq 50$ mL/min; worsening of sleep disturbance, worsening renal insufficiency, and choking, respectively). Two subjects discontinued study drug due to renal AEs (Section 2.1.7.3.2.3.1.1).

No AEs leading to discontinuation of study drug were reported for Cohort 2 ART-naive subjects.

2.1.6.2.4. ART-Naive Adolescent Subjects

2.1.6.2.4.1. Study GS-US-292-0106

No subject in Study GS-US-292-0106 discontinued study drug due to an AE (Table 16).

2.1.6.3. D/C/F/TAF Study

2.1.6.3.1. ART-Naive Subjects

2.1.6.3.1.1. Study GS-US-299-0102

In Study GS-US-299-0102, AEs leading to study drug discontinuation were reported in similar percentages of subjects in each treatment group (D/C/F/TAF 1.9%, 2 subjects; DRV+COBI+TVD 4.0%, 2 subjects; Table 17). Of the AEs resulting in study drug discontinuation, 2 were considered related to study drug by the investigator for 1 subject in the D/C/F/TAF group (SAE of hypersensitivity and AE of rash), and 1 subject in the DRV+COBI+TVD group (AE of worsening of diarrhea). One subject in the DRV+COBI+TVD group discontinued study drug due to an SAE of renal tubular disorder (Section 2.1.7.3.3.1.1.1). No individual AE leading to study drug discontinuation was reported in > 1 subject.

2.1.6.4. Phase 1 TAF Safety Population

Discontinuations due to AEs in the E/C/F/TAF, D/C/F/TAF, TAF and F/TAF Phase 1 studies are summarized in Table 29. No treatment-related trends were observed regarding discontinuations due to AEs in these studies.

Table 29. Phase 1 TAF Safety Population: Discontinuations Due to Adverse Events

Safety Population	Study No.	No. of Subjects Who Discontinued Due to an AE	AEs Leading to Discontinuation (No. of Subjects)	Associated Treatment and Relationship
E/C/F/TAF Phase 1	GS-US-292-0101	1	Elevated creatine phosphokinase (1)	TAF, related
	GS-US-292-0103	0	—	—
	GS-US-292-0108	1	Headache, urticaria, pruritus (1)	E/C/F/TAF, related
	GS-US-292-0110	0	—	—
	GS-US-292-1316	0	—	—
	GS-US-342-1167	1	Urticaria (1)	SOF/TAF, related
D/C/F/TAF Phase 1	GS-US-299-0101	1	Drug eruption (1)	DRV+COBI, related
TAF Phase 1	GS-120-1101	0	—	—
	GS-US-120-0104	0	—	—
	GS-US-120-0107	0	—	—
	GS-US-120-0108	0	—	—
	GS-US-120-0109	0	—	—
	GS-US-120-0114	0	—	—
	GS-US-120-0117	0	—	—
	GS-US-120-0118	0	—	—
	GS-US-120-1538	0	—	—
	GS-US-120-1554	1	Increased hepatic enzymes	RPV followed by TAF+RPV, related
F/TAF Phase 1	GS-US-311-0101	2	Anxiety (1) Joint abscess (1)	F/TAF+EVG, related FTC/TAF, unrelated
	GS-US-311-1088	0	—	—
	GS-US-311-1386	1	Neutropenia (1)	F/TAF (fasted); related
	GS-US-311-1472	1	Macular rash (1)	E/C/F/TAF; related
	GS-US-311-1473	0	—	—

SOF = sofosbuvir
Source: GS-US-292-0101; GS-US-292-0103; GS-US-292-0108; GS-US-292-0110; GS-US-292-1316; GS-US-342-1167; m5.3.1.2, GS-US-299-0101; GS-120-1101; GS-US-120-0104; GS-US-120-0107; GS-US-120-0108; GS-US-120-0109; GS-US-120-0114; GS-US-120-0117; m5.3.3.4, GS-US-120-0118; m5.3.3.4, GS-US-120-1538; m5.3.3.4, GS-US-120-1554; GS-US-311-0101; m5.3.1.2, GS-US-311-1088; m5.3.3.4, GS-US-311-1386; m5.3.1.2, GS-US-311-1472; m5.3.1.2, GS-US-311-1473

2.1.7. Analysis of Adverse Events by Organ System or Syndrome

2.1.7.1. Summary of Analysis of Adverse Events by Organ System or Syndrome

As TAF is associated with >90% lower systemic TFV exposure relative to that associated with TDF, less off-target TFV-associated toxicity was anticipated in subjects receiving E/C/F/TAF in the Phase 2 and Phase 3 randomized studies, including less impact on the nephrotoxicity and reduced BMD. Results from the Phase 2 Studies GS-US-292-0102 (E/C/F/TAF) and GS-US-299-0102 (D/C/F/TAF) supported this, demonstrating that subjects receiving E/C/F/TAF relative to STB or D/C/F/TAF relative to DRV+COBI+TVD had less impact on BMD, bone turnover biomarkers, serum creatinine, and tubular proteins (urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio). After the primary hypothesis of noninferior efficacy of E/C/F/TAF relative to STB was achieved in the E/C/F/TAF Phase 3 comparative studies, multiplicity adjustments were made for 4 safety endpoints with a fallback procedure in sequential order with prespecified 2-sided alpha levels: hip BMD, spine BMD, serum creatinine, and treatment-emergent proteinuria. Statistically significant differences favoring E/C/F/TAF over STB at Week 48 for all key secondary safety endpoints in ART-naive adults and virologically suppressed subjects were observed: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$), mean change from baseline in serum creatinine ($p < 0.001$), 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; $p < 0.001$).

2.1.7.2. Bone Safety

Bone safety was assessed in the E/C/F/TAF Phase 2 and Phase 3 studies and the Phase 2 D/C/F/TAF study due to the accelerated bone loss seen in the HIV-infected population. The initiation of ART in treatment-naive HIV-infected adults is associated with a subsequent decrease in BMD in the first 12 to 24 months of use, after which BMD appears to stabilize or to show some degree of recovery. The decrease in BMD appears to be greater with TDF than with other NRTIs {11882}, {17735}, {29368}, {18854}.

2.1.7.2.1. Methodology

The PTs included in the analysis of fracture events for the E/C/F/TAF studies were defined by the Gilead medical monitor in a blinded fashion prior to database lock, based on both the Standardized MedDRA Query for osteoporosis/osteopenia and on the HLGT for fractures.

In studies that enrolled adults, clinical BMD status was assessed using BMD T-scores; normal bone status was defined by a BMD T-score ≥ -1, osteopenia by a T-score from < -1 to ≥ -2.5, and osteoporosis by a T-score < -2.5 {16957}. Assessment of BMD Z-scores in adolescents is described in Section 2.1.7.2.2.4.1.2.

The 10-year probability of hip fracture and of major osteoporotic fracture (FRAX analysis) was calculated for subjects ≥ 40 years of age, as it is validated only for these subjects.

2.1.7.2.2. E/C/F/TAF Studies

2.1.7.2.2.1. ART-Naive Subjects

2.1.7.2.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Bone safety is described in detail in the respective CSRs for Studies GS-US-292-0104 and GS-US-292-0111 (GS-US-292-0104 Week 48 CSR, Section 11.2.4.1; GS-US-292-0111 Week 48 CSR, Section 11.2.4.1).

2.1.7.2.2.1.1.1. Fracture Events

In Studies GS-US-292-0104 and GS-US-292-0111, the incidence of fracture events was similar in both treatment groups (E/C/F/TAF 1.3%, 11 subjects; STB 1.7%, 15 subjects; E/C/F/TAF ISS, Table 24). One fracture AE in each group was reported as serious: ankle fracture (E/C/F/TAF) and thoracic vertebral fracture (STB) (E/C/F/TAF ISS, Table 14). None of the reported fracture AEs were considered by the investigator as related to the study drugs or resulted in discontinuation of study drugs.

2.1.7.2.2.1.1.2. Bone Mineral Density

Percentage Change from Baseline in Hip and Spine BMD

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111, respectively. Statistical analysis using the fallback procedure confirmed that there were significant differences in the changes from baseline using adjusted alphas that were dependent on the results from preceding tests.

Mean percentage decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48; Figure 1 and Figure 2; E/C/F/TAF ISS, Tables 20.1.2 and 20.2.2). Mean (SD) baseline hip BMD values were similar for each treatment group (E/C/F/TAF 1.041 [0.1557] g/cm^2; STB 1.028 [0.1480] g/cm^2); decreases from baseline at Week 48 were as follows: E/C/F/TAF 0.657% (3.2646%), STB 2.948% (3.4095%). Mean (SD) baseline spine BMD was higher in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 1.135 [0.1759] g/cm^2; STB 1.114 [0.1625] g/cm^2; $p = 0.011$); decreases from baseline at Week 48 were as follows: E/C/F/TAF 1.301% (3.0823%), STB 2.862% (3.2460%).

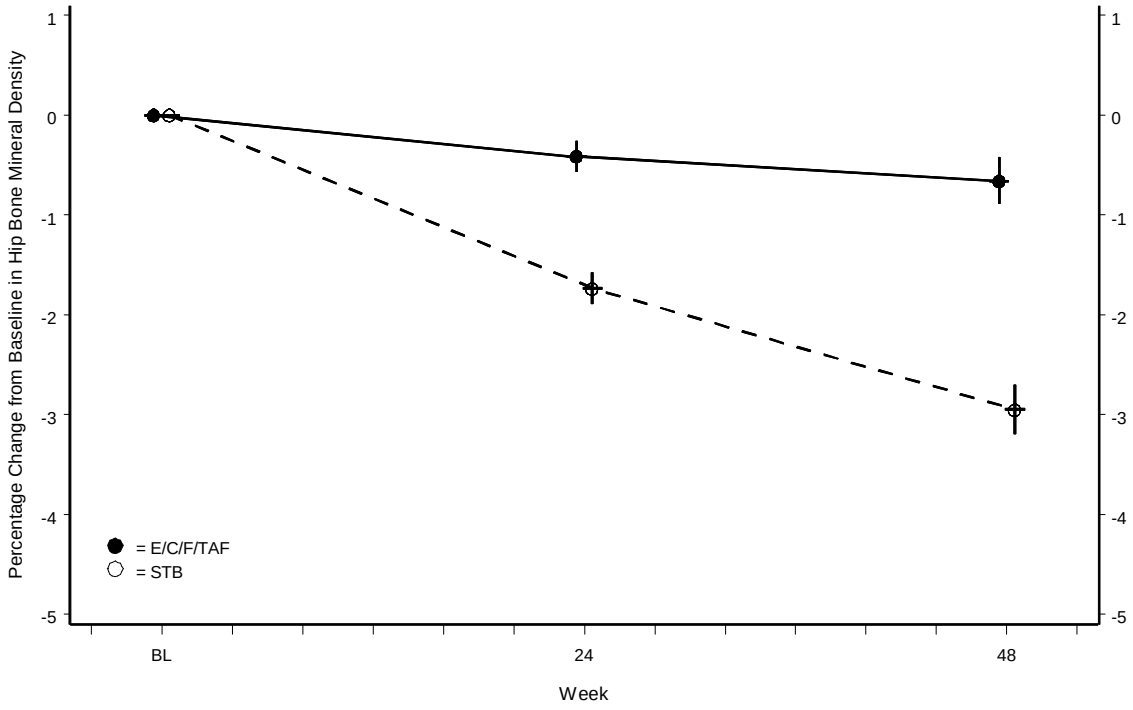
Analysis using the last observation carried forward (LOCF) method to replace missing values showed similar results to the observed data (E/C/F/TAF ISS, Tables 20.1.1 and 20.2.1).

Sensitivity analyses of percentage changes from baseline in BMD at the hip or at the spine were performed to exclude subjects who took osteoporosis medications during the study. Results were similar to those observed for all subjects in the Hip and Spine DXA Analysis Sets (GS-US-292-0104 Week 48 CSR, Section 11.2.4.1.2.1; GS-US-292-0111 Week 48 CSR, Section 11.2.4.1.2.1).

The potential for a differential effect of younger age on changes in BMD for E/C/F/TAF and STB groups was assessed in a subset of subjects aged 18 to 25 years in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102. Like children and adolescents, subjects in this age group have not yet achieved peak bone mass. In a pooled analysis of subjects 18 to 25 years of age from Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102, mean percentage decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48; E/C/F/TAF ISS, Tables Req6799.1.1 and Req6799.1.2). Mean (SD) baseline hip BMD values were similar for each treatment group (E/C/F/TAF 1.073 [0.1599] g/cm^2; STB 1.071 [0.1562] g/cm^2); decreases from baseline at Week 48 were as follows: E/C/F/TAF 1.044% (3.4849%), STB 3.677% (3.3658%). Mean (SD) baseline spine BMD were similar for each treatment group (E/C/F/TAF 1.134 [0.1625] g/cm^2; STB 1.103 [0.1495] g/cm^2); decreases from baseline at Week 48 were as follows: E/C/F/TAF −1.123% (2.9321%), STB −2.597% (2.9819%). These results were similar to that observed in all ART-naive adults.

Decreased bone density was reported as a nonserious AE for 3 subjects (0.3%) in the E/C/F/TAF group and for 4 subjects (0.5%) in the STB group (E/C/F/TAF ISS, Tables 7 and 14). Decreased bone density was considered related to study drugs by the investigator for 2 subjects (0.2%) in each treatment group (E/C/F/TAF ISS, Table 11). No AEs of decreased bone density resulted in discontinuation of study drugs.

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



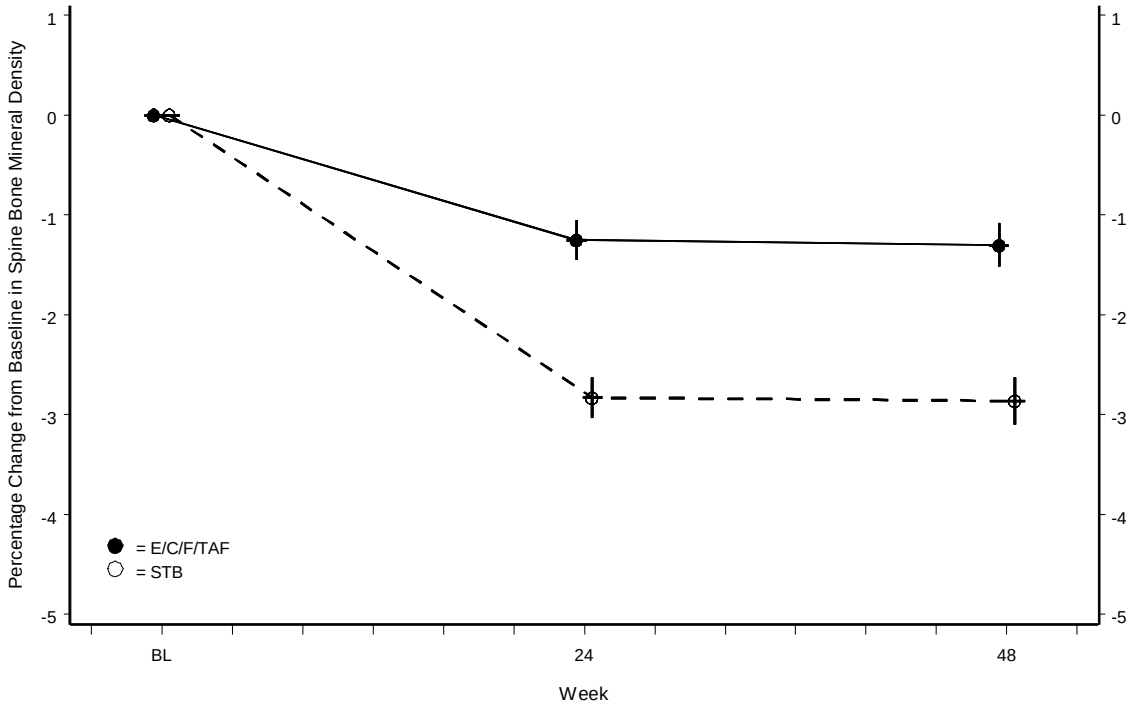
E/C/F/TAF (n=):	836	789	780
STB (n=):	848	815	767

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

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

Source: E/C/F/TAF ISS, Figure 3.2.1

Figure 2. **E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set)**



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

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

Data Extracted: s292-0104: CRF,DXA Data: [redacted], Lab Data: [redacted], s292-0111: CRF,DXA Data: [redacted], Lab Data: [redacted]
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out [redacted] 17:41

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

Categorical Distribution of Percentage Change from Baseline in BMD

Differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were statistically significant ($p < 0.001$ at Weeks 24 and 48). At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a > 3% decrease from baseline in hip BMD (E/C/F/TAF 16.8%, 131 of 780 subjects; STB 50.1%, 384 of 767 subjects) and spine BMD (E/C/F/TAF 26.5%, 208 of 784 subjects; STB 45.8%, 354 of 773 subjects; E/C/F/TAF ISS, Tables 22.1 and 22.2). At Week 48, more subjects in the E/C/F/TAF group compared with the STB group had a > 3% increase from baseline in hip BMD (E/C/F/TAF 6.7%, 52 of 780 subjects; STB 3.3%, 25 of 767 subjects) and spine BMD (E/C/F/TAF 6.5%, 51 of 784 subjects; STB 2.8%, 22 of 773 subjects.

Hip and Spine BMD Clinical Status

The distribution of the clinical BMD status at the hip or spine was similar across the 2 treatment groups at baseline (Table 30 and Table 31). The majority of subjects had normal BMD status measured at the hip (E/C/F/TAF 77.8%, 642 of 826 subjects; STB 74.4%, 626 of 841 subjects) or the spine (E/C/F/TAF 69.8%, 583 of 835 subjects; STB 65.8%, 555 of 843 subjects). Approximately 25% to 30% of subjects had an osteopenic or osteoporotic BMD status at baseline (hip: E/C/F/TAF 22.3%, 184 of 826 subjects; STB 25.6%, 215 of 841 subjects; spine: E/C/F/TAF 30.2%, 252 of 835 subjects; STB 34.2%, 288 of 843 subjects). More subjects in both treatment groups had osteoporotic spine BMD status (E/C/F/TAF: 0.6%, 5 of 826 subjects; STB 0 subjects) compared with osteoporotic hip BMD status (E/C/F/TAF: 4.0%, 33 of 835 subjects; STB 2.7%, 23 of 843 subjects) at baseline.

The distribution of the clinical BMD status adjusted for baseline status was significantly different between treatment groups at Weeks 24 and 48 at the hip or at the spine ($p < 0.001$ at Week 24 and Week 48 for hip and spine). Based on the number of subjects with available data at Week 48, fewer subjects in the E/C/F/TAF group had worsening hip BMD clinical status from baseline (normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis) compared with the STB group (E/C/F/TAF 3.6%, 28 of 768 subjects; STB 7.5%, 57 of 761 subjects). Similarly, fewer subjects in the E/C/F/TAF group had worsening spine BMD clinical status at Week 48 compared with the STB group (E/C/F/TAF 8.0%, 60 of 747 subjects; STB 12.5%, 93 of 746 subjects).

Table 30. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Clinical Hip BMD Status at Baseline and Week 48 (Hip DXA Analysis Set)

	E/C/F/TAF (N=836) Baseline				STB (N=848) Baseline				E/C/F/TAF vs STB p-value
	Normal (N=642)	Osteopenia (N=179)	Osteoporosis (N=5)	Missing (N=10)	Normal (N=626)	Osteopenia (N=215)	Osteoporosis (N=0)	Missing (N=7)	
At Week 48									
Normal	575 (95.8%)	14 (8.3%)	0	4	509 (90.4%)	8 (4.0%)	0	2	<.001
Osteopenia	24 (4.0%)	151 (89.9%)	0	0	54 (9.6%)	187 (94.4%)	0	1	
Osteoporosis	1 (0.2%)	3 (1.8%)	5 (100.0%)	0	0	3 (1.5%)	0	1	
Missing	42	11	0	6	63	17	0	3	

The denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.
Only subjects with nonmissing hip BMD for the baseline visit were included in Hip DXA Analysis Set.
Clinical BMD Status is defined based on T-score, where Normal: >= −1.0; Osteopenia: >= −2.5 to < −1.0; Osteoporosis: < −2.5.
P-value was from rank analysis of covariance adjusting for baseline clinical status for treatment comparison.
Due to age limitation, some subjects had BMD values, but no T-score to define clinical status.
Source: E/C/F/TAF ISS, Table 21.1

Table 31. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Clinical Spine BMD Status at Baseline and Week 48 (Spine DXA Analysis Set)

	E/C/F/TAF (N=845) Baseline				STB (N=850) Baseline				E/C/F/TAF vs STB p-value
	Normal (N=583)	Osteopenia (N=219)	Osteoporosis (N=33)	Missing (N=10)	Normal (N=555)	Osteopenia (N=265)	Osteoporosis (N=23)	Missing (N=7)	
At Week 48									
Normal	493 (91.1%)	14 (6.8%)	0	2	428 (85.3%)	5 (2.0%)	0	2	<.001
Osteopenia	48 (8.9%)	180 (87.4%)	3 (10.0%)	2	74 (14.7%)	220 (90.2%)	2 (9.5%)	1	
Osteoporosis	0	12 (5.8%)	27 (90.0%)	0	0	19 (7.8%)	19 (90.5%)	1	
Missing	42	13	3	6	53	21	2	3	

The denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.
Only subjects with nonmissing spine BMD for the baseline visit were included in Spine DXA Analysis Set.
Clinical BMD Status is defined based on T-score, where Normal: >= −1.0; Osteopenia: >= −2.5 to < −1.0; Osteoporosis: < −2.5.
P-value was from rank analysis of covariance adjusting for baseline clinical status for treatment comparison.
Due to age limitation, some subjects had BMD values, but no T-score to define clinical status.
Source: E/C/F/TAF ISS, Table 21.2

The incidences of osteopenia and osteoporosis reported as an AE were as follows: osteopenia: E/C/F/TAF 3.7 %, 32 subjects; STB 5.1%, 44 subjects; osteoporosis: E/C/F/TAF 1.3%, 11 subjects; STB 1.5%, 13 subjects (E/C/F/TAF ISS, Table 7). Osteopenia was considered related to study drugs by the investigator for 25 subjects: E/C/F/TAF 8 subjects (0.9%), STB 17 subjects (2.0%); osteoporosis was considered related to study drugs by the investigator for 7 subjects: E/C/F/TAF 3 subject (0.3%), STB 4 subjects (0.5%) (E/C/F/TAF ISS, Table 11). Nineteen of the 32 subjects in the E/C/F/TAF group and 18 of the 44 subjects in the STB group who had AEs of osteopenia were reported prior to Day 30 (GS-US-292-0104 Week 48 CSR, Appendix 16.2, Listing 17; GS-US-292-0111 Week 48 CSR, Appendix 16.2, Listing 17). Nine of the 11 subjects in the E/C/F/TAF group and 8 of the 13 subjects in the STB group who had AEs of osteoporosis were reported prior to Day 30. The reporting of these events was temporally related to the baseline DXA scan. All AEs of osteopenia or osteoporosis were nonserious, and none resulted in discontinuation of study drugs (E/C/F/TAF ISS, Tables 14 and 16).

2.1.7.2.2.1.1.3. Fracture Probability (FRAX Analysis)

For subjects aged ≥ 40 years, the mean (SD) baseline 10-year probability of a hip fracture by FRAX analysis was low for both treatment groups based on the Hip DXA Analysis Set (E/C/F/TAF 0.34% [0.614%]; STB 0.47% [0.760%]; p = 0.030; E/C/F/TAF ISS, Table 25.1.1). Mean (SD) increase from baseline at Week 48 in hip fracture risk was smaller for the E/C/F/TAF group compared with the STB group (E/C/F/TAF 0.09% [0.311%]; STB 0.17% [0.406%]; difference in LSM −0.08%, 95% CI: - 0.15% to −0.02%; p = 0.008).

For subjects aged ≥ 40 years, the baseline 10-year probability of a major osteoporotic fracture by FRAX analysis was low for both treatment groups based on the Hip DXA Analysis Set, with a lower mean fracture risk observed for the E/C/F/TAF group compared with the STB group (mean [SD] E/C/F/TAF: 2.82% [2.029%]; STB: 3.21% [2.344%]; p = 0.033; E/C/F/TAF ISS, Table 25.2.1). Mean (SD) increase from baseline at Week 48 in major osteoporotic fracture risk was smaller for the E/C/F/TAF group compared with the STB group (E/C/F/TAF 0.26% [0.533%]; STB 0.38% [0.622%]; difference in LSM −0.12%, 95% CI: −0.22% to −0.02%; p = 0.014).

2.1.7.2.2.1.1.4. Bone Laboratory Parameters

Increases from baseline in the bone turnover biomarkers C-telopeptide (bone resorption biomarker) and P1NP (bone formation), as well as PTH, a hormone involved in bone metabolism, were smaller in the E/C/F/TAF group compared with the STB group at both Weeks 24 and 48 ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline; E/C/F/TAF ISS, Tables 23.1, 23.2, and 23.3). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows: C-telopeptide: E/C/F/TAF 9.1% (−9.4%, 32.7%), STB 21.1% (0.0%, 44.6%); P1NP: E/C/F/TAF 26.86% (3.42%, 60.18%), STB 72.85% (41.28%, 120.58%); PTH: E/C/F/TAF 23.0% (−4.5%, 58.7%), STB 41.9% (8.9%, 88.0%).

2.1.7.2.2.1.2. Study GS-US-292-0102

Bone safety for Study GS-US-292-0102 is described in detail in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.2.4.1).

2.1.7.2.2.1.2.1. Fracture Events

In the randomized phase of Study GS-US-292-0102, 1 subject in the E/C/F/TAF group and 2 subjects in the STB group had a fracture event (E/C/F/TAF: pelvic fracture, upper limb [arm] fracture, STB: thoracic vertebral fracture, ankle fracture). Pelvic fracture, upper limb fracture (both in 1 subject), and thoracic vertebral fracture (1 subject) were serious, while the ankle fracture (1 subject) was nonserious. All reported fracture AEs were the result of trauma, considered by the investigator as unrelated to the study drugs, and none resulted in discontinuation of study drugs.

2.1.7.2.2.1.2.2. Bone Mineral Density

Percentage Change from Baseline in Hip and Spine BMD

In the randomized phase of Study GS-US-292-0102, decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups in mean percentage changes from baseline in hip or spine BMD at Weeks 24 and 48; Figure 3 and Figure 4). Mean (SD) percentage decreases from baseline in hip BMD were as follows:

- At Week 24: E/C/F/TAF 0.42% (1.678), STB 2.02% (2.664)
- At Week 48: E/C/F/TAF 0.67% (2.180), STB 3.12% (3.367)

Mean (SD) percentage decreases from baseline in spine BMD were as follows:

- At Week 24: E/C/F/TAF 0.93% (2.965), STB 2.55% (2.507)
- At Week 48: E/C/F/TAF 1.02% (3.447), STB 3.24% (3.219)

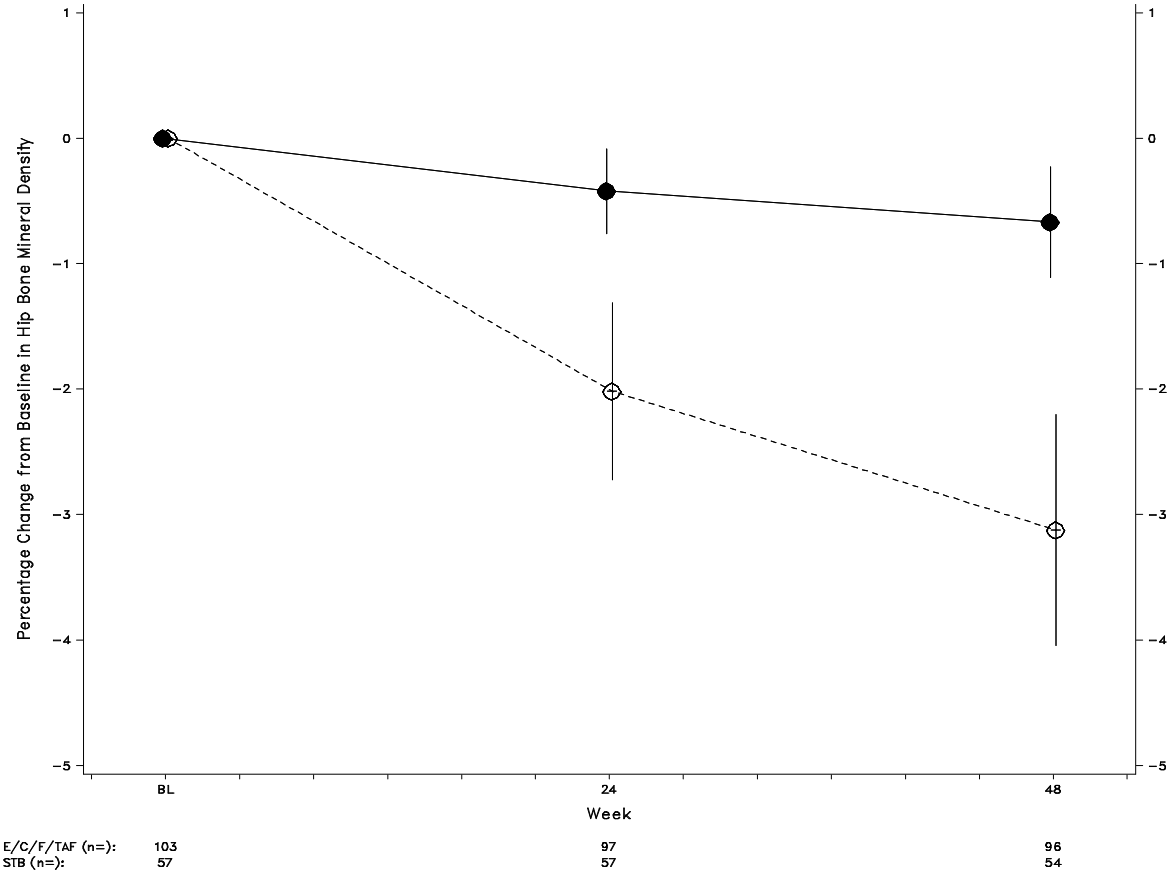
Analysis using LOCF to replace missing values showed similar results to the observed data for the randomized phase.

In the E/C/F/TAF group at Week 96, mean (SD) percentage decreases from baseline in hip or spine BMD were consistent with results at Week 48, as follows: hip 0.78% (2.452%); spine 0.71% (3.697%).

In the randomized phase, differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were statistically significant ($p < 0.001$ for both parameters at Weeks 24 and 48). At Week 48, fewer subjects in the E/C/F/TAF group compared with the STB group had a > 3% decrease from baseline in both hip (E/C/F/TAF 11.5%, STB 44.4%) and spine BMD (E/C/F/TAF 24.3%, STB 53.6%).

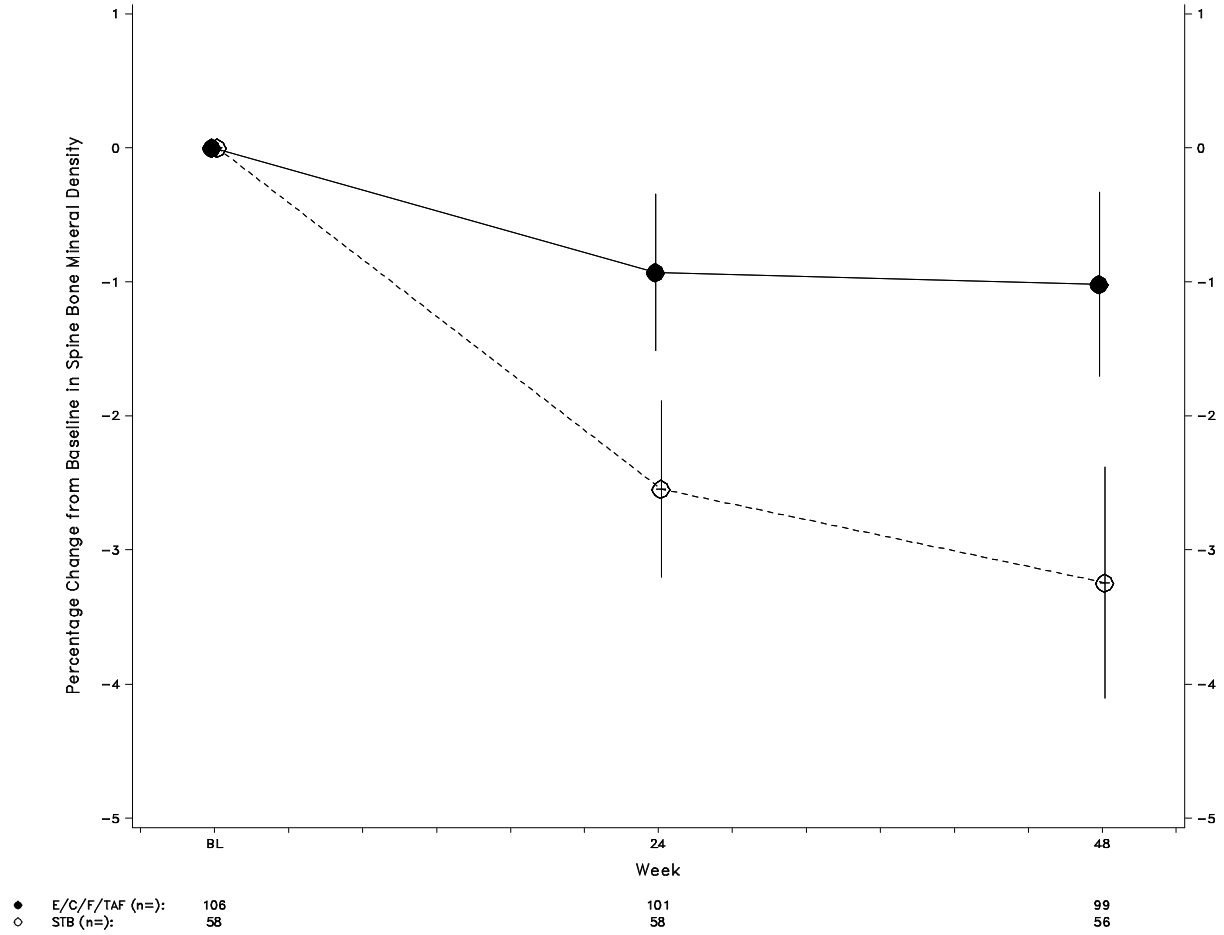
In the E/C/F/TAF group at Week 96, the categorical distributions of percentage change from baseline in hip or spine BMD were consistent with results at Week 48.

Figure 3. E/C/F/TAF Study GS-US-292-0102: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)



Source: GS-US-292-0102 Week 48 CSR, Section 15.1, Figure Req6660.1.1

Figure 4. E/C/F/TAF Study GS-US-292-0102: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)



Source: GS-US-292-0102 Week 48 CSR, Section 15.1, Figure Req6660.2.1

Hip and Spine BMD Clinical Status

In the randomized phase of Study GS-US-292-0102, few subjects in either group had worsening hip or spine BMD clinical status (at Week 48: hip: E/C/F/TAF 3.3%, 3 subjects; STB 9.3%, 5 subjects; spine: E/C/F/TAF 7.4%, 7 subjects; STB 7.1%, 4 subjects).

In the E/C/F/TAF group at Week 96, the numbers of subjects with shifts in hip or spine BMD clinical status were consistent with results at Week 48.

2.1.7.2.2.1.2.3. Bone Laboratory Parameters

In the randomized phase of Study GS-US-292-0102, increases from baseline in the bone biomarkers C-telopeptide and P1NP were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline at Weeks 24 and 48).

Serum bone specific alkaline phosphatase and osteocalcin were only measured at Week 24; results were consistent with those for C-telopeptide and P1NP at this time point.

In the E/C/F/TAF group at Week 96, median percentage changes from baseline in P1NP and C-telopeptide were consistent with results at Week 48.

2.1.7.2.2.2. Virologically Suppressed Subjects

2.1.7.2.2.2.1. Study GS-US-292-0109

Bone safety for Study GS-US-292-0109 is described in detail in the CSR (GS-US-292-0109 Week 48 CSR, Section 11.2.4.1).

2.1.7.2.2.2.1.1. Fracture Events

The percentages of subjects in each group of Study GS-US-292-0109 who had a fracture event were comparable (E/C/F/TAF 1.5%, 14 subjects; FTC/TDF+3rd Agent 0.6%, 3 subjects; $p = 0.20$). In the E/C/F/TAF group 3 fractures were reported as SAEs: skull fracture (Subject *DJ), radius fracture (Subject *DK), and hip fracture (Subject *DL). All the other fracture events reported for subjects in both groups were nonserious. All reported fracture AEs were the result of trauma and considered by the investigator as unrelated to the study drugs; none were indicative of fragility fractures, and none resulted in permanent discontinuation of study drugs.

2.1.7.2.2.2.1.2. Bone Mineral Density

Percentage Change from Baseline in Hip and Spine BMD

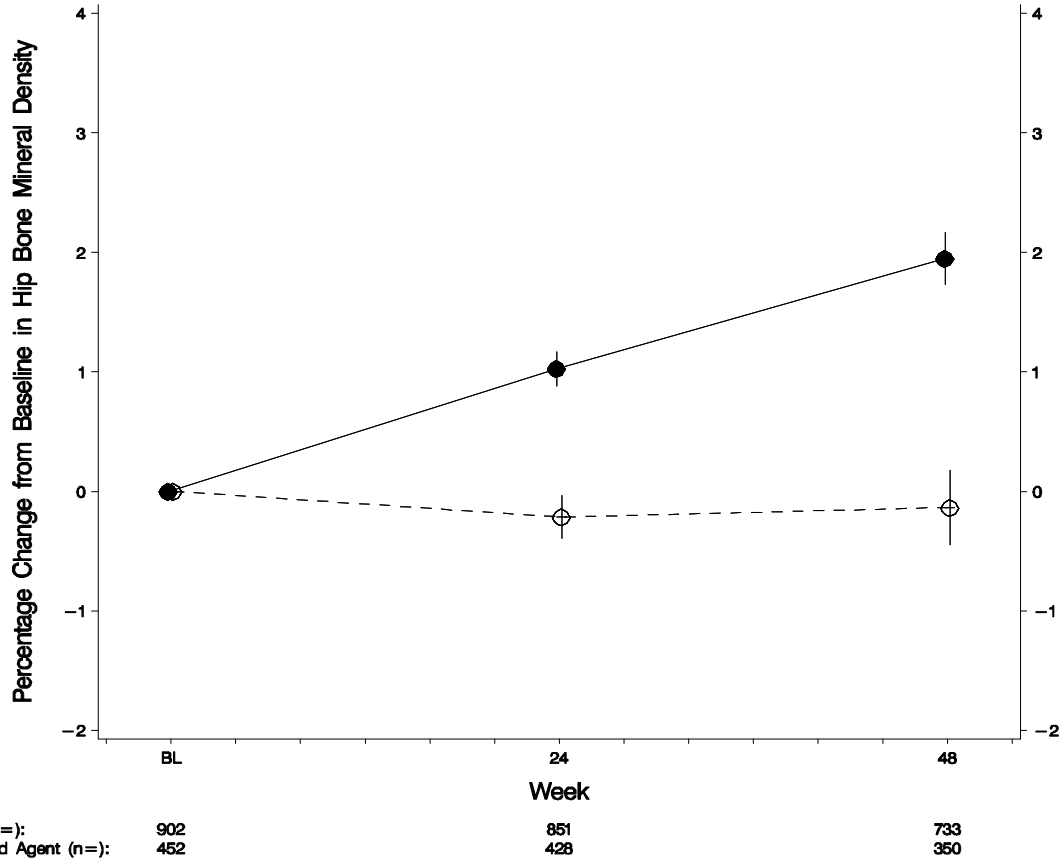
The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for Study GS-US-292-0109, respectively. Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which were dependent on the results from preceding tests. There were increases from baseline in mean (SD) BMD at the hip or at the spine in the E/C/F/TAF group as compared with minimal changes from baseline in both parameters in the FTC/TDF+3rd Agent group at both Weeks 24 and 48 ($p < 0.001$ for the differences between groups; Figure 5 and Figure 6).

Mean (SD) percentage changes from baseline in BMD at Week 48 were as follows:

- Hip: E/C/F/TAF 1.949% (2.9956); FTC/TDF+3rd Agent −0.136% (2.9890)
- Spine: E/C/F/TAF 1.861% (3.0889); FTC/TDF+3rd Agent −0.110% (3.7415)

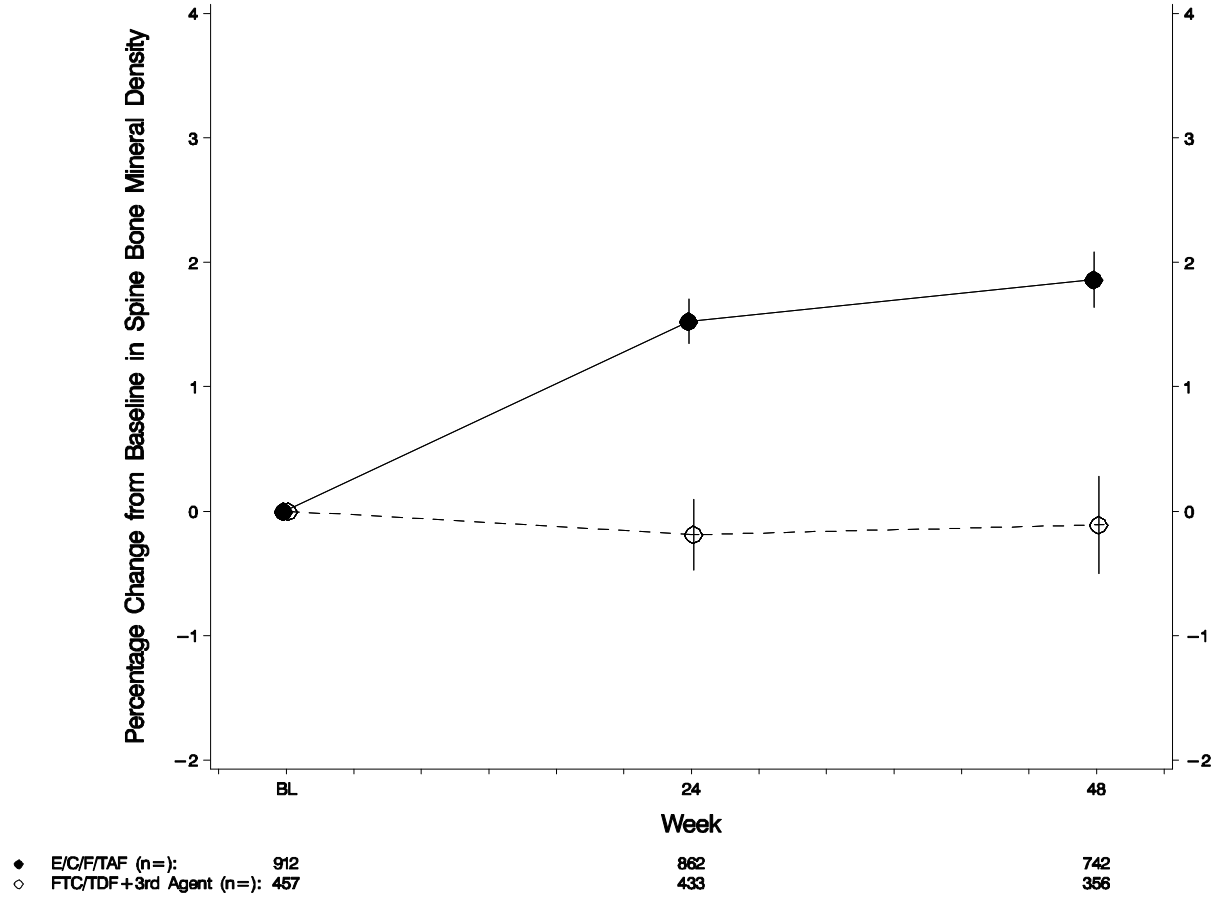
Similar results were obtained when the data were analyzed using the LOCF approach for the Week 48 Hip and Spine DXA Analysis Sets.

Figure 5. **E/C/F/TAF Study GS-US-292-0109: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)**



Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Figure 8.2.1

Figure 6. **E/C/F/TAF Study GS-US-292-0109: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)**



Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Figure 8.2.2

Percentage Change from Baseline in Hip and Spine BMD by Prior Treatment Subgroup

An increase from baseline in BMD was consistently observed for subjects in the E/C/F/TAF group at the hip or at the spine at Weeks 24 and 48, regardless of prior treatment regimen. In contrast, there were minimal changes from baseline in both parameters for subjects who continued on their baseline regimen. Significant differences between the E/C/F/TAF and FTC/TDF+3rd Agent groups were observed at Weeks 24 and 48 for the percentage changes from baseline in hip or spine BMD in each subgroup by prior treatment ($p < 0.001$).

Mean (SD) percentage changes from baseline in hip BMD at Week 48 by prior treatment group were as follows:

- STB: E/C/F/TAF 1.622% (3.0016); FTC/TDF+3rd Agent 0.014% (3.1113); difference in LSM: 1.609%, 95% CI: 0.949% to 2.268%

- ATR: E/C/F/TAF 2.398% (3.3332); FTC/TDF+3rd Agent 0.035% (2.8713); difference in LSM: 2.363%, 95% CI: 1.607% to 3.118%

- ATV/boosted+TVD: E/C/F/TAF 1.883% (2.6358); FTC/TDF+3rd Agent −0.415% (2.9637); difference in LSM: 2.298%, 95% CI: 1.715% to 2.882%

Mean (SD) percentage changes from baseline in spine BMD at Week 48 by prior treatment group were as follows:

- STB: E/C/F/TAF 1.735% (2.9805); FTC/TDF+3rd Agent −0.276% (3.1363); difference in LSM 2.011%, 95% CI: 1.353% to 2.669%

- ATR: E/C/F/TAF 1.686% (3.3176); FTC/TDF+3rd Agent 0.059% (3.3071); difference in LSM 1.626%, 95% CI: 0.858% to 2.395%

- ATV/boosted+TVD: E/C/F/TAF 2.127% (2.9818); FTC/TDF+3rd Agent −0.091% (4.5460); difference: in LSM 2.218%, 95% CI: 1.465% to 2.971%

Similar results were obtained when the data in each subgroup by prior treatment were analyzed using the LOCF approach for the Week 48 Hip and Spine DXA Analysis Sets.

Percentage Change from Baseline in Hip and Spine BMD by Osteoporosis Medication Use

Similar percentages of subjects in each treatment group were taking osteoporosis medications at study entry (E/C/F/TAF 8.7%, 83 subjects; FTC/TDF+3rd Agent 8.0%, 38 subjects). During the study, 7.4% (n = 71) of subjects in the E/C/F/TAF group and 4.0% (n = 19) of subjects in the FTC/TDF+3rd Agent group initiated osteoporosis medications.

Categorical Distribution of Percentage Change from Baseline in BMD

Differences between the 2 treatment groups in the categorical distribution of percentage change from baseline in hip or spine BMD were statistically significant ($p < 0.001$ for both parameters at Weeks 24 and 48.

Higher percentages of subjects in the E/C/F/TAF group had increases from baseline in BMD of > 3% relative to the FTC/TDF+3rd Agent group at Week 24 (hip: E/C/F/TAF 12.0%; FTC/TDF+3rd Agent 2.8%; spine: E/C/F/TAF 28.2%, FTC/TDF+3rd Agent 11.1%) and at Week 48 (hip: E/C/F/TAF 25.2%; FTC/TDF+3rd Agent 8.6%; spine: E/C/F/TAF 33.6%, FTC/TDF+3rd Agent 13.8%; Table 32).

Smaller percentages of subjects in the E/C/F/TAF group had decreases from baseline in BMD of > 3% relative to the FTC/TDF+3rd Agent group at Week 24 (hip: E/C/F/TAF 1.3%, FTC/TDF+3rd Agent 6.5%; spine: E/C/F/TAF 4.6%, FTC/TDF+3rd Agent 14.3%) and at Week 48 (hip: E/C/F/TAF 1.9%; FTC/TDF+3rd Agent 11.1%; spine: E/C/F/TAF 5.8%, FTC/TDF+3rd Agent 17.4%).

Table 32. E/C/F/TAF Study GS-US-292-0109: Percentage of Subjects with > 3% Change in Hip and Spine BMD by Visit (Hip and Spine DXA Analysis Sets)

Percentage Change	Visit	E/C/F/TAF n/N (%)	FTC/TDF+3rd Agent n/N (%)
Hip BMD[a]			
> 3% Decrease	Week 24	11/851 (1.3%)	28/428 (6.5%)
	Week 48	14/733 (1.9%)	39/350 (11.1%)
> 3% Increase	Week 24	102/851 (12.0%)	12/428 (2.8%)
	Week 48	185/733 (25.2%)	30/350 (8.6%)
Spine BMD[b]			
> 3% Decrease	Week 24	40/862 (4.6%)	62/433 (14.3%)
	Week 48	43/742 (5.8%)	62/356 (17.4%)
> 3% Increase	Week 24	243/862 (28.2%)	48/433 (11.1%)
	Week 48	249/742 (33.6%)	49/356 (13.8%)

a The Hip DXA Analysis Set is defined as subjects who received at least 1 dose of study drug and had nonmissing hip BMD for the baseline visit.
b The Spine DXA Analysis Set is defined as subjects who received at least 1 dose of study drug and had nonmissing spine BMD for the baseline visit.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 43.1 and 43.2

Hip and Spine BMD Clinical Status

The majority of subjects in both treatment groups had normal hip and spine BMD clinical status at baseline and retained that status at Week 24 and Week 48.

The distribution of the clinical BMD status adjusted for baseline status was significantly different between treatment groups at Weeks 24 and 48 at the hip ($p \leq 0.002$) or at the spine ($p \leq 0.002$). Based on results for subjects with available data at Week 48, a higher percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had an improvement in hip BMD clinical status (E/C/F/TAF 5.6%, 41 of 733 subjects; FTC/TDF+3rd Agent 2.0%, 7 of 350 subjects), and a lower percentage of subjects in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had worsening hip BMD clinical status (E/C/F/TAF 0.7%, 5 subjects; FTC/TDF+3rd Agent 4.3%, 15 subjects).

Similarly, based on results for subjects with available data at Week 48, a higher percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had an improvement in spine BMD clinical status (E/C/F/TAF 7.5%, 56 of 742 subjects; FTC/TDF+3rd Agent 3.7%, 13 of 356 subjects) and a lower percentage of subjects in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had worsening spine BMD clinical status (E/C/F/TAF 0.9%, 7 subjects; FTC/TDF+3rd Agent 5.1%, 18 subjects).

2.1.7.2.2.2.1.3. Fracture Probability (FRAX Analysis)

For subjects aged ≥ 40 years, the mean (SD) baseline 10-year probability of a hip fracture by FRAX analysis was lower in the E/C/F/TAF group than in the FTC/TDF+3rd Agent group. The mean (SD) change from baseline in fracture risk at Week 48 was 0.00% (0.242) in the E/C/F/TAF group and 0.10% (0.438) in the FTC/TDF+3rd Agent group ($p < 0.001$ for the difference between groups). The change from baseline in the 10-year probability of major osteoporotic fracture at Week 48 was 0.10% (0.386) in the E/C/F/TAF group and 0.23% (0.549) in the FTC/TDF+3rd Agent group ($p = 0.002$ for the difference between groups).

2.1.7.2.2.2.1.4. Bone Laboratory Parameters

There was a decrease from baseline in serum levels of the bone formation biomarker P1NP and also in PTH, involved in bone formation and resorption, in the E/C/F/TAF group as compared with an increase from baseline in both parameters in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). There was no change from baseline in serum levels of the bone resorption biomarker C-telopeptide in the E/C/F/TAF group compared with an increase from baseline in the FTC/TDF+3rd Agent at Week 48 ($p = 0.007$ for the difference between groups).

Median (Q1, Q3) percentage changes from baseline in P1NP, C-telopeptide, and PTH at Week 48 were as follows:

- P1NP: E/C/F/TAF −26.89% (−41.41, −10.63); FTC/TDF+3rd Agent 4.48% (−12.54, 25.36)
- C-telopeptide: E/C/F/TAF 0.0% (−16.0, 18.2); FTC/TDF+3rd Agent 2.9% (−10.0, 22.6)
- PTH: E/C/F/TAF −3.3% (−24.6, 21.7); FTC/TDF+3rd Agent 7.1% (−12.6, 39.4)

2.1.7.2.2.2.2. Study GS-US-292-0102 Open-Label Extension

2.1.7.2.2.2.2.1. Fracture Events

Two subjects in the DRV+COBI+TVD to E/C/F/TAF group had a fracture event (ankle fracture, hand [finger] fracture) during the extension phase. The hand (finger) fracture (Subject *DM) was nonserious while the ankle fracture (Subject *DN) was serious; both events were traumatic, considered by the investigator as unrelated to the study drug, and no action was taken with study drug as a result of either event.

2.1.7.2.2.2.2.2. Bone Mineral Density

Percentage Change from Baseline in Hip and Spine BMD

In contrast to the ART-naive population, increases from baseline in hip or spine BMD were observed at Week 24 of the extension phase in the all TDF to TAF switch group. The mean (SD) percentage increases from baseline in hip or spine BMD at Week 24 were 0.58% (1.963) and 1.18% (3.426), respectively. In the D/C/F/TAF to E/C/F/TAF group, the mean (SD) percentage

changes from baseline in BMD at Week 24 of the extension phase were 0.22% (2.467) at the hip and 0.71% (3.930).

A majority of subjects in the all TDF to TAF group had increases from baseline in BMD at Week 24 of the extension phase (hip: 62.6%; spine: 68.2%; Table 33 and Table 34). Few subjects in this switch group had > 3% decrease from baseline in hip BMD (1.6%) or spine BMD (7.5%).

Table 33. E/C/F/TAF Study GS-US-292-0102: Categorical Distribution of Changes in Hip BMD at Week 24 of the Extension Phase (All E/C/F/TAF Hip DXA Analysis Set)

Percentage Change at Week 24	All TDF to TAF (N=87)	STB to E/C/F/TAF (N=52)	DRV+COBI+TVD to E/C/F/TAF (N=35)	D/C/F/TAF to E/C/F/TAF (N=68)
> 5% Decrease	0/64	0/51	0/13	1/31 (3.2%)
> 3 to <= 5% Decrease	1/64 (1.6%)	1/51 (2.0%)	0/13	0/31
> 1 to <= 3% Decrease	13/64 (20.3%)	11/51 (21.6%)	2/13 (15.4%)	8/31 (25.8%)
> 0 to <= 1% Decrease	10/64 (15.6%)	7/51 (13.7%)	3/13 (23.1%)	5/31 (16.1%)
>=0 to <= 1% Increase	17/64 (26.6%)	11/51 (21.6%)	6/13 (46.2%)	6/31 (19.4%)
> 1 to <= 3% Increase	17/64 (26.6%)	16/51 (31.4%)	1/13 (7.7%)	9/31 (29.0%)
> 3 to <= 5% Increase	3/64 (4.7%)	2/51 (3.9%)	1/13 (7.7%)	1/31 (3.2%)
> 5% Increase	3/64 (4.7%)	3/51 (5.9%)	0/13	1/31 (3.2%)

Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 37.3.1.2

Table 34. E/C/F/TAF Study GS-US-292-0102: Categorical Distribution of Changes in Spine BMD at Week 24 of the Extension Phase (All E/C/F/TAF Spine DXA Analysis Set)

Percentage Change at Week 24	All TDF to TAF (N=89)	STB to E/C/F/TAF (N=53)	DRV+COBI+TVD to E/C/F/TAF (N=36)	D/C/F/TAF to E/C/F/TAF (N=69)
> 5% Decrease	2/66 (3.0%)	2/53 (3.8%)	0/13	3/31 (9.7%)
> 3 to <= 5% Decrease	3/66 (4.5%)	2/53 (3.8%)	1/13 (7.7%)	1/31 (3.2%)
> 1 to <= 3% Decrease	9/66 (13.6%)	6/53 (11.3%)	3/13 (23.1%)	7/31 (22.6%)
> 0 to <= 1% Decrease	7/66 (10.6%)	4/53 (7.5%)	3/13 (23.1%)	0/31
>=0 to <= 1% Increase	11/66 (16.7%)	11/53 (20.8%)	0/13	5/31 (16.1%)
> 1 to <= 3% Increase	16/66 (24.2%)	12/53 (22.6%)	4/13 (30.8%)	5/31 (16.1%)
> 3 to <= 5% Increase	12/66 (18.2%)	10/53 (18.9%)	2/13 (15.4%)	8/31 (25.8%)
> 5% Increase	6/66 (9.1%)	6/53 (11.3%)	0/13	2/31 (6.5%)

Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table 37.3.2.2

Hip and Spine BMD Clinical Status

At Week 24 of the extension phase, few subjects in the switch groups had shifts in hip or spine BMD clinical status.

2.1.7.2.2.2.2.3. Bone Laboratory Parameters

In the all TDF to TAF group, median percentage decreases from baseline were observed for the bone biomarkers serum C-telopeptide and serum P1NP at Week 24 of the extension phase. Serum bone specific alkaline phosphatase and osteocalcin were not measured for the switch groups during the extension phase.

2.1.7.2.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.7.2.2.3.1. Study GS-US-292-0112

Bone safety for Study GS-US-292-0112 is described in detail in the CSR (GS-US-292-0112 Week 24 CSR, Section 11.3.4.1).

2.1.7.2.2.3.1.1. Fracture Events

A total of 5 subjects (2.1%) experienced 6 fracture events, of whom 4 were subjects with pre-switch TDF use and 1 was a subject without pre-switch TDF use. All reported fracture AEs were considered unrelated to study drug by the investigator and none resulted in discontinuation of study drug. One fracture event (spinal compression fracture) was serious. All fracture events were the result of trauma, and none were reported as fragility fractures.

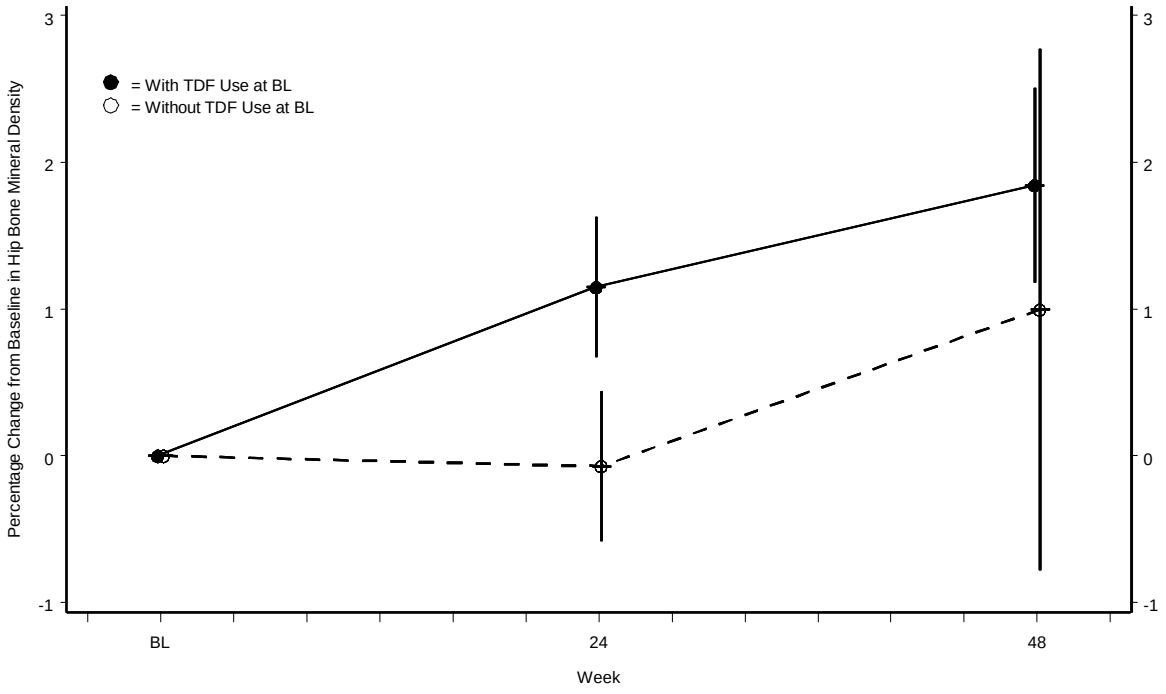
No fracture events occurred in Cohort 2 ART-naive subjects.

2.1.7.2.2.3.1.2. Bone Mineral Density

Percentage Change from Baseline in Hip and Spine BMD

Overall, hip and spine BMD increased for Cohort 1 subjects after switching to E/C/F/TAF. Mean (SD) percentage increases from baseline were observed in hip BMD (Week 24: 0.733% [2.7674]; Week 48: 1.575% [4.5738]) and spine BMD (Week 24: 1.643% [3.6250]; Week 48: 2.368 % [4.2582]; Figure 7 and Figure 8). Mean percentage changes from baseline in hip and spine BMD for those with pre-switch TDF use compared with those without pre-switch TDF use were 1.151% versus −0.071% for hip BMD and 2.370% versus 0.291% for spine BMD at Week 24 and 1.843% versus 0.997% for hip BMD and 2.994% versus 1.104% for spine BMD at Week 48.

Figure 7. E/C/F/TAF Study GS-US-292-0112: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)



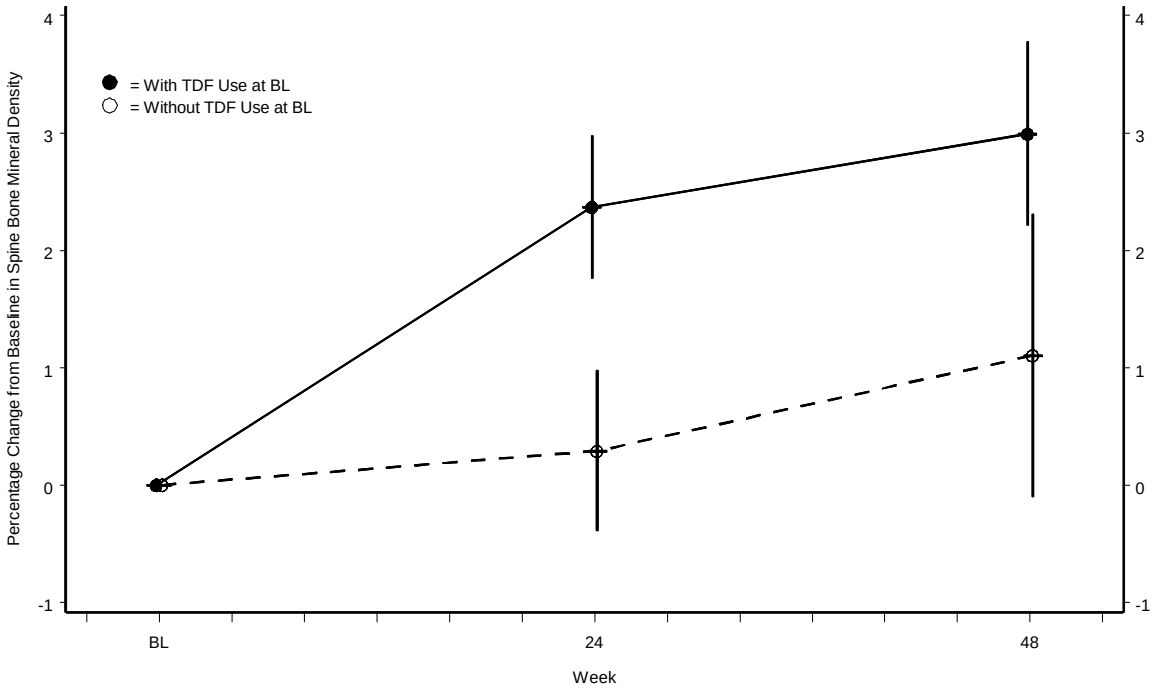
With TDF Use at BL (n=):	154	148	110
Without TDF Use at BL (n=):	82	77	51

BL = Baseline.
Only subjects with nonmissing baseline hip BMD value were included in hip DXA analysis set.

Data Extracted: CRF Data: [redacted], Lab Data: [redacted], Dexa Data: [redacted]
Source: .../version1/prog/t-dexa-bmd.sas v9.2 Output file: g-dexa-hip-bmd-mean.out [redacted]:10:37

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Figure 22.1.2

Figure 8. E/C/F/TAF Study GS-US-292-0112: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)



With TDF Use at BL (n=):	154	147	107
Without TDF Use at BL (n=):	82	79	53

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

Data Extracted: CRF Data: [redacted]20[redacted], Lab Data: [redacted]20[redacted], Dexa Data: [redacted]20[redacted]
Source: .../version1/prog/t-dexa-bmd.sas v9.2 Output file: g-dexa-spine-bmd-mean.out [redacted]P20[redacted]:10:37

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Figure 22.2.2

There was evidence for an improvement in hip and spine BMD after switch to E/C/F/TAF. When assessed using a threshold of 3% for changes from baseline, higher percentages of subjects had increases versus decreases from baseline in BMD at both the hip (Week 24: 13.8% versus 7.2%; Week 48: 22.4% versus 6.3%) and the spine (Week 24: 33.7% versus 8.0%; Week 48: 38.8% versus 4.4%).

Mean (SD) percentage changes from baseline were observed in hip BMD (Week 24: −0.022% [1.6853]; Week 48: −0.222% [2.3207]) and spine BMD (Week 24: −2.686 [4.5755]; Week 48: −4.538 [6.8917]) for Cohort 2 ART-naive subjects. Change from baseline for hip and spine BMD was < 3% in Cohort 2.

2.1.7.2.2.3.1.3. Hip and Spine BMD Clinical Status

Overall, few Cohort 1 switch subjects or Cohort 2 ART-naive subjects had changes from baseline in hip and spine BMD clinical status.

2.1.7.2.2.3.2. Fracture Probability (FRAX Analysis)

FRAX scores were calculated for subjects in Cohort 1 (switch) only.

For subjects aged ≥ 40 years, the mean (SD) baseline 10-year probability of hip fracture was lower in subjects with pre-switch TDF use than subjects without pre-switch TDF use based on the Hip DXA Analysis Set (with TDF use 1.40% [1.814]; without pre-switch TDF use 1.92% [3.237]; difference in LSM −0.52%, 95% CI: −1.18% to 0.15%; p = 0.13). Mean (SD) change from baseline at Week 24 in hip fracture risk slightly decreased in subjects with pre-switch TDF use and increased in subjects without pre-switch TDF use (with pre-switch TDF use −0.02% [0.383]; without pre-switch TDF use 0.19% [0.785]; difference in LSM −0.21%, 95% CI: −0.36% to −0.05%; p = 0.010). Mean (SD) change from baseline at Week 48 in hip fracture risk slightly decreased in subjects with pre-switch TDF use and slightly increased in subjects without pre-switch TDF use (with pre-switch TDF use −0.09% [0.505]; without pre-switch TDF use 0.07% [0.605]; difference in LSM −0.16%, 95% CI: −0.34% to 0.02%; p = 0.087).

For subjects aged ≥ 40 years, the mean (SD) baseline 10-year probability of major osteoporotic fracture was lower in subjects with pre-switch TDF use than subjects without pre-switch TDF use based on the Hip DXA Analysis Set (with pre-switch TDF use 5.12% [3.665]; without pre-switch TDF use 6.54% [5.436]; difference in LSM −1.42%, 95% CI: −2.62% to −0.22%; p = 0.020). Mean (SD) change from baseline at Week 24 in major osteoporotic fracture risk slightly increased in subjects with pre-switch TDF use and increased in subjects without pre-switch TDF use (with pre-switch TDF use 0.01% [0.470]; without pre-switch TDF use 0.27% [0.863]; difference in LSM −0.26%, 95% CI: −0.44% to −0.08%; p = 0.005). Mean (SD) from baseline at Week 48 in major osteoporotic fracture risk slightly decreased in subjects with pre-switch TDF use and slightly increased in subjects without pre-switch TDF use (with pre-switch TDF use −0.04% [0.603]; without pre-switch TDF use 0.06% [0.769]; difference in LSM −0.11%, 95% CI: −0.33% to 0.12%; p = 0.35).

2.1.7.2.2.3.3. Bone Laboratory Parameters

Overall, median percentage decreases from baseline for Cohort 1 switch subjects at Weeks 24 and 48 were observed in the bone biomarkers C telopeptide (bone resorption) and PINP (bone formation), as well as PTH, a hormone involved in bone metabolism. For each of the bone laboratory parameters, Cohort 1 switch subjects with pre-switch TDF use had median percentage decreases from baseline at Week 24, whereas those without pre-switch TDF use had median percentage increases from baseline at Week 24. Median (Q1, Q3; baseline value) percentage changes from baseline at Week 24 for subjects with and without pre-switch TDF use were as follows: C-telopeptide: with pre-switch TDF use −5.4% (−19.2%, 7.1%; 4.8 µg/L), without pre-switch TDF use 5.2% (−8.1%, 21.3%; 5.1 µg/L); PINP: with pre-switch TDF use −24.27% (−39.98%, 8.34%; 57.21 ng/mL), without pre-switch TDF use 8.94% (−15.64%, 43.64%; 45.43 ng/mL); PTH: with pre-switch TDF use −15.9% (−32.0%, 8.1%; 48.3 pg/mL), without pre-switch TDF use 14.6% (−9.3%, 65.2%; 43.4 pg/mL).

Overall, median percentage increases from baseline for Cohort 2 ART-naive subjects at Weeks 24 and 48 were observed in C-telopeptide, P1NP, and PTH.

2.1.7.2.2.4. ART-Naive Adolescent Subjects

2.1.7.2.2.4.1. Study GS-US-292-0106

Bone safety for Study GS-US-292-0106 is described in detail in the CSR (GS-US-292-0106 Interim CSR, Section 11.2.4.1).

2.1.7.2.2.4.1.1. Fracture Events

No fractures were reported in Study GS-US-292-0106.

2.1.7.2.2.4.1.2. Bone Mineral Density

Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD

Mean and median baseline values and percentage changes from baseline at Week 24 in spine and TBLH BMD are shown in Table 35.

Table 35. E/C/F/TAF Study GS-US-292-0106: Baseline Value and Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD at Week 24 (Spine and TBLH DXA Analysis Sets)

	Spine (N = 23)		TBLH (N = 23)	
Time Point	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
Baseline (g/cm^2)	0.779 (0.2102)	0.778 (0.677, 0.838)	0.872 (0.1305)	0.856 (0.805, 0.935)
% Change at Week 24	1.726 (4.2840)	2.773 (−1.182, 4.557)	0.772 (2.5631)	0.340 (−1.228, 2.122)

Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 36.1 and 36.2

Two of 23 subjects (8.7%) had a ≥ 4% decrease from baseline in spine BMD at the Week 24 assessment. One of these subjects had a height-age adjusted BMD Z-score > −2 at both baseline and Week 24; the other subject had a height-age adjusted BMD Z-score > −2 at baseline and ≤ 2 at Week 24. No subject had a ≥ 4% decrease from baseline in TBLH BMD at Week 24.

Change from Baseline in Bone Mineral Density Z-Scores

BMD status was also assessed using BMD Z-scores. The Z-score for any BMD value is the number of SDs that value lies below or above the mean BMD of an age-, sex-, and race-matched control group. A Z-score ≤ –2.0 is "below the expected range for age" and is considered to reflect a low bone mass or BMD, while a Z-score > –2.0 is "within the expected range for age." In clinical terms, a Z-score ≤ –2.0 reflects a low bone mass or BMD {30329}. BMD Z-scores were also calculated adjusted for height-age. For both spine and TBLH, height-age adjusted mean and median Z-scores at baseline were closer to zero than unadjusted Z-scores, and changes from baseline in each at Week 24 were numerically smaller than for unadjusted Z-scores. Both

spine and TBLH median (Q1, Q3) height-age adjusted BMD Z-scores were within the expected range for age.

Change from baseline in height-age adjusted spine BMD Z-score was as follows: mean (SD) −0.08 (0.391); median −0.02 (−0.15, 0.13). Change from baseline in height-age adjusted TBLH BMD Z-score was as follows: mean (SD) −0.10 (0.256); median −0.09 (−0.26, 0.10).

Spine and Total-Body-Less-Head Clinical Status

Two subjects showed a worsening (change from > −2 to ≤ −2) in their spine or TBLH height-age adjusted BMD Z-scores from baseline at Week 24.

2.1.7.2.3. D/C/F/TAF Study

2.1.7.2.3.1. ART-Naive Subjects

2.1.7.2.3.1.1. Study GS-US-299-0102

Bone safety for Study GS-US-299-0102 is described in detail in the CSR (GS-US-299-0102, Section 11.2.4.1).

2.1.7.2.3.1.1.1. Fracture Events

No fractures were reported in Study GS-US-299-0102.

2.1.7.2.3.1.1.2. Bone Mineral Density

Percentage Change from Baseline in Hip and Spine BMD

Decreases from baseline in BMD at the hip or spine were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group ($p < 0.001$ for the differences between the 2 groups in mean percentage changes from baseline in hip BMD at Weeks 24 and 48; $p < 0.001$ for the differences between the 2 groups in mean percentage changes from baseline in spine BMD at Week 24 and $p = 0.003$ at Week 48; Figure 9 and Figure 10). Mean (SD) percentage decreases from baseline in hip BMD were as follows:

- At Week 24: D/C/F/TAF 0.53% (2.410), DRV+COBI+TVD 2.09% (2.283)
- At Week 48: D/C/F/TAF 0.84% (2.582), DRV+COBI+TVD 3.82% (2.651)

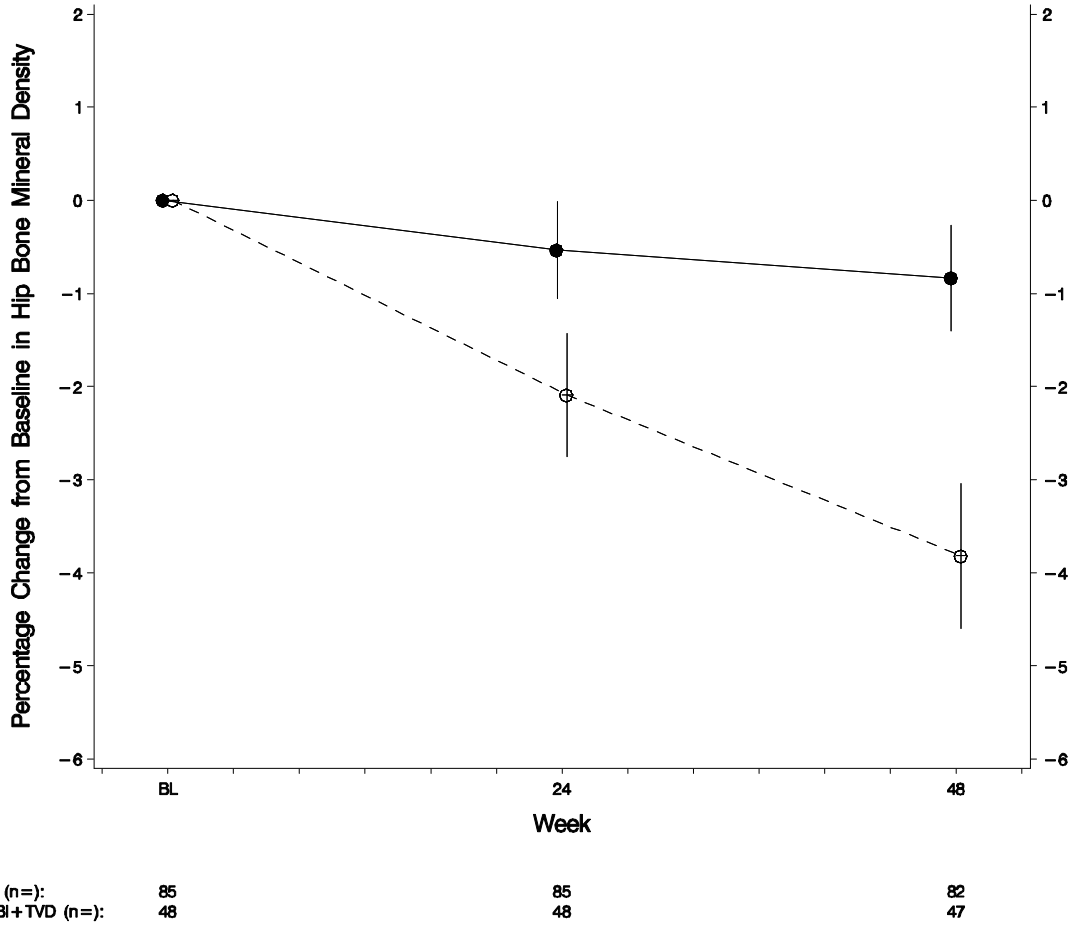
Mean (SD) percentage decreases from baseline in spine BMD were as follows:

- At Week 24: D/C/F/TAF 1.09% (2.972), DRV+COBI+TVD 3.82% (3.633)
- At Week 48: D/C/F/TAF 1.57% (3.920), DRV+COBI+TVD 3.62% (3.128)

Differences between groups in the categorical distribution of percentage change from baseline in hip or spine BMD were statistically significant ($p \leq 0.002$ for both parameters at Weeks 24 and

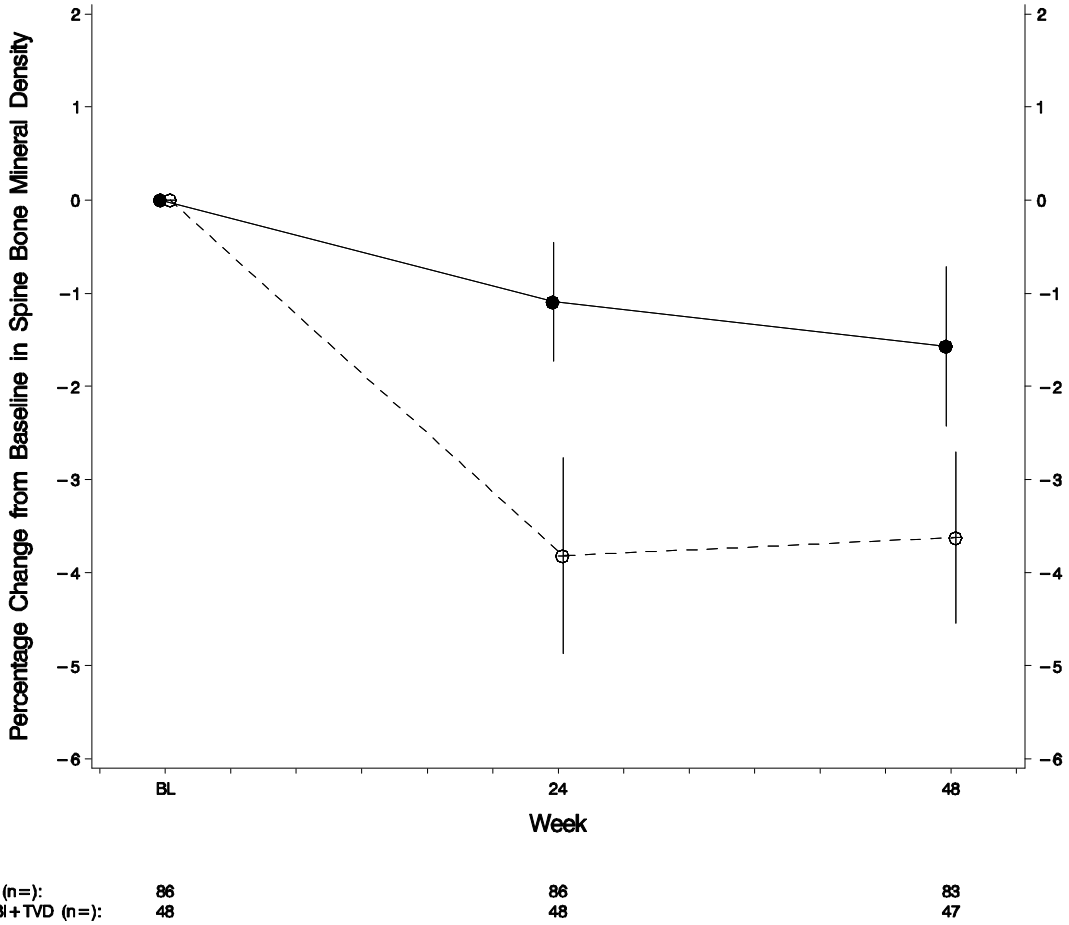
48; m5.3.5.1, GS-US-299-0102, Section 11.2.4.1.2.1). At Week 48, fewer subjects in the D/C/F/TAF group compared with the DRV+COBI+TVD group had a > 3% decrease from baseline in both hip (D/C/F/TAF 18.3%, DRV+COBI+TVD 61.7%) and spine BMD (D/C/F/TAF 32.5%, DRV+COBI+TVD 55.3%).

Figure 9. **D/C/F/TAF Study GS-US-299-0102: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Hip DXA Analysis Set)**



Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Figure Req6835.1

Figure 10. D/C/F/TAF Study GS-US-299-0102: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Spine DXA Analysis Set)



Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Figure Req6835.2

Hip and Spine BMD Clinical Status

The distribution of the clinical BMD status adjusted for baseline status was significantly different between treatment groups at Week 48 at the hip (p = 0.010) and at Weeks 24 and 48 at the spine (p = 0.019 at Week 24; p = 0.024 at Week 48). Fewer subjects in the D/C/F/TAF group had worsening hip or spine BMD clinical status (at Week 48: hip: D/C/F/TAF 2.4%, 2 subjects; DRV+COBI+TVD 15.2%, 7 subjects; spine: D/C/F/TAF 7.2%, 6 subjects; DRV+COBI+TVD 21.7%, 10 subjects).

2.1.7.2.3.1.2. Bone Laboratory Parameters

Median percentage increases from baseline in the bone biomarkers C-telopeptide and P1NP were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group (p < 0.001 for the differences between the 2 groups at Weeks 24 and 48).

Median (Q1, Q3) percentage changes from baseline in C-telopeptide were as follows:

- At Week 24: D/C/F/TAF 33.0% (0.3, 68.0), DRV+COBI+TVD 79.2% (33.7, 149.8)
- At Week 48: D/C/F/TAF 23.2% (−12.2, 77.2), DRV+COBI+TVD 74.4% (34.9, 154.7)

Median (Q1, Q3) percentage changes from baseline in P1NP were as follows:

- At Week 24 : D/C/F/TAF 10.95% (−14.93, 34.18), DRV+COBI+TVD 49.19% (24.68, 75.06)
- At Week 48: D/C/F/TAF 4.73% (−18.68, 27.12), DRV+COBI+TVD 52.47% (20.57, 92.04)

Results for serum bone specific alkaline phosphatase and osteocalcin were consistent with those for C-telopeptide and P1NP at Weeks 24 and 48.

2.1.7.3. Renal Safety

Renal toxicity has been associated with TDF use, and COBI inhibits tubular secretion of creatinine, leading to an increase in serum creatinine and a decrease in eGFR without an effect on aGFR.

2.1.7.3.1. Methodology

In order to ensure a comprehensive assessment of renal safety, a thorough review was performed of all relevant data in the E/C/F/TAF studies for subjects with clinically significant AEs (SAEs and AEs leading to study drug discontinuation) in the renal and urinary disorders SOC and the renal function analyses HLT in the investigations SOC.

There is no commonly accepted laboratory definition of PRT to identify cases in which tubulopathy is likely to evolve clinically in a specific subject. STB clinical studies identified subjects with confirmed increases in serum creatinine plus confirmed increases in 2 of the 3 markers of tubular dysfunction for clinical review. In E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109, the same thresholds for creatinine and tubular dysfunction were used, but the sensitivity was increased, with subclinical renal tubulopathy defined as confirmed abnormalities in any 2 out of the 4 renal parameters (serum creatinine and 3 markers of tubular dysfunction) as follows:

- Increase in serum creatinine ≥ 0.40 mg/dL from baseline (≥ 0.24 mg/dL for the subjects in Study GS-US-292-0109 switching to E/C/F/TAF from therapies other than ATR). The serum creatinine cutoffs were based on the mean + 2 SD of the change in serum creatinine from baseline at Week 48 using pooled data from STB Phase 3 Studies GS-US-236-0102 and GS-US-236-0103. The cutoff of 0.40 mg/dL was based on results from the STB group, and the cutoff of 0.24 mg/dL was based on results from the ATR group.
- Confirmed ≥ 2 grade level increase from baseline in proteinuria

- Confirmed ≥ 1 grade level increase from baseline in hypophosphatemia
- Confirmed ≥ 1 grade level increase from baseline in glycosuria concurrent with serum glucose ≤ 100 mg/dL (normoglycemic glycosuria)

A confirmed laboratory abnormality was defined as an abnormality observed at 2 consecutive postbaseline measurements or an abnormality observed at 1 measurement followed by study drug discontinuation.

Given the known specificity of TFV nephrotoxicity at the proximal tubule cells, changes in tubular proteinuria were assessed by urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio.

2.1.7.3.2. E/C/F/TAF Studies

2.1.7.3.2.1. ART-Naive Subjects

2.1.7.3.2.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Renal safety is described in detail in the respective CSRs for Studies GS-US-292-0104 and GS-US-292-0111 (GS-US-292-0104 Week 48 CSR, Section 11.2.4.2; GS-US-292-0111 Week 48 CSR, Section 11.2.4.2).

2.1.7.3.2.1.1.1. Renal Events

Two subjects in Study GS-US-292-0104, 1 in each treatment group, had a renal SAE, neither of which resulted in discontinuation of study drugs nor was considered related to study drugs by the investigator: Grade 2 nephrotic syndrome (E/C/F/TAF) and Grade 2 acute renal failure (reported as acute kidney injury; STB). In Study GS-US-292-0111, 1 renal SAE (ureteric calculus) was reported for 1 subject in the E/C/F/TAF group, and the event was not considered related to study drugs by the investigator.

Three subjects in Study GS-US-292-0104, all in the STB group, had renal AEs that resulted in discontinuation of study drugs (nephropathy, renal failure, and decreased GFR); the events were nonserious and considered related to study drugs by the investigator. One subject in the STB group in Study GS-US-292-0111 had a renal AE that resulted in discontinuation of study drugs: nonserious, Grade 3 renal failure (reported as renal insufficiency) with concurrent AEs of hypertensive crises and cerebrovascular accident. The renal failure was considered related to study drugs by the investigator.

There were no subjects who reported proximal tubulopathy (including Fanconi syndrome) (E/C/F/TAF ISS, Table 7).

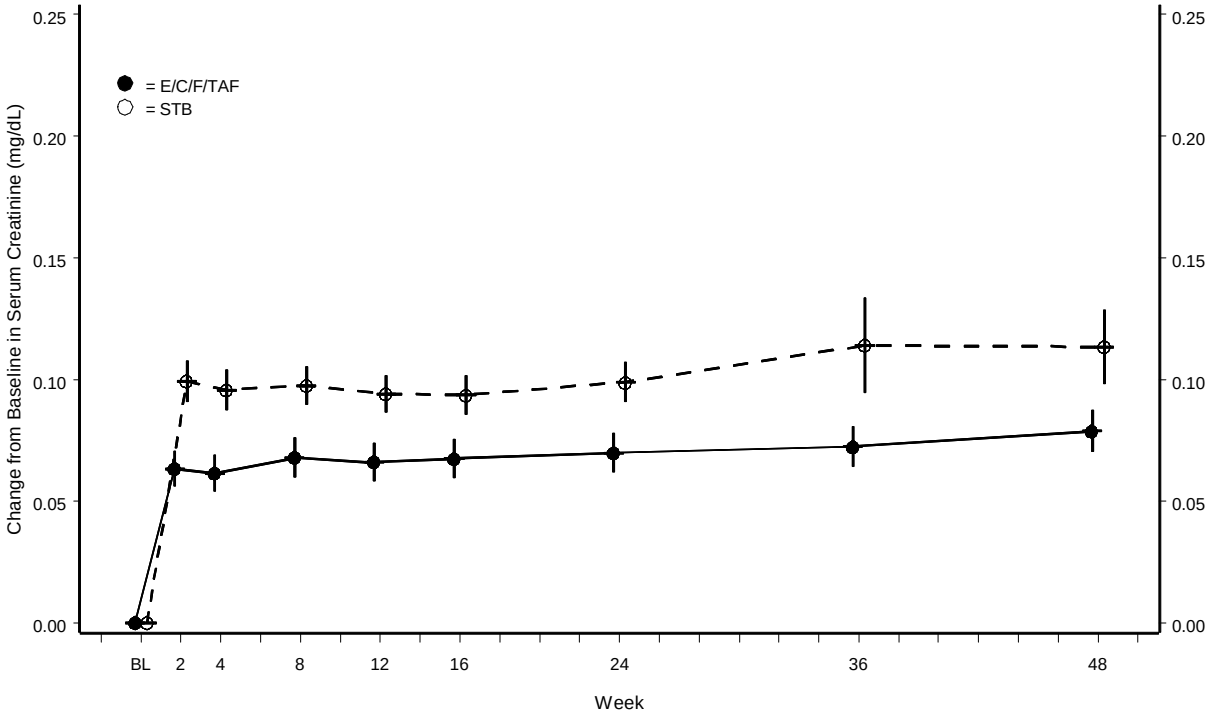
2.1.7.3.2.1.1.2. Renal Laboratory Parameters

Serum Creatinine

The change from baseline in serum creatinine at Week 48 was the third alpha-protected key safety endpoint for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111. Statistical analysis using the fallback procedure confirmed significance using an adjusted alpha, which was dependent on the results from preceding tests. Overall, increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group (Figure 11). Mean (SD) baseline serum creatinine values were as follows: E/C/F/TAF 0.93 (0.172) mg/dL, STB 0.94 (0.169) mg/dL (E/C/F/TAF ISS, Table 26.2). Increases were observed by Week 2 for each treatment group, and remained stable through Week 48. Mean (SD) changes from baseline were as follows: Week 2, E/C/F/TAF 0.06 (0.105) mg/dL, STB 0.10 (0.121) mg/dL ($p < 0.001$); Week 48, E/C/F/TAF 0.08 (0.124) mg/dL, STB 0.11 (0.217) mg/dL ($p < 0.001$). The difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48.

Analysis using LOCF to replace missing values showed similar results to the observed data (E/C/F/TAF ISS, Table 26.1).

Figure 11. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data; Safety Analysis Set)



Source: E/C/F/TAF ISS, Figure 5.2

Graded laboratory abnormalities for serum creatinine were reported for 3.7% of subjects (n = 32) in the E/C/F/TAF group and 5.0% of subjects (n = 43) in the STB group (E/C/F/TAF ISS, Table 18). Most of these abnormalities were Grade 1. Grade 2 serum creatinine abnormalities were reported for 1 subject in the E/C/F/TAF group and 4 subjects in the STB group. Two subjects, both in the STB group, had a Grade 4 serum creatinine abnormality.

Estimated Glomerular Filtration Rate

Overall, decreases from baseline in median $eGFR_{CG}$ values were smaller in the E/C/F/TAF group compared with the STB group (Table 36 and Figure 12). Median (Q1, Q3) baseline $eGFR_{CG}$ values were as follows: E/C/F/TAF 117.0 (99.6, 135.6) mL/min, STB 113.9 (99.0, 133.6) mL/min. Decreases were observed by Week 2 for each treatment group and remained stable through Week 48. Median (Q1, Q3) changes from baseline were as follows: Week 2, E/C/F/TAF −7.2 (−15.0, 0.5) mL/min, STB −10.2 (−17.9, −3.1) mL/min ($p < 0.001$); Week 48, E/C/F/TAF −6.4 (−15.4, 2.4) mL/min, STB −11.2 (−20.2, −2.3) mL/min ($p < 0.001$). The

difference between the treatment groups was statistically significant at all time points from Weeks 2 to 48.

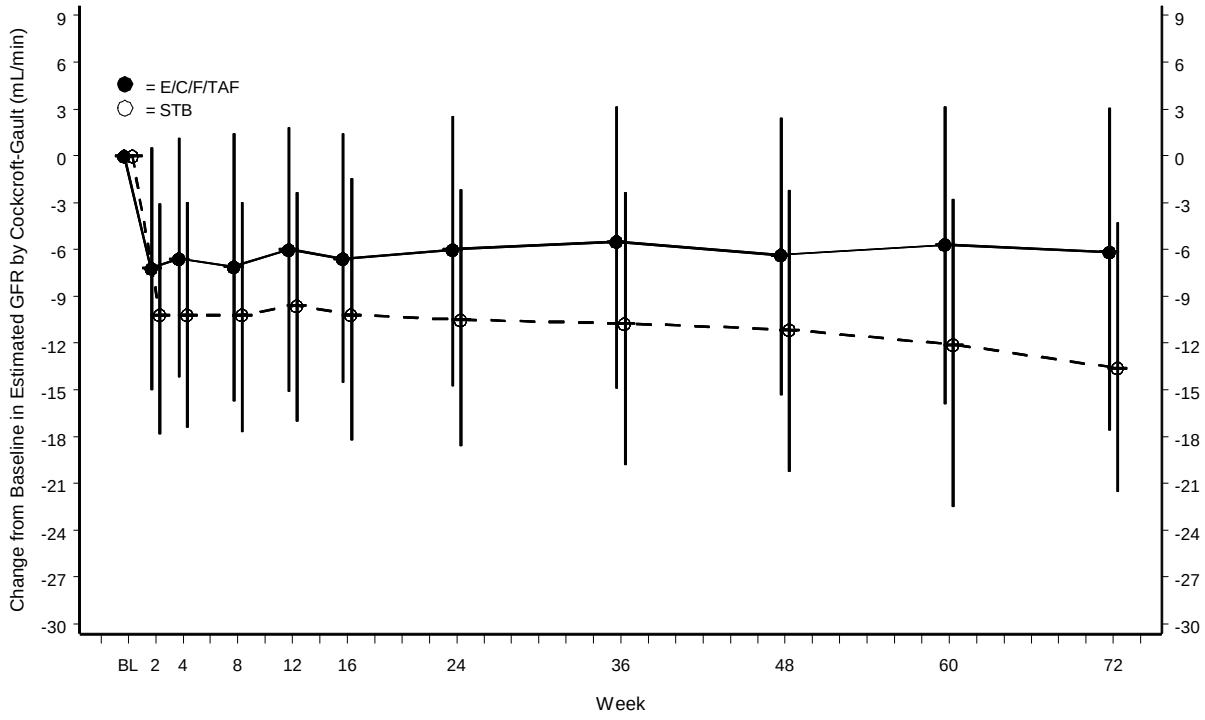
Observations for changes from baseline in $eGFR_{CKD\text{-}EPI,\ creatinine}$ support those seen for $eGFR_{CG}$ (E/C/F/TAF ISS, Table 27.2).

Table 36. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Changes from Baseline in $eGFR_{CG}$ at Weeks 24 and 48 (Safety Analysis Set)

	E/C/F/TAF (N=866)	STB (N=867)	p-value
Baseline			
N	866	867	0.082
Mean (SD)	120.8 (30.87)	118.7 (30.73)	
Median	117.0	113.9	
Q1, Q3	99.6, 135.6	99.0, 133.6	
Change at Week 24			
N	836	833	<0.001
Mean (SD)	−6.3 (14.63)	−10.2 (14.28)	
Median	−6.0	−10.5	
Q1, Q3	−14.8, 2.5	−18.6, −2.2	
Change at Week 48			
N	820	804	<0.001
Mean (SD)	−6.6 (15.37)	−11.2 (15.01)	
Median	−6.4	−11.2	
Q1, Q3	−15.4, 2.4	−20.2, −2.3	

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: E/C/F/TAF ISS, Table 27.1

Figure 12. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Median (Q1, Q3) Change from Baseline in $eGFR_{CG}$ (mL/min) by Visit (Safety Analysis Set)



E/C/F/TAF (n=):	866	825	854	847	842	845	836	829	820	396	128
STB (n=):	867	844	858	850	841	843	833	814	804	375	117

BL = Baseline.

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-lab.sas v9.2 Output file: g-labc-creatclr.out [redacted]20[redacted]:17:46

Source: E/C/F/TAF ISS, Figure 6.1

Proteinuria by Urinalysis (Dipstick)

Proteinuria by urinalysis (dipstick) through Week 48 data cut was the fourth key alpha-protected safety endpoint for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111. Fewer subjects in the E/C/F/TAF group than in the STB group had at least 1 recorded, graded proteinuria by dipstick during the study (E/C/F/TAF 31.2% [269 of 862 subjects]; STB 36.8% [318 of 865 subjects]; p = 0.022; E/C/F/TAF ISS, Table 28). Of the subjects who had proteinuria by urinalysis, most were Grade 1.

Eight subjects (0.9%) in the E/C/F/TAF group and 14 subjects (1.6%) in the STB group had AEs of proteinuria; in addition, 1 subject in the E/C/F/TAF group and 2 subjects in the STB group had an AE of protein urine present (E/C/F/TAF ISS, Table 7). Three subjects (E/C/F/TAF 2 subjects, STB 1 subject) had AEs of proteinuria assessed by the investigator as Grade 2; all other AEs of proteinuria were Grade 1. The AEs of proteinuria were considered related to study

drugs by the investigator for 7 subjects in the E/C/F/TAF group and 10 subjects in the STB group (E/C/F/TAF ISS, Table 11).

Proteinuria by Quantitative Assessment

There was a decrease from baseline in median UPCR for the E/C/F/TAF group that was observed at Week 2 and persisted through Week 48. In contrast, there was an increase from baseline in UPCR in the STB group (median [Q1, Q3] percentage change from baseline at Week 48: E/C/F/TAF: −3.4% [−34.5%, 42.6%]; STB: 19.8% [−23.0%, 75.8%]; Table 37). The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

There was a decrease from baseline in median UACR for the E/C/F/TAF group at Week 48 compared with an increase in the STB group (median [Q1, Q3] percentage change from baseline at Week 48: E/C/F/TAF −4.7% [−32.9%, 35.6%]; STB 7.1% [−26.5%, 62.1%]; $p = 0.001$; Table 37).

A summary of UACR to UPCR ratios from baseline to Week 48 in Study GS-US-292-0104 showed no change in the median percentage change from baseline for the E/C/F/TAF group compared with a decrease for the STB group at Week 48; the difference was statistically significant between treatment groups at Week 48 ($p = 0.022$). In Study GS-US-292-0111, there were no differences in UACR to UPCR ratio between treatment groups at Week 48. In both studies, urine creatinine was similar for both treatment groups at each measured time point.

Table 37. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Renal Biomarkers at Week 48

Parameter	Median Percentage Change (%) (Q1, Q3)		p-value[a]
	E/C/F/TAF	STB	
UPCR (mg/g)	−3.4% (−34.5%, 42.6%)	19.8% (−23.0%, 75.8%)	<0.001
UACR (mg/g)	−4.7% (−32.9%, 35.6%)	7.1% (−26.5%, 62.1%)	0.001
RBP to Urine Creatinine Ratio (µg/g)	9.2% (–23.0%, 48.6%)	51.2% (2.9%, 132.9%)	<0.001
Beta-2-microglobulin to Urine Creatinine Ratio (µg/g)	−31.7% (–57.3%, 3.7%)	24.1% (–33.8%, 167.9%)	<0.001

a p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: E/C/F/TAF ISS, Tables 29.1 to 29.4

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

There was an initial decrease from baseline in RBP to creatinine ratio, followed by a small increase after Week 12 for the E/C/F/TAF group, and a progressive increase from baseline to Week 48 for the STB group (median percentage change from baseline at Week 48: E/C/F/TAF

9.2% [−23.0%, 48.6%]; STB 51.2% [2.9%, 132.9%]; Table 37). The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

The median percentage change from baseline in beta-2-microglobulin to creatinine ratio decreased for the E/C/F/TAF group and increased for the STB group through Week 48 (median percentage change from baseline at Week 48: E/C/F/TAF −31.7% [–57.3%, 3.7%], STB 24.1% [−33.8%, 167.9%]; Table 37). The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

Other Renal Biomarkers

Other renal biomarkers included the marker of proximal renal tubular function, FEUA, and measures of renal phosphate handling, TmP/GFR, and $FEPO_4$, each using unadjusted and adjusted serum creatinine values.

There was no change from baseline in median (Q1, Q3) FEUA using adjusted serum creatinine at Week 48 in the E/C/F/TAF group, compared with an increase in the STB group (E/C/F/TAF 0.0% [–1.3%, 1.1%]; STB 0.4% [–0.8%, 2.0%]; E/C/F/TAF ISS, Table 33.2). The difference between treatment groups was statistically significant at all time points ($p < 0.001$ at Week 48).

At Week 48, there were no differences in median (Q1, Q3) TmP/GFR between treatment groups (E/C/F/TAF −0.1% [−0.6%, 0.4%]; STB −0.2% [−0.6%, 0.3%]; $p = 0.18$; E/C/F/TAF ISS, Table 31.2).

Median (Q1, Q3) $FEPO_4$ using adjusted serum creatinine was increased relative to baseline through Week 48 for both groups (E/C/F/TAF 0.9% [–2.0%, 4.5%]; STB 1.7% [–1.6%, 5.3%]; E/C/F/TAF ISS, Table 32.2). The increase was significantly greater in the STB group relative to the E/C/F/TAF group ($p = 0.005$ at Week 48).

Similar results for FEUA, TmP/GFR, and $FEPO_4$ were observed when values were calculated using unadjusted serum creatinine (E/C/F/TAF ISS, Tables 31.1, 32.1, and 33.1).

Markers of Subclinical Proximal Renal Tubulopathy

No subjects in the E/C/F/TAF group met the criteria for PRT.

2.1.7.3.2.1.2. Study GS-US-292-0102

Renal safety for Study GS-US-292-0102 is described in detail in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.2.4.2).

2.1.7.3.2.1.2.1. Renal Events

In the randomized phase, no subjects discontinued study drugs due to a renal AE.

Two subjects in the E/C/F/TAF group had events of renal failure, considered unrelated to study drugs by the investigator. Neither event resulted in discontinuation of study drugs. No cases of renal failure were reported for subjects in the STB group. Subject *DO in the E/C/F/TAF

group had a Grade 1, nonserious AE of renal failure (reported as renal insufficiency; maximum serum creatinine 1.5 mg/dL) related to volume depletion and the SAE of pyelonephritis. The event resolved within 2 days of onset. Subject *DP in the E/C/F/TAF group had an SAE of acute renal failure due to volume depletion during the extension phase. Renal function returned to normal and treatment with the study drugs, which was interrupted for 6 days, was resumed.

There were no cases of PRT reported (including Fanconi syndrome) in either treatment group.

2.1.7.3.2.1.2.2. Renal Laboratory Parameters

Serum Creatinine

In the randomized phase, increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. Increases were observed at Week 2 for each treatment group and remained stable through Week 48. Mean (SD) increases from baseline at Week 48 were as follows: E/C/F/TAF 0.08 (0.112) mg/dL, STB 0.12 (0.144) mg/dL (p = 0.011). No graded abnormalities of serum creatinine were reported.

Analysis using LOCF to replace missing values showed similar results to the observed data for the randomized phase.

In the E/C/F/TAF group at Week 96, increases from baseline in mean values for serum creatinine were consistent with results at Week 48.

Estimated Glomerular Filtration Rate

In the randomized phase, decreases from baseline in median $eGFR_{CG}$ were smaller in the E/C/F/TAF group compared with the STB group. Decreases were observed at Week 2 for each treatment group and remained stable through Week 48. Median decreases from baseline at Week 48 were as follows: E/C/F/TAF 5.5 mL/min, STB 10.1 mL/min; p = 0.041.

Observations for changes from baseline in $eGFR_{CKD\text{-}EPI,\ creatinine}$ and $eGFR_{CKD\text{-}EPI,\ cysC}$ support those seen for $eGFR_{CG}$.

In the E/C/F/TAF group at Week 96, changes from baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ were consistent with results at Week 48.

Proteinuria by Urinalysis (Dipstick)

In the randomized phase, proteinuria was reported for 26.1% of subjects (n = 29) in the E/C/F/TAF group and 34.5% of subjects (n = 20) in the STB group. Most proteinuria by dipstick was Grade 1 (E/C/F/TAF 23 subjects; STB 19 subjects). One subject in the E/C/F/TAF group had a laboratory abnormality of Grade 3 proteinuria that was also reported as a Grade 1, nonserious AE. The event was not considered related to study drugs by the investigator, and did not result in discontinuation of treatment with study drugs. The subject had negative proteinuria at baseline, which increased to Grade 1 at Week 8, was negative at Weeks 12 and 16, and was

Grade 3 at Week 24. Values fluctuated between negative, trace and 1+ until Week 62, and then remained negative through Week 96. There were no clinically relevant changes in serum creatinine or eGFR after Week 4; quantitative urine protein declined through Week 96; and there was no laboratory or clinical evidence of renal dysfunction.

Proteinuria by Quantitative Assessment

In the randomized phase, no statistically significant differences were observed between the 2 treatment groups in median percentage change from baseline in UPCR or UACR (at Week 48, median percentage changes from baseline for UPCR: E/C/F/TAF −7.2%, STB 13.5%; p = 0.092, for UACR: E/C/F/TAF −6.9%, STB 8.1%; p = 0.089).

In the E/C/F/TAF group at Week 96, median percentage changes from baseline in UPCR and UACR were consistent with results at Week 48.

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

In the randomized phase, there was no change from baseline at Week 48 in RBP to creatinine ratio for the E/C/F/TAF group; however, an increase from baseline was seen for the STB group (E/C/F/TAF −0.1%, STB 36.2%; p = 0.002 for the difference between groups). The median percentage change from baseline in beta-2-microglobulin to creatinine ratio decreased for the E/C/F/TAF group compared with no change for the STB group through Week 48 (change from baseline at Week 48: E/C/F/TAF −40%, STB −1%; p = 0.007 for the difference between groups).

At Week 96, there was a transient increase in median RBP to creatinine ratio for the E/C/F/TAF group (change from baseline at Week 96 was 20.6%). The median decrease from baseline in beta-2-microglobulin to creatinine ratio at Week 96 was consistent with that at Week 48.

Other Renal Biomarkers

There were no changes from baseline in median values for the other renal biomarkers in either group during the randomized phase, with no statistically significant differences between the 2 groups.

There were no changes from baseline at Week 96 in median values for the other renal biomarkers for the E/C/F/TAF group.

2.1.7.3.2.2. Virologically Suppressed Subjects in E/C/F/TAF Studies

2.1.7.3.2.2.1. Study GS-US-292-0109

Renal safety for Study GS-US-292-0109 is described in detail in the CSR (GS-US-292-0109 Week 48 CSR, Section 11.2.4.2).

2.1.7.3.2.2.1.1. Renal Events

One subject in the FTC/TDF+3rd Agent group had a study drug-related SAE of acute renal failure that did not result in discontinuation of study drug. In the E/C/F/TAF group, 2 subjects had nonserious renal AEs (tubulointerstitial nephritis [subject had recurrent hematuria on and off treatment and was diagnosed with Hodgkin's disease after treatment discontinuation] and acute renal failure [event was prerenal, linked to Hodgkin's disease and generalized worsening]) that resulted in discontinuation of the study drug; both events were considered by the investigator as not related to study drug.

There were no AEs of PRT (including Fanconi Syndrome) reported in the E/C/F/TAF group. One subject in the FTC/TDF+3rd Agent group (taking ATV+COBI+TVD) had a study drug-related, nonserious AE of acquired Fanconi syndrome that resulted in discontinuation of study drug.

2.1.7.3.2.2.1.2. Renal Laboratory Parameters

Serum Creatinine

There were decreases or no changes from baseline in mean serum creatinine values in the E/C/F/TAF group as compared with increases or no changes from baseline in the FTC/TDF+3rd Agent group after excluding subjects switching from ATR ($p \leq 0.014$ for the differences between treatment groups at Weeks 2 through 48). At Week 48, the mean (SD) changes from baseline in serum creatinine were as follows: E/C/F/TAF −0.01 (0.117) mg/dL; FTC/TDF+3rd Agent 0.04 (0.123) mg/dL ($p < 0.001$ for the difference between groups).

For changes in serum creatinine analyzed by prior treatment regimen, decreases from baseline were observed among subjects who switched to E/C/F/TAF from STB, and either increases or no changes from baseline at most time points among the subjects who switched to E/C/F/TAF from ATV/boosted regimens. In contrast, among subjects who switched to E/C/F/TAF from ATR, increases in serum creatinine were observed at Week 2 (consistent with the established COBI effect on serum creatinine), and through Week 48.

Estimated Glomerular Filtration Rate

There were increases from baseline in $eGFR_{CG}$ values in the E/C/F/TAF group compared with decreases from baseline in the FTC/TDF+3rd Agent group at Weeks 2 through 48 after excluding subjects switching from ATR. Median changes from baseline at Week 48 were: E/C/F/TAF 1.8 mL/min, FTC/TDF+3rd Agent −3.7 mL/min ($p < 0.001$ for the difference between groups). The changes from baseline in $eGFR_{CG}$ corresponded with those observed for serum creatinine at most time points in both treatment groups among subjects with STB or ATR as their prior regimen and among subjects who remained on ATV/boosted+TVD regimens. Among subjects who switched to E/C/F/TAF from ATV/boosted+TVD regimens, increases from baseline in $eGFR_{CG}$ were observed at most time points, and there was generally no correspondence between $eGFR_{CG}$ and serum creatinine values.

Proteinuria by Urinalysis (Dipstick)

Based on results for subjects with available data at Week 48, a higher percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had improvements from baseline in proteinuria (E/C/F/TAF 7.1%, 55 of 772 subjects; FTC/TDF+3rd Agent 5.6%, 21 of 374 subjects) and a lower percentage in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had worsening proteinuria (E/C/F/TAF 4.3%, 33 of 772 subjects; FTC/TDF+3rd Agent 7.0%, 26 of 374 subjects).

Proteinuria was reported as an AE for a similar percentage of subjects in each treatment group (E/C/F/TAF 1.4%; FTC/TDF+3rd Agent 1.3%); all AEs of proteinuria were Grade 1 or 2 in severity and none resulted in discontinuation of study drugs.

Proteinuria by Quantitative Assessment

There were decreases from baseline in UPCR and UACR in the E/C/F/TAF group as compared with increases from baseline in the FTC/TDF+3rd Agent group at Week 48 ($p < 0.001$ for the differences between groups). Median (Q1, Q3) percentage changes from baseline at Week 48 were as follows:

- UPCR: E/C/F/TAF −18.5% (−45.5, 18.1); FTC/TDF+3rd Agent 9.4% (−16.9, 51.8)
- UACR: E/C/F/TAF −18.4% (−45.1, 21.0); FTC/TDF+3rd Agent 5.3% (−25.5, 58.5)

Decreases from baseline in UPCR and UACR were observed in the E/C/F/TAF group regardless of prior treatment regimen.

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

There were decreases from baseline in the E/C/F/TAF group in urine RBP to creatinine and beta-2-microglobulin to creatinine ratios compared with increases from baseline in both parameters at most time points in the FTC/TDF+3rd Agent group ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline at Week48).

Median (Q1, Q3) percentage changes from baseline in RBP to creatinine and beta-2-microglobulin to creatinine ratios at Week 48 were as follows:

- RBP to creatinine ratio: E/C/F/TAF −32.9% (−63.9, 0.0); FTC/TDF+3rd Agent 15.7% (−22.9, 75.1)
- Beta-2-microglobulin to creatinine ratio: E/C/F/TAF −49.2% (−80.0, −4.9); FTC/TDF+3rd Agent 14.4% (−33.6, 92.9)

Decreases from baseline in both the RBP to creatinine and beta-2-microglobulin to creatinine ratios were observed in the E/C/F/TAF group regardless of prior treatment regimen ($p < 0.001$ for the differences between the 2 groups in median percentage changes from baseline at Week48).

Other Renal Biomarkers

The magnitude of the decrease from baseline in TmP/GFR at Week 48 was comparable in both treatment groups, excluding subjects previously on ATR (median change from baseline at Week 48: E/C/F/TAF −0.1 mg/dL, FTC/TDF+3rd Agent −0.1 mg/dL; p = 0.63). There was minimal change from baseline in $FEPO_4$ at Week 48 in the E/C/F/TAF compared with an increase from baseline the FTC/TDF+3rd Agent group, excluding subjects previously on ATR (median change from baseline at Week 48: E/C/F/TAF 0.1%, FTC/TDF+3rd Agent 0.7%; p = 0.023).

There was a decrease from baseline in FEUA at Week 48 in the E/C/F/TAF group compared with minimal change from baseline in the FTC/TDF+3rd Agent group, excluding subjects previously on ATR (median change from baseline at Week 48: E/C/F/TAF −0.8%, FTC/TDF+3rd Agent 0.1%; p < 0.001). A decrease from baseline in FEUA was observed in the E/C/F/TAF group regardless of prior treatment regimen.

Markers of Subclinical Renal Tubulopathy

No subjects in the E/C/F/TAF group had laboratory findings consistent with subclinical renal tubulopathy. One subject (*DQ) in the FTC/TDF+3rd Agent (taking ATV+COBI+TVD) had all 4 confirmed renal laboratory abnormalities as well as a renal AE of Fanconi syndrome.

2.1.7.3.2.2.2. Study GS-US-292-0102 Open-Label Extension

2.1.7.3.2.2.2.1. Renal Events

There were no cases of renal failure, and no subjects discontinued study drug due to renal AEs in the switch groups during the extension phase of Study GS-US-292-0102.

There were no cases of PRT (including Fanconi Syndrome).

2.1.7.3.2.2.2.2. Renal Laboratory Parameters

Serum Creatinine

In the all TDF to TAF group, decreases from baseline in mean values for serum creatinine were observed as early as Week 2 of the extension phase and were maintained through Week 24 (the mean baseline value was 1.12 mg/dL; mean changes from baseline by visit at Weeks 2 through 24 ranged from −0.02 to −0.05 mg/dL). In the D/C/F/TAF to E/C/F/TAF group, a decrease from baseline in serum creatinine was observed at Week 24 of the extension phase (−0.03 mg/dL).

Estimated Glomerular Filtration Rate

In the all TDF to TAF group, increases from baseline in median values for $eGFR_{CG}$ were observed at as early as Week 2 of the extension phase and were maintained through Week 24: the median baseline value was 99.0 mL/min; the median changes from baseline by visit at

Weeks 2 through 24 ranged from 3.2 to 5.8 mL/min. In the D/C/F/TAF to E/C/F/TAF group, the median changes from baseline in $eGFR_{CG}$ from Week 4 through Week 24 by visit ranged from 0.4 to 3.8 mL/min.

Proteinuria by Urinalysis (Dipstick)

All urine protein abnormalities reported in the switch groups were Grade 1 or Grade 2, and none were reported as an AE.

Proteinuria by Quantitative Assessment

In the all TDF to TAF group, decreases from baseline in UPCR and UACR were seen at Week 24; the median percentage change from baseline at Week 24 for UPCR was −13.0% and for UACR was −10.3%. In the D/C/F/TAF to E/C/F/TAF group, there were no consistent changes from baseline in median values for these parameters.

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

In the all TDF to TAF group, the median percentage change from baseline at Week 24 for the RBP to creatinine ratio was −12.5% and for the beta-2-microglobulin to creatinine ratio was −32.0%. In the D/C/F/TAF to E/C/F/TAF group, the median percentage change from baseline at Week 24 for the RBP to creatinine ratio was −2.5% and for the beta-2-microglobulin to creatinine ratio was −12.0%.

Other Renal Biomarkers

In the switch groups, there were no changes from baseline in median values for the other renal biomarkers.

Markers of Subclinical Proximal Renal Tubulopathy

There were no laboratory findings consistent with subclinical renal tubulopathy.

2.1.7.3.2.3. Subjects with Mild to Moderate Renal Impairment

2.1.7.3.2.3.1. Study GS-US-292-0112

Renal safety for Study GS-US-292-0112 is described in detail in the CSR (GS-US-292-0112 Week 24 CSR, Section 11.2).

2.1.7.3.2.3.1.1. Renal Events

One subject (0.4%) in Cohort 1 had an SAE in the renal and urinary disorders SOC. Subject *DR (baseline $eGFR_{CG} \geq 50$ mL/min group) had a single Grade 3 serum creatinine elevation concurrent with an SAE of acute renal failure; the event was considered unrelated to study drug by the investigator and did not result in discontinuation of study drug. The SAE of

acute renal failure resolved 2 days after onset and the subject's serum creatinine values decreased to below the baseline value (1.85 mg/dL) at each subsequent visit.

Two of 242 subjects (0.8%) in Cohort 1 (both in the baseline $eGFR_{CG}$ < 50 mL/min group) had an AE in the renal and urinary disorders SOC that led to study drug discontinuation (renal failure and renal failure chronic). Both discontinuations were due to declining GFR, 1 subject had labile hypertension and was using concomitant ramipril and valsartan, and the discontinuation for another subject was assessed as likely related to progression of CKD and not related to study drug.

No renal SAEs or AEs in the renal and urinary disorders SOC that led to study drug discontinuation were reported for Cohort 2 ART-naive subjects.

There were no AEs of proximal tubulopathy (including Fanconi Syndrome).

2.1.7.3.2.3.1.2. Renal Laboratory Parameters

Actual GFR

The aGFR was directly measured at baseline, Week 2, 4, and/or 8, and Week 24 using $CL_{iohexol}$ for subjects enrolled in the PK/PD substudy (N = 32). Median (Q1, Q3) changes from baseline in aGFR were −1.8 (−5.3, 3.7) mL/min at Week 2, 4, or 8 and 0.1 (−4.3, 4.4) at Week 24. The GLSM ratios (90% CIs) for Week 2, 4, or 8 and Week 24 versus baseline were 98.94 (93.71, 104.46) and 102.66 (97.11, 108.53), respectively, indicating aGFR was not affected by E/C/F/TAF over 24 weeks of treatment. There was no mean change in aGFR between subjects with baseline $eGFR_{CG}$ < 50 mL/min compared with subjects with baseline $eGFR_{CG} \geq 50$ mL/min. There was also no change in aGFR between subjects with or without pre-switch TDF use. The 90% CIs of the GLSM ratios in all cases were within 80% to 125%.

Serum Creatinine, Cystatin C, and Phosphorus

Median changes from baseline at each time point through Week 48 ranged from −0.01 to 0.04 mg/dL for serum creatinine, −0.06 to −0.01 mg/dL for serum cystatin C, and 0 to 0.3 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters. In subjects whose last prior ART regimen did not include TDF (N = 84), mean (SD) change from baseline in serum creatinine at Week 24 was 0.05 (0.280) mg/dL (E/C/F/TAF ISS, Table Req6909.4).

In Cohort 2 (ART-naive) subjects, median changes from baseline in serum creatinine at each time point through Week 48 ranged from −0.01 to 0.13 mg/dL, indicating no clinically significant changes in serum creatinine in these subjects. Graded serum creatinine laboratory abnormalities (Grade 1 only) were reported for 1 subject. Median changes from baseline at each time point through Week 48 ranged from −0.13 to 0.19 mg/dL for serum cystatin C and −0.6 to 0.2 mg/dL for serum phosphorus, indicating no clinically significant increases or decreases in these parameters.

Estimated Glomerular Filtration Rate

The primary renal endpoints for Study GS-US-292-0112 were defined as change from baseline at Week 24 in $eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ cysC}$, and $eGFR_{CKD\text{-}EPI,\ creatinine}$. No clinically significant changes from baseline eGFR through Week 24 were observed using any of the 3 equations in the Cohort 1 switch and Cohort 2 ART-naive subjects.

In Cohort 1 (switch), the overall median (Q1, Q3) change from baseline in $eGFR_{CG}$ at Week 24 was −0.4 (−4.7, 4.5) mL/min for $eGFR_{CG}$, −1.8 (−6.1, 4.9) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.8 (−4.8, 11.2) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ cysC}$. The baseline $eGFR_{CG}$ < 50 mL/min group had median increases from baseline at Weeks 24 and 48 using any of the 3 equations. The baseline $eGFR_{CG} \geq 50$ mL/min group had an increase in eGFR as assessed by $eGFR_{CKD\text{-}EPI,\ cysC}$ and decreases as assessed by $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ at Weeks 24 and 48.

In Cohort 2 (ART-naive), the median (Q1, Q3) change from baseline in eGFR at Week 24 (primary endpoint) was −0.3 (−3.6, 1.3) mL/min for $eGFR_{CG}$, −2.6 (−11.1, −0.9) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 3.9 (−3.3, 13.2) mL/min/1.73 m^2 for $eGFR_{CKD\text{-}EPI,\ cysC}$.

Proteinuria by Urinalysis (Dipstick)

Most subjects in Cohort 1 had either no change or an improvement (toxicity grade decreased at least 1 grade from baseline) from the baseline proteinuria toxicity grade at Week 24. For 75.0% of subjects (57 of 76) with nonmissing values, the proteinuria grade improved from baseline at Week 24, of whom 22 of 33 (66.7%) had baseline $eGFR_{CG} < 50$ mL/min and 35 of 43 (81.4%) had baseline $eGFR_{CG} \geq 50$ mL/min. For only 5.7% of subjects (13 of 230) with nonmissing values, proteinuria grade worsened from baseline at Week 24, of whom 9 of 75 (12.0%) had baseline $eGFR_{CG} < 50$ mL/min and 4 of 155 (2.6%) had baseline $eGFR_{CG} \geq 50$ mL/min. At Week 24, most subjects had either no change or an improvement (decrease) from the baseline proteinuria toxicity grade irrespective of pre-switch TDF use. In subjects whose last prior antiretroviral regimen did not include TDF, 53% of subjects had an improvement (ie, decrease at least 1 toxicity grade) from baseline in proteinuria as measured by urine dipstick at Week 24 (E/C/F/TAF ISS, Table Req6756.16).

No changes from the baseline proteinuria toxicity grade were observed for Cohort 2 ART-naive subjects.

Proteinuria by Quantitative Assessment

In Cohort 1 (switch subjects), decreases in UPCR from the baseline median of 160.6 mg/g were observed at Week 1 (median of 110.3 mg/g) and persisted through Week 48 (median of 80.1 mg/g). Median (Q1, Q3) UPCR percentage change from baseline at Week 24 was −35.3% (−62.3%, 9.4%). For subjects with baseline $eGFR_{CG} < 50$ mL/min, median (Q1, Q3) baseline UPCR was 270.0 (105.5, 499.5) mg/g, and median (Q1, Q3) percentage change from baseline at Week 24 was −27.6% (−64.8%, 12.2%); for subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median (Q1, Q3) baseline UPCR was 138.5 (68.4, 269.3) mg/g, and median (Q1, Q3) percentage change from baseline format Week 24 was −38.5% (−62.3%, 8.9%). Similar to UPCR, decreases

in UACR from the baseline median (Q1, Q3) of 28.8 (7.9, 83.9) mg/g were observed at Week 1 (median of 16.6 mg/g) and persisted through Week 48 (median of 8.3 mg/g). Median (Q1, Q3) UACR percentage changes from baseline at Week 24 was −38.8% (−72.7%, −0.8%). For subjects with baseline $eGFR_{CG}$ < 50 mL/min, median (Q1, Q3) baseline UACR was 53.2 (14.6, 240.8) mg/g, and median (Q1, Q3) percentage change from baseline at Week 24 was −28.6% (−69.9%, 10.2%). For subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median (Q1, Q3) baseline UACR was 22.7 (6.0, 60.6) mg/g, and median (Q1, Q3) percentage changes from baseline at Week 24 was −43.6% (−73.8%, −6.0%).

Clinically significant proteinuria (UPCR > 200 mg/g) was reported for 42.2% of subjects (101 of 239) with nonmissing values at baseline and 21.2% of subjects (48 of 226) with nonmissing values at Week 24. Clinically significant albuminuria (UACR ≥ 30 mg/g) was reported for 48.9% of subjects (115 of 235) with nonmissing values at baseline and 27.0% of subjects (62 of 230) with nonmissing values at Week 24. In subjects whose last prior antiretroviral regimen did not include TDF, median percentage change from baseline at Week 24 was 0.1% and −19.5%, respectively, for UPCR and UACR (E/C/F/TAF ISS, Tables Req6909.8 and Req6909.9).

In Cohort 2 (ART-naive subjects), changes from baseline in median UPCR and UACR were observed, but no subject developed new clinically significant proteinuria (UPCR > 200 mg/g) or clinically significant albuminuria (UACR ≥ 30 mg/g). Changes in UPCR from the baseline median of 45.9 mg/g were observed from Weeks 1 to 48, with medians of 50.8, 48.8, 48.7, 48.4, 55.0, 43.2, 58.2, 48.9, and 59.9 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively. Changes in UACR from the baseline median of 12.3 mg/g were observed from Weeks 1 to 48, with medians of 5.3, 7.8, 10.4, 8.1, 8.9, 7.2, 12.4, 7.1, and 8.6 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively.

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

Decreases in median percentage change from baseline in urine RBP to creatinine ratio (baseline of 800.5 µg/g) and beta-2-microglobulin to creatinine ratio (baseline of 1562.5 µg/g) were observed from Weeks 1 to 48: RBP to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −71.9% to −43.4%; beta-2-microglobulin to creatinine ratio median percentage changes from baseline from Weeks 1 to 48 ranged from −80.5% to −48.2%. In subjects whose last prior antiretroviral regimen did not include TDF, median percentage change from baseline at Week 24 was −5.5% and −11.8%, respectively, for RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio (E/C/F/TAF ISS, Tables Req6909.6 and Req6909.7).

Changes in urine RBP to creatinine ratio were observed from Weeks 1 to 48 for Cohort 2 ART-naive subjects, with median percentage changes from baseline of 12.1%, −20.8%, −5.0%, −9.6%, 68.8%, and 69.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively. Changes in beta-2-microglobulin to creatinine ratio were observed from Weeks 1 to 48, with median percentage changes from baseline of −15.2%, 43.4%, −47.1%, −10.2%, −19.5%, and 34.3% at Weeks 1, 2, 4, 12, 24, and 48, respectively.

Other Renal Biomarkers

Other renal biomarkers included TmP/GFR ratio, $FEPO_4$, urine FEUA, and urine creatinine. In Cohort 1 (switch), no clinically significant changes from baseline through Week 48 were observed for TmP/GFR, $FEPO_4$, FEUA, or urine creatinine or for the baseline $eGFR_{CG}$ < 50 mL/min and $eGFR_{CG} \geq 50$ mL/min groups; similar results were observed for Cohort 2 (ART-naive).

Markers of Subclinical Proximal Renal Tubulopathy

There were no laboratory findings consistent with subclinical renal tubulopathy.

2.1.7.3.2.4. ART-Naive Adolescent Subjects

2.1.7.3.2.4.1. Study GS-US-292-0106

Renal safety for Study GS-US-292-0106 is described in detail in the CSR (GS-US-292-0106 Interim CSR, Section 11.2.4.2).

2.1.7.3.2.4.2. Renal Events

In Study GS-US-292-0106, there were no renal AEs that led to discontinuation of study drug. One subject had urinary retention of 6 days' duration reported as an SAE considered unrelated to study drug by the investigator; study drug dosing was not interrupted.

No AEs of PRT (including Fanconi syndrome) were reported.

2.1.7.3.2.4.3. Renal Laboratory Parameters

Serum Creatinine

The median (Q1, Q3) change from baseline in serum creatinine was 0.06 (0.00, 0.13) mg/dL at Week 1 (baseline median [Q1, Q3], 0.57 [0.50, 0.71] mg/dL). Creatinine subsequently stabilized without progressive changes; median (Q1, Q3) change from baseline at Week 24 was 0.08 (0.04, 0.17) mg/dL. No graded abnormalities of serum creatinine were reported.

Estimated Glomerular Filtration Rate

The median (Q1, Q3) change from baseline in eGFR (calculated using the Schwartz formula) at Week 1 was −14.0 (−27.0, −1.0) mL/min/1.73 m^2 (baseline median [Q1, Q3], 157.5 [133.0, 187.0] mL/min/1.73 m^2). The median (Q1, Q3) change from baseline at Week 24 was −20.0 (−32.0, −12.0) mL/min/1.73 m^2.

When eGFR was calculated using the modified Schwartz formula, the median (Q1, Q3) change from baseline at Week 2 (the first time point) was −2.6 (−8.4, 5.5) mL/min/1.73 m^2 (baseline median [Q1, Q3], 110.9 [95.8, 118.8] mL/min/1.73 m^2). The median (Q1, Q3) change from baseline at Week 24 was −5.1 (−8.2, 4.5) mL/min/1.73 m^2.

Proteinuria by Urinalysis (Dipstick)

At baseline, 2 of 48 subjects (4.2%) had Grade 1 or Grade 2 proteinuria as assessed by dipstick analysis. Postbaseline, treatment-emergent Grade 1 or Grade 2 proteinuria, generally isolated and transient, was reported for 20.9% (10 of 48 subjects).

Proteinuria by Quantitative Assessment

There were no clinically meaningful changes from baseline in proteinuria as assessed by UPCR (median [Q1, Q3]: baseline, 86.14 [41.49, 139.29] mg/g; percentage change at Week 24, 9.29% [−27.59%, 47.83%]).

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

A reduction from baseline was observed at Week 24 in the urine beta-2-microglobulin to creatinine ratio (median [Q1, Q3]: baseline, 179.16 [92.31, 264.71] µg/g; percentage change from baseline at Week 24, −44.61% [−72.46%, −21.00%]). No clinically meaningful change from baseline in urine RBP to creatinine ratio was observed through Week 24.

Other Renal Biomarkers

No clinically meaningful change from baseline in TmP/GFR, $FEPO_4$, or FEUA was observed through Week 24.

Markers of Subclinical Proximal Renal Tubulopathy

No subject had laboratory findings consistent with PRT.

2.1.7.3.3. D/C/F/TAF Study

2.1.7.3.3.1. ART-Naive Subjects

2.1.7.3.3.1.1. Study GS-US-299-0102

Renal safety for the Phase 2 Study GS-US-299-0102 is described in detail in m5.3.5.1, GS-US-299-0102, Section 11.2.4.2.

2.1.7.3.3.1.1.1. Renal Events

In the D/C/F/TAF Phase 2 Study GS-US-299-0102, there was 1 AE of PRT, which was reported in a subject in the DRV+COBI+TVD group. The event was an SAE of Grade 2 renal tubular disorder (reported as PRT) that resulted in discontinuation of study drug. The event resolved and was not considered by the investigator to be related to study drug. No other subjects discontinued study drug due to a renal AE.

2.1.7.3.3.1.1.2. Renal Laboratory Parameters

Serum Creatinine

Increases from baseline in mean values for serum creatinine in Study GS-US-299-0102 were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group. Mean (SD) baseline serum creatinine was 0.97 (0.139) mg/dL for the D/C/F/TAF group and 1.02 (0.189) mg/dL for the DRV+COBI+TVD group. Increases were observed at Week 2 for each treatment group, and remained stable through Week 48. Mean (SD) increases from baseline at Week 48 were as follows: D/C/F/TAF 0.06 (0.101) mg/dL, DRV+COBI+TVD 0.09 (0.161) mg/dL; p = 0.053). No graded abnormalities of serum creatinine were reported.

Estimated Glomerular Filtration Rate

Decreases from baseline in median $eGFR_{CG}$ in Study GS-US-299-0102 were smaller in the D/C/F/TAF group compared with the DRV+COBI+TVD group. Decreases were observed at Week 2 for each treatment group, and remained stable through Week 48. Median (Q1, Q3) decreases from baseline at Week 48 were as follows: D/C/F/TAF 2.9 (−11.8, 6.2) mL/min, DRV+COBI+TVD 10.6 (−22.4, −0.5) mL/min; p = 0.017.

Observations for changes from baseline in $eGFR_{CKD\text{-}EPI,\ creatinine}$ and $eGFR_{CKD\text{-}EPI,\ cysC}$ support those seen for $eGFR_{CG}$.

Proteinuria by Urinalysis (Dipstick)

Proteinuria was reported for 32.4% of subjects (n = 33) in the D/C/F/TAF group and 34.0% of subjects (n = 17) in the DRV+COBI+TVD group, of which all but 1 were Grade 1 or 2. One subject in the DRV+COBI+TVD group had Grade 3 proteinuria, which was not associated with an AE. Proteinuria (Grade 1) was reported as an AE (considered unrelated to study drug by the investigator) for 1 subject in the DRV+COBI+TVD group.

Proteinuria by Quantitative Assessment

No statistically significant differences were observed between the 2 treatment groups in median percentage change from baseline in UPCR or UACR (at Week 48, median [Q1, Q3] percentage changes from baseline for UPCR: D/C/F/TAF −8.22% [−35.10%, 21.31%], DRV+COBI+TVD −27.52% [−48.28%, 29.36%]; p = 0.19; for UACR: D/C/F/TAF −13.1% [−39.7%, 28.2%], DRV+COBI+TVD −22.6% [−58.8%, 25.9%]; p = 0.17).

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

There was no change from baseline at Week 48 in RBP to creatinine ratio for the D/C/F/TAF group; however, an increase from baseline was seen for the DRV+COBI+TVD group (D/C/F/TAF 9% [−22%, 51%], DRV+COBI+TVD 54% [5%, 152%]; p = 0.003 for the difference between groups). The beta-2-microglobulin to creatinine ratio decreased for the D/C/F/TAF group compared with no change for the DRV+COBI+TVD group through Week 48

(median [Q1, Q3] change from baseline at Week 48: D/C/F/TAF −42.0% [−66.4%, −11.0%]; DRV+COBI+TVD 2.3% [−53.5%, 100.3%]; p = 0.002 for the difference between groups).

Other Renal Biomarkers

There were no clinically relevant changes from baseline in median values for $FEPO_4$ or FEUA (using serum creatinine adjusted or unadjusted values) in either group in Study GS-US-299-0102 and no statistically significant differences between the 2 groups.

2.1.7.4. Ocular Safety

2.1.7.4.1. Summary of Ocular Safety

In a 9-month toxicology study conducted in dogs, some animals administered the highest dose of TAF (12-18 mg/kg) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation. This finding did not occur in animals given lower doses, and it has not occurred in other animal studies. This nonclinical finding has also not been observed in humans, where the dose is much lower, nor have there been reports of posterior uveitis in human clinical studies.

Across all E/C/F/TAF studies, eye disorders were uncommon, balanced between treatment arms, and were considered by the investigator as unrelated to the study drugs. None were indicative of posterior uveitis, and none resulted in permanent discontinuation of study drugs. One subject in Study GS-US-292-0106 had an AE of intermediate uveitis that was considered related to study drug by the investigator but was resolving while the subject continued on study drug without interruption.

In the D/C/F/TAF Phase 2 Study GS-US-299-0102, 6 subjects (5.8%) receiving D/C/F/TAF had nonserious AEs in the eye disorders SOC compared with none of the subjects in the DRV+COBI+TVD group. There were no AEs of uveitis in the study.

2.1.7.4.2. Methodology

Any ophthalmic AE reported by subjects who received at least 1 dose of study drug in the E/C/F/TAF studies was included in an analysis using the SOC term eye disorders, which includes all AEs related to the eye. An additional analysis was performed to detect AEs where the symptoms reported may potentially represent posterior uveitis. This was done by selecting a subset of nonspecific eye disorder PTs, and this list of terms was reviewed and edited by an external ophthalmologist for comprehensiveness.

2.1.7.4.3. E/C/F/TAF Studies

2.1.7.4.3.1. ART-Naive Subjects

2.1.7.4.3.1.1. Studies GS-US-292-0104 and GS-US-292-0111

The incidence of AEs in the eye disorders SOC across Studies GS-US-292-0104 and GS-US-292-0111 was similar for both treatment groups (E/C/F/TAF 7.0%, 61 subjects; STB 7.3%, 63 subjects; Table 38).

Sixteen subjects (1.8%) in the E/C/F/TAF group and 9 subjects (1.0%) in the STB group had AEs in the eye disorders SOC considered related to study drugs by the investigator (E/C/F/TAF ISS, Table 11). One subject in each treatment group had AEs in the eye disorders SOC resulting in discontinuation of study drugs, one of which was also reported as an SAE (for the subject in the STB group (E/C/F/TAF ISS, Table 16). Subject *DS , in the E/C/F/TAF group in Study GS-US-292-0111, had 3 nonserious AEs of Grade 2 eye irritation, eye pain, and eye pruritus. All 3 AEs were considered related to study drugs by the investigator. Subject *DT , in the STB group, had an SAE of Grade 2 iridocyclitis considered unrelated to study drugs by the investigator. Subject *DU , in the STB group, also had an SAE of Grade 2 retinal detachment considered unrelated to study drugs by the investigator; treatment with study drugs continued. Additionally, Subject *DV in the E/C/F/TAF group in Study GS-US-292-0104 had an SAE of retinal detachment following trauma considered unrelated to study drugs by the investigator.

There were no AEs of uveitis in the E/C/F/TAF group in either study (E/C/F/TAF ISS, Table 7). There was 1 uveitis event reported in the STB group in Study GS-US-292-0111 (iridocyclitis, reported as right and left sided anterior uveitis, detailed above). Twenty-three subjects (2.7%) in the E/C/F/TAF group and 15 subjects (1.7%) in the STB group had AEs from the list of identified terms that could represent symptoms of uveitis (E/C/F/TAF ISS, Table 17). The most common potential uveitis AE was vision blurred (E/C/F/TAF 1.3%, 11 subjects; STB 1.0%, 9 subjects). Blurred vision was considered related to study drugs by the investigator for 4 subjects (0.5%) in the E/C/F/TAF group, and 3 subjects (0.3%) in the STB group (E/C/F/TAF ISS, Table 11). Other than the SAE of iridocyclitis detailed above; all other potential uveitis AEs were nonserious, Grade 1 or 2, and did not result in discontinuation of study drugs (E/C/F/TAF ISS, Tables 10, 14, 16, and 17). Other than the SAE of iridocyclitis in the STB group, no other potential uveitis AEs were considered representative of an actual clinical case of uveitis.

Table 38. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Summary of Adverse Events: Eye Disorders (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term	E/C/F/TAF (N=866)	STB (N=867)
Eye disorders	61 (7.0%)	63 (7.3%)
Vision blurred	11 (1.3%)	9 (1.0%)
Eye pain	7 (0.8%)	8 (0.9%)
Dry eye	3 (0.3%)	10 (1.2%)
Eye irritation	6 (0.7%)	2 (0.2%)
Eye pruritus	3 (0.3%)	5 (0.6%)
Conjunctivitis allergic	3 (0.3%)	4 (0.5%)
Blepharitis	2 (0.2%)	4 (0.5%)
Chalazion	3 (0.3%)	2 (0.2%)
Visual acuity reduced	3 (0.3%)	2 (0.2%)
Blepharospasm	1 (0.1%)	3 (0.3%)
Ocular hyperaemia	2 (0.2%)	2 (0.2%)
Photophobia	3 (0.3%)	1 (0.1%)
Visual impairment	4 (0.5%)	0
Astigmatism	1 (0.1%)	1 (0.1%)
Cataract	1 (0.1%)	1 (0.1%)
Conjunctival hyperaemia	1 (0.1%)	1 (0.1%)
Eye discharge	0	2 (0.2%)
Lacrimation increased	2 (0.2%)	0
Periorbital oedema	1 (0.1%)	1 (0.1%)
Pterygium	0	2 (0.2%)
Retinal detachment	1 (0.1%)	1 (0.1%)
Vitreous floaters	1 (0.1%)	1 (0.1%)
Abnormal sensation in eye	0	1 (0.1%)
Asthenopia	1 (0.1%)	0
Blepharitis allergic	1 (0.1%)	0
Blindness	0	1 (0.1%)
Conjunctival haemorrhage	1 (0.1%)	0
Conjunctival pallor	1 (0.1%)	0
Dark circles under eyes	1 (0.1%)	0
Exophthalmos	0	1 (0.1%)

Adverse Events by System Organ Class and Preferred Term	E/C/F/TAF (N=866)	STB (N=867)
Eye allergy	0	1 (0.1%)
Eye disorder	0	1 (0.1%)
Eye swelling	0	1 (0.1%)
Eyelid oedema	0	1 (0.1%)
Eyelid rash	1 (0.1%)	0
Glaucoma	1 (0.1%)	0
Iridocyclitis	0	1 (0.1%)
Photopsia	0	1 (0.1%)
Strabismus	0	1 (0.1%)
Vitritis	1 (0.1%)	0

Adverse events were coded using MedDRA 17.0.
System organ class (SOC) was presented alphabetically, and PT was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: E/C/F/TAF ISS Table 7

2.1.7.4.3.1.2. Study GS-US-292-0102

In the randomized phase of Study GS-US-292-0102, AEs in the eye disorders SOC were reported for 7.1% of subjects (n = 8) in the E/C/F/TAF group (Table 39). No AE in the eye disorders SOC was reported in the STB group.

One nonserious AE of photophobia reported for Subject *DW in the E/C/F/TAF group was considered related to study drugs by the investigator (further details below). All other eye disorder AEs were considered not related to study drugs by the investigator. All eye disorder AEs resolved without treatment and none resulted in discontinuation of study drugs.

Table 39. E/C/F/TAF Study GS-US-292-0102: Summary of Adverse Events: Eye Disorders (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c,d]	E/C/F/TAF (N=112)	STB (N=58)	p-value[e]
Eye disorders	8 (7.1%)	0	0.052
Vision blurred	2 (1.8%)	0	
Conjunctival haemorrhage	1 (0.9%)	0	
Diplopia	1 (0.9%)	0	
Lacrimation increased	1 (0.9%)	0	
Photophobia	1 (0.9%)	0	
Retinal detachment	1 (0.9%)	0	
Visual impairment	1 (0.9%)	0	

a Adverse events were coded using MedDRA 17.0.
b Preferred term was presented by descending order of the total frequencies.
c Eye disorder was defined to be any event with SOC of Eye Disorders.
d Only PTs with at least 1 subject having the event in any treatment group are presented in this table.
e p-value was from the Fisher exact test.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Table Req6674.1

In the SOC of infections and infestations, conjunctivitis was reported for 8.0% of subjects (n = 9) in the E/C/F/TAF group and no subjects in the STB group. All AEs of conjunctivitis were Grade 1 or Grade 2, were nonserious, and resolved without interruption to, or discontinuation of, study drugs. No AE of conjunctivitis was considered related to study drugs by the investigator.

Four subjects in the E/C/F/TAF group had AEs from the list of identified terms that could represent symptoms of anterior or posterior uveitis, none of which resulted in discontinuation of study drugs. These were as follows:

- Subject *DX : a 35-year-old female, had Grade 1 blurred vision on Day 285 that was considered unrelated to study drugs by the investigator and resolved on Day 290 without treatment.

- Subject *DY : a 26-year-old male, had Grade 1 blurred vision and fatigue that began after the first dose of study drugs. The events were considered unrelated to study drugs by the investigator and resolved within 1 month without treatment (exact dates not reported).

- Subject *DW : a 28-year-old male had Grade 1 photophobia (reported as “intermittent light sensitivity”) as well as Grade 1 diarrhea, vomiting, nausea, decreased appetite, headache, and hot flush, which all began on Day 2. All of these AEs were considered related to study drugs by the investigator. The event of photophobia resolved on Day 38 without treatment.

- Subject *DZ : a 40-year-old male had Grade 1 visual impairment (clinically documented as "decreased near vision"; AE reported as "unspecified visual disturbance") on Day 398 (continuing). The event was considered unrelated to study drugs by the investigator. The subject was referred to an ophthalmologist but did not follow up with the referral. The subject's last study visit was Day 642. No further information on the event of visual impairment is available.

2.1.7.4.3.2. Virologically Suppressed Subjects

2.1.7.4.3.2.1. Study GS-US-292-0109

In Study GS-US-292-0109, AEs in the SOC of eye disorders were reported for similar percentages of subjects in the 2 groups (E/C/F/TAF 5.5%, 53 of 959 subjects; FTC/TDF+3rd Agent 4.6%, 22 of 477 subjects; Table 40).

Subject *EA in the E/C/F/TAF group had an SAE of retinal detachment with onset on Day 167; the event resolved with treatment on Day 168. This SAE was considered by the investigator as unrelated to the study drug and did not result in discontinuation of the study drug. This subject had a history of retinal detachment.

Nonserious AEs reported for 2 subjects in the E/C/F/TAF group and for 5 subjects in the FTC/TDF+3rd Agent group were considered by the investigator as related to study drugs. In the E/C/F/TAF group, Subject *EB had two Grade 1 AEs of visual acuity reduced and vision blurred, with exact onset dates unknown; and Subject *EC had a Grade 1 AE of vision blurred with onset on Day 279. All 3 events were listed as ongoing at the time of the data cut date for this study, and none resulted in discontinuation of study drug. In the FTC/TDF+3rd Agent group, ocular icterus was reported for 5 subjects taking ATV/boosted+TVD regimens: Subjects *ED (Grade 1, onset Day 252), *EE (Grade 1, onset Day 85), *EF (Grade 1, onset Day 174), *EG (Grade 1, onset Day 295), and *EH (Grade 2, exact onset date unknown). Four of these events were listed as ongoing at the time of the writing of this summary document, and none resulted in discontinuation of study drug.

All other eye disorder AEs were considered by the investigator as not related to study drugs. Most eye disorder AEs resolved and none resulted in discontinuation of study drugs.

Table 40. E/C/F/TAF Study GS-US-292-0109: Summary of Adverse Events in the SOC of Eye Disorders (Safety Analysis Set)

Adverse Events by Preferred Term[a,b,c,d]	E/C/F/TAF (N=959)	FTC/TDF+3rd Agent (N=477)
Number of Subjects Experiencing Any Eye Disorders	53 (5.5%)	22 (4.6%)
Vision Blurred	10 (1.0%)	1 (0.2%)
Ocular Icterus	1 (0.1%)	7 (1.5%)
Eye Irritation	4 (0.4%)	1 (0.2%)
Blepharospasm	3 (0.3%)	1 (0.2%)
Conjunctival Haemorrhage	2 (0.2%)	2 (0.4%)
Vitreous Floaters	1 (0.1%)	3 (0.6%)
Cataract	3 (0.3%)	0
Conjunctivitis Allergic	2 (0.2%)	1 (0.2%)
Visual Impairment	3 (0.3%)	0
Chalazion	2 (0.2%)	0
Dacryostenosis Acquired	1 (0.1%)	1 (0.2%)
Eye Discharge	2 (0.2%)	0
Ocular Discomfort	2 (0.2%)	0
Ocular Hyperaemia	1 (0.1%)	1 (0.2%)
Visual Acuity Reduced	2 (0.2%)	0
Arcus Lipoides	1 (0.1%)	0
Astigmatism	0	1 (0.2%)
Blepharitis	1 (0.1%)	0
Blindness	1 (0.1%)	0
Corneal Scar	1 (0.1%)	0
Diplopia	1 (0.1%)	0
Eye Allergy	1 (0.1%)	0
Eye Pain	1 (0.1%)	0
Eye Pruritus	1 (0.1%)	0
Eyelid Oedema	1 (0.1%)	0
Glare	1 (0.1%)	0
Keratitis	0	1 (0.2%)
Lacrimation Increased	1 (0.1%)	0
Macular Hole	0	1 (0.2%)

Adverse Events by Preferred Term[a,b,c,d]	E/C/F/TAF (N=959)	FTC/TDF+3rd Agent (N=477)
Mydriasis	1 (0.1%)	0
Myopia	0	1 (0.2%)
Optic Disc Disorder	0	1 (0.2%)
Panophthalmitis	1 (0.1%)	0
Photophobia	1 (0.1%)	0
Pigment Dispersion Syndrome	1 (0.1%)	0
Presbyopia	1 (0.1%)	0
Pterygium	1 (0.1%)	0
Retinal Detachment	1 (0.1%)	0
Scleral Hyperaemia	1 (0.1%)	0
Ulcerative Keratitis	1 (0.1%)	0

a Adverse events were coded using MedDRA 17.0.
b Preferred term was presented by descending order of the total frequencies.
c Eye disorder was defined as any event within the SOC of eye disorders.
d Only PTs with at least 1 subject having the event in any treatment group are presented in this table.
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Table 22

There were no reports of uveitis during the study. Adverse events from a list of identified terms that could represent symptoms of uveitis were reported for similar percentages of subjects in the 2 groups (E/C/F/TAF 1.9%; FTC/TDF+3rd Agent 0.8%). These events were all Grade 1 or 2 and none resulted in discontinuation of study drugs. Two subjects in the E/C/F/TAF group had nonspecific ocular AEs (Subjects *EB [visual acuity reduced and vision blurred] and *EC [vision blurred]) that were considered by the investigator as related to study drug.

Among the subjects who participated in the ophthalmologic substudy (E/C/F/TAF 32 subjects; FTC/TDF+3rd Agent 15 subjects), most had normal ophthalmologic central reading assessments at baseline (E/C/F/TAF 25 subjects; FTC/TDF+3rd Agent 13 subjects). Of the subjects with available postbaseline data, most had normal assessments at Week 24 (E/C/F/TAF 26 of 31 subjects; FTC/TDF+3rd Agent 12 of 14 subjects) and Week 48 (E/C/F/TAF 14 of 18 subjects; FTC/TDF+3rd Agent 6 of 8 subjects). Subject *EI in the E/C/F/TAF group had a shift from normal at baseline to abnormal at Week 24 in the central reading assessment due to the detection of a retinal hemorrhage in the left eye. No subjects in the ophthalmic substudy had fundoscopic findings consistent with uveitis.

2.1.7.4.3.2.2. Study GS-US-292-0102 Open-Label Extension

Few subjects in the switch groups of Study GS-US-292-0102 had ocular AEs in the SOC of eye disorders.

2.1.7.4.3.3. Subjects with Mild to Moderate Renal Impairment

2.1.7.4.3.3.1. Study GS-US-292-0112

In Study GS-US-292-0112, AEs in the eye disorders SOC were reported in 22 of 242 subjects (9.1%) in Cohort 1 (switch) (6 of 80 subjects [7.5%] with baseline $eGFR_{CG}$ < 50 mL/min and 16 of 162 [9.9%] of subjects with baseline $eGFR_{CG} \geq 50$ mL/min) and no subjects in Cohort 2 (ART-naive). None of the AEs in the eye disorders SOC were serious or resulted in discontinuation of study drug. Two ocular AEs reported for 1 subject (vitreous floaters and photopsia; Subject *EJ) were considered related to study drugs by the investigator. All other ocular AEs were considered unrelated to the study drugs by the investigator.

Four Cohort 1 subjects, 3 with baseline $eGFR_{CG} \geq 50$ mL/min and 1 with baseline $eGFR_{CG}$ < 50 mL/min, had AEs from the list of identified terms that could represent symptoms of uveitis, none of which resulted in discontinuation of study drug.

None of these AEs were considered representative of an actual case of clinical uveitis.

2.1.7.4.3.4. ART-Naive Adolescent Subjects

2.1.7.4.3.4.1. Study GS-US-292-0106

In Study GS-US-292-0106, Subject *DE , a 13-year-old Ugandan female, had Grade 3 intermediate uveitis. This subject had been infected with HIV-1 via vertical transmission, and entered the study with a baseline CD4 cell count of 1110 cells/μL. At Day 14 the subject presented with visual field changes and conjunctival hyperemia. Grade 3 chorioretinitis was reported as low-grade posterior uveitis considered related to study drug by the investigator. Symptoms improved significantly with antibiotic/steroid and nonsteroidal anti-inflammatory eye drops, and oral steroid and antihistamine therapy. Concurrent eye disorders reported on Day 14 were Grade 1 allergic conjunctivitis, and Grade 2 visual impairment (reported as an SAE considered related to study drug by the investigator) and cataracts. Following repeat fundoscopic examination on Day 27, the chorioretinitis was reassessed as Grade 2 intermediate uveitis, reported as an SAE, and still considered related to study drug by the investigator. Throughout, the subject continued on study drug without interruption. At the time of the data cut for the Week 24 analysis, intermediate uveitis was ongoing but resolving; visual impairment and recurrent allergic conjunctivitis were ongoing, and the subject was continuing on study drug.

The only other AEs within the Eye Disorders SOC were Grade 1 allergic conjunctivitis and giant papillary conjunctivitis, both considered unrelated to study drug by the investigator, in 1 subject.

2.1.7.4.4. D/C/F/TAF Study

2.1.7.4.4.1. ART-Naive Subjects

2.1.7.4.4.1.1. Study GS-US-299-0102

In the D/C/F/TAF Phase 2 Study GS-US-299-0102, there were no AEs of uveitis. Adverse events in the eye disorders SOC were reported for 5.8% of subjects (n = 6) in the D/C/F/TAF group (Table 41). No AE in the eye disorders SOC was reported in the DRV+COBI+TVD group. One nonserious AE of photophobia in the D/C/F/TAF group was considered by the investigator to be related to study drug. All other eye disorders were not considered by the investigator to be related to study drug. No eye disorder resulted in discontinuation of study drug.

Table 41. D/C/F/TAF Study GS-US-299-0102: Summary of Adverse Events: Eye Disorders (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c,d]	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)
Eye disorders	6 (5.8%)	0
Eye irritation	2 (1.9%)	0
Lacrimation increased	1 (1.0%)	0
Eye pruritus	1 (1.0%)	0
Ocular hyperaemia	1 (1.0%)	0
Photophobia	1 (1.0%)	0

a Adverse events were coded using MedDRA 17.0.
b Preferred term was presented by descending order of the total frequencies.
c Eye disorder was defined to be any event with SOC of Eye Disorders.
d Only PTs with at least 1 subject having the event in any treatment group are presented in this table.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 22

In the SOC of infections and infestations, conjunctivitis was reported for 1.9% of subjects (n = 2) in the D/C/F/TAF group and no subjects in the DRV+COBI+TVD group. AEs of conjunctivitis were Grade 1 or 2, were nonserious, and resolved without interruption to, or discontinuation of, study drugs. No AE of conjunctivitis was considered related to study drugs by the investigator.

One subject in the D/C/F/TAF group had an AE from the list of identified terms that could represent symptoms of uveitis: Subject *EK had Grade 1 photophobia and Grade 1 nausea, which both began on Day 1. Both AEs were considered by the investigator to be related to study drug but did not result in discontinuation of study drug. Both events resolved on the same day without treatment.

2.2. Narratives

For all Gilead-sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, pregnancies, and fractures, if applicable, are provided in the relevant CSRs.

3. CLINICAL LABORATORY EVALUATIONS

In the following sections, a summary of the clinical laboratory evaluations relevant for the F/TAF FDC based on the E/C/F/TAF Phase 2 and Phase 3 studies as well as the D/C/F/TAF Phase 2 study are presented. All laboratory abnormalities discussed in the following sections were treatment emergent and are referred to as laboratory abnormalities in this document.

3.1. E/C/F/TAF Studies

Table 42 presents an overall summary of Grade 3 and 4 laboratory abnormalities for the E/C/F/TAF Phase 2 and Phase 3 studies. Approximately 20% of subjects across all E/C/F/TAF 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 the E/C/F/TAF studies were creatinine kinase, and fasting LDL. In ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111, 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 and were not consistently present for individual subjects, and no case of clinical rhabdomyolysis was reported. Grade 3 or 4 creatinine kinase laboratory abnormalities were reported for a similar percentage of subjects in both treatment groups for virologically suppressed subjects (E/C/F/TAF 5.2%, 50 of 959 subjects; FTC/TDF+3rd Agent 5.0%, 24 of 477 subjects). In subjects with mild to moderate renal impairment, Grade 3 or 4 creatinine kinase abnormalities were reported for 10 subjects (4.1%) in Cohort 1 (switch) and 1 subject (16.7%) in Cohort 2 (ART-naive). No Grade 3 or 4 creatinine kinase abnormalities were reported for ART-naive adolescent subjects.

In E/C/F/TAF ART-naive subjects, Grade 3 LDL abnormalities were reported for 5.0% of subjects (n = 42) in the E/C/F/TAF group and 2.2% of subjects (n = 18) in the STB group. No Grade 4 fasting LDL laboratory abnormalities were reported in either treatment group. In virologically suppressed subjects, more subjects in the E/C/F/TAF group than in the comparator groups had Grade 3 fasting LDL abnormalities (E/C/F/TAF 7.2%, 67 subjects; FTC/TDF+3rd Agent 0.9%, 4 subjects). In subjects with mild to moderate renal impairment, Grade 3 fasting LDL abnormalities were reported for 14 subjects (6.0%), which is consistent with the incidence reported for ART-naive subjects and virologically suppressed subjects. No Grade 3 or 4 fasting LDL abnormalities were reported for ART-naive adolescent subjects.

Lipase testing was only performed in subjects with serum amylase > 1.5 × upper limit of normal (ULN). In ART-naive subjects and virologically suppressed subjects in the E/C/F/TAF studies, Grade 3 or 4 lipase abnormalities were reported less frequently in the E/C/F/TAF groups than in the comparator groups.

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.

The incidence of all other Grade 3 or 4 laboratory abnormalities were generally similar across the 2 treatment groups in each study with a comparator group.

Among subjects with mild to moderate renal impairment, 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.

Table 42. E/C/F/TAF Studies 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: Grade 3 and 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group from Any Study (Safety Analysis Set)

	ART-Naive Adult Subjects				Virologically Suppressed Subjects Who Switched Treatment		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
	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)	ART Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Maximum Postbaseline Toxicity Grade	862	865	111	58	959	477	242	6	48
Grade 3 or 4	172 (20.0%)	171 (19.8%)	31 (27.9%)	11 (19.0%)	190 (19.8%)	121 (25.4%)	64 (26.4%)	1 (16.7%)	4 (8.3%)
Hematology									
Neutrophils	862	865	111	58	959	477	242	6	48
Grade 3 or 4	13 (1.5%)	21 (2.4%)	7 (6.3%)	2 (3.4%)	11 (1.1%)	3 (0.6%)	2 (0. 8%)	0	3 (6.3%)
Chemistry									
ALT	862	865	111	58	959	477	242	6	48
Grade 3 or 4	10 (1.2%)	12 (1.4%)	1 (0.9%)	1 (1.7%)	5 (0.5%)	3 (0.6%)	2 (0.8%)	0	0
Amylase	862	865	111	58	959	477	242	6	–
Grade 3 or 4	13 (1.5%)	26 (3.0%)	3 (2.7%)	2 (3.4%)	11 (1.1%)	9 (1.9%)	6 (2.5%)	1 (16.7%)	–
AST	862	865	111	58	959	477	242	6	48
Grade 3 or 4	13 (1.5%)	16 (1.8%)	1 (0.9%)	0	12 (1.3%)	5 (1.0%)	1 (0.4%)	0	0

	ART-Naive Adult Subjects				Virologically Suppressed Subjects Who Switched Treatment		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
	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)	ART Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Creatine Kinase	862	865	111	58	959	477	242	6	48
Grade 3 or 4	59 (6.8%)	49 (5.7%)	7 (6.3%)	2 (3.4%)	50 (5.2%)	24 (5.0%)	10 (4.1%)	1 (16.7%)	0
Creatinine	862	865	111	58	959	477	242	6	48
Grade 3 or 4	0	2 (0.2%)	0	0	0	0	5 (2.1%)	0	0
GGT	862	865	111	58	959	477	242	6	–
Grade 3 or 4	3 (0.3%)	12 (1.4%)	1 (0.9%)	1 (1.7%)	4 (0.4%)	5 (1.0%)	3 (1.2%)	0	–
Lipase[b]	90	113	8	10	46	30	33	2	–
Grade 3 or 4	4 (4.4%)	9 (8.0%)	0	1 (10.0%)	4 (8.7%)	3 (10.0%)	4 (12.1%)	0	–
Serum Glucose (Fasting, Hyperglycemia)	860	865	111	58	958	475	242	6	31
Grade 3 or 4	7 (0.8%)	4 (0.5%)	2 (1.8%)	1 (1.7%)	7 (0.7%)	2 (0.4%)	6 (2.5%)	0	0
Serum Glucose (Nonfasting, Hyperglycemia)[c]	858	857	–	–	959	475	241	6	48
Grade 3 or 4	7 (0.8%)	10 (1.2%)	–	–	5 (0.5%)	6 (1.3%)	10 (4.1%)	0	0

	ART-Naive Adult Subjects				Virologically Suppressed Subjects Who Switched Treatment		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
	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)	ART Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Total Bilirubin (Hyperbilirubinemia)	862	865	111	58	959	477	242	6	48
Grade 3 or 4	0	4 (0.5%)	0	0	1 (0.1%)	68 (14.3%)	0	0	0
Total Cholesterol (Fasting, Hypercholesterolemia)	835	834	110	58	930	454	232	6	23
Grade 3 or 4	15 (1.8%)	10 (1.2%)	3 (2.7%)	0	28 (3.0%)	0	10 (4.3%)	0	0
Triglycerides (Fasting)	835	834	110	58	930	454	232	6	23
Grade 3 or 4	4 (0.5%)	2 (0.2%)	1 (0.9%)	1 (1.7%)	8 (0.9%)	2 (0.4%)	1 (0.4%)	0	0
LDL (Fasting)	835	833	110	58	930	454	232	6	23
Grade 3 or 4	42 (5.0%)	18 (2.2%)	10 (9.1%)	3 (5.2%)	67 (7.2%)	4 (0.9%)	14 (6.0%)	0	0
Uric Acid (Hyperuricemia)	862	865	111	58	959	477	242	6	48
Grade 3 or 4	0	2 (0.2%)	0	0	2 (0.2%)	0	4 (1.7%)	0	0
Urinalysis[d]									
Urine Glucose (Glycosuria)	862	865	111	58	959	476	242	6	48
Grade 3 or 4	11 (1.3%)	13 (1.5%)	2 (1.8%)	0	11 (1.1%)	5 (1.1%)	8 (3.3%)	0	0

	ART-Naive Adult Subjects				Virologically Suppressed Subjects Who Switched Treatment		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
	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)	ART Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)	E/C/F/TAF (N=48)
Urine RBC (Hematuria, Quantitative)	862	865	111	58	959	476	242	6	48
Grade 3 or 4	15 (1.7%)	19 (2.2%)	2 (1.8%)	0	18 (1.9%)	3 (0.6%)	4 (1.7%)	0	1 (2.1%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LDL = low density lipoprotein; RBC = red blood cell
Denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value (for the test).
Subjects were counted once for the maximum postbaseline severity for each laboratory test.

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. Laboratory abnormalities during the open-label extension were similar to the laboratory abnormalities observed in the randomized phase.

b Lipase test was only performed for subjects with serum amylase > 1.5 x ULN.

c Nonfasting glucose was not collected at baseline, therefore, treatment emergent cannot be determined. Maximum postbaseline grade was summarized.

d For Urinalysis (ie, urine glucose and urine RBC), the highest grade is up to Grade 3.

Source: E/C/F/TAF ISS, Table 19; GS-US-292-0102 Week 96 CSR, Section 15.1, Table 32.1; GS-US-292-0109 Week 48 CSR, Section 15.1, Table 33; GS-US-292-0112 Week 24 CSR, Section 15.1, Table 45; GS-US-292-0106 Interim CSR, Section 15.1, Table 27

3.2. D/C/F/TAF Study

In the D/C/F/TAF Phase 2 Study GS-US-299-0102, Grade 3 or 4 laboratory abnormalities occurred in 27.5% of subjects in the D/C/F/TAF group and 28.0% of subjects in the DRV+COBI+TVD group (Table 43). The most commonly reported Grade 3 or 4 laboratory abnormality was elevation in creatine kinase (D/C/F/TAF 8.8%, 9 subjects; DRV+COBI+TVD 12.0%, 6 subjects). These results are consistent with those from the E/C/F/TAF studies in ART-naive subjects.

Table 43. D/C/F/TAF Study GS-US-299-0102: Grade 3 and 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)

Laboratory Panel, Laboratory Parameter, Grade [a,b]	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)
Maximum post-baseline toxicity grade	102	50
Grade 3 or 4	28 (27.5%)	14 (28.0%)
Hematology		
Neutrophils	102	50
Grade 3 or 4	4 (3.9%)	1 (2.0%)
Platelets	102	50
Grade 3 or 4	1 (1.0%)	0
Chemistry		
ALT	102	50
Grade 3 or 4	1 (1.0%)	0
Amylase	102	50
Grade 3 or 4	1 (1.0%)	1 (2.0%).
AST	102	50
Grade 3 or 4	1 (1.0%)	2 (4.0%)
Corrected calcium (hypocalcemia)	102	50
Grade 3 or 4	0	1 (2.0%)
Creatine kinase	102	50
Grade 3 or 4	9 (8.8%)	6 (12.0%)
Gamma-glutamyl transferase	102	50
Grade 3 or 4	3 (2.9%)	1 (2.0%)
Serum glucose (hyperglycemia)	102	50
Grade 3 or 4	3 (2.9%)	0
Serum sodium (hypernatremia)	102	50
Grade 3 or 4	1 (1.0%)	0
Total cholesterol (fasting, hypercholesterolemia)	99	49
Grade 3 or 4	4 (4.0%)	1 (2.0%)
Triglycerides (fasting)	99	49
Grade 3 or 4	4 (4.0%)	1 (2.0%)
LDL (fasting)	99	49
Grade 3 or 4	5 (5.1%)	4 (8.2%)
Urinalysis[c]		
Urine glucose (glycosuria)	102	50
Grade 3 or 4	2 (2.0%)	1 (2.0%)
Urine protein (proteinuria)	102	50
Grade 3 or 4	0	1 (2.0%)

a Denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value (for the test).
b Subjects were counted once for the maximum postbaseline severity for each laboratory test.
c For Urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade was up to Grade 3.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Table 33

3.3. Laboratory Abnormalities

3.3.1. E/C/F/TAF Studies

3.3.1.1. ART-Naive Subjects

3.3.1.1.1. Studies GS-US-292-0104 and GS-US-292-0111

Detailed clinical laboratory evaluation results for Studies GS-US-292-0104 and GS-US-292-0111 may be found in the respective CSRs (GS-US-292-0104 Week 48 CSR, Section 11.6; GS-US-292-0111 Week 48 CSR, Section 11.6).

Fasting Lipid Parameters

Increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct LDL, HDL, and triglycerides at Weeks 24 and 48 (Table 44). The median increase from baseline for those parameters was greater in the E/C/F/TAF group compared with the STB group at Week 48 ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, HDL, direct LDL, and triglycerides). Median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.1 (–0.3, 0.5) in the E/C/F/TAF group and 0.0 (−0.5, 0.4) in the STB group ($p < 0.001$ for the difference between treatment groups).

Consistent with these results, greater percentages of subjects in the E/C/F/TAF group than the STB group had categorical changes in the following NCEP ATP III lipid classifications from baseline: fasting total cholesterol (< 200 mg/dL to ≥ 200 mg/dL): E/C/F/TAF 31.0%, 204 of 659 subjects; STB 17.2%, 111 of 646 subjects; fasting direct LDL (< 130 mg/dL to ≥ 130 mg/dL): E/C/F/TAF 23.3%, 143 of 615 subjects; STB 14.8%, 91 of 613 subjects; and triglycerides (< 200 mg/dL to ≥ 200 mg/dL): E/C/F/TAF 13.5%, 98 of 724 subjects; STB 9.1%, 63 of 695 subjects (E/C/F/TAF ISS, Tables 34.1.2, 34.2.2, and 34.4.2). Based on the number of subjects with available data at Week 48, fewer percentages of subjects in the E/C/F/TAF group than the STB group had categorical changes in fasting HDL (≥ 40 mg/dL to < 40 mg/dL): E/C/F/TAF 4.3%, 23 of 532 subjects; STB 7.9%, 41 of 518 subjects (E/C/F/TAF ISS, Table 34.3.2). These small lipid categorical changes were clinically irrelevant and consistent with data from other studies of abacavir, d4T, and other non TDF-based NRTIs in ART-naive patients {11417}.

The majority of these lipid abnormalities were Grade 1 or 2.

Graded fasting hypercholesterolemia was more common in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 42.9%, 358 subjects; STB 25.1%, 209 subjects; E/C/F/TAF ISS, Table 18). The majority of hypercholesterolemia abnormalities were Grade 1 (E/C/F/TAF 216 subjects; STB 138 subjects). Grade 2 hypercholesterolemia was reported for 15.2% of subjects (n = 127) in the E/C/F/TAF group and 7.3% of subjects (n = 61) in the STB group. Grade 3 hypercholesterolemia was infrequent and was reported for similar percentages of subjects in each treatment group (E/C/F/TAF 1.8%, 15 subjects; STB 1.2%, 10 subjects). No subject had Grade 4 hypercholesterolemia.

More subjects in the E/C/F/TAF group compared with the STB group had graded abnormalities in fasting LDL (E/C/F/TAF 37.6%, 314 subjects; STB 23.4%, 195 subjects). The majority of these abnormalities were Grade 1 (E/C/F/TAF 176 subjects; STB 127 subjects). Grade 2 fasting LDL laboratory abnormalities were reported for 11.5% of subjects (n = 96) in the E/C/F/TAF group and 6.0% of subjects (n = 50) in the STB group. Grade 3 LDL abnormalities were reported for 5.0% of subjects (n = 42) in the E/C/F/TAF group and 2.2% of subjects (n = 18) in the STB group. No Grade 4 fasting LDL laboratory abnormalities were reported in either treatment group.

Graded abnormalities in fasting triglycerides were infrequent, and reported for similar percentages of subjects in each treatment group (E/C/F/TAF 1.9%, 16 subjects; STB 1.7%, 14 subjects). There were no Grade 1 fasting triglyceride abnormalities. Grade 2 abnormalities were reported for 1.4% of subjects (n = 12) in each treatment group. Grade 3 and 4 triglyceride abnormalities were as follows: Grade 3: 0.1%, 1 subject in each treatment group; Grade 4 E/C/F/TAF 0.4%, 3 subjects; STB 0.1%, 1 subject.

A similar percentage of subjects in both treatment groups had graded fasting hyperglycemia (E/C/F/TAF 15.5%, 133 subjects; STB 14.0%, 121 subjects). The majority of these abnormalities were Grade 1.

AEs related to lipid laboratory test abnormalities were as follows: hyperlipidemia (E/C/F/TAF 1.2%, 10 subjects; STB 0.5%, 4 subjects); dyslipidemia (E/C/F/TAF 1.2%, 10 subjects; STB 0.3%, 3 subjects); hypertriglyceridemia (E/C/F/TAF 0.6%, 5 subjects; STB 0.2%, 2 subjects); hypercholesterolemia (0.3%, 3 subjects in each group); LDL increased and blood triglycerides increased (each 0.1%, 1 subject in each group), lipids abnormal (E/C/F/TAF 0.1%, 1 subject; STB 0 subjects), Type V hyperlipidemia (E/C/F/TAF 0.1%, 1 subject; STB 0 subjects), and blood cholesterol increased (E/C/F/TAF 0 subjects; STB 0.2%, 2 subjects; E/C/F/TAF ISS, Table 7). None of these lipid laboratory test abnormality AEs were serious, and blood triglycerides increased in 1 subject in the E/C/F/TAF group was the only lipid abnormality AE that led to discontinuation of study drugs (E/C/F/TAF ISS, Tables 14 and 16). The following lipid laboratory test abnormality AEs were considered related to study drugs by the investigator: dyslipidemia (E/C/F/TAF 0.2%, 2 subjects; STB 0 subjects), hyperlipidemia (0.2%, 2 subjects in each group), hypertriglyceridemia (E/C/F/TAF 0.2%, 2 subjects; STB 0.1%, 1 subjects), hypercholesterolemia (0.1%, 1 subject in each group), and blood triglycerides increased (E/C/F/TAF 0.1%, 1 subject; STB 0 subjects) (E/C/F/TAF ISS, Table 11).

In the E/C/F/TAF group, 4.4% of subjects (n = 32) were taking lipid modifying medications at study entry, and 3.6% of subjects (n = 31) initiated treatment during the study (E/C/F/TAF ISS, Tables Req6742.3.1 and Req6742.3.2). In the STB group, 5.0% of subjects (n = 43) were taking lipid modifying medications at study entry, and 2.9% of subjects (n = 25) initiated treatment during the study.

One subject in Study GS-US-292-0104 (Subject *EL in the E/C/F/TAF group, a 57-year-old male with chronic tobacco use) had an SAE of acute myocardial infarction (MI) on Day 213, as well as a nonserious AE of coronary artery disease (ongoing). Both events were considered unrelated to the study drugs by the investigator. The subject had Grade 1 elevations of total cholesterol and LDL on Day 171.After initiating pravastatin on Day 213, values were

within the normal range by Day 333. The SAE of acute MI resolved on Day 215 and the subject continued to receive study drugs. One subject in Study GS-US-292-0111 (Subject *EM in the E/C/F/TAF group) had SAEs of cerebrovascular accident and transient ischemic attack, a nonserious AE of hypertension, and a concurrent nonserious AE of Grade 1 hypercholesterolemia. The subject had Grade 1 abnormalities in total cholesterol and LDL at baseline, and both laboratory values were normal around the time of the events. None of the events were considered related to study drugs by the investigator. No other subject with an AE indicative of cardiovascular disease had any AE related to lipid laboratory tests.

Table 44. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Summary of Fasting Metabolic Assessments Change from Baseline at Week 24 and Week 48 (Safety Analysis Set)

	E/C/F/TAF (N=866)	STB (N=867)	p-value
Fasting Total Cholesterol (mg/dL)			
Baseline			
N	841	848	0.14
Mean (SD)	164 (36.2)	166 (37.1)	
Median	160	163	
Q1, Q3	138, 186	140, 189	
Change at Week 48			
N	789	781	<.001
Mean (SD)	31 (29.5)	14 (29.9)	
Median	29	13	
Q1, Q3	13, 48	−6, 31	
Fasting HDL (mg/dL)			
Baseline			
N	841	848	0.47
Mean (SD)	46 (13.1)	45 (12.6)	
Median	44	44	
Q1, Q3	37, 53	37, 52	
Change at Week 48			
N	789	781	<.001
Mean (SD)	7 (10.9)	4 (10.4)	
Median	7	3	
Q1, Q3	1, 13	−2, 10	

	E/C/F/TAF (N=866)	STB (N=867)	p-value
Fasting Direct LDL (mg/dL)			
Baseline			
N	837	849	0.091
Mean (SD)	105 (31.2)	108 (33.5)	
Median	101	104	
Q1, Q3	81, 125	85, 126	
Change at Week 48			
N	785	783	<.001
Mean (SD)	15 (24.6)	4 (25.4)	
Median	13	2	
Q1, Q3	0, 30	−12, 17	
Fasting Total Cholesterol to HDL Ratio			
Baseline			
N	841	848	0.069
Mean (SD)	3.8 (1.10)	3.9 (1.22)	
Median	3.6	3.6	
Q1, Q3	3.0, 4.3	3.0, 4.5	
Change at Week 48			
N	789	781	<.001
Mean (SD)	0.2 (0.96)	0.0 (1.03)	
Median	0.1	0.0	
Q1, Q3	−0.3, 0.5	−0.5, 0.4	
Fasting Triglycerides (mg/dL)			
Baseline			
N	841	848	0.14
Mean (SD)	116 (82.4)	120 (81.7)	
Median	95	100	
Q1, Q3	70, 137	73, 140	
Change at Week 48			
N	789	781	<.001
Mean (SD)	30 (103.5)	10 (80.2)	
Median	18	6	
Q1, Q3	−9, 50	−21, 36	

Only laboratory measurements under fasting status were summarized.
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: E/C/F/TAF ISS, Tables 34.1.1, 34.2.1, 34.3.1, 34.4.1, and 34.5

3.3.1.1.2. Study GS-US-292-0102

Detailed clinical laboratory evaluation results for Study GS-US-292-0102 may be found in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.6).

Fasting Glucose and Lipid Parameters

In the randomized phase of Study GS-US-292-0102, increases from baseline were observed for fasting total cholesterol, fasting direct LDL cholesterol, and fasting HDL cholesterol at Weeks 24 and 48 for each treatment group (Table 45). The median increase from baseline was greater in the E/C/F/TAF group compared with the STB group at both Week 24 and Week 48. Statistically significant differences between the 2 groups in change from baseline were seen for all 3 lipid parameters at Week 24, and for fasting total cholesterol and fasting HDL cholesterol at Week 48.

There were no changes from baseline or statistically significant differences between treatment groups for median fasting total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose for either treatment group.

In the randomized phase, graded fasting hypercholesterolemia was more commonly reported in the E/C/F/TAF group compared with the STB group (E/C/F/TAF 56.4%, 62 subjects; STB 29.3%, 17 subjects). The majority of the hypercholesterolemia abnormalities were Grade 1 (E/C/F/TAF 44 subjects; STB 8 subjects). More subjects in the E/C/F/TAF group compared with the STB group had graded abnormalities in fasting LDL (E/C/F/TAF 50.9%, 56 subjects; STB 36.2%, 21 subjects). The majority of these abnormalities were Grade 1 (E/C/F/TAF 32 subjects; STB 10 subjects). Grade 2 fasting LDL was reported for 12.7% of subjects (n = 14) in the E/C/F/TAF groups and 13.8% of subjects (n = 2) in the STB group. Grade 3 fasting LDL was reported for 9.1% of subjects (n = 10) in the E/C/F/TAF group and 5.2% of subjects (n = 3) in the STB group. No Grade 4 fasting LDL abnormalities were reported in either group.

Two subjects (1.8%) in the E/C/F/TAF group and 1 subject (1.7%) in the STB group had AEs of hyperlipidemia considered related to study drugs by the investigator.

More subjects in the E/C/F/TAF group compared with the STB group received concomitant lipid-modifying agents during the randomized phase (E/C/F/TAF 13.4%, 15 subjects; STB 3.4%, 2 subjects). In the E/C/F/TAF group, 8 of the 15 subjects were continuing treatment from baseline, while 7 initiated treatment during the study. In the STB group, 1 subject was continuing treatment from baseline, and 1 subject initiated treatment during the study.

Table 45. E/C/F/TAF Study GS-US-292-0102: Summary of Fasting Metabolic Assessments Change from Baseline at Week 24 and Week 48 (Safety Analysis Set)

Metabolic Assessment	E/C/F/TAF (N=112)	STB (N=58)	p-value[a]
Fasting Total Cholesterol (mg/dL)			
Baseline			
N	111	58	0.32
Median	152	156	
Q1, Q3	135, 172	137, 188	
Change at Week 24			
N	105	58	<.001
Median	30	13	
Q1, Q3	11, 45	−7, 31	
Change at Week 48			
N	104	55	0.007
Median	30	17	
Q1, Q3	8, 52	2, 35	
Fasting Direct LDL Cholesterol (mg/dL)			
Baseline			
N	111	58	0.39
Median	96	98	
Q1, Q3	79, 114	81, 121	
Change at Week 24			
N	105	58	<.001
Median	16	3	
Q1, Q3	4, 33	−10, 20	
Change at Week 48			
N	104	55	0.11
Median	17	11	
Q1, Q3	1, 38	−4, 24	
Fasting HDL Cholesterol (mg/dL)			
Baseline			
N	111	58	0.66
Median	42	43	
Q1, Q3	35, 51	36, 53	

Metabolic Assessment	E/C/F/TAF (N=112)	STB (N=58)	p-value[a]
Change at Week 24			
N	105	58	0.010
Median	6	2	
Q1, Q3	1, 14	−2, 7	
Change at Week 48			
N	104	55	0.023
Median	7	3	
Q1, Q3	1, 13	−1, 8	
Fasting Total Cholesterol to HDL Ratio			
Baseline			
N	111	58	0.94
Median	3.7	3.7	
Q1, Q3	2.9, 4.5	3.1, 4.5	
Change at Week 24			
N	105	58	0.42
Median	0.1	0.1	
Q1, Q3	−0.3, 0.6	−0.3, 0.4	
Change at Week 48			
N	104	55	0.34
Median	0.2	0.1	
Q1, Q3	−0.2, 0.5	−0.3, 0.5	
Fasting Triglycerides (mg/dL)			
Baseline			
N	111	58	0.33
Median	100	85	
Q1, Q3	63, 137	58, 124	
Change at Week 24			
N	105	58	0.45
Median	24	21	
Q1, Q3	−3, 68	−9, 54	
Change at Week 48			
N	104	55	0.65
Median	15	22	

Metabolic Assessment	E/C/F/TAF (N=112)	STB (N=58)	p-value[a]
Q1, Q3	−8, 61	−2, 44	
Fasting Glucose			
Baseline			
N	111	58	0.54
Median	89	91	
Q1, Q3	85, 96	84, 97	
Change at Week 24			
N	105	58	0.70
Median	3	3	
Q1, Q3	−3, 10	−3, 7	
Change at Week 48			
N	104	55	0.75
Median	4	3	
Q1, Q3	−2, 9	−3, 13	

Only laboratory measurements under fasting status were summarized
a p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-292-0102 Week 96 CSR, Section 15.1, Tables 35.1.1, 35.2.1, 35.3.1, 35.4.1, 35.5.1, and 35.6.1

3.3.1.2. Virologically Suppressed Subjects

3.3.1.2.1. Study GS-US-292-0109

Detailed clinical laboratory evaluation results for Study GS-US-292-0109 may be found in the CSR (GS-US-292-0109 Week 48 CSR, Section 11.7).

Fasting Glucose and Lipid Parameters

There were increases from baseline in fasting values of total cholesterol, LDL cholesterol, and triglycerides in the E/C/F/TAF group, while these parameters remained unchanged or were changed to a relatively smaller extent in the FTC/TDF+3rd Agent group at both Week 24 and Week 48 ($p < 0.001$ for the differences between groups; Table 46).

Consistent with these results, of subjects with available data at Week 48, higher percentages in the E/C/F/TAF group than the FTC/TDF+3rd Agent group had the following categorical shifts from baseline based on NCEP ATP III classifications: total cholesterol (< 200 mg/dL to ≥ 200 mg/dL: E/C/F/TAF 34.0%, 168 of 494 subjects; FTC/TDF+3rd Agent 20.2%, 53 of 262 subjects), LDL cholesterol (< 130 mg/dL to ≥ 130 mg/dL: E/C/F/TAF 23.6%, 114 of 483 subjects; FTC/TDF+3rd Agent 13.6%, 34 of 250 subjects), and triglycerides (< 200 mg/dL to ≥ 200 mg/dL: E/C/F/TAF 13.0%, 81 of 621 subjects; FTC/TDF+3rd Agent 8.2%, 25 of 305 subjects).

Increases from baseline in median fasting values for total cholesterol, LDL cholesterol, and triglycerides at Weeks 24 and 48 were consistently observed in the E/C/F/TAF group, regardless of prior treatment regimen.

There were increases in HDL cholesterol in both treatment groups at Week 48 (median [Q1, Q3] changes from baseline: E/C/F/TAF 2 [−4, 8] mg/dL; FTC/TDF+3rd Agent 1 [−4, 5] mg/dL; p = 0.025 for the difference between groups); the increases were not considered clinically relevant.

There were no clinically relevant changes from baseline in the median fasting values for total cholesterol to HDL ratio, or glucose in either treatment group.

Graded fasting hypercholesterolemia was more commonly reported in the E/C/F/TAF group compared with the FTC/TDF+3rd Agent group (E/C/F/TAF 46.7%, 434 of 930 subjects; FTC/TDF+3rd Agent 24.2%, 110 of 454 subjects). The majority of the hypercholesterolemia abnormalities were Grade 1 or Grade 2. Grade 3 hypercholesterolemia was reported only for subjects in the E/C/F/TAF group (3.0%, 28 subjects). Graded abnormalities in fasting LDL cholesterol were also reported for a higher percentage of subjects in the E/C/F/TAF group than the FTC/TDF+3rd Agent group (E/C/F/TAF 37.8%, 352 subjects; FTC/TDF+3rd Agent 16.7%, 76 subjects). The majority of the abnormalities in fasting LDL cholesterol were Grade 1 or Grade 2. Grade 3 fasting LDL abnormalities were reported for 7.2% of subjects (n = 67) in the E/C/F/TAF group and 0.9% of subjects (n = 4) in the FTC/TDF+3rd Agent group. No Grade 4 fasting total cholesterol or fasting LDL abnormalities were reported in either group.

Similar percentages of subjects in each group had hypertriglyceridemia (E/C/F/TAF 2.3%, 21 subjects; FTC/TDF+3rd Agent 0.9%, 4 subjects); Grade 3 or 4 abnormalities of fasting triglycerides were uncommon (E/C/F/TAF 0.9%, 8 subjects; FTC/TDF+3rd Agent 0.4%, 2 subjects; Table 42).

Adverse events related to lipid abnormalities were more commonly reported in the E/C/F/TAF group compared with the FTC/TDF+3rd Agent group: hyperlipidemia (E/C/F/TAF 1.9%, 18 subjects; FTC/TDF+3rd Agent 0.8%, 4 subjects); hypercholesterolemia (E/C/F/TAF 2.0%, 19 subjects; FTC/TDF+3rd Agent 0%); dyslipidemia (E/C/F/TAF 0.4%, 4 subjects; FTC/TDF+3rd Agent 0.4%, 2 subjects); hypertriglyceridemia (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); and blood cholesterol increased (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject). All of these AEs were nonserious and none led to discontinuation of study drugs.

The percentage of subjects who received concomitant lipid modifying agents during the study (ie, between the first dose date and the last dose date of study drug, inclusive) was comparable between treatment groups (E/C/F/TAF 14.9%, 143 subjects; FTC/TDF+3rd Agent 13.4%, 64 subjects). Similar percentages of subjects in both treatment groups were taking treatment with lipid modifying agents at study entry (E/C/F/TAF 10.7%, 103 subjects; FTC/TDF+3rd Agent 10.5%, 50 subjects) and initiated treatment with lipid modifying agents during the study (E/C/F/TAF 5.4%, 52 subjects; FTC/TDF+3rd Agent 3.8%, 18 subjects). In this analysis, subjects who stopped treatment that was ongoing at study entry and reinitiated treatment during the study with the same or different lipid modifying agent were counted twice, ie, once as taking

a lipid modifying agent at study entry and the second time as initiating a lipid modifying agent during the study.

Table 46. E/C/F/TAF Study GS-US-292-0109: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set)

Metabolic Assessment	E/C/F/TAF (N = 959)		FTC/TDF+3rd Agent (N = 477)		P-Value[a]
	N	Median (Q1, Q3)	N	Median (Q1, Q3)	
Fasting Total Cholesterol (mg/dL)					
Baseline	942	182 (156, 208)	467	181 (158, 205)	0.60
Change at Week 24	911	21 (4, 40)	444	1 (−13, 16)	< 0.001
Change at Week 48	758	20 (1, 41)	367	6 (−9, 19)	< 0.001
Fasting Direct LDL Cholesterol (mg/dL)					
Baseline	942	116 (94, 142)	467	116 (96, 139)	0.97
Change at Week 24	911	11 (−3, 27)	444	−2 (−15, 9)	< 0.001
Change at Week 48	757	9 (−9, 25)	367	0 (−13, 11)	< 0.001
Fasting HDL Cholesterol (mg/dL)					
Baseline	942	50 (42, 59)	466	49 (42, 58)	0.48
Change at Week 24	911	2 (−3, 8)	443	0 (−5, 5)	< 0.001
Change at Week 48	758	2 (−4, 8)	366	1 (−4, 5)	0.025
Fasting Total Cholesterol to HDL Ratio					
Baseline	942	3.6 (2.9, 4.5)	466	3.6 (3.0, 4.4)	0.98
Change at Week 24	911	0.2 (−0.1, 0.7)	443	0.1 (−0.3, 0.4)	< 0.001
Change at Week 48	758	0.2 (−0.2, 0.7)	366	0.1 (−0.3, 0.4)	< 0.001
Fasting Triglycerides (mg/dL)					
Baseline	942	120 (82, 169)	466	114 (81, 164)	0.31
Change at Week 24	911	10 (−21, 47)	443	2 (−29, 28)	< 0.001
Change at Week 48	758	10 (−18, 48)	366	0 (−28, 27)	< 0.001
Fasting Glucose (mg/dL)					
Baseline	940	92 (85, 99)	466	92 (86, 100)	0.40
Change at Week 24	908	2 (−5, 8)	447	1 (−6, 7)	0.12
Change at Week 48	759	2 (−5, 8)	370	0 (−6, 7)	0.19

a P-values comparing the 2 treatment groups were from the 2-sided Wilcoxon rank sum test.
Only laboratory measurements under fasting status were summarized
Source: GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 38.1 to 38.6

3.3.1.2.2. Study GS-US-292-0102 Open-Label Extension

Detailed clinical laboratory evaluation results for Study GS-US-292-0102 may be found in the CSR (GS-US-292-0102 Week 96 CSR, Section 11.6).

Fasting Lipid Parameters

In the all TDF to TAF group of Study GS-US-292-0102, increases from baseline at Week 24 were observed for the following (median change from baseline):

- Fasting total cholesterol: 24 mg/dL
- Fasting direct LDL cholesterol: 16 mg/dL
- Fasting HDL cholesterol: 5 mg/dL
- Fasting triglycerides: 10 mg/dL

No changes from baseline were observed in median fasting total cholesterol to HDL ratio.

In the D/C/F/TAF to E/C/F/TAF group, decreases from baseline at Week 24 were observed for the following (median change from baseline):

- Fasting direct LDL cholesterol: −10 mg/dL
- Fasting triglycerides: −12 mg/dL

In the D/C/F/TAF to E/C/F/TAF group, no changes from baseline were observed in fasting total cholesterol or median fasting total cholesterol to HDL ratio.

Serious AEs of acute myocardial infarction and congestive cardiac failure were reported on Day 92 for Subject *EN in the D/C/F/TAF to E/C/F/TAF group. This 55-year-old African American female had a pre-existing history of uncontrolled Type 2 diabetes, hypertension, obesity (BMI 33.8 kg/m^2), coronary artery disease, and hyperlipidemia. The events resolved on Day 101, were not considered related to the study drugs by the investigator, and did not result in discontinuation of study treatment.

3.3.1.3. Subjects with Mild to Moderate Renal Impairment

3.3.1.3.1. Study GS-US-292-0112

Detailed clinical laboratory evaluation results for Study GS-US-292-0112 may be found in the CSR (GS-US-292-0112 Week 24 CSR, Section 11.7).

Fasting Glucose and Lipid Parameters

For each baseline eGFR group among Cohort 1 switch subjects and for ART-naive subjects in Cohort 2, changes from baseline to Weeks 24 or 48 were observed for fasting total cholesterol,

fasting direct LDL cholesterol, and fasting HDL cholesterol, fasting total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose that demonstrated a trend toward increase in most parameters evaluated (Table 47).

Among Cohort 1 switch subjects, Grade 3 fasting hypercholesterolemia was reported in 4 subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 6 subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group. Grade 3 fasting triglyceridemia was reported in 1 subject in the baseline $eGFR_{CG} < 50$ mL/min group only. Grade 3 fasting LDL was reported in 4 subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 10 subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group. No Grade 4 fasting total cholesterol, triglycerides, or LDL abnormalities were reported in either group. Grade 3 fasting serum glucose (hyperglycemia only) was reported in 4 subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 2 subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group. No Grade 4 fasting serum glucose (both hyperglycemia and hypoglycemia) was reported in either group.

Consistent with these results, based on the number of subjects with available data at Week 48, the following percentages of subjects had categorical changes in the following NCEP ATP III lipid classifications from baseline: fasting total cholesterol (< 200 mg/dL to ≥ 200 mg/dL): 33.7%, 29 of 86 subjects; fasting direct LDL (< 130 mg/dL to ≥ 130 mg/dL): 21.0%, 21 of 100 subjects; fasting HDL (≥ 40 mg/dL to < 40 mg/dL): 12.7%, 18 of 142 subjects; and triglycerides (< 200 mg/dL to ≥ 200 mg/dL): 13.6%, 17 of 125 subjects.

Two subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group had AEs of hypercholesterolemia and 1 subject in the baseline $eGFR_{CG} \geq 50$ mL/min group had an AE of hyperlipidemia considered related to study drugs by the investigator.

A similar percentage of subjects in the baseline eGFR groups received concomitant lipid-modifying agents (56.3% of subjects in the baseline $eGFR_{CG} < 50$ mL/min group and 46.3% of subjects in the baseline $eGFR_{CG} \geq 50$ mL/min group).

Table 47. E/C/F/TAF Study GS-US-292-0112: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set)

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min	**Baseline $eGFR_{CG}$ ≥ 50 mL/min**	**Total**
Fasting Total Cholesterol (mg/dL)			
Baseline			
N	79	160	239
Median	196	201	198
Q1, Q3	173, 240	174, 229	173, 230
Change at Week 24			
N	73	154	227
Median	9	12	10
Q1, Q3	−20, 34	−12, 31	−15, 32
Change at Week 48			
N	42	120	162
Median	11	13	13
Q1, Q3	−7. 35	−15, 35	−12, 35
Fasting Direct LDL Cholesterol (mg/dL)			
Baseline			
N	79	160	239
Median	122	125	123
Q1, Q3	94, 152	99, 151	98, 151
Change at Week 24			
N	73	154	227
Median	2	7	5
Q1, Q3	−20, 21	−13, 21	−16, 21
Change at Week 48			
N	42	120	162
Median	2	5	4
Q1, Q3	−10, 27	−11, 29	−11, 28
Fasting HDL Cholesterol (mg/dL)			
Baseline			
N	79	160	239

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min	**Baseline $eGFR_{CG}$ ≥ 50 mL/min**	**Total**
Median	55	54	54
Q1, Q3	42, 71	46, 65	44, 67
Change at Week 24			
N	73	154	227
Median	−1	0	0
Q1, Q3	−8, 4	−6, 7	−7, 6
Change at Week 48			
N	42	120	162
Median	−3	1	−1
Q1, Q3	−10, 1	−6, 7	−7, 6
Fasting Total Cholesterol to HDL Ratio			
Baseline			
N	79	160	239
Median	3.7	3.6	3.6
Q1, Q3	2.7, 4.8	2.9, 4.6	2.9, 4.7
Change at Week 24			
N	73	154	227
Median	0.2	0.2	0.2
Q1, Q3	−0.3, 0.6	−0.3, 0.6	−0.3, 0.6
Change at Week 48			
N	42	120	162
Median	0.5	0.1	0.3
Q1, Q3	0.2, 1.2	−0.3, 0.7	−0.2, 0.8
Fasting Triglycerides (mg/dL)			
Baseline			
N	79	160	239
Median	143	138	141
Q1, Q3	102, 220	92, 198	95, 202
Change at Week 24			
N	73	154	227
Median	4	4	4
Q1, Q3	−39, 42	−41, 36	−41, 38
Change at Week 48			

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min	**Baseline $eGFR_{CG}$ ≥ 50 mL/min**	**Total**
N	42	120	162
Median	43	6	10
Q1, Q3	1, 86	−31, 37	−18, 45
Fasting Glucose (mg/dL)			
Baseline			
N	78	159	237
Median	95	94	95
Q1, Q3	89, 103	87, 103	87, 103
Change at Week 24			
N	73	153	226
Median	3	−1	0
Q1, Q3	−5, 14	−9, 5	−8, 8
Change at Week 48			
N	43	121	164
Median	2	−1	0
Q1, Q3	−11, 8	−8, 6	−9, 7

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 49.1.1 to 49.1.6

Subjects in Cohort 1 with pre-switch TDF use were compared with subjects who did not receive TDF at baseline, change from baseline at Week 24 for fasting total cholesterol, fasting direct LDL cholesterol, and fasting HDL cholesterol, fasting total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose (Table 48). For the metabolic laboratory parameters evaluated, median changes from baseline at Weeks 24 and 48 demonstrated a trend toward increase in all parameters for subjects with pre-switch TDF use and a decrease in most parameters for subjects without pre-switch TDF use.

Table 48. E/C/F/TAF Study GS-US-292-0112: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 With or Without TDF or Without TDF Use at Baseline (Cohort 1 switch Subjects Only, Safety Analysis Set)

	With TDF Use at Baseline[a] N=158	Without TDF Use at Baseline N=84
Fasting Total Cholesterol (mg/dL)		
Change at Week 24		
N	150	77
Median	20	−11
Q1, Q3	−1, 37	−28, 19
Change at Week 48		
N	110	52
Median	21	−9
Q1, Q3	2, 44	−26, 15
Fasting Direct LDL Cholesterol (mg/dL)		
Change at Week 24		
N	150	77
Median	11	−10
Q1, Q3	−5, 25	−30, 12
Change at Week 48		
N	110	52
Median	9	−3
Q1, Q3	−5, 30	−26, 5
Fasting HDL Cholesterol (mg/dL)		
Change at Week 24		
N	150	77
Median	2	−4
Q1, Q3	−4, 7	−10, 2
Change at Week 48		
N	110	52
Median	1	−3
Q1, Q3	−5, 7	−9, 3

	With TDF Use at Baseline[a] N=158	Without TDF Use at Baseline N=84
Fasting Total Cholesterol to HDL Ratio		
Change at Week 24		
N	150	77
Median	0.2	0.2
Q1, Q3	−0.2 0.6	−0.5, 0.6
Change at Week 48		
N	110	52
Median	0.4	0.2
Q1, Q3	−0.2, 0.8	−0.1, 0.7
Fasting Triglycerides (mg/dL)		
Change at Week 24		
N	150	77
Median	9	−10
Q1, Q3	−33, 42	−55, 27
Change at Week 48		
N	110	52
Median	18	−1
Q1, Q3	−13, 48	−28, 35
Fasting Glucose (mg/dL)		
Change at Week 24		
N	150	76
Median	0	−1
Q1, Q3	−6, 8	−10, 8
Change at Week 48		
N	113	51
Median	0	−3
Q1, Q3	−8, 7	−11, 6

a With TDF use at baseline defined as subjects who took TDF containing regimen (such as Stribild, Atripla, Complera/Eviplera, Truvada, and Viread) immediately prior to the first dose date of study drug.

Source: GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 49.2.1 to 49.2.6

Among the 6 ART-naive subjects in Cohort 2, no Grade 3 to 4 fasting total cholesterol, triglycerides, or LDL abnormalities were reported, and no subjects had graded triglyceride values. Based on the number of subjects with available data at Week 48, no Cohort 2 ART-naive subject had a categorical change in NCEP ATP III lipid classifications from baseline for fasting HDL (≥ 40 mg/dL to < 40 mg/dL) or triglycerides (< 200 mg/dL to ≥ 200 mg/dL). Three of 3 subjects and 1 of 2 subjects had a categorical change in NCEP ATP III lipid classifications from baseline for fasting total cholesterol (< 200 mg/dL to ≥ 200 mg/dL) and fasting direct LDL (<130 mg/dL to ≥ 130 mg/dL), respectively. One subject had an AE of hyperlipidemia considered related to study drug by the investigator and 1 subject received a concomitant lipid-modifying agent (pravastatin).

3.3.1.4. ART-Naive Adolescent Subjects

3.3.1.4.1. Study GS-US-292-0106

Detailed clinical laboratory evaluation results for Study GS-US-292-0106 may be found in the CSR (GS-US-292-0106 Interim CSR, Section 11.6).

Fasting Glucose and Lipid Parameters

Median (Q1, Q3) values at baseline and Week 24, and median changes from baseline at Week 24 in fasting glucose and lipid parameters in Study GS-US-292-0106 are shown in Table 49.

Table 49. E/C/F/TAF Study GS-US-292-0106: Summary of Fasting Glucose and Lipid Parameters at Week 24 (Safety Analysis Set)

Fasting Parameter[a]	Baseline (N = 46)	Week 24 (N = 23)	Change from Baseline at Week 24 (N = 22)
Total Cholesterol (mg/dL)	130 (116, 148)	162 (138, 192)	34 (22, 41)
LDL Cholesterol (mg/dL)	83 (68, 99)	96 (80, 123)	18 (5, 30)
HDL Cholesterol (mg/dL)	36 (32, 40)	51 (41, 57)	10 (4, 21)
Total Cholesterol to HDL Cholesterol Ratio	3.68 (3.32, 4.17)	3.49 (2.85, 4.06)	0.01 (−0.64, 0.34)
Triglycerides (mg/dL)	85 (69, 113)	95 (77, 112)	5 (−18, 30)
Glucose (mg/dL)[b]	81 (77, 85)	84 (81, 89)	6 (−1, 12)

a All values are median (Q1, Q3).
b Baseline n = 47
Source: GS-US-292-0106 Interim CSR, Section 15.1, Tables 31.1 to 31.6

There were no graded abnormalities in fasting glucose values. Graded abnormalities in fasting total cholesterol and fasting LDL cholesterol were reported for 30.4% of subjects, all of which were Grade 1 or Grade 2 in severity and transient.

For 22 subjects who had nonmissing values at each time point, the following shifts were noted based on NCEP Expert Panel on Cholesterol Levels in Children criteria:

- Total cholesterol: 31.8% of subjects were in a higher category at Week 24 than at baseline
- LDL cholesterol: 31.8% of subjects were in a higher category at Week 24 than at baseline
- HDL cholesterol: 68.2% of subjects were in a higher category at Week 24 than at baseline
- Triglycerides: 36.4% of subjects were in a higher category at Week 24 than at baseline, 13.6% of subjects were in a lower category at Week 24 than at baseline

3.3.2. D/C/F/TAF Study

3.3.2.1. ART-Naive Subjects

3.3.2.1.1. Study GS-US-299-0102

Detailed clinical laboratory evaluation results for the D/C/F/TAF Phase 2 Study GS-US-299-0102 may be found in m5.3.5.1, GS-US-299-0102, Section 11.6.

Fasting Glucose and Lipid Parameters

In Study GS-US-299-0102, increases from baseline were observed for fasting lipid parameters total cholesterol, direct LDL cholesterol, HDL cholesterol, and triglycerides at Weeks 24 and 48 for each treatment group, with the exception of no change in fasting triglycerides at Week 48 for the DRV+COBI+TVD group (Table 50). The median increase from baseline was greater in the D/C/F/TAF group compared with the DRV+COBI+TVD group at both Week 24 and Week 48. Statistically significant differences between the 2 groups in change from baseline were seen for fasting total cholesterol and fasting direct LDL cholesterol at Week 24, and for all 4 lipid parameters at Week 48.

There were no clinically relevant changes from baseline for either treatment group or statistically significant differences in changes form baseline between treatment groups for median fasting total cholesterol to HDL ratio or fasting glucose.

Graded fasting hypercholesterolemia was more common in the D/C/F/TAF group compared with the DRV+COBI+TVD group (D/C/F/TAF 57.6%, 57 subjects; DRV+COBI+TVD 36.7%, 18 subjects). The majority of the hypercholesterolemia abnormalities were Grade 1 (D/C/F/TAF 38.4%, 38 subjects; DRV+COBI+TVD 22.4%, 11 subjects). More subjects in the D/C/F/TAF group compared with the DRV+COBI+TVD group had graded abnormalities in fasting LDL (D/C/F/TAF 53.5%, 53 subjects; DRV+COBI+TVD 34.7%, 17 subjects). The majority of these abnormalities were Grade 1 (D/C/F/TAF 29.3%, 29 subjects; DRV+COBI+TVD 16.3%, 8 subjects). Grade 2 fasting LDL was reported for 19.2% of subjects (n = 19) in the D/C/F/TAF group and 10.2% of subjects (n = 5) in the DRV+COBI+TVD group. Grade 3 fasting LDL was reported for 5.1% of subjects (n = 5) in the D/C/F/TAF group and 8.2% of subjects (n = 4) in the DRV+COBI+TVD group. No Grade 4 fasting LDL abnormalities were reported in either group.

A similar percentage of subjects in each treatment group had AEs of hyperlipidemia (D/C/F/TAF 4.9%, 5subjects; DRV+COBI+TVD 4.0%, 2 subjects); events were considered by the investigator to be related to study drug for 1 subject in each treatment group.

A similar percentage of subjects in each treatment group received concomitant lipid-modifying agents (D/C/F/TAF 14.6%, 15 subjects; DRV+COBI+TVD 14.0%, 7 subjects). In the D/C/F/TAF group, 10 of the 15 subjects were continuing treatment from baseline, while 5 initiated treatment during the study. In the DRV+COBI+TVD group, 3 subjects were continuing treatment from baseline, and 4 subjects initiated treatment during the study.

Table 50. D/C/F/TAF Study GS-US-299-0102: Summary of Fasting Metabolic Assessments Change from Baseline at Week 24 and Week 48 (Safety Analysis Set)

Metabolic Assessment	n	D/C/F/TAF (N = 103)	n	DRV+COBI+TVD (N = 50)	p-value[a]
Fasting Total Cholesterol (mg/dL)					
Baseline, median (Q1, Q3)	100	156 (137, 174)	49	158 (137, 190)	0.27
Change at Week 24	88	31 (10, 49)	47	14 (0, 32)	0.014
Change at Week 48	83	40 (13, 58)	45	5 (−9, 26)	<0.001
Fasting Direct LDL Cholesterol (mg/dL)					
Baseline, median (Q1, Q3)	100	93 (81, 108)	49	101 (79, 136)	0.14
Change at Week 24	88	22 (9, 37)	47	7 (–5, 28)	0.004
Change at Week 48	83	26 (9,44)	45	4 (–9, 17)	<0.001
Fasting HDL Cholesterol (mg/dL)					
Baseline, median (Q1, Q3)	100	42 (33, 50)	49	42 (37, 53)	0.20
Change at Week 24	88	3 (–1, 10)	47	2 (–2, 10)	0.35
Change at Week 48	83	7 (1, 14)	45	3 (–3, 7)	0.009
Fasting Total Cholesterol to HDL Ratio					
Baseline, median (Q1, Q3)	100	3.8 (3.1, 4.7)	49	3.8 (3.1, 4.8)	0.87
Change at Week 24	88	0.3 (–0.1, 0.8)	47	0.2 (–0.3, 0.7)	0.47
Change at Week 48	83	0.0 (–0.2, 0.5)	45	–0.2 (–0.5, 0.4)	0.15
Fasting Triglycerides (mg/dL)					
Baseline, median (Q1, Q3)	100	99 (76, 156)	49	99 (69, 129)	0.54
Change at Week 24	88	24 (–4, 55)	47	10 (–17, 38)	0.13
Change at Week 48	83	29 (–6, 72)	45	–5 (–23, 29)	0.007
Fasting Glucose (mg/dL)					
Baseline, median (Q1, Q3)	100	89 (81, 95)	49	91 (84, 96)	0.28
Change at Week 24	88	2 (–4, 11)	47	1 (–4, 8)	0.69
Change at Week 48	83	5 (–4, 11)	45	2 (–3, 11)	0.33

a p-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: m5.3.5.1, GS-US-299-0102, Section 15.1, Tables 37.1 to 37.6

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Detailed information on vital signs, physical findings, and other observations related to safety may be found in the respective CSRs for each study (GS-US-292-0104 Week 48 CSR, Section 11.7; GS-US-292-0111 Week 48 CSR, Section 11.7; GS-US-292-0102 Week 96 CSR, Section 11.7; GS-US-292-0109 Week 48 CSR, Section 11.8; GS-US-292-0112 Week 24 CSR, Section 11.8; GS-US-292-0106 Interim CSR, Section 11.7; and m5.3.5.1, GS-US-299-0102, Section 11.7).

4.1.1. ECG Findings

4.1.1.1. E/C/F/TAF Studies

4.1.1.1.1. ART-Naive Subjects

4.1.1.1.1.1. Studies GS-US-292-0104 and GS-US-292-0111

In Study GS-US-292-0104, clinically significant ECG abnormalities were reported for 2 subjects in the E/C/F/TAF group and 1 subject in the STB group. Clinically significant ECG abnormalities were reported as an AE for 1 subject in the E/C/F/TAF group. Subject *EO , who had a normal ECG at baseline, had clinically significant abnormal sinus rhythm with sinus arrhythmia and first degree atrioventricular block at Week 48, which was also reported as a nonserious AE of ECG abnormal considered. The event was ongoing at the time of the data cutoff, considered unrelated to study drugs by the investigator, and did not result in discontinuation of study drugs.

In Study GS-US-292-0111, clinically significant ECG abnormalities were reported as an AE for 1 subject in the E/C/F/TAF group. Subject *EP , who had an abnormal ECG at baseline (premature supraventricular complexes with aberrant ventricular conduction), had clinically significant atrial fibrillation on Day 305, which was reported as a nonserious AE of ECG abnormal. The event resolved the same day, was considered unrelated to study drugs by the investigator, and did not result in discontinuation of study drugs.

4.1.1.1.1.2. Study GS-US-292-0102

There were no clinically significant ECG findings reported for subjects during the randomized phase of Study GS-US-292-0102.

Two subjects in the E/C/F/TAF group had AEs related to ECG findings: Subject *EQ had a nonserious ST segment elevation concurrent with pericarditis, sinus bradycardia, and upper respiratory tract infection; Subject *ER had a nonserious ECG abnormality that was not associated with any AE. Neither event was related to study drugs or resulted in discontinuation of study treatment.

There were no clinically significant ECG findings reported for subjects in the E/C/F/TAF group in the extension phase.

4.1.1.1.2. Virologically Suppressed Subjects

4.1.1.1.2.1. Study GS-US-292-0109

In Study GS-US-292-0109, clinically significant ECG findings were reported for 6 subjects in the E/C/F/TAF group and 1 subject in the FTC/TDF+3rd Agent group. These ECG findings were reported as AEs for 2 subjects in the E/C/F/TAF group. Subject *ES in the E/C/F/TAF group, with normal ECG at baseline, had clinically significant abnormal nonspecific ST and T wave abnormality, with normal sinus rhythm on Day 331. The wave abnormality was reported as a nonserious, Grade 1 AE of ECG abnormal. The event was ongoing at the time of the data cutoff, considered by the investigator as unrelated to study drug, and did not result in discontinuation of study drug. Subject *ET in the E/C/F/TAF group, with normal ECG at baseline, had clinically significant abnormal sinus rhythm with possible premature atrial complexes, aberrant conduction, possible left atrial enlargement, and incomplete right bundle branch block on Day 333. The bundle branch block right and arrhythmia were reported as nonserious, Grade 1 AEs. The events were ongoing at the time of the data cutoff, were considered by the investigator as unrelated to study drug, and did not result in discontinuation of study drug.

In addition, 5 subjects in the E/C/F/TAF group and 3 subjects in the FTC/TDF+3rd Agent group had AEs related to ECG findings. In the E/C/F/TAF group, the AEs were supraventricular extrasystoles and atrial fibrillation (both reported for Subject *EU), sinus tachycardia (Subject *EV), tachycardia (Subject *DD), and sinus bradycardia (reported for Subjects *EW and *EX). In the FTC/TDF+3rd Agent group, the reported AEs were extrasystoles (Subject *EY), arrhythmia (Subject *EZ), and sinus bradycardia (Subject *FA). All of these AEs were nonserious and Grade 1 or 2; none led to discontinuation of study drugs. The AEs of supraventricular extrasystoles and atrial fibrillation reported for Subject *EU in the E/C/F/TAF group were assessed as related to study drug by the investigator.

4.1.1.1.2.2. Study GS-US-292-0102 Open-Label Extension

There were no clinically significant ECG findings or AEs related to ECG findings reported for subjects in the switch groups.

4.1.1.1.3. Subjects with Mild to Moderate Renal Impairment

4.1.1.1.3.1. Study GS-US-292-0112

There were no clinically significant ECG findings reported in Study GS-US-292-0112.

A total of 14 Cohort 1 switch subjects and 1 Cohort 2 ART-naive subject had AEs related to ECGs or cardiac conditions. Of those, 1 Cohort 1 switch subject had an AE related to ECGs or cardiac conditions that was considered by the investigator to be related to study drug (intermittent palpitations on study Day 4 non-serious and resolved within 4 days of onset).

4.1.1.1.4. ART-Naive Adolescent Subjects

4.1.1.1.4.1. Study GS-US-292-0106

Physical examination data were not collected in eCRFs for Study GS-US-292-0106. There were no clinically relevant changes in any vital signs parameter in any subject during the study.

4.1.1.2. D/C/F/TAF Study

4.1.1.2.1. ART-Naive Subjects

4.1.1.2.1.1. Study GS-US-299-0102

There were no clinically significant ECG findings reported in Study GS-US-299-0102.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

5.1.1. Summary of Intrinsic Factors

The safety profile of F/TAF was not affected by sex, age, race, HIV-1 RNA level, or CD4 count based on subgroup analyses of the Phase 3 E/C/F/TAF studies. Sex, age, and race did not have clinically relevant effects on TAF (25 mg or 10 mg), TFV, or FTC exposures based on population PK analyses of the Phase 3 studies and integrated PK analyses.

Although TAF and FTC are renally eliminated, F/TAF does not require dose adjustment above an $eGFR_{CG}$ of 30 mL/min, as in Study GS-US-292-0112, subjects with $eGFR_{CG} < 50$ mL/min receiving E/C/F/TAF did not have a different safety profile compared with subjects with $eGFR_{CG} \geq 50$ mL/min.

The effect of mild to moderate hepatic impairment (Child Pugh Class A or B) on TAF was evaluated in Study GS-US-120-0114, and no dose adjustment is necessary for patients. The effect of severe hepatic impairment on the PK of TAF has not been studied.

FTC has not been studied in hepatically impaired subjects, but renal excretion of unchanged drug is the major route of elimination of FTC with metabolism representing a minor pathway for the elimination (< 13% of oral dose). Therefore, in patients with various degrees of hepatic dysfunction, little change in FTC clearance is expected.

5.1.2. Sex

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in males and females for both treatment groups (E/C/F/TAF: male 90.2%, 661 of 733 subjects; female 88.0%, 117 of 133 subjects; STB: male 90.8%, 672 of 740 subjects; female 86.6%, 110 of 127 subjects) (E/C/F/TAF ISS, Table 8.2). Individual AEs were generally similar in males and females for both treatment groups.

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects experiencing any AE were comparable in males and females for both treatment groups (E/C/F/TAF: male 80.3%, 687 of 856 subjects; female 74.8%, 77 of 103 subjects; FTC/TDF+3rd Agent: male 76.8%, 328 of 427 subjects; female 80.0%, 40 of 50 subjects).

5.1.2.1. TAF

TAF

Sex did not have an effect on TAF exposures in subjects and was not a statistically significant or clinically relevant covariate based on population PK analyses of the Phase 3 E/C/F/TAF studies (m2.7.2, Section 3.2.2.6). Based on the integrated ad hoc PK analysis, a statistically significant

effect of sex on TAF PK parameters was observed, with higher exposure in females (mean [%CV] AUC_{last} TAF 25 mg 305.7 [47.69] ng•h/mL; TAF 10 mg + COBI 355.9 [36.30] ng/mL) than in males (mean [%CV] AUC_{last} TAF 25 mg 241.8 [49.02] ng•h/mL; TAF 10 mg + COBI 276.1 [42.40] ng/mL). Because of the wide range of safe and efficacious TAF exposure established and the larger and more robust dataset used for population PK analyses, which concluded no effect of sex on TAF PK, the relationship between sex and TAF exposure is not considered clinically relevant.

TFV

Based on covariate analyses, a statistically significant effect of sex on TFV PK parameters was observed. However, the range of TFV exposure across males and females was comparable. As such, the observed relationship between sex and TFV exposure is not considered to be clinically relevant.

5.1.2.2. FTC

For FTC, there were no major differences with respect to range and distribution of AUC values between males and females (m2.7.2, Section 3.2.2.6). The 16% higher mean AUC and the ~20% higher C_{max} in female subjects as compared with males are not considered clinically relevant. In addition, all C_{max} data points in female subjects were within the C_{max} data range of male subjects.

5.1.3. Age

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects with any AE were comparable in subjects < 50 and ≥ 50 years in the E/C/F/TAF group (< 50 years 90.0%, 699 of 777 subjects; ≥ 50 years 88.8%, 79 of 89 subjects) and the STB group (< 50 years 89.8%, 676 of 753 subjects; ≥ 50 years 93.0%, 106 of 114 subjects) (E/C/F/TAF ISS, Table 8.1). In a pooled analysis of subjects aged ≥ 65 years in Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102, all 4 subjects in the E/C/F/TAF group and 9 subjects (90%) in the STB group had at least 1 AE (E/C/F/TAF ISS, Table Req6744.2). One subject in each group (E/C/F/TAF 25%; STB 10%) had a Grade 3 or 4 AE; 1 subject (25%) in the E/C/F/TAF group and 2 subjects (20%) in the STB group had an SAE. No subject aged ≥ 65 years died or had any AE leading to study drug discontinuation.

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects with any AE were comparable in subjects < 50 and ≥ 50 years in the E/C/F/TAF group (< 50 years 79.2%, 610 of 770 subjects; ≥ 50 years 81.5%, 154 of 189 subjects) and the FTC/TDF+3rd Agent group (< 50 years 78.3%, 292 of 373 subjects; ≥ 50 years 73.1%, 76 of 104 subjects). In the subset of 19 subjects aged ≥ 65 years, at least 1 AE was reported in 11 subjects (91.7%) in the E/C/F/TAF group and 5 subjects (71.4%) in the FTC/TDF+3rd Agent group (E/C/F/TAF ISS, Table Req6758.2.2). No subject aged ≥ 65 years died or had an SAEs. In the E/C/F/TAF group, no subject had a Grade 3 or 4 AE or an AE that led to study drug discontinuation. In the FTC/TDF+3rd Agent group, 1 subject (14.3%) had a Grade 3 or 4 AE, and 1 subject (14.3%) had an AE that led to discontinuation of study drugs.

In E/C/F/TAF Study GS-US-292-0112, at least 1 AE was reported in 86.4% of subjects (n = 209: 67 [83.8%] with baseline $eGFR_{CG}$ < 50 mL/min and 142 [87.7%] with baseline $eGFR_{CG}$ ≥ 50 mL/min). In the subset of 63 subjects aged ≥ 65 years, at least 1 AE was reported in 92.1% of subjects (22 [88.0%] with baseline $eGFR_{CG}$ < 50 mL/min and 36 [94.7%] with baseline $eGFR_{CG}$ ≥ 50 mL/min) (E/C/F/TAF ISS, Table Req6756.11).

In the adolescent E/C/F/TAF Study GS-US-292-0106, at least 1 AE was reported in 81.3% of subjects (39 of 48 subjects).

5.1.3.1. TAF

TAF

As demonstrated in the Phase 3 E/C/F/TAF studies, age did not have an effect on TAF exposures in subjects and was not a statistically significant or clinically relevant covariate based on population PK analyses (m2.7.2, Section 3.2.2.2). No clinically relevant or statistically significant differences in TAF exposure were observed between age groups (18 to < 55 years of age; ≥ 55 years of age), and age (as a continuous covariate) did not have an effect on TAF exposure in healthy or HIV-infected subjects based on population PK analyses and integrated PK analyses.

In adolescent subjects, TAF exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration (PK substudy in Study GS-US-292-0102 [m2.7.3, Section 2.1.1.3]), indicating no relevant effect of age (≥ 12 and < 18 years) on the exposure of TAF (m2.7.2, Section 3.2.2.5). Additionally, in the pooled E/C/F/TAF Phase 2 and Phase 3 study populations used for population PK analyses, HIV-infected adolescent subjects had comparable TAF exposures versus HIV-infected adult subjects, respectively, again confirming that age was not a clinically relevant covariate.

TFV

As age is often correlated with renal function and TFV is primarily renally eliminated, there was a modest dependence of TFV exposure on age (mean [%CV] AUC_{tau} 18 to < 55 years of age 322.3 [44.2] ng*h/mL; ≥ 55 years of age 522.9 [37.1] ng*h/mL); however age was not found to be a statistically significant covariate after adjusting for $eGFR_{CG}$. Moreover, this age-dependent exposure difference was not considered clinically relevant, since TFV exposure observed in subjects ≥ 55 years of age receiving E/C/F/TAF was still at least 80% lower than TFV exposures observed following STB administration in Studies GS-US-292-0104 and GS-US-292-0111.

In adolescent subjects, TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration (PK substudy in Study GS-US-292-0102 [m2.7.3, Section 2.1.1.3]). Additionally, in the pooled E/C/F/TAF Phase 2 and Phase 3 study populations used for population PK analyses, HIV-infected adolescent subjects had comparable TFV exposures versus HIV-infected adult subjects, respectively, again confirming that age was not a clinically relevant covariate.

5.1.3.2. FTC

For FTC PK, there were no relevant differences with respect to range and distribution of AUC values between age groups examined (m2.7.2, Section 3.2.2.2). Subjects > 40 years had slightly higher (< 10%) mean/median AUC and C_{max} values than subjects ≤ 40 years of age. There were no major differences in the overall range and distribution of $t_{1/2}$ values between the 2 age groups. However, subjects > 40 years of age had a longer mean or median $t_{1/2}$ than subjects ≤ 40 years by 26% or 30%.

5.1.4. Race

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in black and nonblack subjects for both treatment groups (E/C/F/TAF: black 90.6%, 202 of 223 subjects; nonblack 89.6%, 576 of 643 subjects; STB: black 91.5%, 195 of 213 subjects; nonblack 89.8%, 587 of 654 subjects) (E/C/F/TAF ISS, Table 8.3).

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects experiencing any AE were comparable in black and nonblack subjects for both treatment groups (E/C/F/TAF: black 77.5%, 131 of 169 subjects; nonblack 80.2%, 632 of 788 subjects; FTC/TDF+3rd Agent: black 72.5%, 74 of 102 subjects; nonblack 78.3%, 293 of 374 subjects).

In E/C/F/TAF Study GS-US-292-0108, 6 Japanese subjects (60.0%) and 9 white subjects (90.0%) experienced at least 1 AE. No significant differences in safety parameters between Japanese and white subjects were noted.

5.1.4.1. TAF

TAF

As demonstrated in the Phase 3 E/C/F/TAF studies, race did not have an effect on TAF (25 mg or 10 mg) exposures in subjects and was not a statistically significant or clinically relevant covariate based on population PK analyses and integrated PK analyses (m2.7.2, Section 3.2.2.4).

The PK of TAF were comparable between Japanese and white subjects, both after a single dose of E/C/F/TAF and upon multiple dosing of E/C/F/TAF (Study GS-US-292-0108).

TFV

Based on covariate analyses, a statistically significant effect of race (black versus nonblack) on TFV PK parameters was observed. However, the range of TFV exposure across race was comparable and overall > 80% lower than TFV exposure observed following STB administration. As such, the observed relationship between race and TFV exposure is not considered to be clinically relevant.

The PK of TFV were comparable between Japanese and white subjects, both after a single dose of E/C/F/TAF and upon multiple dosing of E/C/F/TAF (Study GS-US-292-0108).

5.1.4.2. FTC

No clinically important PK differences in FTC exposure due to gender or race have been identified {23270}, {30162}.

5.1.5. HIV-1 RNA Stratum at Baseline

In in ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in subjects with baseline HIV-1 RNA level ≤ 100,000 copies/mL and > 100,000 copies/mL for both treatment groups (E/C/F/TAF: HIV-1 RNA level ≤ 100,000 copies/mL 89.6%, 600 of 670 subjects; > 100,000 copies/mL 90.8%, 178 of 196 subjects; STB: HIV-1 RNA level ≤ 100,000 copies/mL 89.6%, 602 of 672 subjects; > 100,000 copies/mL 92.3%, 180 of 195 subjects) (E/C/F/TAF ISS, Table 8.4).

5.1.6. CD4 Cell Count at Baseline

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in subjects with baseline CD4 count < 200 cells/μL and ≥ 200 cells/μL for both treatment groups (E/C/F/TAF: CD4 count < 200/μL 90.2%, 101 of 112 subjects; ≥ 200/μL 89.8%, 676 of 753 subjects; STB: CD4 count < 200/μL 88.0%, 103 of 117 subjects; ≥ 200/μL 90.5%, 679 of 750 subjects) (E/C/F/TAF ISS, Table 8.5).

5.1.7. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

The PK-PD analyses of the TAF and TFV exposure:safety relationship were performed in ART-naive HIV-infected subjects in E/C/F/TAF pivotal Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 using TAF and TFV exposures derived from population PK modeling versus safety parameters that included commonly observed AEs, namely diarrhea and nausea (very common ≥ 10%), and vomiting and gastrointestinal (GI)/abdominal pain (common ≥ 1% and < 10%). The relationships between plasma TAF and TFV exposures and ΔΔQTcF were evaluated in a thorough QT/QTc study of TAF single agent (Study GS-US-120-0107) (m2.7.2, Section 3.3.2).

5.1.7.1. TAF

TAF

TAF exposure was comparable regardless of the presence or absence of diarrhea and/or GI/abdominal pain, and no relevant exposure-AE trends were observed with these AEs. TAF exposure was generally comparable in the presence or absence of nausea and/or vomiting, but logistic regression analysis showed a trend between the highest TAF exposure and the presence of these AEs (nausea correlated with the highest 4% of TAF exposure; vomiting correlated with

the highest 19% of TAF exposure). No trend was observed between exposure and severity. The overall incidence of nausea and vomiting was similar between treatment groups in the pivotal Phase 3 studies (E/C/F/TAF ISS, Table 7).

Percentage change from baseline in BMD at the hip and at the spine at Week 48 were also key safety endpoints of Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TAF exposure quartiles and changes in BMD at the hip and spine were evaluated. Across all TAF AUC_{tau} quartiles, percentage change from baseline at the hip and at the spine at Week 48 in BMD were comparable; no trends in exposure changes in BMD were noted.

The change from baseline in serum creatinine at Week 48 was a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. The relationship between TAF exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated. Across all TAF AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable; no trends in exposure-changes in serum creatinine were noted.

A linear mixed-effect model of the relationship between plasma concentrations of TAF and ΔΔQTcF suggest there is no statistically significant or pharmacologically meaningful association between TAF plasma concentration and ΔΔQTcF interval (Study GS-US-120-0107).

TFV

For diarrhea, GI/abdominal pain, nausea, and vomiting, TFV exposure was comparable regardless of the presence or absence of either of those symptoms, and no exposure-AE trends were observed with these AEs.

The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were also key safety endpoints in Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationships between TFV exposure quartiles and changes in BMD at the hip and spine were evaluated. The percentage change from baseline at Week 48 was comparable across all TFV AUC_{tau} quartiles for both hip and spine BMD; no exposure-changes in BMD trends were noted.

Change from baseline in serum creatinine at Week 48 was a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. The relationship between TFV exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated. Maximum increase from baseline in serum creatinine was comparable across TFV AUCtau quartiles; no exposure changes in serum creatinine trends were noted.

A linear mixed-effect model of the relationship between plasma concentrations of TFV and ΔΔQTcF suggest there is no pharmacologically meaningful association between plasma concentrations of TFV and ΔΔQTcF, ΔQTcF, or raw QTcF (Study GS-US-120-0107).

5.1.7.2. FTC

The PK-PD analyses of the FTC exposure safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2 and Phase 3 studies using FTC exposures derived from

intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea. The relationship between FTC exposure quartiles and changes in renal laboratory parameters was also evaluated.

FTC exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed. As observed for the other agents, across all FTC AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable, and no trends in exposure-changes in laboratory parameters were noted. Importantly, the range of FTC exposures explored in these PK/PD analyses covered the individual FTC exposures observed in the renally impaired, HIV-infected subjects with $eGFR_{CG} < 50$ mL/min receiving E/C/F/TAF in Phase 3 Study GS-US-292-0112. Moreover, as demonstrated in Study GS-US-292-0112, subjects with $eGFR_{CG} < 50$ mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG} \geq 50$ mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

5.1.8. Renal Impairment

Pharmacokinetic and relevant safety data support administration of F/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) (m2.7.2, Section 3.2.2.1.1). Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, baseline eGFR was not a statistically significant or clinically relevant covariate influencing TAF PK. As expected due to renal elimination, FTC PK parameters were higher in subjects with mild to moderate renal impairment compared with those having normal renal function in the Phase 2 and 3 E/C/F/TAF studies in ART naive subjects. However, the FTC PK parameters were comparable to the mean FTC PK parameters achieved in subjects with mild renal impairment not requiring dose adjustment {23270}, {30162}. Moreover, subjects with $eGFR_{CG} < 50$ mL/min receiving E/C/F/TAF did not have a different safety profile compared with subjects with $eGFR_{CG} \geq 50$ mL/min.

No additional measures outside of standard clinical practice guidelines for routine monitoring renal safety in subjects with mild to moderate renal impairment are indicated.

5.1.8.1. TAF

TAF

In the Phase 1 Study GS-US-120-0108, the PK of TAF and TFV was analyzed in non−HIV-infected subjects with severe renal impairment (defined as subjects with $eGFR_{CG}$ between 15 mL/min and 29 mL/min [inclusive], not on dialysis) and in age- and sex-matched non–HIV-infected subjects with normal renal function ($eGFR_{CG} \geq 90$ mL/min) following a single dose of TAF. Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure (as assessed by AUC_{inf}) relative to age- and sex-matched subjects with normal renal function. These data supported the conduct of a clinical study to evaluate the safety and efficacy of E/C/F/TAF in HIV-infected patients with mild to moderate renal impairment (Study GS-US-292-0112).

A Phase 3 PK substudy (n = 30) evaluating the PK of TAF following administration of E/C/F/TAF was performed in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min at screening, and showed mean (%CV) TAF and TFV exposures (AUC) of 254.2 (54.1) ng*h/mL (n = 29) (GS-US-292-0112). The TAF exposure was numerically higher in subjects with baseline eGFRCG < 50 versus ≥ 50 mL/min. These Phase 3 data are also consistent with results from the renal impairment study, GS-US-120-0108.

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, baseline eGFR was not a statistically significant or clinically relevant covariate influencing TAF PK. Although TAF exposure was higher in HIV-infected subjects with lower baseline $eGFR_{CG}$ ($30 \leq eGFR_{CG} < 60$ mL/min; mean [%CV] AUC 305.0 [112.5] ng•h/mL; C_{max} 208.6 [53.0] ng/mL) relative to those with normal renal function (> 90 mL/min) the difference between those with moderate renal impairment and those with normal renal function was less than 50% (mean [%CV] AUC 210.4 [94.1] ng•h/mL; C_{max}158.9 [57.1] ng/mL).

TFV

Following a single dose of TAF, non–HIV-infected subjects with severe renal impairment in Study GS-US-120-0108 had a 6.05-fold mean increase in systemic TFV exposure (as assessed by AUC_{inf}) relative to age- and sex-matched non–HIV-infected subjects with normal renal function. The mean (%CV) TFV exposure observed in this study in subjects with severe renal impairment (2073.8 [47.1] ng*h/mL) was within or below the ranges of TFV plasma exposure observed in historical studies after administration of TDF 300 mg in both HIV-infected and non−HIV-infected subjects with normal renal function.

In the Phase 3 PK substudy (n = 30) of E/C/F/TAF in HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min (Study GS-US-292-0112) at screening, mean (%CV) TFV exposure (AUC) was 552.7 (32.0) ng*h/mL (n = 29) (Study GS-US-292-0112). The TFV exposure was numerically higher in subjects with baseline $eGFR_{CG} < 50$ versus ≥ 50 mL/min. These Phase 3 data are also consistent with results from the renal impairment study, GS-US-120-0108.

Based on population PK analyses of pooled data from Phase 1, 2, and 3 studies in healthy and HIV-infected subjects, a statistically significant effect of baseline $eGFR_{CG}$ on TFV exposure was observed based on covariate analyses; this result was expected with TFV being primarily renally eliminated. Although TFV exposure was higher in HIV-infected subjects with lower baseline $eGFR_{CG}$ relative to those with normal renal function, the TFV exposure observed in subjects with $eGFR_{CG} < 50$ mL/min was within or below the ranges of exposure observed in historical studies after administration of TDF 300 mg in both HIV-infected and non−HIV-infected subjects with normal renal function {26885}, {34210}.

5.1.8.2. FTC

Since renal excretion of the unchanged drug is the principal route of elimination for FTC, it is anticipated that the PK profiles of FTC in subjects with altered or deficient renal function may vary or deviate from those in subjects with normal renal function. Adult subjects with varying degrees of renal impairment (or insufficiency), as determined by $eGFR_{CG}$ values, were evaluated in Study FTC-107.

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

The percentage of dose excreted as unchanged FTC in urine for the normal and mild renal impairment groups ($eGFR_{CG}$ 50-80 mL/min) was similar to that observed with healthy subjects (FTC-106) and HIV-infected subjects with normal renal function (FTC-101). In subjects with moderate and severe impairment ($eGFR_{CG}$ < 50 mL/min), the urinary recovery was lower (approximately 30%-50% of the dose) over a 72-hour collection period, primarily due to slower excretion of FTC by the impaired kidneys, which, in the absence of clinical experience of FTC in HIV-infected subjects with $eGFR_{CG}$ < 60 mL/min, led to a dose interval adjustment recommendation.

A Phase 3 efficacy and safety study was conducted to evaluate the effect of the E/C/F/TAF on renal parameters in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min (Study GS-US-292-0112 [Section 1.1.4.1.1]). This study included an intensive PK substudy evaluating the PK of FTC following administration of E/C/F/TAF in subjects with $eGFR_{CG}$ of 30 to 69 mL/min (n = 30) and showed mean (%CV) FTC exposure AUC and C_{max} of 20,968.6 (25.5) ng*h/mL and 2645.3 (24.7) ng/mL, respectively, which were in the range of exposures where dose modification was not warranted in FTC-107. Importantly, the mean FTC AUC and C_{max} observed in GS-US-292-0112 subjects with $eGFR_{CG}$ of 30 to 69 mL/min were comparable with the AUC and C_{max} of 19,900 (6.2) ng*h/mL and 3800 (2.3) ng/mL, respectively, for subjects with $eGFR_{CG}$ of 50 to 80 mL/min who do not require dose adjustment {23270}, {30162}. Subjects with $eGFR_{CG}$ < 50 mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG} \geq 50$ mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

The totality of these data support the recommendation that F/TAF may be safely administered once daily without dose adjustment in patients with renal impairment ($eGFR_{CG}$ 30 to 69 mL/min).

5.1.9. Hepatic Impairment

Pharmacokinetic and relevant safety data support administration of F/TAF once daily without dose adjustment in HIV-infected subjects with mild to moderate hepatic impairment (CPT Class A or B) (m2.7.2, Section 3.2.2.1.2).

The PK of TAF and its metabolite TFV was evaluated in non-HIV-infected subjects with mild or moderate hepatic impairment (CPT Class A or B) and in age- and sex-matched non–HIV-infected subjects with normal hepatic function following a single dose of TAF in Study GS-US-120-0114. The effect of severe hepatic impairment on the PK of TAF has not been studied.

5.1.9.1. TAF

TAF

The plasma exposure parameters of TAF were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 12.69%, 15.06%, and 18.70% higher, respectively) in non–HIV-infected subjects with moderate hepatic impairment relative to age- and sex-matched control subjects with normal hepatic function; the observed increases were not considered to be clinically relevant.

TFV

The plasma exposure parameters of TFV were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 10.84%, 10.69%, and 2.97% lower, respectively) in non–HIV-infected subjects with mild hepatic impairment relative to age- and sex-matched control subjects with normal hepatic function; the observed decreases were not considered to be clinically relevant. The plasma exposure parameters of TFV were comparable (AUC_{inf}, AUC_{last}, and C_{max} were 2.78%, 4.45%, and 12.44% lower, respectively) in non–HIV-infected subjects with moderate hepatic impairment relative to age- and sex-matched control subjects with normal hepatic function; the observed decreases were not considered to be clinically relevant.

5.1.9.2. FTC

The PK of FTC has not been studied in hepatically impaired subjects. Renal excretion of unchanged drug is the major route of elimination of FTC in humans with metabolism representing a minor pathway for the elimination (< 13% of oral dose) (Study FTC-106). Therefore, in patients with various degrees of hepatic dysfunction, little change in FTC clearance is expected.

5.1.10. Coinfection with HIV-1 and Hepatitis B and/or Hepatitis C Virus

Subjects with HBV or HCV coinfection were excluded from the E/C/F/TAF clinical development program. The exclusion criteria for Phase 3 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. In Study GS-US-292-0104, Subject *FB in the STB group tested positive for HBV surface antigen at screening and discontinued study drugs on Day 32 due an SAE of Grade 3 immune inflammatory syndrome due to HBV, which resulted in unblinding of study drug.

Subject *FC in the E/C/F/TAF group of Study GS-US-292-0104 had normal liver function tests (LFTs) at screening, and high aspartate aminotransferase (AST; Grade 2) and alanine aminotransferase (ALT; Grade 3) at baseline (AST = 117 U/L, ALT = 237 U/L). AST returned to within the normal range on Day 18, and ALT was within the normal range by Day 26. On Day 84, ALT was again elevated (55 U/L, Grade 1). On Day 113, the subject had a nonserious AE of Grade 2 hepatitis C (ALT = 788 U/L, Grade 4; AST = 383 U/L, Grade 4) considered unrelated to the study drugs by the investigator. On Day 133 the subject tested positive for HCV

antigen. On Day 181, the subject commenced treatment with subcutaneous pegylated interferon and oral ribavirin (treatment ongoing). By Day 253, all LFTs were within the normal range; however the event of hepatitis C was ongoing.

The PK of FTC was evaluated in a Phase 1 study in subjects with chronic HBV (Study FTCB-101). Based on the steady-state data from FTCB-101, FTC PK in HBV-infected subjects are generally similar to those determined previously in healthy subjects and in HIV-infected subjects.

5.2. Extrinsic Factors

5.2.1. Summary of Extrinsic Factors

Data pertinent to drug interactions are described in Section 5.3.

The safety profile of F/TAF was not affected by prior treatment regimen, food, or region.

5.2.2. Prior Treatment Regimen

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects with any AE were comparable in subjects who received prior treatment with STB (E/C/F/TAF 79.1%, 242 of 306 subjects; FTC/TDF+3rd Agent 77.1%, 118 of 153 subjects), ATR (E/C/F/TAF 82.1%, 206 of 251 subjects; FTC/TDF+3rd Agent 76.8%, 96 of 125 subjects), or ATV/boosted+TVD (E/C/F/TAF 78.6%, 316 of 402 subjects; FTC/TDF+3rd Agent 77.4%, 154 of 199 subjects).

5.2.3. Effect of Food

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

In Study GS-US-311-1386, administration of F/TAF under fed conditions resulted in increased overall TAF exposure, lower C_{max}, and delayed T_{max}. Administration of F/TAF (200/25 mg) under fed conditions resulted in an increase in TAF exposure (AUC_{last}) by 77% compared with administration under fasting conditions, with a decrease of 15% in TAF C_{max} and delay in TAF T_{max} from 0.50 hour under fasting conditions to 1.00 hour under fed conditions (m5.3.3.4, GS-US-311-1386). Given the wide range of safe and efficacious TAF exposure established in the Phase 3 E/C/F/TAF studies (predicted individual steady-state mean [95% CI, %CV] AUC 206.4 ng*h/mL [55.6 to 526.1 ng*h/mL, 71.8%]), the differences in TAF PK under fed and fasting conditions were not considered clinically relevant.

In Study GS-US-292-0110, administration of E/C/F/TAF under fed conditions did not affect overall TAF exposure, but resulted in a lower C_{max} and delayed T_{max}. Administration of E/C/F/TAF with a high-fat meal resulted in an increase of 17% in TAF exposure (AUC_{last}) compared with administration following an overnight fast, with a 37% decrease in TAF C_{max} and

a delay in TAF T_{max} from 0.50 hour under fasting conditions to 1.00 hour under fed conditions. These modest changes in TAF PK parameters upon E/C/F/TAF administration with food (versus fasted) are not considered clinically relevant.

The differential effect of food observed between Studies GS-US-311-1386 and GS-US-292-0110 is likely due to the oral bioavailability of TAF when administered in the absence or presence of a boosting agent. Although the absolute bioavailability of TAF has not been evaluated in humans, it is expected to be modest (~40%). TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI or RTV) reduces P-gp−mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. As a result, the effect of food on TAF absorption is smaller when administered in the presence of a boosting agent.

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

5.2.4. Region

In ART-naive subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111, the percentages of subjects experiencing any AE were comparable in subjects from the United States (US) and ex-US regions for both treatment groups (E/C/F/TAF: US 90.0%, 479 of 532 subjects; ex-US 89.5%, 299 of 334 subjects; STB: US 91.9%, 489 of 532 subjects; ex-US 87.5%, 293 of 335 subjects; E/C/F/TAF ISS, Table 8.6).

In virologically suppressed subjects in E/C/F/TAF Study GS-US-292-0109, the percentages of subjects experiencing any AE were comparable in subjects from the US and ex-US regions for both treatment groups (E/C/F/TAF: US 79.9%, 518 of 648 subjects; ex-US 79.1%, 246 of 311 subjects; FTC/TDF+3rd Agent: US 75.3%, 238 of 316 subjects; ex-US 80.7%, 130 of 161 subjects).

5.3. Drug Interactions

Drug interaction studies involving TAF and/or FTC have been conducted and pertinent findings and/or recommendations are as follows (m2.7.2, Section 3.2.3.2).

5.3.1. TAF

TAF

The potential for TAF to affect human cytochrome P450 enzyme (CYP)-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities. TAF weakly inhibited CYP3A-mediated oxidation of midazolam (MDZ) or

testosterone with concentration that resulted in 50% inhibition (IC_{50}) values of 7.6 and 7.4 μM, respectively.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A was assessed at TAF concentration at 50 μM (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.

Study GS-US-120-1538 demonstrated that multiple-dose TAF does not exhibit CYP3A inhibition or induction activity, either presystemically or systemically, when assessed using MDZ as a CYP3A probe drug (m5.3.3.4, GS-US-120-1538).

TAF is transported by P-glycoprotein (P-gp) and metabolized by esterases expressed in the intestine {21545}, {21546}. Drugs that strongly affect P-gp activity may lead to changes in TAF bioavailability. Coadministration with COBI or RTV can lead to near-maximal inhibition of P-gp, resulting in increased TAF exposure. Coadministration with COBI-boosted EVG, RTV-boosted ATV, or RTV-boosted LPV resulted in an increase in TAF exposure of 122%, 91%, and 47%, respectively, compared with FTC+TAF or TAF single agent. Notably, coadministration with RTV- or COBI-boosted DRV had almost no effect on TAF exposure (6% increase and 2% decrease in AUC_{last}, respectively); this lack of effect may have been due to a mixed inhibitory/inductive effect of D/C/F/TAF on TAF absorption. It was because of the effect of P-gp inhibitors on TAF exposure that 2 F/TAF FDC dosage strengths were developed. Results from Studies GS-US-311-1472 and GS-US-311-1473, demonstrate bioequivalence in TAF exposure between TAF 25 mg and TAF 10 mg + COBI; the results of the integrated ad hoc PK analysis support this conclusion.

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

Exposure to TAF may be affected by inhibitors of organic anion transporting polypeptide (OATP)1B1 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.

Following the coadministration of E/C/F/TAF and sertraline, no clinically relevant alterations in the PK of TAF, TFV, or sertraline were observed relative to the administration of E/C/F/TAF or sertraline alone (m2.7.2, Section 2.5.3.2). A lack of CYP-mediated drug interaction was observed upon coadministration of E/C/F/TAF and sertraline. Overall, the exposures of all analytes following E/C/F/TAF and/or sertraline were consistent with historical data.

TFV

The potential for TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (V990172-104). TFV at 100 μM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

Coadministration of TAF with a modest CYP3A inducer (ie, EFV) resulted in slightly lower TFV exposure (20% to 25%; GS-US-311-0101), likely due to P-gp induction. As such, administration of F/TAF with a modest CYP3A inducer may result in lower TFV exposure. Coadministration of TAF with a weak CYP inducer (ie, RPV) resulted in no clinically relevant change in TFV exposure (GS-US-120-1554). As such, no effect on TFV exposure is expected upon coadministration of F/TAF with a weak CYP3A inducer.

5.3.2. FTC

There are no clinically significant interactions when FTC is coadministered with TDF, EFV, DRV+COBI, sertraline, ledipasvir/sofosbuvir, tacrolimus, zidovudine (ZDV), d4T, or famciclovir.

FTC is primarily excreted via glomerular filtration and active tubular secretion. With the exception of famciclovir and TDF, the effect of coadministration of FTC with medicinal products that are excreted by the renal route, or other medicinal products known to affect renal function, has not been evaluated. Coadministration of FTC with medicinal products that are eliminated by active tubular secretion may lead to an increase in serum concentrations of either FTC or a coadministered medicinal product due to competition for this elimination pathway.

5.4. Use in Pregnancy and Lactation

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

In animal studies, it has been shown that TFV is excreted into milk. In humans, samples of breast milk obtained from 5 HIV-infected mothers given TVD show that TFV is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the TFV IC_{50}){17083}. The same samples show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of FTC. Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown. Tenofovir-associated risks, including the risk of viral resistance to TFV, in infants breastfed by mothers being treated with TAF are unknown. 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 the F/TAF FDC.

5.4.1. E/C/F/TAF

No pregnancies were reported in Phase 1 studies with the E/C/F/TAF FDC.

Two pregnancies were reported in the Phase 2 Study GS-US-292-0102. One subject (Subject *FD , E/C/F/TAF) had a confirmed ectopic pregnancy on Day 689 that was reported as an SAE. The subject underwent emergency surgery to remove the ectopic pregnancy and she recovered on Day 690. One subject (Subject *FE , STB) had a confirmed pregnancy on Day 741 for which further details were not available.

Six pregnancies were reported in Phase 3 Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0112, and GS-US-292-0109; all were due to nonadherence to protocol-specified contraception.

Pregnancy in 1 subject enrolled in Study GS-US-292-0104 (Subject *AR , STB) resulted in the birth at 40 weeks gestation of a live-born female neonate; there were no reported complications.

Pregnancy in 1 subject enrolled in Study GS-US-292-0111 (Subject *FF , STB) reported severe intrauterine growth restriction. The subject delivered a live male infant at 37 weeks gestational age; no labor or delivery complications, nor prolonged neonatal hospitalization were noted.

Pregnancies in 3 subjects enrolled in Study GS-US-292-0111 (Subjects *FG , *FH , and *FI ; STB) were reported as ongoing at the time of the report.

Pregnancy in 1 subject enrolled in Study GS-US-292-0109 (Subject *FJ , E/C/F/TAF) was terminated by an elective abortion.

No pregnancies were reported in Study GS-US-292-0112 or GS-US-292-0106.

5.4.2. D/C/F/TAF

No pregnancies were reported in the Phase 1 Study GS-US-299-0101 or Phase 2 Study GS-US-299-0102 with the D/C/F/TAF FDC.

5.4.3. F/TAF

Pregnancy in 1 subject (Subject *DG , F/TAF) enrolled in Study GS-US-311-1386 was terminated in a spontaneous abortion (SAE considered related to study drug by the investigator).

5.4.4. TAF

No pregnancies were reported in clinical studies for TAF single agent.

5.4.5. FTC

Pregnancies in clinical studies are described in individual CSRs. The safety of the use of FTC during pregnancy or breast-feeding is reflected in the approved drug label for Emtriva. This product should only be used in pregnancy if the potential benefit justifies the potential risk.

Cumulative Antiretroviral Pregnancy Registry (APR) interim analysis reports are produced at 6-month intervals, and the latest report was issued in [redacted] 20[redacted] (data to [redacted] 20[redacted]). The cumulative data for FTC are provided below.

A total of 1721 first trimester and 818 second/third trimester prospective cases of live births involving exposure to FTC were presented. There were 41 cases of birth defects following first trimester exposure and 18 cases of a birth defects following second/third trimester exposure.

The main conclusions from the latest APR report were as follows:

Primary Registry Analysis (Prospective Reports)

For FTC, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date.

For the overall population exposed to ARV drugs in this registry, no increases in risk of overall birth defects or specific defects have been detected to date when compared with observed rates in the 2 population-based birth defects surveillance systems (Centers for Disease Control and Prevention's [CDC's] birth defects surveillance system, the Metropolitan Atlanta Congenital Defects Program [MACDP]) and the Texas Birth Defects Registry (TBDR) or with rates among those with earliest exposure in the second and third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis with the exception of didanosine (ddI) and nelfinavir, no increases in risk of concern have been detected.

Retrospective Reports

No pattern of defects (isolated or syndromic) associated with FTC exposure has been found in the overall evaluation of retrospective reports and registry cases of birth defects.

Reports from Clinical Studies in Pregnancy

Events from clinical studies involving FTC were not analysed separately. In the analysis of reports from clinical studies in pregnancy involving all products in the APR, 14 infants with defects were identified among 310 live births with first trimester exposures to an antiretroviral therapy. The prevalence of birth defects per 100 live births among women with first trimester exposures to an antiretroviral (primarily NRTIs) is 4.5 (95% CI: 2.5-7.5). The number of defects identified with an initial exposure in the second or third trimester is 23 among 1567 live births, and the prevalence of birth defects per 100 live births is 1.5 (95% CI: 0.9-2.2). The high rate of birth defects in clinical studies is attributed to the patient population enrolling in clinical studies

compared with either the MACDP or the TBDR. Differences include severity of disease at the time of maternal enrollment in clinical studies and rigorous infant follow-up and evaluation. In addition, women with first trimester exposures appeared to have more advanced disease. Forty-nine prospective cases of ventricular septal defects, distributed across trimesters and drug exposures, have been received to date. The overall rate remains low and there is no apparent excess of cases among ZDV or any drug exposure group or relevant trimester of exposure.

Reports from the Published Literature

The registry has not identified a signal in any of the published studies reviewed to date.

5.5. Overdose

If an overdose with F/TAF occurs, the patient must be monitored for evidence of toxicity, and general supportive measures applied as necessary, including observation of the clinical status of the patient and monitoring of vital signs. Limited clinical experience is available at doses higher than the therapeutic doses of FTC or TAF. No Grade 3 adverse reactions were reported at supratherapeutic doses in studies of FTC.

Up to 30% of the FTC dose may be removed by hemodialysis. TFV is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether FTC or TFV may be removed by peritoneal dialysis.

Cases of overdose are assessed within postmarketing surveillance of FTC are discussed in the periodic safety update reports for this product. No new safety issues have been identified regarding overdose.

Within the Phase 1, 2 and 3 studies included in this submission, most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of study medication and not associated with clinical symptoms or sequelae. Cases with additional relevant details are described below:

- In Study GS-US-292-0104, 2 subjects had AEs associated with overdose: (E/C/F/TAF: Grade 1 headache [Subject *FK], and event not specified [Subject *FL]).

- In Study GS-US-292-0111, 2 subjects had AEs associated with overdose (E/C/F/TAF: dizziness [Subject *FM], STB: vomiting [Subject *FN]).

- In Study GS-US-292-0102, Subject *BR in the STB group had an SAE of suicidal ideation by taking 3 pills from each bottle of the study drugs instead of the prescribed dose of 1 dose form daily. The subject also took an overdose of naproxen by taking more than 6 pills at the same time on the same day. The SAE of suicidal ideation resolved on the day of onset.

- In Study GS-US-292-0109, Subject *FO in the E/C/F/TAF group took almost an entire bottle of study drug in a suicidal gesture (intentional overdose). The suicide attempt was reported as an SAE that resolved on the same day as onset. Study drug was discontinued, and the subject recovered fully.

5.6. Drug Abuse

No safety issues concerning the abuse or misuse of F/TAF tablets are anticipated from the available data.

5.7. Withdrawal and Rebound

The safety and efficacy of F/TAF have not been established in patients coinfected with HIV-1 and HBV. Discontinuation of F/TAF therapy in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis. Patients coinfected with HIV-1 and HBV who discontinue F/TAF should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since posttreatment exacerbation of hepatitis may lead to hepatic decompensation.

5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been conducted to evaluate the effects of FTC or TAF on the ability to drive or operate machinery.

6. POSTMARKETING DATA

F/TAF has not been marketed in any country at the time of this application.

7. APPENDICES

Appendix Number	Appendix Title
7.1	Tabular Summary of E/C/F/TAF Studies Relevant for Safety
7.1.2	Tabular Summary of TAF Studies Relevant for Safety
7.1.3	Tabular Summary of FTC Studies Relevant for Safety
7.2	E/C/F/TAF FDC: Integrated Safety Analyses

7.1. Tabular Summary of Studies Relevant for Safety

7.1.1. E/C/F/TAF Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	GS-US-292-0106 (synopsis)	Part A: Evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC Part B: Evaluate the safety and tolerability of the E/C/F/TAF FDC	Phase 2/3, open-label, multicenter, 2-part, single-group study	• E/C/F/TAF (150/150/200/10 mg) QD PO	48 weeks Extension Phase: Subjects have option to continue study drug until subject turns 18 and E/C/F/TAF is commercially available for adults in country of enrollment, E/C/F/TAF becomes commercially available for adolescents in country of enrollment, or E/C/F/TAF development is terminated in country of enrollment	Enrolled: 48 Part A: 24 Part B: 24 Safety Analysis Set: 48 Continuing study drug at Week 24: Main study: 47 Extension: 1	HIV-infected, ART-naive adolescents (12 to < 18 years of age)	Study ongoing; Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	GS-US-292-0112 (synopsis)	Evaluate the effect of the E/C/F/TAF FDC on renal parameters	Phase 3, open-label, multicenter, multi-cohort study	• E/C/F/TAF (150/150/200/10 mg) QD PO	96 weeks Extension Phase: Subjects have option to continue study drug until E/C/F/TAF is commercially available or development is terminated	Enrolled: 252 Safety Analysis Set: Cohort 1: 242 Cohort 2: 6 Continuing study drug at Week 24 Cohort 1: 226 Cohort 2: 6	HIV-infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min Cohort 1: ART-experienced Cohort 2: ART-naive	Study ongoing; Week 24 Interim CSR

7.1.2. TAF Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-0117 (synopsis)	Evaluate the PK of RPV and TAF following single-dose administration of RPV and TAF alone and in combination in healthy subjects	Phase 1, open-label, single-center, single-dose, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatment: <u>Cohort 1:</u> • TAF 25 mg QD PO (A) • TAF 25 mg + RPV 25 mg QD PO (B) <u>Cohort 2:</u> • TAF 25 mg + RPV 25 mg QD PO (B) • RPV 25 mg QD PO (C)	2 days (Day 1 and 12)	Randomized: 36 Completed: 36 Safety Analysis Set: Cohort 1: 18 Cohort 2: 18	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-0118 (synopsis)	Evaluate the effect of common boosted PIs ATV+RTV; DRV+RTV; LPV/r, or the INSTI DTG on the PK of TAF, and evaluate the PK of ATV, DRV, LPV, and DTG alone and in combination with FTC and TAF	Phase 1, open-label, DDI study	Cohort 1: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • ATV 300 mg + RTV 100 mg QD PO (Days 2-14) (B) • A + B (Day 15) Cohort 2: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • DRV 800 mg + RTV 100 mg QD PO (Days 2-14) (C) • A + C (Day 15) Cohort 3: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • LPV/r (4 × 200/50 mg) QD PO (Days 2-14) (D) • A + D (Day 15) Cohort 4: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (F) • DTG 50 mg QD PO (Days 2-14) (E) • F + E (Day 15)	15 days	Enrolled: 40 Completed: 39 Safety Analysis Set: Cohort 1: 10 Cohort 2: 10 Cohort 3: 10 Cohort 4: 10 (1 subject excluded from the FTC+TAF+DTG safety analysis)	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Patient PD and PK/PD	GS-120-1101 (synopsis)	Investigate the safety of TAF over 14 days, and evaluate the antiviral potency of escalating doses of TAF compared with TDF in ART-naive HIV-infected subjects	Phase 1/2, randomized, double-blind, active-controlled, dose-escalation study	Within each cohort, subjects were randomized to 1 of the following treatments: Cohort 1: • TAF 50 mg (2 × 25 mg) + placebo-to-match TDF QD PO (A) • Placebo-to-match TAF + TDF 300 mg QD PO (B) Cohort 2: • TAF 150 mg (6 × 25 mg) + placebo-to-match TDF QD PO (C) • Placebo-to-match TAF + TDF 300 mg QD PO (D)	14 days	Randomized: 30 Completed: 30 Safety Analysis Set: A: 10 B + D: 10 C: 10	HIV-infected, ART-naive adult subjects	Study completed; Final CSR

7.1.3. FTC Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-301A (synopsis)	Compare the safety and efficacy of FTC and d4T within a triple drug combination containing ddI and EFV	Phase 3, randomized (1:1), double-blind, active-controlled equivalence study	• FTC 200 mg QD PO (A) • d4T 40 mg BID PO if ≥ 60 kg; 30 mg BID PO if < 60 kg (B) Both groups: ddI 400 mg QD PO if ≥ 60 kg; 250 mg QD PO if < 60 kg and EFV 600 mg QD PO	48 weeks: Last subject completed 48 weeks on 24 Oct 2002; all subjects subsequently rolled to an open-label FTC-containing regimen or an alternative regimen off study	Randomized and received ≥ 1 dose of study drug (ITT): 571 A: 286 B: 285	HIV-infected, ART-naive subjects	Study completed; Interim Week 48 CSR (Volume 1 and Volume 2)

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-302 (synopsis)	Compare the safety and efficacy of FTC and 3TC within a triple drug combination containing d4T and NVP+EFV	Phase 3, randomized (1:1), open-label, active-controlled switch study	• FTC 200 mg QD PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 194) or EFV 600 mg QD PO (n = 40) (A) • 3TC 150 mg BID PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg BID and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 191) or EFV 600 mg once daily PO (n = 43) (B)	48 weeks	Randomized: 512 ITT: 468 A: 234 B: 234	HIV-infected, ART-naive adult subjects	Study completed; Final CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-303 (synopsis)	Compare FTC to 3TC in HIV-infected subjects with HIV-1 RNA ≤ 400 copies/mL on a stable (≥ 12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI	Phase 3, randomized (2:1) open-label, multi-center equivalence study	• Subjects switch from 3TC to FTC PO while continuing on current background therapy (A) • Subjects continue on current 3TC-containing regimen (B)	48 weeks	Randomized: 459 ITT: 440 A: 294 B: 146	HIV-infected, 3TC-experienced, adult subjects with stable HIV-1 RNA	Study completed; Final CSR and Addendum

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	FTC-203 (synopsis)	Obtain long-term safety, PK, and antiviral activity of FTC in pediatric subjects	Phase 2, multicenter, open-label study in ART-naive and ART-experienced male or female pediatric subjects. ART-naive subjects had no or very limited prior ART exposure.	ART-naive (triple-drug ART regimen): FTC (6 mg/kg QD; up to 200 mg capsule or 240 mg oral solution QD) d4T (mg/kg BID dosage based on weight): 1 mg/kg (< 30 kg); 30 mg/kg (30–59 kg); 40 mg/kg (≥ 60 kg) LPV/r (mg/kg BID dosage based on weight): 12/3 mg/kg (7-< 15 kg); 10/2.5 mg/kg (15-40 kg); 400/100 mg/kg (> 40 kg) ART-experienced: FTC (same dosage as above) plus background ART medications (no 3TC) No control regimen	96 weeks	Enrolled: 117 ITT: 116 ART-naive: 71 ART-experienced: 45 Age groups: 3–24 mo: 16 25 mo–6 y: 68 7–12 y: 29 13–17 y: 3	Pediatric subjects (3 mo-17 y) with HIV infection, $CD4^+$ > 200 cells/mm^3; ART-naive: Plasma HIV-1 RNA 5,000-600,000 copies/mL ART-experienced: HIV-1 RNA ≤ 400 copies/mL, stable on 3TC regimen for ≥ 3 mo	Study completed; Final Week 48 CSR

3TC = lamivudine; ART = antiretroviral therapy; BID = twice daily; DGT = dolutegravir; DRV = darunavir; ITT = intent-to-treat; LPV = lopinavir; LPV/r = lopinavir boosted with ritonavir; NPV = nevirapine; PO = orally; QD = once daily

7.2. E/C/F/TAF FDC: Integrated Safety Analyses

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SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.5—LITERATURE REFERENCES

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

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

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SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES

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

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

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1. TABULAR LISTING OF CLINICAL STUDIES

1.1. F/TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-311-1088 (synopsis)	Evaluate the bioequivalence between F/TAF FDC and FTC + TAF coadministered as individual agents	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/25 mg FDC PO (A) • FTC 200 mg + TAF 25 mg PO (B)	2 days (Single doses on Days 1 and 15)	Enrolled: 56 Completed: 54 Safety Analysis Set: A: 56 B: 55	Healthy adult subjects	Study completed; m5.3.1.2 Final CSR
Comparative BA/BE	GS-US-311-1472 (synopsis)	Evaluate the bioequivalence of FTC and TAF administered as F/TAF FDC + EVG + COBI, or as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/10 mg FDC + EVG 150 mg + COBI 150 mg PO (A) • E/C/F/TAF (150/150/200/10 mg) FDC PO (B)	2 days (Single doses on Days 1 and 7)	Enrolled: 100 Completed: 99 Safety Analysis Set: A: 99 B: 100	Healthy adult subjects	Study completed; m5.3.1.2 Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-311-1473 (synopsis)	Evaluate the bioequivalence of FTC and TAF administered as F/TAF FDC, or as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/25 mg FDC PO (A) • E/C/F/TAF (150/150/200/10 mg) FDC PO (B)	2 days (Single doses on Days 1 and 7)	Enrolled: 116 Completed: 116 Safety Analysis Set: A: 116 B: 116	Healthy adult subjects	Study completed; m5.3.1.2 Final CSR
Extrinsic Factor PK	GS-US-311-0101 (synopsis)	Cohort 1: Evaluate the PK of TAF, TFV, and FTC following once-daily coadministration of F/TAF FDC and EFV relative to the administration of F/TAF FDC alone Cohorts 2 and 3: Evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF FDC and DRV+COBI relative to the administration of these agents alone Cohort 4: Evaluate the PK of TAF, TFV, and COBI following once-daily	Phase 1, nonrandomized, open-label, crossover, multicohort, multiple-dose study	Cohort 1: • F/TAF (200/40 mg) QD PO (Days 1-12, fasted) (A) • F/TAF (200/40 mg) + EFV 600 mg QD PO (Days 13-26, fasted) (B) Cohort 2: • F/TAF (200/25 mg) QD PO (Days 1-12, fed) (C) • F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 13-22, fed) (D) Cohort 3: • DRV 2 × 400 mg + COBI 150 mg QD PO (Days 1-10, fed) (E) • F/TAF (200/25 mg) +	Cohort 1: 26 days Cohorts 2-4: 22 days	Enrolled:50 Completed: 48 Safety Analysis Set: A: 12 B: 12 C: 12 D: 25[a] E: 14 F: n/a G: 12 H: 12 [a] Includes 11 subjects who received Treatment D and 14 subjects who received Treatment F	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
		coadministration of TAF+COBI relative to the administration of TAF alone		DRV 2 × 400 mg + COBI 150 mg QD PO (Days 11-22, fed) (F) <u>Cohort 4:</u> • TAF 8 mg QD PO (Days 1-12, fed) (G) • TAF 8 mg + COBI 150 mg QD PO (Days 13-22, fed) (H)				
Extrinsic Factor PK	GS-US-311-1386 (synopsis)	Determine the effect of food on the PK of TAF and FTC when administered as F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-period, crossover study	Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments: • F/TAF 200/25 mg FDC PO fasted (A) • F/TAF 200.25 mg FDC PO fed (B)	2 days (Single doses on Days 1 and 8)	Enrolled: 40 Completed: 38 Safety Analysis Set: A: 40 B: 38	Healthy adult subjects	Study completed; m5.3.3.4 Final CSR

1.2. TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Tolerability	GS-US-120-0109 (synopsis)	Determine the mass balance of TAF following administration of a single, oral dose of radiolabeled [^{14}C]TAF	Phase 1, open-label, mass-balance study	• TAF 25 mg (mixture of unlabeled TAF and [^{14}C]TAF) PO	Single dose	Enrolled: 8 Completed: 8 Safety Analysis Set: 8	Healthy adult male subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0108 (synopsis)	Evaluate the PK of TAF and its metabolite TFV following administration of TAF in subjects with and without severe renal impairment	Phase 1, open-label, parallel-design, single-dose, PK study	• TAF 25 mg PO	Single dose	Enrolled: 27 Completed: 27 Safety Analysis Set: Subjects with severe renal impairment: 14 Age and sex matched controls: 13	Adult subjects with severe renal impairment ($eGFR_{CG}$ of 15 to ≤ 29 mL/min) or healthy matched control subjects ($eGFR_{CG}$ of ≥ 90 mL/min)	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0114 (synopsis)	Evaluate the PK of TAF in subjects with normal and impaired hepatic function	Phase 1, open-label, 2-cohort, parallel-group, single-dose, multicenter study	• TAF 25 mg PO	Single dose	Enrolled: 40 Completed: 40 Safety Analysis Set: Cohort 1: Subjects with mild hepatic impairment: 10 Matched controls: 10 Cohort 2:	Cohort 1: Adult subjects with mild hepatic impairment (CPT Class A) and healthy matched control subjects Cohort 2: Adult subjects with moderate hepatic impairment	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
						Subjects with moderate hepatic impairment: 10 Matched controls: 10	(CPT Class B) and healthy matched control subjects	
Extrinsic Factor PK	GS-US-120-0117 (synopsis)	Evaluate the PK of RPV and TAF following single-dose administration of RPV and TAF alone and in combination in healthy subjects	Phase 1, open-label, single-center, single-dose, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments: <u>Cohort 1:</u> • TAF 25 mg QD PO (A) • TAF 25 mg + RPV 25 mg QD PO (B) <u>Cohort 2:</u> • TAF 25 mg + RPV 25 mg QD PO (B) • RPV 25 mg QD PO (C)	2 days (Days 1 and 12)	Randomized: 36 Completed: 36 Safety Analysis Set: Cohort 1: 18 Cohort 2: 18	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-0118 (synopsis)	Evaluate the effect of common boosted PIs ATV+RTV; DRV+RTV; LPV/r, or the INSTI DTG on the PK of TAF, and evaluate the PK of ATV, DRV, LPV, and DTG alone and in combination with FTC and TAF	Phase 1, open-label, DDI study	Cohort 1: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • ATV 300 mg + RTV 100 mg QD PO (Days 2-14) (B) • A + B (Day 15) Cohort 2: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • DRV 800 mg + RTV 100 mg QD PO (Days 2-14) (C) • A + C (Day 15) Cohort 3: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • LPV/r (4 × 200/50 mg) QD PO (Days 2-14) (D) • A + D (Day 15) Cohort 4: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (F) • DTG 50 mg QD PO (Days 2-14) (E) • F + E (Day 15)	15 days	Enrolled: 40 Completed: 39 Safety Analysis Set: Cohort 1: 10 Cohort 2: 10 Cohort 3: 10 Cohort 4: 10 (1 subject excluded from the FTC+TAF+ DTG safety analysis)	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-1538 (synopsis)	Evaluate the PK and drug interaction potential between TAF and MDZ (Oral and IV)	Phase 1, open-label, multiple-dose, single-center study	Subjects received the following treatments in a fixed sequence under fed conditions in the morning: • Day 1: MDZ_{oral} 2.5 mg syrup (A) • Day 3: MDZ_{IV} 1 mg solution (B) • Days 4-15 and 17: TAF 25 mg PO (C) • Day 16: TAF 25 mg PO + MDZ_{oral} 2.5 mg syrup coadministered (D) • Day 18: TAF 25 mg PO + MDZ_{IV} 1 mg solution administered within 5 min of each other (E)	18 days (Day 1, washout on Day 2, and doses on Days 3-18)	Enrolled: 18 Completed: 18 Safety Analysis Set: A: 18 B: 18 C: 18 D: 18 E: 18 F: 18	Healthy adult subjects	Study completed; m5.3.3.4 Final CSR
Extrinsic Factor PK	GS-US-120-1554 (synopsis)	Evaluate the PK and drug interaction potential between TAF and RPV	Phase 1, open-label, randomized, fixed-sequence, 2-cohort, 2-period, multiple-dose study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments under fed conditions: <u>Cohort 1:</u> • TAF 25 mg QD PO (Days 1-14) (A) • TAF 25 mg + RPV 25 mg QD PO (Days 15-	28 days	Randomized: 34 Completed: 32 Safety Analysis Set: Cohort 1: 17 Cohort 2: 17	Healthy adult subjects	Study completed; m5.3.3.4 Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				28) (C) <u>Cohort 2:</u> • RPV 25 mg QD PO (Days 1-14) (B) • TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C)				
Healthy Subjects PK and PK/PD	GS-US-120-0107 (synopsis)	Evaluate the effects of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, randomized, partially-blinded, placebo- and positive-controlled, 4-period, single-dose crossover study	Subjects were randomized to 1 of 8 treatment sequences and received the following treatments: • TAF 25 mg + 4 × placebo-to-match TAF QD PO (A) • TAF 125 mg (5 × 25 mg) QD PO (B) • Placebo-to-match TAF (C) • Moxifloxacin 400 mg PO, administered open-label (D)	37 days (4 single-dose treatment days separated by 11 days of washout between doses)	Randomized: 59 Completed: 58 Safety Analysis Set: A: 58 B: 58 C: 59 D: 58	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Patient PD and PK/PD	GS-US-120-0104 (synopsis)	Evaluate the short-term antiviral potency of TAF 8 mg, 25 mg, and 40 mg compared to placebo-to-match TAF or TDF 300 mg	Phase 1, randomized, partially-blinded, active- and placebo-controlled study	• TAF 8 mg QD PO (A) • TAF 25 mg QD PO (B) • TAF 40 mg QD PO (C) • TDF 300 mg QD PO (D) • Placebo-to-match TAF QD PO (E)	10 days	Randomized: 40 Completed: 37 Safety Analysis Set: A: 9 B: 8 C: 8 D: 6 E: 7	HIV-infected adult subjects, who had not received ART within 90 days of screening	Study completed; Final CSR
Patient PD and PK/PD	GS-US-120-1101 (synopsis)	Investigate the safety of TAF over 14 days, and evaluate the antiviral potency of escalating doses of TAF compared with TDF in ARTnaive HIV infected subjects	Phase 1/2, randomized, double-blind, active controlled, dose-escalation study	Within each cohort, subjects were randomized to 1 of the following treatments: Cohort 1: • TAF 50 mg (2 × 25 mg) + placebo-tomatch TDF QD PO (A) • Placebo-to-match TAF + TDF 300 mg QD PO (B) Cohort 2: • TAF 150 mg (6 × 25 mg) + placebo-tomatch TDF QD PO (C) • Placebo-to-match TAF + TDF 300 mg QD PO • (D)	14 days	Randomized: 30 Completed: 30 Safety Analysis Set: A: 10 B + D: 10 C: 10	HIV infected, ART-naive adult subjects	Study completed; m5.3.4.2, Final CSR

1.3. E/C/F/TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-292-0103 (synopsis)	Evaluate the PK and relative bioavailability of EVG, COBI, FTC, TAF, and TFV administered as E/C/F/TAF FDC relative to the administration of the individual components	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort, 2-period, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments: Cohort 1: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • EVG 150 mg + COBI 150 mg QD PO (B) Cohort 2: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • FTC 200 mg + TAF 25 mg QD PO (C)	24 days (12 days for each treatment period within a sequence)	Randomized: 34 Completed: 33 Safety Analysis Set: Cohort 1: 14 Cohort 2: 20	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-292-0101 (synopsis)	Evaluate the relative bioavailability of EVG, COBI, FTC, and TFV when administered as 1 of 2 formulations of E/C/F/TAF FDC vs STB STR and TAF alone	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort study	Within each cohort, subjects were randomized to 1 of 4 treatment sequences and received the following treatments: Cohort 1: • Formulation 1 E/C/F/TAF (150/150/200/25 mg) QD PO (A)	54 days (4 12-day treatment sequences with a 2-day washout period between each sequence)	Randomized: 40 Completed: 36 Safety Analysis Set: Cohort 1: 20 Cohort 2: 20	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				• Formulation 1 E/C/F/TAF (150/150/200/40 mg) QD PO (B) • STB STR (150/150/200/ 300 mg) QD PO (C) • TAF 25 mg QD PO (D) <u>Cohort 2:</u> • Formulation 2 E/C/F/TAF (150/150/200/25 mg) QD PO (E) • Formulation 2 E/C/F/TAF (150/150/200/40 mg) QD PO (F) • STB STR (150/150/200/ 300 mg) QD PO (C) • TAF 25 mg QD PO (D)				
Healthy Subject PK and Tolerability	GS-US-292-0108 (synopsis)	Investigate the PK of EVG, COBI, FTC, TAF, and TFV when administered as E/C/F/TAF FDC in healthy Japanese and Caucasian subjects	Phase 1, open-label, sequential single- and multiple-dose study	• E/C/F/TAF (150/150/200/10 mg) QD PO	13 days (1 single dose on Day 1, followed by a washout and then once-daily doses of study treatment on Days 8 to 19	Enrolled: 20 Completed: 17 Safety Analysis Set: Single-dose phase: 20 (10 Japanese; 10 Caucasian)	Healthy adult Japanese (first generation Japanese descent) or Caucasian (not of Japanese or Asian descent)	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
						Multiple-dose phase: 18 (10 Japanese; 8 Caucasian)	subjects	
Extrinsic Factor PK	GS-US-292-0110 (synopsis)	Evaluate the effect of food (high-calorie/high-fat meal or light/low-fat meal) on the PK of TAF when administered as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-center, 3-period, 6-sequence, crossover, food-effect study	Subjects were randomized to 1 of 6 treatment sequences and received E/C/F/TAF (150/150/200/10 mg) QD PO administered under the following meal conditions: • Fasted (A) • Light/low-fat meal (B) • High-calorie/high-fat meal (C)	15 days (study drug was administered on Days 1, 8, and 15)	Randomized: 43 Completed: 42 Safety Analysis Set: 43	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-292-1316 (synopsis)	Evaluate the PK of EVG, TAF, and SER following the coadministration of E/C/F/TAF FDC and SER relative to the administration of E/C/F/TAF or SER alone	Phase 1, open-label, 3-period, fixed-sequence, single-center study	• SER 50 mg QD PO (Day 1) (A) • E/C/F/TAF (150/150/200/10 mg) QD PO (Days 2-13) (B) • SER 50 mg + E/C/F/TAF (150/150/200/10 mg) QD PO (Day 14) (C)	14 days	Enrolled: 20 Completed: 19 Safety Analysis Set: 20	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-342-1167 (synopsis)	Evaluate the PK of SOF and metabolites GS-566500 and GS-331007, and GS-5816 upon administration of	Phase 1, open-label, multiple-dose, 4-cohort study	Cohorts 1-3: Subjects were randomized to treatments that did not include E/C/F/TAF.	Cohort 4: 24 days	Randomized to Cohort 4: 24 Completed: 23 Safety Analysis Set: 24	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
		SOF/GS-5816 FDC with ATR STR, CPA STR, DTG, or E/C/F/TAF, and evaluate the PK of COBI, DTG, EFV, EVG, FTC, RPV, TAF and/or TFV upon administration of ATR, CPA, DTG, or E/C/F/TAF with SOF/GS-5816 FDC		Cohort 4: Subjects were randomized to 1 of 6 treatment sequences and received the following treatments with a moderate fat meal: • SOF/GS-5816 (400/100 mg) QD PO (8 days) (J) • E/C/F/TAF (150/150/200/10 mg) QD PO (8 days) (K) • SOF/GS-5816 (400/100 mg) + E/C/F/TAF (150/150/200/10 mg) QD PO (8 days) (L)				
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0102 (synopsis)	Evaluate the efficacy of a regimen containing E/C/F/TAF FDC versus STB STR	Phase 2, randomized, double-blind and open-label, multicenter, active-controlled study	Randomized Phase: • E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/ 300 mg) + placebo-to-match E/C/F/TAF QD PO (B) Open-Label Extension Phase: • E/C/F/TAF (150/150/200/10 mg)	Randomized Phase: 48 weeks until unblinding Open-Label Extension Phase: Until E/C/F/TAF is commercially available or development is terminated	Randomized: 171 Completed: 158 Safety Analysis Set: A: 112 B: 58 Entered Open-Label Extension: A: 105 B: 53 299-0102: 108 Continuing study drug at Week 96:	Randomized Phase: HIV-infected, ART-naive adult subjects Open-Label Extension Phase: Additional HIV-infected adult subjects had received a DRV+COBI containing regimen in Study GS-US-	Study ongoing; Week 96 Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				QD PO (C)		A: 104 B: 53 299-0102: 107	299-0102 and were ART-naive at the time of entry into that study.	
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0104 (synopsis)	Evaluate the efficacy of E/C/F/TAF FDC versus STB STR	Phase 3, randomized, double-blind, active-controlled, multicenter study	• E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/ 300 mg) + placebo-to-match E/C/F/TAF QD PO (B)	96 weeks Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 872 Safety Analysis Set: A: 435 B: 432 Continuing study drug at Week 48: A: 413 B: 400	HIV-infected, ART-naive adult subjects	Study ongoing; Week 48 Interim CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0109 (synopsis)	Evaluate the noninferiority of switching to a TAF-containing FDC relative to maintaining TDF-containing regimens in virologically suppressed, HIV-infected subjects	Phase 3, randomized, open-label, active-controlled, multicenter study	• Switch to E/C/F/TAF (150/150/200/10 mg) QD PO from a predefined FTC/TDF regimen (A) • Stay on pre-existing FTC/TDF+3rd Agent regimen (B): STB STR (150/150/200/ 300 mg) QD PO; ATR STR (600/200/300 mg) QD PO; ATV 300 mg +	96 weeks Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 1443 Safety Analysis Set: A: 959 B: 477 Continuing study drug at Week 48: A: 939 B: 447	HIV-infected adult subjects from a predefined set of Gilead clinical studies receiving ARV regimens for at least 6 consecutive months, and who had maintained plasma HIV-1 RNA levels at undetectable	Study ongoing; Week 48 Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				COBI 150 mg + FTC/TDF (200/300 mg) QD PO; or ATV 300 mg + RTV 100 mg + FTC/TDF (200/300 mg) QD PO			levels for ≥ 6 consecutive months prior to screening	
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-292-0111 (synopsis)	Evaluate the efficacy of E/C/F/TAF FDC versus STB STR	Phase 3, randomized, double-blind, active-controlled, multicenter study	• E/C/F/TAF (150/150/200/10 mg) + placebo-to-match STB QD PO (A) • STB STR (150/150/200/ 300 mg) + placebo-to-match E/C/F/TAF QD PO (B)	96 weeks Open-Label Extension Phase: Subjects have option to receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 872 Safety Analysis Set: A: 431 B: 435 Continuing study drug at Week 48: A: 408 B: 396	HIV-infected, ART-naive adult subjects	Study ongoing; Week 48 Interim CSR
Uncontrolled Clinical Studies	GS-US-292-0106 (synopsis)	Part A: Evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC Part B: Evaluate the safety and tolerability of the E/C/F/TAF FDC	Phase 2/3, open-label, multicenter, 2-part, single-group study	• E/C/F/TAF (150/150/200/10 mg) QD PO	48 weeks Extension Phase: Subjects have option to continue study drug until subject turns 18 and E/C/F/TAF is commercially available for adults in	Enrolled: 48 Part A: 24 Part B: 24 Safety Analysis Set: 48 Continuing study drug at Week 24: Main study: 47 Extension: 1	HIV-infected, ART-naive adolescents (12 to < 18 years of age)	Study ongoing; Week 24 Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
					country of enrollment, E/C/F/TAF becomes commercially available for adolescents in country of enrollment, or E/C/F/TAF development is terminated in country of enrollment			
Uncontrolled Clinical Studies	GS-US-292-0112 (synopsis)	Evaluate the effect of the E/C/F/TAF FDC on renal parameters	Phase 3, open-label, multicenter, multi-cohort study	• E/C/F/TAF (150/150/200/10 mg) QD PO	96 weeks Extension Phase: Subjects have option to continue study drug until E/C/F/TAF is commercially available or development is terminated	Enrolled: 252 Safety Analysis Set: Cohort 1: 242 Cohort 2: 6 Continuing study drug at Week 24 Cohort 1: 226 Cohort 2: 6	HIV-infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min Cohort 1: ART-experienced Cohort 2: ART-naive	Study ongoing; Week 24 Interim CSR

1.4. D/C/F/TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-299-0101 (synopsis)	Evaluate the bioavailability of 3 formulations of D/C/F/GS-7340 STR relative to the administration of individual components DRV/co, FTC, and GS-7340	Phase 1, randomized, open-label, multiple-dose, 3-part, multiple-cohort, single-center study	**Part 1:** Subjects were randomized (1:1:1) to 1 of 3 treatments: • DRV/COBI/FTC/ GS-7340 STR Formulation 1 monolayer (800/150/200/25) (A) • DRV/COBI/FTC/ GS-7340 STR Formulation 2 bilayer (800/150/200/25) (B) • DRV/COBI/FTC/ GS-7340 STR Formulation 3 monolayer (800/150/200/10) (C) **Part 2:** Subjects were randomized (1:1) to treatment sequences within Cohort 1 or Cohort 2: Cohort 1 treatments: • DRV 800 mg + COBI 150 mg +	**Part 1:** 21 days **Part 2:** 20 days (10 days/ treatment) **Part 3:** 24 days (12 days/ treatment)	**Part 1:** Randomized: 30 Safety Analysis Set: A: 10 B: 10 C: 10 **Part 2, Cohort 1:** Randomized: 20 Safety Analysis Set: DE: 10 ED: 10 **Part 2, Cohort 2:** Randomized: 16 Safety Analysis Set: DF: 8 FD: 8 **Part 3, Cohort 1:** Randomized: 20 Safety Analysis Set: CE: 10 EC: 9 **Part 3, Cohort 2:** Randomized: 16 Safety Analysis	Healthy adult subjects	Study completed; m5.3.5.2 Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				TVD (FTC 200 mg/TDF 300 mg) (D) • DRV 800 mg + COBI 150 mg (E) Cohort 2 treatments: • DRV 800 mg + COBI 150 mg + TVD (FTC 200 mg/TDF 300 mg) (D) • TVD (FTC 200 mg/TDF 300 mg) (F) **Part 3:** Subjects were randomized (1:1) to treatment sequences within Cohort 1 or Cohort 2: Cohort 1 treatments: • DRV/COBI/FTC/ GS-7340 STR Formulation 3 monolayer (800/150/200/10) (C) • DRV 800 mg + COBI 150 mg (E) Cohort 2 treatments: • DRV/COBI/FTC/ GS-7340 STR Formulation 3		Set: CG: 8 GC: 8		

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				monolayer (800/150/200/10) (C) • FTC 200 mg + GS-7340 25 mg (G)				
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-299-0102 (synopsis)	Evaluate the efficacy of D/C/F/TAF FDC versus DRV+COBI+TVD	Phase 2, randomized, double-blind, active-controlled, multicenter, study	Subjects were randomized in a 2:1 ratio to 1 of 2 treatment groups as follows: • D/C/F/TAF (800/150/200/10 mg) + placebo-to-match DRV+COBI+FTC/TDF QD PO (A) • DRV (800 mg) + COBI (150 mg) + FTC/TDF (200/300 mg) + placebo-to-match D/C/F/TAF QD PO (B)	48 weeks Extension Phase: Subjects continued to receive blinded drug until unblinding and then were given option to participate in Study GS-US-292-0102 and receive E/C/F/TAF until it is commercially available or development is terminated	Randomized: 153 Safety Analysis Set: A: 103 B: 50	HIV-infected, ART-naive adult subjects	Study completed; m5.3.5.1 Final CSR

1.5. FTC

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
BA	FTC-110 (synopsis)	Evaluate relative and absolute BA of FTC	Phase 1, open-label, randomized, 3-way crossover, single 200-mg doses administered as IV solution, oral solution, or oral capsule	• FTC 1 × 200-mg capsule, PO, fasted (A) • 20 mL of FTC 10 mg/mL solution, PO, fasted (B) • 20 mL of FTC 10 mg/mL solution, IV infused over 1 hour, fasted (C)	3 single doses	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Comparative BA/BE	FTC-109 (synopsis)	Pilot study to evaluate the BE/BA of FTC between the 100-and 200-mg capsules	Phase 1, open-label, randomized, 2-way crossover, single 200-mg dose study	• FTC 2 × 100-mg capsules, PO, single dose (Formulation C) (A) • FTC 1 × 200-mg capsule, PO, single dose (Formulation B) (B)	2 single doses	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Comparative BA/BE	FTC-111 (synopsis)	Determine the BA/BE of 100- and 200-mg capsules, and the effect of food on the BA of FTC administered as a 200-mg capsule	Phase 1, open-label, randomized, 3-way crossover, single 200-mg dose, food-effect study	• FTC 2 × 100 mg capsules, PO, single dose (fasted state) (Formulation C) (A) • FTC 1 × 200 mg capsule, PO single dose (fasted state) (Formulation B) (B) • FTC 1 × 200 mg capsule, PO, single dose (fed state) (Formulation B) (C)	3 single doses	Enrolled: 24 Completed: 24 Safety Analysis Set: 24	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Tolerability	FTC-106 (synopsis)	Evaluate ADME of [^{14}C]FTC, mass balance by urinary and fecal recovery, plasma and PBMCs (FTC-triphosphate)	Phase 1, open-label, single-dose and 8-day repeated doses of FTC (with a single [^{14}C]FTC dose) in healthy adult volunteers	• Day 1: 200 mg single dose PO (N = 6) • Days 3−11: 200 mg QD PO for 8 days, single 250 µCi [^{14}C]FTC dose PO on the last day (N = 5)	11 days	Enrolled: 6 Completed: 5 Safety Analysis Set: 6	Healthy male subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	Burroughs Wellcome 143-001 (synopsis)	Assess the safety, PK, and effect of food on the BA of FTC	Phase 1, randomized, single-blind, single-dose, placebo-controlled, escalating doses (100 to 1200 mg)	• Single escalating oral doses of FTC administered as capsules: 100, 200, 400 (± food), 800, and 1200 mg, PO • Placebo, PO	6 total doses, each given 1 week apart	Enrolled: 18 Active: 12 Placebo: 6 Completed: 17	HIV-infected adult subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	FTC-101 (synopsis)	Evaluate the safety, tolerance, PK, and antiviral activity of repeat doses of FTC	Phase 1, open-label, dose-ranging study with 14 days of repeated doses of monotherapy	Multiple escalating oral doses of FTC administered as capsules for: 25 mg BID (N=9) 100 mg BID (N=8) 200 mg BID (N=8) 100 mg QD (N=8) 200 mg QD (N=8)	14 days	Enrolled: 41 Completed: 41	HIV-infected, therapy-naive adult subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	FTC-102 (synopsis)	Safety, antiviral activity, dose-defining, comparison with 3TC	Phase 1/2, randomized, open-label, 3TC-controlled, 3 doses of FTC, 10-day repeated doses of	• FTC 25 mg QD PO (N = 20) (A) • FTC 100 mg QD PO (N = 21) (B) • FTC 200 mg QD PO (N = 19) (C)	10 days	As treated: 81 Completed: 81 Safety Analysis Set: 81	HIV-infected adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
			monotherapy in adult HIV infected, ART-naive patients	• 3TC 150 mg BID PO (N = 21) (D)				
Intrinsic Factor PK	FTC-107 (synopsis)	Assess the PK profiles in subjects with various degrees of renal insufficiency (for potential dosage adjustment) and effect of hemodialysis	Phase 1, open-label, single-dose study of FTC in adult volunteers with varying degrees of renal insufficiency without and with hemodialysis	One single dose of FTC 200 mg administered PO in capsule formulation to: • Group 1 (normal renal function, CL_{cr} > 80 mL/min, N=6) • Group 2 (mild renal impairment, CL_{cr} = 50−80 mL/min, N=6) • Group 3 (moderate renal impairment, CL_{cr} = 30−49 mL/min, N=6) • Group 4 (severe renal impairment, CL_{cr} < 30 mL/min, N=5) • Group 5 (end-stage renal disease, requiring hemodialysis, N=6) For Group 5 subjects, a second FTC 200 mg dose PO was administered ~1.5 hour before the start of a 3-hour hemodialysis	1−2 single doses	Enrolled: 29 Completed: 29	Adult subjects with varying degrees of renal insufficiency with and without hemodialysis	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Intrinsic Factor PK	FTCB-101 (synopsis)	Assess the safety, tolerance, antiviral activity, and PK of FTC	Phase 1, open-label, dose-escalation, multiple repeat doses, 8 week study	• FTC 25 mg QD PO • FTC 50 mg QD PO • FTC 100 mg QD PO • FTC 200 mg QD PO • FTC 300 mg QD PO	56 days with 28 day follow up	Enrolled: 49 Completed: 45 Safety Analysis Set: 49	HBV-infected adult subjects	Study completed; Final CSR
Extrinsic Factor PK	FTC-103 (synopsis)	Evaluate PK interactions of FTC, ZDV, and d4T	Phase 1, randomized, open-label, single-dose, 3-period crossover study	Subjects were assigned to 1 of 2 treatment cohorts, then randomized into 1 of 3 single oral dosing sequences per cohort in a 3-period crossover design using treatments as follows: Cohort 1: • FTC 200 mg • ZDV 300 mg • Combination of FTC 200 mg and ZDV 300 mg Cohort 2: • FTC 200 mg • d4T 40 mg • Combination of FTC 200 mg and d4T 40 mg	3 single doses (Days 1, 3, and 5)	Enrolled: 13 Completed: 12 Safety Analysis Set: Cohort 1: 6 Cohort 2: 7	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	FTC-108 (synopsis)	Assess potential PK interactions with concomitant antiviral drug (ie, famciclovir) with extensive renal excretion	Phase 1, randomized, open-label, single-dose, 3-way crossover study	3 single crossover doses (all PO) of: • FTC 200 mg alone • FCV 500 mg alone • FTC 200 mg + FCV 500 mg 1-week washout interval between doses	Single dose	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	FTC-114 (synopsis)	Evaluate the steady-state PK interaction of FTC and TDF when administered alone and in combination	Single-center, open-label, randomized, 3-way crossover study	Subjects received each of the following 3 treatments: • FTC 200 mg QD (A) • TDF 300 mg QD (B) • FTC 200 mg + TDF 300 mg QD (C)	21 days (7 days/treatment)	Enrolled: 19 Completed: 17 Safety Analysis Set: 19	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-174-0105 (synopsis)	Evaluate the PK interactions between FTC/TDF FDC and TCL when administered alone and together	Single-center, open-label, randomized, 3-way crossover study	Subjects received each of the following treatments: • FTC/TDF (200/300 mg) QD PO • TCL 0.1 mg/kg/day in 2 divided doses BID PO	21 days (7 days FTC/TDF FDC, 7 days TCL, 7 days FTC/TDF FDC + TCL)	Enrolled: 31 Completed: 21 Safety Analysis Set: 31	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-301A (synopsis)	Compare the safety and efficacy of FTC and d4T within a triple drug combination containing ddI and EFV	Phase 3, randomized (1:1), double-blind, active-controlled equivalence study	• FTC 200 mg QD PO (A) • d4T 40 mg BID PO if ≥ 60 kg; 30 mg BID PO if < 60 kg (B) Both groups: ddI 400 mg QD PO if ≥ 60 kg; 250 mg QD PO if < 60 kg and EFV 600 mg QD PO	48 weeks: Last subject completed 48 weeks on 24 Oct 2002; all subjects subsequently rolled to an open-label FTC-containing regimen or an alternative regimen off study	Randomized and received ≥ 1 dose of study drug (ITT): 571 A: 286 B: 285	HIV-infected, ART-naive subjects	Study completed; Interim Week 48 CSR (Volume 1 and Volume 2)
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-302 (synopsis)	Compare the safety and efficacy of FTC and 3TC within a triple drug combination containing d4T and NVP+EFV	Phase 3, randomized (1:1), open-label, active-controlled switch study	• FTC 200 mg QD PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 194) or EFV 600 mg QD PO (n = 40) (A) • 3TC 150 mg BID PO plus d4T 30 mg BID PO if < 60 kg or 40 mg BID PO if ≥ 60 kg BID and NVP 200 mg QD PO for 14 days then 200 mg BID PO (n = 191) or EFV 600 mg once daily PO (n = 43) (B)	48 weeks	Randomized: 512 ITT: 468 A: 234 B: 234	HIV-infected, ART-naive adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-303 (synopsis)	Compare FTC to 3TC in HIV-infected subjects with copies/mL (HIV-1 RNA ≤ 400) on a stable (≥ 12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI	Phase 3, randomized (2:1) open-label, multi-center equivalence study	• Subjects switch from 3TC to FTC PO while continuing on current background therapy (A) • Subjects continue on current 3TC-containing regimen (B)	48 weeks	Randomized: 459 ITT: 440 A: 294 B: 146	HIV-infected, 3TC-experienced, adult subjects with stable HIV-1 RNA	Study completed; Final CSR and Addendum
Uncontrolled Clinical Studies	FTC 203 (synopsis)	Obtain long-term safety, PK, and antiviral activity of FTC in pediatric subjects	Phase 2, multicenter, open-label study in ART-naive and ART-experienced male or female pediatric patients. ART-naive patients had no or very limited prior ART exposure.	ART-naive (triple-drug ART regimen): • FTC (6 mg/kg QD; up to 200 mg capsule or 240 mg oral solution QD) • d4T (mg/kg BID dosage based on weight): 1 mg/kg (< 30 kg); 30 mg/kg (30-59 kg); 40 mg/kg (≥ 60 kg) • LPV/r (mg/kg BID dosage based on weight): 12/3 mg/kg (7- < 15 kg); 10/2.5 mg/kg (15-40 kg); 400/100 mg/kg (> 40 kg)	96 weeks	Enrolled: 117 ITT: 116 ART-naive: 71 ART-experienced: 45 Age groups: 3–24 mo: 16 25 mo–6 y: 68 7–12 y: 29 13–17 y: 3	Pediatric subjects (3 mo-17 y) with HIV infection, $CD4^+$ > 200 cells/mm^3 ART-naive: Plasma copies/mL (HIV-1 RNA 5,000-600,000) ART-experienced: Copies/mL (HIV-1 RNA ≤ 400), stable on 3TC regimen for ≥ 3 mo	Study completed; Final Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
				ART-experienced: • FTC (same dosage as above) plus background ART medications (no 3TC) No control regimen				

3TC = lamivudine; ADME = absorption, distribution, metabolism, and excretion; ART = antiretroviral therapy; ARV = antiretroviral; ATR = efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®); ATV = atazanavir; BID = twice daily; BA = bioavailability; BE = bioequivalence; ^{14}C = radiolabeled carbon 14; CL_{cr} = creatinine clearance; COBI = cobicistat (Tybost®); CPA = emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®); CPT = Child-Pugh-Turcotte; CSR = clinical study report; d4T = stavudine; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated); ddI = didanosine; DDI = drug-drug interaction; DRV = darunavir; DRV/co = darunavir booster with cobicistat; DTG = dolutegravir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated); EFV = efavirenz; $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; EVG = elvitegravir (Vitekta®); FCV = famciclovir; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); FTC = emtricitabine (Emtriva®); F/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); HBV = hepatitis B virus; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; INSTI = integrase strand-transfer inhibitor; ITT = intent-to-treat; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir boosted with ritonavir; MDZ = midazolam; NNRTI = nonnucleoside reverse transcriptase inhibitor; NVP = nevirapine; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamics(s); PI = protease inhibitor; PK = pharmacokinetic(s); PO = orally; QD = once daily; QT = electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur; QTcF = QT interval corrected for heart rate using the Fridericia formula; RNA = ribonucleic acid; RPV = rilpivirine; RTV = ritonavir; SER = sertraline; SOF = sofosbuvir; STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®); STR = single-tablet regimen; TAF = tenofovir alafenamide; TCL = tacrolimus; TDF = tenofovir disoproxil fumarate (Viread®); TFV = tenofovir; TVD = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); ZDV = zidovudine