SECTION 2.7.1—SUMMARY OF BIOPHARMACEUTICAL STUDIES AND ASSOCIATED ANALYTICAL METHODS

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (E/C/F/TAF FDC)

Gilead Sciences

[redacted] **20**[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.1—SUMMARY OF BIOPHARMACEUTICAL STUDIES AND ASSOCIATED ANALYTICAL METHODS 1

TABLE OF CONTENTS 2

LIST OF IN-TEXT TABLES 3

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 5

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS 7

1. SUMMARY OF BIOPHARMACEUTICAL STUDIES AND ASSOCIATED ANALYTICAL METHODS 8

   1.1. Background and Overview 8
      1.1.1. Formulation Development 9
      1.1.2. Dissolution Profile 11
      1.1.3. Bioanalytical Methods 12
      1.1.4. Cross Validations 25
      1.1.5. Long-Term Stability 25

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES 28

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES 29

   3.1. Bioavailability 29
      3.1.1. Bioavailability of TAF 29
      3.1.2. Bioavailability of EVG 29
      3.1.3. Bioavailability of COBI 29
      3.1.4. Bioavailability of FTC 30
      3.1.5. Bioavailability of E/C/F/TAF Tablets 30
   3.2. Effect of Food 30
   3.3. Conclusions 31

4. APPENDICES 32

   4.1. Quantitative Composition of the Proposed Commercial Formulation of E/C/F/TAF FDC Tablets 33
   4.2. Summary of In Vitro Dissolution Profiles for the Formulation of E/C/F/TAF FDC Tablets Lot No. CP[redacted]01B 34
   4.3. Tabular Summary of Biopharmaceutic Studies 35
   4.4. Summary of Analytical Methods for Individual Studies 36
   4.5. Summary of Long-Term Storage Stability Data for Individual Studies 55
   4.6. Determination of Coadministered Drugs in Human Plasma Supporting E/C/F/TAF Studies 79
      4.6.1. Determination of GS-5816 in Human Plasma 79
      4.6.2. Determination of LDV in Human Plasma 79
      4.6.3. Determination of SOF, GS-566500, and GS-331007 in Human Plasma 80
      4.6.4. Determination of ATV in Human Plasma 81
      4.6.5. Determination of ATV and RTV in Human Plasma 81
      4.6.6. Determination of BUP and norBUP in Human Plasma 82
      4.6.7. Determination of Carbamazepine and Carbamazepine-10,11-Epoxide in Human Plasma 82
      4.6.8. Determination of Desipramine in Human Plasma 83
      4.6.9. Determination of Digoxin in Human Plasma 83
      4.6.10. Determination of EFV in Human Plasma 83
      4.6.11. Determination of Ethinyl Estradiol in Human Plasma 84
      4.6.12. Determination of Iohexol in Human Plasma 84
      4.6.13. Determination of Ketoconazole in Human Plasma 85
      4.6.14. Determination of MDZ in Human Plasma 85

4.6.15. Determination of Methadone in Human Plasma 86
4.6.16. Determination of NLX in Human Plasma 87
4.6.17. Determination of Omeprazole in Human Plasma 87
4.6.18. Determination of Rifabutin in Human Plasma 88
4.6.19. Determination of RTV in Human Plasma 88
4.6.20. Determination of Rosuvastatin in Human Plasma 90
4.6.21. Determination of Sertraline in Human Plasma 90
4.6.22. Determination of 17-Desacetyl Norgestimate in Human Plasma 91
4.6.23. Determination of TVR in Human Plasma 91

5. REFERENCES 93

LIST OF IN-TEXT TABLES

Table 1. Formulation Summary for Key Studies with TAF and E/C/F/TAF 11
Table 2. Biopharmaceutics Classification of EVG, COBI, FTC, and TAF 12
Table 3. Bioanalytical Method Validation for Determination of TAF in Human Plasma at [redacted] 12
Table 4. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted] 13
Table 5. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted] 13
Table 6. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted] 14
Table 7. Bioanalytical Method Validation for Determination of TFV in Human Urine at [redacted] 14
Table 8. Bioanalytical Method Validation for Determination of TAF and TFV in Human Urine at [redacted] 15
Table 9. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma at Gilead 15
Table 10. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma at [redacted] 16
Table 11. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma at [redacted] 16
Table 12. Bioanalytical Method Validation for Determination of EVG in Human Plasma at Gilead 17
Table 13. Bioanalytical Method Validation for Determination of EVG, GS-9200, GS-9202, and RTV in Human Plasma at Gilead 17
Table 14. Bioanalytical Method Validation for Determination of EVG, GS-9200, GS-9202, and RTV in Human Plasma at [redacted] 18
Table 15. Bioanalytical Method Validation for Determination of EVG, GS-9200, GS-9202, and RTV in Human Plasma at [redacted] 18
Table 16. Bioanalytical Method Validation for Determination of EVG, GS-9200, and GS-9202 in Human Plasma at [redacted] 19
Table 17. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma at [redacted] 19
Table 18. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma at [redacted] 20
Table 19. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma at [redacted] 20
Table 20. Bioanalytical Method Validation for Determination of COBI in Human Plasma at [redacted] 21
Table 21. Bioanalytical Method Validation for Determination of COBI and GS-8374 in Human Plasma at Gilead 21

Table 22. Bioanalytical Method Validation for Determination of COBI in Human Urine at [redacted] 22
Table 23. Bioanalytical Method Validation for Determination of COBI and GS-9612 in Human Plasma at Gilead 22
Table 24. Bioanalytical Method Validation for Determination of FTC in Human Plasma at Gilead 23
Table 25. Bioanalytical Method Validation for Determination of FTC and Emivirine in Human Plasma at Gilead 23
Table 26. Bioanalytical Method Validation for Determination of FTC in Human Urine at Gilead 24
Table 27. Bioanalytical Method Validation for Determination of FTC in Human Urine at Gilead 24
Table 28. Long-Term Stability of TAF, TFV, EVG, COBI, and FTC 25
Table 29. Combination Stability of TAF, TFV, EVG, COBI, and FTC 26

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

1'-OH MDZ	midazolam metabolite (1′-hydroxymidazolam)
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
BCS	Biopharmaceutics Classification System
BUP	buprenorphine
C	cobicistat (Tybost®)
CD	cluster determinant
CI	confidence interval
COBI	cobicistat (Tybost®)
CSR	clinical study report
CV	coefficient of variation
DCF	drug correction factor
DRV	darunavir
E	elvitegravir (Vitekta®)
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
EFV	efavirenz
EVG	elvitegravir (Vitekta®)
F	emtricitabine (Emtriva®)
FDC	fixed-dose combination
F/TAF	emtricitabine/tenofovir alafenamide (coformulated)
FTC	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
IQ_{95}	95% inhibitory quotient
INSTI	integrase strand-transfer inhibitor
LC-MS/MS	liquid chromatography/[redacted] mass spectrometry
LDV	ledipasvir
LLOQ	lower limit of quantitation
LTSS	long-term storage stability
m	Module
MDZ	midazolam
MS/MS	[redacted] mass spectrometry
NF	National Formulary
NLX	naloxone
NNRTI	nonnucleoside reverse transcriptase inhibitor

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
norBUP	norbuprenorphine
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopeia
PI	protease inhibitor
PK	pharmacokinetic
[redacted]	[redacted]
RE	relative error
RPV	rilpivirine
RTV	ritonavir
SOF	sofosbuvir (Sovaldi®)
SPE	solid phase extraction
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
TAF	tenofovir alafenamide
TAF fumarate	tenofovir alafenamide fumarate, GS-7340-03
TAF monofumarate	tenofovir alafenamide monofumarate, GS-7340-02
TDF	tenofovir disoproxil fumarate (Viread®)
TFV-DP	tenofovir diphosphate
TFV	tenofovir
TVR	telaprevir
UPLC	ultra-high performance liquid chromatography
USA	United States of America
USP	United States Pharmacopeia
vs	versus

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

AUC	area under the plasma/serum/PBMC concentration versus time curve
$AUC_{0\text{-}last}$, 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 (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 the optimization of tolerability, long-term safety, and adherence of potent ART regimens {29705}. In addition, there remains a significant medical need for new, effective therapies that take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, non-HIV comorbidities, and regimen simplification.

For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI) {28776}, {27621}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {21053}, {29702}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailablity that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density have been shown that are larger than those seen with other NRTIs {26885}. Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF.

Gilead Sciences (Gilead) has coformulated TAF with the HIV-1 INSTI elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), and the NRTI emtricitabine (FTC; F) into an FDC tablet that is suitable for once-daily use. The E/C/F/TAF FDC may provide a potent, convenient, well-tolerated, and practical regimen for the long-term treatment of patients infected with HIV.

This Summary of Biopharmaceutical Studies and Associated Analytical Methods is being submitted in support of a marketing application for the E/C/F/TAF FDC tablet for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

To facilitate the review, the focus of this document is on data relevant to E/C/F/TAF and its components with the greatest detail on that for the new chemical entity, TAF. This includes data from studies conducted with E/C/F/TAF, as well as studies conducted with the individual components, TAF (also referred to as GS-7340), EVG, COBI, FTC, FTC coformulated with TAF (F/TAF), and the FDC tablet EVG/COBI/FTC/TDF (coformulated; Stribild®; STB).

A summary of the bioanalytical methods for quantitation of the components of E/C/F/TAF in the clinical development program are described in Sections 1.1.3.1 to 1.1.3.15 with links to the current method validation reports.

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

A tabular summary of the long-term storage stability (LTSS) program for the analytes of E/C/F/TAF is presented in Section 1.1.5. A detailed tabular summary presented by clinical study that includes 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 is provided in Appendix 4.5.

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

1.1.1. Formulation Development

The proposed commercial drug product consists of an FDC containing 150 mg EVG, 150 mg COBI, 200 mg FTC, and 10 mg TAF (hereafter referred to as E/C/F/TAF tablets). EVG is fluid-bed granulated with intragranular excipients to yield EVG granulation. FTC and TAF are dry-granulated with intragranular excipients to yield FTC/TAF granulation. Both granulations are blended with COBI drug substance and extragranular excipients prior to compression into monolayer tablets. The E/C/F/TAF tablets are film-coated with [redacted].

Two forms of the TAF drug substance were used in the development of TAF single agent and E/C/F/TAF tablets: TAF monofumarate (GS-7340-02), synonymous for GS-7340 as the monofumarate form (1:1 ratio of GS-7340 to fumarate), and TAF fumarate (GS-7340-03), synonymous for the hemifumarate form (2:1 ratio of GS-7340 to fumarate). As shown in Table 1, TAF single-agent formulation development included several formulations of drug product: TAF monofumarate tablets (8-, 25-, and 40-mg strengths) and TAF fumarate tablets (25-mg strength). TAF fumarate drug substance was selected for commercialization based on the following: (1) enhanced purging capability of the process impurity GS-7339, (2) increased thermodynamic stability in organic solvents, and (3) improved thermal stability compared with TAF monofumarate drug substance.

E/C/F/TAF tablet formulation development included several formulations of drug product (Table 1). In Study GS-US-292-0101 (m2.7.2, Section 2.2.1.1), monolayer and bilayer E/C/F/TAF tablet formulations were evaluated containing either 25 or 40 mg of TAF as TAF monofumarate. Based on similar bioperformance and chemical stability of the monolayer and bilayer tablet formulation, the monolayer was selected for further development. Following

Study GS-US-292-0101, the TAF dose was adjusted to 10 mg in the E/C/F/TAF tablets based on the increase in exposure of TAF in the presence of COBI.

The E/C/F/TAF tablet core formulation containing 10 mg of TAF, as 11.2 mg of TAF fumarate (the form selected for commercialization of TAF), was developed prior to the initiation of Phase 2 clinical studies using TAF fumarate. The E/C/F/TAF tablet formulation demonstrated similar pharmacokinetic (PK) performance to the coadministered single-agent tablets, EVG 150-mg strength, COBI 150-mg strength, FTC 200-mg strength, and TAF 25-mg strength, in Study GS-US-292-0103 (m2.7.2, Section 2.2.1.2).

The E/C/F/TAF monolayer tablet core formulation was subsequently used in the Phase 2 clinical study (GS-US-292-0102, m2.7.3, Section 2.1.3).

The proposed commercial E/C/F/TAF tablets are green, capsule-shaped, film-coated tablets, debossed with “GSI” on one side and “510” on the other side, containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF. Each tablet core contains the following inactive ingredients: microcrystalline cellulose, silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and hydroxypropyl cellulose. The tablet film-coat contains polyvinyl alcohol (E1203), titanium dioxide (E171), polyethylene glycol (E1521), talc (E553B), FD&C Blue #2/indigo carmine aluminum lake (E132), and iron oxide yellow (E172). This is the tablet formulation used in all primary and registration stability batches and in the pivotal Phase 3 clinical studies (GS-US-292-0104 and GS-US-292-0111, m2.7.3, Sections 2.1.1 and 2.1.2). The quantitative composition of E/C/F/TAF tablet is summarized in Appendix 4.1.

Table 1. Formulation Summary for Key Studies with TAF and E/C/F/TAF

Product	Drug Substance Form	Formulation	Study	Summary of Results Location
TAF Single Agent	TAF monofumarate	[redacted], 8, 25, 40 mg	GS-US-120-0104 Safety, PK, and antiviral activity of TAF monotherapy GS-US-292-0101 Relative bioavailability E/C/F/TAF vs STB and TAF	m2.7.2, Sections 2.3.1.1 and 2.2.1.1
	TAF fumarate	[redacted], 25 mg	GS-US-292-0103 Bioavailability of E/C/F/TAF FDC relative to individual components	m2.7.2, Section 2.2.1.2
E/C/F/TAF FDC	TAF monofumarate	[redacted], EVG 150 mg/COBI 150 mg/FTC 200 mg/ TAF 25 mg FDC; [redacted], EVG 150 mg/COBI 150 mg/FTC 200 mg/ TAF 40 mg FDC	GS-US-292-0101 Relative bioavailability E/C/F/TAF vs STB and TAF	m2.7.2, Section 2.2.1.1
		[redacted], EVG 150 mg/ COBI 150 mg/FTC 200 mg/TAF 25 mg FDC; [redacted], EVG 150 mg/ COBI 150 mg/FTC 200 mg/TAF 40 mg FDC		
	TAF fumarate	[redacted], EVG 150 mg/COBI 150 mg/FTC 200 mg/ TAF 10 mg FDC	GS-US-292-0103 Bioavailability of E/C/F/TAF FDC relative to individual components	m2.7.2, Section 2.2.1.2

COBI = cobicistat; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic(s); STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild); TAF = tenofovir alafenamide; vs = versus

1.1.2. Dissolution Profile

According to the Biopharmaceutics Classification System (BCS), EVG and COBI are low solubility, high permeability (BCS 2) compounds. 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] % [redacted] °C. The amount of each active ingredient dissolved was [redacted]

Dissolution profiles for the proposed commercial tablet formulation (Lot No. CP[redacted]01B) are summarized in Appendix 4.2. The dissolution profile showed [redacted] % [redacted] minutes. EVG showed [redacted] % [redacted] minutes.

Table 2. Biopharmaceutics Classification of EVG, COBI, FTC, and TAF

EVG	COBI	FTC	TAF
2	2	1	3

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide

1.1.3. Bioanalytical Methods

1.1.3.1. Determination of TAF in Human Plasma

The TAF bioanalytical method was validated at [redacted] 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/[redacted] mass spectrometry (LC-MS/MS) with positive ionization. Method validation parameters are summarized in Table 3.

Table 3. Bioanalytical Method Validation for Determination of TAF in Human Plasma at [redacted]

	TAF
Linear 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-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-311-0101, and GS-US-342-1167

TAF = tenofovir alafenamide
Source: [redacted] 60-1115 Amendment 4

1.1.3.2. Determination of TFV in Human Plasma

The 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. Method validation parameters are summarized in Table 4.

Table 4. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted]

	TFV
Linear 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-292-0101, GS-US-292-0102, GS-US-292-0103, GS-US-292-0104, GS-US-292-0108, and GS-US-311-0101

TFV = tenofovir
Source: [redacted] 60-1116 Amendment 3

The original TFV bioanalytical method was improved and validated at [redacted] using the improved liquid chromatographic separation method to support the E/C/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. Method validation parameters are summarized in Table 5.

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

	TFV
Linear Range (ng/mL)	0.3 to 300
LLOQ (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 and GS-US-292-0110

TFV = tenofovir
Source: [redacted] 60-1352

This original TFV bioanalytical method ([redacted] 60-1116) was improved and validated at [redacted] using a smaller sample volume and an improved liquid chromatographic separation method to support the E/C/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. Method validation parameters are summarized in Table 6.

Table 6. Bioanalytical Method Validation for Determination of TFV in Human Plasma at [redacted]

	TFV
Linear 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-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-342-1167

TFV = tenofovir
Source: [redacted] 60-1368

1.1.3.3. Determination of TFV in Human Urine

The bioanalytical method for the determination of TFV in human urine was validated at [redacted]. The method involved protein precipitation extraction of TFV and its internal standard ([redacted]) from human urine followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 7.

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

	TFV
Linear Range (ng/mL)	500 to 200,000
Lower Limit of Quantitation (ng/mL)	500
Interassay Precision Range (%CV)	1.9% to 8.5%
Interassay Accuracy Range (%RE)	-1.5% to 4.9%
Studies Supported	GS-US-216-0134

TFV = tenofovir
Source: [redacted] 60-1270 Amendment 2

1.1.3.4. 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. Method validation parameters are summarized in Table 8.

Table 8. Bioanalytical Method Validation for Determination of TAF and TFV in Human Urine at [redacted]

	TAF	TFV
Linear 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	

TAF = tenofovir alafenamide; TFV = tenofovir
Source: [redacted] 60-1220 Amendment 1

1.1.3.5. 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 fully validated 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. Method validation parameters are summarized in Table 9.

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

	TFV	FTC
Linear 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	GS-US-183-0103 and GS-US-236-0105	

FTC = emtricitabine; TFV = tenofovir
Source: Gilead V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)

A combined TFV and FTC bioanalytical method was developed and validated at [redacted] and 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. Method validation parameters are summarized in Table 10.

Table 10. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma at [redacted]

	TFV	FTC
Linear 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-236-0110, GS-US-236-0120, GS-US-292-0101, GS-US-292-0102, GS-US-292-0104, GS-US-292-0106, GS-US-292-0111, GS-US-292-0112, GS-US-292-1316, and GS-US-342-1167 GS-US-120-0104 and GS-US-216-0134 (TFV only) GS-US-292-0103, GS-US-292-0108, and GS-US-311-0101 (FTC only)	

FTC = emtricitabine; TFV = tenofovir
Source: [redacted] 42-0831 Amendment 5

A bioanalytical method for determination of TFV and FTC in human plasma was validated at [redacted] USA). This method involved protein precipitation extraction of TFV, FTC, and the internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 11.

Table 11. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma at [redacted]

	TFV	FTC
Linear Range (ng/mL)	5 to 3000	5 to 3000
Lower Limit of Quantitation (ng/mL)	5	5
Interassay Precision Range (%CV)	0.6% to 3.8%	0.0% to 2.8%
Interassay Accuracy Range (%RE)	-3.3% to 0.0%	-1.3% to 5.3%
Studies Supported	GS-US-236-0135	

FTC = emtricitabine; TFV = tenofovir
Source: [redacted] 114

1.1.3.6. Determination of EVG in Human Plasma

The original EVG bioanalytical method developed and validated at Gilead involved the extraction of EVG and its internal standard ([redacted]) from human plasma using SPE followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 12.

Table 12. Bioanalytical Method Validation for Determination of EVG in Human Plasma at Gilead

	EVG
Linear Range (ng/mL)	1 to 1000
Lower Limit of Quantitation (ng/mL)	1.0
Interassay Precision Range (%CV)	4.6% to 20%
Interassay Accuracy Range (%RE)	-3.3% to 0.8%
Studies Supported	GS-US-183-0101, GS-US-183-0102, and GS-US-183-0103

EVG = elvitegravir
Source: Gilead V-GS-9137-16447v2

The EVG bioanalytical method was further developed and validated at Gilead and a different bioanalytical laboratory ([redacted] USA) for the determination of EVG and its metabolites (GS-9200 and GS-9202) plus ritonavir (RTV) in human plasma samples collected during specific clinical pharmacology studies. Refer to Section 1.1.3.7 for the bioanalytical method used for the determination of EVG, GS-9200, GS-9202, and RTV in plasma.

1.1.3.7. Determination of EVG, GS-9200, GS-9202, and RTV in Human Plasma

The EVG bioanalytical method was also developed and validated at Gilead for the simultaneous determination of EVG, GS-9200, GS-9202, and RTV concentrations in human plasma. The LC-MS/MS method involved the extraction of the analytes and internal standards ([redacted] and [redacted]) from human plasma using SPE followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 13.

Table 13. Bioanalytical Method Validation for Determination of EVG, GS-9200, GS-9202, and RTV in Human Plasma at Gilead

	EVG		GS-9200	GS-9202	RTV	
Linear Range (ng/mL)	0.5 to 50	20 to 10,000	20 to 1000	20 to 1000	0.5 to 50	5 to 5000
Lower Limit of Quantitation (ng/mL)	0.5	20	20	20	0.5	5
Interassay Precision Range (%CV)	7.5% to 12.5%	2.1% to 6.3%	4.7% to 14.7%	3.5% to 10.9%	5.3% to 7.7%	8.0% to 11.6%
Interassay Accuracy Range (%RE)	3.0% to 6.7%	-13.0% to -2.4%	-4.5% to 1.5%	-5.1% to -3.3%	-2.8% to 4.0%	-2.0% to 9.4%
Studies Supported	GS-US-183-0113, GS-US-183-0119, GS-183-0128, and GS-US-183-0146 GS-US-183-0140 (EVG and RTV only)					

EVG = elvitegravir; RTV = ritonavir
Source: Gilead V_GS9137_METABS_RTV_HUMAN_PLASMA_V7 (16555v7) and V-GS-9137-16566V2

This EVG, GS-9200, GS-9202, and RTV bioanalytical method was later transferred and validated at [redacted] This validated bioanalytical method was used for the determination of EVG, GS-9200, GS-9202, and RTV in human plasma samples collected in Study GS-US-183-0126. Method validation parameters are summarized in Table 14.

Table 14. Bioanalytical Method Validation for Determination of EVG, GS-9200, GS-9202, and RTV in Human Plasma at [redacted]

	EVG	GS-9200	GS-9202	RTV
Linear Range (ng/mL)	20 to 10,000	20 to 1000	20 to 1000	5 to 2500
Lower Limit of Quantitation (ng/mL)	20	20	20	5
Interassay Precision Range (%CV)	3.1% to 5.6%	2.0% to 4.6%	2.0% to 9.5%	2.6% to 4.6%
Interassay Accuracy Range (%RE)	-8.4% to 6.0%	-5.5% to 4.0%	-10.4% to 3.3%	-4.5% to 4.7%
Studies Supported	GS-US-183-0126 GS-US-236-0135 (RTV only)			

EVG = elvitegravir; RTV = ritonavir
Source: [redacted]009, Amendment 1, and Amendment 2; [redacted]156; and [redacted]204

This EVG, GS-9200, GS-9202, and RTV bioanalytical method was transferred and validated at [redacted] for the simultaneous determination of EVG, GS-9200, GS-9202, and RTV concentrations in human plasma. The LC-MS/MS method involved the extraction of the analytes and internal standards [redacted] and [redacted]) from human plasma using SPE followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 15.

Table 15. Bioanalytical Method Validation for Determination of EVG, GS-9200, GS-9202, and RTV in Human Plasma at [redacted]

	EVG	GS-9200	GS-9202	RTV
Linear Range (ng/mL)	20 to 10,000	17.5 to 875.5	20 to 1000	5 to 5000
Lower Limit of Quantitation (ng/mL)	20	17.5	20	5
Interassay Precision Range (%CV)	3.3% to 5.5%	4.1% to 12.1%	3.8% to 4.8%	3.1% to 14.6%
Interassay Accuracy Range (%RE)	-0.4% to 9.2%	1.4% to 7.8%	0.4% to 8.1%	-3.7% to 7.6%
Studies Supported	GS-US-216-0116 (EVG and RTV only) GS-US-236-0105 (EVG only)			

EVG = elvitegravir; RTV = ritonavir
Source: [redacted] 60-0811 Amendment 4

1.1.3.8. Determination of EVG, GS-9200, and GS-9202 in Human Plasma

A combined EVG, GS-9200, and GS-9202 bioanalytical method was developed and validated at [redacted] and involved the extraction of EVG, GS-9200, GS-9202, and stable isotope internal standards ([redacted] and [redacted] respectively) from human plasma using SPE followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 16.

Table 16. Bioanalytical Method Validation for Determination of EVG, GS-9200, and GS-9202 in Human Plasma at [redacted]

	EVG	GS-9200	GS-9202
Linear Range (ng/mL)	20 to 10,000	20 to1000	20 to1000
Lower Limit of Quantitation (ng/mL)	20	20	20
Interassay Precision Range (%CV)	2.0% to 4.3%	2.5% to 4.1%	1.8% to 4.1%
Interassay Accuracy Range (%RE)	-0.3% to 2.4%	2.0% to 7.4%	3.7% to 4.0%
Studies Supported	GS-US-183-1004		

EVG = elvitegravir
Source: [redacted] 60-1378

1.1.3.9. Determination of EVG and COBI in Human Plasma

A combined EVG and COBI bioanalytical method was developed and validated at [redacted] and 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. Method validation parameters are summarized in Table 17.

Table 17. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma at [redacted]

	EVG	COBI
Linear 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-183-0133, GS-US-216-0116, GS-US-216-0120, GS-US-216-0122, GS-US-216-0123, GS-US-216-0124, GS-US-216-0125, GS-US-236-0106, GS-US-236-0110, GS-US-236-0120, GS-US-292-0101, GS-US-292-0102, GS-US-292-0103, GS-US-292-0104, and GS-US-292-0108 GS-US-216-0112, GS-US-216-0116, GS-US-216-0121, GS-US-216-0134, and GS-US-311-0101 (COBI only)		

COBI = cobicistat; EVG = elvitegravir
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 E/C/F/TAF program. This method involved SPE extraction of EVG, COBI, and stable isotope internal standards ([redacted] and [redacted] respectively) from human plasma followed by LC-MS/MS with positive ionization. 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
Linear 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-216-0137, GS-US-292-0106, GS-US-292-0112, GS-US-292-1316, and GS-US-342-1167	

COBI = cobicistat; EVG = elvitegravir
Source: [redacted] 60-1343 Amendment 1

A bioanalytical method for simultaneous determination of EVG and COBI in human plasma was validated at [redacted] This method involved SPE of EVG, COBI, and the internal standards ([redacted] and [redacted] respectively) from human plasma followed by LC-MS/MS with positive ionization. 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
Linear Range (ng/mL)	20 to 10,000	5 to 2500
Lower Limit of Quantitation (ng/mL)	20	5
Interassay Precision Range (%CV)	1.8% to 7.0%	2.1% to 5.8%
Interassay Accuracy Range (%RE)	-6.5% to 1.6%	2.0% to 5.0%
Studies Supported	GS-US-236-0135 and GS-US-344-0102	

COBI = cobicistat; EVG = elvitegravir
Source: [redacted] 165

1.1.3.10. Determination of COBI in Human Plasma

The original COBI bioanalytical LC-MS/MS method developed and validated at [redacted] ([redacted] USA) involved the extraction of COBI and its internal standard ([redacted]) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 20.

Table 20. Bioanalytical Method Validation for Determination of COBI in Human Plasma at [redacted]

	COBI
Linear Range (ng/mL)	5 to 1000
Lower Limit of Quantitation (ng/mL)	5
Interassay Precision Range (%CV)	1.6% to 2.8%
Interassay Accuracy Range (%RE)	-1.5% to 8.0%
Studies Supported	GS-US-216-0101

COBI = cobicistat
Source: [redacted] 6511-369 Addendum 2

Another COBI bioanalytical method was developed and validated at Gilead for the simultaneous determination of COBI and GS-8374 in human plasma. The LC-MS/MS method involved the extraction of COBI, GS-8374, and internal standards from human plasma using SPE followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 21.

Table 21. Bioanalytical Method Validation for Determination of COBI and GS-8374 in Human Plasma at Gilead

	COBI	GS-8374
Linear Range (ng/mL)	10 to 5000	20 to 10,000
Lower Limit of Quantitation (ng/mL)	10	20
Interassay Precision Range (%CV)	3.7% to 9.5%	4.8% to 9.4%
Interassay Accuracy Range (%RE)	-2.7% to 4.4%	0.0% to 6.0%
Studies Supported	GS-US-216-0107 (COBI only)	

COBI = cobicistat
Source: Gilead V_GS9350_AND_GS8374_HUMAN_PLASMA_V2 (20199v2); GS-US-216-0107 CSR, Table 5-6

A third COBI bioanalytical method was developed and validated at [redacted] as part of EVG and COBI bioanalytical method ([redacted] validation report 60-0949) and was used for the determination of COBI concentrations in human samples collected in Studies GS-US-216-0112, GS-US-216-0116, and GS-US-216-0121. Refer to Section 1.1.3.9 for the bioanalytical method used for the determination of EVG and COBI in plasma.

1.1.3.11. Determination of COBI in Human Urine

The bioanalytical method for the determination of COBI in human urine was developed and validated at [redacted] The method involved protein precipitation extraction of COBI and its internal standard ([redacted]) from human urine followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 22.

Table 22. Bioanalytical Method Validation for Determination of COBI in Human Urine at [redacted]

	COBI
Linear Range (ng/mL)	50 to 25,000
Lower Limit of Quantitation (ng/mL)	50
Interassay Precision Range (%CV)	1.7% to 6.9%
Interassay Accuracy Range (%RE)	-8.9% to -0.2%
Studies Supported	GS-US-216-0134

COBI = cobicistat
Source: [redacted] 60-1268 Amendment 2

1.1.3.12. Determination of COBI Metabolites in Human Plasma

The COBI and GS-9612 bioanalytical method for measurement of COBI and its metabolite GS-9612 was developed and validated at Gilead and involved the extraction of COBI, GS-9612, and the internal standard ([redacted]) from human plasma using SPE followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 23.

Table 23. Bioanalytical Method Validation for Determination of COBI and GS-9612 in Human Plasma at Gilead

	COBI	GS-9612
Linear Range (ng/mL)	5 to 2500	5 to 2500
Lower Limit of Quantitation (ng/mL)	5	5
Interassay Precision Range (%CV)	4.0% to 6.1%	4.6% to 6.3%
Interassay Accuracy Range (%RE)	-2.0% to 2.0%	-3.4% to 2.0%
Studies Supported	GS-US-216-0113 and GS-US-236-0105	

COBI = cobicistat
Source: Gilead V_GS9350_AND_GS9612_HUMAN_PLASMA_V3 (20150v3)

1.1.3.13. Determination of FTC in Human Plasma

The initial FTC human plasma bioanalytical method was developed and validated at Gilead (formerly [redacted]) for the analysis of all FTC clinical study samples except for 1 study (Study 143-001) conducted by [redacted] in [redacted]. This proprietary method used by [redacted] to analyze plasma samples collected from Study 143-001 was a high-performance liquid chromatography with ultraviolet 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 FTC plasma method involved SPE of FTC and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 24.

Table 24. Bioanalytical Method Validation for Determination of FTC in Human Plasma at Gilead

	FTC
Linear Range (ng/mL)	5 to 5000
Lower Limit of Quantitation (ng/mL)	5
Interassay Precision Range (%CV)	4.9% to 5.7%[a]
Interassay Accuracy Range (%RE)	2.8% to 5.2%[a]
Studies Supported	FTC-101, FTC-106, FTC-107, FTC-108, FTC-109, FTC-110, and FTC-111 FTC-107 (human dialysate)

FTC = emtricitabine
a Did not include lower limit of quantitation data
Source: Gilead V-00-BIO-TP0006-01 (7536v6)

1.1.3.14. Determination of FTC and Emivirine in Human Plasma

A combined FTC and emivirine bioanalytical method was developed and validated at Gilead and involved SPE of FTC, emivirine, and internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Table 25.

Table 25. Bioanalytical Method Validation for Determination of FTC and Emivirine in Human Plasma at Gilead

	FTC	Emivirine
Linear 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	

FTC = emtricitabine
Source: Gilead 6879v4

1.1.3.15. Determination of FTC in Human Urine

The initial FTC human urine bioanalytical method was developed and validated at Gilead (formerly [redacted]) for the analysis of all FTC clinical study samples except for 1 study (Study 143-001) conducted by [redacted] in [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. Method validation parameters are summarized in Table 26.

Table 26. Bioanalytical Method Validation for Determination of FTC in Human Urine at Gilead

	FTC
Linear 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

FTC = emtricitabine
Source: Gilead 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. Method validation parameters are summarized in Table 27.

Table 27. Bioanalytical Method Validation for Determination of FTC in Human Urine at Gilead

	FTC
Linear 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

FTC = emtricitabine
Source: Gilead 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 assay 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 P&A run acceptance criteria stated in method validation standard operating procedures.

1.1.5. Long-Term Stability

Analytical support for the E/C/F/TAF program includes extensive long-term stability studies (Table 28), including combination stability of TAF, TFV, EVG, COBI, and FTC (Table 29) within biological matrices studied.

Table 28. Long-Term Stability of TAF, TFV, EVG, COBI, and FTC

Analyte	Matrix	LTSS Data Available	Most Current Validation Report
TAF	Plasma	520 days at -70°C	[redacted] 60-1115 Amendment 4
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	V_FTC_TFV_Human_and_Canine_Plasma_V9
FTC	Urine	664 days at -70°C	[redacted] 42-1236 Amendment 2
EVG	Plasma	585 days at -70°C	[redacted] 60-0949 Amendment 5
GS-9200	Plasma	834 days at -70°C	[redacted] 60-1378
GS-9202	Plasma	834 days at -70°C	[redacted] 60-1378
COBI	Plasma	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2

COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TFV = tenofovir

Table 29. Combination Stability of TAF, TFV, EVG, COBI, 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
TFV[a]	TAF FTC EVG COBI EFV RPV ATV DRV	Plasma	485 days at -70°C	[redacted] 60-1325
FTC	TAF TFV EVG COBI EFV RPV ATV DRV	Plasma	485 days at -70°C	[redacted] 60-1325
TFV[b]	TAF FTC EVG COBI EFV RPV ATV DRV	Plasma	485 days at -70°C	[redacted] 60-1325
EVG	TAF FTC TFV COBI EFV RPV ATV DRV	Plasma	485 days at -70°C	[redacted] 60-1325

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

ATV = atazanavir; COBI = cobicistat; DRV = darunavir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RPV = rilpivirine; TAF = tenofovir alafenamide; TFV = tenofovir
a At an assay range of 5 to 3000 ng/mL.
b At an assay range of 0.3 to 300 ng/mL as a metabolite of TAF.
Note: Non-Gilead/pertinent analytes (eg, EFV, RPV, ATV, DRV) are included and tested as ongoing potential combination drug programs.
Source: [redacted] 60-1325

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

In all but one instance (telaprevir [TVR] in Study GS-US-236-0135), LTSS covered transpired time, calculated between the date of the first sample collection and the date of the last sample analysis for a study. In Study GS-US-236-0135, study samples were analyzed in batches during study conduct in the established LTSS timeframe.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Summaries of clinical studies included in this marketing application may be found 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

The bioavailability of TAF when administered alone is estimated to be ≤ 40%. TAF is transported by P-glycoprotein (P-gp) and metabolized by esterases expressed in the intestine {21545}, {21546}. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly inhibit P-gp activity increase TAF availability. Upon coadministration of TAF with COBI single agent, near maximal inhibition of P-gp by COBI is achieved, leading to increased availability of TAF (Study GS-US-311-0101, m2.7.2, Section 2.5.2.1). In the context of E/C/F/TAF containing TAF 10 mg, TAF bioavailability is increased approximately 2.3-fold, providing resultant exposures comparable with TAF 25 mg single agent (Study GS-US-292-0103, m2.7.2, Section 2.2.1.2).

3.1.2. Bioavailability of EVG

The bioavailability of EVG is approximately 6- to 7-fold higher upon coadministration with a pharmacoenhancer (eg, COBI, RTV) relative to its administration alone, primarily due to a reduction in first-pass effect (Study GS-US-183-0102).

Study GS-US-183-0140 demonstrated that the Phase 3 and commercial formulation of the stand-alone 150-mg tablet of EVG boosted with 100 mg of RTV provided bioequivalent exposures relative to the Phase 2 125-mg tablet of EVG boosted with 100 mg of RTV. Therefore, the 150-mg dose of EVG boosted with 100 mg of RTV was selected as the dose evaluated for clinical development of EVG single agent. The 150-mg dose of EVG boosted with 150 mg of COBI was also the dose used in clinical development of STB and the E/C/F/TAF FDC. Additionally, the formulation of EVG used in the stand-alone 150-mg tablet in the relative bioavailability Study GS-US-292-0103 (m2.7.2, Section 2.2.1.2), the intrinsic factor Study GS-US-183-1004 (m2.7.2, Section 2.4.3.1), and the drug interaction Studies GS-US-216-0137 (m2.7.2, Section 2.5.3.1) and GS-US-344-0102 was representative of the Phase 2, Phase 3, and commercial formulation of the E/C/F/TAF FDC, as well as the commercial formulation of STB.

3.1.3. Bioavailability of COBI

The bioavailability of COBI increases with dose (before reaching a plateau ≥ 200 mg) and upon single-dose to multiple-dose administration, consistent with its metabolic autoinhibition properties as a pharmacoenhancer (Studies GS-US-216-0101 and GS-US-216-0113). The relative bioavailability of the Phase 3 test tablet (Formulation 2) of COBI, which was 15% smaller and simplified the manufacturing relative to the reference formulation used in the Phase 2 study, was determined to be similar to the Phase 2 tablet (Formulation 1) in Study GS-US-216-0116. Further, EVG exposures were shown to be similar following coadministration with the COBI Phase 3 test tablet (Formulation 2) versus RTV. As such,

Formulation 2 was selected for use in subsequent studies for COBI single agent, STB, and E/C/F/TAF clinical development. Additionally, the formulation of COBI used in the stand-alone 150-mg tablet in the relative bioavailability Study GS-US-292-0103 (m2.7.2, Section 2.2.1.2), the intrinsic factor Study GS-US-183-1004 (m2.7.2, Section 2.4.3.1), and the drug interaction Studies GS-US-311-0101 (m2.7.2, Section 2.5.2.1), GS-US-216-0137 (m2.7.2, Section 2.5.3.1) and GS-US-344-0102 was representative of the Phase 2, Phase 3, and commercial formulation of the E/C/F/TAF FDC, as well as the commercial formulation of STB.

3.1.4. Bioavailability of FTC

In Study FTC-110, the relative bioavailability of the commercial oral solution formulation (Formulation C-1) and the commercial capsule formulation (200 mg – Formulation B) were investigated in healthy subjects compared with that of an intravenous solution (from which the absolute bioavailability of FTC was derived in the same study). The bioequivalence of the capsule and oral solution were also assessed. The PK parameters for FTC, together with the results of the bioequivalence comparisons, are provided in m2.7.2, Sections 3.1.1.2 and 3.1.2.2.

The geometric mean AUC_{inf} ratios indicate that the relative bioavailability (in comparison with the intravenous solution) of the capsule was 93% (90% CIs: 87% to 99%), whereas the equivalent figure for the oral solution was 75% (90% CIs: 70% to 80%). Based on AUC_{inf} ratios, the relative bioavailability of the capsule formulation compared with oral solution was 124% (90% CIs: 117% to 133%).

At 93%, the relative bioavailability of the capsule is high, indicating excellent absorption via the oral route. The finding of a lower bioavailability of the solution compared with the capsules was unexpected and difficult to explain, although the magnitude (approximately 24%) of the difference between the 2 oral formulations is considered unlikely to be of any clinical importance. Furthermore, data concerning the FTC oral solution are not directly relevant to the present application, which concerns a combination tablet formulation.

3.1.5. Bioavailability of E/C/F/TAF Tablets

Following the administration of E/C/F/TAF, the exposures of EVG, COBI, and FTC were equivalent to those observed following administration of EVG, COBI, or FTC single agents. Moreover, EVG, COBI, and FTC exposures following E/C/F/TAF were comparable with those observed historically following administration of STB (Study GS-US-292-0103, m2.7.2, Section 2.2.1.2). Due to the near maximal TAF bioavailability achieved upon administration under strong P-gp inhibitory conditions (ie, with COBI), E/C/F/TAF provided equivalent exposures of TAF and TFV relative to TAF 25 mg single agent (Study GS-US-292-0103).

3.2. Effect of Food

The effect of food on the absorption/bioavailability of boosted TAF was evaluated when given as part of E/C/F/TAF (Study GS-US-292-0110, m2.7.2, Section 2.5.1.1). Administration of E/C/F/TAF under fed versus fasting conditions did not affect overall exposure of TAF, but resulted in a modestly lower C_{max} and delayed T_{max}. The geometric least-squares mean (GLSM) ratios (90% CIs) of the AUC_{last} of TAF when administered with a light/low-fat or

high-calorie/high-fat were 114.95% (106.82% to 123.69%) and 116.65% (108.40% to 125.52%), respectively, and within the predefined no-effect boundary. The GLSM (90% CIs) ratios of the C_{max} of TAF were 68.04% (58.96% to 78.52%) and 63.20% (54.76% to 72.93%) when administered under light/low-fat or high-calorie/high-fat conditions, respectively. These modest changes in TAF PK parameters upon E/C/F/TAF administration with food (versus fasted) were not considered clinically relevant.

The effect of food on EVG, COBI, and FTC was evaluated following administration of STB in Study GS-US-236-0105.

Relative to the fasted condition, EVG AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max} increased by 34%, 36%, and 22%, respectively, for the light meal condition and increased by 87%, 91%, and 56%, respectively, for the high-calorie/high-fat meal condition. EVG AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max} increased by 39%, 40%, and 28%, respectively, when STB was administered with a high-calorie/high-fat meal relative to a light meal. The higher EVG exposure when administered with high-calorie/high-fat meal is not considered to be clinically relevant given the safety profile of EVG at doses up to 300 mg. Additionally, the clinical development of EVG entailed a recommendation for administration with food with no requirements on the type of meal. COBI exposure parameters were bioequivalent under light meal and fasted conditions. For the high-calorie/high-fat meal condition, COBI C_{max} and AUC decreased by 19% to 27% relative to the light meal condition and by 17% to 24% relative to the fasted condition, which are not considered to be clinically significant, as evidenced by the maintenance of boosted EVG exposure (in fact, higher) upon administration with a high-calorie/high-fat meal, indicating that the effect of food on COBI did not affect EVG exposure. Mean FTC AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max} were bioequivalent between the 3 treatment conditions, consistent with the established PK profile of FTC.

Although boosted TAF (when administered as E/C/F/TAF) is unaffected by food and does not require a food restriction, it is recommended that boosted EVG be administered with food to achieve EVG exposure that provides a high mean 95% inhibitory quotient (IQ_{95}) (EVG trough concentration (C_{tau}) / I_{95}).

As such, E/C/F/TAF was administered with food in its clinical development program to align with the dosing recommendation for EVG and for STB, the comparator in the pivotal Phase 3 studies.

3.3. Conclusions

Administration of E/C/F/TAF results in comparable exposures of EVG, COBI, and FTC relative to singles agents. E/C/F/TAF provides comparable exposures of TAF and TFV, relative to TAF 25 mg single agent.

Although TAF is unaffected by food when administered as E/C/F/TAF, it is recommended that E/C/F/TAF be administered with food to achieve exposures of EVG that maintain a high inhibitory quotient.

4. APPENDICES

Appendix Number	Appendix Title
4.1	Quantitative Composition of the Proposed Commercial Formulation of E/C/F/TAF FDC Tablets
4.2	Summary of In Vitro Dissolution Profiles for the Formulation of E/C/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 E/C/F/TAF Studies

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

Component	Composition (% w/w)	Unit Formula (mg/tablet)	Reference Quality Standard	Function
Tablet Core				
EVG[a]	[redacted]	150.0	In-house	Active ingredient
COBI on Silicon Dioxide[c]	[redacted]	[redacted][e]	In-house	Active ingredient
FTC[c]	[redacted]	200.0	In-house	Active ingredient
TAF Fumarate[c]	[redacted]	11.2[d]	In-house	Active ingredient
Lactose Monohydrate[a]	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Microcrystalline Cellulose[c]	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Croscarmellose Sodium	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Hydroxypropyl Cellulose	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Sodium Lauryl Sulfate	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
Magnesium Stearate	[redacted]	[redacted]	NF, Ph. Eur.	[redacted]
[redacted][b]	[redacted]	[redacted]	USP, Ph. Eur.	[redacted]
Film Coat				
[redacted][f]	[redacted][g]	[redacted]	In-house	[redacted]
[redacted][b]	[redacted]	[redacted]	USP, Ph. Eur.	[redacted]

COBI = cobicistat; DCF = drug correction factor; EVG = elvitegravir; FTC = emtricitabine; Ph. Eur. = European Pharmacopeia; NF = National Formulary; TAF = tenofovir alafenamide; USP = United States Pharmacopeia

a [redacted]

b [redacted]

c [redacted]

d 11.2 mg of TAF fumarate corresponds to 10 mg of TAF.

e [redacted] of COBI on silicon dioxide corresponds to 150 mg of COBI.

f [redacted] is prepared as a [redacted] for [redacted]. [redacted] contains [redacted] polyvinyl alcohol [redacted], [redacted] titanium dioxide [redacted], [redacted] polyethylene glycol [redacted], [redacted] talc [redacted], [redacted] FD&C Blue #2/indigo carmine aluminum lake, and [redacted] iron oxide yellow [redacted].

g [redacted]

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

4.2. Summary of In Vitro Dissolution Profiles for the Formulation of E/C/F/TAF FDC Tablets Lot No. CP[redacted]01B

Time (minutes)	% Dissolved			
	EVG	COBI	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]

COBI = cobicistat; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EVG = elvitegravir;
FDC = fixed-dose combination; FTC = emtricitabine; TAF = tenofovir alafenamide
Dissolution condition: 1000 mL 2.0% w/v polysorbate 80 in 50 mM sodium citrate; pH 5.5. Paddle rotation speed was 100 rpm.
Source: m3.2.P.5.4, Table 23

4.3. Tabular Summary of Biopharmaceutic Studies

Tabular summaries of biopharmaceutic studies included in this marketing application may be found in m2.7.2.

4.4. Summary of Analytical Methods for Individual Studies

A tabular summary of analytical methods, method validation reports, and sample analysis reports for individual studies are provided below for studies conducted to support the E/C/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	Limits of Quantitation	Sample Analysis Report
143-001	Human Plasma	FTC	Method documents not available (property of [redacted].)	HPLC-UV	80 ng/mL	Sample analysis reports not available (property of [redacted].)
	Human Urine	FTC		HPLC-UV	1000 ng/mL	
FTC-101	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	[redacted] 8200v4
	Human Urine	FTC	[redacted] 2638v1	LC/MS (SIM) [redacted] 2638v1	250-5000 ng/mL	
FTC-102	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS [redacted] 6879v4	10-2500 ng/mL	[redacted] 7027v3
FTC-106	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	[redacted] 8603v2
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS [redacted] 8361v2	2.5-250 µg/mL	
FTC-107	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	[redacted] 10824v1
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS [redacted] 8361v2	2.5-250 µg/mL	
	Human Dialysate	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
FTC-108	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	[redacted] 11088v1
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS [redacted] 8361v2	2500-250,000 ng/mL	
FTC-109	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	[redacted] 8737v2
FTC-110	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	[redacted] 11694v1
	Human Urine	FTC	[redacted] 8361v2	LC/MS-MS [redacted] 8361v2	2500-250,000 ng/mL	
FTC-111	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS [redacted] 7536v6	5-5000 ng/mL	[redacted] 11378v1
FTC-303	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS [redacted] 6879v4	10-2500 ng/mL	[redacted] 6564v3
FTCB-101	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS [redacted] 6879v4	10-2500 ng/mL	[redacted] 6525v2
GS-US-120-0104	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1128A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1128B
		TFV	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1128C

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-120-0107	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1230A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1230B
GS-US-120-0108	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1269A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1269B
	Human Urine	TAF	[redacted] 60-1220 Amendment 1	LC-MS/MS [redacted] 60-1220 Amendment 1	2-1000 ng/mL	[redacted] 60-1269C
		TFV			10-5000 ng/mL	
GS-US-120-0109	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1245A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1245B
	Human Urine	TAF	[redacted] 60-1220 Amendment 1	LC-MS/MS [redacted] 60-1220 Amendment 1	2-1000 ng/mL	[redacted] 60-1245C
		TFV			10-5000 ng/mL	
GS-US-120-0114	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1344A
		TFV	[redacted] 60-1352	LC-MS/MS [redacted] 60-1352	0.3-300 ng/mL	[redacted] 60-1344B Amendment 1

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-183-0101	Human Plasma	EVG	V-GS-9137-16447V2	LC-MS/MS M-GS-9137-16407V1-V4	1.00-1000 ng/mL	S-183-04 V1
GS-US-183-0102	Human Plasma	EVG	V-GS-9137-16447V2	LC-MS/MS M-GS-9137-16407V1, V2	1.00-1000 ng/mL	[redacted] 60-0507A
		RTV	[redacted] 42-0316 42-0212	LC-MS/MS [redacted] 42-0316	1.00-1000 ng/mL	[redacted] 60-0507
GS-US-183-0103	Human Plasma	EVG	V-GS-9137-16447V2 (16447v2)	LC-MS/MS M-GS-9137-16443V4	1.00-1000 ng/mL	S-183-03
		FTC	V_FTC_TFV_HUMAN_ AND_CANINE_PLASMA V9 (15401v9)	LC-MS/MS M-02-BIO-TP0006-02v5	5.00-2000 ng/mL	
		TFV			10.0-1000 ng/mL	

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-183-0113	Human Plasma	EVG	V-GS-9137-16566V2	LC-MS/MS M-GS-9137-16553	0.5-50.0 ng/mL	S-183-15V2
			V-GS-9137-16555V7	LC-MS/MS M-GS-9137-16511V3,V4	20-10,000 ng/mL	
		JTP-71051 (M4, GS-9200)	V-GS-9137-16555V7	LC-MS/MS M-GS-9137-16511	20-1000 ng/mL	
		JTP-71081 (M1, GS-9202)				
		RTV	V-GS-9137-16566V2	LC-MS/MS M-GS-9137-16553V2	0.5-50.0 ng/mL	
			V-GS-9137-16555V7	LC-MS/MS M-GS-9137-16511	5.0-5000 ng/mL	
		MDZ	[redacted] 42-0624 Addendum 3	LC-MS/MS [redacted] 42-0624 Addendum 3	0.1-100 ng/mL	[redacted] 60-0623
GS-US-183-0119	Human Plasma	EVG	V-GS-9137-16555V7	LC-MS/MS M-GS-9137-16511V4	20-10,000 ng/mL	S-183-17V2
		JTP-71051 (M4, GS-9200)			20-1000 ng/mL	
		JTP-71081 (M1, GS-9202)			20-1000 ng/mL	
		RTV			5.0-5000 ng/mL	
		Omeprazole	[redacted] 42-0510 Addendum 1	LC-MS/MS [redacted] 42-0510 Addendum 1	20-2000 ng/mL	[redacted] 60-0632

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-183-0126	Human Plasma	EVG	[redacted]009 Amendment 2 and [redacted]156	LC-MS/MS TSLM05194	20-10,000 ng/mL	[redacted]180
		JTP-71051 (M4, GS-9200)				
		JTP-71081 (M1, GS-9202)				
		RTV	[redacted]204	LC-MS/MS TSLM06121	5.0-2500 ng/mL	
GS-US-183-0128	Human Plasma	EVG	V-GS-9137-16555V7	LC-MS/MS M-GS-9137-16511V1-4	20-10,000 ng/mL	S-183-19V2
		JTP-71051 (M4, GS-9200)			20-1000 ng/mL	
		JTP-71081 (M1, GS-9202)			20-1000 ng/mL	
		RTV			5.0-5000 ng/mL	
GS-US-183-0133	Human Plasma	EVG	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	20-10,000 ng/mL	[redacted] 60-1035
		COBI			5-2500 ng/mL	
GS-US-183-0140	Human Plasma	EVG	V-GS-9137-16555V7	LC-MS/MS M-GS-9137-16511V7	20-10,000 ng/mL	S-183-24
		RTV			5.0-5000 ng/mL	

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-183-0146	Human Plasma	EVG	V-GS-9137-16555V7	LC-MS/MS M-GS-9137-16511V7	20-10,000 ng/mL	S_GSUS1830146_ PLASMA_V1
		JTP-71051 (M4, GS-9200)			20-1000 ng/mL	
		JTP-71081 (M1, GS-9202)			20-1000 ng/mL	
		RTV			5.0-5000 ng/mL	
		MDZ	[redacted] 42-0624 Addendum 3	LC-MS/MS [redacted] 42-0624 Addendum 3	0.1-100 ng/mL	[redacted] 60-0719A
		1′-OH MDZ			0.1-100 ng/mL	
		Ketoconazole	[redacted] 42-0719	LC-MS/MS [redacted] 42-0719	20-10,000 ng/mL	[redacted] 60-0719B
GS-US-183-1004	Human Plasma	EVG	[redacted] 60-1378	LC-MS/MS [redacted] 60-1378	20-10,000 ng/mL	[redacted] 60-1386
		GS-9200				
GS-US-216-0101	Human Plasma	COBI	[redacted] 6511-369 Addendum 2	LC-MS/MS G93HPP V001 and 002	5-1000 ng/mL	[redacted] 6511-387
		RTV	[redacted] 2100-620 2100-371	LC-MS/MS LIHP V006	10-2000 ng/mL	
		MDZ	[redacted] 2100-229	LC-MS/MS MHHP V011 and 012	0.1-100 ng/mL	
		1′-OH MDZ				
GS-US-216-0107	Human Plasma	COBI	V_GS9350_AND_ GS8374_HUMAN_PLASMA V2	LC-MS/MS M_GS9350_AND _GS8374_HUMAN PLASMA_v1-3	10-5000 ng/mL	S_GSUS2160107_ PLASMA_V1

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-216-0112	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1003A
		Desipramine	[redacted] 42-0319 Amendment 4	LC-MS/MS [redacted] 42-0319 Amendment 4	1-2000 ng/mL	[redacted] 60-1003B
		Digoxin	[redacted] 42-1016	LC-MS/MS [redacted] 42-1016	100-30,000 pg/mL	[redacted] 60-1003C
		EFV	[redacted] 42-0827 Amendment 3	LC-MS/MS [redacted] 42-0827 Amendment 3	5-5000 ng/mL	[redacted] 60-1003D
GS-US-216-0113	Human Plasma	COBI	V_GS9350_AND_GS9612 _HUMAN_PLASMA_V3	LC-MS/MS M_GS9350_AND_ GS9612_HUMAN _PLASMA	5-2500 ng/mL	S_GSUS2160113_ PLASMA_V1
GS-US-216-0116	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-0951A
		EVG	[redacted] 60-0811 Amendment 4	LC-MS/MS [redacted] 60-0811 Amendment 4	20-10,000 ng/mL	[redacted] 60-0951B
		RTV			5.0-5000 ng/mL	
		EVG	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	20-10,000 ng/mL	[redacted] 60-0951C
		COBI			5-2500 ng/mL	
		MDZ	[redacted] 42-0624 Addendum 3	LC-MS/MS [redacted] 42-0624 Addendum 3	0.1-100 ng/mL	[redacted] 60-0951D
		1′-OH MDZ				

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-216-0120	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-0964
		EVG			20-10,000 ng/mL	
GS-US-216-0121	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-0965A
		RTV	[redacted] 42-0830 Amendment 2	LC-MS/MS [redacted] 42-0830 Amendment 2	5-2500 ng/mL	[redacted] 60-0965B
		Iohexol	[redacted] 2100-775 Addendum 7	LC-MS/MS eDOCs, IOHHPC	1000-500,000 ng/mL	[redacted] 8221988 and 8221988 Addendum 1
GS-US-216-0122	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1031
		EVG			20-10,000 ng/mL	
GS-US-216-0123	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1050A
		EVG			20-10,000 ng/mL	
		Rosuvastatin	[redacted] 42-1043 Amendment 2	LC-MS/MS [redacted] 42-1043 Amendment 2	0.05-50 ng/mL	[redacted] 60-1050B
		ATV	[redacted] 42-0830 Amendment 2	LC-MS/MS [redacted] 42-0830 Amendment 2	10-5000 ng/mL	[redacted] 60-1050C
		RTV			5-2500 ng/mL	
		Rifabutin	[redacted] 42-0724 Amendment 1	LC-MS/MS [redacted] 42-0724 Amendment 1	1-1000 ng/mL	[redacted] 60-1050D
		25-0-deacetyl rifabutin				

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-216-0124	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1109A
		EVG			20-10,000 ng/mL	
GS-US-216-0125	Human Plasma	EVG	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	20-10,000 ng/mL	[redacted] 60-1124A
		COBI			5-2500 ng/mL	
		R-Methadone	[redacted] 42-1105 Amendment 2	LC-MS/MS [redacted] 42-1105 Amendment 2	0.1-100 ng/mL	[redacted] 60-1124B
		S-Methadone				
		Buprenorphine	[redacted] 42-0217 Amendment 1	LC-MS/MS [redacted] 42-0217 Amendment 1	20-5000 ng/mL	[redacted] 60-1124C
		Norbuprenorphine				
		Naloxone	[redacted] VS-00948	LC-MS/MS [redacted] VS-00948	20-2000 ng/mL	[redacted] 60-1124D
GS-US-216-0134	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1253A
		TFV	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1253B
	Human Urine	COBI	[redacted] 60-1268 Amendment 2	LC-MS/MS [redacted] 60-1268 Amendment 2	50-25,000 ng/mL	[redacted] 60-1253C
		TFV	[redacted] 60-1270 Amendment 2	LC-MS/MS [redacted] 60-1270 Amendment 2	0.5-200 µg/mL	[redacted] 60-1253D

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-216-0137	Human Plasma	Carbamazepine	[redacted] 42-1371	LC-MS/MS [redacted] 42-1371	20-20,000 mg/mL	[redacted] 60-1395A
		Carbamazepine-10,11-epoxide			5-5000 ng/mL	
		COBI	[redacted] 60-1343 Amendment 1	LC-MS/MS [redacted] 60-1343 Amendment 1	5-2500 ng/mL	[redacted] 60-1395B
		EVG			20-10,000 ng/mL	
GS-US-236-0105	Human Plasma	EVG	[redacted] 60-0811 Amendment 4	LC-MS/MS [redacted] 60-0811 Amendment 4	20-10,000 ng/mL	[redacted] 60-0850
		COBI	V_GS9350_AND_ GS9612_HUMAN_ PLASMA_V1 (20150v3)	LC-MS/MS M_GS9350_AND_ GS9612_HUMAN_ PLASMA (20114v3)	5-2500 ng/mL	S_GSUS2360105_ GS9350_PLASMA _V1
		FTC	V_FTC_TFV_HUMAN_ AND_CANINE_PLASMA _V9 (15401v9)	LC-MS/MS M-02-BIO-TP0006-02 (14832v8)	5-2000 ng/mL	S_GSUS2360105_ FTC_TFV_ PLASMA_V1
		TFV			10-1000 ng/mL	
GS-US-236-0106	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-0952A
		EVG			20-10,000 ng/mL	
		Ethinyl estradiol	[redacted] 42-0931 Amendment 1	LC-MS/MS [redacted] 42-0931 Amendment 1	2.5-500 pg/mL	[redacted] 60-0952B
		17-desacetyl noregestrimate	[redacted] 42-0728	LC-MS/MS [redacted] 42-0728	20-10,000 pg/mL	[redacted] 60-0952C

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-236-0110	Human Plasma	EVG	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	20-10,000 ng/mL	[redacted] 60-0948A
		COBI			5-2500 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-0948B
		TFV				
GS-US-236-0120	Human Plasma	EVG	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	20-10,000 ng/mL	[redacted] 60-1136A
		COBI			5-2500 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1136B
		TFV				
		EFV	[redacted] 42-0827 Amendment 3	LC-MS/MS [redacted] 42-0827 Amendment 3	5-5000 ng/mL	[redacted] 60-1136C
GS-US-236-0135	Human Plasma	ATV	[redacted]204	LC-MS/MS [redacted]204	10-5000 ng/mL	[redacted] 232A
		RTV			5-2500 ng/mL	
		EVG	[redacted]165 [redacted] 60-0949 Amendment 5	LC-MS/MS [redacted]165	20-10,000 ng/mL	[redacted] 232B
		COBI			5-2500 ng/mL	
		FTC	[redacted]114 [redacted] 42-0831 Amendment 5 Gilead 15401v9	LC-MS/MS [redacted]114	5-3000 ng/mL	[redacted] 232C
		TFV				
		Telaprevir	[redacted]164 Amendment 1	LC-MS/MS [redacted]164 Amendment 1	10-5000 ng/mL	[redacted] 232D

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-292-0101	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1119A
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1119B
		TFV				
		TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1119C
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1119D
GS-US-292-0102	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1222A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1222B
		COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1222C
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1222D [redacted] 60-1222E
		TFV				

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-292-0103	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1142A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1142B
		COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1142C
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1142D
GS-US-292-0104	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1312A Amendment 1
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1312B
		TFV	[redacted] 60-1368	LC-MS/MS [redacted] 60-1368		
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1312C
		TFV				

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-292-0106	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1314A
		TFV	[redacted] 60-1368	LC-MS/MS [redacted] 60-1368	0.3-300 ng/mL	[redacted] 60-1314B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1314C
		TFV				
		EVG	[redacted] 60-1343 Amendment 1	LC-MS/MS [redacted] 60-1343 Amendment 1	20-10,000 ng/mL	[redacted] 60-1314D
		COBI			5-2500 ng/mL	
GS-US-292-0108	Human Plasma	COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-12103A
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-12103B
		TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-12103C
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-12103D
GS-US-292-0109	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1315A
		TFV	[redacted] 60-1368	LC-MS/MS [redacted] 60-1368	0.3-300 ng/mL	[redacted] 60-1315B

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-292-0110	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1358A
		TFV	[redacted] 60-1352	LC-MS/MS [redacted] 60-1352	0.3-300 ng/mL	[redacted] 60-1358B
GS-US-292-0111	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1313A
		TFV	[redacted] 60-1368	LC-MS/MS [redacted] 60-1368	0.3-300 ng/mL	[redacted] 60-1313B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1313C
		TFV				
GS-US-292-0112	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1316A
		TFV	[redacted] 60-1368	LC-MS/MS [redacted] 60-1368	0.3-300 ng/mL	[redacted] 60-1316B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1316C
		TFV				
		EVG	[redacted] 60-1343 Amendment 1	LC-MS/MS [redacted] 60-1343 Amendment 1	20-10,000 ng/mL	[redacted] 60-1316D
		COBI			5-2500 ng/mL	
		Iohexol	[redacted] 2100-775 Addendum 7	LC-MS/MS eDOCs, IOHHPC	1000-500,000 ng/mL	[redacted] 8283389

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-292-1316	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1411A
		TFV	[redacted] 60-1368	LC-MS/MS [redacted] 60-1368	0.3-300 ng/mL	[redacted] 60-1441B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1411C
		TFV				
		EVG	[redacted] 60-1343 Amendment 1	LC-MS/MS [redacted] 60-1343 Amendment 1	20-10,000 ng/mL	[redacted] 60-1411D
		COBI			5-2500 ng/mL	
		Sertraline	[redacted] 42-1402	LC-MS/MS [redacted] 42-1402	0.2-200 ng/mL	[redacted] 60-1411E
GS-US-311-0101	Human Plasma	TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1125A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS [redacted] 60-1116 Amendment 3	0.3-300 ng/mL	[redacted] 60-1125B
		FTC	[redacted] 42-0831 Amendment 5	LC-MS/MS [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1125C
		EFV	[redacted] 42-0827 Amendment 3	LC-MS/MS [redacted] 42-0827 Amendment 3	5-5000 ng/mL	[redacted] 60-1125E
		COBI	[redacted] 60-0949 Amendment 5	LC-MS/MS [redacted] 60-0949 Amendment 5	5-2500 ng/mL	[redacted] 60-1125F

Study Number[a]	Matrix	Analyte	Most Current Method Validation Report[b]	Analytical Method	Limits of Quantitation	Sample Analysis Report
GS-US-342-1167	Human Plasma	SOF	[redacted] 60-1323 Amendment 1	LC-MS/MS [redacted] 60-1323 Amendment 1	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 [redacted] 42-0831 Amendment 5	5-3000 ng/mL	[redacted] 60-1390B [redacted] 60-1390C
		TFV				
		TAF	[redacted] 60-1115 Amendment 4	LC-MS/MS [redacted] 60-1115 Amendment 4	1-1000 ng/mL	[redacted] 60-1390G
		TFV	[redacted] 60-1368	LC-MS/MS [redacted] 60-1368	0.3-300 ng/mL	[redacted] 60-1390H
		COBI	[redacted] 60-1343 Amendment 1	LC-MS/MS [redacted] 60-1343 Amendment 1	5-2500 ng/mL	[redacted] 60-1390I
		EVG			20-10,000 ng/mL	
		GS-5816	[redacted]-102 Amendment 1	LC-MS/MS [redacted]-102 Amendment 1	1-1000 ng/mL	[redacted]-278
GS-US-344-0102	Human Plasma	EVG	[redacted]-165	LC-MS/MS [redacted]-165	20-10,000 ng/mL	[redacted]-159-G
		COBI			5-2500 ng/mL	
		SOF	[redacted]-103 Amendment 2	LC-MS/MS [redacted]-103 Amendment 2	5-5000 ng/mL	[redacted]-159-H Amendment 1
		GS-566500			8.7-4350 ng/mL	
		GS-331007			10-5000 ng/mL	
		LDV	[redacted]-209	LC-MS/MS [redacted]-209	1-2000 ng/mL	[redacted]-159-I

1'-OH MDZ = midazolam metabolite (1'-hydroxymidazolam); ATV = atazanavir; COBI = cobicistat; CSR = clinical study report; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HPLC-UV = high-performance liquid chromatography with ultraviolet detection; LC-MS/MS = liquid chromatography-[redacted] mass spectrometry; LDV = ledipasvir; MDZ = midazolam; [redacted] RTV = ritonavir; SOF = sofosbuvir; 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
143-001	Human Plasma	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	Not reported	—	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	Not reported
	Human Urine	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	Not reported	—	664 days at -70°C	[redacted] 42-1236 Amendment 2	Not reported
FTC-101	Human Plasma	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	[redacted] 19[redacted] through [redacted] 20[redacted]	814 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] 11714v1
	Human Urine	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	[redacted] 19[redacted]	469 days at -80°C	664 days at -70°C	[redacted] 42-1236 Amendment 2	
FTC-102	Human Plasma	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	[redacted] 19[redacted] through [redacted] 19[redacted]	222 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] 7027v3
FTC-106	Human Plasma	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	[redacted] 19[redacted] through [redacted] 20[redacted]	325 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] 8603v2
	Human Urine	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	[redacted] 19[redacted] through [redacted] 20[redacted]	325 days at -70°C	664 days at -70°C	[redacted] 42-1236 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
FTC-107	Human Plasma	FTC	[redacted] 19[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	373 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] S-01-TP0006-01
	Human Urine	FTC	[redacted] 19[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	373 days at -80°C	664 days at -70°C	[redacted] 42-1236 Amendment 2	
	Human Dialysate	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	275 days at -80°C	460 days at -80°C	[redacted] 20050v1_V_FTC_D DI_Human_Plasma_ V1	
FTC-108	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	154 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] S-01-TP0006-03
		Penciclovir	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	236 days at -80°C	Not reported	V-01-BIO-T00260-01	
	Human Urine	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	222 days at -80°C	294 days at -80°C	V-00-BIO-T0006-02 (8361v2)	
		Peniclovir	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	258 days at -80°C	Not reported	V-01-BIO-T00260-01	
FTC-109	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	41 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] S-00-TP0006-03

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-110	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	38 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] S-01-BIO-TP0006-07
	Human Urine	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	45 days at -80°C	664 days at -70°C	[redacted] 42-1236 Amendment 2	
FTC-111	Human Plasma	FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	44 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] S-01-BIO-TP0006-05
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	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] 6564v3
FTCB-101	Human Plasma	FTC	[redacted] 19[redacted] through [redacted] 19[redacted]	[redacted] 19[redacted] through [redacted] 19[redacted]	346 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] 6525v2
GS-US-120-0104	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	218 days at -70°C	520 days at -70°C	[redacted] 60-1115 Amendment 4	[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

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-120-0107	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 4	[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
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 4	[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	103 days at –70°C	[redacted] 60-1220 Amendment 1	
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 4	[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	103 days at –70°C	[redacted] 60-1220 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-120-0114	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 4	[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
GS-US-183-0101	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	222 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	Gilead S-183-04 V1
GS-US-183-0102	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	Not reported	—	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-0507A
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	45 days at -70°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	[redacted] 60-0507
GS-US-183-0103	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	68 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	Gilead S-183-03
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	68 days at -70°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	68 days at -70°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	

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-183-0113	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	76 days at -80°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	Gilead S-183-15V2
		JTP-71051 (M4, GS-9200)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	76 days at -80°C	834 days at -70°C	[redacted] 60-1378	
		JTP-71081 (M1, GS-9202)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	76 days at -80°C	834 days at -70°C	[redacted] 60-1378	
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	76 days at -80°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
		MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	72 days at -70°C	135 days at -70°C	[redacted] 42-0624 Addendum 3	[redacted] 60-0623
GS-US-183-0119	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	82 days at -80°C	585 days at-70°C	[redacted] 60-0949 Amendment 5	Gilead S-183-17V2
		JTP-71051 (M4, GS-9200)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	82 days at -80°C	834 days at -70°C	[redacted] 60-1378	
		JTP-71081 (M1, GS-9202)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	82 days at -80°C	834 days at -70°C	[redacted] 60-1378	
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	82 days at -80°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
		Omeprazole	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	35 days at -20°C	88 days at -20°C	[redacted] 42-0510 Addendum 1	[redacted] 60-0632

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-183-0126	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	37 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] [redacted]180
		JTP-71051 (M4, GS-9200)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	37 days at -70°C	834 days at -70°C	[redacted] 60-1378	
		JTP-71081 (M1, GS-9202)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	37 days at -70°C	834 days at -70°C	[redacted] 60-1378	
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	37 days at -70°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
GS-US-183-0128	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -80°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	Gilead S-183-19V2
		JTP-71051 (M4, GS-9200)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -80°C	834 days at -70°C	[redacted] 60-1378	
		JTP-71081 (M1, GS-9202)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -80°C	834 days at -70°C	[redacted] 60-1378	
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -80°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
GS-US-183-0133	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	113 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1035
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	113 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 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-183-0140	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	59 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	Gilead S-183-24V1
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	59 days at -70°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
GS-US-183-0146	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	Gilead S_GSUS1830146_Plasma_V1
		JTP-71051 (M4, GS-9200)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -70°C	834 days at -70°C	[redacted] 60-1378	
		JTP-71081 (M1, GS-9202)	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -70°C	834 days at -70°C	[redacted] 60-1378	
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -70°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
		MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	48 days at -20°C	135 days at -20°C	[redacted] 42-0624 Addendum 3	[redacted] 60-0719A
		1′-OH MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	48 days at -20°C	135 days at -20°C	[redacted] 42-0624 Addendum 3	
		Ketoconazole	[redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	26 days at -20°C	58 days at -20°C	[redacted] 42-0719	[redacted] 60-0719B

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-183-1004	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	54 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1386
		GS-9200	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	54 days at -70°C	834 days at -70°C	[redacted] 60-1378	
GS-US-216-0101	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	146 days at -60°C to -80°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 6511-387
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	146 days at -60°C to -80°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
		MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	146 days at -60°C to -80°C	2143 days at -60°C to -80°C	[redacted] 8280288	
		1′-OH MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	146 days at -60°C to -80°C	2143 days at -60°C to -80°C	[redacted] 8280288	
GS-US-216-0107	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	51 days at -80°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	Gilead S_GSUS2160107_Plasma_V1

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-216-0112	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	60 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 60-1003A
		Desipramine	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	51 days at -20°C	122 days at -70°C	[redacted] 42-0319 Amendment 4	[redacted] 60-1003B
		Digoxin	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	57 days at -70°C	75 days at -70°C	[redacted] 42-1016	[redacted] 60-1003C
		EFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	60 days at -70°C	1301 days at -70°C	[redacted] 42-0827 Amendment 3	[redacted] 60-1003D
GS-US-216-0113	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	42 days at -80°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	Gilead S_GSUS2160113_PLASMA_V 1
GS-US-216-0116	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 60-0951A
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	39 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-0951B 60-0951C
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	24 days at -70°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	[redacted] 60-0951B
		MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	43 days at -70°C	2143 days at -60°C to -80°C	[redacted] 8280288	[redacted] 60-0951D
		1′-OH MDZ	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	43 days at -70°C	2143 days at -60°C to -80°C	[redacted] 8280288	

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-216-0120	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	35 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-0964
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	35 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	
GS-US-216-0121	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	345 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 60-0965A
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	16 days at -70°C	834 days -70°C	[redacted] 60-0811 Amendment 4	[redacted] 60-0965B
		Iohexol	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	398 days at -60°C to -80°C	1260 days -60°C to -80°C	[redacted] 2100-775 Addendum 7	[redacted] 8221988 and Addendum 1
GS-US-216-0122	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	21 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1031
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	21 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 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-216-0123	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	93 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1050A
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	93 days at -70°C	1297 days at –60°C to -80°C	[redacted] 6511-369 Addendum 2	
		Rosuvastatin	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	79 days at -70°C	175 days at -70°C	[redacted] 42-1043 Amendment 2	[redacted] 60-1050B
		ATV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -70°C	721 days at -70°C	[redacted] 42-0830 Amendment 2	[redacted] 60-1050C
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	61 days at -70°C	834 days at -70°C	[redacted] 60-0811 Amendment 4	
		Rifabutin	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	81 days at -70°C	332 days at -70°C	[redacted] 42-0724 Amendment 1	[redacted] 60-1050D
		25-O-Deacetyl Rifabutin	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	81 days at -70°C	332 days at -70°C	[redacted] 42-0724 Amendment 1	
GS-US-216-0124	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	126 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1109A
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	126 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 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-216-0125	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	253 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1124A
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	253 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	
		Methadone	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	259 days at -70°C	378 days at -70°C	[redacted] 42-1105 Amendment 2	[redacted] 60-1124B
		Buprenorphine	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	308 days at -70°C	391 days at -70°C	[redacted] 42-0217 Amendment 1	[redacted] 60-1124C
		Norbuprenorphine	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	308 days at -70°C	391 days at -70°C	[redacted] 42-0217 Amendment 1	
		Naloxone	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	343 days at -70°C	449 days at -70°C	[redacted] VS-00948-01 Amendment 1	[redacted] 60-1124D
GS-US-216-0134	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	36 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 60-1253A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	52 days at -70°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1253B
	Human Urine	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	54 days at -70°C	377 days at -70°C	[redacted] 60-1268 Amendment 2	[redacted] 60-1253C
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	54 days at -70°C	225 days at -70°C	[redacted] 60-1270 Amendment 2	[redacted] 60-1253D

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-216-0137	Human Plasma	Carbamazepine	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	26 days at -70°C	96 days at -70°C	[redacted] 42-1371	[redacted] 60-1395A
		Carbamazepine-10, 11-epoxide	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	26 days at -70°C	96 days at -70°C	[redacted] 42-1371	
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	47 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 60-1395B
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	47 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	
GS-US-236-0105	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	58 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-0850
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	65 days at -80°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	S_GSUS2360105_ GS9350_PLASMA_V1
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	65 days at -80°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	S_GSUS2360105_ FTC_TFV_PLASMA_V1
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	65 days at -80°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	

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-236-0106	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	113 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-0952A
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	113 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	
		Ethinyl Estradiol	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	151 days at -70°C	182 days at -70°C	[redacted] 42-0931 Amendment 1	[redacted] 60-0952B
		17-Desacetyl Noregestrimate	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	147 days at -70°C	153 days at -70°C	[redacted] 42-0728	[redacted] 60-0952C
GS-US-236-0110	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	49 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-0948A
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	49 days at -70°C	1297 days at –60°C to -80°C	[redacted] 6511-369 Addendum 2	
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	46 days at -70°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] 60-0948B
		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	

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-236-0120	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	95 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1136A
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	95 days at -70°C	1297 days at -60˚C to -80˚C	[redacted] 6511-369 Addendum 2	
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	95 days at -70°C	1426 days at -80˚C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] 60-1136B
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	95 days at -70°C	1092 days at -70˚C	[redacted] 60-1116 Amendment 3	
		EFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	51 days at -70°C	1301 days at -70˚C	[redacted] 42-0827 Amendment 3	[redacted] 60-1136C
GS-US-236-0135	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	111 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] [redacted] 232B
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	111 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	114 days at -70°C	1426 days at -80°C	V_FTC_TFV_ HUMAN_AND_ CANINE_PLASMA _V9 (15401v9)	[redacted] [redacted] 232C
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	114 days at -70°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Transpired Time[a]	Supporting LTSS Data	Most Current Validation Report[b]	Sample Analysis Report
		ATV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	146 days at -70°C	721 days at -70°C	[redacted] 42-0830 Amendment 2	[redacted] [redacted] 232A
		RTV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	146 days at -70°C	721 days at -70°C	[redacted] 60-0811 Amendment 4	
		TVR	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	110 days at -70°C	98 days at -70°C[c]	[redacted] 164 Amendment 1	[redacted] [redacted] 232D
GS-US-292-0101	Human Plasma	COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	81 days at -70°C	1297 days at –60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 60-1119A
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	81 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]	88 days at -70°C	1297 days at –60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[redacted] 60-1119B
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	88 days at -70°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	
		TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	67 days at -70°C	520 days at -70°C	[redacted] 60-1115 Amendment 4	[redacted] 60-1119C
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	86 days at -70°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1119D

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-292-0102	Human Plasma	TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	446 days at –70°C	520 days at -70°C	[redacted] 60-1115 Amendment 4	[redacted] 60-1222A
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	446 days at –70°C[c]	1092 days at -70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1222B
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	452 days at -70°C	1297 days at -60°C to -80°C	[redacted] 6511-369 Addendum 2	[redacted] 60-1222C
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	452 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]	444 days at -70°C	1297 days at –60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[redacted] 60-1222D
		FTC-TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	194 days at -70°C	340 days at -70°C	[redacted] 42-0831 Amendment 5	[redacted] 60-1222E
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 4	[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] 6511-369 Addendum 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	
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	45 days at -70°C	1297 days at -60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[redacted] 60-1142D

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-292-0104	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 4	[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
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 4	[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	1297 days at –60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[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] 6511-369 Addendum 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	

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-292-0108	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] 6511-369 Addendum 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	1297 days at -60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[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 4	[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
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 4	[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 4	[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

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-292-0111	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 4	[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
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 4	[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	1297 days at –60°C to -80◦C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[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] 6511-369 Addendum 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 Addendum 7	[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 4	[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	1297 days at -60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[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] 6511-369 Addendum 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
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 4	[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	1297 days at -60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[redacted] 60-1125C
		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] 6511-369 Addendum 2	[redacted] 60-1125F

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	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	47 days at -70°C	813 days at -70°C	[redacted] 60-1323 Amendment 1	[redacted] 60-1390A
		GS-566500	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	47 days at -70°C	497 days at -70°C	[redacted] 60-1323 Amendment 1	
		GS-331007	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	47 days at -70°C	813 days at -70°C	[redacted] 60-1323 Amendment 1	
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	54 days at -70°C	1297 days at -60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[redacted] 60-1390B
		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	
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	46 days at -70°C	1297 days at -60°C to -80°C	V_FTC_TFV_HUMAN_AND_CANINE_PLASMA_V9 (15401v9)	[redacted] 60-1390C
		TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	57 days at -70°C	520 days at -70°C	[redacted] 60-1115 Amendment 4	[redacted] 60-1390G
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	44 days at -70°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1390H
		EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	50 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 60-1390I
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	50 days at -70°C	1297 days –60°C to –80°C	[redacted] 6511-369 Addendum 2	
		GS-5816	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	26 days at -70°C	570 days at -70°C	[redacted] [redacted] 102 Amendment 1	[redacted] [redacted] 278

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-344-0102	Human Plasma	EVG	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	100 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 5	[redacted] 159G
		COBI	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	100 days at -70°C	1297 days at –60°C to -80°C	[redacted] 6511-369 Addendum 2	
		SOF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	142 days at -70°C	813 days at -70°C	[redacted] 60-1323 Amendment 1	[redacted] 159H Amendment 1
		GS-566500	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	142 days at -70°C	497 days at -70°C	[redacted] 60-1323 Amendment 1	
		GS-331007	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	142 days at -70°C	813 days at -70°C	[redacted] 60-1323 Amendment 1	
		LDV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	195 days at -70°C	623 days at -70°C	[redacted] 60-1028 Amendment 3	[redacted] 159I

1'-OH MDZ = midazolam metabolite (1′-hydroxymidazolam); ATV = atazanavir; COBI = cobicistat; CSR = clinical study report; DRV = darunavir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LDV = LTSS = long-term storage stability; MDZ = midazolam; RTV = ritonavir; [redacted]
SOF = sofosbuvir; TAF = tenofovir alafenamide; TFV = tenofovir; TVR = telaprevir

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.

c All study samples were analyzed for TVR within the established LTSS of 98 days at -70°C.

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

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

4.6.1. Determination of GS-5816 in Human Plasma

The bioanalytical method for quantitation of GS-5816 in human plasma was developed and validated at [redacted] This method involved liquid-liquid precipitation extraction of GS-5816 and internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized Appendix Table 1.

Appendix Table 1. Bioanalytical Method Validation for Determination of GS-5816 in Human Plasma at [redacted]

	GS-5816
Linear 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]102 Amendment 1

4.6.2. Determination of LDV in Human Plasma

A bioanalytical method for determination of ledipasvir (LDV) in human plasma was validated at [redacted] The method involved liquid-liquid extraction of LDV and internal standard ([redacted]) from human plasma followed by LC/MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 2.

Appendix Table 2. Bioanalytical Method Validation for Determination of LDV in Human Plasma at [redacted]

	LDV
Linear Range (ng/mL)	1 to 2000
LLOQ (ng/mL)	1
Interassay Precision Range (%CV)	1.4% to 3.2%
Interassay Accuracy Range (%RE)	0.0% to 2.8%
Studies Supported	GS-US-344-0102

LDV = ledipasvir
Source: [redacted]209

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

The bioanalytical method for simultaneous quantitation of sofosbuvir (SOF) and its 2 metabolites, GS-566500 and GS-331007, in human plasma was developed and validated at [redacted] This method involved protein precipitation extraction of SOF, GS-566500, and GS-331007 and internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 3.

Appendix Table 3. Bioanalytical Method Validation for Determination of SOF, GS-566500, and GS-331007 in Human Plasma at [redacted]

	SOF	GS-566500	GS-331007
Linear Range (ng/mL)	5 to 2500	10 to 5000	10 to 5000
Lower Limit of Quantitation (ng/mL)	5	10	10
Interassay Precision Range (%CV)	2.4% to 9.7%	5.1% to 7.7%	2.5% to 7.2%
Interassay Accuracy Range (%RE)	-5.1% to 3.4%	-2.2% to 2.9%	-1.0% to 2.5%
Studies Supported	GS-US-342-1167		

SOF = sofosbuvir
Source: [redacted] 60-1323 Amendment 1

The bioanalytical method for simultaneous quantitation of SOF, GS-566500, and GS-331007, in human plasma was also developed and validated at [redacted] This method involved protein precipitation extraction of SOF, GS-566500, and GS-331007 and internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 4.

Appendix Table 4. Bioanalytical Method Validation for Determination of SOF, GS-566500, and GS-331007 in Human Plasma at [redacted]

	SOF	GS-566500	GS-331007
Linear Range (ng/mL)	5 to 5000	8.70 to 4350	10 to 5000
LLOQ (ng/mL)	5	8.70	10
Interassay Precision Range (%CV)	0.0% to 1.4%	0.0% to 1.3%	0.0% to 3.5%
Interassay Accuracy Range (%RE)	0.0% to 3.5%	0.0% to 3.5%	-2.0% to 1.0%
Studies Supported	GS-US-344-0102		

Source: [redacted] 103 Amendment 2

4.6.4. Determination of ATV in Human Plasma

A commercially available atazanavir (ATV) bioanalytical method was developed at [redacted] for the simultaneous determination of ATV and RTV. The LC-MS/MS 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. Method validation parameters are summarized in Appendix Table 5.

Appendix Table 5. Bioanalytical Method Validation for Determination of ATV in Human Plasma at [redacted]

	ATV	RTV
Linear 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-216-0123	

ATV = atazanavir; RTV = ritonavir
Source: [redacted] 42-0830 Amendment 2

4.6.5. Determination of ATV and RTV in Human Plasma

A commercial bioanalytical method for simultaneous determination of ATV and RTV in human plasma was validated at [redacted] This method involved liquid-liquid extraction of RTV and ATV and internal standards ([redacted] and [redacted] respectively) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 6.

Appendix Table 6. Bioanalytical Method Validation for Determination of ATV and RTV in Human Plasma at [redacted]

	ATV	RTV
Linear Range (ng/mL)	10 to 5000	5 to 2500
Lower Limit of Quantitation (ng/mL)	10	5
Interassay Precision Range (%CV)	2.3% to 3.0%	2.4% to 3.4%
Interassay Accuracy Range (%RE)	-2.0% to -1.5%	-3.0% to -1.8%
Studies Supported	GS-US-236-0135	

ATV = atazanavir; RTV = ritonavir
Source: [redacted] 204

4.6.6. Determination of BUP and norBUP in Human Plasma

A bioanalytical method for the simultaneous determination of buprenorphine (BUP) and norbuprenorphine (norBUP) in human plasma was developed and validated at [redacted]. This method involved liquid-liquid extraction of BUP and norBUP and internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 7.

Appendix Table 7. Bioanalytical Method Validation for Determination of BUP and norBUP in Human Plasma at [redacted]

	BUP	norBUP
Linear Range (ng/mL)	20 to 5000	20 to 5000
Lower Limit of Quantitation (ng/mL)	20	20
Interassay Precision Range (%CV)	3.8% to 7.2%	5.2% to 9.0%
Interassay Accuracy Range (%RE)	-3.3% to 3.5%	-3.7% to 10.5%
Studies Supported	GS-US-216-0125	

BUP = buprenorphine; norBUP = norbuprenorphine
Source: [redacted] 42-0217 Amendment 1

4.6.7. Determination of Carbamazepine and Carbamazepine-10,11-Epoxide in Human Plasma

A commercial bioanalytical method for determination of carbamazepine and carbamazepine-10,11-epoxide in human plasma was developed and validated at [redacted]. This method involved protein precipitation extraction of carbamazepine and carbamazepine-10,11-epoxide and internal standards ([redacted] and [redacted], respectively) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 8.

Appendix Table 8. Bioanalytical Method Validation for Determination of Carbamazepine and Carbamazepine-10,11-Epoxide in Human Plasma at [redacted]

	Carbamazepine	Carbamazepine-10,11-Epoxide
Linear Range (ng/mL)	20 to 20,000	5 to 5000
Lower Limit of Quantitation (ng/mL)	20	5
Interassay Precision Range (%CV)	2.8% to 6.0%	3.6% to 5.2%
Interassay Accuracy Range (%RE)	-1.3% to 6.4%	-3.5% to 4.7%
Studies Supported	GS-US-216-0137	

Source: [redacted] 42-1371

4.6.8. Determination of Desipramine in Human Plasma

A commercially available desipramine bioanalytical method involving the extraction of desipramine 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]. Method validation parameters are summarized in Appendix Table 9.

Appendix Table 9. Bioanalytical Method Validation for Determination of Desipramine in Human Plasma at [redacted]

	Desipramine
Linear Range (ng/mL)	1 to 2000
Lower Limit of Quantitation (ng/mL)	1
Interassay Precision Range (%CV)	1.5% to 13.8%
Interassay Accuracy Range (%RE)	-1.9% to -9.7%
Studies Supported	GS-US-216-0112

Source: [redacted] 42-0319 Amendment 4

4.6.9. Determination of Digoxin in Human Plasma

A commercially available digoxin bioanalytical method involving the extraction of digoxin and its internal standard ([redacted]) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Method validation parameters are summarized in Appendix Table 10.

Appendix Table 10. Bioanalytical Method Validation for Determination of Digoxin in Human Plasma at [redacted]

	Digoxin
Linear Range (pg/mL)	100 to 30,000
Lower Limit of Quantitation (pg/mL)	100
Intraassay Precision Range (%CV)	0.9% to 6.1%[a]
Intraassay Accuracy Range (%RE)	-6.0% to 7.2%
Studies Supported	GS-US-216-0112

a Intraassay data
Source: [redacted] 42-1016

4.6.10. 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. Method validation parameters are summarized in Appendix Table 11.

Appendix Table 11. Bioanalytical Method Validation for Determination of EFV in Human Plasma at [redacted]

	EFV
Linear 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-216-0112, GS-US-236-0120, and GS-US-311-0101

EFV = efavirenz
Source: [redacted] 42-0827 Amendment 3

4.6.11. Determination of Ethinyl Estradiol in Human Plasma

A commercially available ethinyl estradiol method involving the extraction of ethinyl estradiol and its internal standard ([redacted]) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted] Method validation parameters are summarized in Appendix Table 12.

Appendix Table 12. Bioanalytical Method Validation for Determination of Ethinyl Estradiol in Human Plasma at [redacted]

	Ethinyl Estradiol
Linear Range (pg/mL)	2.5 to 500
Lower Limit of Quantitation (pg/mL)	2.5
Interassay Precision Range (%CV)	3.8% to 7.9%
Interassay Accuracy Range (%RE)	-4.1% to 1.2%
Studies Supported	GS-US-236-0106

Source: [redacted] 42-0931 Amendment 1

4.6.12. 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] Method validation parameters are summarized in Appendix Table 13.

Appendix Table 13. Bioanalytical Method Validation for Determination of Iohexol in Human Plasma at [redacted]

	Iohexol
Linear 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-216-0121, GS-US-292-0112

Source: [redacted] 2100-775 and Addendum 7

4.6.13. Determination of Ketoconazole in Human Plasma

A commercially available ketoconazole bioanalytical method involving the extraction of ketoconazole and its internal standard ([redacted]) from human plasma using a protein precipitation extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted] Method validation parameters are summarized in Appendix Table 14.

Appendix Table 14. Bioanalytical Method Validation for Determination of Ketoconazole in Human Plasma at [redacted]

	Ketoconazole
Linear Range (ng/mL)	20 to 10,000
Lower Limit of Quantitation (ng/mL)	20
Interassay Precision Range (%CV)	5.9% to 9.9%
Interassay Accuracy Range (%RE)	-8.9% to -0.8%
Studies Supported	GS-US-183-0146

Source: [redacted] 42-0719

4.6.14. Determination of 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] Method validation parameters are summarized in Appendix Table 15.

Appendix Table 15. Bioanalytical Method Validation for Determination of MDZ and 1′-OH MDZ in Human Plasma at [redacted]

	MDZ	1′-OH MDZ
Linear 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-183-0146 and GS-US-216-0116	

1'-OH MDZ = midazolam metabolite (1′-hydroxymidazolam); MDZ = midazolam
Source: [redacted] 42-0624 Addendum 3

A commercially available MDZ bioanalytical method was also developed and validated at [redacted] for determination of MDZ and 1′-OH MDZ concentrations in human plasma. Method validation parameters are summarized in Appendix Table 16.

Appendix Table 16. Bioanalytical Method Validation for Determination of MDZ and 1'-OH MDZ in Human Plasma at [redacted]

	MDZ	1′-OH MDZ
Linear 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)	4.9% to 7.9%	3.4% to 7.5%
Interassay Accuracy Range (%RE)	-4.4% to 6.0%	-8.3% to 1.3%
Studies Supported	GS-US-216-0101	

1'-OH MDZ = midazolam metabolite (1′-hydroxymidazolam); MDZ = midazolam
Source: [redacted] 2100-229

4.6.15. Determination of Methadone in Human Plasma

A bioanalytical method for the simultaneous determination of (R)-(+)-methadone and (S)-(-)-methadone in human plasma was developed and validated at [redacted] This method involved the liquid-liquid extraction of (R)-(+)-methadone and (S)-(–)-methadone and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 17.

Appendix Table 17. Bioanalytical Method Validation for Determination of (R)-(+)-Methadone and (S)-(–)-Methadone in Human Plasma

	(R)-(+)-Methadone	(S)-(–)-Methadone
Linear 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)	0.7% to 4.5%	0.6% to 7.8%
Interassay Accuracy Range (%RE)	-11% to -0.1%	-10.4% to -5.7%
Studies Supported	GS-US-216-0125	

Source: [redacted] 42-1105 Amendment 2

4.6.16. Determination of NLX in Human Plasma

A commercial naloxone (NLX) bioanalytical method for the determination of NLX in human plasma was developed and validated at [redacted] This method involved liquid-liquid extraction of NLX and its internal standard ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 18.

Appendix Table 18. Bioanalytical Method Validation for Determination of NLX in Human Plasma

	NLX
Linear Range (ng/mL)	20 to 2000
Lower Limit of Quantitation (ng/mL)	20
Interassay Precision Range (%CV)	15.7% at LLOQ and 4.0% to 7.2% above LLOQ
Interassay Accuracy Range (%RE)	-6.3% at LLOQ and -8.2% to -1.3% above LLOQ
Studies Supported	GS-US-216-0125

NLX = naloxone
Source: [redacted] VS-00948

4.6.17. Determination of Omeprazole in Human Plasma

A commercially available omeprazole bioanalytical method involving the extraction of omeprazole 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] Method validation parameters are summarized in Appendix Table 19.

Appendix Table 19. Bioanalytical Method Validation for Determination of Omeprazole in Human Plasma at [redacted]

	Omeprazole
Linear Range (ng/mL)	20 to 2000
Lower Limit of Quantitation (ng/mL)	20
Interassay Precision Range (%CV)	5.1% to 12.5%
Interassay Accuracy Range (%RE)	-5.8% to 5.5%
Studies Supported	GS-US-183-0119

Source: [redacted] 42-0510 Addendum 1

4.6.18. Determination of Rifabutin in Human Plasma

A commercially available rifabutin and metabolite 25-O-desacetyl rifabutin bioanalytical method involving the extraction of rifabutin, 25-O-desacetyl rifabutin, and internal standard ([redacted]) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted] Method validation parameters are summarized in Appendix Table 20.

Appendix Table 20. Bioanalytical Method Validation for Determination of Rifabutin and 25-O-Desacetyl rifabutin in Human Plasma at [redacted]

	Rifabutin	25-O-Desacetyl rifabutin
Linear Range (ng/mL)	1 to 1000	1 to 1000
Lower Limit of Quantitation (ng/mL)	1	1
Interassay Precision Range (%CV)	4.2% to 9.4%	3.8% to 9.3%
Interassay Accuracy Range (%RE)	-4.3% to 3.9%	-6.7% to 5.0%
Studies Supported	GS-US-216-0123	

Source: [redacted] 42-0724 Amendment 1

4.6.19. Determination of RTV in Human Plasma

A commercial [redacted] RTV bioanalytical method involving the extraction of RTV and its internal standard ([redacted]) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted] Method validation parameters are summarized in Appendix Table 21.

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

	RTV
Linear Range (ng/mL)	1 to 1000
Lower Limit of Quantitation (ng/mL)	1
Interassay Precision Range (%CV)	6.4% to 7.4%
Interassay Accuracy Range (%RE)	-7.7% to 1.6%
Studies Supported	GS-US-183-0102

RTV = ritonavir
Source: [redacted] 42-0316 and Addendum 1

A second commercial [redacted] stand-alone RTV bioanalytical method involving the extraction of RTV and its internal standard ([redacted]) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was also developed and validated at [redacted] Method validation parameters are summarized in Appendix Table 22.

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

	RTV
Linear Range (ng/mL)	10 to 2000
Lower Limit of Quantitation (ng/mL)	10
Interassay Precision Range (%CV)	7.1% to 10.3%
Interassay Accuracy Range (%RE)	-3.7 % to 5.7%
Studies Supported	GS-US-216-0101

RTV = ritonavir
Source: [redacted] 2100-620 and 2100-371

The commercial [redacted] RTV bioanalytical method was validated at [redacted] for the simultaneous determination of RTV and ATV in human plasma using the stable isotope labeled internal standard ([redacted] and [redacted] respectively). The method involved protein precipitation extraction followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 23.

Appendix Table 23. Bioanalytical Method Validation for Determination of RTV and ATV in Human Plasma at [redacted]

	RTV	ATV
Linear Range (ng/mL)	5 to 2500	10 to 5000
Lower Limit of Quantitation (ng/mL)	5	10
Interassay Precision Range (%CV)	4.0% to 8.4%	3.8% to 5.5%
Interassay Accuracy Range (%RE)	-6.6 % to -0.5%	-2.4 % to -0.1%
Studies Supported	GS-US-216-0123 GS-US-216-0121 (RTV only)	

ATV = atazanavir; RTV = ritonavir
Source: [redacted] 42-0830 Amendment 2

4.6.20. Determination of Rosuvastatin in Human Plasma

A commercially available rosuvastatin bioanalytical method involving the extraction of rosuvastatin and its internal standard ([redacted]) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted] Method validation parameters are summarized in Appendix Table 24.

Appendix Table 24. Bioanalytical Method Validation for Determination of Rosuvastatin in Human Plasma at [redacted]

	Rosuvastatin
Linear Range (ng/mL)	0.05 to 50
Lower Limit of Quantitation (ng/mL)	0.05
Interassay Precision Range (%CV)	1.9% to 5.7%
Interassay Accuracy Range (%RE)	1.2% to 6.0%
Studies Supported	GS-US-216-0123

Source: [redacted] 42-1043 Amendment 2

4.6.21. 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] Method validation parameters are summarized in Appendix Table 25.

Appendix Table 25. Bioanalytical Method Validation for Determination of Sertraline in Human Plasma at [redacted]

	Sertraline
Linear 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

4.6.22. Determination of 17-Desacetyl Norgestimate in Human Plasma

A commercially available 17-desacetyl norgestimate bioanalytical method involving the extraction of 17-desacetyl norgestimate and its internal standard ([redacted]) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted] Method validation parameters are summarized in Appendix Table 26.

Appendix Table 26. Bioanalytical Method Validation for Determination of 17-Desacetyl Norgestimate in Human Plasma at [redacted]

	17-Desacetyl Norgestimate
Linear Range (pg/mL)	20 to 10,000
Lower Limit of Quantitation (pg/mL)	20
Interassay Precision Range (%CV)	2.3% to 8.0%
Interassay Accuracy Range (%RE)	-5.2% to 3.1%
Studies Supported	GS-US-236-0106

Source: [redacted] 42-0728

4.6.23. Determination of TVR in Human Plasma

A commercial bioanalytical method for simultaneous determination of TVR in human plasma was developed and validated at [redacted] This method involved protein-precipitation extraction of TVR and internal standards ([redacted]) from human plasma followed by LC-MS/MS with positive ionization. Method validation parameters are summarized in Appendix Table 27.

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

	TVR
Linear Range (ng/mL)	10 to 5000
Lower Limit of Quantitation (ng/mL)	10
Interassay Precision Range (%CV)	1.1% to 1.5%
Interassay Accuracy Range (%RE)	8.0% to 10.5%
Studies Supported	GS-US-236-0135

TVR = telaprevir
Source: [redacted]164 Amendment 1

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SECTION 2.7.2— SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (E/C/F/TAF FDC)

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.2— SUMMARY OF CLINICAL PHARMACOLOGY STUDIES 1
TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 3
LIST OF IN-TEXT FIGURES 8
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 11
PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS 18
1. BACKGROUND AND OVERVIEW 19
1.1. Human Biomaterials Studies 20
1.2. Clinical Pharmacology Studies 20
1.2.1. E/C/F/TAF 21
1.2.2. F/TAF 25
1.2.3. TAF 26
1.2.4. EVG 28
1.2.5. COBI 31
1.2.6. EVG+COBI 35
1.2.7. FTC 35
1.2.8. STB 38
1.3. Bioanalytical Methods 39
1.4. Absorption, Distribution, Metabolism, and Elimination 40
1.5. Population Pharmacokinetics 40
1.5.1. TAF 40
1.5.2. EVG 41
1.5.3. COBI 41
1.5.4. FTC 41
1.6. Pharmacokinetics/Pharmacodynamics 42
1.7. Virology 42
1.7.1. Nonclinical Virology 42
1.7.2. Clinical Virology 42
2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES 43
2.1. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials 43
2.2. Studies in Healthy Subjects 43
2.2.1. E/C/F/TAF 43
2.2.2. TAF 54
2.3. Studies in HIV-Infected Subjects 61
2.3.1. TAF 61
2.4. Intrinsic Factor Pharmacokinetic Studies 67
2.4.1. E/C/F/TAF 67
2.4.2. TAF 70
2.4.3. EVG 78
2.5. Extrinsic Factor Pharmacokinetic Studies/Drug-Drug Interaction Pharmacokinetic Studies 80
2.5.1. E/C/F/TAF 80
2.5.2. F/TAF 86
2.5.3. EVG+COBI 93
3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES 97
3.1. ADME Characteristics 98
3.1.1. Absorption 98
3.1.2. Distribution 103

3.1.3. Metabolism and Elimination 105
3.2. Pharmacokinetics 124
3.2.1. Pharmacokinetic Profile 124
3.2.2. Effect of Intrinsic Factors 140
3.2.3. Effect of Extrinsic Factors 159
3.3. Pharmacokinetics/Pharmacodynamics 170
3.3.1. Pharmacokinetic-Pharmacodynamic Relationship for Efficacy Parameters 170
3.3.2. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters 184

4. VIROLOGY SUMMARY 205

4.1. Nonclinical Virology 205
4.1.1. Primary Pharmacodynamics 205
4.1.2. Secondary Pharmacodynamics 273
4.1.3. Pharmacodynamic Drug Interactions 284
4.1.4. Discussion and Conclusions 292
4.2. Clinical Virology 297
4.2.1. Virology Resistance Analyses at Baseline and in the Resistance Analysis Population from Phase 2 and 3 Studies 299
4.2.2. Integrated Virology Analyses at Baseline and in Subjects Experiencing Virologic Failure 329
4.2.3. Conclusions 341

5. REFERENCES 342

6. APPENDIX 355

6.1. Tabular Summary of Clinical Pharmacology Studies 356
6.1.1. E/C/F/TAF 356
6.1.2. F/TAF 360
6.1.3. TAF 361
6.1.4. EVG 363
6.1.5. COBI 368
6.1.6. EVG+COBI 373
6.1.7. FTC 380
6.1.8. STB 385
6.2. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses 388
6.3. Tabular Summary of Nonclinical Virology Studies 398
6.3.1. TAF Tabular Summary of Nonclinical Virology Studies 398
6.3.2. EVG, COBI, and STB Tabular Summary of Nonclinical Virology Studies 400
6.3.3. FTC Tabular Summary of Nonclinical Virology Studies 405
6.3.4. TDF Tabular Summary of Nonclinical Virology Studies 410
6.3.5. FTC/TDF Tabular Summary of Nonclinical Virology Studies 416

LIST OF IN-TEXT TABLES

Table 1. Overview of E/C/F/TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology 23
Table 2. Overview of F/TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology 26
Table 3. Overview of TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology 27
Table 4. Overview of EVG Clinical Studies Contributing Information to the Summary of Clinical Pharmacology 29
Table 5. Overview of COBI Clinical Studies Contributing Information to the Summary of Clinical Pharmacology 32

Table 6. Overview of FTC Clinical Studies Contributing Information to the Summary of Clinical Pharmacology 36
Table 7. Overview of STB Clinical Studies Contributing Information to the Summary of Clinical Pharmacology 39
Table 8. Studies Used in the Population PK Analysis of E/C/F/TAF 40
Table 9. Clinical Studies Supporting the Clinical Pharmacology of E/C/F/TAF Listed by Study Type and by Individual Components of E/C/F/TAF 97
Table 10. Mean Urinary Recovery and Renal Clearance Estimates for FTC 102
Table 11. Percent of Total ^{14}C-Radioactivity Present as [^{14}C]TAF Metabolites in Pooled Feces From All Sampling Intervals by HPLC 108
Table 12. Percent of Total ^{14}C-Radioactivity Present as [^{14}C]TAF Metabolites in Pooled Urine From All Sampling Intervals by HPLC 109
Table 13. Percentage of Total ^{14}C-Radioactivity Present as [^{14}C]EVG Metabolites in Pooled Urine from All Sampling Intervals by HPLC Radiochemical Analysis 111
Table 14. Percentage of Total ^{14}C-Radioactivity Present as [^{14}C]COBI Metabolites in Pooled Feces from All Sampling Intervals by HPLC 114
Table 15. Percentage of Total ^{14}C-Radioactivity Present as [^{14}C]COBI Metabolites in Pooled Urine from All Sampling Intervals by HPLC 115
Table 16. Effect of COBI and RTV on Various Activities Catalyzed by Human Hepatic Microsomal CYP3A Enzymes 120
Table 17. IC_{50} Values for Inhibition of Major Human Cytochrome P450 Enzymes by COBI, RTV, and Positive Control Inhibitors 121
Table 18. Transporter Substrate Assessment of E/C/F/TAF Components 122
Table 19. Transporter Inhibition Assessment of E/C/F/TAF Components 123
Table 20. Single- and Multiple-Dose PK of TAF Following Administration of TAF as a Single Agent or as E/C/F/TAF in Healthy Subjects 125
Table 21. Single- and Multiple-Dose PK of TFV Following Administration of TAF as a Single Agent or as E/C/F/TAF in Healthy Subjects 125
Table 22. GS-US-292-0104 and GS-US-292-0111: Statistical Comparisons of TFV PK Parameter Estimates Between E/C/F/TAF and STB in Pooled Phase 3 Studies (PK Substudy Analysis Set) 126
Table 23. GS-US-292-0104 and GS-US-292-0111: Statistical Comparisons of TFV-DP PK Parameter Estimate Between E/C/F/TAF and STB in Pooled Phase 3 Studies (PK Substudy Analysis Set) 127
Table 24. Single- and Multiple-Dose (Twice Daily) PK of EVG 100 mg Following Administration Alone or in Combination with RTV 100 mg in Healthy Subjects 128
Table 25. Single- and Multiple-Dose (Once Daily) PK of EVG Administered as EVG+RTV Using the Phase 2 (125 mg) or Phase 3 (150 mg) Formulations in Healthy Subjects 129
Table 26. Single- and Multiple-Dose (Once Daily) PK of EVG Administered as STB Using the Phase 3 Formulation in Healthy Subjects 129
Table 27. Summary of EVG PK Parameters Across the EVG+RTV Dose Range 130
Table 28. Summary of EVG PK Parameters Following STB or E/C/F/TAF Administration 130
Table 29. COBI Single-Dose PK in Healthy Subjects from Studies GS-US-216-0101 and GS-US-216-0113 131
Table 30. COBI Multiple-Dose PK in Healthy Subjects from Studies GS-US-216-0101 and GS-US-216-0113 132
Table 31. Summary of COBI PK Parameters Following STB or E/C/F/TAF Administration 132
Table 32. Single-Dose PK of FTC 200 mg Administered as the Capsule Formulation in Healthy and HIV-Infected Subjects 133
Table 33. Summary of Steady-State PK Parameter Estimates for FTC Following 200 mg Once-Daily Dose 134
Table 34. Summary of FTC PK Parameters Following STB or E/C/F/TAF Administration 134
Table 35. TAF PK Parameters After Once-Daily Administration of E/C/F/TAF in Healthy or HIV-Infected Subjects 138

Table 36. TFV PK Parameters After Once-Daily Administration of E/C/F/TAF in Healthy or HIV-Infected Subjects 138
Table 37. Steady-State EVG PK Parameters After Once-Daily Administration of STB in HIV-Infected Subjects in STB Phase 2 and Phase 3 Studies or in Healthy Subjects from Study GS-US-236-0110 138
Table 38. Steady-State COBI PK After Once-Daily Administration of STB in HIV-Infected Subjects from Intensive PK Substudies of STB Phase 2 and Phase 3 Studies or in Healthy Subjects from Study GS-US-236-0110 139
Table 39. Summary of Steady-State PK Parameter Estimates for FTC Following 200 mg Once-Daily Dose 140
Table 40. Statistical Comparisons of TAF PK Parameters in Subjects with Severe Renal Impairment or Normal Renal Function 141
Table 41. Statistical Comparisons of TFV PK Parameters in Subjects with Severe Renal Impairment or Normal Renal Function 141
Table 42. TAF PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects by Renal Function 142
Table 43. TFV PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects by Renal Function 142
Table 44. Mean (%CV) EVG Exposure by HBV or HCV Coinfection Following Administration of STB in HIV-Infected Subjects 146
Table 45. Summary of Steady-State PK Parameter Estimates for FTC Following 200 mg Once-Daily Dose in Various Populations 148
Table 46. TAF PK Parameters by Age Group After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects (Population PK Analysis from Phase 2 and 3 Studies) 149
Table 47. TFV PK Parameters by Age Group After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects (Population PK Analysis from Phase 2 and 3 Studies) 149
Table 48. Mean (%CV) TAF Exposure Across Weight Ranges Following Administration of E/C/F/TAF in HIV-Infected Subjects 150
Table 49. Mean (%CV) TFV Exposure Across Weight Ranges Following Administration of E/C/F/TAF in HIV-Infected Subjects 151
Table 50. Mean (%CV) EVG Exposures Across Quartiles of Body Surface Area Following Administration of STB in HIV-Infected Subjects 151
Table 51. Mean (%CV) TAF Exposure by Race Following Administration of E/C/F/TAF in HIV-Infected Subjects 152
Table 52. Mean (%CV) TFV Exposure by Race Following Administration of E/C/F/TAF in HIV-Infected Subjects 153
Table 53. Mean (%CV) EVG Exposure by Race Following Administration of STB in HIV-Infected Subjects 153
Table 54. Mean (%CV) COBI Exposure by Race Following Administration of COBI in Healthy Subjects and HIV-Infected Subjects 154
Table 55. Multiple-Dose TAF Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects 154
Table 56. Multiple-Dose TFV Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects 155
Table 57. TAF PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Adolescent and Adult Subjects 155
Table 58. TFV PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Adolescent and Adult Subjects 155
Table 59. Multiple-Dose EVG Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects 156
Table 60. Multiple-Dose COBI Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects 156
Table 61. Multiple-Dose FTC Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects 157

Table 62. Mean (%CV) TAF Exposure by Sex Following Administration of E/C/F/TAF in HIV-Infected Subjects 157
Table 63. Mean (%CV) TFV Exposure by Sex Following Administration of E/C/F/TAF in HIV-Infected Subjects 158
Table 64. Mean (%CV) EVG Exposure by Sex Following Administration of STB in HIV-Infected Subjects 158
Table 65. Mean (%CV) COBI Exposure by Sex Following Administration of COBI in Healthy Subjects and HIV-Infected Subjects 158
Table 66. Drug Interaction Information for E/C/F/TAF with Potential Concomitant Drugs 164
Table 67. Percentage of Virologic Success at Week 48 Across Quartiles of TAF Exposure (TAF PK/PD Analysis Set) 172
Table 68. Percentage of Pure Virologic Responders Across Quartiles of EVG Exposure (N = 373) (EVG PK/PD Analysis Set) 175
Table 69. Summary of MDZ PK Parameters Across Treatments (PK Analysis Set) 179
Table 70. Single-Dose MDZ PK Parameters Following Coadministration with COBI or RTV in Study GS-US-216-0101 and Historical Data with RTV and/or Other CYP3A Inhibitors 180
Table 71. Metabolism of 10 μM TFV Either Alone or in Combination with 10 μM ABC 206
Table 72. Metabolism of 10 μM ABC Either Alone or in Combination with 10 μM TFV 206
Table 73. TFV and Metabolites in Selected Lymph Nodes of a Monkey 48 Hours After Administration of a Single Dose of [^{14}C]TFV 208
Table 74. Kinetic Inhibition Constants of TFV-DP Against HIV-1 Reverse Transcriptase 209
Table 75. TAF Antiviral Activity Against Primary HIV-1 Isolates 210
Table 76. Characteristics and Drug Susceptibilities of Selected Viruses 212
Table 77. Initial Drug Concentrations Used in Selection Experiments 213
Table 78. Characteristics and Drug Susceptibilities of Selected Viruses 215
Table 79. Replication Capacity of Primary HIV-1 Isolates Without Protease Inhibitor Resistance 217
Table 80. Antiviral Susceptibilities of Molecular Clones of HIV-1 Expressing Nucleoside-Associated Resistance Mutations in Reverse Transcriptase 218
Table 81. Phenotypic Susceptibilities of 24 Recombinant HIV-1 Isolates with NRTI Mutations Against TAF and TFV 220
Table 82. Drug Susceptibilities of Nucleoside-Resistant Primary HIV-1 Isolates 222
Table 83. TAF Antiviral Activity Against Primary HIV-2 Isolates 224
Table 84. Genotypic and Phenotypic Characteristics of the Viral Isolates 225
Table 85. Time to Viral Breakthrough 226
Table 86. TAF Antiviral Activity Against Drug-Resistant Primary HIV-1 Isolates 227
Table 87. Anti-HIV Activity (EC_{50}) and Cytotoxicity (CC_{50}) of TAF, TFV, and TDF 228
Table 88. Inhibitory Activity of EVG Against Recombinant HIV-1 Integrase 230
Table 89. Kinetic Constants for EVG and RAL Binding and Dissociation with Integrase-DNA Complexes 232
Table 90. Effects of EVG on the Generation of Full-Length, Integrated, and 2-LTR Circle Forms of HIV-1 DNA in Infected MT-4 Cells 233
Table 91. Effects of EVG on the Accumulation of Late-RT and Alu-PCR Products in Single-Cycle HIV-1 Vector-Infected SupT1 Cells 234
Table 92. Antiviral Activity of EVG and Control Compounds Against Wild-Type HIV-1 in T-Lymphocytoid Cell Lines 234
Table 93. Anti-HIV-1 Activity of EVG and Control Compounds Against HIV-1 M-tropic Laboratory Strains in Monocyte/Macrophage Cells 235
Table 94. Anti-HIV Activity of EVG and Control Compounds Against 8 Subtypes of HIV-1 Clinical Isolates and an HIV-2 Isolate in PBMCs 236
Table 95. Intracellular Antiviral Persistence of EVG, RAL, TFV, and LPV 237
Table 96. Effects of Human Serum on the Anti-HIV-1 Activity and Cytotoxicity of EVG and EFV in Human PBMC Cultures 238

Table 97. Effects of Human Plasma Components on the Anti-HIV-1 Activity of EVG and Control Compounds in MT-4 and MT-2 Cells 238
Table 98. Human Serum-Adjusted Antiviral EC_{50} and EC_{95} of EVG in Human T Cells 238
Table 99. Genotypic Analysis of the Integrase Genes from HIV-1_{IIIB} Variants Selected in the Presence of EVG 240
Table 100. Phenotypic Analysis for EVG Against Wild-Type HIV-1_{IIIB} or EVG-Resistant Mutant HIV-1 241
Table 101. Genotypic Analysis of the Integrase Genes from HIV-1_{HXB2} Variants Selected in the Presence of EVG or RAL During Breakthrough Selections 242
Table 102. Antiviral Activity of EVG and Control Compounds Against Emergent HIV-1 NL4-3 Site-Directed Integrase Mutations 245
Table 103. Antiviral Activity of EVG, M1, M4, and Control Compounds Against HIV-1 NL4-3 Site-Directed Integrase Mutant Viruses 247
Table 104. EVG Susceptibility of Reverse Transcriptase and Protease Resistant Patient-Derived Recombinant HIV-1 Molecular Clones 249
Table 105. Anti-HIV Activity of EVG and Control Compounds Against Drug-Resistant HIV-1 Clinical Isolates in PBMCs 250
Table 106. Drug Susceptibility of Recombinant HIV-1 Molecular Clones Containing Mutations Associated with NRTI Resistance 251
Table 107. Drug Susceptibility of Recombinant HIV-1 Molecular Clones Containing Mutations Associated with NNRTI Resistance 252
Table 108. Drug Susceptibility of Recombinant HIV-1 Molecular Clones Containing Mutations Associated with Protease Inhibitor Resistance 252
Table 109. IC_{50} Values for EVG, its Metabolites, and L-870,810 against Strand-Transfer Activity of Wild-Type HIV-1 Integrase 253
Table 110. Kinetic Constants for the Incorporation of dCTP, FTC-TP, and 3TC-TP into an RNA/DNA Template/Primer 257
Table 111. Inhibitory Effect of FTC on the Replication of Laboratory Strains of HIV-1 and HIV-2 259
Table 112. Comparison of the Antiviral Activities of FTC and 3TC Against Various Laboratory Strains of HIV-1 259
Table 113. Inhibition of HIV-1 Clinical Isolates by FTC 260
Table 114. Comparative Potency of RT Inhibitors in HIV-1 Infected PBMCs Using a Coculture Method 260
Table 115. EC_{50} Values of NRTIs Against HIV-1 Group M and Group O Isolates in PBMCs and MAGI-CCR5 Cells 261
Table 116. Phenotypic Analysis of a Panel of Recombinant Viruses 266
Table 117. Phenotypic Analysis of Recombinant Viruses Generated from Clinical Isolates 267
Table 118. Metabolism of 10 μM TFV Either Alone or in Combination with 10 μM FTC 269
Table 119. Metabolism of 10 μM FTC Either Alone or in Combination with 10 μM TFV 269
Table 120. Mean EC_{50} and EC_{90} Values for TFV and FTC Against HIV-1_{LAI} and HIV-1_{MM-317} Strains 271
Table 121. In Vitro Selection of TFV and FTC Resistant HIV-1 272
Table 122. Kinetic Inhibition Constants of TFV-DP Against DNA Polymerases α, β, γ, δ, and ε 273
Table 123. Relative Efficiencies of Incorporation into DNA of TFV-DP and NRTI-Triphosphates by Human DNA Polymerases α, β, and γ 274
Table 124. TAF and TFV Antiviral Activity Against Human Viruses and SIV 276
Table 125. Effect of EVG Against HIV-1 Reverse Transcriptase and HIV-1 Protease 277
Table 126. Anti-HIV Activity of COBI and RTV 278
Table 127. Activity of COBI and RTV Against Primary HIV Isolates in Human PBMCs 279
Table 128. Antiviral Activity of COBI Metabolites Identified In Vitro 280
Table 129. Anti-HBV Activity of COBI in WT-42 Cells 280
Table 130. Anti-HCV Activity and Cytotoxicity of COBI in Huh-Luc Replicon Cells 281
Table 131. Anti-HBV Activity in HepG2 2.2.15 Cells of Compounds Approved and Under Development for HBV Infection 282

Table 132. TAF Anti-HIV-1 Activity in Combination with Selected ARVs 285
Table 133. Two-Drug Combination Anti-HIV Activity of EVG with Other Anti-HIV Antiretroviral Compounds 287
Table 134. Two-Drug Combination Anti-HIV Activity of EVG with Other Anti-HBV Antiretroviral Compounds 289
Table 135. Antiviral Activity of Several Antiretroviral Drugs in the Presence of COBI 290
Table 136. Synergistic Activity of FTC with Other Antiretroviral Agents 291
Table 137. Resistance Mutations by Antiretroviral Class 298
Table 138. GS-US-292-0104: Summary of Pretreatment HIV-1 Subtype and PR, RT, and IN Resistance Mutations Detected 300
Table 139. GS-US-292-0104: Summary of HIV-1 Genotypic Resistance Observed Through Week 48 303
Table 140. GS-US-292-0104: Details of Subjects in the Resistance Analysis Population 304
Table 141. GS-US-292-0111: Summary of Pretreatment HIV-1 Subtype and PR, RT, and IN Resistance Mutations Detected 306
Table 142. GS-US-292-0111: Summary of HIV-1 Genotypic Resistance Observed Through Week 48 309
Table 143. GS-US-292-0111: Details of Subjects in the Resistance Analysis Population 310
Table 144. GS-US-292-0102: Summary of Pretreatment HIV-1 Subtype and PR and RT Resistance Mutations Detected 312
Table 145. GS-US-292-0102: Summary of HIV-1 Genotypic Resistance Observed Through Week 48 315
Table 146. GS-US-292-0102: Details of Subjects in the Resistance Analysis Population 316
Table 147. GS-US-292-0109: Summary of Pretreatment HIV-1 Subtype and PR and RT Resistance Mutations Detected 317
Table 148. GS-US-292-0109: Summary of HIV-1 Genotypic Resistance Observed Through Week 48 320
Table 149. GS-US-292-0109: Details of Subjects in the Resistance Analysis Population 321
Table 150. GS-US-292-0112: Summary of Pretreatment HIV-1 Subtype and PR, RT, and IN Resistance Mutations Detected 322
Table 151. GS-US-292-0112: Summary of HIV-1 Genotypic Resistance Observed Through Week 24 325
Table 152. GS-US-292-0112: Details of Subjects with Resistance Testing at Week 24 326
Table 153. GS-US-292-0106: Summary of Pretreatment HIV-1 Subtype, and PR, RT, and IN Resistance Mutations 327
Table 154. GS-US-292-0106: Summary of HIV-1 Genotypic Resistance Observed Through Week 24 328
Table 155. E/C/F/TAF Integrated Analysis: Summary of PR and RT Resistance Mutations Detected Pretreatment 330
Table 156. E/C/F/TAF Integrated Analyses: Summary of HIV-1 Subtypes 331
Table 157. E/C/F/TAF Integrated Analyses: Proportion of Subjects with Treatment Success at Week 48 by Baseline Virologic Category 332
Table 158. E/C/F/TAF Integrated Analyses: Summary of HIV-1 Genotypic Resistance Through Week 48 335
Table 159. E/C/F/TAF Integrated Analysis: Details of Subjects With Available Data in the Final Resistance Analysis Population 336

LIST OF IN-TEXT FIGURES

Figure 1. E/C/F/TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type 22
Figure 2. TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type 26

Figure 3. EVG Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type....28
Figure 4. COBI Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type....31
Figure 5. FTC Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type....35
Figure 6. STB Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type....38
Figure 7. Biotransformation Pathway of TAF....106
Figure 8. Proposed Biotransformation Pathway of TAF in Humans....110
Figure 9. Proposed Biotransformation Pathway of EVG in Humans....112
Figure 10. Proposed Biotransformation Pathway of COBI in Humans....115
Figure 11. Putative Metabolites of FTC....116
Figure 12. 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 in Pooled Phase 3 Studies (Semilogarithmic Scale, PK Substudy Analysis Set)....126
Figure 13. GS-US-292-0104 and GS-US-292-0111: Median (Q1, Q3) PBMC TFV-DP Concentrations: TFV-DP PK Profile After Administration of E/C/F/TAF or STB in Pooled Phase 3 Studies (Semilogarithmic Scale, PK Substudy Analysis Set)....127
Figure 14. GS-US-120-0104: Median (Q1, Q3) of Change from Baseline in HIV-1 RNA (log_{10} copies/mL) by Visit (Full Analysis Set)....171
Figure 15. 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)....172
Figure 16. EVG Dose-Response Model Based on Monotherapy and Phase 2 Dose-Ranging Studies....174
Figure 17. Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) by EVG C_{tau} (ng/mL) Quartile Subgroup (EVG PK/PD Analysis Set)....176
Figure 18. Effect of CYP3A Inhibition by COBI or RTV on the Probe Substrate MDZ (PK Analysis Set)....178
Figure 19. FTC-101: Dose-Response Relationship of Anti-HIV Activity of FTC: Plots of Log_{10} HIV-1 RNA AAUCMB Versus FTC Daily Dose....183
Figure 20. FTC-101: Correlation of Antiviral Activity of FTC and FTC-Triphosphate Levels in PBMCs....184
Figure 21. Box Plot of TAF AUC_{tau} (ng•hr/mL) by Selected Adverse Events (TAF PK/PD Analysis Set)....185
Figure 22. Box Plot of TAF C_{max} (ng/mL) by Selected Adverse Events Subgroup (TAF PK/PD Analysis Set)....186
Figure 23. Box Plot of TFV AUC_{tau} (ng•h/mL) by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set)....187
Figure 24. Box Plot of TFV C_{max} (ng/mL) by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set)....188
Figure 25. Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)....189
Figure 26. Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)....190
Figure 27. Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)....191
Figure 28. Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)....192
Figure 29. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)....193
Figure 30. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)....194

Figure 31. Box Plot of EVG AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (EVG PK/PD Analysis Set) 195
Figure 32. Box Plot of EVG C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (EVG PK/PD Analysis Set) 196
Figure 33. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by EVG AUC_{tau} (ng•h/mL) Quartile Subgroup (EVG PK/PD Analysis Set) 197
Figure 34. Box Plot of COBI AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (COBI PK/PD Analysis Set) 199
Figure 35. Box Plot of COBI C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (COBI PK/PD Analysis Set) 200
Figure 36. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by COBI AUC_{tau} (ng•h/mL) Quartile Subgroup (COBI PK/PD Analysis Set) 201
Figure 37. Box Plot of FTC AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set) 202
Figure 38. Box Plot of FTC C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set) 203
Figure 39. 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) 204
Figure 40. TFV Intracellular Metabolism in Human PBMCs 206
Figure 41. 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 208
Figure 42. Resistance Profile Comparison Between TAF and TFV in the Monogram PhenoSense Assay 221
Figure 43. Inhibition of the Strand-Transfer Reaction by EVG 231
Figure 44. Binding and Dissociation of EVG and RAL from Integrase-DNA Complexes 231
Figure 45. Effects of EVG on the Generation of 3 Different Forms of HIV-1 DNA in Infected Cells 233
Figure 46. Effect of EVG-Selected Mutations on HIV-1 Strand-Transfer Activity and Inhibition by EVG and L-870,810 243
Figure 47. Intracellular Levels of FTC-TP as a Function of Extracellular FTC Concentration 256
Figure 48. Effect of Multiplicity of Infection on the EC_{50} of FTC in MAGI-CCR5 Cells 262
Figure 49. Effect of Multiplicity of Infection on the EC_{50} of FTC in PBMCs 262
Figure 50. Fold Change in FTC EC_{50} as a Function of Time of Addition 263
Figure 51. HIV-1 Breakthrough in the Presence of FTC and 3TC 264
Figure 52. Formation of the Active Metabolites of TFV and FTC 270
Figure 53. GS-US-292-0104: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48 302
Figure 54. GS-US-292-0111: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48 308
Figure 55. GS-US-292-0102: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48 314
Figure 56. GS-US-292-0109: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48 319
Figure 57. GS-US-292-0112: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 24 324
Figure 58. GS-US-292-0106: Resistance Analysis Population Inclusion Criteria Through Week 24 328
Figure 59. E/C/F/TAF Integrated Analysis: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48 334

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

1′-OH MDZ	midazolam metabolite (1'- hydroxymidazolam)
3TC	lamivudine
3TC-TP	lamivudine 5'-triphosphate
AAG	α_1-acid glycoprotein
AAUCMB	average area under the curve minus baseline
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AF	assay failure
aGFR	actual glomerular filtration rate
AhR	aryl hydrocarbon receptor
AK	adenylate kinase
ALT	alanine aminotransferase
ANOVA	analysis of variance
APV	amprenavir
ART	antiretroviral treatment or 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
BDC	bile duct-cannulated
BE	bioequivalence
BID	twice daily
BL	baseline
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
bpm	beats per minute
BSEP	bile salt excretory pump
BUP	buprenorphine
CatA	cathepsin A
CBV-TP	carbovir triphosphate
CBZ	carbamazepine
CBZE	carbamazepine-10,11-epoxide
CC_{50}	concentration that results in 50% cytotoxicity
CCR5	chemokine receptor type 5

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

CD4	cluster determinant 4
cDNA	complementary DNA
CI	confidence interval
CL	clearance
CL_{cr}	creatinine clearance
CL_r	renal clearance
CNS	central nervous system
COBI or C	cobicistat (GS-9350; Tybost®)
+COBI	cobicistat-boosted (not coformulated)
COWS	Clinical Opiate Withdrawal Scale
CPI	comparator protease inhibitor
CPK	creatine phosphokinase
CPT	Child-Pugh-Turcotte
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450 enzyme
cysGFR	cystatin C-derived glomerular filtration rate
d4T	stavudine
d4T-TP	stavudine triphosphate
dATP	deoxyadenosine triphosphate
$DAVG_{XX}$	time-weighted average change from baseline at Week xx
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	darunavir
DTG	dolutegravir
EC_{xx}	concentration of a compound inhibiting virus replication by xx%
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
ECG	electrocardiogram
ECHO	echocardiogram
EE	ethinyl estradiol
EFV	efavirenz

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
$eGFR_{MDRD}$	estimated glomerular filtration rate calculated using the modification of diet in renal disease equation
ELISA	enzyme-linked immunosorbent assay
ESDD	Early Study Drug Discontinuation
ESRD	end-stage renal disease
ETV	etravirine
EVG or E	elvitegravir (GS-9137; Vitekta®)
FBS	fetal bovine serum
FC	fold change
FDA	Food and Drug Administration
FDC	fixed-dose combination
FSH	follicle-stimulating hormone
F/TAF	emtricitabine/tenofovir alafenamide (coformulated)
FTC or F	emtricitabine (GS-9019; Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®/Eviplera®)
FTC-TP	emtricitabine 5'-triphosphate
GGT	gamma-glutamyltransferase
Gilead	Gilead Sciences
GI	gastrointestinal
GLSM	geometric least-squares mean
GMR	geometric mean ratio
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, HIV type 1, HIV type 2
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPLC, HPLC-UV	high-performance liquid chromatography, HPLC with ultraviolet detection
HS	human serum
HSA	human serum albumin
HSV, HSV-1, HSV-2	herpes simplex virus, HSV type 1, HSV type 2
IC_{xx}	concentration that results in xx% inhibition
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

IDV	indinavir
IN	integrase
INR	international normalized ratio
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
IV	intravenous or Roman numeral 4
K_d	equilibrium binding or affinity constant
K_i	kinetic inhibition constant
K_m	Michaelis-Menton constant
K_{off}	dissociation rate
k_{pol}	incorporation rate
KTZ	ketoconazole
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LDV	ledipasvir
LF	low fat
LH	luteinizing hormone
LLOQ	lower limit of quantitation
LPV	lopinavir
LPV/r	lopinavir/ritonavir (coformulated, Kaletra®)
LTR	long terminal repeat
m	module
M1	elvitegravir metabolite (hydroxylation of the chlorofluorophenyl group); also named GS-9202
M4	elvitegravir metabolite (glucuronide conjugate of the carboxylic acid); also named GS-9200
MATE	multidrug and toxin extrusion
MDM	monocyte-derived macrophage
MDR	multidrug resistance
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
mGFR	measured glomerular filtration rate (determined using 24-hour urinary output and serum creatinine concentration)
MOI	multiplicity of infection
mRNA	messenger RNA
MRP	multidrug resistance protein
MVC	maraviroc
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate, reduced
NC	not calculable

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

ND	not determined or not done
NFV	nelfinavir
NGM	norgestimate
NGMN	norelgestromin
NLX	naloxone
NNRTI	nonnucleoside reverse transcriptase inhibitor
norBUP	norbuprenorphine
NRTI	nucleoside reverse transcriptase inhibitor
NS5A	nonstructural protein 5A
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OCTN1	organic cation transporter novel, type 1
OOAS	Opiate Overdose Assessment Scale
OOWS	Objective Opiate Withdrawal Scale
P	passage
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics(s)
PDE5	phosphodiesterase-5
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	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PR	protease
PVR	pure virologic response
PXR	pregnane X receptor
Q1, Q3	first quartile, third quartile
QD	once daily

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

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 using the individual correction formula
QTcM	model-derived, individual-specific, corrected QT
QTcN	QT interval corrected for heart rate using population-specific correction formula
ΔΔQTc	time-matched, baseline-adjusted, placebo-corrected QTc
ΔΔQTcF	time-matched, baseline-adjusted, placebo-corrected QTcF
-R	resistant
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
RTV	ritonavir
+RTV	ritonavir boosted (not coformulated)
SAE	serious adverse event
SD	standard deviation
SER	sertraline
SI	selectivity index
SIV	simian immunodeficiency virus
SOF	sofosbuvir (Sovaldi®)
SOWS	Subjective Opiate Withdrawal Scale
SQV	saquinavir
SSRI	selective serotonin reuptake inhibitor
ST	QT interval minus the QRS duration
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
STR	single-tablet regimen (also referred to as FDC for E/C/F/TAF)
T-20	enfuvirtide
TAF	tenofovir alafenamide (GS-7340)
TAM	thymidine analog mutation

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

TCA	tricyclic antidepressant
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TFV	tenofovir (previously referred to as PMPA)
TFV-DP	tenofovir diphosphate (previously referred to as PMPApp)
TFV-MP	tenofovir monophosphate (previously referred to as PMPAp)
TLOVR	time to loss of virologic response
TPV	tipranavir
TVR	telaprevir
UGT	uridine diphosphate glucuronosyltransferase
US	United States
UTP	uridine triphosphate
V_{max}	maximum velocity
vs	versus
VZV	varicella zoster virus
WHV	woodchuck hepatitis virus
WHVsAG	woodchuck hepatitis virus surface antigen
WT	wild-type
ZDV	zidovudine
ZDV-TP	zidovudine 5’ triphosphate

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

A_e	amount of unchanged drug excreted in urine calculated either over a specific interval ($A_{e(interval)}$) or cumulatively over all collection intervals, calculated as (concentration of unchanged drug in urine) × (volume of urine collected)
AUC	area under the plasma/PBMC concentration versus time curve
$AUC_{0–last}$, AUC_{last}	area under the plasma/PBMC concentration versus time curve from time zero to the last quantifiable concentration
$AUC_{inf,}$ $AUC_{0\text{-}inf}$	area under the plasma/PBMC concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0–last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the plasma/ PBMC concentration versus time curve over the dosing interval
$AUC_{x–xx}$	partial area under the plasma/PBMC concentration versus time curve from time "x" to time "xx"
C_0	predose concentration
C_{24}	observed plasma/PBMC concentration at time 24 hours
CL	systemic clearance of the drug after intravenous administration
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
CL_{ss}/F	apparent steady-state clearance
C_{last}	last observed quantifiable plasma/PBMC concentration of the drug
CL_r	renal clearance of unchanged drug in a specific interval ($CL_{r\ (interval)}$) or cumulatively over all collection intervals
C_{max}	maximum observed plasma/PBMC concentration of drug
$C_{max,ss}$	maximum observed plasma/PBMC concentration of drug at steady state
C_{min}	minimum observed plasma/PBMC concentration over a dosing interval
$C_{min,ss}$	minimum observed plasma/PBMC concentration over a dosing interval at steady state
C_{tau} or C_{trough}	observed drug concentration at the end of the dosing interval
E_{max}	maximum (pharmacodynamic) effect
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
T_{maxss}	time (observed time point) of C_{max} at steady state
V_c/F	apparent volume of central compartment
V_p/F	apparent volume of peripheral compartment
V_{ss}	steady-state volume of distribution
V_z	volume of distribution of the drug after intravenous administration
V_z/F	apparent volume of distribution of the drug

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 (ARV) therapy (ART) to suppress viral replication to below detectable limits, increase cluster determinant 4 (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 the optimization of tolerability, long-term safety, and adherence of potent ART regimens {29705}. In addition, there remains a significant medical need for new, effective therapies that take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, non-HIV comorbidities, and regimen simplification.

For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI) {28776}, {27621}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {21053}, {29702}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NtRTI for use in combination with other ARV agents for the treatment of HIV-1 infection. 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}. Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and at the 10-mg dose contained within the E/C/F/TAF FDC tablet yields approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF.

Gilead Sciences (Gilead) has coformulated TAF with the HIV-1 INSTI elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), and the NRTI emtricitabine (FTC; F) into an FDC tablet that is suitable for once-daily use. The E/C/F/TAF FDC may provide a potent, convenient, well-tolerated, and practical regimen for the long-term treatment of patients infected with HIV.

This Summary of Clinical Pharmacology presents pharmacokinetic (PK) and pharmacodynamic (PD) data that supports the E/C/F/TAF FDC tablet for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. These data are based on clinical studies and supportive nonclinical studies, as well as analyses of PK and PD data across studies.

The nonclinical and clinical virology studies conducted as part of the clinical development program for E/C/F/TAF are summarized in Sections 4.1 and 4.2, respectively. Integrated analyses of the virology resistance data from the Phase 2 and Phase 3 studies (GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111) are included in Section 4.2.2. Nonclinical studies conducted using human biomaterials that assist in the interpretation of the PK data are discussed in the Nonclinical Pharmacokinetics Written Summary (m2.6.4). Pharmacokinetic studies related to biopharmaceutics are referenced in this summary and are also discussed in detail in the Summary of Biopharmaceutic Studies (m2.7.1).

To facilitate review, the focus of this document is on data relevant to E/C/F/TAF and its components with the greatest detail on that for the new chemical entity, TAF. Data from studies with the other components, EVG, COBI, and FTC, are included as needed to describe their PK and PD profiles within the context of E/C/F/TAF.

Clinical studies discussed in this document include biopharmaceutic and clinical pharmacology studies conducted with E/C/F/TAF, as well as studies conducted with the individual components, TAF (also referred to as GS-7340), EVG, COBI, FTC, FTC coformulated with TAF (F/TAF), and the FDC tablet, EVG/COBI/FTC/TDF (coformulated; Stribild®; STB). Clinical studies are listed and described further by drug or drug combination and study type in Section 1.2; results from individual studies, presented by study drug, are provided in Section 2. A summary of data for each individual component within E/C/F/TAF is presented in Section 3, beginning with the new chemical entity, TAF.

Many clinical studies have been previously submitted to regulatory agencies in at least 1 region. These studies are described at a level of detail appropriate to the context in which the data contribute to the understanding of the PK and PD of the combination E/C/F/TAF tablet. Studies that have not been previously submitted are designated as “new” in this document. These studies are described in appropriate greater detail within this document and/or other clinical summary documents within this marketing application.

1.1. Human Biomaterials Studies

Studies pertinent to the PK of E/C/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 E/C/F/TAF and its components.

In total, 60 clinical studies provide PK data in support of this marketing application. Of these, 12 studies were conducted with E/C/F/TAF and 6 studies were conducted with F/TAF (1) or TAF (5). The other 42 studies (2 of which are new) were conducted with EVG, COBI, EVG+COBI, FTC, or STB. Twelve studies were conducted in HIV-infected subjects, including 6 studies conducted with E/C/F/TAF in subjects 12 to > 80 years of age (and including subjects

with mild-to-moderate renal impairment). Forty-eight studies were conducted in healthy subjects, including the following:

- Single- and multiple-dose PK and PK/PD studies with E/C/F/TAF (2), EVG (3), COBI (3), FTC (3), and STB (1).
- Mass balance studies with TAF, EVG, COBI, and FTC
- QT/QTc interval studies with TAF, EVG, and COBI
- Cytochrome p450 enzyme (CYP) and drug efflux transporter P-glycoprotein (P-gp) study with COBI
- Food effect studies with E/C/F/TAF and STB
- Drug-interaction studies with E/C/F/TAF (2), F/TAF (1), EVG (3), COBI (7), FTC (1), and STB (3).

In addition, the following special population studies were conducted:

- Renal-impairment studies with TAF (1), COBI (2), and FTC (1)
- Hepatic-impairment studies with TAF, EVG, and FTC
- Uridine diphosphate glucuronosyltransferase (UGT) 1A1-activity study with EVG
- Japanese PK bridging study with E/C/F/TAF

Clinical pharmacology studies of E/C/F/TAF, individual component drugs, and/or STB entailed single and/or multiple dosing and clinically relevant exposure of the drug(s) to assess PK, PK/PD relationships, and/or the effects of intrinsic and extrinsic factors. Drug-interaction studies were performed using designs with adequate sample size to provide appropriate statistical comparisons and allow assessment of the clinical relevance of findings. Intensive PK sampling was used in healthy subject and HIV-infected subject studies (except Study GS-US-292-0109, which used only sparse sampling). Additionally, sparse sampling was performed in Phase 2 and Phase 3 studies and used for population PK analysis, including the effects of relevant covariates, as described further in Section 1.5.

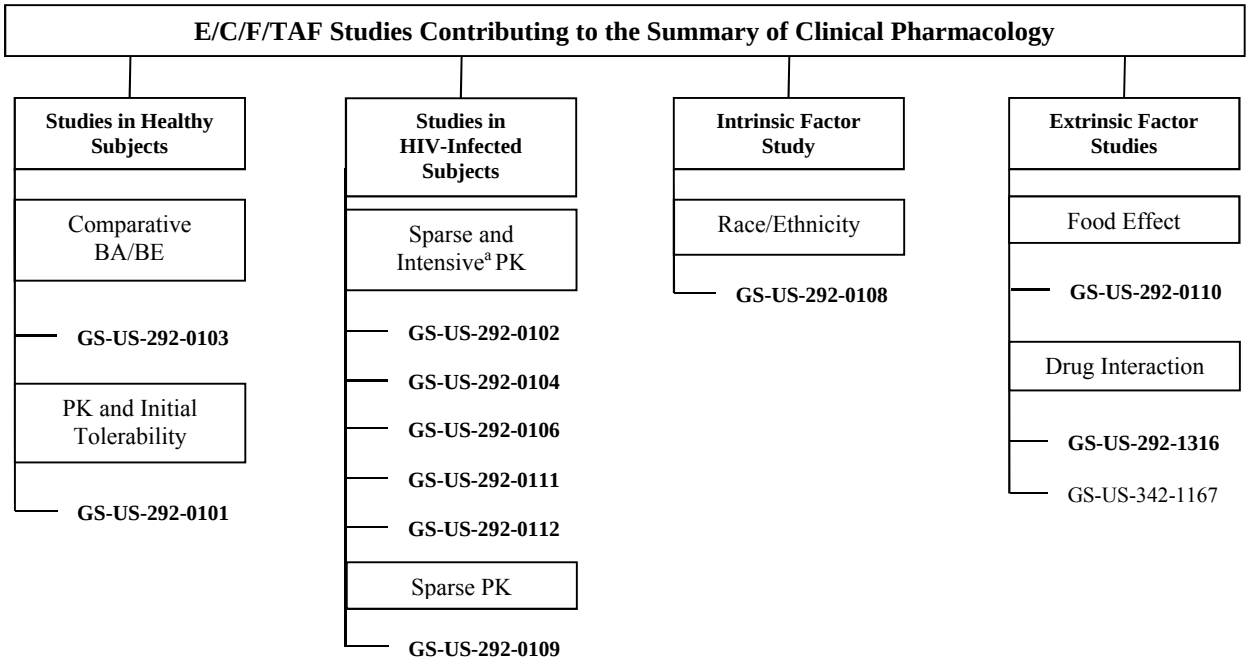
The studies contributing information to this summary are described by study drug in Sections 1.2.1 to 1.2.8.

1.2.1. E/C/F/TAF

The 12 clinical studies conducted with E/C/F/TAF contributing information to this Summary of Clinical Pharmacology are listed by study type in Figure 1 and in Table 1, which includes the dosage form, lot number, dose, and number of subjects administered drug. Study narratives for

the new (bolded) studies in Figure 1 are provided in Section 2 of this document, the Summary of Clinical Efficacy (m2.7.3), or the Summary of Clinical Safety (m2.7.4) as indicated in Table 1.

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



BA = bioavailability; BE = bioequivalence
a Intensive PK sampling was conducted in PK substudies
Study numbers in bold text (new studies) have narratives provided in Section 2 of this document, Section 2 of m2.7.3, or Section 1 of m2.7.4

Table 1. Overview of E/C/F/TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

Type of Study/ Study Number/ Phase/Narrative Location	E/C/F/TAF				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Studies in Healthy Subjects					
Comparative Bioavailability/Bioequivalence Study					
GS-US-292-0103 Phase 1 (Section 2.2.1.2)	E/C/F/TAF FDC 150/150/200/10-mg tablet	CP[redacted]05B1	150/150/ 200/10 mg	33	EVG 150-mg tablet COBI 150-mg tablet FTC 200-mg capsule TAF 25-mg tablet
Multiple-Dose Study PK and Initial Tolerability Study					
GS-US-292-0101 Phase 1 (Section 2.2.1.1)	E/C/F/TAF FDC 150/150/200/25-mg tablet E/C/F/TAF FDC 150/150/200/40-mg tablet (2 formulations each)	25 mg Form 1: CP[redacted]03B1 Form 2: CP[redacted]01B1 40 mg: Form 1: CP[redacted]04B1 Form 2: CP[redacted]02B1	150/150/ 200/25 mg 150/150/ 200/40 mg	38	STB (EVG/COBI/FTC/TDF) 150/150/200/300-mg tablet TAF 25-mg tablet
Studies in HIV-Infected Subjects					
Controlled Multiple-Dose Studies with Intensive PK Sampling					
GS-US-292-0102 Phase 2; ART-naive subjects (m2.7.3, Section 2)	E/C/F/TAF FDC 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	150/150/ 200/10 mg	112	E/C/F/TAF placebo tablet STB (EVG/COBI/FTC/TDF) 150/150/200/300-mg tablet and matching placebo tablet
GS-US-292-0104 Phase 3; ART-naive subjects (m2.7.3, Section 2)	E/C/F/TAF FDC 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	150/150/ 200/10 mg	435	E/C/F/TAF placebo tablet STB (EVG/COBI/FTC/TDF) 150/150/200/300-mg tablet and matching placebo tablet

Type of Study/ Study Number/ Phase/Narrative Location	E/C/F/TAF				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
GS-US-292-0111 Phase 3; ART-naive subjects (m2.7.3, Section 2)	E/C/F/TAF FDC 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	150/150/ 200/10 mg	431	E/C/F/TAF placebo tablet STB (EVG/COBI/FTC/TDF) 150/150/200/300-mg tablet and matching placebo tablet
Uncontrolled Multiple-Dose Studies with Intensive PK Sampling					
GS-US-292-0106 Phase 2/3; ART-naive subjects (m2.7.4, Section 1)	E/C/F/TAF FDC 150/150/200/10-mg tablet	CP[redacted]05B1 CP[redacted]03B1 CP[redacted]08B1 CP[redacted]10B1 CP[redacted]11B1 CP[redacted]13B1	150/150/ 200/10 mg	48	Not applicable
GS-US-292-0112 Phase 3; renally impaired subjects (m2.7.4, Section 1)	E/C/F/TAF FDC 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	150/150/ 200/10 mg	248	Not applicable
Controlled Multiple-Dose Study with Sparse PK Sampling					
GS-US-292-0109 Phase 3; virologically suppressed subjects (m2.7.3, Section 2)	E/C/F/TAF FDC 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	150/150/ 200/10 mg	959	FTC/TDF+3rd Agent regimen (STB, ATR, ATV/co+TVD or ATV+RTV+TVD)

Type of Study/ Study Number/ Phase/Narrative Location	E/C/F/TAF				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Intrinsic Factor PK Study					
Study of the Effect of Race/Ethnicity in Healthy Subjects					
GS-US-292-0108 Phase 1 (Section 2.4.1.1)	E/C/F/TAF FDC 150/150/200/10-mg tablet	CP[redacted]01B1	150/150/ 200/10 mg	20	Not applicable
Extrinsic Factor PK Studies					
Study of the Effect of Food in Healthy Subjects					
GS-US-292-0110 Phase 1 (Section 2.5.1.1)	E/C/F/TAF FDC 150/150/200/10-mg tablet	CP[redacted]09B1	150/150/ 200/10 mg	43	Not applicable
Drug Interaction Study Between E/C/F/TAF and Sertraline in Healthy Subjects					
GS-US-292-1316 Phase 1 (Section 2.5.1.2)	E/C/F/TAF FDC 150/150/200/10-mg tablet	CP[redacted]10B1	150/150/ 200/10 mg	20	Sertraline 50-mg tablet
Drug Interaction Study Between E/C/F/TAF and Sofosbuvir/GS-5816 FDC in Healthy Subjects					
GS-US-342-1167 Phase 1	E/C/F/TAF FDC 150/150/200/10-mg tablet	CP[redacted]09B1	150/150/ 200/10 mg	24	SOF/GS-5816 400/100-mg tablet ATR 600/200/300-mg tablet FTC/RPV/TDF 200/25/300-mg tablet DTG 50-mg tablet

ATR = efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®); DTG = dolutegravir; FTC/RPV/TDF = emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®/Eviplera®); n = number of subjects administered E/C/F/TAF; SOF = sofosbuvir; STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; coformulated; Stribild)

1.2.2. F/TAF

The clinical study conducted with F/TAF contributing information to this Summary of Clinical Pharmacology was Study GS-US-311-0101, which was a Phase 1 study evaluating the drug interaction potential between once-daily F/TAF and efavirenz (EFV) or COBI-boosted darunavir (DRV) (DRV+COBI). The dosage form, lot number, dose, number of subjects administered drug, and locations of the study narrative and report are listed in Table 2.

Table 2. Overview of F/TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

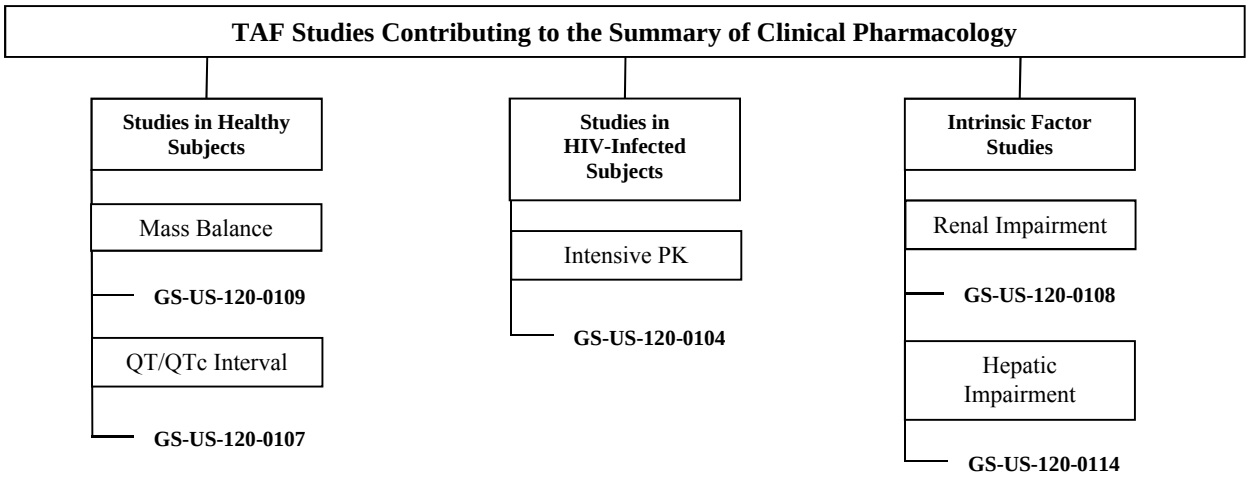
Type of Study/ Study Number/ Phase/Narrative Location[a]	F/TAF				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Extrinsic Factor PK Study					
Drug Interaction Study Between F/TAF and EFV or DRV+COBI in Healthy Subjects					
GS-US-311-0101 Phase 1 (Section 2.5.2.1)	F/TAF 200/25-mg tablet	200/25: CR[redacted]06B1	200/25 mg	50	COBI 150-mg tablet TAF 8-mg tablet EFV 600-mg tablet DRV 400-mg tablet
	F/TAF 200/40-mg tablet	200/40: CR[redacted]07B1	200/40 mg		

DRV = darunavir; EFV = efavirenz; n = number of subjects administered F/TAF
a Location of narrative for Study GS-US-311-0101 in Section 2 of this document

1.2.3. TAF

The 5 clinical studies conducted with TAF contributing information to this Summary of Clinical Pharmacology are listed by study type in Figure 2 and in Table 3, which includes the dosage form, lot number, dose, and number of subjects administered drug. Study narratives for each new (bolded) study are provided in Section 2 of this document as indicated in Table 3.

Figure 2. TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type



Study numbers in bold text (new studies) have narratives provided in Section 2 of this document

Table 3. Overview of TAF Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

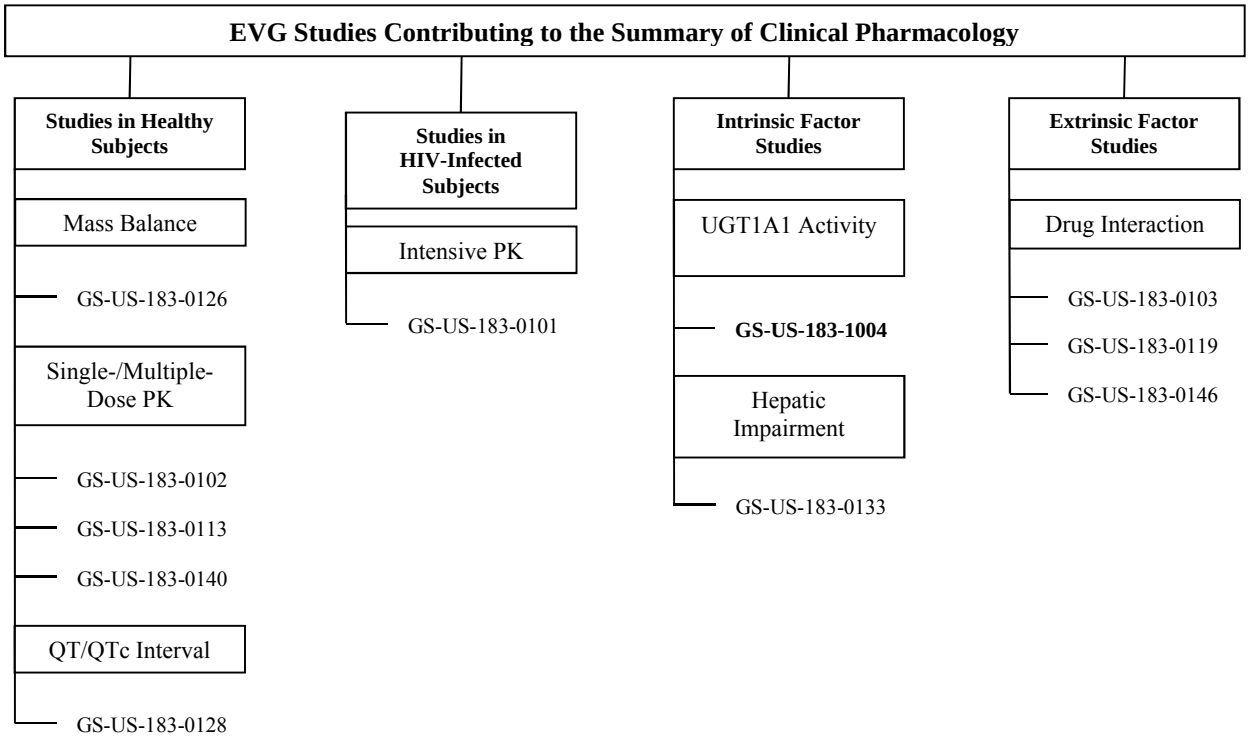
Type of Study/ Study Number/ Phase/Narrative Location	TAF				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Studies in Healthy Subjects					
Mass Balance Study (PK, Metabolism, and Excretion)					
GS-US-120-0109 Phase 1 (Section 2.2.2.2)	TAF [^{14}C]-labeled, 25-mg capsule (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	25 mg	8	Not applicable
QT/QTc Interval Study					
GS-US-120-0107 Phase 1 (Section 2.2.2.1)	TAF 25-mg tablet	CM[redacted]02B1	25, 125 mg	58	TAF placebo tablet Moxifloxacin 400-mg tablet
Studies in HIV-Infected Subjects					
Controlled Multiple-Dose Studies With Intensive PK Sampling					
GS-US-120-0104 Phase 1 (Section 2.3.1.1)	TAF 8-mg tablet TAF 25-mg tablet TAF 40-mg tablet	CM[redacted]02B1 CM[redacted]03B1 CM[redacted]04B1	8, 25, 40 mg	25	TDF 300-mg tablet TAF placebo tablet
Intrinsic Factor PK Studies					
Renal Impairment Study					
GS-US-120-0108 Phase 1 (Section 2.4.2.1)	TAF 25-mg tablet	CM[redacted]02B1 CM[redacted]02B1 CM[redacted]02B1-A	25 mg	27	Not applicable
Hepatic Impairment Study					
GS-US-120-0114 Phase 1 (Section 2.4.2.2)	TAF 25-mg tablet	[redacted]	25 mg	40	Not applicable

ATV = atazanavir; DRV = darunavir; DTG = dolutegravir; n = number of subjects administered TAF; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

1.2.4. EVG

The 11 clinical studies conducted with EVG contributing information to this Summary of Clinical Pharmacology are listed by study type in Figure 3 and in Table 4, which includes the dosage form, lot number, dose, and number of subjects administered drug. The study narrative for the new (bolded) study in Figure 3 is provided in Section 2 of this document as indicated in Table 4.

Figure 3. EVG Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type



UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1
Study number in bold text (new study) has narrative provided in Section 2 of this document

Table 4. Overview of EVG Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

Type of Study/ Study Number/ Phase/Narrative Location	EVG				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Studies in Healthy Subjects					
Mass Balance Study (PK, Metabolism, and Excretion)					
GS-US-183-0126 Phase 1	EVG 25-mg capsule (each containing a mixture of unlabeled EVG plus 50 µCi of [^{14}C]EVG)	37702E21	50 mg	8	RTV 100-mg soft gelatin capsule
Single- and Multiple-Dose PK and Initial Tolerability Studies					
GS-US-183-0102 Phase 1	EVG 50-mg tablets	071-4	100 mg	12	RTV 100-mg soft gelatin capsules
GS-US-183-0113 Phase 1	EVG 125-mg tablet	AJ[redacted]03A1	125 mg	24	RTV 20-, 50-, 100-, 200-mg oral solutions MDZ hydrochloride 1 mg, IV injection
GS-US-183-0140 Phase 1	EVG 125-mg tablet EVG 150-mg tablet	AJ[redacted]03A1 AJ[redacted]01D1	125, 150 mg	26	RTV 100-mg soft gelatin capsules
QT/QTc Interval Study					
GS-US-183-0128 Phase 1	EVG 125-mg tablet	AJ[redacted]03A1	125, 250 mg	83	RTV 100-mg soft gelatin capsule and matching placebo capsule EVG placebo tablet Moxifloxacin 400-mg tablet and matching placebo tablet
Studies in HIV-Infected Subjects					
Controlled Multiple-Dose Study With Intensive PK Sampling (PK and PK/PD relationships)					
GS-US-183-0101 Phase 1/2	EVG 50-mg tablet EVG 200-mg tablet	071-4, 070-4	50, 200, 400, 800 mg	30	RTV 100-mg soft gelatin capsule Placebo tablet

Type of Study/ Study Number/ Phase/Narrative Location	EVG				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Intrinsic Factor PK Studies					
UGT1A1 Activity Study					
GS-US-183-1004[a] Phase 1 (Section 2.4.3.1)	EVG 150-mg tablet COBI 150-mg tablet	AJ[redacted]01G1 BB[redacted]05B1	EVG: 150 mg COBI: 150 mg	36	Not applicable
Hepatic Impairment Study					
GS-US-183-0133 Phase 1	EVG 150-mg tablet COBI 150-mg tablet	EVG: AJ[redacted]02D1 COBI: BB[redacted]04B1	EVG: 150 mg COBI: 150 mg	20	Not applicable
Extrinsic Factor PK Studies					
Drug Interaction Study Between EVG+RTV and FTC/TDF or an Antacid in Healthy Subjects					
GS-US-183-0103 Phase 1	EVG 50-mg tablet	071-4	50 mg	26	RTV 100-mg soft gelatin capsule FTC/TDF 200/300-mg tablet Maalox Max antacid 20-mL suspension
Drug Interaction Study Between EVG+RTV and Antacid or Omeprazole in Healthy Subjects					
GS-US-183-0119 Phase 1	EVG 50-mg tablet	AJ[redacted]02A1	50 mg	60	RTV 100-mg soft gelatin capsule Maalox Max 20-mL suspension Omeprazole 40-mg capsule
Drug Interaction Study Between EVG+RTV and KTZ in Healthy Subjects					
GS-US-183-0146 Phase 1	EVG 150-mg tablet	AJ[redacted]01D1	150 mg	18	RTV 100-mg soft gelatin capsule KTZ 200-mg tablet MDZ hydrochloride 2-mg/mL syrup

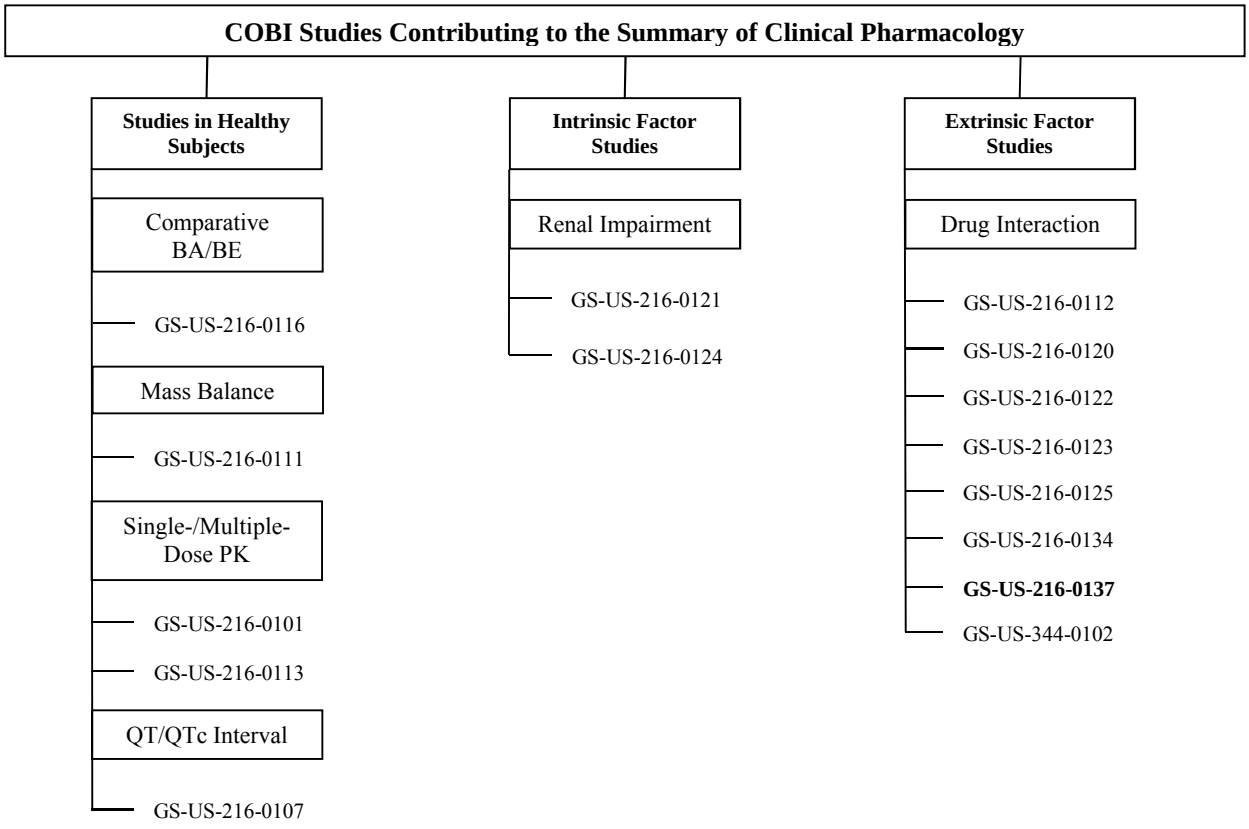
ABC = abacavir; ATV = atazanavir; d4T = stavudine; ddI = didanosine; DRV = darunavir; IV = intravenous; KTZ = ketoconazole; MDZ = midazolam; MVC = maraviroc; n = number of subjects administered EVG (or EVG+COBI); PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; +RTV = ritonavir-boosted; TPV = tipranavir; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

a Location of narrative for new study provided in Section 2 of this document

1.2.5. COBI

The 15 clinical studies conducted with COBI contributing information to this Summary of Clinical Pharmacology are listed by study type in Figure 4 and in Table 5, which includes the dosage form, lot number, dose, and number of subjects administered drug. Study narratives for the new (bolded) studies in Figure 4 are provided in Section 2 of this document as indicated in Table 5.

Figure 4. COBI Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type



Study number in bold text (new study) has narrative provided in Section 2 of this document

Table 5. Overview of COBI Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

Type of Study/ Study Number/ Phase/Narrative Location	COBI				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Studies in Healthy Subjects					
Comparative Bioavailability/Bioequivalence Study					
GS-US-216-0116 Phase 1	COBI 150-mg tablet (original formulation 1 and new formulation 2)	BB[redacted]02A1 BB[redacted]04B1	150 mg	62	EVG 150-mg tablet RTV 100-mg soft gelatin capsule MDZ hydrochloride 5 mg oral syrup
Mass Balance Study (PK, Metabolism, and Excretion)					
GS-US-216-0111 Phase 1	COBI 150-mg tablet COBI 150-mg capsule (each containing 148.5 mg nonradiolabeled COBI plus 100 μCi [1.5 mg] [^{14}C]COBI)	BB[redacted]01A1-A, 9350-AC-2E CR2, G01-025-0564-A-20[redacted]-PV	150 mg	8	Not applicable
Multiple-Dose PK and Initial Tolerability Studies (including PK/PD Relationships)					
GS-US-216-0101 Phase 1	COBI 25-mg tablet COBI 100-mg tablet	BB[redacted]03A1 BB[redacted]02A1	50, 100, 200 mg	42	RTV 100-mg soft gelatin capsule (overencapsulated) and matching placebo capsule COBI placebo tablet MDZ hydrochloride 5 mg (2.5 mL of a 2-mg/mL oral syrup)
GS-US-216-0113 Phase 1	COBI 100-mg tablet	BB[redacted]03A1	300, 400 mg	24	Not applicable
QT/QTc Interval Study					
GS-US-216-0107 Phase 1	COBI 100-mg tablet COBI 150-mg tablet	BB[redacted]03A1-B BB[redacted]02A1	250, 400 mg	48	COBI placebo tablet Moxifloxacin 400-mg tablet

Type of Study/ Study Number/ Phase/Narrative Location	COBI				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Intrinsic Factor PK Studies					
Renal Impairment Studies					
GS-US-216-0121 Phase 1 Multiple-dose PK and PK/PD of COBI in healthy subjects and subjects with mild/moderate renal impairment	COBI 150-mg tablet	BB[redacted]04B1 BB[redacted]04B1	150 mg	30	RTV 100-mg soft gelatin capsule and matching placebo capsule COBI placebo tablet Iohexol 1500 mg (5 mL of 300-mg iodine/mL solution) as IV bolus over 1 to 2 minutes
GS-US-216-0124 Phase 1 Multiple-dose PK of EVG and COBI in healthy subjects and subjects with severely impaired renal function	EVG 150-mg tablet COBI 150-mg tablet	AJ[redacted]02D1 BB[redacted]04B1	EVG: 150 mg COBI: 150 mg	24	Not applicable
Extrinsic Factor PK Studies					
Drug Interaction Study Between COBI and P450 Enzymes or Drug Efflux Transporter P-gp in Healthy Subjects					
GS-US-216-0112 Phase 1	COBI 150-mg tablet	BB[redacted]01B1	150 mg	48	Desipramine 50-mg tablet Digoxin 0.25-mg tablet EFV 600-mg tablet
Drug Interaction Study Between EVG+COBI and H2-receptor Antagonist or Proton Pump Inhibitor in Healthy Subjects					
GS-US-216-0120 Phase 1	EVG 150-mg tablet COBI 150-mg tablet	AJ[redacted]05E1 BB[redacted]04B1	EVG: 150 mg COBI: 150 mg	33	Famotidine 40-mg tablet Omeprazole 20-mg capsule
Drug Interaction Study Between EVG+COBI and H2-Receptor Antagonist in Healthy Subjects					
GS-US-216-0122 Phase 1	EVG 150-mg tablet COBI 150-mg tablet	AJ[redacted]05E1 BB[redacted]04B1	EVG: 150 mg COBI: 150 mg	16	Famotidine 40-mg tablet

Type of Study/ Study Number/ Phase/Narrative Location	COBI				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Drug Interaction Study Between EVG+COBI and ATV (vs ATV+RTV), Rosuvastatin, or Rifabutin in Healthy Subjects					
GS-US-216-0123 Phase 1	EVG 85- or 150-mg tablet COBI 150-mg tablet	AJ[redacted]02C1, AJ[redacted]02D1 BB[redacted]04B1-A	EVG: 85, 150 mg COBI: 150 mg	34	Rosuvastatin 10-mg tablet ATV 300-mg capsule RTV 100-mg capsules Rifabutin 150-mg capsule
Drug Interaction Study Between EVG+COBI and Methadone or BUP/NLX in Healthy Subjects					
GS-US-216-0125 Phase 1	EVG 150-mg tablet COBI 150-mg tablet	AJ[redacted]02D1 BB[redacted]04B1 BB[redacted]04B1-A	EVG: 150 mg COBI: 150 mg	28	BUP/NLX 2/0.5-mg or 8/2-mg tablet Methadone 80- to 100-mg in tablet or 10-mg/mL liquid solution formulation
Drug Interaction Study Between COBI and TDF in Healthy Subjects					
GS-US-216-0134 Phase 1	COBI 150-mg tablet	BB[redacted]04B2	150 mg	45	TDF 300-mg tablet
Drug Interaction Study Between EVG+COBI and Carbamazepine in Healthy Subjects					
GS-US-216-0137 [a] Phase 1 (Section 2.5.3.1)	EVG 150-mg tablet COBI 150-mg tablet	AJ[redacted]01G1 BB[redacted]05B1	EVG: 150 mg COBI: 150 mg	14	CBZ 100-mg tablet
Drug Interaction Study Between EVG+COBI and LDV/SOF in Healthy Subjects					
GS-US-344-0102 Phase 1	EVG 150-mg tablet COBI 150-mg tablet	AJ[redacted]01G1 BB[redacted]04B2	EVG: 150 mg COBI: 150 mg	30	LDV/SOF 400/90-mg tablet LDV 90-mg tablet ATR 600/200/300-mg tablet DRV 400-mg tablet RTV 100-mg tablet RAL 400-mg tablet RPV 25-mg tablet ATV 300-mg capsule

ATR = efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated, Atripla); ATV = atazanavir; BUP/NLX = buprenorphine/naloxone; CBZ = carbamazepine; DRV = darunavir; EFV = efavirenz; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); IV = intravenous; LDV = ledipasvir; MDZ = midazolam; n = number of subjects administered COBI (or EVG+COBI); P-gp = P-glycoprotein; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SOF = sofosbuvir; TDF = tenofovir disoproxil fumarate

a Location of narratives for new studies provided in Section 2 of this document

1.2.6. EVG+COBI

Clinical studies conducted with EVG+COBI that contribute information to this Summary of Clinical Pharmacology are included in the lists of EVG and COBI studies in Sections 1.2.4 and 1.2.5, respectively. These studies include the previously submitted Studies GS-US-183-0133 (under EVG) and GS-US-216-0120, GS-US-216-0122, GS-US-216-0123, GS-US-216-0124, and GS-US-216-0125 (under COBI), and GS-US-344-0102 (a study with ledipasvir/sofosbuvir [LDV/SOF] listed under COBI), as well as the new Studies GS-US-183-1004 (under EVG) and GS-US-216-0137 (under COBI), which are described further in Section 2.

1.2.7. FTC

The 11 clinical studies conducted with FTC contributing information to this Summary of Clinical Pharmacology are listed by study type in Figure 5 and in Table 6, which includes the dosage form, lot number, dose, and number of subjects administered drug. In addition to these studies, Study GS-US-311-0101 with F/TAF contributed information to this document and is described in Section 1.2.2.

Figure 5. FTC Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type

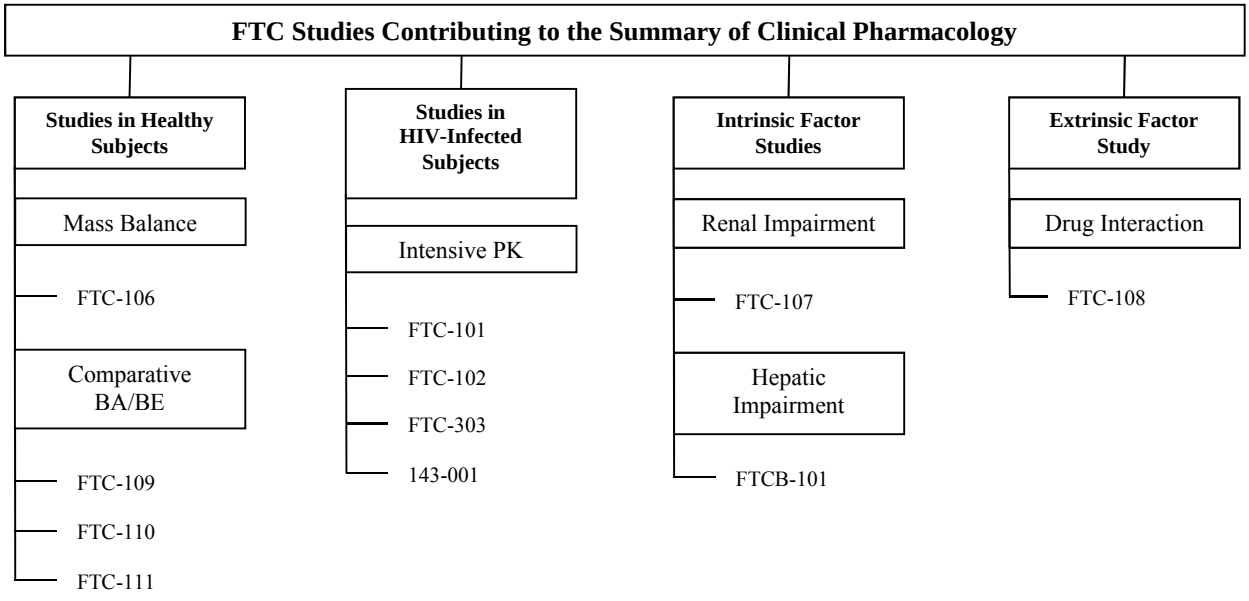


Table 6. Overview of FTC Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

Type of Study/ Study Number/ Phase	FTC				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Studies in Healthy Subjects					
Mass Balance Study (PK, Metabolism, and Excretion)					
FTC-106 Phase 1	FTC 100-mg capsule FTC 200-mg in oral solution containing 250 μCi [^{14}C]FTC)	TP-0006-99044 TP-0006/96/WW TP-0006-99084 (3361001)	200 mg	6	Not applicable
Comparative Bioavailability/Bioequivalence Studies					
FTC-109 Phase 1	FTC 100-mg capsule FTC 200-mg capsule	TP-0006-99099 TP-0006-99125	200 mg	12	Not applicable
FTC-110 Phase 1	FTC 200-mg capsule FTC 10-mg/mL oral solution FTC 10-mg/mL IV solution	TP-0006-00205 TP-0006-00211 TP-0006-00093	200 mg	12	Not applicable
FTC-111 Phase 1	FTC 100-mg capsule FTC 200-mg capsule	TP-0006-00120 TP-0006-00205	200 mg	24	Not applicable
Studies in HIV-Infected Subjects					
Patient PK and Initial Tolerability Studies (including PD and PK/PD relationships)					
FTC-101 Phase 1	FTC 25-mg capsule FTC 100-mg capsule	25947 26172	25, 100, 200 mg	41	Not applicable
FTC-102 Phase 1/2	FTC 25-mg capsule FTC 100-mg capsule	29087 29408	25, 100, 200 mg	60	3TC 150-mg tablet
143-001 Phase 1	FTC 100-mg capsule	2T2722	100, 200, 400, 800, 1200 mg	12	FTC placebo capsule
Controlled Multiple-Dose Study With Intensive PK Sampling					
FTC-303 Phase 3	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	200 mg	294	3TC (150 mg) and background regimen containing either d4T or ZDV and a PI or NNRTI

Type of Study/ Study Number/ Phase	FTC				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Intrinsic Factor PK Study					
Renal Impairment Study					
FTC-107 Phase 1	FTC 100-mg capsule	TP-0006-99044	200 mg	29	Not applicable
Study in Hepatitis B Virus Infected Subjects					
FTCB-101 Phase 1	FTC 25-mg capsule FTC 100-mg capsule	TP-0006/96/AA TP-0006/96/BB	25, 50, 100, 200, 300 mg	49	Not applicable
Extrinsic Factor PK Study					
Drug Interaction Study Between FTC and Famciclovir in Healthy Subjects					
FTC-108 Phase 1	FTC 100-mg capsule	TP-0006-99099	200 mg	12	Famciclovir 500-mg tablet

3TC = lamivudine; BID = twice daily; d4T = stavudine; IV = intravenous; n = number of subjects administered FTC; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

1.2.8. STB

The 5 clinical studies conducted with STB contributing information to this Summary of Clinical Pharmacology are listed by study type in Figure 6 and in Table 7, which includes the dosage form, lot number, dose, and number of subjects administered drug.

Figure 6. STB Clinical Studies Contributing Information to the Summary of Clinical Pharmacology by Study Type

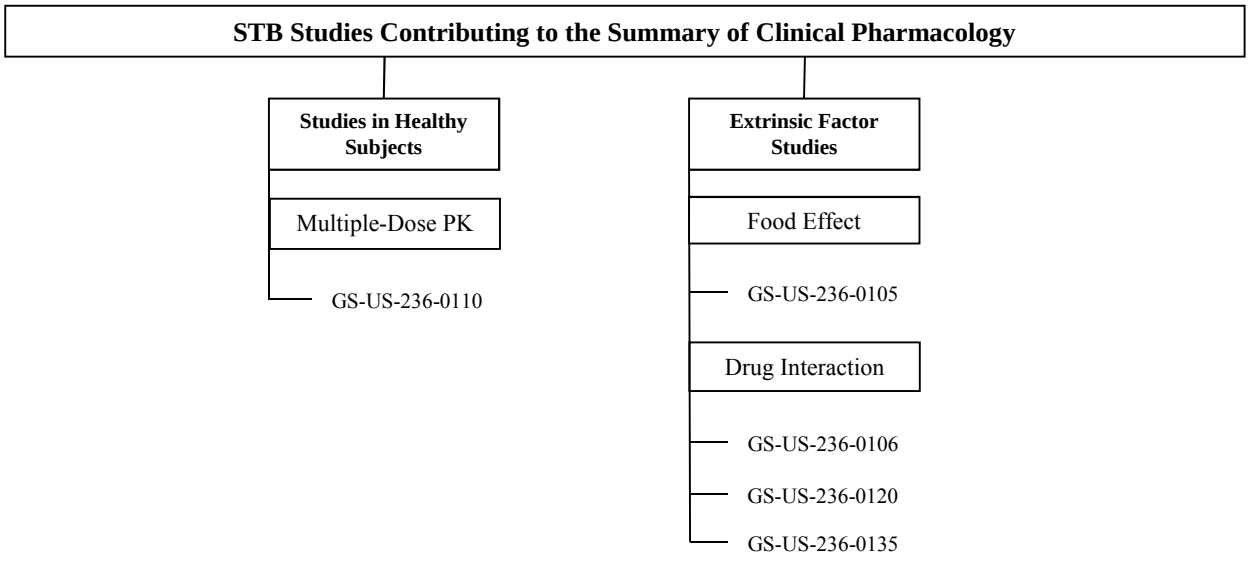


Table 7. Overview of STB Clinical Studies Contributing Information to the Summary of Clinical Pharmacology

Type of Study/ Study Number/ Phase	STB				Dosage Form of Coadministered or Control Drugs
	Dosage Form	Lot Number	Dose	n	
Studies in Healthy Subjects					
Multiple-Dose PK and Initial Tolerability Study					
GS-US-236-0110 Phase 1	STB (EVG/COBI/FTC/ TDF) 150/150/200/ 300-mg tablet (2 formulations)	BK[redacted]01B1 BK[redacted]02B1	150/150/ 200/300 mg	42	FTC 200-mg capsule TDF 300-mg tablet
Extrinsic Factor PK Study					
Study of the Effect of Food in Healthy Subjects					
GS-US-236-0105 Phase 1	STB 150/150/200/ 300-mg tablet	BK[redacted]03B1	150/150/ 200/ 300 mg	24	Not applicable
Drug Interaction Study Between STB and Hormonal Contraceptive Medication in Healthy Subjects					
GS-US-236-0106 Phase 1	STB 150/150/200/ 300-mg tablet	BK[redacted]03B1	150/150/ 200/ 300 mg	16	Ortho Tri-Cyclin Lo tablet (norgestimate 0/0.180/ 0.215/0.250 mg/ ethinyl estradiol 0/0.025 mg)
Drug Interaction Study Between STB and Telaprevir in Healthy Subjects					
GS-US-236-0135 Phase 1	STB 150/150/200/ 300-mg tablet	BK[redacted]05B1-A	150/150/ 200/ 300 mg	16	EVG 85-mg tablet EVG 150-mg tablet ATV 300-mg gelatin capsule RTV 100-mg tablet TVR 375-mg tablet
Drug Interaction Study Between STB and Previous Efavirenz/FTC/TDF Treatment in Healthy Subjects					
GS-US-236-0120 Phase 1	STB 150/150/200/ 300-mg tablet	BK[redacted]03B1	150/150/ 200/ 300 mg	32	EFV/FTC/TDF FDC 600/200/300-mg tablet

ATV = atazanavir; EFV/FTC/TDC = efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated); n = number of subjects administered STB; RTV = ritonavir; STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF; coformulated; Stribild); TVR = telaprevir

1.3. Bioanalytical Methods

The bioanalytical methods used for the determination of E/C/F/TAF and individual components and metabolites during the clinical development programs are described in m2.7.1, Section 1.1.3. An overview of the validated analytical methods for E/C/F/TAF and individual components, 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 absorption, distribution, metabolism, and elimination (ADME) of E/C/F/TAF and its components are described in Section 3.1.

Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure of CYP3A substrates, such as EVG, consistent with the PK enhancement or "boosting" effect of COBI. Inhibition of intestinal P-gp by COBI also results in increased exposure to TAF upon coadministration. For simplicity in this summary document, PK results from studies of EVG or TAF in the presence/absence of a PK enhancer are described as boosted/unboosted, respectively.

1.5. Population Pharmacokinetics

1.5.1. TAF

To evaluate the population PK of boosted TAF (and TFV metabolite) and identify intrinsic factors influencing TAF and TFV PK, population PK analyses of TAF and TFV were performed using pooled intensive and sparse data from Phase 1, 2, and 3 studies following administration of E/C/F/TAF, which included 1543 HIV-infected subjects (Table 8). 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 3.2.1.2.1. Select population PK analyses findings are included in the discussion of the effect on intrinsic factors (Section 3.2.2).

Further details on the population PK model are described in the m5.3.3.5, TAF Population PK Report.

Table 8. Studies Used in the Population PK Analysis of 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: m5.3.3.5, TAF Population PK Report

1.5.2. EVG

To evaluate the population PK of boosted EVG and identify any intrinsic factors or extrinsic effects influencing EVG PK, population PK analyses of COBI-boosted EVG were performed using pooled intensive and sparse data from Phase 1, 2, and 3 studies following administration of STB or EVG+COBI, which included 419 HIV-infected subjects (EVG Population PK Report). Intensive PK sampling was conducted in all Phase 1 studies. In Phase 2 and Phase 3 studies, intensive sampling entailed serial blood sampling at steady-state at one of the study visits (Week 2, 4, or 8). Sparse sampling (targeted trough sample or anytime postdose) entailed blood collection at all study visits up to Week 48. A mixed-effect modeling approach using NONMEM Version 7.2 software was applied and the results of the population PK analyses are discussed in Section 3.2.1.2.2. Select population PK analyses findings are included in the discussion of the effect on intrinsic factors (Section 3.2.2). EVG population PK was previously submitted in support of the clinical pharmacology of STB.

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

1.5.3. COBI

To evaluate the population PK of COBI and identify any intrinsic factors or extrinsic effects influencing COBI PK, population PK analyses of COBI were performed using pooled intensive and sparse data from Phase 1, 2, and 3 studies following administration of STB or COBI. Data from a total of 643 adult subjects (341 HIV-infected) were used in the analyses (COBI Population PK Report). Intensive PK sampling was conducted in all Phase 1 studies. In the Phase 2 and Phase 3 studies, intensive sampling entailed serial blood sampling at steady state at one of the study visits from Week 2 through Week 8. Sparse sampling entailed blood collection (targeted trough sample or anytime postdose) at all study visits up to Week 48. The final dataset used in the final model building steps included data from the COBI 150-mg dose level. A mixed-effect modeling approach using NONMEM Version 7.2 software was applied and the results of the population PK analyses are discussed in Section 3.2.1.2.3. Select population PK analyses findings are included in the discussion of the effect on intrinsic factors (Section 3.2.2). COBI population PK was previously submitted in support of the clinical pharmacology of COBI.

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

1.5.4. 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 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 one or more independent demographic variables with a single dependent PK parameter estimate of FTC. The results of these analyses are discussed in Section 3.2.1.2.4. Select population PK analyses findings are included in the discussion of the

effect on intrinsic factors (Section 3.2.2). These findings were previously submitted in support of the clinical pharmacology of FTC.

1.6. Pharmacokinetics/Pharmacodynamics

The PK/PD relationships of the individual analytes TAF and TFV, EVG, COBI, and FTC were evaluated for efficacy and safety in HIV-infected subjects. These PK/PD analyses are presented in Section 3.3.1 and Section 3.3.2, respectively.

1.7. Virology

A comprehensive program of nonclinical experiments and clinical studies characterized the antiviral activity of E/C/F/TAF and its individual components, as described in Sections 1.7.1 and 1.7.2, respectively.

1.7.1. Nonclinical Virology

Nonclinical virology studies characterized the antiviral activity of the E/C/F/TAF components, TAF, EVG, COBI, 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, peripheral blood mononuclear cells [PBMCs]). These studies characterized the following specific PD characteristics, the results of which are provided in Sections 4.1.1, 4.1.2, and 4.1.3, respectively.

- Primary pharmacodynamics: mechanism of action and antiviral activity against HIV-1 (wild-type and drug-resistant strains), including drug-resistance selection, for all except COBI

- Secondary pharmacodynamics: effect against host enzymes (eg, DNA polymerases and proteases) and non-HIV viruses (as well as anti-HIV-1 activity for COBI)

- Pharmacodynamic drug interactions

Conclusions from these nonclinical virology studies are provided in Section 4.1.4.

1.7.2. 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). 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 study (GS-US-292-0102) and 2 Phase 3 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 new studies providing information for this Summary of Clinical Pharmacology are provided in Sections 2.2 to 2.5, except Studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0109, and GS-US-292-0111 for which narratives are provided in Section 2 of Module 2.7.3, and Studies GS-US-292-0106 and GS-US-292-0112, for which narratives are provided in Section 1 of Module 2.7.4.

2.1. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Studies pertinent to the PK of E/C/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. E/C/F/TAF

2.2.1.1. 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 STR 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 mg and 40 mg TAF) versus STB STR or TAF 25 mg alone in healthy male and female volunteer 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: FDC Formulation 1 containing 150 mg EVG/150 mg COBI/200 mg FTC/25 mg TAF
- Treatment B: FDC Formulation 1 containing 150 mg EVG/150 mg COBI/200 mg FTC/40 mg TAF
- Treatment C: STB STR containing 150 mg EVG/150 mg COBI/200 mg FTC/300 mg TDF
- 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: FDC Formulation 2 containing 150 mg EVG/150 mg COBI/200 mg FTC/25 mg TAF
- Treatment F: FDC Formulation 2 containing 150 mg EVG/150 mg COBI/200 mg FTC/40 mg TAF
- Treatment C: STB STR containing 150 mg EVG/150 mg COBI/200 mg FTC/300 mg TDF
- 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 clinical study report (CSR) (m5.3.3.1, 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 adverse event (AE).

In Cohort 1, 10 (50%) were male, and the mean age was 37 years (range: 25 to 45 years). Seventeen of the subjects (85%) were white and 3 (15%) were black; all were Hispanic/Latino. Mean values for weight, height, and a body mass index (BMI) at screening were 80.1 kg, 170.5 cm, and 27.5 kg/m^2, respectively. Baseline estimated glomerular filtration rate (eGFR) by Cockcroft-Gault ($eGFR_{CG}$) was 137.6 mL/min (range: 102.5 to 170.0 mL/min) and $eGFR_{CG}$ by modification of diet in renal disease ($eGFR_{MDRD}$) was 109.2 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 mean age was 36 years (range: 26 to 45 years). Seventeen of the subjects (85%) were white and 3 (15%) were black; 19 (95%) were Hispanic/Latino. Mean values for weight, height, and BMI at screening were 71.1 kg, 165.0 cm, and 26.0 kg/m^2, respectively. Baseline $eGFR_{CG}$ was 120.9 mL/min (range: 84.3 to 154.6 mL/min) and $eGFR_{MDRD}$ was 108.9 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 below. Comparisons of exposure parameters are made primarily for treatments containing TAF 25 mg, which represent the target exposures that provide robust antiviral activity {20420}.

TAF PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Cohort 1				
E/C/F/TAF Formulation 1 (25 mg) (Test) vs TAF (25 mg) (Reference)	N = 19	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 (25 mg) (Test) vs TAF (25 mg) (Reference)	N = 18	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

CI = confidence interval; CV = coefficient of variation; GLSM = geometric least-squares mean

TFV PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Cohort 1				
E/C/F/TAF Formulation 1 (25 mg) (Test) vs STB (Reference)	N = 19	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
E/C/F/TAF Formulation 1 (25 mg) (Test) vs TAF (25 mg) (Reference)	N = 19	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 (25 mg) (Test) vs STB (Reference)	N = 18	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
E/C/F/TAF Formulation 2 (25 mg) (Test) vs TAF (25 mg) (Reference)	N = 17	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

CI = confidence interval; CV = coefficient of variation; GLSM = geometric least-squares mean

EVG PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Cohort 1				
E/C/F/TAF Formulation 1 (25 mg) (Test) vs STB (Reference)	N = 19	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 (25 mg) (Test) vs STB (Reference)	N = 18	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

CI = confidence interval; CV = coefficient of variation; GLSM = geometric least-squares mean

COBI PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Cohort 1				
E/C/F/TAF Formulation 1 (25 mg) (Test) vs STB (Reference)	N = 19	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 (25 mg) (Test) vs STB (Reference)	N = 18	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

CI = confidence interval; CV = coefficient of variation; GLSM = geometric least-squares mean

FTC PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Cohort 1				
E/C/F/TAF Formulation 1 (25 mg) (Test) vs STB (Reference)	N = 19	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 (25 mg) (Test) vs STB (Reference)	N = 18	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

CI = confidence interval; CV = coefficient of variation; GLSM = geometric least-squares mean

Following administration of E/C/F/TAF (25 mg) Formulations 1 and 2, geometric mean TAF and TFV exposures were substantially higher relative to TAF 25-mg single agent. With both formulations of E/C/F/TAF 25 mg, 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 2.5.2.1) when dosed as TAF (8 mg) plus COBI (150 mg) 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 (40 mg) versus E/C/F/TAF (25 mg). TFV exposure parameters were lower following administration of E/C/F/TAF Formulations 1 and 2 (25 and 40 mg) 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 approximately 90% lower compared with STB.

Following administration of E/C/F/TAF Formulations 1 and 2 containing TAF 25 mg and 40 mg, the geometric mean ratio (GMR) and 90% confidence intervals (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 bioequivalence 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 serious adverse events (SAEs) occurred during the study. One subject discontinued from the study because of a nonserious AE of Grade 3 increased creatine phosphokinase (CPK) 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 electrocardiograms (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 approximately 90% lower compared with STB.

- Administration of E/C/F/TAF Formulations 1 and 2 containing TAF (25 mg and 40 mg) provided similar EVG, COBI, and FTC exposures compared with STB.

- E/C/F/TAF Formulations 1 and 2, as well as STB STR and TAF alone, were generally safe and well tolerated in healthy subjects.

2.2.1.2. 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: FDC containing E/C/F/TAF (150/150/200/10 mg)

Treatment B: EVG 150 mg + COBI 150 mg

Cohort 2

Treatment A: FDC containing 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 (m5.3.1.2, 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 and 36 years, respectively, and the proportions of non-Hispanic/Latino subjects were 57% and 65%, respectively. As regards other characteristics, the 2 cohorts were comparable in terms of sex (approximately 71% male), race (approximately 59% white, 41% black), weight (overall mean at baseline: 74.9 kg), BMI (overall mean at baseline: 25.2 kg/m^2), and $eGFR_{CG}$ (overall mean at baseline: 126.9 mL/min).

Pharmacokinetic Results

Primary PK exposure parameters of TAF, TFV, EVG, COBI, and FTC following administration of E/C/F/TAF 10 mg, EVG+COBI, and EVG+TAF 25 mg, and statistical comparisons of each between treatments, are presented below.

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (%) (90% CI)
Cohort 2 E/C/F/TAF 10 mg (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 10 mg (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 10 mg (Test) vs EVG+COBI (Reference) (N = 14)			
AUC_{tau} (ng•h/mL)	22067.1 (26.3)	23099.2 (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 10 mg (Test) vs EVG+COBI (Reference) (N = 14)			
AUC_{tau}(ng•h/mL)	11209.8 (27.4)	10931.2 (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 10 mg (Test) vs FTC+TAF 25 mg (Reference) (N = 19)			
AUC_{tau}(ng•h/mL)	12352.6 (13.5)	10520.9 (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)

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 2.5.2.1] and GS-US-292-0101 [Section 2.2.1.1]). 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 10 mg (test treatment), the 90% CIs of the geometric least-squares mean (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 (percentage coefficient of variation [%CV]) TFV exposure parameters (AUC and C_{max}) following multiple doses of E/C/F/TAF 10 mg 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 10 mg, 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 the E/C/F/TAF 10 mg FDC (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 10 mg or FTC+TAF 25 mg was markedly lower than historical TFV exposure following administration of the STB STR, administration of E/C/F/TAF 10 mg resulted in comparable TAF and TFV exposures relative to FTC+TAF 25 mg.

- Administration of E/C/F/TAF 10 mg 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 the STB STR.

- E/C/F/TAF 10 mg was generally safe and well tolerated by healthy subjects.

2.2.2. TAF

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 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): 25 mg TAF (1 × 25-mg TAF tablet plus 4 × TAF placebo to match)

Treatment B (supratherapeutic exposure): 125 mg TAF (5 × 25-mg TAF tablets)

Treatment C (placebo control): 5 × TAF placebo to match

Treatment D (positive control): 1 × 400 mg moxifloxacin

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 (m5.3.4.1, 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 mean age of 35 years (range: 18 to 44 years).

Pharmacokinetic Results

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

GS-US-120-0107: Statistical Analysis of Dose Proportionality

PK Parameter	GLSM		GLSM Ratio (%)	90% CI (%)
	TAF 125 mg (Test) (n = 48)	TAF 25 mg (Reference) (n = 48)		
TAF				
AUC_{last} (ng•h/mL)	1149.38	208.28	551.85	(525.61, 579.40)
AUC_{inf} (ng•h/mL)	1161.31[a]	214.25[a]	542.04	(517.16, 568.13)
C_{max} (ng/mL)	809.94	155.05	522.37	(475.94, 573.33)
TFV				
AUC_{last} (ng•h/mL)	1121.29	190.91	587.35	(566.51, 608.96)
AUC_{inf} (ng•h/mL)	1505.60	250.08	602.04	(578.15, 626.92)
C_{max} (ng/mL)	49.17	8.40	585.28	(556.34, 615.71)

a n = 47

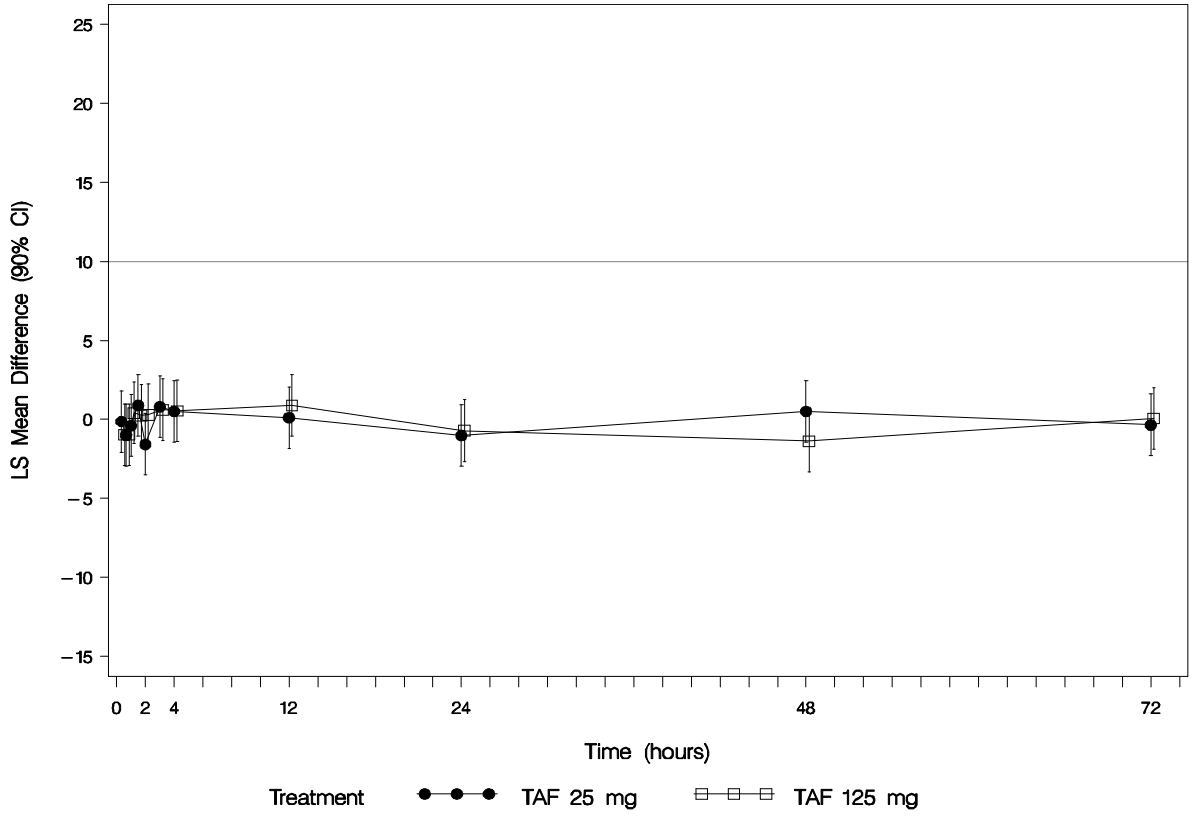
Pharmacodynamic Results

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 (see figure below). 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.

GS-US-120-0107: Noninferiority Evaluation for Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF (PD Analysis Set)



Categorical Analyses: Results from categorical analyses of QTcF, QTcB, QTcN, and QTcI are summarized below. 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.

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)

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 mild 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 (m5.3.3.1, 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 ± standard deviation (SD) recovery of [^{14}C]-radioactivity in feces plus urine was 84.4% ± 2.45% (N = 7), with the percent of radioactive dose recovered from feces at 47.2% ± 4.62% (N = 7) and the percent 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 percent of radioactive dose recovered from feces at 47.2% ± 4.62% (N = 7) and the percent 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.

2.3. Studies in HIV-Infected Subjects

2.3.1. TAF

2.3.1.1. Study GS-US-120-0104

Title

A Phase I 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 Week 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 tablet

Treatment Group 2: TAF 25-mg tablet

Treatment Group 3: TAF 40-mg tablet

Treatment Group 4: TDF 300-mg tablet

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 (m5.3.4.2, 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 mean age was 38 years (range: 20 to 57 years), the mean BMI was 26.8 kg/m^2 (range: 19.9 to 37.3 kg/m^2), and the mean $eGFR_{CG}$ was 118.2 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 (log10 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 $DAVG_{11}$ (log10 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 TAF, TFV, and TFV-DP (previously abbreviated PMPApp) are presented below.

TAF PK Parameter	TAF Multiple-Dose PK Day 10		
	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)

Q1 = first quartile; Q3 = third quartile
a n = 8
Notes: AUC_{last} is presented for multiple-dose PK because TAF concentrations are below the limit of quantitation (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.

TFV PK Parameter	TFV Single-Dose PK[a] Day 1				TFV Multiple-Dose PK Day 10			
	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_{inf} for single dose or AUC_{tau} for multiple dose (ng•h/mL), 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)	0.69 (19.8)	2.4 (23.5)	4.0 (27.2)	23.9 (57.5)	2.1 (33.8)	9.21 (26.1)	13.3 (16.0)[b]	38.7 (44.7)
T_{max} (h), 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)[b]	29.83 (26.87, 44.00)[b]	24.55 (20.33, 28.25)	15.56 (14.17, 17.07)	30.77 (26.90, 55.61)[c]	40.19 (28.98, 44.84)	35.95 (26.38, 42.90)[b]	14.86 (12.18, 16.81)

Q1 = first quartile; Q3 = third quartile
a AUC_{inf} and C_{24h} are presented for single dose PK
b n = 7
c n = 8

TFV-DP PK Parameter	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)	3.50 (77.6)	21.38 (76.8)	74.47 (92.7)	2.98 (118.4)
AUC_{tau} (μM•h), Median (Q1, Q3)	2.50 (1.60, 5.80)	15.80 (9.60, 33.15)	53.40 (28.30, 104.70)	1.60 (1.00, 4.95)

Q1 = first quartile; Q3 = third quartile
Note: To account for the variability in the data, the mean and median AUC_{tau} are presented.

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. Peripheral blood mononuclear cell 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 TFV-DP AUC_{tau} values were approximately 7-fold and approximately 25-fold higher, 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. Peripheral blood mononuclear cell 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 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. E/C/F/TAF

2.4.1.1. 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 (m5.3.3.1, 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 mean age (range) in each group was 36 years (23 to 51 years) for Caucasians and 40 years (26 to 51 years) for Japanese. There were similar proportions 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. The PK data generated were consistent with historical data following the administration of E/C/F/TAF.

PK Parameter Mean (%CV)	Japanese Subjects		Caucasian Subjects	
	Single Dose N = 10	Multiple Dose N = 9	Single Dose N = 10	Multiple Dose N = 8
EVG AUC[a] (ng•h/mL)	24629.2 (19%)	31194.5 (38%)	31144.1 (41%)	35803.7 (29%)
EVG AUC_{last} (ng•h/mL)	23377.9 (22%)	NA	30453.0 (43%)	NA
EVG C_{max} (ng/mL)	2143.4 (16%)	2964.1 (33%)	2495.9 (43%)	3698.2 (32%)
EVG C_{tau} (ng/mL)	NA	379.6 (64%)	NA	557.6 (40%)
COBI AUC[a] (ng•h/mL)	6273.4 (38%)	8228.2 (19%)	5680.0 (56%)	10643.7 (39%)
COBI AUC_{last} (ng•h/mL)	6220.3 (38%)	NA	5615.2 (57%)	NA
COBI C_{max} (ng/mL)	958.4 (37%)	1293.1 (17%)	809.7 (44%)	1456.6 (35%)
COBI C_{tau} (ng/mL)	NA	17.8 (28%)	NA	28.5 (47%)
FTC AUC[a] (ng•h/mL)	12019.8 (13%)	13142.1 (12%)	12646.9 (17%)	14827.0 (23%)
FTC AUC_{last} (ng•h/mL)	11792.5 (13%)	NA	12277.4 (17%)	NA
FTC C_{max} (ng/mL)	2652.4 (21%)	2944.6 (12%)	2381.2 (21%)	2744.3 (15%)
FTC C_{tau} (ng/mL)	NA	75.4 (29%)	NA	101.6 (44%)
TAF AUC[a] (ng•h/mL)	242.1 (22%)	253.7 (26%)	235.8 (30%)	292.0 (28%)
TAF AUC_{last} (ng•h/mL)	240.7 (22%)	NA	233.6 (30%)	NA
TAF C_{max} (ng/mL)	359.8 (29%)	317.3 (19%)	258.6 (39%)	319.0 (45%)
TAF C_{last} (ng/mL)	NA	2.1 (46%)	NA	2.4 (63%)
TFV AUC[a] (ng•h/mL)	338.7 (19%)	330.6 (12%)	337.5 (16%)	411.8 (37%)
TFV AUC_{last} (ng•h/mL)	215.3 (10%)	NA	227.8 (19%)	NA
TFV C_{max} (ng/mL)	20.3 (55%)	24.5 (32%)	11.5 (39%)	23.1 (31%)
TFV 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.

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, 150/150/200/10 mg 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.

2.4.2. TAF

2.4.2.1. 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 x 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 (m5.3.3.3, 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. 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. 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 (mean percent 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 percent unbound ranged from 97% to 99% at both time points in both groups).

Pharmacokinetic Parameters for TAF and TFV after 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)

Statistical Comparisons of TAF and TFV PK Parameters in Subjects with Severe Renal Impairment or Normal Renal Function

GLSM Ratio % (90% CI) Severe Renal Impairment (Test) vs Normal Renal Function (Reference)		
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)

N =14 for the renal impairment group and N = 13 for the matched control group

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 $\geq$ 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 mild.

- 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.

2.4.2.2. 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 5-6) (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 7-9) (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 (m5.3.3.3, 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

Geometric least-squares means and the 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 the tables below.

PK Parameter	GLSMs		GLSM Ratio (%) (90% CI)
	Reference Treatment: Normal Matched Control Group (N = 10)	Test Treatment: Mild Hepatic Impairment Group (N = 10)	
TAF			
AUC_{inf} (ng•h/mL)	223.08	206.30	92.48 (66.25, 129.09)
AUC_{last} (ng•h/mL)	218.93	201.04	91.83 (65.15, 129.43)
C_{max} (ng/mL)	162.51	144.65	89.01 (57.69, 137.33)
TFV			
AUC_{inf} (ng•h/mL)	289.73	258.32	89.16 (67.20, 118.30)
AUC_{last} (ng•h/mL)	256.74	229.30	89.31 (67.30, 118.53)
C_{max} (ng/mL)	8.06	7.82	97.03 (75.93, 124.00)

GLSMs were obtained using a mixed-effects model.

PK Parameter	GLSMs		GLSM Ratio (%) (90% CI)
	Reference Treatment: Normal Matched Control Group (N = 10)	Test Treatment: Moderate Hepatic Impairment Group (N = 10)	
TAF			
AUC_{inf} (ng•h/mL)	173.14	195.10	112.69 (87.29, 145.47)
AUC_{last} (ng•h/mL)	167.71	192.96	115.06 (88.50, 149.57)
C_{max} (ng/mL)	104.07	123.53	118.70 (78.94, 178.47)
TFV			
AUC_{inf} (ng•h/mL)	238.16	231.53	97.22 (77.03, 122.70)
AUC_{last} (ng•h/mL)	212.39	202.95	95.55 (75.20, 121.42)
C_{max} (ng/mL)	8.10	7.09	87.56 (70.49, 108.76)

GLSMs were obtained using a mixed-effects model.

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 percent 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 percent 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 2.4.2.1), the percent 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 percent 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 percent 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 [INR]).

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 mild and unrelated to study drug.

2.4.3. EVG

2.4.3.1. Study GS-US-183-1004

Title

A Phase 1, Multiple-Dose Study to Evaluate the Pharmacokinetics of Cobicistat-Boosted Elvitegravir in Subjects with Decreased UGT1A1 Activity

Objectives

The primary objective of this study was as follows:

- To evaluate the PK of EVG and GS-9200, the glucuronidated metabolite of EVG (M4), following the administration of EVG+COBI in subjects with decreased UGT1A1 activity (as identified by UGT1A1*28 genotype) and wild-type matched control subjects

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of EVG and COBI following the administration of EVG+COBI in subjects with decreased UGT1A1 activity (as identified by UGT1A1*28 genotype) and wild-type matched control subjects

Study Design

This was a Phase 1, open-label, nonrandomized, parallel-design, multiple-dose, single-center study to evaluate the PK of EVG and its metabolite GS-9200, and the safety and tolerability of EVG+COBI in subjects with decreased UGT1A1 activity.

Eligible subjects were identified through genomic screening of the TATA region of the UGT1A1 promoter, no more than 45 days prior to the scheduled first dose of study drug. Only subjects homozygous for the UGT1A1*28 allele (TA7/TA7) were enrolled in the UGT1A1*28 group. Each subject in the UGT1A1*28 group was matched by sex, age (± 20%), and BMI (± 20%) with a subject in the wild-type matched control group. Matched control subjects that exhibited wild type UGT1A1*1 enzyme (TA6/TA6) were identified through genomic screening no more than 45 days prior to scheduled first dose.

Subjects received study treatment (EVG 150 mg + COBI 150 mg) once daily in the morning with food for 10 days (Days 1-10).

Further details on the design and results of this study are available in the CSR (m5.3.3.3, GS-US-183-1004).

Study Population

A total of 36 subjects were enrolled in the study: 18 subjects each in the UGT1A1*28 and UGT1A1*1 groups. All 36 subjects completed the study and were recorded as having received

all doses of study drugs. However, 1 subject in the UGT1A1*28 group had EVG and GS-9200 concentration profiles indicative of a missed dose on Day 10.

In the safety analysis set, the majority of subjects were male (88.9%, 32 of 36 subjects). The mean age of subjects was 37 years (range: 20 to 53 years); half of the subjects were white (50%) and the majority of the remainder were black (44.4%), and two-thirds were non-Hispanic/Latino (66.7%). At baseline, the mean BMI was 25.8 kg/m^2 and the mean $eGFR_{CG}$ was 119.9 mL/min.

Pharmacokinetic Results

The steady-state mean and %CV of the primary PK parameters for EVG and GS-9200 after administration of 10 daily doses of EVG+COBI, and the results of the statistical analysis, are summarized below.

EVG PK Parameter	UGT1A1*28 (Test)[a] (N = 18)	UGT1A1*1 (Reference)[a] (N = 18)	GLSM Ratio (%)	90% CI
AUC_{tau} (ng•h/mL)	27,832.5 (35.5)	24,743.1 (22.8)	103.67	(79.93, 134.46)
C_{max} (ng/mL)	2204.9 (35.3)	2201.7 (32.2)	97.63	(78.38, 121.61)
C_{tau} (ng/mL)	589.0 (60.8)	507.1 (36.6)	120.60	(95.49, 152.32)

a Data are presented as mean (%CV).

GS-9200 PK Parameter	UGT1A1*28 (Test)[a] (N = 18)	UGT1A1*1 (Reference)[a] (N = 18)	GLSM Ratio (%)	90% CI
AUC_{tau} (ng•h/mL)	1363.1 (30.6)[b]	2135.2 (28.3)	63.26	(53.67, 74.57)
C_{max} (ng/mL)	127.6 (37.5)	207.5 (24.6)	57.88	(46.82, 71.56)
C_{tau} (ng/mL)	13.9 (127.2)	30.6 (63.3)	85.67	(65.54, 111.97)

a Data are presented as mean (%CV).
b N = 17. The value for Subject [redacted] was missing since terminal half-life could not be reliably calculated.

Following multiple-dose administration of EVG+COBI in subjects with decreased UGT1A1 activity (as identified by the UGT1A1*28 homozygous genotype versus matched control subjects with wild-type UGT1A1*1), EVG AUC_{tau} and C_{max} were unaffected: GLSM ratios (90% CI) for AUC_{tau} was 103.67% (79.93%, 134.46%) and C_{max} was 97.63% (78.38%, 121.61%). EVG C_{tau} was approximately 20% higher in the UGT1A1*28 group (GLSM ratio [90% CI] for C_{tau} was 120.60% [95.49%, 152.32%]), but this is not considered to be clinically meaningful, as C_{tau} in the UGT1A1*28 group (mean [%CV] for C_{tau} was 589.0 [60.8] ng/mL) was consistent with historical data on EVG C_{trough} {26526}. EVG $t_{1/2}$ was comparable between UGT1A1 activity groups (median [first quartile (Q1), third quartile (Q3)] for UGT1A1*28 was 9.66 [8.74, 12.91] hours and UGT1A1*1 was 10.94 [9.71, 11.98] hours), indicating that EVG elimination was unchanged. Mean GS-9200 plasma exposure (AUC_{tau}) was modestly lower (37%) in the UGT1A1*28 group versus the UGT1A1*1 group. The lower GS-9200 exposure is attributed to the decreased UGT1A1 activity, resulting in less formation of the glucuronidated metabolite, which does not contribute to the efficacy of EVG.

Safety Results

Adverse events were reported for 6 subjects (33.3%) in the UGT1A1*28 group and 1 subject (5.6%) in the UGT1A1*1 group. All AEs were Grade 1 in severity. No deaths, SAEs, AEs leading to study drug discontinuation, or pregnancies were reported for this study. The majority of laboratory abnormalities were Grade 1 in severity. Three subjects had Grade 3 laboratory abnormalities (low neutrophils in 1 subject in the UGT1A1*28 group; high amylase and lipase in 1 subject in the UGT1A1*1 group; and urine blood consistent with menses in 1 female subject in the UGT1A1*1 group). The Grade 3 laboratory abnormalities returned to baseline grades or normalized. None of the graded laboratory abnormalities were associated with signs and/or symptoms, or were reported as an AE. There were no clinically relevant changes in median values for hematology and the majority of the chemistry parameters assessed in this study. There were no notable changes in vital sign parameters reported during the study.

Conclusions

- EVG PK parameters were comparable and $t_{1/2}$ was unchanged following multiple-dose administration of boosted EVG in subjects with decreased UGT1A1 activity (UGT1A1*28), relative to matched control subjects with wild-type UGT1A1*1 activity, while exposures of the glucuronidated metabolite of EVG (GS-9200) were modestly lower in subjects with decreased UGT1A1 activity.

- UGT1A1 activity does not influence overall EVG clearance, negating the need to screen for UGT1A1 polymorphisms.

- No dose modification of EVG is necessary in patients with UGT1A1 polymorphisms receiving EVG as part of a boosted antiviral regimen.

- EVG and COBI were generally well tolerated with no differences in the safety profiles between the UGT1A1 activity groups. No new safety concerns were identified.

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

2.5.1. E/C/F/TAF

2.5.1.1. 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 an FDC containing 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 an FDC of 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 and light/low-fat meal). 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 (m5.3.3.4, 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}. 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. 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.

Treatment Condition (N = 42)	TAF PK Parameter		
	AUC_{inf} (ng•h/mL)	AUC_{last} (ng•h/mL)	C_{max} (ng/mL)
Test Treatment: Light/LF Meal GLSM	238.94	236.73	200.65
Test Treatment: HC/HF Meal GLSM	243.71	240.22	186.36
Reference Treatment: Fasted GLSM	207.37	205.94	294.90
Light/LF Meal vs. Fasted GLSM ratio (90% CI), %	115.22 (107.14, 123.91)	114.95 (106.82, 123.69)	68.04 (58.96, 78.52)
HC/HF Meal vs. Fasted GLSM ratio (90% CI), %	117.53 (109.28, 126.39)	116.65 (108.40, 125.52)	63.20 (54.76, 72.93)
HC/HF Meal vs. Light/LF Meal GLSM ratio (90% CI), %	102.00 (94.85, 109.69)	101.48 (94.30, 109.20)	92.88 (80.49, 107.18)

HC/HF = high-calorie/high-fat; LF = low-fat
GLSMs were obtained using a mixed-effects model.

Similarly, food did not affect the overall TFV exposure. 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. 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).

Treatment Condition (N = 42)	TFV PK Parameter		
	AUC_{inf} (ng•h/mL)	AUC_{last} (ng•h/mL)	C_{max} (ng/mL)
Test Treatment: Light/LF Meal GLSM	316.09	177.76	12.06
Test Treatment: HC/HF Meal GLSM	313.69	177.76	12.01
Reference Treatment: Fasted GLSM	278.40	175.33	14.34
Light/LF Meal vs Fasted GLSM ratio (90% CI), %	113.54 (108.23, 119.11)	101.38 (97.77, 105.13)	84.11 (75.71, 93.45)
HC/HF Meal vs Fasted GLSM ratio (90% CI), %	112.68 (107.40, 118.21)	101.39 (97.77, 105.13)	83.76 (75.39, 93.05)
HC/HF Meal vs Light/LF Meal GLSM ratio (90% CI), %	99.24 (94.60, 104.11)	100.00 (96.44, 103.70)	99.58 (89.63, 110.63)

HC/HF = high-calorie/high-fat; LF = low-fat
GLSMs were obtained using a mixed-effects model.

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

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.

2.5.1.2. 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 (SER) following the coadministration of E/C/F/TAF FDC and SER relative to the administration of E/C/F/TAF or SER 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 SER relative to the administration of E/C/F/TAF or SER alone

- To evaluate the safety and tolerability of administration of E/C/F/TAF or SER alone or in combination as E/C/F/TAF+SER

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 SER in healthy adult subjects. Following completion of screening and Day -1 procedures, eligible subjects were enrolled. The following study treatments were administered:

- Treatment A: SER 50-mg tablet, single dose, administered orally in the morning with food
- Treatment B: E/C/F/TAF (150/150/200/10 mg) tablet, single dose, administered orally in the morning with food for 12 days
- Treatment C: SER 50-mg tablet, single dose plus E/C/F/TAF (150/150/200/10 mg) tablet, 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 (m5.3.3.4, 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 SER (Treatment A) and ≥ 1 dose of E/C/F/TAF (Treatment B). Nineteen of the 20 subjects received E/C/F/TAF+SER (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 mean age of 35 years (range: 23 to 44 years). The majority of subjects were white (18 subjects [90%]) and of Hispanic/Latino ethnicity (18 subjects [90%]). The mean (SD) value for BMI at baseline was 26.1 (2.47) kg/m^2.

Pharmacokinetic Results

The mean and %CV of the primary PK parameters for EVG, COBI, FTC, TAF, TFV, and SER following the administration E/C/F/TAF and SER alone or in combination, and the results of the statistical analysis, are summarized in the table below.

EVG PK Parameter	Mean (%CV) by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF+SER (Test) (N = 19)	**E/C/F/TAF (Reference) (N = 19)**		
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	**E/C/F/TAF+SER (Test) (N = 19)**	**E/C/F/TAF (Reference) (N = 19)**		
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	**E/C/F/TAF+SER (Test) (N = 19)**	**E/C/F/TAF (Reference) (N = 19)**		
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	**E/C/F/TAF+SER (Test) (N = 19)**	**E/C/F/TAF (Reference) (N = 19)**		
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	**E/C/F/TAF+SER (Test) (N = 19)**	**E/C/F/TAF (Reference) (N = 19)**		
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)
SER PK Parameter	**E/C/F/TAF+SER (Test) (N = 19)**	**SER (Reference) (N = 20)**		
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)

Following the coadministration of E/C/F/TAF and SER, no clinically relevant alterations in the PK of EVG, COBI, FTC, TAF, TFV, or SER were observed relative to the administration of E/C/F/TAF or SER alone. The 90% CIs for the relevant PK parameters of EVG, COBI, FTC, TAF, TFV, and SER 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 SER. Overall, the exposures of all analytes following E/C/F/TAF and/or SER were consistent with historical data. Based on these study results, no dose adjustment is needed when coadministrating E/C/F/TAF and SER.

Safety Results

Onset of ≥ 1 AE was reported for 10.0% (2 of 20) of subjects after a single-dose administration of SER 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+SER. 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 SER had no effect on the PK of SER, EVG, COBI, FTC, TAF, or TFV.
- Coadministration of SER 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 SER was generally well tolerated in these healthy subjects.
- Since no clinically relevant drug interactions were observed upon coadministration of E/C/F/TAF and SER, no dose adjustments are needed when coadministrating E/C/F/TAF and SER.

2.5.2. F/TAF

2.5.2.1. 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 FDC (200/40 mg) and EFV 600 mg relative to administration of F/TAF FDC alone (Cohort 1)
- To evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF FDC (200/25 mg) and DRV+COBI (DRV 800 mg plus COBI 150 mg) relative to administration of these agents alone (Cohorts 2 and 3)
- To evaluate the PK of TAF, TFV, and COBI following once-daily coadministration of TAF 8 mg and COBI 150 mg 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 FDC administered alone or in combination with EFV (Cohort 1)
- To explore the PK of EFV following its coadministration with F/TAF FDC (Cohort 1)
- To evaluate the safety of F/TAF FDC and DRV+COBI when each is administered alone or in combination with each other (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 FDC 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:

Cohort 1	Days 1 to 12: Treatment A, FDC oral tablet containing F/TAF (200/40 mg) once daily in the morning, fasted	Days 13 to 26: Treatment B, FDC oral tablet containing F/TAF (200/40 mg) plus EFV (600 mg) oral tablet once daily in the morning, fasted
Cohort 2	Days 1 to 12: Treatment C, FDC oral tablet containing F/TAF (200/25 mg) once daily in the morning, fed	Days 13 to 22: Treatment D, FDC oral tablet containing F/TAF (200/25 mg) plus DRV (2 × 400 mg) + COBI (1 × 150 mg) oral tablets once daily in the morning, fed
Cohort 3	Days 1 to 10: Treatment E, DRV (2 × 400 mg) + COBI (1 × 150 mg) oral tablets once daily in the morning, fed	Days 11 to 22: Treatment F, FDC oral tablet containing F/TAF (200/25 mg) plus DRV (2 × 400 mg) + COBI (1 × 150 mg) oral tablets once daily in the morning, fed
Cohort 4	Days 1 to 12: Treatment G, Oral tablet containing single-agent TAF 8 mg once daily in the morning, fed	Days 13 to 22: Treatment H, Oral tablet containing single-agent TAF (8 mg) plus COBI (150 mg) oral tablet once daily in the morning, 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 (m5.3.3.4, 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 plus EFV 600 mg), 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 mean age was 35 years (range: 21 to 45 years), the mean BMI was 26.5 kg/m^2 (range: 20.4 to 31.0 kg/m^2), and the mean $eGFR_{CG}$ was 130.8 mL/minute (range: 87.2 to 190.7 mL/minute).

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 the tables below by cohort.

TAF PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI
Cohort 1: F/TAF 200/40 mg + EFV (Test) vs F/TAF 200/40 mg (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 (Test) vs F/TAF 200/25 mg (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 and COBI (Test) vs TAF 8 mg (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)

Note: DRV+COBI was administered as DRV 800 mg (two 400-mg tablets) plus COBI 150-mg tablet.

TFV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI
Cohort 1: **F/TAF 200/40 mg + EFV (Test) vs F/TAF 200/40 mg (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 and DRV+COBI (Test) vs F/TAF 200/25 mg (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 and COBI (Test) vs TAF 8 mg (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)

Note: DRV+COBI was administered as DRV 800 mg (two 400-mg tablets) plus COBI 150-mg tablet.

COBI PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI
Cohort 3: **F/TAF 200/25 mg and DRV+COBI (Test) vs DRV+COBI (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)

Note: DRV+COBI was administered as DRV 800 mg (two 400-mg tablets) plus COBI 150-mg tablet.

FTC PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI
Cohort 1: **F/TAF 200/40 mg + EFV (Test) vs F/TAF 200/40 mg (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 and DRV+COBI (Test) vs F/TAF 200/25 mg (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)

Note: DRV+COBI was administered as DRV 800 mg (two 400-mg tablets) plus COBI 150-mg tablet.

DRV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI
Cohort 3: **F/TAF 200/25 mg and DRV+COBI (Test) vs DRV+COBI (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)

Note: DRV+COBI was administered as DRV 800 mg (two 400-mg tablets) plus COBI 150-mg tablet.

Following administration of F/TAF FDC (200/40 mg) plus EFV 600 mg 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 the F/TAF FDC 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 2.3.1.1]), 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 FDC.

Following administration of F/TAF FDC (200/25 mg) plus DRV+COBI (800 mg + 150 mg) in Cohort 2, the GLSM ratio and 90% CIs for TAF and FTC were within the lack of interaction boundary, relative to the F/TAF FDC 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 150 mg versus TAF 8 mg alone) and with E/C/F/TAF versus TAF 25 mg single agent in Study GS-US-292-0101 (Section 2.2.1.1). 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 DRV+COBI plus F/TAF FDC, as compared with a single dose of F/TAF FDC 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 DRV+COBI (800 mg + 150 mg) plus F/TAF FDC (200/25 mg) 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 bioequivalence 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 (800 mg + 150 mg) plus F/TAF FDC (200/25 mg) in Cohort 2. COBI and FTC exposures were consistent with historical data from previous studies.

Following coadministration of TAF (8 mg) single agent plus COBI (150 mg) 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 (800 mg + 150 mg) (Cohort 3: no AE reported). 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 600 mg] and Grade 2 joint abscess with Treatment C). 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 FDC plus EFV resulted in no clinically relevant changes in FTC, TFV, TAF, or EFV exposure, as compared with F/TAF FDC dosed alone. Based on these data, it is concluded that no dose adjustments are needed when EFV is coadministered with the F/TAF FDC or the TAF single agent.

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

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

- Administration of TAF plus 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 the F/TAF FDC 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) plus EFV 600 mg. EFV has been shown to have central nervous system (CNS)-related side effects. Additionally, multiple doses of TAF 8 mg administered alone or coadministered with COBI 150 mg were well tolerated.

2.5.3. EVG+COBI

2.5.3.1. Study GS-US-216-0137

Title

A Phase 1, Multiple-Dose Study to Evaluate the Pharmacokinetics and Drug Interaction Potential between Carbamazepine and Cobicistat Boosted Elvitegravir in Healthy Subjects

Objectives

The primary objective of this study was as follows:

- To evaluate the PK of carbamazepine (CBZ), carbamazepine-10,11-epoxide (CBZE), EVG, and COBI following the coadministration of CBZ plus COBI-boosted EVG (EVG+COBI+CBZ) relative to the administration of CBZ alone or EVG+COBI alone

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of CBZ and EVG+COBI administered alone or in combination.

Study Design

This was a Phase 1, open-label, fixed-sequence, single-cohort, multiple-dose, single-center study to evaluate the PK and drug interaction profile, safety, and tolerability of EVG+COBI once daily plus CBZ twice daily compared with EVG+COBI once daily alone or CBZ twice daily alone, in healthy subjects.

Subjects received the following treatments: EVG 150 mg + COBI 150 mg once daily in the morning on Days 1 to 10 (Treatment A, Period 1); CBZ 100 mg twice daily in the morning and evening on Days 11 to 13, then CBZ 200 mg twice daily in the morning and evening on Days 14 to 31 (Treatment B, Period 2); EVG 150 mg + COBI 150 mg once daily in the morning, plus CBZ 200 mg twice daily in the morning and evening from Days 32 to 41 (Treatment C, Period 3). All doses were administered with a standard meal.

Further details on the design and results of this study are available in the CSR (m5.3.3.4, GS-US-216-0137).

Study Population

A total of 14 subjects were enrolled in the study and received at least one dose of study drug. Of these, 12 subjects received all doses of study drugs and completed the study, and 2 subjects discontinued in Period 3 (EVG+COBI+CBZ); 1 subject discontinued due to an AE, and 1 subject withdrew consent.

In the safety analysis set, the majority of subjects were males (12 subjects). The mean age was 39 years (range: 22 to 55 years); the majority of subjects were white (64.3%) and were not Hispanic or Latino (71.4%). The mean BMI at baseline was 25.6 kg/m^2. The mean $eGFR_{CG}$ at baseline was 116.1 mL/min.

Pharmacokinetic Results

Consistent with the characterization of CBZ as a potent inducer of CYP3A, following administration of EVG+COBI+CBZ, EVG and COBI exposures were markedly decreased relative to EVG+COBI (69.30% and 83.83% decreases in AUC_{tau} for EVG and COBI, respectively). The 90% CIs for the GLSMs for both EVG and COBI AUC_{tau}, C_{max}, and C_{tau} were well below the lack of interaction bounds (70%-143%), indicating the presence of a substantial drug interaction. Importantly, EVG C_{tau}, the parameter best associated with antiviral activity, was BLQ in 8 of 12 subjects following administration of EVG+COBI+CBZ, resulting in a mean (%CV) EVG C_{tau} of 20.4 (94.0) ng/mL, which was below the protein binding-adjusted concentration that resulted in 95% inhibition (IC_{95}) for wild-type virus (44.5 ng/mL).

Following administration of EVG+COBI+CBZ, CBZ exposure (AUC) were modestly increased (43.38%) relative to CBZ alone. The 90% CIs for the GLSMs for CBZ AUC_{tau}, C_{max}, and C_{tau} were above the lack of interaction bounds (70%−143%). Correspondingly, the exposure (AUC) of the CYP3A-mediated metabolite, CBZE, was modestly decreased (35.27%). The 90% CIs for the GLSMs for CBZE AUC_{tau}, C_{max}, and C_{tau} were below the lack of interaction bounds

(70%-143%). These results were expected, as metabolism of CBZ and the formation of CBZE is mediated by CYP3A, which is inhibited by COBI.

Further details of key PK results are summarized below.

EVG PK Parameter	**EVG+COBI+CBZ (Test)**	**EVG+COBI (Reference)**	**GLSM Ratio (%)**	**90% CI**
AUC_{tau}[a] (ng•h/mL)	8588.7 (43.0)	27,261.6 (33.2)	30.70	(28.23, 33.39)
C_{max} (ng/mL)	1184.8 (40.4)	2091.4 (29.1)	54.77	(48.92, 61.32)
C_{tau}[b] (ng/mL)	20.4 (94.0)	591.5 (51.7)	2.99	(2.25, 3.97)
COBI PK Parameter	**EVG+COBI+CBZ (Test)**	**EVG+COBI (Reference)**	**GLSM Ratio (%)**	**90% CI**
AUC_{tau}[a] (ng•h/mL)	1905.7 (46.2)	10,898.9 (33.0)	16.17	(14.33, 18.26)
C_{max} (ng/mL)	423.0 (40.4)	1392.9 (22.2)	28.22	(24.40, 32.63)
C_{tau}[c] (ng/mL)	4.0 (59.2)	52.8 (91.8)	9.78	(6.76, 14.17)
CBZ PK Parameter	**EVG+COBI+CBZ (Test)**	**CBZ (Reference)**	**GLSM Ratio (%)**	**90% CI**
AUC_{tau}[a] (ng•h/mL)	101,909.4 (27.1)	70,293.1 (18.4)	143.38	(135.55, 151.67)
C_{max} (ng/mL)	9171.7 (27.5)	6684.3 (22.7)	140.24	(132.22, 148.75)
C_{tau} (ng/mL)	8208.3 (28.1)	5317.9 (20.8)	151.37	(141.47, 161.97)
CBZE PK Parameter	**EVG+COBI+CBZ (Test)**	**CBZ (Reference)**	**GLSM Ratio (%)**	**90% CI**
AUC_{tau}[a] (ng•h/mL)	5875.5 (23.0)	9081.5 (18.5)	64.73	(63.05, 66.45)
C_{max} (ng/mL)	612.8 (27.2)	848.8 (20.3)	73.47	(69.56, 77.61)
C_{tau} (ng/mL)	426.1 (22.3)	717.2 (22.5)	59.18	(57.09, 61.35)

LLOQ = lower limit of quantitation
Data presented are mean (%CV).
a AUC_{tau} is AUC_{0-24} for EVG and COBI. AUC_{tau} is AUC_{0-12} for CBZ and CBZE.
b C_{tau} values of EVG that were BLQ were treated as LLOQ/2 = 10 ng/mL.
c C_{tau} values of COBI that were BLQ were treated as LLOQ/2 = 2.5 ng/mL.
EVG+COBI+CBZ (N = 12): EVG 150 mg + COBI 150 mg once daily in the morning + CBZ 200 mg twice daily in the morning and evening.
EVG+COBI (N = 14): EVG 150 mg + COBI 150 mg once daily in the morning.
CBZ (N = 14): CBZ 200 mg twice daily in the morning and evening.

Safety Results

Adverse events were reported for 0 subjects in Period 1 (EVG+COBI), for 4 subjects (28.6%) in Period 2 (CBZ), and for 5 subjects (35.7%) in Period 3 (EVG+COBI+CBZ). No deaths or SAEs were reported for this study. One subject discontinued due to an AE of hepatic enzyme increased in Period 3. All AEs were Grade 1 or 2 in severity. For the laboratory evaluations, there were no clinically relevant changes in median laboratory values throughout the study. The subject who discontinued due to an AE of hepatic enzyme increased had Grade 1 elevated gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels at the end of Period 2 (CBZ), and elevated Grade 3 GGT and Grade 2 ALT and AST levels in Period 3 (EVG+COBI+CBZ). The investigator considered the AE related to the study drugs. There were no clinically relevant changes in vital signs, body weight, or ECGs, and there were no indications of suicidal ideation from the Columbia Suicide Severity Rating Score (C-SSRS) questionnaire results.

Conclusions

- Following administration of EVG+COBI+CBZ, relative to the administration of EVG+COBI, exposures of EVG and COBI were markedly decreased likely due to the strong induction of CYP3A by CBZ, and mean EVG trough concentrations were below the protein binding-adjusted IC_{95} for HIV-1.

- Following administration of EVG+COBI+CBZ, relative to the administration of CBZ, exposure of CBZ was modestly increased and exposure of the CYP3A-mediated metabolite CBZE was modestly decreased.

- The study drugs were generally well tolerated in this short-term study in healthy subjects, and there were no new or unexpected safety findings.

- Based on these data, coadministration of CBZ with products containing EVG and/or COBI may result in loss of therapeutic effect and development of resistance.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

The following section discusses the clinical pharmacology of E/C/F/TAF across all supporting studies by individual component (Table 9). The studies are subcategorized by study type and highlight new, previously unsubmitted studies in bold.

Table 9. Clinical Studies Supporting the Clinical Pharmacology of E/C/F/TAF Listed by Study Type and by Individual Components of E/C/F/TAF

	TAF	EVG	COBI	FTC
Studies in Healthy Subjects				
Single/Multiple Dose PK and/or Initial Tolerability	**GS-US-292-0101**	GS-US-183-0102 GS-US-183-0113 GS-US-183-0140 GS-US-236-0110	GS-US-216-0101 GS-US-216-0113	—
Comparative BA/BE	**GS-US-292-0103**	GS-US-216-0116	—	FTC-109 FTC-110 FTC-111
Mass Balance	**GS-US-120-0109**	GS-US-183-0126	GS-US-216-0111	FTC-106
QT/QTc Interval	**GS-US-120-0107**	GS-US-183-0128	GS-US-216-0107	—
Studies in HIV-Infected Subjects				
Sparse and/or Intensive PK	**GS-US-292-0102** **GS-US-292-0104** **GS-US-292-0106** **GS-US-292-0111** **GS-US-292-0112** **GS-US-120-0104** **GS-US-292-0109**	GS-US-183-0101	—	FTC-101 FTC-102 FTC-303 143-001
Intrinsic Factor Studies				
Race/Ethnicity	**GS-US-292-0108**	—	—	—
Renal Impairment	**GS-US-120-0108**	—	GS-US-216-0121 GS-US-216-0124	FTC-107
Hepatic Impairment	**GS-US-120-0114**	GS-US-183-0133	—	FTCB-101
UGT1A1	—	**GS-US-183-1004**	—	—
Extrinsic Factor Studies				
Food Effect	**GS-US-292-0110**	GS-US-236-0105	—	—
Drug Interaction	**GS-US-311-0101** GS-US-342-1167	GS-US-183-0103 GS-US-183-0119 GS-US-183-0146 GS-US-216-0120 GS-US-216-0122 GS-US-236-0106 GS-US-236-0120 GS-US-236-0135	**GS-US-292-1316** GS-US-216-0112 GS-US-216-0123 GS-US-216-0125 GS-US-216-0134 **GS-US-216-0137** GS-US-344-0102	FTC-108

BA = bioavailability; BE = bioequivalence
Study numbers in bold text (new studies) have narratives provided in Section 2 of this document, Section 2 of m2.7.3, or Section 1 of m2.7.4.

3.1. ADME Characteristics

3.1.1. Absorption

3.1.1.1. In Vitro/Nonclinical Studies

TAF PK has been extensively characterized in vitro and in nonclinical species. TAF PK is characterized by rapid absorption across species with a time to peak plasma concentration (T_{max}) of 0.08 hours in mouse and dog and 0.5 hours in monkey. TAF was undetectable in any of the rat plasma samples. TAF plasma concentrations decline rapidly with a $t_{1/2}$ of < 1 hour, with concentrations undetectable in plasma by 5 hours postdose in both dog and monkey, respectively. 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 bioavailability of TAF increased with increasing dose in dogs and the observed oral bioavailability 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 (BDC) dog, the fraction absorbed was at least 41% based on excretion in urine and bile. Therefore, hepatic extraction was calculated to be approximately 65%.

EVG shows moderate oral bioavailability in rats and dogs with values similar in fasted and nonfasted animals. From studies with [^{14}C]EVG, this likely reflects moderate absorption of EVG and modest first-pass elimination. Studies in vitro also showed EVG to have modest permeability in LLC-PK1 cell monolayers. EVG was subject to polarized efflux in P-gp–expressing cells, but in clinical studies with coadministration of EVG with known inhibitors or inducers of P-gp, there were no clinically meaningful interactions attributable to effects on P-gp.

COBI is well absorbed with estimated fraction absorbed in vivo to be > 50%. After moderate doses, oral bioavailability in nonclinical species is low due to metabolic instability and resulting high first-pass elimination. COBI can act as a substrate for P-gp and breast cancer resistance protein (BCRP) intestinal efflux transporters, but this likely does not play a significant role during its absorption since COBI has high passive permeability, as demonstrated in Caco-2 cells.

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

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 absolute bioavailability of TAF has not been evaluated.

TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by COBI reduces P-gp–mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed. Cumulative results from Studies GS-US-292-0103 (Section 2.2.1.2), GS-US-292-0101 (Section 2.2.1.1), and GS-US-311-0101 (Section 2.5.2.1) 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 alone.

The effect of food on the absorption/bioavailability of boosted TAF was evaluated when given as part of E/C/F/TAF (GS-US-292-0110 [Section 2.5.1.1]) and the modest changes in TAF exposure upon E/C/F/TAF administration with food (versus fasted) are unlikely to be clinically relevant (approximately 15% and 18% higher AUC with light or high-fat meal, respectively, versus fasted).

EVG

The absolute bioavailability of EVG, in the context of the E/C/F/TAF formulation, has not been evaluated, but it is likely to be high based on the evaluation of EVG PK following unboosted versus boosted administration in human subjects.

The pharmacophore of HIV integrase (IN) inhibitors such as EVG forms a complex with divalent cations (Mg^{2+}) at the active site of the IN enzyme. Such binding with cations predisposes EVG and IN inhibitors, in general, to local gastrointestinal (GI) drug-antacid interactions upon coadministration due to high concentrations of divalent and trivalent cations in antacids. Due to the prevalent use of acid-reducing agents in the HIV-infected population, clinical studies were performed to assess the effect of antacid-based interactions and to delineate them from the general influence of gastric pH on EVG absorption.

As a result, the PK of boosted EVG in the presence of acid-reducing agents was evaluated using simultaneous or staggered administration of antacid (20 mL of magnesium hydroxide/aluminum hydroxide; 2000 mg each total dose), staggered or coadministration with a representative proton pump inhibitor, omeprazole (40 mg once daily), using different boosters for EVG (ritonavir [RTV] or COBI), and staggered or coadministration with a representative H_2-receptor antagonist, famotidine (40 mg once daily) (Studies GS-US-183-0119, GS-US-216-0120, and GS-US-216-0122).

The effect of food on the absorption/bioavailability of boosted EVG was evaluated using STB. EVG exposure was higher with food compared with fasted dosing, likely due to improved solubility under fed conditions. The increase in EVG exposures between a light meal and a high-calorie/high-fat meal is not considered to be clinically relevant. However, it is

recommended that E/C/F/TAF be administered with food to achieve the EVG exposure that provides a high mean 95% inhibitory quotient (IQ_{95}; EVG trough concentration [C_{tau}]/IC_{95}). The results are summarized in the CSR (GS-US-236-0105). Boosted EVG, specifically, STB and, as a result, E/C/F/TAF were administered with food throughout their respective clinical development programs.

COBI

The absolute bioavailability of COBI has not been evaluated; COBI displays greater than dose-proportional increases in plasma exposure due to a combination of reduced systemic clearance and higher bioavailability via autoinhibition of its own metabolism by CYP3A, which is its desired PD effect.

COBI has 3 basic ionizable groups with pKa of 6.4, 2.5, and 1.8. The intrinsic aqueous solubility of COBI free base (0.075 mg/mL, pH ~7) is significantly enhanced under acidic conditions at pH 2 (70 mg/mL). Being a mechanism-based inhibitor of CYP3A, COBI exhibits both dose/concentration- and time-dependent inhibition of CYP3A, and its ability to effectively boost EVG or any other CYP3A substrate is dependent on the concentrations that are achieved presystemically and/or systemically. Accordingly, clinical studies were conducted to examine the relative bioavailability and disposition of COBI (in combination with EVG) when coadministered with acid-reducing agents (Studies GS-US-216-0120 and GS-US-216-0122).

The effect of food on the absorption/bioavailability of COBI and its pharmacoenhancing abilities on EVG was evaluated using STB (GS-US-236-0105). The effect of food on COBI exposure did not negatively affect EVG exposure. These data support the selection of the COBI 150-mg dose, and the overall dosing recommendation of COBI administration with food.

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).

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 10) 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 ~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 (~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 ~0.075 μg/mL, which is approximately 5-fold higher than the mean in vitro 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 10. 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 BID	59.5 (42%)	253 (41%)
	8 (7M/1F) HIV-infected 40 (27-59) years	100 mg BID	72.8 (27%)	244 (38%)
	8 (6M/2F) HIV-infected 33 (25-41) years	200 mg BID	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%)

F = female; M = male
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 the percent 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 percent 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 (m4.2.2.3, 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.

EVG plasma protein binding was high in all species and showed no clear concentration dependence. In humans, the unbound fraction in plasma was 0.6% to 0.7%. Similar binding was found in ex vivo clinical plasma samples. For humans, the whole blood to plasma ratio for EVG was 0.7, reflecting modest distribution into the cellular components of human blood. Following oral administration of [^{14}C]EVG to rats, radioactivity was rapidly and widely distributed. Tissue to plasma concentration ratios were > 1 for the liver and GI tract, but were in the range 0.2 to 0.5 in most other tissues. Radioactivity was largely excluded from the CNS and eye. Tissue concentrations of radioactivity declined largely in parallel with those in plasma, with almost complete elimination by 96 hours postdose. Treatment of rats with RTV had no effect on the exclusion of [^{14}C]EVG-derived radioactivity from the CNS.

COBI shows moderately high plasma binding. After oral dosing with [^{14}C]COBI, radioactivity is widely distributed, and volumes of distribution of COBI are close to those for body water. COBI is relatively excluded from the cellular fraction of blood (whole blood to plasma ratios are approximately 0.6) and from brain, testes, and the eye. Exclusion from the brain may be due to the action of P-gp and/or BCRP at the blood:brain barrier. COBI shows preferential binding in melanin-containing tissues, but this is reversible.

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 CNS tissues reach approximately 2% to 9% of those in plasma.

The results of nonclinical studies investigating the distribution of TAF, EVG, COBI, and FTC 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 with the percent unbound value of 20% based on multiple human ex vivo studies with the mean percent unbound TAF ranged 14% to 23% (GS-US-120-0108 [Section 2.4.2.1] and GS-US-120-0114 [Section 2.4.2.2]). 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.

EVG

Based on equilibrium dialysis studies (in vitro and plasma samples from HIV-infected subjects and healthy subjects from clinical studies, including subjects with renal or hepatic impairment), EVG was, on average, 98% to 99% bound to human plasma proteins regardless of concentration, with preferential binding to albumin over α_1-acid glycoprotein (AAG) (JTK303-AD-013). After a single oral 50-mg dose of boosted [^{14}C]EVG in healthy subjects, the blood-to-plasma ratio of total ^{14}C-radioactivity was time-independent and approximately 0.73, indicating that EVG and its metabolites are predominantly distributed to plasma relative to the cellular components of the blood (GS-US-183-0126).

The distribution of EVG into compartments other than plasma (eg, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated.

COBI

Consistent with observations in nonclinical species, the plasma protein binding of COBI was 97.3% in samples from clinical studies with healthy human subjects, which occurred in a concentration-independent manner (AD-216-2076 and AD-216-2026). After an oral 150-mg dose of [^{14}C]COBI in healthy subjects, the blood-to-plasma ratio of ^{14}C-radioactivity was time-independent and approximately 0.5, indicating that COBI and its metabolites are excluded from the cellular components of the blood (GS-US-216-0111).

The distribution of COBI 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 bioavailability (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 bioavailability (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 (0.02-200 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 (~5 μg/mL on average) than plasma concentrations determined at 1.5 to 3.5 hours postdosing.

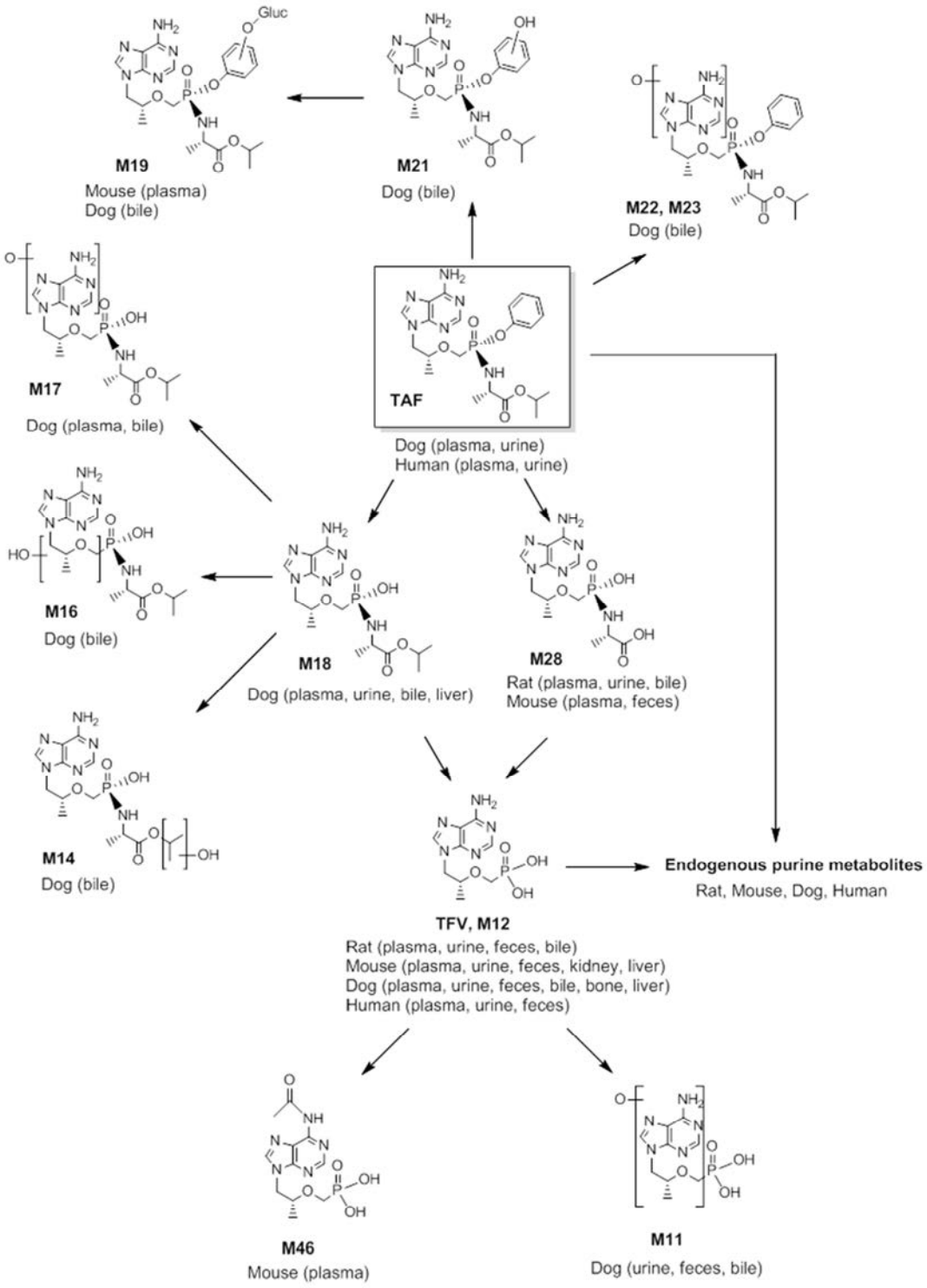
3.1.3. Metabolism and Elimination

3.1.3.1. In Vitro/Nonclinical Studies

The biotransformation of TAF was studied in mice, rats, dogs, and humans (Figure 7). 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 is recovered in the feces or urine in all species. The elimination of a large amount of radioactivity in bile of BDC dogs indicates that biliary excretion is a major route of elimination of [^{14}C]TAF-derived radioactivity in dogs. Total recovery of radiolabel is 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 7. Biotransformation Pathway of TAF



EVG is metabolized extensively in rats and dogs by oxidation and glucuronidation. In samples from rats and dogs in vivo, and in samples from hepatic microsomal fractions from a variety of species, the majority of the biotransformation can be accounted for by 8 metabolites (M1-M8). The most abundant metabolite is M1 (GS-9202, p-hydroxylated-EVG), with lesser amounts of M4 (GS-9200, EVG acyl glucuronide) and M7 (JTP-74488, M1 glucuronide), but parent EVG is the most abundant component circulating in plasma. In bile from rats dosed with [^{14}C]EVG, the majority of the radiolabel was associated with glucuronide metabolites. However, in rat and dog feces from animals dosed with [^{14}C]EVG, the majority of the radioactivity was accounted for by EVG and oxidative metabolites, suggesting that biliary conjugates were cleaved in the intestine. The excretion of radioactivity, following IV or oral administration of [^{14}C]EVG, was studied in rats and dogs. Excretion in bile and feces were the major routes with ≤ 1% excreted in the urine. In all cases, excretion of radioactivity was largely complete by 48 hours postdose. There was low potential for enterohepatic recirculation of radioactivity. Low levels of EVG were excreted in rat milk, in proportion to plasma concentrations.

COBI is an intended mechanism-based inhibitor of human CYP3A enzymes. Due to the species specificity, COBI shows high clearance in nonclinical species due to a lack of self-inhibition of metabolism. The primary routes of metabolism of COBI are oxidation by CYP3A (major) and CYP2D6 (minor) enzymes. Metabolites M21, M26, and M31 were identified in mouse, rat, dog, and human samples in vitro, and were later identified in excreta from these species. One other primary metabolite, M39, was also identified in all species in vivo. Other metabolites arise from secondary metabolism, due to combinations of these primary pathways, and from other minor primary metabolites. Parent COBI is the major component circulating in plasma in all species. After oral dosing of mice, rats, dogs, and humans with [^{14}C]COBI, the majority of the radiolabel is recovered in the feces or bile with little in the urine. Total recovery of the radiolabel is high for all species. Excretion of COBI into milk was detected in rats.

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. Because of the highly restricted substrate specificity of the enzymes catalyzing the phosphorylation of FTC and TFV, inhibition of pharmacological activation by EVG or COBI is unlikely. Since FTC and TFV are almost exclusively eliminated by renal excretion, while very little EVG or COBI is excreted in the urine, interactions between the compounds during excretion are unlikely.

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.

The mass balance and PK of TAF following administration of an oral dose of [^{14}C]TAF in healthy subjects were evaluated in Study GS-US-120-0109 (Section 2.2.2.2). Serial blood (whole blood and plasma), urine, and stool samples were obtained. Metabolism is a major elimination pathway for TAF in humans, accounting for > 80% of an oral dose. TFV, the major metabolite, emerges in plasma with time to peak ranging from 0.25 to 3 hours postdose. TAF and TFV have a median plasma half-life of 0.51 and 32.37 hours, respectively.

Following administration of [^{14}C]TAF in humans, TAF is extensively metabolized and excreted in feces and urine as major metabolite, TFV. The predominant species detected in feces and urine was TFV. All other metabolites detected in the feces and urine were in trace amounts, with no values exceeding 2% of the administered radioactive dose (Table 11 and Table 12, respectively). Renal excretion of TAF as parent drug was a minor pathway (< 1%) (GS-US-120-0108 [Section 2.4.1.1]). The human data are consistent with the established nonclinical profile of TAF.

Table 11. Percent of Total ^{14}C-Radioactivity Present as [^{14}C]TAF Metabolites in Pooled Feces From All Sampling Intervals by HPLC

[^{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)

Note: M29 = unknown; M43 = unknown
Source: m5.3.3.1, GS-US-120-0109, Section 15.1, Table 8.1

Table 12. Percent of Total ^{14}C-Radioactivity Present as [^{14}C]TAF Metabolites in Pooled Urine From All Sampling Intervals by HPLC

[^{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)

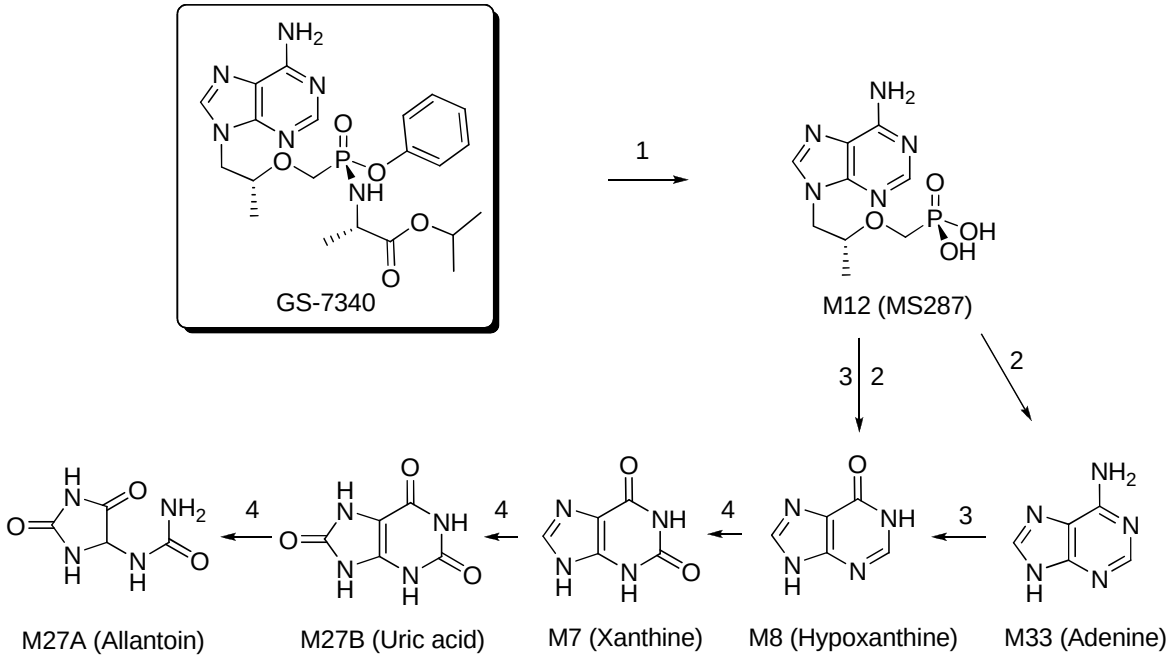
Note: M27B = uric acid; M7 = xanthine; M8 = hypoxanthine
Source: m5.3.3.1, GS-US-120-0109, Section 15.1, Table 7.1

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 8. TAF is primarily metabolized via the purine catabolic pathway following conversion to TFV.

Figure 8. Proposed Biotransformation Pathway of TAF in Humans



Note: GS-7340 = TAF; M12 = TFV
Note: Pathways are proposed based on general knowledge of metabolism and do not imply definitive pathways. Direct experimentation was not performed.
Source: m5.3.3.1, GS-US-120-0109, Section 10.8.4, Figure 10-8

EVG

The mass balance, PK, and metabolite profile of EVG following administration of an oral dose of boosted [^{14}C]EVG in healthy subjects were evaluated in Study GS-US-183-0126. Serial blood (whole blood and plasma), urine, and stool samples were obtained for analysis while subjects were confined to the clinic during sample collection, with the exact interval based on the measured recovery of radioactivity. Quantifiable levels of ^{14}C-radioactivity in whole blood and plasma were observed for up to 36 and 48 hours, respectively, following a single dose of boosted [^{14}C]EVG.

Following administration of boosted [^{14}C]EVG, recovery of the radioactive dose was primarily from the feces (94.8%) relative to urine (6.7%), suggesting primarily hepatobiliary excretion of EVG. The combined fecal and urinary recovery (101.4% ± 4.2%) accounted for the entire administered radioactive dose.

In plasma, the predominant circulating species was EVG (approximately 94%), with the remaining radioactivity made up of low levels of metabolites from hydroxylation and/or glucuronidation pathways, including GS-9200 and GS-9202 (the M4 and M1 metabolites of

EVG, respectively). Quantifiable levels of GS-9200 were observed only up to 8 hours postdose, and represented < 5% of the parent exposure. Plasma exposures of the CYP3A-mediated metabolite, GS-9202, were generally BLQ, consistent with its inhibition by pharmacoenhancers such as RTV or COBI. Low levels of minor metabolites M7 (phenyl-hydroxylated-EVG-glucuronide) and M19 (isopropylhydroxylated-EVG-glucuronide-3) were observed at a few postdose time points (< 3% of parent exposure). Trace levels of glucuronides and hydroxylated metabolites were also observed.

Radioactivity in urine (approximately 6.7% of the administered dose) consisted primarily of 4 minor metabolites each representing > 1% of the administered dose. Several trace metabolites (< 1% of the dose) were observed. No parent drug was detected in urine. The 4 minor metabolites, M19, M7, M20 (quinolone-hydroxylated-EVG-glucuronide), and GS-9200 accounted for means of 1.48%, 1.44%, 1.41%, and 1.26% of the administered dose, respectively (Table 13). Consistent with the minimal excretion of EVG in the urine, no clinically relevant changes in EVG PK were noted in subjects with severe renal impairment in Study GS-US-216-0124.

Table 13. Percentage of Total ^{14}C-Radioactivity Present as [^{14}C]EVG Metabolites in Pooled Urine from All Sampling Intervals by HPLC Radiochemical Analysis

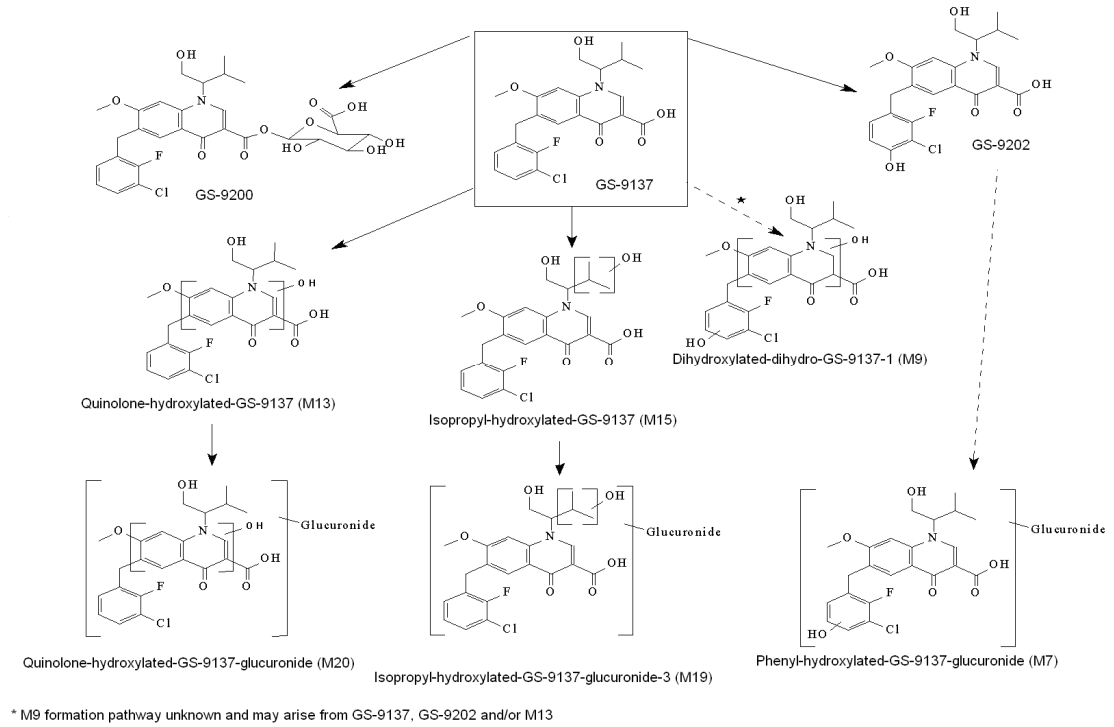
[^{14}C]EVG Metabolite	Mean (%CV) Percent of Total Radioactivity
GS-9200 (M4)	1.26 (22.7)
GS-9202 (M1)	0.2[a]
M7	1.44 (30.7)
M19	1.48 (33.3)
M20	1.41 (37.3)

a n = 1
Source: GS-US-183-0126, Section 11.1, Table 6.1

The radioactivity in feces (pooled samples) was accounted for mainly by EVG and hydroxylation products. The presence of EVG in feces (30.8%) is likely a combination of unabsorbed drug from the GI tract, biliary secretion of EVG, and biliary secretion of GS-9200 converted back to EVG by the β-glucuronidases in the intestinal microflora. Metabolites in the feces included GS-9202 (33.8%) and low levels of M9 (dihydroxylated-dihydro-EVG-1; 1.49%-3.26%), M13 (quinolone-hydroxylated-EVG; 1.44%-2.83%), and M15 (isopropylhydroxylated-EVG; 3.48%-7.37%) in some samples.

A proposed biotransformation pathway for [^{14}C]EVG is shown in Figure 9. EVG is primarily metabolized via aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation.

Figure 9. Proposed Biotransformation Pathway of EVG in Humans



Source: GS-US-183-0126, Figure 7-10

The rates of metabolism of [^{14}C]EVG by recombinant baculovirus-expressed human CYPs (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5) were determined by quantifying the loss of parent and the formation of mono- and di-hydroxylated metabolites (JTK303-AD-017 and JTK303-AD-017 Amendment). EVG was predominantly metabolized by CYP3A4, and the resulting pattern of metabolites most closely resembled that generated by human hepatic microsomal fractions. EVG was also incubated with microsomal fractions containing 12 individual recombinant baculovirus-expressed human UGTs (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, and 2B17) (AD-183-2034). UGT1A1 and UGT1A3 generated appreciable amounts of GS-9200, suggesting that these would be the major catalysts for the glucuronidation of EVG in humans.

COBI

The mass balance, PK, and metabolite profile of COBI following administration of an oral dose of boosted [^{14}C]COBI in healthy subjects were evaluated in Study GS-US-216-0111. Serial blood (whole blood and plasma), urine, and stool samples were obtained for analysis while subjects were confined to the clinic during sample collection. Quantifiable levels of ^{14}C-radioactivity in whole blood and plasma were observed for up to 28 and 32 hours, respectively, following administration of [^{14}C]COBI.

Following oral administration of [^{14}C]COBI in humans, COBI is extensively metabolized. COBI is primarily metabolized via CYP3A- and/or CYP2D6-mediated oxidation, with no evidence of Phase 2 metabolism. The total combined mean (SD) recovery of ^{14}C-radioactivity in feces and urine was 94.4% (3.75%), with most of the radioactive dose recovered from the feces (86.2% [3.95%]), consistent with the hepatobiliary excretion of COBI and primarily as parent drug or metabolites M21 (GS-9454, or E1) or M31 (GS-9612, or E3); 8.2% of the administered dose was recovered in urine, primarily as unchanged parent drug and with low levels of metabolites M21 and M31. The predominant species circulating in plasma was COBI, which accounted for 98.6% of the total ^{14}C-radioactivity over 24 hours. In some instances at individual time points (≤ 2 time points), low levels of radioactive metabolite(s) were detected in pooled plasma samples; however, composite concentration-time profiles could not be drawn, precluding quantification of these metabolites.

Analysis by high-performance liquid chromatography (HPLC) radiometry and liquid chromatography/tandem mass spectrometry (LC/MS/MS) showed that COBI was the major species in the feces (27%), followed by known oxidative metabolites, E3 (14%), which results from hydroxylation of isopropyl thiazole; and E1 (5.5%), which results from carbamate cleavage. All other metabolites detected in the feces were in trace amounts, with no values exceeding 3% of the administered radioactive dose as shown in Table 14.

Table 14. Percentage of Total ^{14}C-Radioactivity Present as [^{14}C]COBI Metabolites in Pooled Feces from All Sampling Intervals by HPLC

[^{14}C]COBI Metabolite	Mean (SD) Percent of Total Radioactivity
M10	1.20 (0.53)
M57	0.21 (0.40)
M14	2.40 (0.42)
M59	0.10 (0.28)
M60	0.11 (0.30)
M21	5.47 (0.88)
M48	1.09 (0.26)
M26	2.37 (0.78)
M49	1.90 (1.34)
M72	0.34 (0.46)
M73	1.15 (0.10)
M31	14.04 (3.20)
M64	0.80 (0.55)
M74	1.16 (0.75)
M75	0.16 (0.46)
M76	0.41 (0.45)
M39	2.41 (0.42)
COBI	26.94 (2.82)

M57, M59, M60, M72, M73, M64, and M75 are unknown; M10 is N-des isopropyl-4-methylthiazole-GS-342006; M14 is Oxy GS-342006; M21 is E1 (GS-9454, GS-342006); M31 is E3 (GS-9612, GS-364751); M48 is Dioxy GS-9350-1; M26 is E5 (GS-341842); M49 is Dioxy GS-9350-2; M74 is Oxy GS-9350-3; M76 is Desmethyl GS-9350; and M39 is Desethyl COBI.
Source: GS-US-216-0111, Section 11.1, Table 6.1

The renal excretion of COBI was a minor pathway for elimination. In urine samples pooled for individual subjects by collection interval and analyzed by HPLC, a mean (SD) of 6.31% (1.15%) of the total radioactive dose was quantified and was comprised primarily of COBI. Known metabolites E1 (M21, GS-9454, GS-342006) and E3 (M31, GS-9612, GS-364751) were present in low amounts (ie, < 10% of the administered dose was present in urine as parent drug plus metabolites) as shown in Table 15.

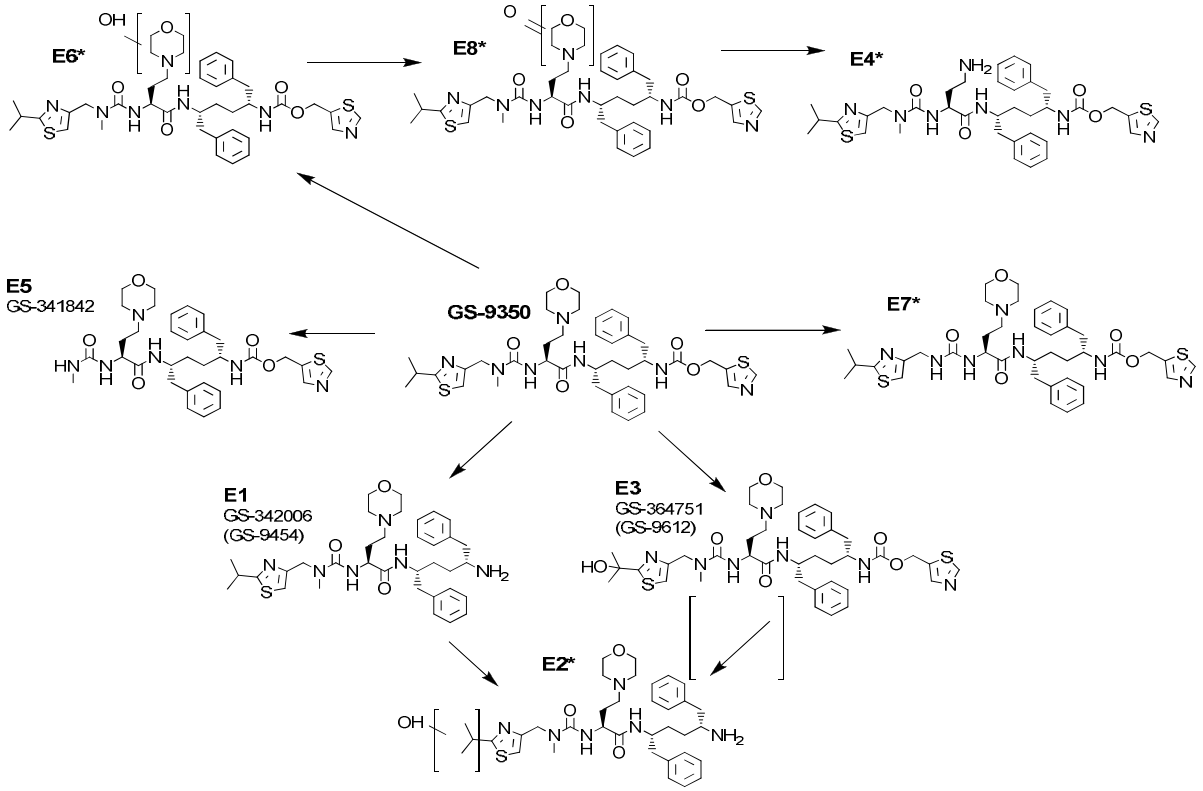
Table 15. Percentage of Total ^{14}C-Radioactivity Present as [^{14}C]COBI Metabolites in Pooled Urine from All Sampling Intervals by HPLC

[^{14}C]COBI Metabolite	Mean (SD) Percent of Total Radioactivity
M55	0.03 (0.05)
M56	0.01 (0.03)
M10	0.01 (0.02)
M14	0.01 (0.02)
M21	0.09 (0.04)
M31	0.7 (0.20)
COBI	5.45 (0.99)
M77	0.02 (0.04)

M55 and M56 are unknown; M10 is N-des isopropyl-4-methylthiazole-GS-342006; M14 is Oxy GS-342006; M21 is E1 (GS-9454, GS-342006); M31 is E3 (GS-9612, GS-364751); and M77 is Oxy COBI-4.
Source: GS-US-216-0111, Section 11.1, Table 5.1

A proposed biotransformation pathway for [^{14}C]COBI is shown in Figure 10. COBI is primarily metabolized via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation, with no evidence of Phase 2 metabolism.

Figure 10. Proposed Biotransformation Pathway of COBI in Humans

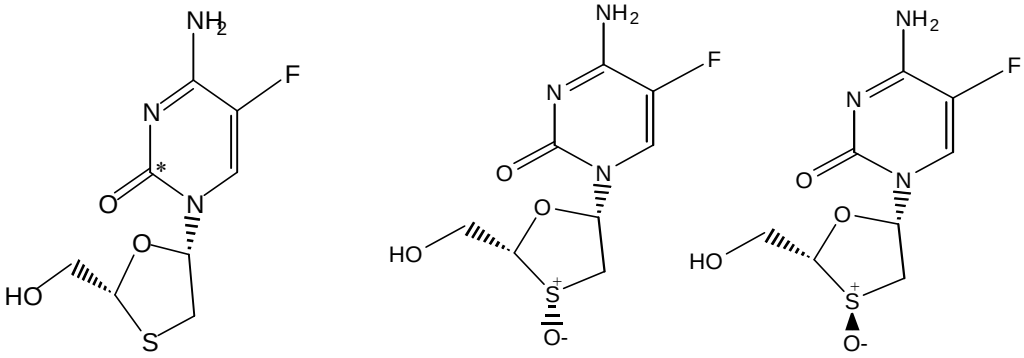


E1, E3, and E5 were generated by humans, mice, rats, and dogs; E2, E4, E6, E7, and E8 were generated exclusively by dogs.
Source: GS-US-216-0111, Figure 7-8

FTC

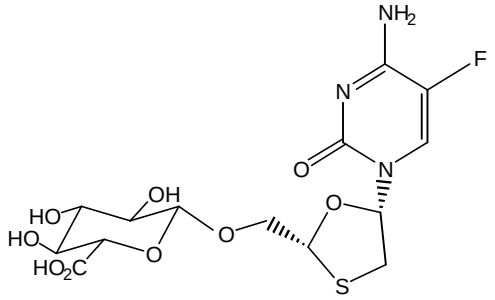
FTC is primarily eliminated from the plasma via renal excretion as unchanged drug (~65% of an oral dose and ~73% of an IV dose). Metabolism is a minor route of elimination. In a mass balance study with [^{14}C]FTC, an average of 65% to 70% of an oral FTC dose was excreted in urine as unchanged drug, 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 (Study FTC-106). Three putative metabolites were isolated, with structures tentatively identified by mass spectrometry (Figure 11).

Figure 11. Putative Metabolites of FTC



Emtricitabine (FTC) **M1 and M2** (3'-Sulfoxide Diastereomers of Emtricitabine)

*:indicates the site of ^{14}C label



M3 (2'-O-Glucuronide of Emtricitabine)

Source: FTC-106, 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 (Study 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 (Report 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 multi-exponential (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 10).

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

3.1.3.3.1. Key Cytochrome P450 Interaction Potential for TAF

The potential for TAF and TFV to inhibit or induce major human drug metabolizing CYPs was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (m4.2.2.6, AD-120-2003 and V990172-104). Based on the totality of data, TAF administered as E/C/F/TAF is not expected to have clinically meaningful CYP-mediated interaction potential. The clinical drug-drug interaction (DDI) potential of E/C/F/TAF is discussed further in Section 3.2.3.2.

3.1.3.3.2. Key Cytochrome P450 Interaction Potential for EVG

The potential for EVG to inhibit major human drug metabolizing CYPs was evaluated using pooled human hepatic microsomal fractions and enzyme-specific activities (JTK303-AD-027 and AD-183-2035). EVG showed no detectable inhibition of human hepatic microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 activity (IC_{50} > 30 μg/mL), and weak inhibition of CYP3A at concentrations > 10-fold above the C_{max} observed in HIV-infected subjects (IC_{50} 28.3 μg/mL). EVG is thus unlikely to cause drug interactions through inhibition of the metabolism of other drugs.

EVG is a weak inhibitor of human P-gp and organic anion transporting polypeptide (OATP) 1B1, but was a more potent inhibitor of human OATP1B3 (IC_{50} 0.44 μM) (JTK303-AD-026 and AD-183-2030). From these data, EVG is predicted to have very low liability to cause drug interactions through inhibition of human CYPs or P-gp.

The potential for EVG to cause drug interactions through induction was assessed in primary cultures of human hepatocytes (JTK303-AD-023). EVG at concentrations up to 10 μg/mL resulted in a ≤ 1.6-fold increase of CYP1A2 activity compared with approximately 48-fold increase for the positive control. These data indicate that, at clinically relevant concentrations,

EVG does not induce CYP1A2 and is very unlikely to cause interactions through activation of aryl hydrocarbon receptor (AhR).

Treatment with EVG resulted in concentration-dependent increases of CYP3A activity, with calculated mean increases of 18.9% of the positive control at EVG 1 μg/mL, which increased to a mean of 46.8% of the positive control at EVG 10 μg/mL (JTK303-AD-023). These data suggest that EVG is a weak inducer of CYP3A activity, which is countered upon coadministration with potent CYP3A-inhibiting PK enhancers, such as RTV or COBI. As such, any increases in CYP3A expression by EVG would be masked and, hence, net inhibitory effects are expected.

The effects of enzyme-selective inhibitors on the oxidative metabolism of [^{14}C]EVG by human hepatic microsomal fraction were determined (JTK303-AD-018). While the CYP2C9-selective inhibitor, sulfaphenazole, and the CYP2D6-selective inhibitor, quinidine, displayed relatively little effect on EVG metabolism, the CYP3A-selective inhibitor, ketoconazole (KTZ), showed potent, concentration-dependent inhibition of EVG and the formation of oxidative metabolites.

The effects of KTZ and the UGT1A1-selective inhibitor, atazanavir (ATV), on the formation of GS-9200 (M4) were determined using human hepatic microsomal fractions (AD-183-2028). ATV was a potent inhibitor of EVG glucuronidation with an IC_{50} value of 0.4 μM. KTZ also inhibited EVG glucuronidation with an IC_{50} of 9.6 μM, consistent with previous reports on inhibition of UGT1A1 by this compound. Collectively, the data indicate that both UGT1A1 and UGT1A3 are responsible for the human hepatic microsomal metabolism of EVG, with UGT1A1 playing a quantitatively more important role. The rates of formation of GS-9200 (M4) from EVG were potently and extensively inhibited by ATV, a selective and potent UGT1A1 inhibitor. Thus, other potent clinical UGT1A1 inhibitors may affect the glucuronidation of EVG in vivo.

The clinical DDI potential of E/C/F/TAF is discussed further in Section 3.2.3.2.

3.1.3.3.3. Key Cytochrome P450 Interaction Potential for COBI

The intended pharmacological effect of COBI is inhibition of human CYP3A enzyme activity. CYP3A inhibition studies in human hepatic microsomal fractions, using an established clinical CYP3A inhibitor, RTV, as a comparator, demonstrated that COBI is a potent inhibitor of all human hepatic microsomal CYP3A activities tested including established CYP3A probe activities (midazolam [MDZ] 1′-hydroxylase, testosterone 6β-hydroxylase, and terfenadine *t*-butyl hydroxylase) and clinically relevant interactions (eg, EVG hydroxylase, ATV oxidase) (AD-216-2028). Studies with MDZ 1′-hydroxylase and testosterone 6β-hydroxylase showed that the apparent inhibitory potency could be increased in a preincubation time-dependent and nicotinamide adenine dinucleotide phosphate, reduced (NADPH) cofactor-dependent manner, suggesting that COBI is a mechanism-based inhibitor of human CYP3A enzymes.

Detailed enzyme inactivation kinetic studies were performed with COBI and RTV (AD-216-2028). COBI was found to be an efficient inactivator of human hepatic microsomal CYP3A activity, with kinetic parameters (k_{inact} = 0.47 min^{-1}, K_I = 1.1 μM) similar to those of

RTV (k_{inact} = 0.23 min^{-1}, K_I = 0.26 μM), but with a higher theoretical maximal inactivation rate and a lower affinity.

COBI does not inhibit CYP2C9 or CYP2C19, and is a weaker inhibitor of CYP2D6 than RTV (AD-216-2029 and AD-216-2070). COBI is expected to be a potent inhibitor of CYP3A activity in humans and to show weak inhibition of CYP2D6 activity. COBI is a weak inhibitor of CYP2C8 activity, with a potency lower than RTV. Although COBI inhibits CYP2B6 activity with a potency very similar to RTV, the IC_{50} lies above the expected human plasma C_{max} value. At clinically relevant plasma concentrations, COBI is unlikely to cause drug interactions by inhibition of CYP2C8, and interactions with CYP2D6 (C_{max}/IC_{50} = 0.16) and CYP2B6 (C_{max}/IC_{50} = 0.53) are likely to be modest and brief. These results are consistent with clinical drug interaction studies in which COBI was found to be a weak inhibitor of CYP2D6 (assessed with desipramine as the probe substrate) and did not inhibit CYP2B6 (assessed with EFV as the probe substrate) (GS-US-216-0112).

3.1.3.3.4. Key Cytochrome P450 Interaction Potential for 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. Based on the totality of data, FTC administered as E/C/F/TAF does not have CYP-mediated interaction potential.

3.1.3.4. Inhibition and Induction Potential of E/C/F/TAF and its Components on Cytochrome P450, Uridine Glucuronosyltransferase, and Human Drug Transporters

3.1.3.4.1. Inhibition Potential of COBI on CYP3A and Other Cytochrome P450 and Uridine Glucuronosyltransferase Isoenzymes

The intended pharmacological effect of COBI is inhibition of human CYP3A enzyme activity. COBI is a potent mechanism-based inhibitor of human CYP3A based on all the human hepatic microsomal activities tested, including established CYP3A probe activities (MDZ 1′-hydroxylase, testosterone 6β-hydroxylase, and terfenadine *t*-butyl hydroxylase) and clinically relevant interactions (EVG hydroxylase, ATV oxidase) (AD-216-2028). The CYP3A inactivation kinetics of COBI are similar to RTV as shown in Table 16.

Table 16. Effect of COBI and RTV on Various Activities Catalyzed by Human Hepatic Microsomal CYP3A Enzymes

	Calculated IC_{50} (μM)	
Activity	**COBI**	**RTV**
MDZ 1′-hydroxylase	0.15	0.11
Testosterone 6β-hydroxylase	0.15	0.12
Terfenadine *t*-butyl-hydroxylase	0.29	0.28
EVG hydroxylase (to metabolite M1)	0.03	0.03
ATV oxidation	0.04	0.04

Source: Report AD-216-2028

The potential for COBI to inhibit various common CYP isoforms is shown in Table 17, and RTV data are presented for comparison. At concentrations up to 25 μM, COBI did not inhibit CYP1A2, CYP2C8, CYP2C9, or CYP2C19 activities. Although COBI displayed weak inhibition of CYP2D6 and relatively stronger inhibition of CYP2B6, the IC_{50} lies above the expected human plasma C_{max} value, and at clinically relevant plasma concentrations, drug interactions with CYP2D6 (C_{max}/IC_{50} = 0.16) or CYP2B6 (C_{max}/IC_{50} = 0.53) are either unlikely or to be modest and brief, as supported by the clinical probe drug interaction study (GS-US-216-0112) in which COBI was found to be a weak inhibitor of CYP2D6 (assessed with desipramine as the probe substrate) and did not inhibit CYP2B6 (assessed with EFV as the probe substrate), and dose modifications are not considered necessary. In contrast, RTV was a much more potent inhibitor of CYP2C8, CYP2C9, and CYP2D6.

Overall, these data indicate that COBI is a selective CYP3A inhibitor, with relatively minimal off-target inhibitory effects on other CYP isoforms and, consequently, fewer drug interactions.

COBI does not inhibit UGT1A1, based on an assessment of β-estradiol metabolism (AD-216-2075).

Table 17. IC_{50} Values for Inhibition of Major Human Cytochrome P450 Enzymes by COBI, RTV, and Positive Control Inhibitors

Enzyme	Activity	Calculated IC_{50} (μM)[a]		
		Control Inhibitor[b]	COBI	RTV
CYP1A2	Ethoxyresorufin O-deethylase	0.03	> 25	> 25
CYP2B6	Bupropion 4-hydroxylase	2.8	2.8	2.9
CYP2C8	Paclitaxel 6α-hydroxylase	0.06	30.1	5.5
CYP2C9	Tolbutamide hydroxylase	1.6	> 25	3.9
CYP2C19	(S) Mephenytoin 4'-hydroxylase	10.8	> 25	> 25
CYP2D6	Dextromethorphan O-demethylase	0.04	9.2	3.4
CYP3A	Midazolam 1'-hydroxylase	0.07	0.15	0.10
	Testosterone 6β-hydroxylase	0.09	0.15	0.11

a Data are presented as mean, N = 6.
b Control Inhibitors: CYP1A2, α-Naphthoflavone (0-100 μM); CYP2B6, Triethylenethiophosphoramide (0-30 μM); CYP2C8 Montelukast (0-30 μM); CYP2C9, Sulfaphenazole (0-10 μM); CYP2C19, Tranylcypromine (0-100 μM); CYP2D6, Quinidine (0-10 μM); CYP3A, Ketoconazole (0-10 μM)
Source: Reports AD-216-2029 and AD-216-2070

3.1.3.4.2. Inhibition Potential of E/C/F/TAF Components on Human Drug Transporters

Results from all the transporter substrate and inhibition studies are summarized in Table 18 and Table 19. FTC, TAF, and TFV do not inhibit any of the transporters tested at clinically relevant concentrations in vitro. Therefore, FTC, TAF, and TFV are unlikely to be a perpetrator of transporter-mediated drug interactions.

COBI is a moderate inhibitor of uptake transporters, OATP1B1 and OATP1B3, and is a weak inhibitor of organic cation transporter (OCT) 2 (Table 19). It also inhibits the renal efflux transporters OCT N1 (organic cation transporter novel, type 1) and multidrug and toxin extrusion (MATE) 1. COBI shows weak or undetectable inhibition of multidrug resistance-associated proteins-1, -2, and -4 (MRP1, MRP2, and MRP4, respectively), BCRP, MATE 2-K (MATE2-K), and the renal uptake transporters, organic anion transporters 1 and 3 (OAT1 and OAT3, respectively), so systemic concentrations of COBI would be insufficient to inhibit their activity. Inhibition of OATP transporters is consistent with a clinical drug interaction study (GS-US-216-0123) in which, after dosing with 150 mg COBI and 150 mg EVG, there was a modest increase in exposure of coadministered rosuvastatin (AUC_{inf} increased approximately 38% compared with the reference treatment).

Table 18. Transporter Substrate Assessment of E/C/F/TAF Components

	Substrate Assessment (y/n)				
Transporter	**EVG**	**COBI**	**FTC**	**TAF**	**TFV**
P-gp	y	y	n	y	n
BCRP	y	y	n	y	n
OATP1B1	y	y	ND	y	ND
OATP1B3	y	y	ND	y	ND
OAT1	ND	ND	n	n	y
OAT3	ND	ND	y	n	y
OCT1	n	n	ND	n	n
OCT2	ND	y	n	ND	n
MRP1	ND	ND	ND	ND	n
MRP2	ND	ND	ND	ND	n
MRP3	ND	ND	n	ND	ND
MRP4	ND	ND	ND	ND	y

BCRP = breast cancer resistance protein; MRP1 2, 3, or 4 = multidrug resistance associated protein 1, 2, or 4; n = no; ND = not determined; OAT1 or 3 = organic anion transporter 1 or 3; OATP1B1 or B3 = organic anion transporting polypeptide 1B1 or B3; OCT1 or 2 = organic cation transporter 1; y = yes
Source: m2.6.4, Section 7

Table 19. Transporter Inhibition Assessment of E/C/F/TAF Components

Transporter	IC_{50} (μM)				
	EVG	COBI	FTC	TAF	TFV
P-gp	69.7	36	> 100	> 100	> 1000
BCRP	88.9	59	> 100	> 100	> 100
BSEP	> 20	6.5	> 100	> 100	> 100
OATP1B1	> 2	3.50	> 100	> 100	> 100
OATP1B3	0.44	1.88	> 100	> 100	> 100
MATE1	2.0	1.87	> 100	> 100	> 300
MATE2-K	ND	33.5	ND	ND	ND
OAT1	> 20	> 100	> 100	> 100	33.8[a]
OAT3	> 20	> 100	> 100	> 100	> 1000
OCT1	> 20	14.7	> 100	> 100	> 100
OCT2	> 20	14.4	> 100	> 100	> 300
OCTN1	ND	2.49	ND	ND	ND
MRP1	ND	45-90	ND	ND	> 500
MRP2	> 20	45-90	> 100	ND	> 100
MRP4	> 20	20.7	> 100	ND	> 1000[b]

BCRP = breast cancer resistance protein; BSEP = bile salt excretory pump; MATE1 or 2-K = multidrug and toxin extrusion protein 1 or 2-K; MRP1 2, or 4 = multidrug resistance associated protein 1, 2, or 4; ND = not determined; OAT1 or 3 = organic anion transporter 1 or 3; OATP1B1 or B3 = organic anion transporting polypeptide 1B1 or B3; OCT1 or 2 = organic cation transporter 1; OCTN1 = organic cation transporter novel, type 1

a Binding constant for uptake into CHO cells reported by Cihlar et al, 2009 {2520}

b Imaoka et al 2007 {10260}

Source: m2.6.4, Section 7

Bidirectional transport experiments were performed in Caco-2 cells using probe substrates digoxin (P-gp) and prazosin (BCRP) to assess the effect of COBI on intestinal transporters (AD-216-2072 and AD-216-2104). At very high concentrations (90 μM), such as those present in the intestinal lumen during drug absorption, COBI reduced the polarized transport of P-gp and BCRP substrates. However, based on the data in Table 19, COBI is a weak inhibitor of these transporters, with no effects expected at concentrations achieved systemically.

3.1.3.4.3. Induction Potential of COBI on Cytochrome P450 and Uridine Glucuronosyltransferase Enzymes

Based on receptor transactivation analysis, COBI showed no significant induction of AhR and weak inhibition of human pregnane X receptor (PXR) (AD-216-2027). Accordingly, induction assays using primary cultures of human hepatocytes indicated no relevant increases in CYP1A2 or CYP2B6 activities over a wide COBI concentration range (1-30 μM). Weak activity was noted for CYP3A at higher concentrations (27% of positive control at 10 μM). At plasma concentrations found in humans, COBI would be expected to have no effect on the expression of secondary targets of PXR, such as CYP2C9, CYP2C19, UGT1A1, and P-gp, and would have

very little effect on the expression of CYP3A4 messenger RNA (mRNA). Any effect on CYP3A enzyme activity would be masked by mechanism-based inhibition.

The clinical DDI potential of E/C/F/TAF is discussed further in Section 3.2.3.2.

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 and TFV After Single- and Multiple-Dose Administration in HIV-Infected and Healthy Subjects

Study GS-US-120-0104 (Section 2.3.1.1) evaluated the PK of TAF and TFV after single and multiple oral dosing of TAF 8, 25, or 40 mg monotherapy (Day 1 and Day 10) in HIV-infected subjects. TAF exhibited linear PK and was rapidly absorbed in a dose proportional manner and eliminated with a median $t_{1/2}$ of approximately 0.40 hours across dose range studied. The PK exposure parameters of TAF were similar within each dose group following single- and multiple-dose administration, as expected given the short plasma half-life of TAF. Consistent with linear PK, TFV single-dose exposures (AUC_{inf}) were comparable with steady-state exposures following multiple dosing (AUC_{tau}).

Following the dose selection of TAF 10 mg for the E/C/F/TAF FDC, a relative bioavailability study was conducted evaluating PK of TAF and TFV after single and multiple oral dosing of FTC+TAF 25 mg or E/C/F/TAF (Day 1 and Day 12) (GS-US-292-0103, Section 2.2.1.2) in healthy subjects (Table 20 and Table 21). The mean TAF exposure following single and multiple dosing was comparable (Day 1 vs Day 12), and the mean TFV exposure following single dosing (AUC_{inf}) was predictive of TFV multiple dose exposure (AUC_{tau}). Additionally, statistical comparisons of TAF and TFV exposures following multiple-dose administration of E/C/F/TAF (test) and FTC+TAF 25 mg (reference) were conducted in Study GS-US-292-0103, demonstrating that the 90% CIs of the GLSM ratios for TAF and TFV exposure were within the predefined lack-of-effect boundary (Table 20 and Table 21) indicating comparability of TAF and TFV exposures following unboosted TAF 25 mg or boosted TAF 10 mg administration.

These data confirmed the dose selection of TAF 10 mg in the context of the E/C/F/TAF FDC, allowing for TAF and TFV exposures that are comparable with the exposures observed with the TAF 25-mg single agent.

Table 20. Single- and Multiple-Dose PK of TAF Following Administration of TAF as a Single Agent or as E/C/F/TAF in Healthy Subjects

TAF PK Parameter	FTC+TAF 25 mg Alone		E/C/F/TAF		GLSM Ratio (%) E/C/F/TAF (Test) vs FTC+TAF 25 mg (Reference) (Multiple Dose) (90% CI)
	Day 1 (Single Dose) (N = 9)	Day 12 (Multiple Dose) (N = 19)	Day 1 (Single Dose) (N = 10)	Day 12 (Multiple Dose) (N = 19)	
AUC (ng•h/mL)[a]	235.7 (29.2)	278.2 (28.8)	244.8 (17.2)	250.2 (24.7)	91.42 (84.12, 99.35)
C_{max} (ng/mL)	158.8 (28.2)	179.5 (33.9)	167.2 (38.6)	176.9 (35.1)	98.68 (84.57, 115.13)

a For TAF, AUC represents AUC_{last} on Days 1 and 12.
Data are presented as mean (%CV).
Source: m5.3.1.2, GS-US-292-0103, Section 10.1, Tables 10-1, 10-2, and 10-3

Table 21. Single- and Multiple-Dose PK of TFV Following Administration of TAF as a Single Agent or as E/C/F/TAF in Healthy Subjects

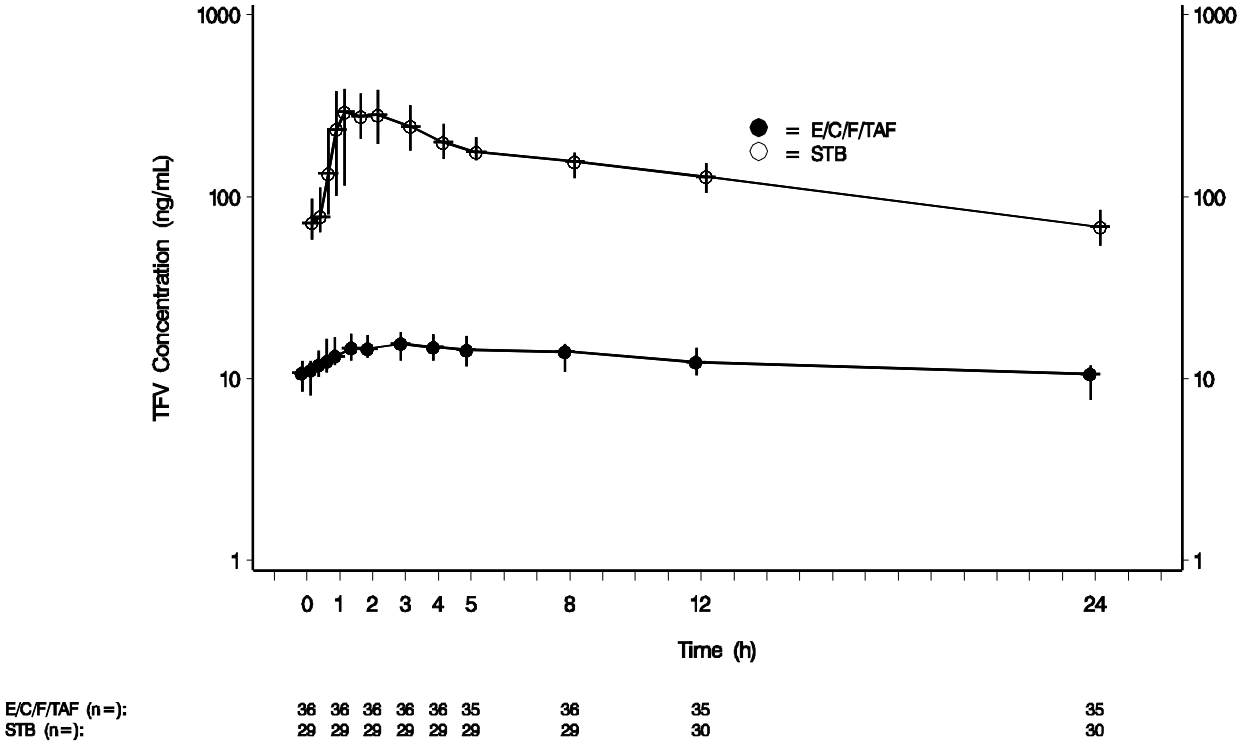
TFV PK Parameter	FTC+TAF 25 mg Alone		E/C/F/TAF		GLSM Ratio (%) E/C/F/TAF (Test) vs FTC+TAF 25 mg (Reference) (Multiple Dose) (90% CI)
	Day 1 (Single Dose) (N = 9)	Day 12 (Multiple Dose) (N = 19)	Day 1 (Single Dose) (N = 10)	Day 12 (Multiple Dose) (N = 19)	
AUC (ng•h/mL)[a]	233.5 (19.7)	265.9 (22.2)	317.0 (27.2)	324.2 (15.4)	123.63 (116.97, 130.67)
C_{max} (ng/mL)	8.6 (20.4)	19.2 (76.0)	8.7 (13.2)	19.6 (13.9)	114.16 (97.52, 133.64)
C_{tau} (ng/mL)[b]	3.0 (16.6)	9.2 (23.5)	3.2 (16.1)	11.4 (17.8)	125.37 (117.72, 133.51)

a For TFV, AUC represents AUC_{inf} on Day 1 and AUC_{tau} on Day 12.
b C_{tau} represents the concentration at the end of the dosing interval for Days 1 and 12
Data are presented as mean (%CV).
Source: m5.3.1.2, GS-US-292-0103, Section 10.1, Tables 10-4, 10-5, and 10-6

3.2.1.1.2. Pharmacokinetics of TFV and TFV-DP After Multiple-Dose Administration of E/C/F/TAF or STB in HIV-Infected Subjects

As discussed 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 each plasma TFV and intracellular TFV-DP 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 12 and Table 22). The distinct metabolism of TAF also provides stable and > 4-fold higher intracellular levels of the active phosphorylated metabolite TFV-DP relative to TDF (Figure 13 and Table 23).

Figure 12. **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 in Pooled Phase 3 Studies (Semilogarithmic Scale, PK Substudy Analysis Set)**



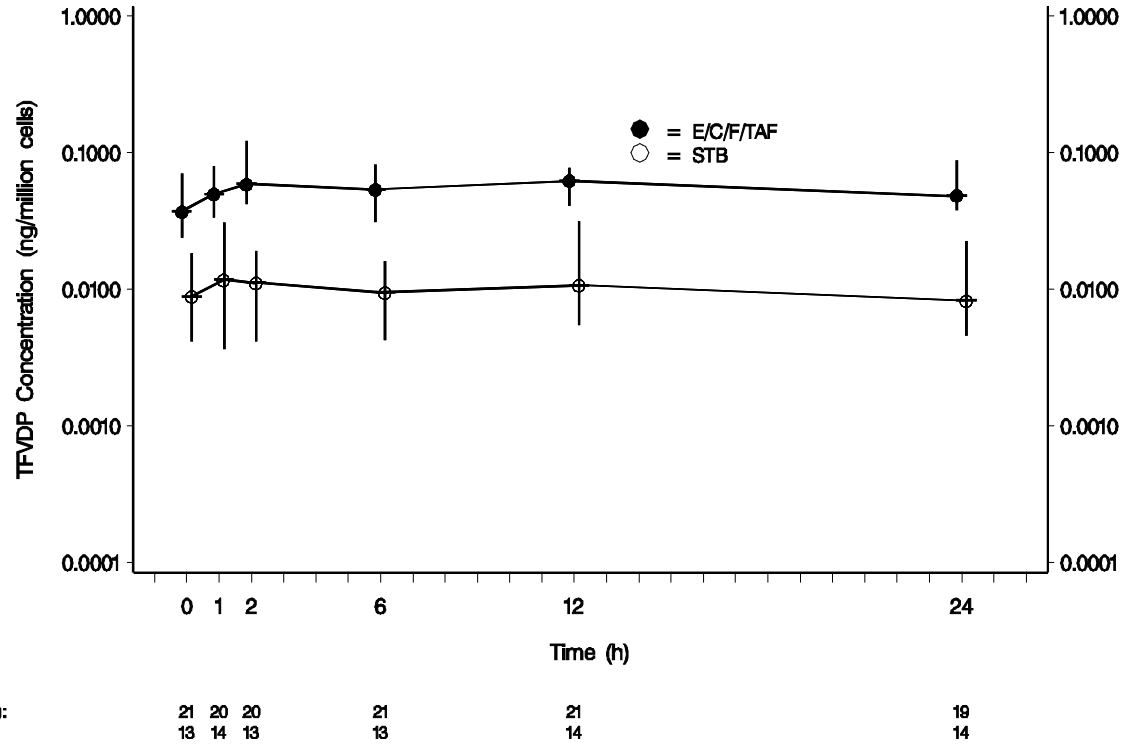
Source: m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Figure 6905.3

Table 22. **GS-US-292-0104 and GS-US-292-0111: Statistical Comparisons of TFV PK Parameter Estimates Between E/C/F/TAF and STB in Pooled Phase 3 Studies (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: m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Table 6905.3

Figure 13. **GS-US-292-0104 and GS-US-292-0111: Median (Q1, Q3) PBMC TFV-DP Concentrations: TFV-DP PK Profile After Administration of E/C/F/TAF or STB in Pooled Phase 3 Studies (Semilogarithmic Scale, PK Substudy Analysis Set)**



Source: m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Figure 6905.4

Table 23. **GS-US-292-0104 and GS-US-292-0111: Statistical Comparisons of TFV-DP PK Parameter Estimate Between E/C/F/TAF and STB in Pooled Phase 3 Studies (PK Substudy Analysis Set)**

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: m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Table 6905.3

Additionally, inclusion of the Phase 2 PK substudy data from Study GS-US-292-0102 following administration with E/C/F/TAF versus STB in HIV-infected subjects showed that results of the pooled Phase 2 and 3 data were consistent with the findings above from pooled Phase 3 data only (GLSM ratio [%] 90% CI [%]: plasma TFV AUC_{tau}: 8.90 [8.20, 9.65]; intracellular TFV-DP AUC_{tau}: 437.25 [285.57, 669.49] (m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Table 6875.3).

3.2.1.1.3. Pharmacokinetics of EVG After Single- and Multiple-Dose Administration in Healthy Subjects

Study GS-US-183-0102 evaluated the PK of EVG after single oral dosing of EVG (100 mg, Day 1) and multiple oral dosing of EVG (100 mg twice daily, Day 10) in the absence or presence of RTV administered orally as a single dose (100 mg, Day 11) or multiple doses (100 mg twice daily, Day 20). During administration of EVG alone, the mean steady-state systemic exposure (AUC_{tau}) to EVG (Day 10) was approximately 20% lower compared with the mean exposure (AUC_{inf}) after a single dose (Day 1), indicating autoinduction of EVG metabolism (Table 24). Coadministration with RTV resulted in a net inhibition of EVG metabolism, as evidenced by both greater-than-predicted steady-state exposures (20-fold higher AUC) and a longer median $t_{1/2}$ (9.5 vs 3.5 hours at steady state). The increase in EVG exposure after coadministration of RTV is likely due to improved oral bioavailability due to decreased first-pass metabolism and reduced systemic clearance, as indicated by a change in observed $t_{1/2}$.

Table 24. Single- and Multiple-Dose (Twice Daily) PK of EVG 100 mg Following Administration Alone or in Combination with RTV 100 mg in Healthy Subjects

	EVG Alone (N = 12)		EVG+RTV (N = 12)	
EVG PK Parameter	Day 1 (Single Dose)	Day 10 (Multiple Dose)	Day 11 (Single Dose)	Day 20 (Multiple Dose)
AUC (ng•h/mL)[a]	908 (28)	719 (26)	6170 (29)[b]	14,300 (24)
C_{max} (ng/mL)	200 (30)	164 (29)	795 (38)	1830 (26)
C_{tau} (ng/mL)[c]	19.2 (53)	12.4 (64)	543 (30)	1040 (32)

a For EVG, AUC represents AUC_{inf} on Day 1 and AUC_{tau} on Days 10, 11, and 20.
b n = 10
c C_{tau} represents the concentration at the end of the dosing interval for Days 1, 10, 11, and 20.
Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: GS-US-183-0102, Section 11.1, Table 5

Study GS-US-183-0140 evaluated the PK of EVG after single and multiple oral dose administration of the EVG+RTV 150/100-mg Phase 3 EVG formulation and 125/100-mg Phase 2 EVG formulation. As shown in Table 25, following dosing, AUC and C_{max} were comparable between single-dose (AUC_{inf}) and multiple-dose (AUC_{tau}) administration of EVG+RTV, indicating substantial inhibition of EVG metabolism/first-pass by RTV with a single dose, consistent with potent CYP3A inhibition. EVG C_{24} was approximately 26% higher (349 to 440 ng/mL), consistent with the development of mechanism-based inhibition of CYP3A by RTV and the consequent reduction in EVG systemic clearance as well as progression to steady-state conditions. EVG T_{max} was similar (approximately 4 hours) following single- or multiple-dose administration.

Table 25. Single- and Multiple-Dose (Once Daily) PK of EVG Administered as EVG+RTV Using the Phase 2 (125 mg) or Phase 3 (150 mg) Formulations in Healthy Subjects

EVG PK Parameter	EVG+RTV Day 1 (N = 12)		EVG+RTV Day 10 (N = 24)	
	125/100 mg	150/100 mg	125/100 mg	150/100 mg
AUC_{inf} or AUC_{tau} (ng•h/mL)	20,800 (59)	20,000 (56)	20,600 (36)	22,100 (32)
C_{max} (ng/mL)	1440 (53)	1410 (50)	2030 (39)	2130 (38)
C_{24} (ng/mL)	361 (67)	349 (62)	408 (51)	440 (48)
T_{max} (h)	4.0 (3.5, 8.0)	4.3 (4.0, 5.0)	4.0 (3.0, 5.0)	4.0 (2.0, 6.0)
$t_{1/2}$ (h)	11 (6.9, 14)	11 (7.3, 14)	8.9 (6.1, 12)	9.1 (6.0, 14)

Data are presented as mean (%CV) or median (min, max) and are shown to 3 significant digits (2 for time parameters).
Source: GS-US-183-0140, Section 11.1, Tables 4.1 and 5.1

The PK data following administration of STB in healthy subjects were obtained from a multiple-dose bioavailability study (GS-US-236-0110), which compared the Phase 3 and intended commercial formulation of STB tablets relative to the formulation used in Phase 2, and also from a single-dose food-effect study (GS-US-236-0105) using the Phase 3 and intended commercial formulation.

EVG AUC and C_{max} were comparable between single (AUC_{inf}) and multiple (AUC_{tau}) doses of STB, indicating substantial inhibition of EVG metabolism by COBI even after a single dose, consistent with potent competitive CYP3A inhibition (Table 26). EVG T_{max} was similar following single- or multiple-dose administration. In comparison, EVG mean C_{24} was approximately 43% higher (508 vs 355 ng/mL) following multiple-dose administration relative to single-dose administration. These results are consistent with those obtained using RTV and mechanism-based inhibition of CYP3A by COBI resulting in reduction in EVG systemic clearance and attainment of steady state.

Table 26. Single- and Multiple-Dose (Once Daily) PK of EVG Administered as STB Using the Phase 3 Formulation in Healthy Subjects

EVG PK Parameter	Day 1[a] (N = 24)	Day 10 (N = 36)
AUC_{inf} or AUC_{tau} (ng•h/mL)	21,100 (28)	22,500 (27)
C_{max} (ng/mL)	1760 (32)	1920 (24)
C_{24} (ng/mL)	355 (54)	508 (41)
T_{max} (h)	4.5 (4.0, 5.0)	4.5 (4.0, 4.5)
$t_{1/2}$ (h)	5.3 (4.7, 6.7)	13 (8.6, 14)

a Data are from the treatment with a light meal.
Data are presented as mean (%CV) or median (Q1, Q3) and are shown to 3 significant digits (2 for time parameters).
Source: GS-US-236-0105, Section 11.1, Tables 3.1 and 4.1; GS-US-236-0110, Section 15.1, Tables 3.1 and 4.1

Clinical data provide evidence for solubility-limited absorption of EVG due to the less than proportional increases in exposures over a wide dose range of 50- to 300-mg equivalent across studies (3- to 4-fold increase EVG AUC over a 6-fold dose range), and also relative to the therapeutic dose (doubling the 150 mg-equivalent therapeutic dose resulted in only approximately 48% increase in EVG AUC) (Table 27).

Table 27. Summary of EVG PK Parameters Across the EVG+RTV Dose Range

EVG PK Parameter	EVG+RTV 50/100 mg (N = 48)	EVG+RTV 125/100 mg (N = 41)	EVG+RTV 250/100 mg (N = 42)
AUC_{tau} (ng•h/mL)	10,700 (28)	24,200 (36)	35,700 (27)
C_{max} (ng/mL)	930 (31)	2270 (35)	3660 (33)
C_{tau} (ng/mL)	211 (40)	450 (49)	632 (38)

Data were generated using the Phase 2 formulation. The 125-mg EVG Phase 2 formulation provides similar exposures as 150 mg of the Phase 3 formulation; the 250-mg dose is expected to provide exposures corresponding to 300 mg of the Phase 3 formulation.
Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: GS-US-183-0119, Section 11.1, Table 5.1; GS-US-183-0128, Section 11.1, Table 25.1

EVG PK and PK/PD have been extensively characterized in the STB development program and EVG exposure was shown to be comparable with STB across E/C/F/TAF Phase 1 and Phase 2 studies (Table 28). Therefore, only the PK of the new study drug TAF was evaluated in the Phase 3 pivotal studies.

Table 28. Summary of EVG PK Parameters Following STB or E/C/F/TAF Administration

EVG PK Parameter	STB[a] (N = 419)	E/C/F/TAF Phase 1 (N = 19)	E/C/F/TAF Phase 2 (N = 19)
AUC_{tau} (ng•h/mL)	23,000 (33)	23,651.0 (33.5)	22,797.0 (34.7)
C_{max} (ng/mL)	1730 (23)	2238.8 (30.2)	2113.1 (33.7)
C_{tau} (ng/mL)	451 (58)	470.4 (44.0)	287.3 (61.7)

a Data shown to 3 significant digits.
Data are presented as mean (%CV).
Source: STB PK/PD Table 1; m5.3.1.2, GS-US-292-0103, Section 10, Table 10-7; m5.3.5.1, GS-US-292-0102, Section 10, Table 10-5

3.2.1.1.4. Pharmacokinetics of COBI After Single- and Multiple-Dose Administration in Healthy Subjects

Pharmacokinetic data following single- and multiple-dose administration of COBI in healthy subjects were obtained from Studies GS-US-216-0101 (COBI dose range: 50 to 200 mg) and GS-US-216-0113 (COBI dose range: 300 to 400 mg).

COBI displayed both dose- and time-dependent changes in CL/F with nonlinear increases in systemic exposure, consistent with the properties of a mechanism-based inhibitor. COBI apparent clearance was 98% lower between the highest and lowest doses in the single-dose range

and 95% lower between the highest and lowest doses in the multiple-dose range, reaching a nadir after single- or multiple-dose administration at ≥ 200 mg. Single doses over an 8-fold dose range yielded a 164-fold range in AUC_{inf} (Table 29). AUC_{inf} increased approximately 6.8-fold as the dose increased 2-fold from 50 to 100 mg, 5.1-fold as dose increased from 100 to 200 mg, and 4.7-fold as dose increased from 200 to 400 mg. The $t_{1/2}$ increased with increasing doses, indicative of a change in the clearance of COBI. Correspondingly, single-dose escalation from COBI 50 to 100 mg and from 100 to 200 mg resulted in dramatic decreases in COBI CL/F (GLSM ratio of 23.55% for 100 vs 50 mg, 38.43% for 200 vs 100 mg, and 68% for 400 vs 300 mg). Nonparametric analyses also showed a large and statistically significant ($p < 0.001$) overall difference in CL/F with increasing dose, indicating changes in COBI relative bioavailability, systemic clearance, or both of these parameters at these doses.

Between 300 and 400 mg, COBI continued to exhibit nonlinear PK with approximately 1.9-fold increase in AUC_{inf}. Overall, these results are consistent with the nonclinical findings in human hepatic microsomes, which demonstrate that COBI is a potent and rapid inactivator of human CYP3A enzymes. Changes in $t_{1/2}$ were modest at COBI doses > 200 mg, suggesting a greater contribution of bioavailability/first-pass exposure increases at higher doses. Increasing doses of COBI were associated with comparable T_{max} values.

Table 29. COBI Single-Dose PK in Healthy Subjects from Studies GS-US-216-0101 and GS-US-216-0113

COBI Dose (mg)	AUC_{inf} (ng•h/mL)	C_{max} (ng/mL)	CL/F (L/h)	$t_{1/2}$ (h)	T_{max} (h)
50	243 (70)	61.6 (57)	435 (92)	1.4 (0.98, 1.8)	3.3 (2.5, 4.3)
100	1650 (48)	343 (35)	77.2 (59)	2.7 (2.3, 3.0)	4.0 (3.5, 4.5)
200	8420 (41)	1200 (30)	29.1 (53)	4.2 (3.3, 5.1)	4.0 (3.5, 4.5)
300	20,800 (28)	2340 (17)	15.5 (29)	5.2 (4.3, 5.8)	3.8 (3.5, 4.5)
400	39,900 (26)	4110 (17)	10.6 (23)	4.8 (4.1, 4.9)	4.3 (3.8, 4.5)

Data are presented as mean (%CV) or median (Q1, Q3) and are shown to 3 significant digits (2 for time parameters).
Source: GS-US-216-0101, Section 11.1, Table 5.1; GS-US-216-0113, Section 11.1, Table 4

Plasma concentrations of COBI increased with increasing doses, and this effect was greater with multiple-dose administration than with single-dose administration. COBI exhibited nonlinear PK with increasing doses and over time. Similarly, COBI exposure following multiple doses increased in a greater-than-proportional manner relative to the increase in dose (Table 30): AUC_{tau} increased 4.2-fold as the dose increased 2-fold from 50 to 100 mg, 4.7-fold as the dose increased from 100 to 200 mg, and 2.4-fold as the dose increased from 200 to 300 mg. Correspondingly, and as observed for single-dose COBI, CL_{ss}/F of COBI at steady state was reduced with increasing dose levels (GLSM ratio of CL_{ss}/F was approximately 34% for COBI 100 vs 50 mg, approximately 43% for 200 vs 100 mg, and approximately 58% for 300 vs 200 mg). COBI $t_{1/2}$ increased with increasing doses and over time, clearly indicative of changes in the clearance of COBI over doses and time. Overall, upon multiple dosing over a 6-fold range, COBI demonstrated a 47-fold range in AUC_{tau}.

Table 30. COBI Multiple-Dose PK in Healthy Subjects from Studies GS-US-216-0101 and GS-US-216-0113

COBI Dose (mg)	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)	CL_{ss}/F (L/h)	$t_{1/2}$ (h)	T_{max} (h)
50	827 (82)	170 (70)	0.4[a] (350)	154 (100)	2.2 (1.3, 2.5)	4.5 (3.5, 4.5)
100	3440 (34)	563 (31)	4.9[a] (87.0)	33.2 (44)	3.1 (2.6, 3.4)	4.5 (4.5, 4.5)
200	16,100 (34)	1850 (28)	127 (75)	14.0 (38)	5.2 (4.1, 6.1)	4.5 (4.5, 4.5)
300	39,100 (28)	3840 (17)	563 (57)	8.28 (30)	8.1 (5.9, 9.0)	4.0 (3.3, 4.5)

a Data are shown to 2 significant digits.
Data are presented as mean (%CV) or median (Q1, Q3) and are shown to 3 significant digits (2 for time parameters).
Source: GS-US-216-0101, Section 11.1, Table 5.1; GS-US-216-0113, Section 11.1, Table 4

Pharmacokinetic data for COBI were also obtained following administration of STB in Studies GS-US-236-0110 (multiple dose) and GS-US-236-0105 (single dose).

COBI AUC and C_{max} were lower following single (AUC_{inf}) versus multiple (AUC_{tau}) doses of STB (8092.3 ng•h/mL and 1243.1 ng/mL vs 11,288.2 ng•h/mL and 1528.0 ng/mL, respectively); however, COBI T_{max} was similar. COBI mean C_{tau} was approximately 64% lower (16.4 vs 45.5 ng/mL) following single-dose administration relative to multiple-dose administration.

COBI PK and PK/PD were extensively characterized in the STB development program and COBI exposures were shown to be comparable with STB across E/C/F/TAF Phase 1 and Phase 2 studies (Table 31). As such, only the PK of the new study drug TAF was evaluated in the Phase 3 pivotal studies of E/C/F/TAF.

Table 31. Summary of COBI PK Parameters Following STB or E/C/F/TAF Administration

COBI 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)	8304.3 (46.1)[a,b]	10273.5 (21.7)	9459.1 (33.9)
C_{max} (ng/mL)	1141.7 (35.6)[c]	1503.5 (19.6)	1450.3 (28.4)
C_{tau} (ng/mL)	49.1 (262.8) [a,d,e]	30.7 (63.0)	20.6 (85.2)

a AUC_{tau} and C_{tau} were not calculated for Subject *AA for any analyte because concentration values were missing for some postdose time points.
b n = 61
c n = 62
d n = 53
e Missing C_{tau} (except for Subject *AA) was due to values BLQ and was excluded from this analysis.
Data are presented as mean (%CV).
Source: STB PK/PD Table 2.2; m5.3.1.2, GS-US-292-0103, Section 10, Table 10-9; m5.3.5.1, GS-US-292-0102, Section 10, Table 10-5

3.2.1.1.5. 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 32 and the steady-state PK parameter estimates of FTC following 200-mg once daily dosing, the therapeutic dose within the E/C/F/TAF FDC, are summarized in Table 33.

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 32. Single-Dose PK of FTC 200 mg Administered as the Capsule Formulation in Healthy and HIV-Infected Subjects

	$AUC_{0\text{-inf}}$ (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 33. Summary of Steady-State PK Parameter Estimates for FTC Following 200 mg Once-Daily Dose

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 34). As such, only the PK of the new study drug TAF was evaluated in the Phase 3 pivotal studies.

Table 34. Summary of FTC PK Parameters Following 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)	12737.0 (35.3)[a]	12352.6 (13.5)	11714.1 (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 *AA 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; m5.3.1.2, GS-US-292-0103, Section 10, Table 10-11; m5.3.5.1, GS-US-292-0102, Section 10, Table 10-5

3.2.1.2. Population Pharmacokinetics

Population PK modeling was conducted to establish a predictive population PK model(s) describing the plasma concentrations of the components of E/C/F/TAF in HIV-infected subjects and healthy subjects and identifying covariates (eg, body weight, age, sex, renal function, and race) influencing plasma concentrations.

These analyses were performed using intensive and sparse PK samples collected in Phase 1, 2, and 3 studies in healthy and HIV-infected subjects. A summary of the methodology is presented in Section 1.5. Additionally, supporting population PK analyses findings related to intrinsic factors are included in Section 3.2.2.

3.2.1.2.1. TAF and TFV

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.

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 subjects versus ART-experienced HIV subjects).

The intersubject variability in TAF exposure varied across studies depending on whether intensive or sparse sampling was employed (%CV: 26%-34% across Phase 1 studies and 58%-118% across Phase 2 and Phase 3 studies).

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 apparent volume of the central compartment (V_c/F) was 1600 L, and the apparent volume of peripheral compartment (V_p/F) was 1670 L. TFV was absorbed at a typical rate of 2.33 h^{-1}.

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, apparent clearance (CL/F), apparent central volume (V_c/F), and apparent peripheral volume (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 L/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.

The intersubject variability in TFV exposure was generally modest/low and comparable across studies (%CV: 18%-41% across Phase 2 and Phase 3 studies).

Further details on the population PK for TAF and TFV are presented in the population PK report (m5.3.3.5, TAF Population PK Report).

3.2.1.2.2. EVG

The final population model that best described EVG PK was a 2-compartment model with a first-order absorption rate constant and absorption lag time.

The typical apparent systemic EVG CL/F was estimated to be 6.6 L/h, the apparent volume of the central compartment (V_c/F) was 12.9 L, and the apparent volume of peripheral compartment (V_p/F) was 125 L. EVG was absorbed at a typical rate of 0.13 h^{-1} with a lag time of 1.6 hours.

Covariate analyses indicated no clinically relevant effects/differences in EVG exposure based on age, sex, race (Asian, black, or white), eGFR, hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection, or HIV-1 positive or negative disease status. Additionally, no relevant effects of COBI exposure (AUC or C_{trough}) were observed with the 150-mg dose, in accordance with consistent exposure from this dose resulting in a robust boosting of EVG exposure, including C_{trough}. A modest, statistically significant relationship was observed between body surface area and EVG exposure; however, EVG AUC, C_{max}, and C_{trough} were generally comparable across the range body surface area values (eg, quartiles), and as such, the observed relationship is not considered to be clinically relevant.

The intersubject variability in EVG exposure was generally modest/low and comparable across studies (%CV: 31%-39% across Phase 2 and Phase 3 studies). Administration of STB resulted in maintenance of robust EVG C_{trough}, generally ~10-fold the protein binding-adjusted IC_{95}.

Further details on the population PK for EVG are presented in the population PK report (EVG Population PK Report).

3.2.1.2.3. COBI

The final population PK model that best described COBI PK in both healthy subjects and HIV-infected subjects was a 1-compartment mammillary PK model with zero- and first-order absorption rate constants and absorption lag time, and including the effect of body weight on the apparent volume of the central compartment (V_c/F) of COBI.

The typical apparent systemic clearance of COBI (CL/F) was estimated to be 15.0 L/h. The typical V_c/F was estimated to be 77.0 L. The COBI absorption profile was modeled using a zero-order absorption process with a duration of 1.16 hours, a first-order absorption rate constant of 0.88 h^{-1}, and a lag time of 0.18 hour.

A statistically significant, positive correlation was observed between body weight and COBI V_c/F. The effect was normalized to the median weight value of 74.4 kg and described with a power function with a population estimate of 0.94. The covariate effect of weight was modest, and the resulting decrease in the intersubject variability term associated with COBI volume was 17%. Relative to the median weight value of 74.4 kg in the entirety of the dataset, the range of observed weights of 57 to 101 kg (5th to 95th percentiles) corresponded to differences of only -22% and 24% in COBI V_c/F, respectively. Such changes are not deemed to be clinically relevant in adults. No other clinically relevant effects of demographic or formulation characteristics were observed on COBI PK.

The intersubject variability in COBI exposure (AUC_{tau} and C_{max}) was generally low/modest and comparable across studies (%CV: 20%-50% and 14%-43%, respectively, across all studies with COBI 150 mg administered once daily). The COBI exposure was consistent with those associated with robust PK enhancement (boosting).

Further details on the population PK for COBI are presented in the population PK report (COBI Population PK Report).

3.2.1.2.4. 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 3.2.2.1.1.4. 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 (FTC 13542v1 Report).

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

3.2.1.3.1. TAF and TFV

TAF and TFV exposures in HIV-infected subjects in the 2 pivotal Phase 3 studies (GS-US-292-0104 and GS-US-292-0111) were compared against those in healthy subjects (GS-US-292-0103, GS-US-292-0108, and GS-US-292-0110) following multiple-dose administration of E/C/F/TAF and are shown in Table 35 and Table 36, respectively.

HIV disease status did not have an effect on TAF exposure in healthy subjects and in HIV-infected subjects and was not a statistically or clinically relevant covariate based on population PK analyses (m5.3.3.5, TAF Population PK Report).

Based on covariate analyses of pooled Phase 1, 2, and 3 healthy and HIV-infected study populations (Table 8), 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 36. As such, the observed relationship between disease status and TFV exposure is not considered to be clinically relevant.

Table 35. TAF PK Parameters After Once-Daily Administration of E/C/F/TAF in Healthy or HIV-Infected Subjects

TAF	AUC_{last} (ng•h/mL)	C_{max} (ng/mL)
Healthy Subjects (N = 79)	250 (31.6)	178 (46.4)
HIV-Infected Subjects (N = 539)[a]	206 (71.8)	162 (51.1)

a Subjects from Studies GS-US-292-0104 and GS-US-292-0111
Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

Table 36. TFV PK Parameters After Once-Daily Administration of E/C/F/TAF in Healthy or HIV-Infected Subjects

TFV	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Healthy Subjects (N = 79)	307 (22.7)	21.2 (23.9)	10.0 (27.6)
HIV-Infected Subjects (N = 841)[a]	293 (27.4)	15.2 (26.1)	10.6 (28.5)

a Subjects from Studies GS-US-292-0104 and GS-US-292-0111
Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

3.2.1.3.2. EVG

EVG exposure in HIV-infected subjects (population PK analyses-derived) were compared against those in healthy subjects (GS-US-236-0110) following multiple-dose administration of STB and are shown in Table 37. EVG AUC_{tau}, C_{max}, and C_{trough} were comparable between the 2 populations. These results are consistent with covariate assessment during the population PK analysis, which indicated no relevant effects of HIV-1 disease state on EVG PK (EVG Population PK Report). The selection of EVG and COBI doses targeted robust exposures in order to achieve high IQ_{95} (C_{trough}/IC_{95} [protein binding-adjusted]) by EVG based on potent CYP3A-inhibitory pharmacoenhancement by COBI.

Table 37. Steady-State EVG PK Parameters After Once-Daily Administration of STB in HIV-Infected Subjects in STB Phase 2 and Phase 3 Studies or in Healthy Subjects from Study GS-US-236-0110

EVG	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
Population PK[a] (N = 419)	23,000 (33)	1730 (23)	451 (58)
Healthy Subjects (N = 36)	22,500 (27)	1920 (24)	508 (41)

a Included STB-treated subjects from Phase 2 and 3 STB studies.
Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: STB PK/PD Table 1; GS-US-236-0110, Section 15.1, Table 4.1

3.2.1.3.3. COBI

Table 38 summarizes COBI PK in a cross-study comparison between HIV-infected subjects (STB Phase 2 and Phase 3 studies) and healthy subjects (GS-US-236-0110) following multiple-dose administration of STB. COBI AUC_{tau} and C_{max} were approximately 25% lower, while T_{max} and $t_{1/2}$ were comparable in HIV-infected subjects compared with healthy subjects (COBI Population PK Report). The reasons for the observed differences are unclear, but these data are consistent with data on other ARV agents, including HIV PIs (eg, ATV, tipranavir [TPV]) {17624}, {18615}. In population PK analyses for EVG, COBI exposure was not associated with differences in EVG exposure at the 150-mg dose, confirming dose selection (COBI Population PK Report).

Table 38. Steady-State COBI PK After Once-Daily Administration of STB in HIV-Infected Subjects from Intensive PK Substudies of STB Phase 2 and Phase 3 Studies or in Healthy Subjects from Study GS-US-236-0110

COBI	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
HIV-Infected Subjects (N = 62)	8300 (46) [a, b]	1140 (36)[c]	49.1 (260)[a, d, e]
Healthy Subjects (N = 36)	11,300 (29)	1530 (26)	45.5 (88)

a AUC_{tau} and C_{tau} were not calculated for Subject *AA for any analyte because concentration values were missing for some postdose time points.
b n = 61
c n = 62
d n = 53
e Missing C_{tau} (except for Subject *AA) was due to values BLQ and was excluded from this analysis.
Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: STB PK/PD Table 2.2; GS-US-236-0110, Section 15.1, Table 4.2

3.2.1.3.4. 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 39). 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 39. Summary of Steady-State PK Parameter Estimates for FTC Following 200 mg Once-Daily Dose

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

Pharmacokinetic data, supported by safety data in HIV-infected subjects with mild-to-moderate renal impairment (Study GS-US-292-0112) support that E/C/F/TAF may be administered once daily without dose adjustment in patients with mild-to-moderate renal impairment ($eGFR_{CG}$ > 30mL/min). Specifically, plasma TFV exposure in these populations are within or below the range of TFV plasma exposure after administration of TDF 300 mg in both healthy, HIV-uninfected subjects and in HIV-infected patients with normal renal function.

3.2.2.1.1.1. TAF and TFV

A study of the PK of TAF and TFV was performed in subjects with severe renal impairment ($eGFR_{CG}$ < 30 mL/min, not on dialysis) and matched healthy adult controls.

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 40). This difference is unlikely to be clinically relevant.

Table 40. Statistical Comparisons of TAF PK Parameters in Subjects with Severe Renal Impairment or 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: m5.3.3.3, GS-US-120-0108, Section 10.1, Tables 10-1 and 10-2

Subjects with severe renal impairment had a 6.05-fold mean increase in systemic TFV exposures as assessed by AUC_{inf} relative to age- and sex-matched subjects with normal renal function (Table 41). The TFV exposure observed 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 exposure measured in historical studies after administration of TDF 300 mg in both healthy, HIV-uninfected subjects and in HIV-infected patients with normal renal function.

Table 41. Statistical Comparisons of TFV PK Parameters in Subjects with Severe Renal Impairment or Normal Renal Function

TFV 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)	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: m5.3.3.3, GS-US-120-0108, Section 10.1, Tables 10-4 and 10-5

A Phase 3 PK substudy (n = 32) evaluating the PK of TAF and 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, and showed mean (%CV) TAF and TFV exposures (AUC) of 254.2 (54.1) ng•h/mL and 552.7 (32.0), respectively (GS-US-292-0112). These Phase 3 data are also consistent with results from the renal impairment study, GS-US-120-0108.

Additionally, population PK analyses of TAF and TFV from pooled Phase 1, 2, and 3 study populations were conducted. Baseline $eGFR_{CG}$ was not a statistically or clinically relevant covariate influencing TAF PK (m5.3.3.5, TAF Population PK Report).The TAF exposure was higher in subjects with lower $eGFR_{CG}$ relative to normal renal function (> 90 mL/min) but less than a 50% change was shown between moderate impairment versus normal renal function (Table 42). As expected with TFV being primarily renally eliminated, a statistically significant effect of baseline $eGFR_{CG}$ on TFV exposure was observed based on covariate analyses. TFV

exposure was higher in subjects with lower $eGFR_{CG}$ relative to normal renal function (Table 43). However, the TFV exposure observed in subjects with $eGFR_{CG}$ < 50 mL/min (775.6 ng•h/mL) was within or below the range of TFV plasma exposure after administration of TDF 300 mg in both healthy, HIV-uninfected subjects and in HIV-infected patients with normal renal function (3300 ng•h/mL) {26885}.

Table 42. TAF PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects by Renal Function

Baseline $eGFR_{CG}$	AUC (ng•h/mL)	C_{max} (ng/mL)
26[a] ≤ $eGFR_{CG}$ < 50 mL/min (N = 69)	343.7 (126.1)	222.4 (50.3)
30 ≤ $eGFR_{CG}$ < 60 mL/min (N = 133)	305.0 (112.5)	208.6 (53.0)
60 ≤ $eGFR_{CG}$ < 90 mL/min (N = 204)	223.9 (86.8)	166.2 (43.7)
$eGFR_{CG}$ ≥ 90 mL/min (N = 769)	210.4 (94.1)	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: m5.3.3.5, TAF Population PK Report, m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Table 6919.1.1

Table 43. TFV PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects by Renal Function

Baseline $eGFR_{CG}$	AUC (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
26[a] ≤ $eGFR_{CG}$ < 50 mL/min (N = 81)	775.6 (31.4)	38.3 (31.1)	27.9 (31.6)
30 ≤ $eGFR_{CG}$ < 60 mL/min (N = 155)	669.7 (29.2)	33.2 (28.7)	24.2 (29.4)
60 ≤ $eGFR_{CG}$ < 90 mL/min (N = 264)	421.4 (30.2)	21.6 (33.4)	15.3 (30.6)
$eGFR_{CG}$ ≥ 90 mL/min (N = 1053)	285.5 (27.1)	14.9 (25.4)	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: m5.3.3.5, TAF Population PK Report, m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Table 6919.1.2

3.2.2.1.1.2. EVG

The PK of EVG and COBI were evaluated in HIV-uninfected subjects with severe renal impairment (EVG and COBI, $eGFR_{CG}$ < 30 mL/min) and a matching cohort of subjects with normal renal function ($eGFR_{CG}$ ≥ 90 mL/min) in Study GS-US-216-0124.

EVG AUC_{tau}, C_{max}, and C_{tau} were approximately 25%, 33%, and 31% lower, respectively, in subjects with severe renal impairment than in matched control subjects. Notably, EVG exposure on Day 7 among subjects with normal renal function was substantially higher than that observed in previous clinical studies with COBI-boosted EVG (GS-US-216-0116, GS-US-216-0123, and GS-US-183-0133).

COBI AUC_{tau}, C_{max}, and C_{tau} were approximately 25%, 22%, and 13% higher, respectively, in subjects with severe renal impairment than in matched control subjects. The differences in exposures between subjects with severe renal impairment and those with normal renal function are not considered clinically relevant. No differences in COBI plasma protein binding were observed between the 2 groups.

Following multiple doses of COBI-boosted EVG, $eGFR_{CG}$ was 10.5% and 8.4% lower compared with baseline in subjects with severe renal impairment and normal renal function, respectively, with values returning to baseline levels upon washout, which was consistent with data in subjects with normal renal function and subjects with mild/moderate renal impairment and was attributed to inhibition of proximal tubular secretion of creatinine by COBI.

Clinically meaningful differences in the PK of EVG and COBI were not observed at the extremes of renal function, and dose adjustment would not be warranted in subjects with renal impairment (GS-US-216-0124).

Additionally, based on pooled STB Phase 2 and Phase 3 study populations used for EVG population PK analyses, baseline $eGFR_{CG}$ did not have an effect on EVG exposure in HIV-infected subjects and was not a statistically or clinically relevant covariate (EVG Population PK Report), likely due to the minimal renal excretion of EVG (~6% to 7%).

3.2.2.1.1.3. COBI

The PK and boosting of COBI (using EVG as the boosted agent) were evaluated in HIV-uninfected subjects with severe renal impairment ($eGFR_{CG}$ < 30 mL/min) and a matching cohort of subjects with normal renal function ($eGFR_{CG}$ ≥ 90 mL/min) in Study GS-US-216-0124.

COBI AUC_{tau}, C_{max}, and C_{tau} were approximately 25%, 22%, and 13% higher, respectively, in subjects with severe renal impairment than in matched control subjects. The differences in exposures between subjects with severe renal impairment and those with normal renal function are not considered clinically relevant.

The mean (SD) percentages for free fraction (unbound concentrations) COBI in the normal matched control subjects and renally impaired subjects were 2.49% (0.29) and 2.47% (0.62), respectively, indicating the lack of effect of severe renal impairment on COBI protein binding.

Following multiple doses of COBI, $eGFR_{CG}$ was 10.5% and 8.4% lower versus baseline among subjects with severe renal impairment and normal renal function, respectively, with values returning to baseline levels upon washout, which was consistent with data in subjects with normal renal function and subjects with mild/moderate renal impairment and was attributed to inhibition of proximal tubular secretion of creatinine by COBI.

Additionally, based on pooled study populations used for population PK analyses, baseline $eGFR_{CG}$ did not have an effect on COBI exposure in healthy and HIV-infected subjects and was not a statistically or clinically relevant covariate (COBI Population PK Report). This was expected in view of the minimal renal excretion of COBI (< 10%) (GS-US-216-0111).

Clinically meaningful differences in the PK of COBI were not observed at the extremes of renal function, and dose adjustment would not be warranted in subjects with renal impairment.

3.2.2.1.1.4. 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 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 percent 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, from the Emtriva® prescribing information for subjects with $eGFR_{CG}$ of 50 to 80 mL/min who do not require dose adjustment. 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 confirms that E/C/F/TAF may be safely administered once daily without dose adjustment in patients with renal impairment ($eGFR_{CG}$ > 30 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 and TFV

The PK of TAF and TFV in HIV-uninfected subjects were evaluated in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) versus matched healthy adult subjects (control) in Study GS-US-120-0114 (Section 2.4.2.2). 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 the subjects with moderate hepatic impairment 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. 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 the subjects with mild hepatic impairment 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. 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 the subjects with moderate hepatic impairment 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. Accordingly, no dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B). The effect of severe hepatic impairment on the PK of TAF has not been studied.

Subjects with HBV or HCV coinfection were excluded from the E/C/F/TAF clinical development program.

3.2.2.1.2.2. EVG

The PK of EVG and COBI in HIV-uninfected subjects were evaluated in subjects with moderate hepatic impairment (CPT Class B, with an additional cohort of matched subjects [age, sex, and BMI] with normal hepatic function) in Study GS-US-183-0133.

The steady-state plasma exposure parameters of EVG were modestly higher (AUC_{tau}, C_{tau}, and C_{max} were 34.99%, 79.63%, and 41.28% higher, respectively) in subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function. The observed increases, however, were well below the protocol-defined clinically significant increase of 100% in EVG AUC_{tau} or C_{max} for subjects with moderate hepatic impairment compared with normal matched control subjects, and were not considered to be clinically relevant.

The AUC_{tau} and C_{max} of COBI were generally comparable in subjects with moderate hepatic impairment relative to normal matched control subjects; COBI C_{tau} was higher (GLSM ratio 207.70%) although not considered to be clinically relevant.

Exploratory analyses indicated no clinically relevant correlations between EVG or COBI exposures versus CPT scores or individual liver function laboratory parameters (ie, albumin, total bilirubin, prothrombin time, and INR) for subjects with moderate hepatic impairment. The mean (SD) percentages for free fraction (unbound concentration) EVG in the normal matched control subjects and moderate hepatic impairment subjects were 1.15% (0.14) and 1.22% (0.23), respectively. These findings are consistent with historical data (GS-US-183-0101) and indicate the lack of effect of hepatic impairment on EVG protein binding. Similar results were observed for COBI (corresponding values were 2.71% [0.56] and 3.23% [0.63], respectively).

In the pooled STB Phase 2 and Phase 3 study populations used for EVG population PK analyses, ~5.7% of subjects were coinfected with HBV or HCV.

HBV or HCV coinfection status did not appear to have an effect on EVG exposure in HIV-infected subjects as shown in Table 44 and was not a statistically or clinically relevant covariate based on population PK analyses (EVG Population PK Report).

Table 44. Mean (%CV) EVG Exposure by HBV or HCV Coinfection Following Administration of STB in HIV-Infected Subjects

HBV or HCV Coinfection Status	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
HBV or HCV Coinfection (N = 24)	21,500 (29)	1650 (23)	421 (46)
No HBV or HCV Coinfection (N = 395)	23,100 (33)	1740 (22)	453 (58)

Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: EVG Population PK Report

3.2.2.1.2.3. COBI

The PK and boosting of COBI (using EVG as the boosted agent) were evaluated in HIV-uninfected subjects with moderate hepatic impairment (CPT Class B) with an additional cohort of matched subjects (age, sex, and BMI) with normal hepatic function in Study GS-US-183-0133.

The AUC_{tau} and C_{max} of COBI were generally comparable in subjects with moderate hepatic impairment relative to normal matched control subjects; COBI C_{tau} was higher (GLSM ratio 207.70%) although not considered to be clinically relevant.

Exploratory analyses indicated no clinically relevant correlations between COBI exposures versus CPT scores or individual liver function laboratory parameters (ie, albumin, total bilirubin, prothrombin time, and INR) for subjects with moderate hepatic impairment. The mean (SD) percentages for free fraction (unbound concentration) COBI in the normal matched control subjects and moderate hepatic impairment subjects were 2.71% (0.56) and 3.23% (0.63), respectively, indicating the lack of effect of hepatic impairment on COBI protein binding.

Clinically meaningful differences in the PK of COBI were not observed in subjects with moderate hepatic impairment versus matched controls, and dose adjustment would not be warranted in subjects with mild to moderate hepatic impairment. The PK of COBI in subjects with severe hepatic impairment have not been evaluated.

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.

3.2.2.1.2.4. 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 45.

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 45. Summary of Steady-State PK Parameter Estimates for FTC Following 200 mg Once-Daily Dose 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 and TFV

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 (m5.3.3.5, TAF Population PK Report; m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Table 6919.2).

Similar to the lack of effect of age (cut off ≥ 55 years) on EVG PK (Section 3.2.2.2.2), age did not have an effect on TAF exposure in HIV-infected subjects and was not a statistically or clinically relevant covariate based on population PK analyses (Table 46). As age is often correlated with renal function and TFV is primarily renally eliminated, there was a modest dependence of TFV exposure on age (Table 47) but this 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 was still at least 80% lower versus STB.

Subjects younger than 18 years are discussed under pediatrics in Section 3.2.2.5.1.

Table 46. TAF PK Parameters by Age Group After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects (Population PK Analysis from Phase 2 and 3 Studies)

Age Group	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)
< 55 Years of Age (N = 915)	221.5 (104)	164.2 (55.8)
≥ 55 Years of Age (N = 197)	239.2 (72.8)	178.2 (51.8)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

Table 47. TFV PK Parameters by Age Group After Once-Daily Administration of E/C/F/TAF in HIV-Infected Subjects (Population PK Analysis from Phase 2 and 3 Studies)

Age Group	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
< 55 Years of Age (N = 1251)	322.3 (44.2)	16.7 (42.9)	11.7 (44.6)
≥ 55 Years of Age (N = 227)	522.9 (37.1)	26.2 (35.6)	18.9 (37.0)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

3.2.2.2.2. EVG

In the pooled Phase 2 and Phase 3 study populations used for EVG population PK analyses, median (Q1, Q3) age was 37 (29, 44) years, with a range of 19 to 72 years, and 27 subjects were ≥ 55 years.

Age did not have an effect on EVG exposure in HIV-infected subjects and was not a statistically or clinically relevant covariate based on EVG population PK analyses (EVG Population PK Report).

Subjects younger than 18 years are discussed under pediatrics in Section 3.2.2.5.2.

3.2.2.2.3. COBI

In the pooled data following once-daily administration of the COBI single-agent tablet from the Phase 1, 2, and 3 study population used for the COBI population PK analyses, median (Q1, Q3) age was 37 (30, 44) years, with a range of 18 to 76 years, and 37 subjects were ≥ 55 years.

Age did not have an effect on COBI exposure in healthy subjects and in HIV-infected subjects and was not a statistically or clinically relevant covariate based on COBI population PK analyses (COBI Population PK Report).

3.2.2.2.4. 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 Surface Area

3.2.2.3.1. TAF and TFV

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 (m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Table 6919.2).

Weight did not have an effect on TAF exposure in HIV-infected subjects and was not a statistically or clinically relevant covariate based on TAF population PK analyses (Table 48). Additionally, body surface area did not have an effect on TAF in HIV-infected subjects and was not a statistically or clinically relevant covariate based on TAF population PK analyses (m5.3.3.5, TAF Population PK Report).

There was a modest dependence of TFV exposure on weight (Table 49) but this was not found to be a statistically significant covariate after adjusting for $eGFR_{CG}$. Moreover, weight was not considered clinically relevant since TFV exposures observed in subjects ≤ 66 kg was still > 80% lower versus STB.

Table 48. Mean (%CV) TAF Exposure Across Weight Ranges Following Administration of E/C/F/TAF in HIV-Infected Subjects

Weight	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)
Weight ≤ 66 kg (N = 301)	237.2 (68.8)	176.7 (50.2)
66 < Weight ≤ 75 kg (N = 260)	248.7 (124)	169.4 (52.6)
75 < Weight ≤ 86 kg (N = 263)	208.4 (85.9)	162.3 (44.4)
Weight > 86 kg (N = 288)	204.6 (104)	157.6 (70.4)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

Table 49. Mean (%CV) TFV Exposure Across Weight Ranges Following Administration of E/C/F/TAF in HIV-Infected Subjects

Weight	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Weight ≤ 66 kg (N = 384)	422.2 (48.4)	21.7 (48.3)	15.3 (47.6)
66 < Weight ≤ 75 kg (N = 355)	355.5 (42.5)	18.2 (40.6)	12.9 (42.7)
75 < Weight ≤ 86 kg (N = 366)	331.9 (37.1)	17.1 (34.3)	12.1 (37.9)
Weight > 86 kg (N = 373)	300.3 (51.8)	15.5 (46.6)	10.9 (53.5)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

3.2.2.3.2. EVG

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 EVG population PK analyses, the median (Q1, Q3) body surface area was 1.92 (1.81, 2.07) m^2.

Based on covariate analyses, a modest, statistically significant effect of body surface area on EVG exposure was observed. However, the range of EVG exposures across quartiles of body surface area was comparable as shown in Table 50. As such, the observed relationship between body surface area and EVG exposure is not considered to be clinically relevant.

Table 50. Mean (%CV) EVG Exposures Across Quartiles of Body Surface Area Following Administration of STB in HIV-Infected Subjects

Body Surface Area (m^2)	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
≤ 1.81 (N = 108)	26,100 (32)	1960 (22)	515 (57)
1.82 to 1.95 (N = 111)	21,700 (34)	1670 (22)	411 (66)
1.96 to 2.07 (N = 98)	22,000 (29)	1650 (19)	440 (52)
> 2.07 (N = 102)	21,800 (30)	1630 (20)	438 (52)

Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: EVG Population PK Report

3.2.2.3.3. COBI

In the pooled study populations used for COBI population PK analyses, the median (Q1, Q3) body surface area was 1.90 (1.73, 2.00) m^2.

Body surface area did not have an effect on COBI exposure in healthy and HIV-infected subjects and was not a statistically or clinically relevant covariate based on COBI population PK analyses (COBI Population PK Report).

3.2.2.3.4. 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 and TFV

In the pooled Phase 1, 2, and 3 study populations used for TAF population PK analyses, the percentages of subjects who were white, black, or other were 59.2%, 24.7%, and 16.2%, respectively.

Race did not have an effect on TAF exposure in HIV-infected subjects as shown in Table 51 and was not a statistically or clinically relevant covariate based on TAF population PK analyses (m5.3.3.5, TAF Population PK Report).

Based on covariate analyses, a statistically significant effect of race (black versus non-black) on TFV PK parameters was observed (Table 52). However, the range of TFV exposure across race was comparable and > 80% lower versus STB as shown in Table 52. As such, the observed relationship between race and TFV exposure is not considered to be clinically relevant.

Table 51. Mean (%CV) TAF Exposure by Race Following Administration of E/C/F/TAF in HIV-Infected Subjects

Race	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)
White (N = 655)	226.0 (98.9)	168.1 (57.1)
Black (N = 265)	229.9 (111)	159.9 (49.8)
Other (N = 192)	212.7 (73.0)	170.9 (54.4)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

Table 52. Mean (%CV) TFV Exposure by Race Following Administration of E/C/F/TAF in HIV-Infected Subjects

Race	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
White (N = 871)	358.6 (48.0)	18.3 (45.1)	13.1 (48.3)
Black (N = 368)	310.3 (37.9)	16.2 (35.1)	11.2 (38.7)
Other (N = 239)	398.7 (50.4)	20.5 (51.9)	14.4 (49.2)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

3.2.2.4.2. EVG

In the pooled Phase 2 and Phase 3 study populations used for EVG population PK analyses, the percentages of subjects who were white, black, or Asian were 70.4%, 21.5%, and 4.3%, respectively.

Race did not have an effect on EVG exposure in HIV-infected subjects as shown in Table 53 and was not a statistically or clinically relevant covariate based on EVG population PK analyses (EVG Population PK Report). Mean (%CV) EVG AUC_{tau}, C_{max}, and C_{trough} values in Asian HIV-infected subjects were 26,700 (33) ng•h/mL, 1970 (22) ng/mL, and 528 (57) ng/mL, respectively.

Table 53. Mean (%CV) EVG Exposure by Race Following Administration of STB in HIV-Infected Subjects

Race	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
Asian (N = 18)	26,700 (33)	1970 (22)	528 (57)
Black (N = 90)	23,400 (33)	1720 (24)	478 (53)
White (N = 295)	22,500 (30)	1710 (21)	435 (55)

Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: EVG Population PK Report

3.2.2.4.3. COBI

In the pooled study populations used for COBI population PK analyses, the percentages of subjects who were white, black, or other were 73%, 24%, and 3%, respectively.

Race did not have an effect on COBI exposure in healthy and HIV-infected subjects as shown in Table 54 and was not a statistically or clinically relevant covariate based on COBI population PK analyses (COBI Population PK Report).

Table 54. Mean (%CV) COBI Exposure by Race Following Administration of COBI in Healthy Subjects and HIV-Infected Subjects

Race	C_{max} (ng/mL)	C_{24} (ng/mL)	$AUC_{0–24}$ (ng•h/mL)
White (N = 213)	1470 (29)	69 (143)	12,400 (41)
Black (N = 69)	1370 (24)	59 (137)	11,600 (36)
Other (N = 9)	1310 (36)	55 (101)	11,300 (42)

Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: COBI Population PK Report

3.2.2.5. Pediatrics

The effect of age for pediatric subjects on the PK of TAF and TFV, EVG, COBI, 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 and TFV

TAF and TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF (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 55 and Table 56).

Table 55. Multiple-Dose TAF Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

	Adolescents	Adults
TAF PK Parameter	E/C/F/TAF (N = 24)	E/C/F/TAF (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: m5.3.5.2, GS-US-292-0106, Section 10.1, Table 10-4; m5.3.5.1, GS-US-292-0102, Section 10.2, Table 10-1

Table 56. Multiple-Dose TFV Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

TFV PK Parameter	Adolescents E/C/F/TAF (N = 24)	Adults E/C/F/TAF (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: m5.3.5.2, GS-US-292-0106, Table 10-1; m5.3.5.1, GS-US-292-0102, Section 10.3, Table 10-2

Additionally, in the pooled Phase 2 and Phase 3 study populations used for TAF population PK analyses, HIV-infected adolescent subjects had comparable TAF and TFV exposures versus HIV-infected adult subjects as shown in Table 57 and Table 58, respectively, again confirming that age was not a clinically relevant covariate.

Table 57. TAF PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Adolescent and Adult Subjects

Age Group	AUC_{last} (ng•h/mL)	C_{max} (ng/mL)
Adolescent Subjects (N = 23)[a]	242.8 (57.8)	121.7 (46.2)
Adult Subjects (N = 539)[b]	206.4 (71.8)	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: m5.3.3.5, TAF Population PK Report

Table 58. TFV PK Parameters After Once-Daily Administration of E/C/F/TAF in HIV-Infected Adolescent and Adult Subjects

Age Group	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Adolescent Subjects (N = 23)[a]	275.8 (18.4)	14.6 (20.0)	10.0 (19.6)
Adult Subjects (N = 841)[b]	292.6 (27.4)	15.2 (26.1)	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: m5.3.3.5, TAF Population PK Report

3.2.2.5.2. EVG

EVG exposure was comparable with values observed in HIV-infected, ART-naive adults following E/C/F/TAF (Study GS-US-292-0102), indicating no relevant effects of pediatrics (age ≥ 12 years) on the exposures of boosted EVG (Table 59).

Table 59. Multiple-Dose EVG Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

	Adolescents	Adults
EVG PK Parameter	**E/C/F/TAF (N = 24)**	**E/C/F/TAF (N = 19)**
AUC_{tau} (ng•h/mL)	23,840.1 (25.5)	22,797.0 (34.7)
C_{max} (ng/mL)	2229.6 (19.2)	2113.1 (33.7)
C_{tau} (ng/mL)	300.8 (81.0)	287.3 (61.7)

Data are presented as mean (%CV).
Source: m5.3.5.2, GS-US-292-0106, Section 10.1, Table 10-1; m5.3.5.1, GS-US-292-0102, Section 10.7, Table 10-5

3.2.2.5.3. COBI

COBI 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 COBI (Table 60).

Table 60. Multiple-Dose COBI Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

	Adolescents	Adults
COBI PK Parameter	**E/C/F/TAF (N = 24)**	**E/C/F/TAF (N = 19)**
AUC_{tau} (ng•h/mL)	8240.8 (36.1)[a]	9459.1 (33.9)
C_{max} (ng/mL)	1202.4 (35.0)	1450.3 (28.4)
C_{tau} (ng/mL)	25.0 (180.0)[b]	20.6 (85.2)

a N = 23
b N = 15
Data are presented as mean (%CV).
Source: m5.3.5.2, GS-US-292-0106, Section 10.1, Table 10-9; m5.3.5.1, GS-US-292-0102, Section 10.7, Table 10-5

3.2.2.5.4. FTC

FTC is approved for use in the pediatric population; however, the effect of age on the PK of FTC in the E/C/F/TAF FDC 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 61).

Table 61. Multiple-Dose FTC Exposure Following Administration of E/C/F/TAF in HIV-Infected, Treatment-Naive Adolescent Versus Adult Subjects

	Adolescents	Adults
FTC PK Parameter	**E/C/F/TAF (N = 24)**	**E/C/F/TAF (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: m5.3.5.2, GS-US-292-0106, Section 10.1, Table 10-11; m5.3.5.1, GS-US-292-0102, Section 10.7, Table 10-5

3.2.2.6. Sex

3.2.2.6.1. TAF and TFV

In the pooled Phase 1, 2, and 3 study populations used for TAF population PK analyses, 16.3% of subjects were female.

Sex did not have an effect on TAF exposure in HIV-infected subjects as shown in Table 62 and was not a statistically or clinically relevant covariate based on TAF population PK analyses (m5.3.3.5, TAF Population PK Report).

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 63. As such, the observed relationship between sex and TFV exposure is not considered to be clinically relevant.

Table 62. Mean (%CV) TAF Exposure by Sex Following Administration of E/C/F/TAF in HIV-Infected Subjects

Sex	**AUC_{tau} (ng•h/mL)**	**C_{max} (ng/mL)**
Male (N = 934)	218.9 (92.7)	165.2 (55.1)
Female (N = 178)	254.9 (117)	174.3 (55.1)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

Table 63. Mean (%CV) TFV Exposure by Sex Following Administration of E/C/F/TAF in HIV-Infected Subjects

Sex	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
Male (N = 1248)	340.5 (44.7)	17.6 (43.0)	12.3 (44.9)
Female (N = 230)	421.2 (53.3)	21.2 (51.5)	15.4 (52.5)

Data are presented as mean (%CV).
Source: m5.3.3.5, TAF Population PK Report

3.2.2.6.2. EVG

In the pooled Phase 2 and Phase 3 study populations used for EVG population PK analyses, ~8.4% of subjects were female.

Sex did not have an effect on EVG exposure in HIV-infected subjects as shown in Table 64 and was not a statistically or clinically relevant covariate based on EVG population PK analyses (EVG Population PK Report).

Table 64. Mean (%CV) EVG Exposure by Sex Following Administration of STB in HIV-Infected Subjects

Sex	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
Female (N = 35)	25,800 (41)	1930 (26)	523 (79)
Male (N = 384)	22,700 (31)	1710 (22)	445 (54)

Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: EVG Population PK Report

3.2.2.6.3. COBI

In the pooled study populations used for COBI population PK analyses, ~34% of subjects were female.

Sex did not have an effect on COBI exposure in healthy and HIV-infected subjects as shown in Table 65 and was not a statistically or clinically relevant covariate based on COBI population PK analyses (COBI Population PK Report).

Table 65. Mean (%CV) COBI Exposure by Sex Following Administration of COBI in Healthy Subjects and HIV-Infected Subjects

Sex	C_{max} (ng/mL)	C_{24} (ng/mL)	$AUC_{0–24}$ (ng•h/mL)
Female (N = 98)	1670 (24)	76 (123)	14,100 (37)
Male (N = 193)	1320 (26)	62 (152)	11,200 (40)

Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: COBI Population PK Report

3.2.2.6.4. 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 E/C/F/TAF or its individual components included food effect and DDIs.

3.2.3.1. Effect of Food

The effect of food on the absorption/bioavailability of boosted TAF was evaluated when given as part of E/C/F/TAF (GS-US-292-0110 [Section 2.5.1.1]).

Administration of E/C/F/TAF under fed versus fasting conditions did not affect overall exposure of TAF, but resulted in a modestly lower C_{max} and delayed T_{max}. The GLSM ratios (90% CIs) of the AUC_{last} of TAF when administered with a light/low-fat or high-calorie/high-fat were 114.95% (106.82% to 123.69%) and 116.65% (108.40% to 125.52%), respectively, and within the predefined no-effect boundary. The GLSM (90% CIs) ratios of the C_{max} of TAF were 68.04% (58.96% to 78.52%) and 63.20% (54.76% to 72.93%) when administered under light/low-fat or high-calorie/high-fat conditions, respectively. These modest changes in TAF PK parameters upon E/C/F/TAF administration with food (versus fasted) were not considered clinically relevant.

The effect of food on EVG, COBI, and FTC was evaluated following administration of STB in Study GS-US-236-0105.

Relative to the fasted condition, EVG AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max} increased by 34%, 36%, and 22%, respectively, for the light meal condition and increased by 87%, 91%, and 56% for the high-calorie/high-fat meal condition. EVG AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max} increased by 39%, 40%, and 28%, respectively, when STB was administered with a high-calorie/high-fat meal relative to a light meal. The higher EVG exposure when administered with high-calorie/high-fat meal is not considered to be clinically relevant given the safety profile of EVG at doses up to 300 mg. Additionally, the clinical development of EVG entailed a recommendation for administration with food with no requirements on the type of meal. COBI exposure parameters were bioequivalent under light meal and fasted conditions. For the high-calorie/high-fat meal condition, COBI C_{max} and AUC decreased by 19% to 27% relative to the light meal condition and by 17% to 24% relative to the fasted condition, which are not considered to be clinically significant, as evidenced by the maintenance of boosted EVG exposure (in fact, higher) upon administration with a high-calorie/high-fat meal, indicating that the effect of food on COBI did

not affect EVG exposure. Mean FTC AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max} were bioequivalent between the 3 treatment conditions, consistent with the established PK profile of FTC.

Although boosted TAF (when administered as E/C/F/TAF) is unaffected by food and does not require a food restriction, it is recommended that boosted EVG be administered with food to achieve EVG exposure that provides a high mean IQ_{95} (EVG trough concentration (C_{tau})/IC_{95}).

As such, E/C/F/TAF was administered with food in its clinical development program to align with the dosing recommendation for EVG and for STB, the comparator in the pivotal Phase 3 studies.

3.2.3.2. Drug Interaction Potential

The results from nonclinical and clinical studies have defined the potential of E/C/F/TAF or its components as perpetrators or victims of DDIs.

The results from in vitro evaluation of E/C/F/TAF 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 E/C/F/TAF are presented below.

3.2.3.2.1. Potential for E/C/F/TAF to Affect Other Drugs

The potential for TAF and TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (m4.2.2.6, AD-120-2003 and V990172-104). The inhibitory activity of TAF with human liver microsomal CYP isozymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed at concentrations up to 25 μM. The inhibition constant (IC_{50}) values calculated for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were greater than 25 μM. TAF weakly inhibited CYP3A-mediated oxidation of MDZ or testosterone with IC_{50} values of 7.6 and 7.4 μM, respectively. TFV at 100 μM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 was assessed at TAF concentration at 50 μM (m4.2.2.6, AD-120-2040). There was no evidence for time- or cofactor-dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control.

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

In vitro, EVG showed no detectable inhibition of human hepatic microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 activity, and weak inhibition of CYP3A. EVG is a weak inhibitor of human P-gp and OATP1B1, but it is a more potent inhibitor of human OATP1B3 (IC_{50} = 0.44 μM). From these data, EVG is predicted to have very low liability to cause drug interactions through inhibition of human CYP or P-gp. Inhibition of OATP transporters is consistent with a clinical drug interaction study (GS-US-216-0123) in which, after dosing with 150 mg COBI and 150 mg EVG, there was a transient effect resulting in a modest increase in exposure of coadministered rosuvastatin (AUC_{inf} increased approximately 38% compared with the reference treatment). Upon coadministration with COBI in E/C/F/TAF, EVG is not expected to contribute further inhibition of CYP3A or P-gp.

At clinically relevant concentrations, EVG does not induce CYP1A2 and CYP2C9 and is a weak inducer of CYP3A activity that is countered by coadministration with COBI (JTK303-AD-023). Additionally, a clinical study in subjects using opioid replacement therapy on an individualized stable dose of methadone demonstrated that COBI-boosted EVG does not induce CYP2B6 or CYP2C19 (GS-US-216-0125). In another clinical evaluation of an alternate opioid, concentrations of buprenorphine and norbuprenorphine were modestly increased and concentrations of naloxone were modestly decreased when coadministered with COBI-boosted EVG. However, there was no effect on opioid PD and the concentration changes were not considered clinically relevant.

COBI is a potent mechanism-based inhibitor of human CYP3A enzymes with inactivation kinetics similar to RTV. As such, drugs subject to extensive metabolism by CYP3A will have substantial increases in exposure with E/C/F/TAF. COBI is a weak inhibitor of CYP2D6 and UGT1A1 and does not inhibit CYP2B6 or CYP2C9 (GS-US-216-0112). As such, drugs not extensively metabolized by CYP2D6 and/or UGT1A1 would not be expected to have clinically meaningful changes in exposure upon coadministration with E/C/F/TAF, as evidence by the lack of effect of E/C/F/TAF on the CYP2D6 substrate sertraline (GS-US-292-1316 [Section 2.5.1.2]). COBI does not activate human AhR, and shows no evidence of induction of CYP1A2 (activity or messenger RNA) in human hepatocytes (AD-216-2027). COBI is a very weak activator of human PXR and will not result in induction of drug metabolizing enzymes or transporters.

At high concentrations present within the intestinal lumen during drug absorption, COBI can inhibit intestinal efflux transporters, such as P-gp and BCRP (GS-US-216-0112, GS-US-216-0134, GS-US-311-0101 [Section 2.5.2.1], GS-US-292-0103 [Section 2.2.1.2], AD-216-2072, and AD-216-2104). COBI was found to increase the C_{max} of coadministered digoxin (41% increase compared with the reference), but to notably have a lesser effect on AUC (7.8% increase in AUC_{inf} compared with the reference), suggesting that the effect was limited to transient inhibition of intestinal P-gp activity (GS-US-216-0112). COBI is a moderate inhibitor of hepatic uptake transporters, OATP1B1 and OATP1B3, which may result primarily in absorption-level interactions (higher peak concentrations/lower first-pass metabolism) of agents that are substrates for these transporters, rather than any changes to their systemic clearance (GS-US-216-0123). It also inhibits OCT2 and the renal efflux transporters OCTN1 and MATE1, which may inhibit the tubular secretion of endogenous substrates such as creatinine (OCT2/MATE1) without affecting overall renal function.

COBI shows weak or undetectable inhibition of P-gp, MRP1, MRP2, MRP4, BCRP, MATE2-K, and the renal uptake transporters, OAT1 and OAT3, so systemic concentrations of COBI would be insufficient to inhibit their activity and no clinically relevant interactions are expected (GS-US-216-0134; AD-216-2030, AD-216-2105, AD-216-2099, and AD-216-2094).

3.2.3.2.2. Potential for Other Drugs to Affect E/C/F/TAF

TAF is transported by P-gp and metabolized by esterases expressed in the intestine {21545}, {21546}. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly affect P-gp activity may lead to changes in TAF availability. However, upon coadministration with COBI in E/C/F/TAF, near maximal inhibition of P-gp by COBI is achieved, leading to increased availability of TAF with resulting exposure comparable with TAF 25 mg single agent. As such, TAF exposure following administration of E/C/F/TAF is not expected to be further increased when used in combination with another P-gp inhibitor. This is supported by a clinical study with E/C/F/TAF and investigation agent GS-5816, a P-gp inhibitor, which showed no clinical relevant changes in TAF or TFV upon coadministration of E/C/F/TAF with GS-5816, relative to E/C/F/TAF alone (GS-US-342-1167). Because TAF was found to be a substrate for hepatic transporters OATP1B1 and OATP1B3, exposure to TAF may be affected by inhibitors of OATP1B1 and OATP1B3 or by genetic polymorphisms affecting their transport activities. The effects of differences in OATP1B1 and OATP1B3 activity are, however, not expected to be clinically relevant given the high passive permeability of TAF.

Coadministration of TAF single agent with a modest CYP inducer, such as EFV, resulted in slightly lower TAF exposure (14%-22%) and a commensurate lowering of TFV exposure (GS-US-311-0101 [Section 2.5.2.1]). As such, administration of E/C/F/TAF with a modest CYP3A inducer may result in lower TAF exposure. However, the magnitude of change in TAF and TFV would be expected to be less following E/C/F/TAF due to the presence of the potent CYP3A inhibitor COBI.

The PK of EVG is likely to be affected by potent inhibitors of UGT1A1/3 (EVG exposure increase) and inducers of CYP3A enzymes (EVG exposure decrease). COBI PK is likely to be affected by potent inhibitors (COBI exposure increase) or inducers (COBI exposure decrease) of CYP3A. The PK of EVG and COBI do not change with acid-reducing agents, with the exception of antacids, as noted below.

The metabolism of EVG is mediated predominantly by CYP3A and secondarily by UGT1A1/3 (JTK303-AD-017 and AD-183-2034). Upon coadministration with COBI, a potent CYP3A inhibitor, the bioavailability of EVG increases as a result of increased absorption/reduced first-pass and the systemic clearance of EVG substantially decreases such that the apparent EVG clearance is approximately 1/20th of hepatic blood flow. The EVG systemic exposures are bioequivalent upon coadministration with COBI 150 mg or RTV 100 mg once daily (GS-US-216-0116). Based on these data and an RTV dose-ranging study (GS-US-183-0113) indicating no additional increases in EVG plasma exposures at RTV doses ≥ 100 mg, coadministration of EVG and COBI with other potent CYP3A inhibitors is not expected to increase EVG exposure, even if COBI exposure is higher. The observed drug interaction between COBI-boosted EVG plus ATV (GS-US-216-0123) or KTZ (GS-US-183-0146) support

the hypothesis that incremental decreases in the systemic clearance of boosted EVG are only evident with agents known to potently inhibit UGT1A1. However, following multiple-dose administration of COBI-boosted EVG in subjects with decreased UGT1A1 activity (UGT1A1*28), EVG PK parameters were comparable and $t_{1/2}$ was unchanged, relative to matched control subjects with wild-type UGT1A1*1 activity, indicating that no dose modification of EVG is necessary in patients with UGT1A1 polymorphisms receiving EVG as part of a boosted antiviral regimen (GS-US-183-1004 [Section 2.4.3.1]).

Coadministration of EVG and COBI with CYP3A inducers, such as rifabutin and carbamazepine, resulted in lower COBI exposure at the end of the dosing interval (ie, C_{tau}) and a consequent lowering of EVG C_{tau} (GS-US-216-0123 and GS-US-216-0137 [Section 2.5.3.1]). As such, administration of COBI-boosted EVG (E/C/F/TAF) with CYP3A inducers may result in lower EVG exposure and the potential for loss of therapeutic activity; therefore, coadministration of E/C/F/TAF with potent CYP3A inducers is contraindicated (eg, rifampin, carbamazepine, phenobarbital, and phenytoin), or not recommended (eg, rifabutin or rifapentine) (Section 3.2.3.2.3).

Coadministration of EVG and COBI with the HCV nonstructural protein 5A (NS5A) inhibitor LDV and the HCV nucleotide analog polymerase inhibitor SOF resulted in increased concentrations of COBI, LDV, SOF, and GS-331007, the predominant circulating metabolite of SOF (GS-US-344-0102). The effect of coadministration of LDV/SOF and E/C/F/TAF on concentrations of all components of these FDCs is unknown. There are insufficient data to make a dosing recommendation for coadministration of E/C/F/TAF with LDV/SOF.

EVG absorption and resulting systemic exposure were lower (40%-50%) upon simultaneous coadministration with antacids containing high concentrations of divalent and trivalent cations, presumably due to local complexation in the GI tract (GS-US-183-0103). This observation is consistent with the pharmacophore of HIV IN inhibitors such as EVG forming a complex with divalent cations (Mg^{2+}) at the active site of the IN enzyme. Staggering EVG and antacid administration by ± 2 hours or ± 4 hours offsets this interaction (GS-US-183-0119), and accordingly, these agents need to be administered ≥ 2 hours apart.

3.2.3.2.3. Management of Known and Potential Drug-Drug Interactions

Based on in vitro and in vivo absorption, metabolism, and elimination properties, and clinical PK of E/C/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, and acid-reducing agents including antacids, H_2-receptor antagonists, and proton pump inhibitors. Drug interaction information (observed or predicted) for E/C/F/TAF with potential concomitant drugs is summarized in Table 66.

Table 66. Drug Interaction Information for E/C/F/TAF with Potential Concomitant Drugs

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Acid Reducing Agents: antacids[b] (eg, aluminum and magnesium hydroxide)	↓ EVG	EVG plasma concentrations are lower with antacids due to local complexation in the GI tract and not to changes in gastric pH. It is recommended to separate E/C/F/TAF and antacid administration by at least 2 hours.
Alpha 1-Adrenoreceptor Antagonist: alfuzosin	↑ alfuzosin	Alfuzosin is primarily metabolized by CYP3A. Coadministration with E/C/F/TAF may result in increased plasma concentrations of alfuzosin, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of E/C/F/TAF and alfuzosin is contraindicated.
Antiarrhythmics: amiodarone bepridil digoxin[b] disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	↑ antiarrhythmics	Concentrations of these antiarrhythmic drugs may be increased when coadministered with COBI. Caution is warranted and clinical monitoring is recommended upon coadministration of these agents with E/C/F/TAF.
Antibacterials: clarithromycin telithromycin	↑ clarithromycin ↑ telithromycin ↑ COBI	Concentrations of clarithromycin and/or COBI may be altered when clarithromycin is coadministered with E/C/F/TAF. Patients with $eGFR_{CG}$ greater than or equal to 60 mL/min: No dose adjustment of clarithromycin is required. Patients with $eGFR_{CG}$ between 30 mL/min and 60 mL/min: The dose of clarithromycin should be reduced by 50%. Concentrations of telithromycin and/or COBI may be increased when telithromycis in coadministered with E/C/F/TAF. Clinical monitoring is recommended upon coadministration with E/C/F/TAF.
Anticoagulants: warfarin	↓ or ↑ warfarin	Concentrations of warfarin may be affected upon coadministration with E/C/F/TAF. It is recommended that the INR be monitored upon coadministration with E/C/F/TAF.

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Anticonvulsants: carbamazepine[b] ethosuximide oxcarbazepine phenobarbital phenytoin	↑ ethosuximide ↓ EVG ↓ COBI ↓ TAF	Carbamazepine, a potent CYP3A inducer, decreases COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of E/C/F/TAF with carbamazepine, phenobarbital, or phenytoin is contraindicated. Coadministration of oxcarbazepine, a CYP3A inducer, may decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered. Concentrations of ethosuximide may be increased when coadministered with COBI. Clinical monitoring is recommended upon coadministration with E/C/F/TAF.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline[b] Tricyclic Antidepressants (TCAs) trazodone	↑ SSRIs ↔ sertraline ↑ TCAs ↑ trazodone	Concentrations of sertraline are not affected upon coadministration with E/C/F/TAF. No dose adjustment is required upon coadministration. Concentrations of other antidepressant agents may be increased when coadministered with COBI. Dose titration may be required for most drugs of the SSRI class. Concentrations of trazodone may increase upon coadministration with COBI. Dose reduction should be considered when trazodone is coadministered with E/C/F/TAF.
Antifungals: itraconazole ketoconazole[b] voriconazole	↑ antifungals ↑ COBI	Concentrations of ketoconazole, itraconazole, and/or COBI may increase with coadministration of E/C/F/TAF. When administering with E/C/F/TAF, the maximum daily dose of ketoconazole and itraconazole should not exceed 200 mg per day. Concentrations of voriconazole may be increased when coadministered with COBI. Clinical monitoring may be needed upon coadministration with E/C/F/TAF.
Antigout: colchicine	↑ colchicine	Dose reductions of colchicine may be required. E/C/F/TAF should not be coadministered with colchicine in patients with renal or hepatic impairment.
Antihistamines: astemizole terfenadine	↑ astemizole ↑ terfenadine	Concentrations of astemizole and terfenadine may be increased when coadministered with COBI. Clinical monitoring is recommended when these agents are coadministered with E/C/F/TAF.

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Antimycobacterials: rifabutin[b] rifampin rifapentine	↓ EVG ↓ COBI ↓ TAF	Coadministration of rifampin, rifabutin, and rifapentine, potent CYP3A inducers, may significantly decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of E/C/F/TAF with rifampin is contraindicated. Coadministration of E/C/F/TAF with rifabutin or rifapentine is not recommended.
Benzodiazepines: diazepam lorazepam midazolam triazolam	↑ diazepam ↔ lorazepam ↑ midazolam ↑ triazolam	Midazolam and triazolam are primarily metabolized by CYP3A. Coadministration with E/C/F/TAF may result in increased plasma concentrations of these drugs, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of E/C/F/TAF and orally administered midazolam and triazolam are contraindicated. Concentrations of other benzodiazepines, including diazepam and parenterally administered midazolam, may be increased when administered with E/C/F/TAF. Coadministration should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction may be necessary. Based on non-CYP-mediated elimination pathways for lorazepam, no effect on plasma concentrations is expected upon coadministration with E/C/F/TAF.
Beta-Blockers: metoprolol timolol	↑ beta-blockers	Concentrations of beta-blockers may be increased when coadministered with COBI. Clinical monitoring is recommended and a dose decrease may be necessary when these agents are coadministered with E/C/F/TAF.
Calcium Channel Blockers: amlodipine diltiazem felodipine nicardipine nifedipine verapamil	↑ calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with COBI. Caution is warranted and clinical monitoring is recommended upon coadministration with E/C/F/TAF.
Systemic Corticosteroid: dexamethasone	↓ EVG ↓ COBI	Coadministration of dexamethasone, a CYP3A inducer, may decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative systemic corticosteroids should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Inhaled/Nasal Corticosteroid: fluticasone	↑ fluticasone	Coadministration of inhaled or nasal fluticasone propionate and E/C/F/TAF is not recommended unless the potential benefit to the patient outweighs the risks. Alternative inhaled or nasal corticosteroids may be considered.
Endothelin Receptor Antagonists: bosentan	↓ EVG ↓ COBI	Coadministration with E/C/F/TAF may lead to decreased EVG and/or COBI exposures and loss of therapeutic effect and development of resistance. Alternative endothelin receptor antagonists may be considered.
Ergot Derivatives: dihydroergotamine ergonovine ergotamine methylergonovine	↑ ergot derivatives	Ergot derivatives are primarily metabolized by CYP3A. Coadministration with E/C/F/TAF may result in increased plasma concentrations of these drugs, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of E/C/F/TAF and dihydroergotamine, ergonovine, ergotamine, and methylergonovine are contraindicated.
GI Motility Agents: cisapride	↑ cisapride	Cisapride is primarily metabolized by CYP3A. Coadministration with E/C/F/TAF may result in increased plasma concentrations of cisapride, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of E/C/F/TAF and cisapride is contraindicated.
HCV Products: ledipasvir/sofosbuvir	↑ COBI ↑ ledipasvir ↑ sofosbuvir ↑ GS-331007	Concentrations of COBI, ledipasvir, sofosbuvir, and GS-331007 (the predominant circulating metabolite of sofosbuvir) are increased when ledipasvir/sofosbuvir is coadministered with EVG and COBI. The effect of coadministration of ledipasvir/sofosbuvir and E/C/F/TAF on concentrations of all components of these FDCs is unknown. There are insufficient data to make a dosing recommendation for coadministration of E/C/F/TAF with ledipasvir/sofosbuvir.
Herbal Products: St John's wort *(Hypericum perforatum)*	↓ EVG ↓ COBI ↓ TAF	Coadministration of St John's wort, a potent CYP3A inducer, may significantly decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of E/C/F/TAF with St John's wort is contraindicated.

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
HMG-CoA Reductase Inhibitors: atorvastatin lovastatin rosuvastatin simvastatin	↑ HMG-CoA reductase inhibitors	HMG-CoA reductase inhibitors are primarily metabolized by CYP3A. Coadministration with E/C/F/TAF may result in increased plasma concentrations of lovastatin or simvastatin, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of E/C/F/TAF with lovastatin and simvastatin are contraindicated. Concentrations of atorvastatin may be increased when coadministered with EVG and COBI. Start with the lowest possible dose of atorvastatin with careful monitoring upon coadministration with E/C/F/TAF. Concentrations of rosuvastatin are transiently increased when coadministered with EVG and COBI. Dose modifications are not necessary when rosuvastatin is administered in combination with E/C/F/TAF.
Hormonal Contraceptives: norgestimate/ethinyl estradiol[b]	↑ norgestimate ↓ ethinyl estradiol	Coadministration of E/C/F/TAF and a norgestimate/ethinyl estradiol-containing hormonal oral contraceptive is expected to decrease plasma concentrations of ethinyl estradiol and increase norgestimate. Use caution when coadministering E/C/F/TAF and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 μg of ethinyl estradiol. The long-term effects of substantial increases in progesterone exposure are unknown. Coadministration of E/C/F/TAF with oral contraceptives or hormonal contraceptives containing progestogens other than norgestimate, or less than 25 μg of ethinyl estradiol, has not been studied.
Immunosuppressants: Cyclosporine rapamycin sirolimus tacrolimus	↑ immunosuppressants	Concentrations of these immunosuppressant agents may be increased when coadministered with COBI. Therapeutic monitoring is recommended upon coadministration with E/C/F/TAF.
Narcotic Analgesics: buprenorphine/ naloxone[b]	↑ buprenorphine ↑ norbuprenorphine ↓ naloxone	Concentrations of buprenorphine and norbuprenorphine are increased when coadministered with E/C/F/TAF. No dose adjustment of buprenorphine/naloxone is required upon coadministration with E/C/F/TAF. Patients should be closely monitored for sedation and cognitive effects.

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration with E/C/F/TAF may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of salmeterol and E/C/F/TAF is not recommended.
Neuroleptics: perphenazine pimozide risperidone thioridazine	↑ neuroleptics	Pimozide is primarily metabolized by CYP3A. Coadministration with E/C/F/TAF may result in increased plasma concentrations of pimozide, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of E/C/F/TAF with pimozide is contraindicated. For other neuroleptics, consider reducing the dose of the neuroleptic upon coadministration with E/C/F/TAF.
Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	PDE5 inhibitors are primarily metabolized by CYP3A. Coadministration with E/C/F/TAF may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE5 inhibitor-associated adverse reactions. Coadministration of E/C/F/TAF with sildenafil for the treatment of pulmonary arterial hypertension is contraindicated. Caution should be exercised, including consideration of dose reduction, when coadministering E/C/F/TAF with tadalafil for the treatment of pulmonary arterial hypertension. For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered with E/C/F/TAF.
Sedative/hypnotics: buspirone orally administered zolpidem	↑ sedatives/hypnotics	With sedative/hypnotics, dose reduction may be necessary upon coadministration with E/C/F/TAF and clinical monitoring is recommended.

HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; PDE5 = phosphodiesterase-5
Note: This table is not all inclusive.
a ↑ = Increase, ↓ = Decrease, ↔ = No Effect
b Indicates that a drug-drug interaction study was conducted.

3.3. Pharmacokinetics/Pharmacodynamics

A list of all tables, figures, and listings related to PK/PD analyses are presented in Appendix 6.2.

3.3.1. Pharmacokinetic-Pharmacodynamic Relationship for Efficacy Parameters

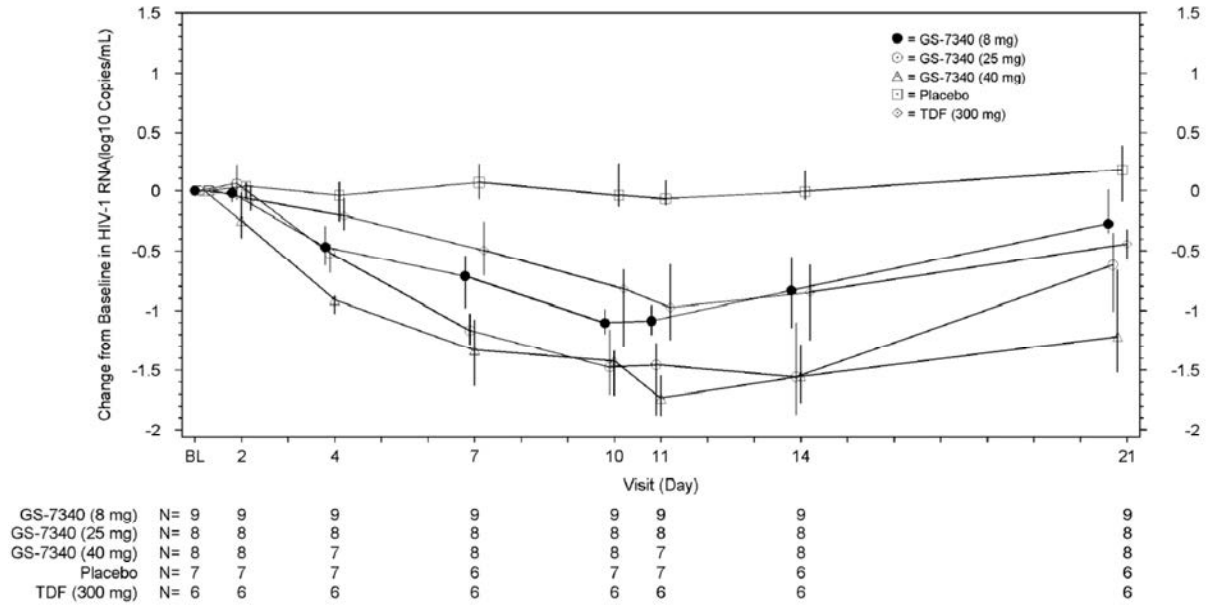
3.3.1.1. TAF and TFV

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.

In the proof of concept Study GS-US-120-0104 (Section 2.3.1.1), following monotherapy treatment of once daily administration of TAF 8, 25, 40 mg, or TDF 300 mg, the mean (± SD) $DAVG_{11}$ was -0.67 ± 0.265, -0.94 ± 0.254, -1.14 ± 0.226, and -0.45 ± 0.340 log_{10} copies/mL, respectively. Mean (± SD) changes from baseline at Day 11 in HIV-1 RNA of -0.98 ± 0.464, -1.50 ± 0.412, and -1.74 ± 0.190 log_{10} copies/mL were observed following TAF 8, 25, or 40 mg treatment, respectively, as compared with a change of -0.81 ± 0.580 log_{10} copies/mL with TDF 300 mg (Figure 14). Mean viral load declines for both the TAF 25 mg and 40 mg doses were statistically greater than for the 8 mg dose.

Figure 14. GS-US-120-0104: Median (Q1, Q3) of Change from Baseline in HIV-1 RNA (log_{10} copies/mL) by Visit (Full Analysis Set)



Note: Baseline HIV-1 RNA is defined to be the geometric mean of the last 2 available nonmissing HIV-1 RNA values before the first dose.
Source: m5.3.4.2, GS-US-120-0104, Section 15.1, Figure 2.1.2

The PK/PD relationships between TAF and TFV plasma exposures and antiviral activity were 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} and AUC and changes 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 show that TAF AUC fits well with an E_{max} model, with an E_{max} of ~1.7 to 1.8 log_{10} decline from baseline and the concentration of drug inhibiting virus replication by 50% (EC_{50}) for AUC of ~32 ng•h/mL. A similar fit/ E_{max} estimate was also obtained using TAF C_{max}, which was somewhat expected given its relatively brief plasma circulation time frame driven by a short half-life and the resulting contribution of the C_{max} to the overall AUC. Upon comparison of antiviral activity with 40 mg and previous data with 120 mg (m5.3.4.2, GS-120-1101), TAF 25 mg is expected to provide near-maximal activity (~1.7 to 1.8 log_{10} copies/mL). Plasma TFV exposure, which was substantially lower with TAF versus TDF, did not correlate with antiviral activity.

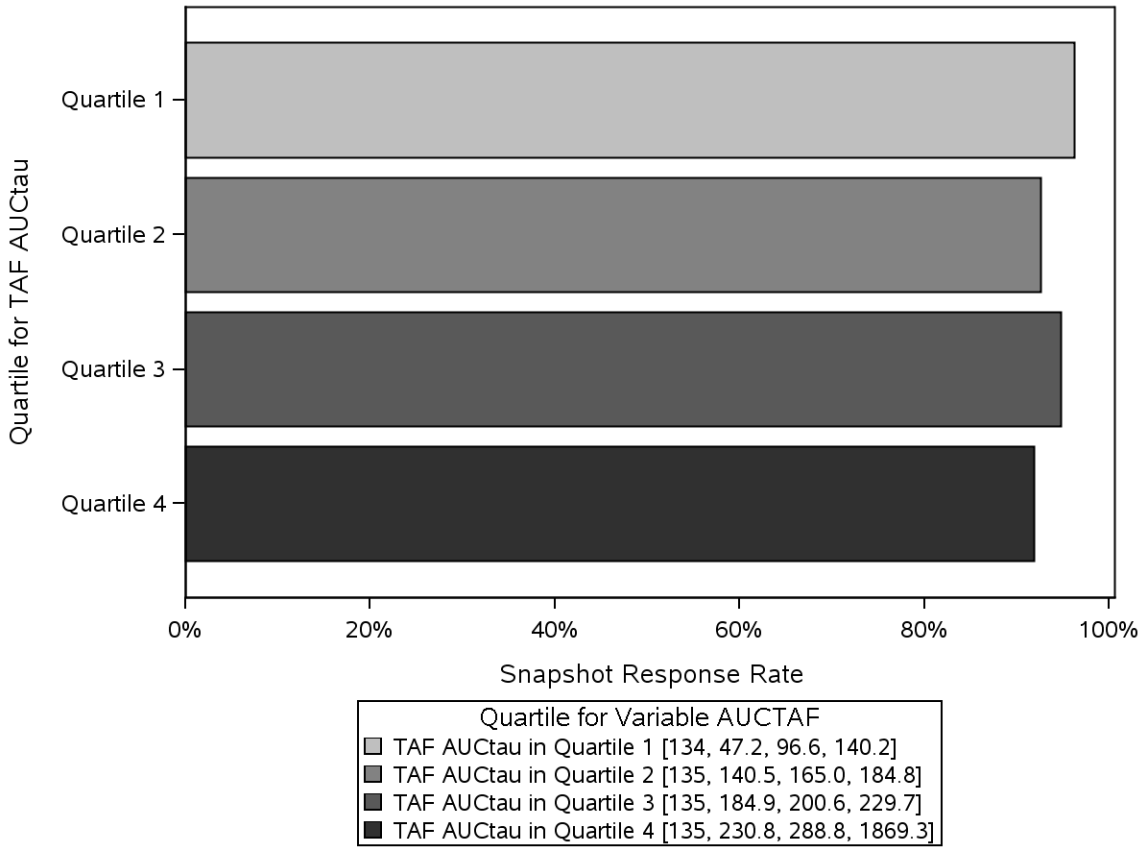
The PK/PD analyses of TAF exposure-efficacy relationship were performed in ART-naive HIV-infected subjects in Studies GS-US-292-0104 and GS-US-292-0111 using TAF exposure (AUC_{tau}) derived from TAF population PK modeling versus efficacy based on percentage of virologic success at Week 48 (HIV-1 RNA < 50 copies/mL, FDA snapshot algorithm); results using quartiles of PK exposure are presented in Table 67. 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 that provides equivalent exposure as the unboosted TAF 25 mg single agent.

Table 67. Percentage of Virologic Success at Week 48 Across Quartiles of TAF Exposure (TAF PK/PD Analysis Set)

TAF AUC_{tau} Quartile (ng•h/mL)	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) (%) (N = 135)
47.2 to 140.2	96.3[a]
140.5 to 184.8	92.6
184.9 to 229.7	94.8
230.8 to 1869.3	91.9

a N = 134
Source: m5.3.4.2, E/C/F/TAF PK/PD Table 2.1

Figure 15. 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: m5.3.4.2, 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 demographics (m2.7.3, Section 3.3).

3.3.1.2. EVG

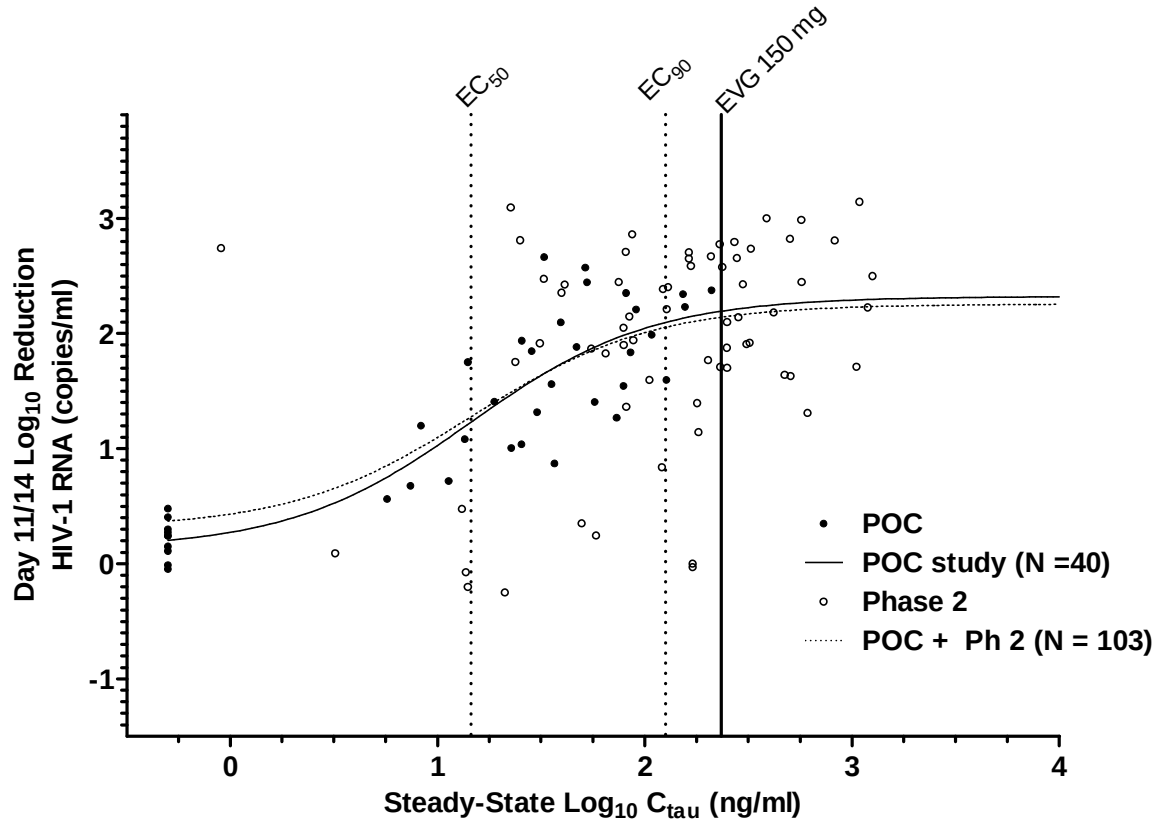
Administration of EVG at doses of 200, 400, or 800 mg twice daily; 800 mg once daily; or EVG 50 mg + RTV 100 mg once daily to INSTI-naive HIV-infected subjects as monotherapy for 10 consecutive days significantly reduced HIV-1 RNA compared with placebo at all dose levels (Study GS-US-183-0101). EVG doses of 400 mg twice daily, 800 mg twice daily, and 50 mg + RTV 100 mg once daily resulted in mean declines from baseline in HIV-1 RNA of 1.94, 1.91, and 1.99 $\log_{10}$ copies/mL, respectively.

When evaluated as short-term monotherapy, EVG exhibited PK supporting twice-daily dosing alone or once-daily dosing with a pharmacoenhancer (low dose [100 mg] RTV evaluated in this study). An EVG exposure-response relationship was identified with EVG C_{tau} values that fit well to a simple E_{max} model. The estimated IQ (C_{trough}/IC_{95}: IQ_{95}) of EVG, calculated using a protein binding-adjusted in vitro IC_{95} of 45 ng/mL, was ~1 at the 400-mg twice-daily and 800-mg twice-daily dose levels, and was ~3 at the 50-mg + RTV once-daily dose level. EVG trough concentrations at these dose levels and dosing regimens exceeded the IC_{95} for the entire dosing interval.

In a Phase 2 dose-finding study designed to assess the noninferiority of EVG+RTV relative to a comparator protease inhibitor (CPI)+RTV, EVG+RTV 50/100-mg and 125/100-mg groups met criteria for noninferiority relative to CPI+RTV for the prespecified primary efficacy endpoint of $DAVG_{24}$. The EVG+RTV 125/100-mg group was statistically superior to CPI+RTV in the analysis of $DAVG_{16}$, $DAVG_{24}$, and in categorical reductions in viral load. EVG mean C_{trough} at the EVG+RTV doses of 20/100 mg, 50/100 mg, and 125/100 mg were ~1.5-, 4.7-, and 6-fold above the IC_{95} (45 ng/mL).

An E_{max} dose-response model for EVG using cumulative data from the monotherapy and dose-ranging data in HIV-infected subjects evaluating antiviral activity as a function of steady-state trough EVG concentrations (C_{tau}: 16-fold dose range and 20-fold mean C_{tau}/C_{trough} range) is shown in Figure 16. Mean C_{trough} values from EVG 150 mg represent the plateau range of this relationship providing near-maximal antiviral activity.

Figure 16. EVG Dose-Response Model Based on Monotherapy and Phase 2 Dose-Ranging Studies



Source: {9320}, {18456}

EVG once daily (at doses of 85 or 150 mg depending on the coadministered PI/r) displayed noninferior antiviral efficacy versus raltegravir (RAL) twice daily when administered to HIV-infected, ART-experienced adults. Mean EVG trough concentrations (C_{tau}, C_{trough}) were ~8.5- to 17.1-fold above the in vitro protein binding-adjusted IC_{95} (45 ng/mL) in a PK substudy, indicating exposures corresponding to near-maximal antiviral activity with either dose. Based on trough sample collection in all subjects over study visits from Week 2 and Week 48, mean EVG 85-mg trough concentrations (n = 57 to 111 subjects) were 9.7- to 12.0-fold and mean EVG 150-mg trough concentrations (n = 58 to 186 subjects) were 6.9- to 9.2-fold above the EVG protein binding-adjusted IC_{95}.

The PK/PD analyses of EVG exposure-efficacy relationship were performed in ART-naive HIV-infected subjects in STB Phase 3 studies using EVG exposure derived from EVG population PK modeling versus efficacy based on HIV-1 RNA < 50 copies/mL using pure virologic response (PVR) criteria by Week 48. Pure virologic response was chosen as the primary PD endpoint for exposure-efficacy analyses as it represents the most appropriate metric assessing virologic response pharmacologically as it is unaffected by nonvirologic factors

(eg, discontinuation for various reasons) that are reasons for the definition of "virologic failure" in composite primary endpoints such as time to loss of virologic response (TLOVR). Because the primary endpoint for efficacy in the Phase 3 studies was based on the FDA snapshot algorithm at Week 48, exposure-efficacy relationships were additionally explored using this endpoint for Phase 2 and Phase 3 studies.

The following criteria were used for classifying a subject as a pure virologic responder at Week 48:

- Had achieved a confirmed suppression (ie, HIV-1 RNA < 50 copies/mL on 2 consecutive visits) prior to or on the upper limit of the Week 48 analysis window
- Had not had a confirmed rebound (ie, HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits or the last available HIV-1 RNA ≥ 50 copies/mL during study followed by premature discontinuation of study) by the upper limit of the Week 48 analysis window after achieving confirmed suppression.

For confirmation of viral suppression or rebound, the first HIV-1 RNA occurred on or before the upper limit of the Week 48 analysis window, and the confirming event (ie, the second of the consecutive HIV-1 RNAs or premature study discontinuation) could occur after the upper limit of the Week 48 analysis window.

EVG PK/PD analyses using EVG C_{trough}-PVR results using quartiles of PK exposure are presented in Table 68. Virologic response was uniformly high across the quartiles of EVG C_{trough} with no trends in exposure-response relationship observed. These results are consistent with the careful and data-driven dose selection of EVG 150 mg that provides exposure corresponding to E_{max} across subjects via provision of potent INSTI antiviral activity with both mean and overall C_{trough} values that exceed (by ~10-fold) the protein binding-adjusted IC_{95} (45 ng/mL).

Table 68. Percentage of Pure Virologic Responders Across Quartiles of EVG Exposure (N = 373) (EVG PK/PD Analysis Set)

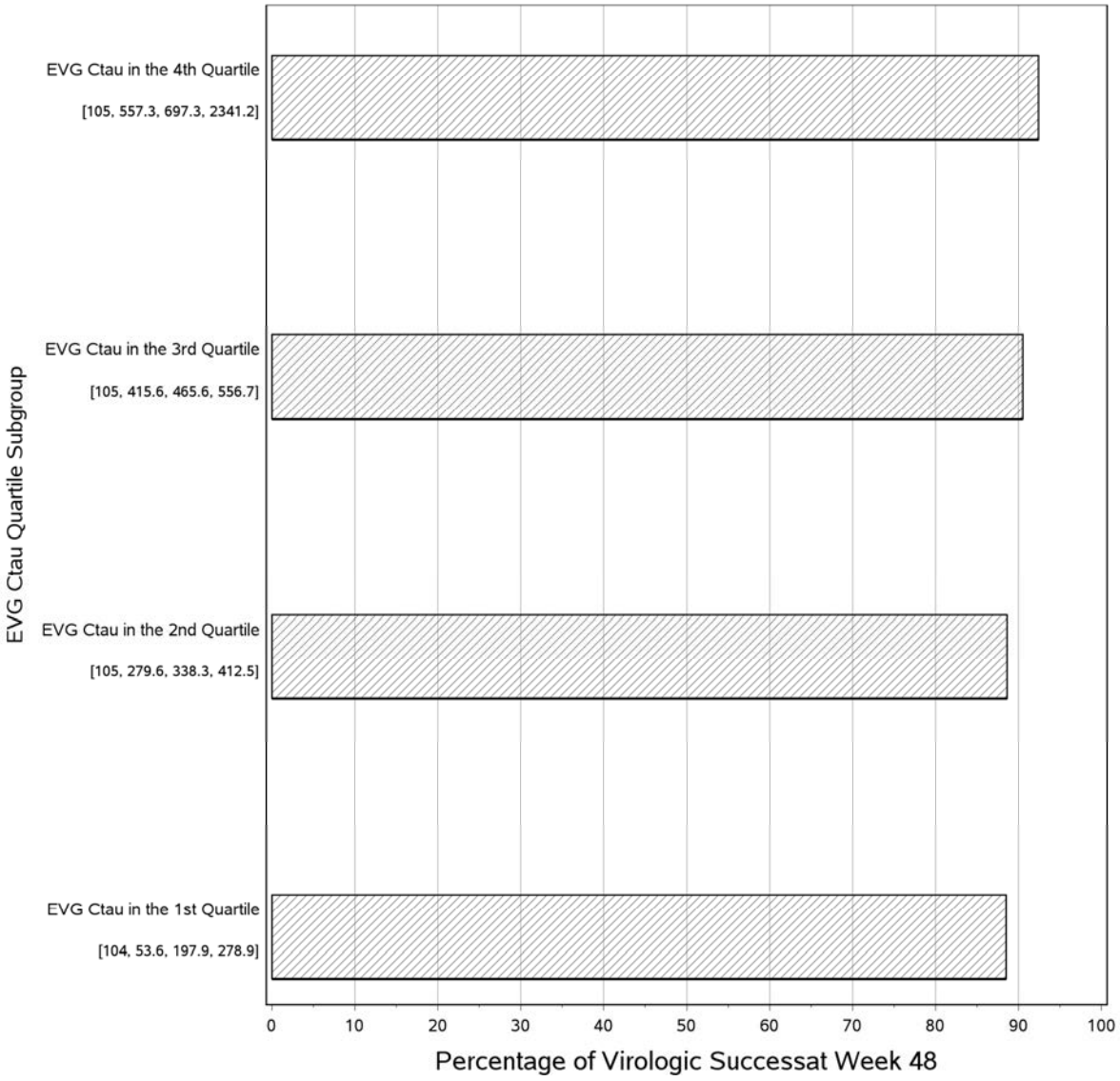
EVG C_{tau} Quartile (ng/mL)	PVR (%) (N= 93)
58 to < 296	89
296 to < 423	88
423 to < 560	93
560 to 2341	87[a]

a N = 94
PVR = pure virologic response
Source: STB PK/PD Tables 3.4

Similar results were obtained using the FDA snapshot algorithm with virologic success rates of 89% and 92% at the lowest and highest C_{trough} quartiles, respectively (Figure 17); 87% and 91% at the lowest and highest C_{trough} quintiles, respectively; and 89% and 93% at the lowest and highest C_{trough} octiles, respectively (STB PK/PD Tables 3.1, 3.2, and 3.3, respectively).

These results are also in accordance with the findings from the EVG population PK analyses that identified no relevant covariates on EVG PK/exposure (Section 3.2.1.2) and the comparable and high rates of efficacy observed across demographics (m2.7.3, Section 3.3).

Figure 17. Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) by EVG C_{tau} (ng/mL) Quartile Subgroup (EVG PK/PD Analysis Set)



Numbers presented in the square bracket were the sample size, minimum, median, and maximum of EVG C_{tau} for subjects included in that subgroup.
Source: STB PK/PD Figure 1.1

3.3.1.3. COBI

The clinical PK/PD of COBI were evaluated in detailed Phase 1 studies using probe or target substrates to identify the COBI dose/exposure range associated with near-maximal/optimal efficacy (ie, CYP3A inhibition resulting in pharmacoenhancement).

COBI PK/PD in the target HIV-infected population were evaluated based on the exposure and the associated efficacy and PK/PD of the boosted agent (ie, EVG in STB) using the COBI dose/exposures used in the STB Phase 2 and Phase 3 studies.

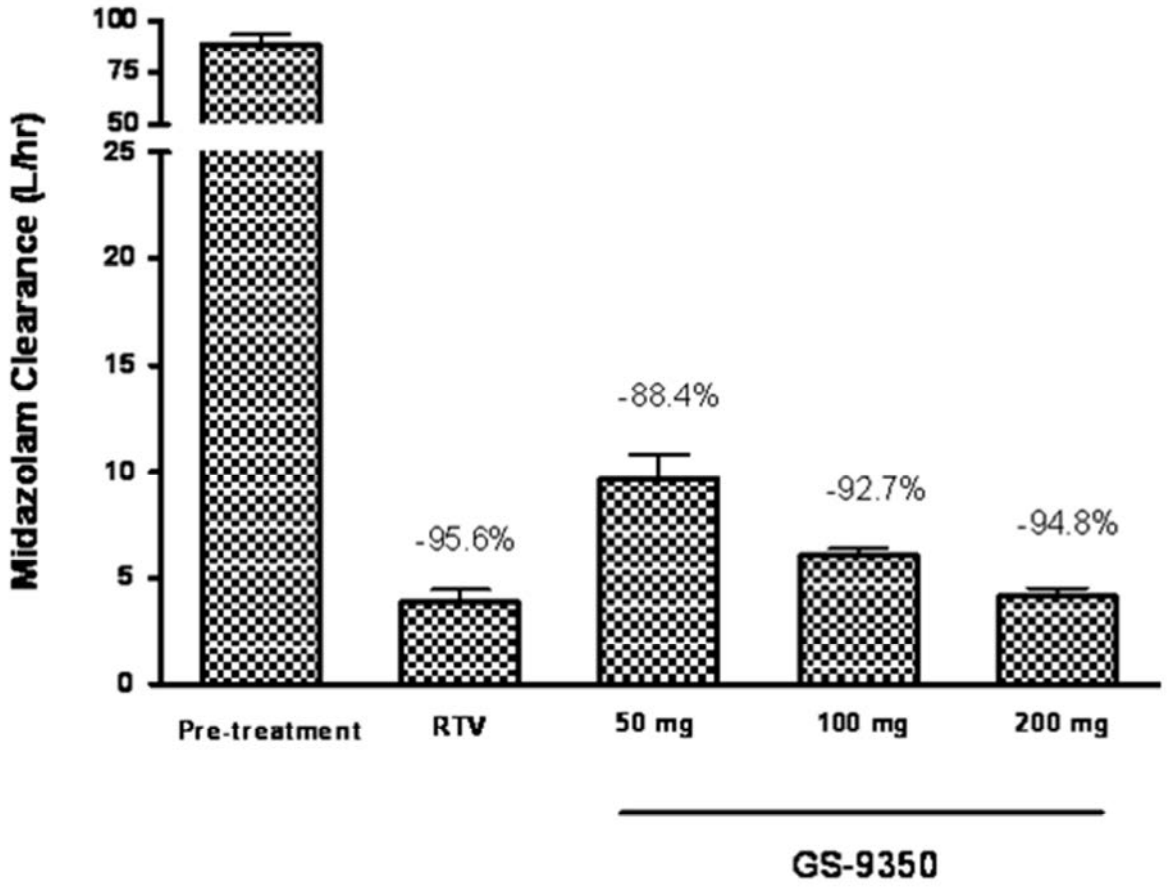
The clinical PK and PD of COBI were evaluated in a Phase 1 study using MDZ as a specific probe CYP3A substrate, administered as a single low dose alone or in combination with multiple doses of COBI over a COBI dose range of 50 to 200 mg, and with RTV, a known CYP3A inhibitor, at 100 mg (GS-US-216-0101).

As expected, MDZ showed increased concentrations when administered with the CYP3A inhibitors, COBI and RTV. Near-maximal inhibition of CYP3A was observed with a low dose of COBI of 100 mg, as evidenced by modest increases in MDZ concentrations with higher COBI doses. The increase in MDZ concentrations following administration of COBI 100 or 200 mg appeared similar to the values observed with 100 mg of RTV.

When MDZ was coadministered with 50 mg of COBI, MDZ CL/F was reduced relative to MDZ administration alone (GLSM ratio 11.6%, or an 88.4% reduction). More modest incremental reductions were observed as the COBI dose was increased to 100 mg and 200 mg (GLSM ratio 7.3% and 5.20% relative to MDZ alone, reflecting 92.7% and 94.8% reductions, respectively), which were comparable with results observed upon coadministration with RTV (GLSM ratio 4.5%, or a 95.6% reduction) (Figure 18 and Table 69).

Overall, comparable near-maximal CYPA3 inhibition (as assessed by the probe substrate MDZ) was achieved at steady state following administration of COBI at dose levels ≥ 100 mg, as evidenced by modest increases in MDZ concentrations with increased COBI doses.

Figure 18. Effect of CYP3A Inhibition by COBI or RTV on the Probe Substrate MDZ (PK Analysis Set)



GS-9350 = cobicistat
Source: GS-US-216-0101, Figure 7-7

Table 69. Summary of MDZ PK Parameters Across Treatments (PK Analysis Set)

MDZ Plasma PK Parameters	MDZ Alone (N = 60)	MDZ+COBI 50 mg (N = 12)	MDZ+COBI 100 mg (N = 11)	MDZ+COBI 200 mg (N = 12)	MDZ+RTV 100 mg (N = 9)
C_{max} (ng/mL) Mean (%CV)	14.5 (29)	45.3 (27)	55.0 (18)	56.0 (21)	58.5 (16)
AUC_{last} (ng•h/mL) Mean (%CV)	58.0 (29)	493 (34)	665 (18)	690 (16)	729 (23)
AUC_{inf} (ng•h/mL) Mean (%CV)	64.1 (33)	626 (50)	856 (18)	1220 (27)[a]	1530 (43)
C_{last} (ng/mL) Mean (%CV)	0.6[b] (69)	7.4[b] (71)	11.8 (27)	16.9 (25)	18.9 (40)
T_{max} (h) Median (Q1, Q3)	1.0 (1.0, 2.0)	1.8 (1.3, 3.8)	4.0 (2.5, 4.5)	2.3 (1.8, 4.3)	3.0 (2.0, 4.0)
$t_{1/2}$ (h) Median (Q1, Q3)	5.2 (3.9, 6.9)	8.9 (6.4, 11)	11 (8.2, 13)	19 (11, 28)[a]	26 (16, 35)
T_{last} (h) Median (Q1, Q3)	16 (16, 16)	24 (24, 24)	24 (24, 24)	24 (24, 24)	24 (24, 24)
CL/F (mL/h) Mean (%CV)	87,300 (35)	9660 (42)	6020 (18)	4350 (24)[a]	3940 (45)

a n = 11
b Data are shown to 2 significant digits.
Data are shown to 3 significant digits (2 for time parameters).
Source: GS-US-216-0101, Section 11.1, Table 5.3

When COBI coadministration was compared directly with RTV coadministration, MDZ clearance was 247%, 166%, and 118% with COBI 50, 100, and 200 mg, respectively, and corresponding exposures were 41%, 60%, and 85%, respectively, relative to those with RTV (GLSM ratio).

Midazolam exposure (AUC_{inf}) was increased 13.8- and 19.2-fold following coadministration with COBI 100 and 200 mg, respectively, and 22.5-fold following coadministration with RTV, relative to administration with MDZ alone (GLSM ratios of 1375.3%, 1921.3%, and 2247.8%, respectively).

In nonparametric analyses, reductions in MDZ CL/F were statistically significant with each dose level of COBI relative to MDZ alone, and between increasing COBI doses over the dose range evaluated. With COBI 50 mg, the effects on MDZ exposure and clearance were significantly different from that of RTV (AUC and CL/F, $p < 0.05$). The effect of COBI 100 mg on MDZ exposure was not statistically significantly different from that of RTV ($p = 0.403$); however, MDZ CL/F results were significantly different for the 2 pharmacoenhancers ($p = 0.019$). The effect of COBI 200 mg on MDZ exposure and clearance was not statistically significantly different from that of RTV (AUC and CL/F, $p > 0.05$).

As expected, 1′-OH MDZ concentrations decreased with increasing doses of COBI, consistent with inhibition of CYP3A and the inhibitory trends exhibited by increasing doses of COBI on its probe substrate, MDZ.

Cumulative assessment of these data indicate that COBI can produce the PD effect of potent inhibition of CYP3A-mediated metabolism of MDZ similar to that observed in other Gilead clinical studies where MDZ was administered with other potent CYP3A inhibitors, including EVG+RTV, and EVG+RTV /high-exposure KTZ (200 mg twice daily; Study GS-US-183-0146), as well as that reported in the literature (Table 70).

Table 70. Single-Dose MDZ PK Parameters Following Coadministration with COBI or RTV in Study GS-US-216-0101 and Historical Data with RTV and/or Other CYP3A Inhibitors

MDZ PK	N	CL/F (L/h)	C_{max} (ng/mL)
MDZ Alone	60	87.3 (35)	14.5 (29)
+ COBI 50 mg	12	9.66 (42)	45.3 (27)
+ COBI 100 mg	11	6.02 (18)	55.0 (18)
+ COBI 200 mg	12	4.35 (24)[a]	56.0 (21)
+ RTV 100 mg	9	3.94 (45)	58.5 (16)
+ EVG+RTV+KTZ (150 mg QD + 100 mg QD + 200 mg BID) (GS-US-183-0146)	18	5.99 (32)	52.7 (26)
+ KTZ 200 mg BID {9064}	9	8.64 (29)[b]	—
+ Troleandomycin 500 mg[c] {12564}	10	9.63 (25)[d]	—

a n = 11
b Apparent clearance in L/h converted from mL min^{-1} kg^{-1} in reference using mean body weight of 68.6 kg.
c Two doses of troleandomycin 500 mg were given, one 2 hours before and one 6 hours after the MDZ dose.
d Apparent clearance in L/h converted from mL min^{-1} kg^{-1} in reference using mean body weight of 74 kg.
Data are presented as mean (%CV) and are shown to 3 significant digits.
Source: GS-US-216-0101, Section 11.1, Table 5.3; GS-US-183-0146, Section 11.1, Table 5.5

The results of Study GS-US-216-0101 led to further evaluation of COBI 100-mg and 150-mg doses and the PD/CYP3A inhibition of EVG. The clinical PK/PD of COBI using EVG as the target drug/substrate were evaluated through a relative bioavailability assessment of the components of STB containing EVG 150 mg, FTC 200 mg, and TDF 300 mg plus the pharmacoenhancer COBI at doses of 100 mg and 150 mg relative to EVG+RTV 150/100 mg, FTC 200 mg, and TDF 300 mg administered as separate components. Administration of EVG as STB with COBI at a dose of 100 mg resulted in bioequivalent exposures as assessed by AUC_{tau} and C_{max} but a 40% lower C_{tau} estimate relative to EVG+RTV. With STB containing COBI 150 mg, EVG exposure was modestly higher with C_{max}, meeting the definition of bioequivalence, and the upper bound of the 90% CI of AUC_{tau} exceeding the criteria by 1%. Importantly, at this COBI dose (150 mg), adequate EVG trough concentrations (C_{tau}) were achieved (upper bound of the 90% CI versus RTV 100 mg: 127%).

Additionally, cumulative study findings demonstrated that EVG 150 mg, ATV 300 mg, and DRV 800 mg steady-state exposures (including C_{trough}) were similar following administration with COBI 150 mg versus RTV 100 mg.

Based on COBI population PK analyses using data from Phase 1 studies in healthy subjects and Phase 2 and Phase 3 studies in HIV-infected subjects, COBI 150-mg exposure did not result in differences in EVG exposure and was considered not to be a clinically relevant covariate. As shown in Section 3.3.1.2, EVG exposure upon coadministration with COBI (as STB) in HIV-infected subjects were associated with high rates of virologic response and corresponded to the plateau phase of its exposure-antiviral efficacy relationship.

3.3.1.4. 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.

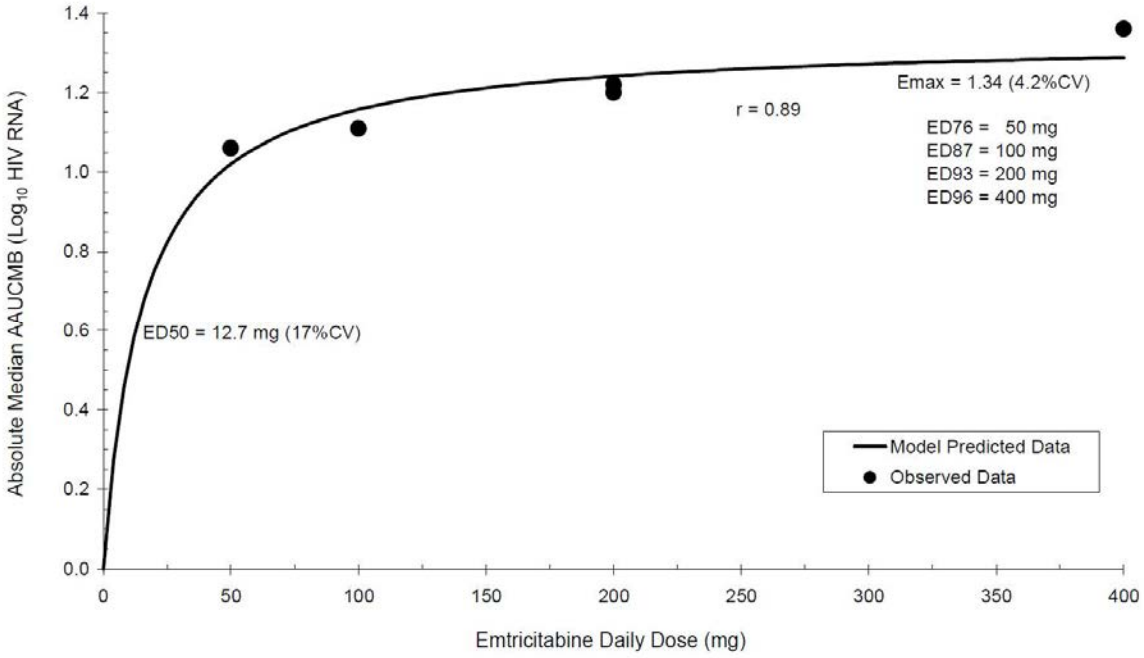
Study FTC-102 was an open-label, randomized, parallel-group study evaluating 3 once-daily dosage regimens of FTC (25, 100, and 200 mg once daily) and the 3TC 150-mg twice-daily regimen during 10 days of monotherapy. A total of 81 subjects, naive to 3TC and ABC, were randomized to 1 of the 4 treatment 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 proportion 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, $E = (E_{max} \times \text{Dose})/(ED_{50} + \text{Dose})$. The pharmacological dose-response curve (Figure 19) 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 19. FTC-101: Dose-Response Relationship of Anti-HIV Activity of FTC: Plots of Log_{10} HIV-1 RNA AAUCMB Versus FTC Daily Dose



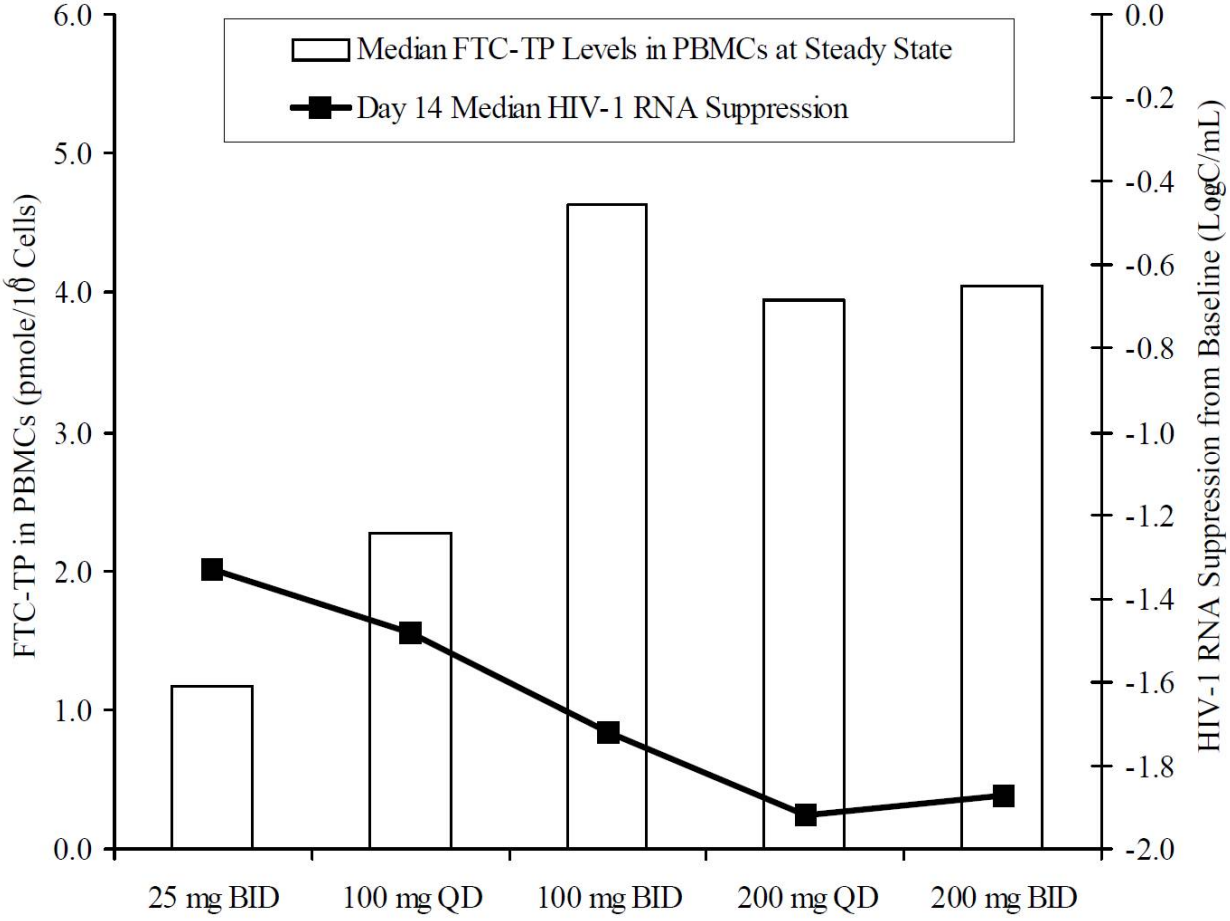
Source: FTC Investigator's Brochure 30 Jul 2010 Table 8

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 20). 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 20. 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 and TFV

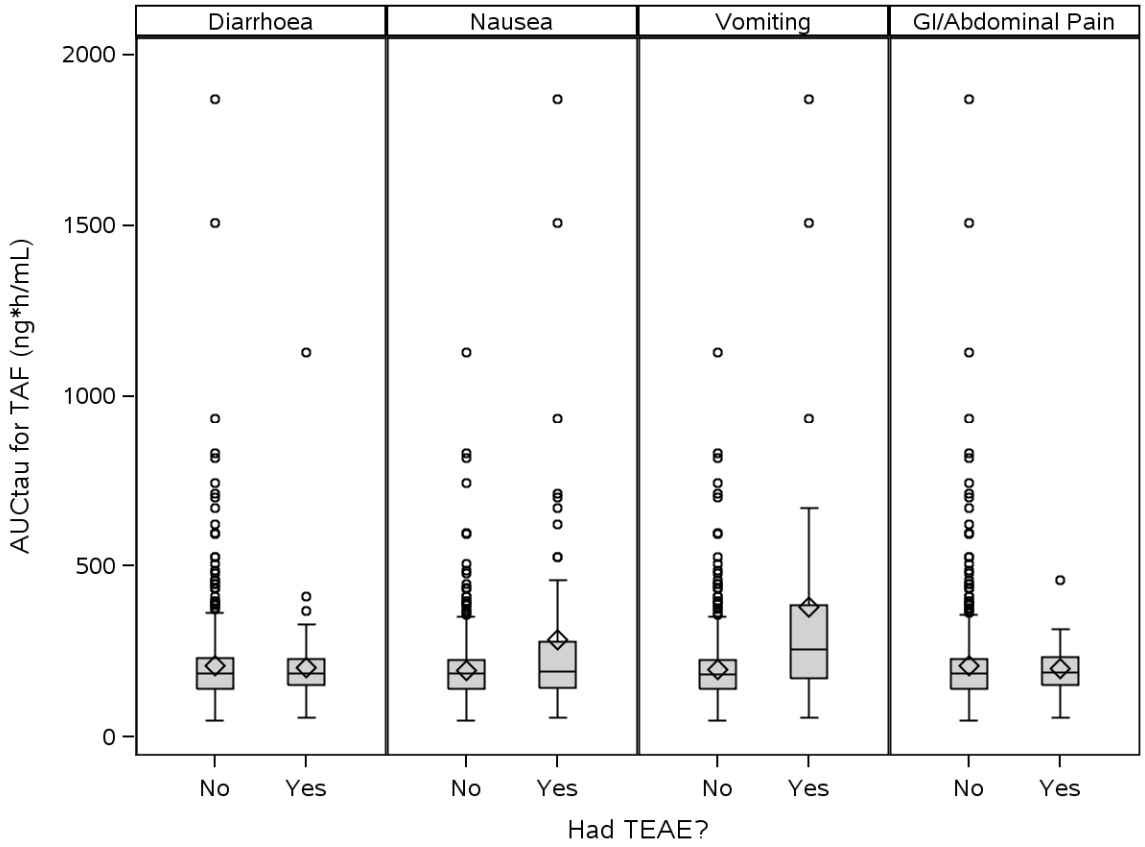
The safety endpoints for the PK/PD analyses were:

- Presence or absence of diarrhea, nausea, vomiting, and 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 and TFV (estimated from population PK modeling for TAF and for TFV).

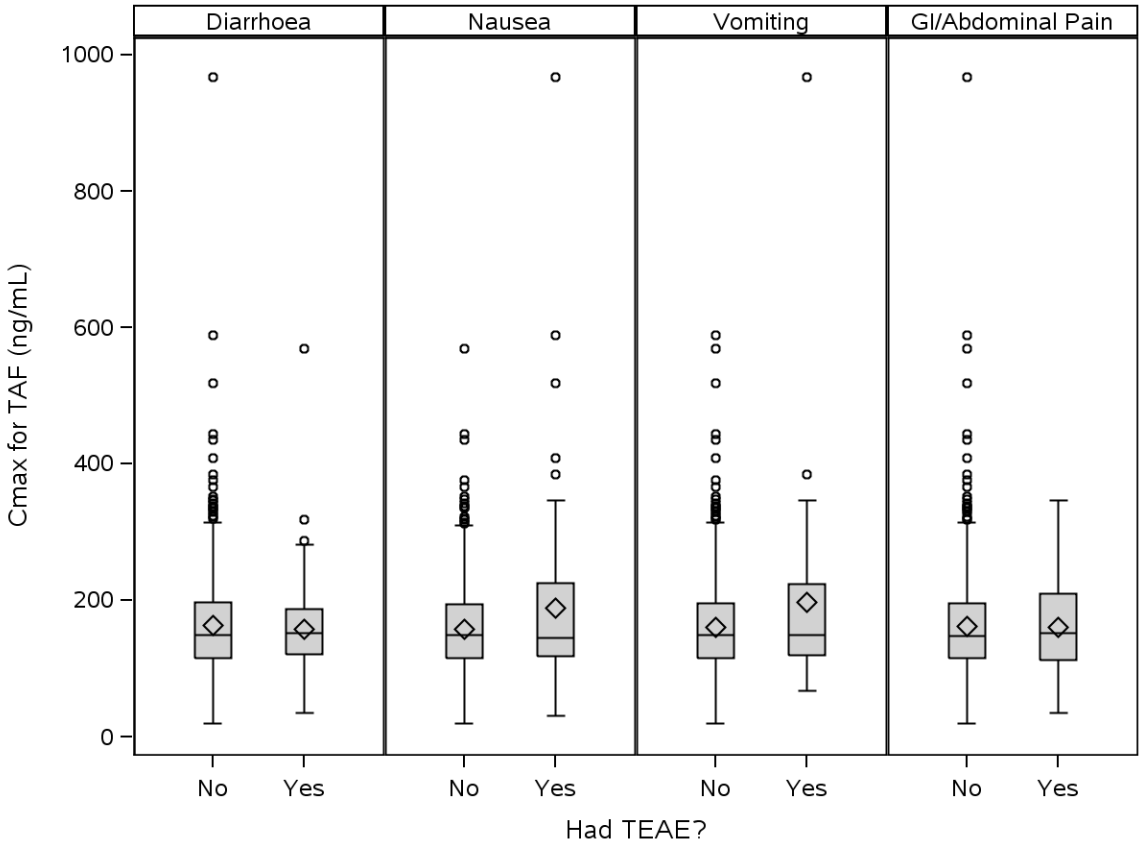
The PK-PD analyses of the TAF and TFV exposure-safety relationship were performed in ART-naive HIV-infected subjects in E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 using TAF and TFV exposures derived from population PK modeling versus safety parameters that included commonly observed AEs, namely diarrhea and nausea (very common ≥ 10%), and vomiting and GI/abdominal pain (common ≥ 1% and < 10%). The relationships between TAF and TFV exposure (AUC_{tau} or C_{max}) and incidence of AEs (present = yes; absent = no) are shown in Figure 21 and Figure 23, Figure 22 and Figure 24, respectively.

Figure 21. Box Plot of TAF AUC_{tau} (ng•hr/mL) by Selected Adverse Events (TAF PK/PD Analysis Set)



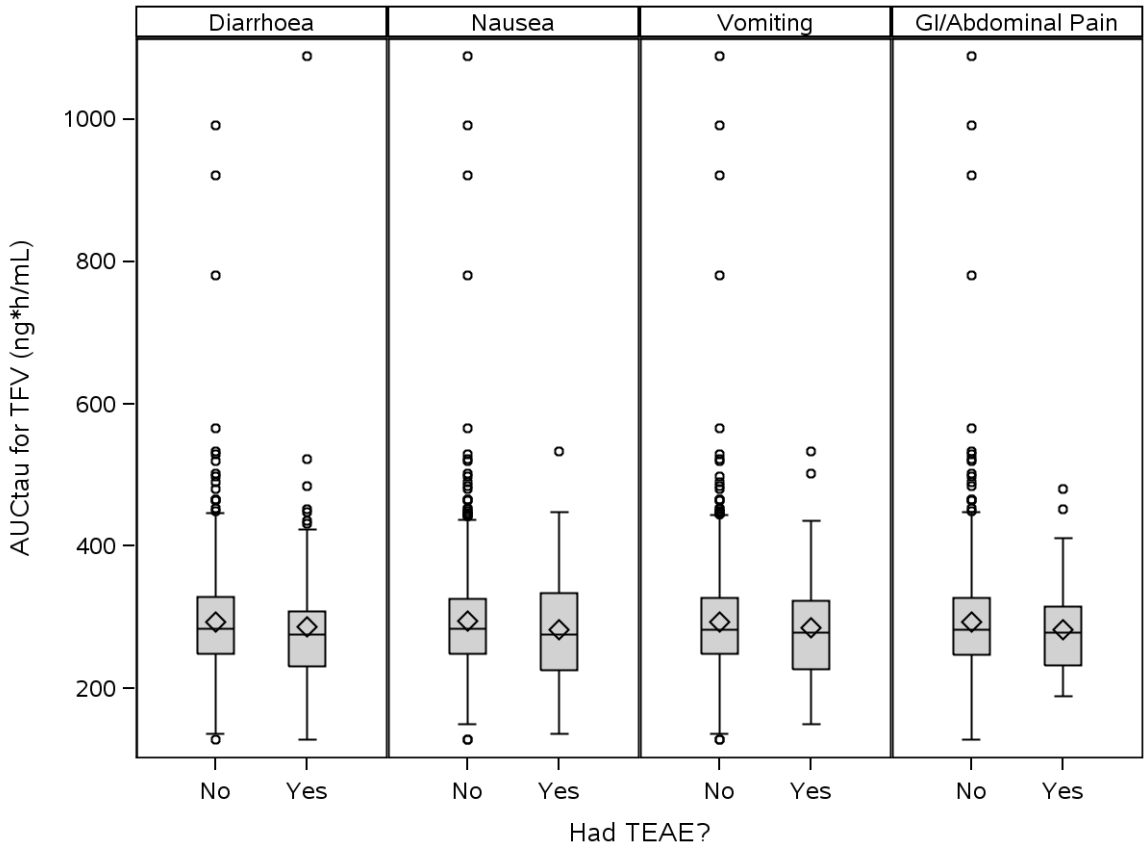
IQR = interquartile range; TEAE = treatment-emergent adverse event
Diarrhea: No (n = 454), Yes (n = 85); Nausea: No (n = 463), Yes (n = 76); Vomiting: No (n = 508), Yes (n = 31); GI/Abdominal Pains: No (n = 512), Yes (n = 27)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum 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: m5.3.4.2, E/C/F/TAF PK/PD, Table 4.1.1 and Figure 2.1.1

Figure 22. Box Plot of TAF C_{max} (ng/mL) by Selected Adverse Events Subgroup (TAF PK/PD Analysis Set)



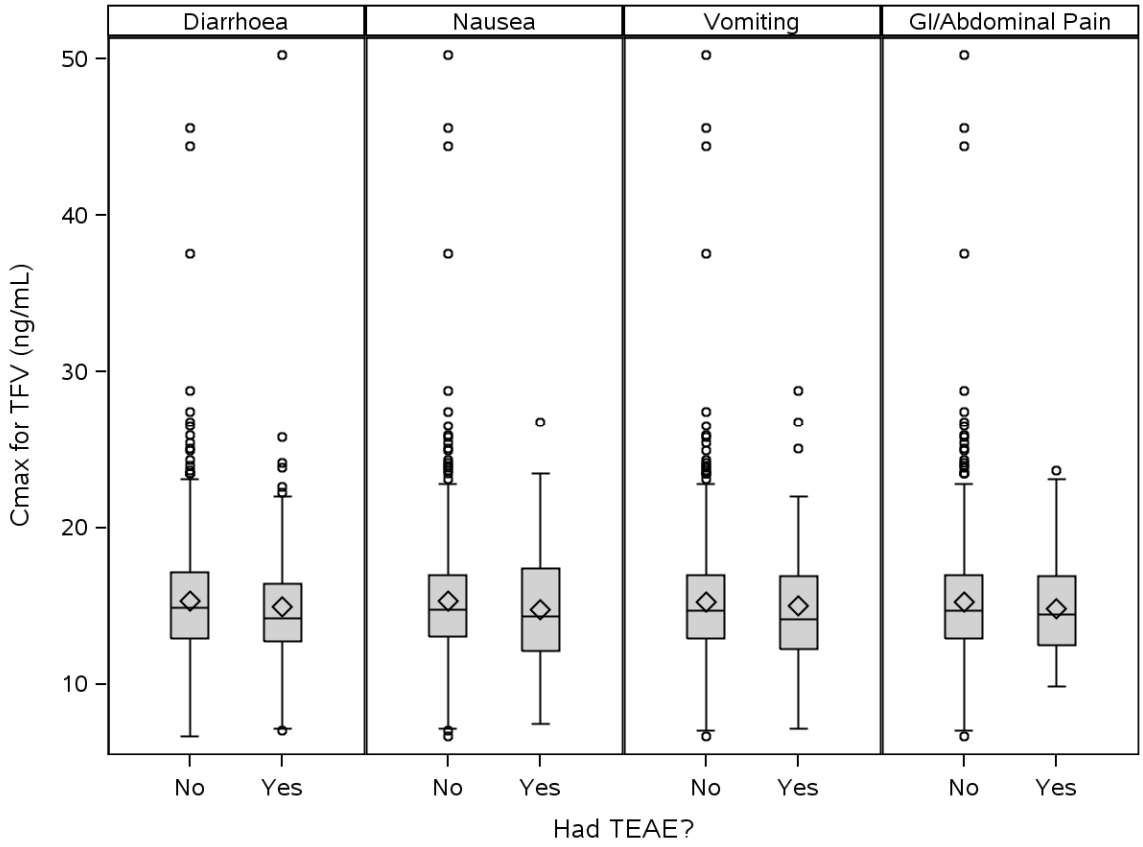
IQR = interquartile range; TEAE = treatment-emergent adverse event
Diarrhea: No (n = 454), Yes (n = 85); Nausea: No (n = 463), Yes (n = 76); Vomiting: No (n = 508), Yes (n = 31); GI/Abdominal Pains: No (n = 512), Yes (n = 27)
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum 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: m5.3.4.2, E/C/F/TAF PK/PD, Table 4.1.1 and Figure 2.1.2

Figure 23. Box Plot of TFV AUC_{tau} (ng•h/mL) by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set)



IQR = interquartile range; TEAE = treatment-emergent adverse event
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: m5.3.4.2, E/C/F/TAF PK/PD, Table 4.2.1 and Figure 2.2.1

Figure 24. Box Plot of TFV C_{max} (ng/mL) by Selected Adverse Events Subgroup (TFV PK/PD Analysis Set)



IQR = interquartile range; TEAE = treatment-emergent adverse event
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: m5.3.4.2, E/C/F/TAF PK/PD, Table 4.2.1 and Figure 2.2.2

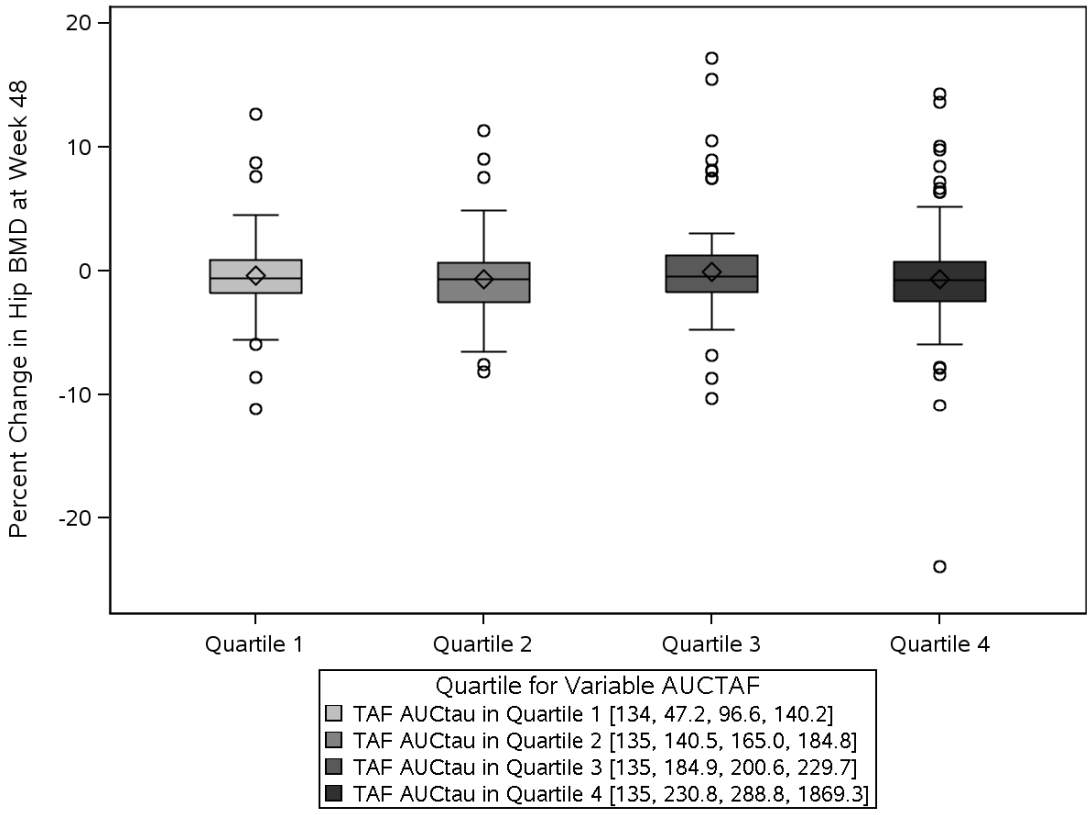
For diarrhea and GI/abdominal pain, both the TAF and TFV exposure was comparable regardless of the presence or absence of either of those symptoms and no exposure-AE trends were observed with these AEs.

For nausea and vomiting, the TFV exposure was comparable regardless of the presence or absence of either of those symptoms with no exposure-AE trends noted. 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) (m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Tables 6918.1.1.1-6918.1.2.2 and 6921.1). No trend was observed between exposure and severity (m5.3.4.2, E/C/F/TAF PK/PD, Ad Hoc Tables 6918.2.1.1-6918.2.2.2). The overall incidence of nausea and vomiting was similar between groups in Studies GS-US-292-0104 and GS-US-292-0111 (m5.3.5.3, E/C/F/TAF ISS, Table 7).

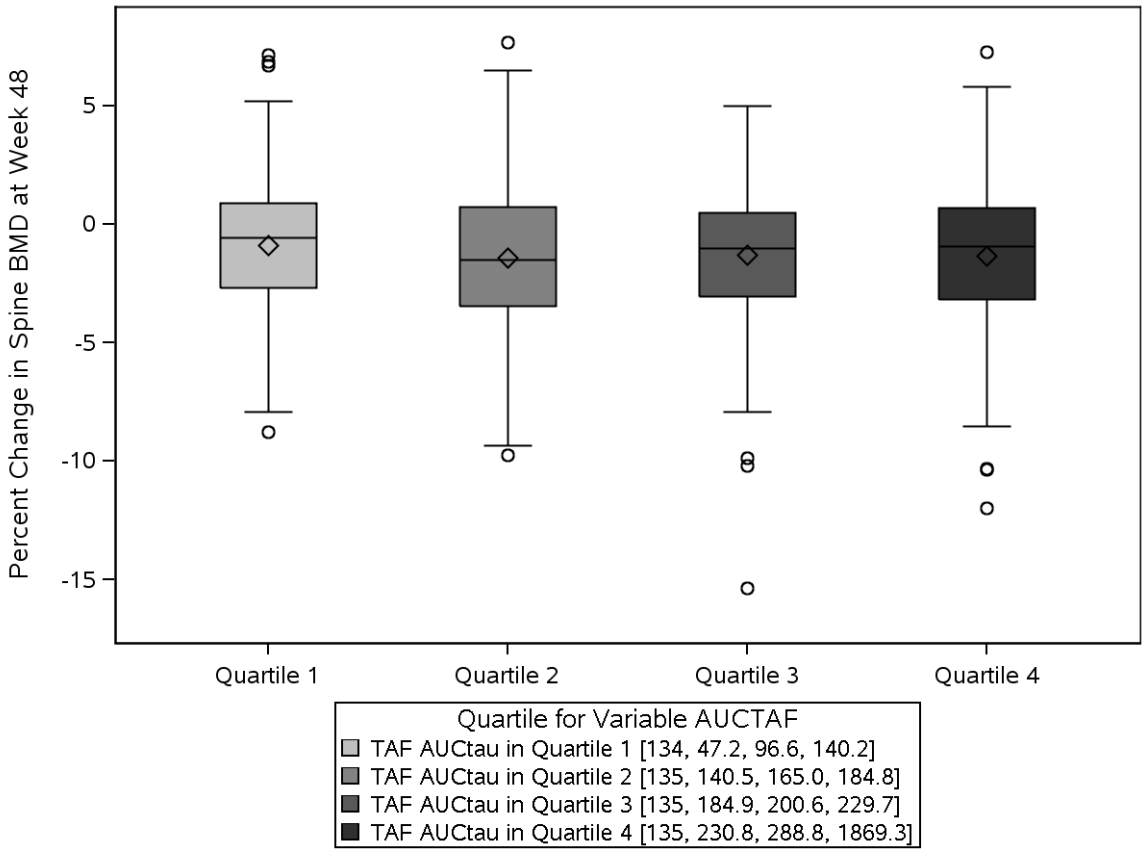
The percent change from baseline in BMD at the hip or at the spine at Week 48 was also a key safety endpoint Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationship between TAF and TFV exposure quartiles and changes in BMD at the hip and spine was evaluated and are shown in Figure 25, Figure 26, Figure 27, and Figure 28. Across all TAF and TFV AUC_{tau} quartiles, the percentage change from baseline at Week 48 in BMD was comparable; no trends in exposure-changes in BMD were noted.

Figure 25. Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)



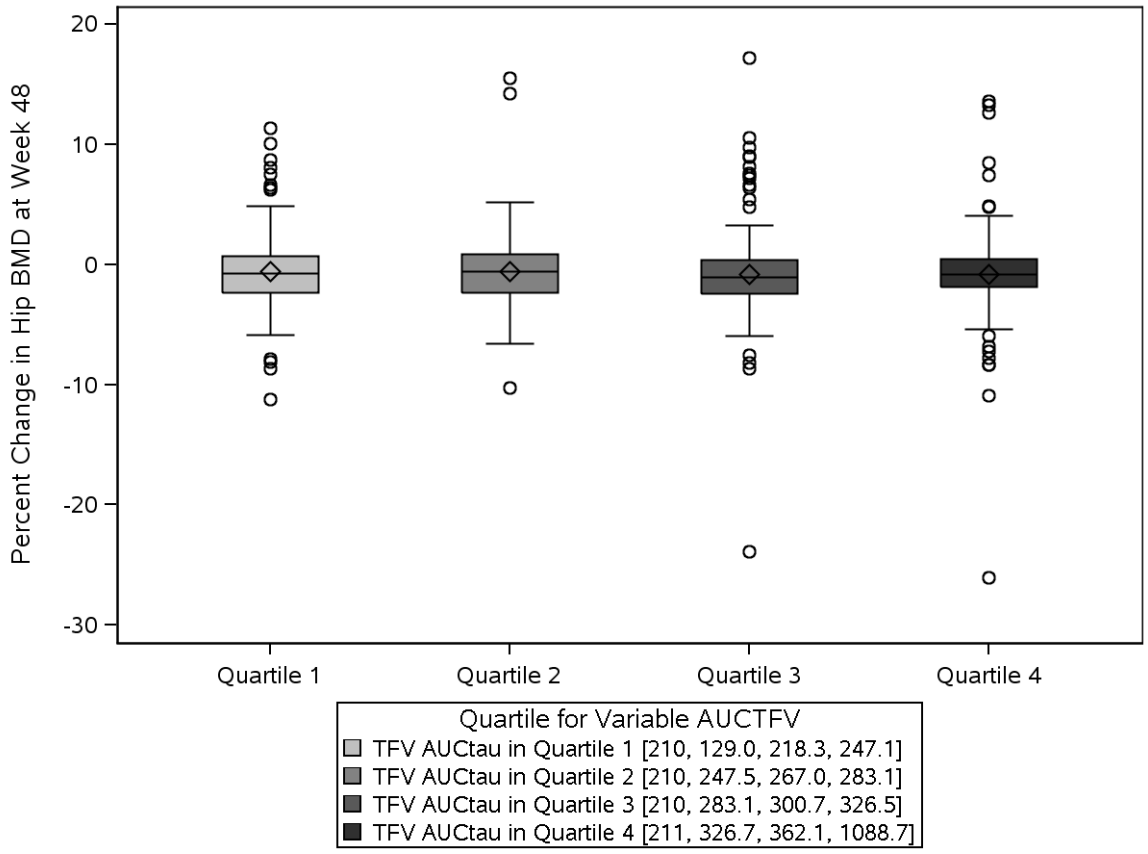
IQR = interquartile range
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TAF PK/PD analysis set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 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: m5.3.4.2, E/C/F/TAF PK/PD, Figure 6.1.1.1

Figure 26. Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)



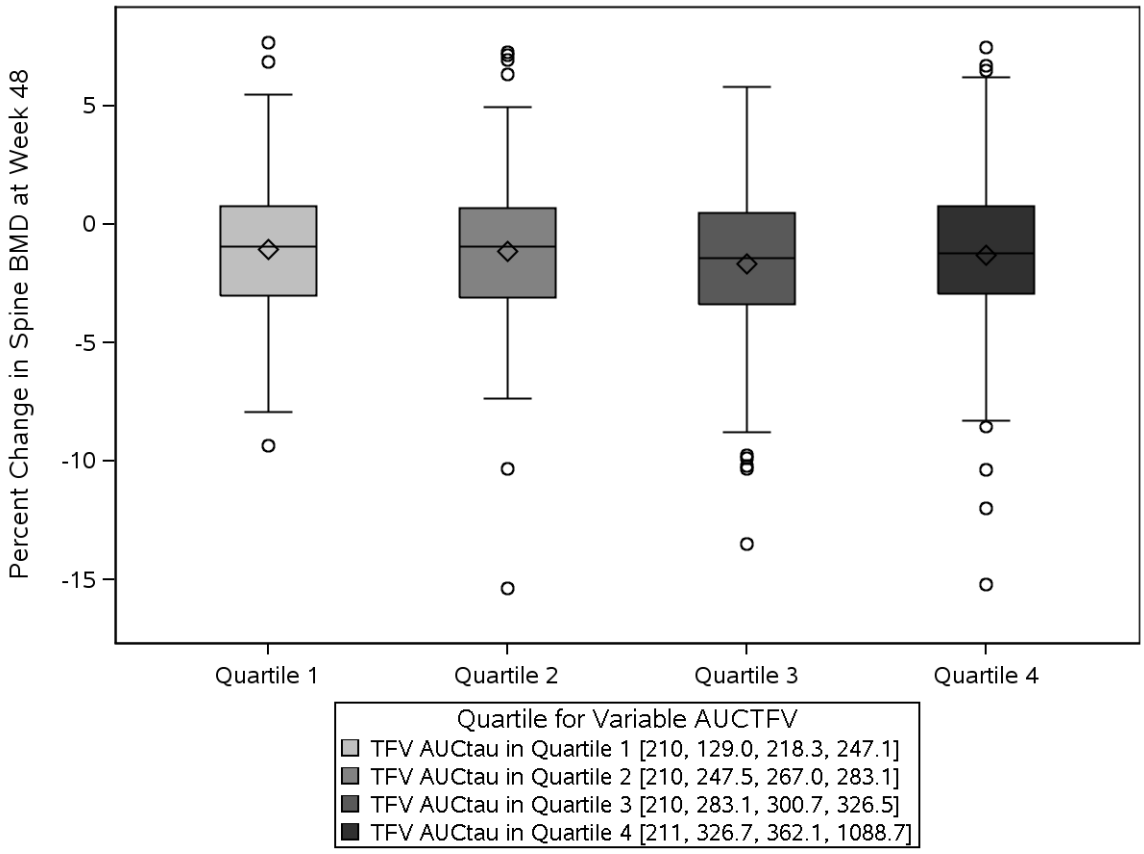
IQR = interquartile range
Box plots denote median and IQR, diamonds denote mean, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
The TAF PK/PD analysis set included all subjects who were randomized and had at least 1 dose of E/C/F/TAF in Study GS-US-292-0104 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: m5.3.4.2, E/C/F/TAF PK/PD, Figure 6.1.1.2

Figure 27. Box Plot of Percentage Change from Baseline at Week 48 in Hip BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)



IQR = interquartile range
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: m5.3.4.2, E/C/F/TAF PK/PD, Figure 6.2.1.1

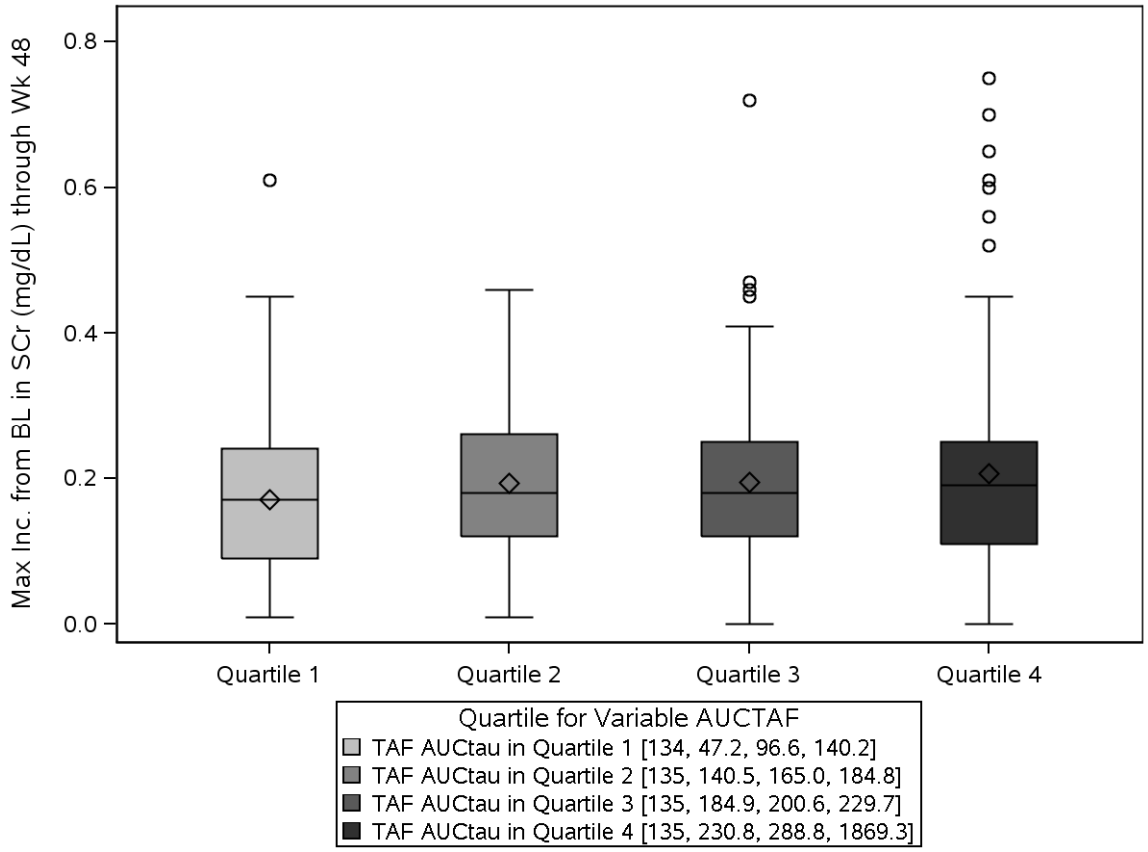
Figure 28. Box Plot of Percentage Change from Baseline at Week 48 in Spine BMD by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)



IQR = interquartile range
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: m5.3.4.2, E/C/F/TAF PK/PD, Figure 6.2.1.2

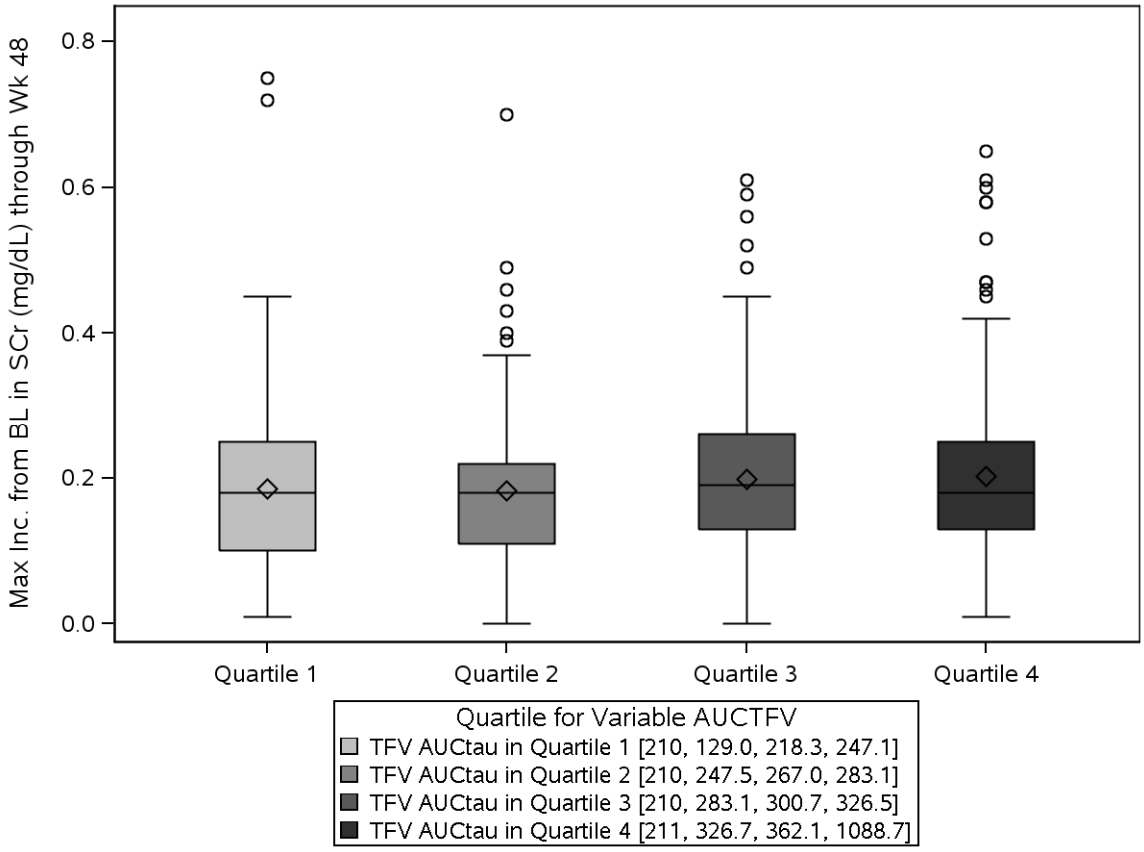
Additionally, the change from baseline in serum creatinine at Week 48 was a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. The relationship between TAF and TFV exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated and is shown in Figure 29 and Figure 30. Across all TAF and TFV AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable; no trends in exposure-changes in serum creatinine were noted.

Figure 29. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by TAF AUC_{tau} Quartile Subgroup (TAF PK/PD Analysis Set)



BL = baseline; IQR = interquartile range
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: m5.3.4.2, E/C/F/TAF PK/PD, Figure 4.1.1

Figure 30. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by TFV AUC_{tau} Quartile Subgroup (TFV PK/PD Analysis Set)



BL = baseline; IQR = interquartile range
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: m5.3.4.2, E/C/F/TAF PK/PD, Figure 4.2.1

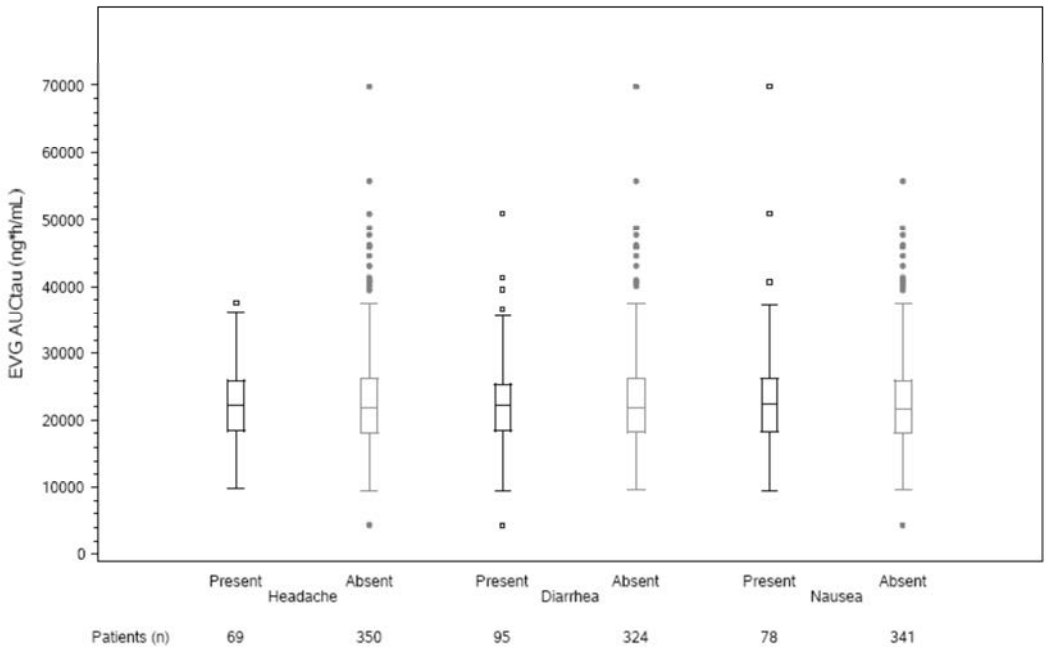
3.3.2.2. EVG

Pharmacokinetic-pharmacodynamic analyses of the EVG exposure-safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2 and Phase 3 studies using EVG exposures derived from EVG population PK modeling versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea.

The relationships between EVG exposure (AUC_{tau} or C_{max}) and incidence of AEs (present/absent) are shown in Figure 31 and Figure 32. EVG exposures were comparable

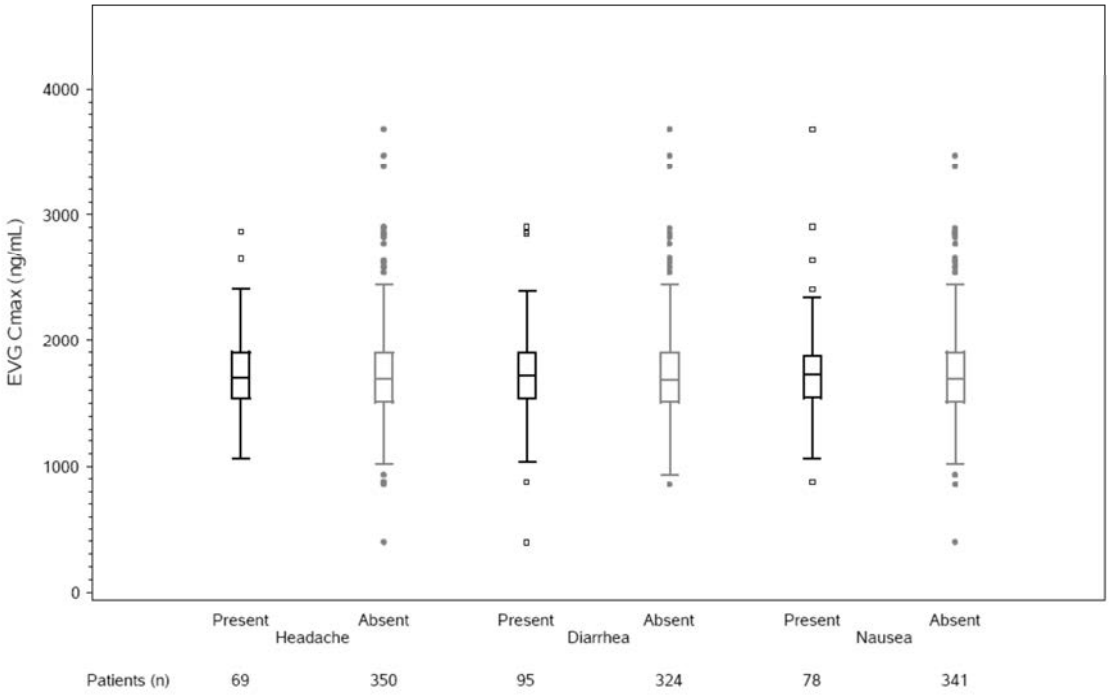
regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed.

Figure 31. Box Plot of EVG AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (EVG PK/PD Analysis Set)



IQR = interquartile range
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 2.1

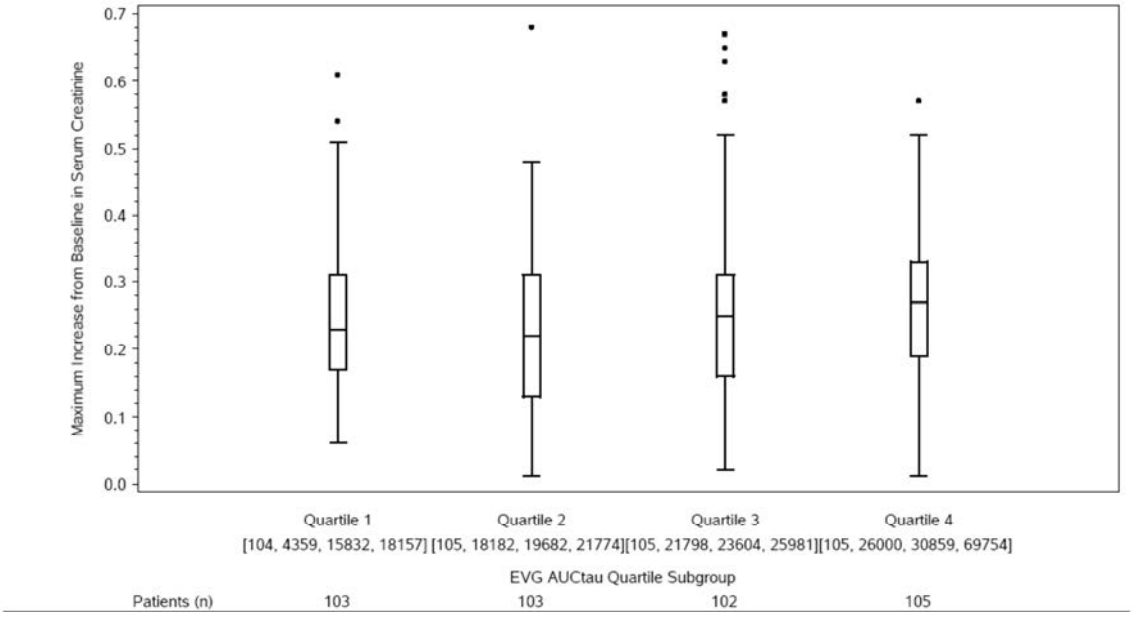
Figure 32. Box Plot of EVG C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (EVG PK/PD Analysis Set)



IQR = interquartile range
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 2.2

The relationship between EVG exposure quartiles and changes in renal laboratory parameters was also evaluated; exposure versus and serum creatinine change is shown in Figure 33. Across all EVG AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable; no trends in exposure-changes in laboratory parameters were noted.

Figure 33. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by EVG AUC_{tau} (ng•h/mL) Quartile Subgroup (EVG PK/PD Analysis Set)



IQR = interquartile range
Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Subject *AB with a maximum increase from baseline in serum creatinine of 2.95 mg/dL in the Quartile 1 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 EVG 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 6.1

3.3.2.3. COBI

The PK of COBI were evaluated in HIV-uninfected subjects with mild/moderate renal impairment (placebo-controlled study evaluating COBI only, $eGFR_{CG}$ 50-79 mL/min, with an additional cohort of subjects with normal renal function, $eGFR_{CG} \geq 80$ mL/min) in Study GS-US-216-0121.

COBI AUC_{tau}, C_{max}, and C_{tau} following once-daily administration for 7 days were 37%, 13%, and 176% higher, respectively, in subjects with mild/moderate renal impairment compared with those with normal renal function ($eGFR_{CG} \geq 80$ mL/min). The $T_{1/2}$ of COBI was significantly longer (7.8 vs 5.0 hours) in subjects with renal impairment compared with those with normal

renal function, suggesting that the observed exposure increases may be due to reductions in COBI clearance with or without a change in its bioavailability.

Following COBI dosing, mean (SD) $eGFR_{CG}$ values decreased 9.9 (13.14) mL/min and 11.9 (6.97) mL/min relative to baseline following 7 days of dosing in subjects with baseline $eGFR_{CG} \geq 80$ mL/min and 50 to 79 mL/min, respectively, but were reversible and returned to baseline values following a 7-day washout period. The time to onset, magnitude, and time to resolution of the observed changes in $eGFR_{CG}$ are consistent with the inhibition of tubular secretion of creatinine by COBI, with the relative contribution of secretion to total clearance increasing with a decline in renal function. In contrast, glomerular filtration probe agent iohexol-based GFR was unchanged on Days 7 and 14 relative to Day 0 following COBI dosing. Similar results were obtained using cystatin C-derived glomerular filtration rate (cysGFR) (an endogenous probe almost exclusively filtered with no secretion or reabsorption), confirming that COBI does not affect actual glomerular function.

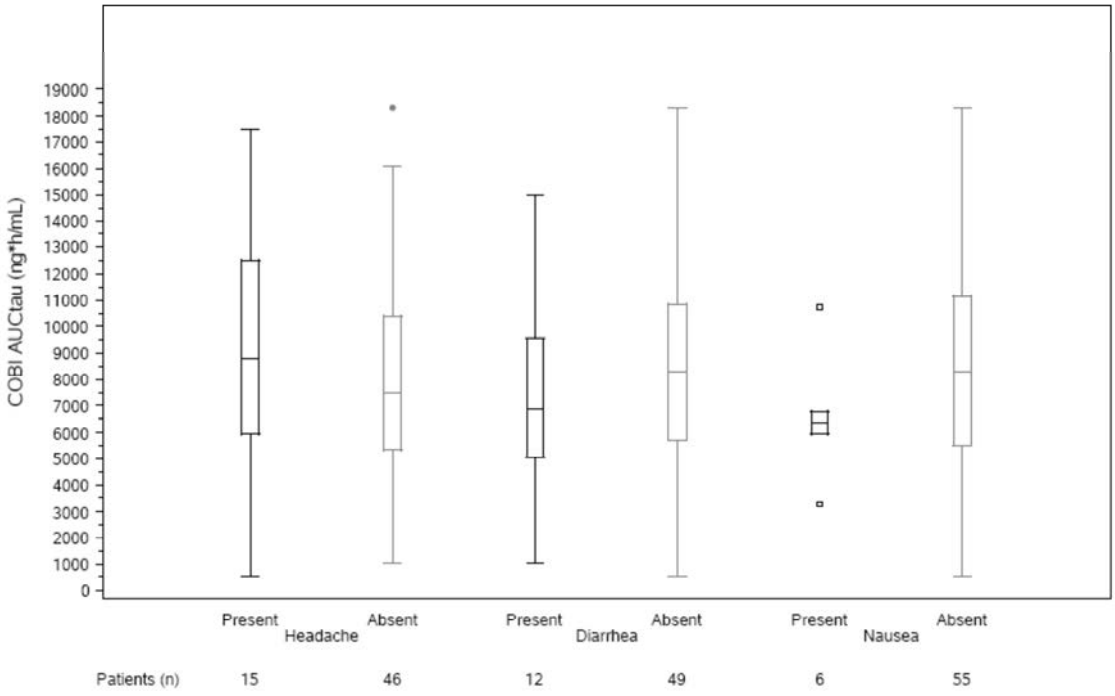
Study GS-US-216-0107, at COBI doses/exposures (AUC_{tau}) ~2- or 4-fold above therapeutic dose/exposures, demonstrated a lack of significant changes in ECG and met the ICH E14 definition of a negative "thorough QT/QTc study." A statistically significant, small, negative association between COBI plasma concentration and QTc interval was observed that is not considered to be clinically significant. An expected modest dosing-related increase in PR interval between 3 and 5 hours after dosing was observed and is not considered to be clinically significant. No clinically significant AEs, ECG abnormalities, or changes in physical exams or vital signs were observed.

Study GS-US-216-0116, at COBI 150-mg dose and corresponding exposures, demonstrated no clinically relevant changes in the left ventricular function, with all 3 measures (end-systolic volume, end-diastolic volume, and ejection fraction) in the normal range based on time-matched echocardiogram (ECHO) assessments.

Pharmacokinetic-pharmacodynamic analyses of the COBI exposure-safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2 and Phase 3 studies using COBI exposures derived from intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea.

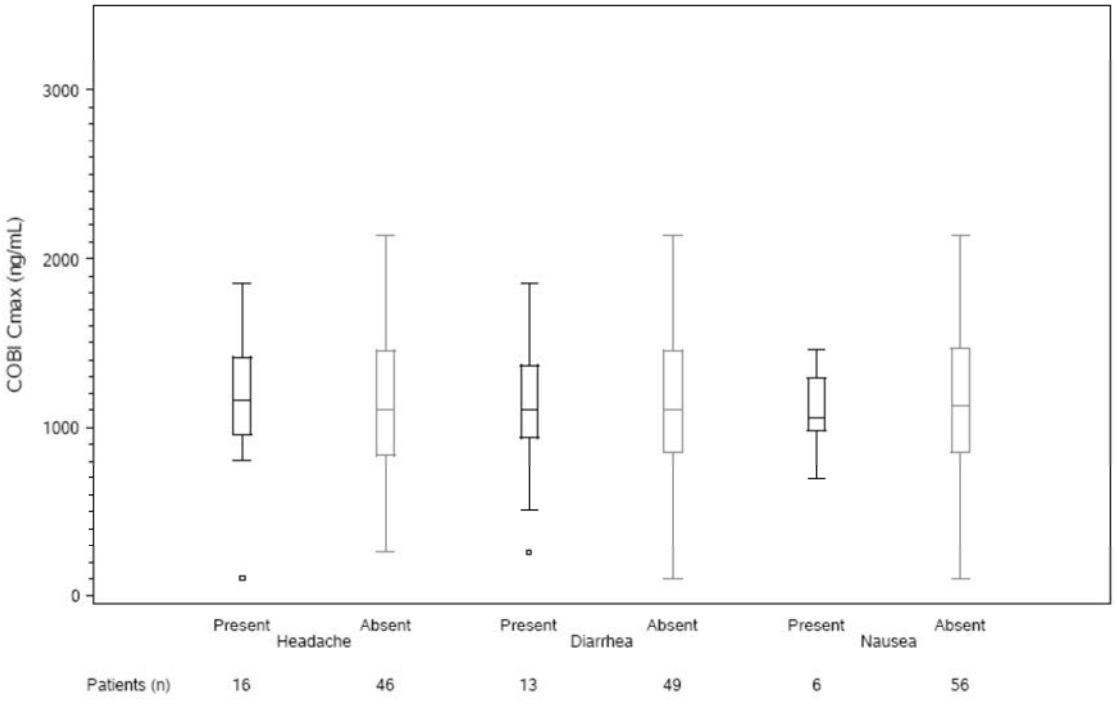
The relationships between COBI exposure (AUC_{tau} or C_{max}) and incidence of AEs (present/absent) are shown in Figure 34 and Figure 35. COBI exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed.

Figure 34. Box Plot of COBI AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (COBI PK/PD Analysis Set)



IQR = interquartile range
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 3.1

Figure 35. Box Plot of COBI C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (COBI PK/PD Analysis Set)

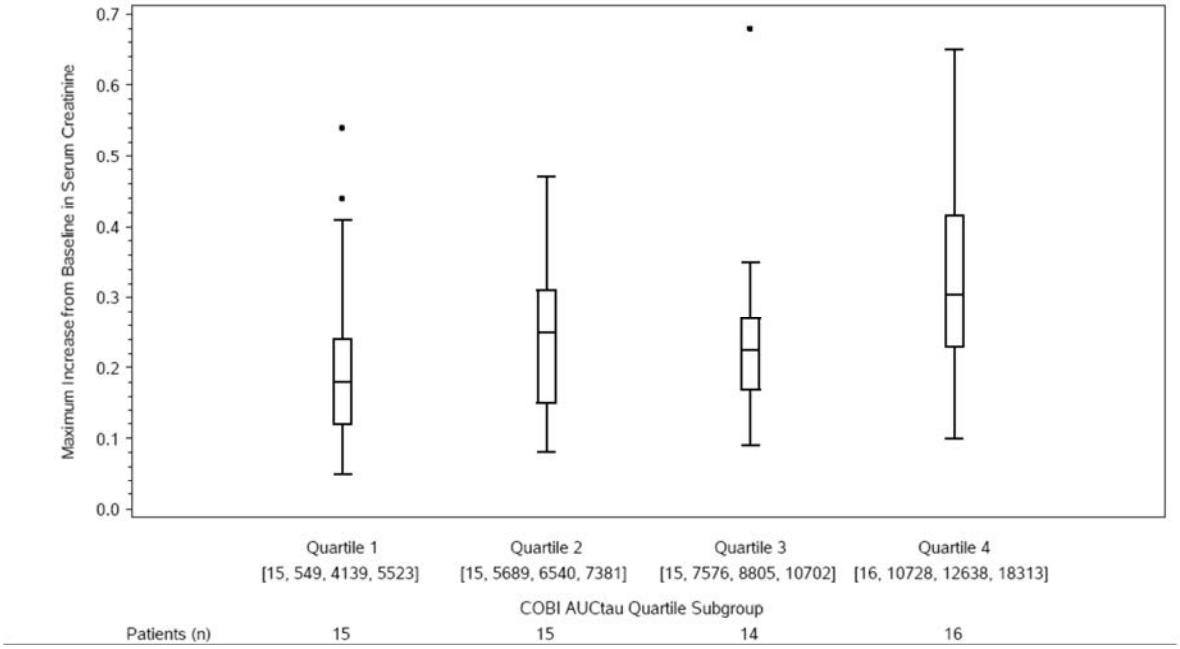


IQR = interquartile range
Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Source: STB PK/PD Figure 3.2

As performed with EVG, the relationship between COBI exposure quartiles and changes in renal laboratory parameters was also evaluated; exposure versus and serum creatinine change is shown in Figure 36.

Across all COBI AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable with overlapping values and greater variability in the fourth quartile (for serum creatinine changes), and no trends in exposure-changes in laboratory parameters were noted.

Figure 36. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by COBI AUC_{tau} (ng•h/mL) Quartile Subgroup (COBI PK/PD Analysis Set)

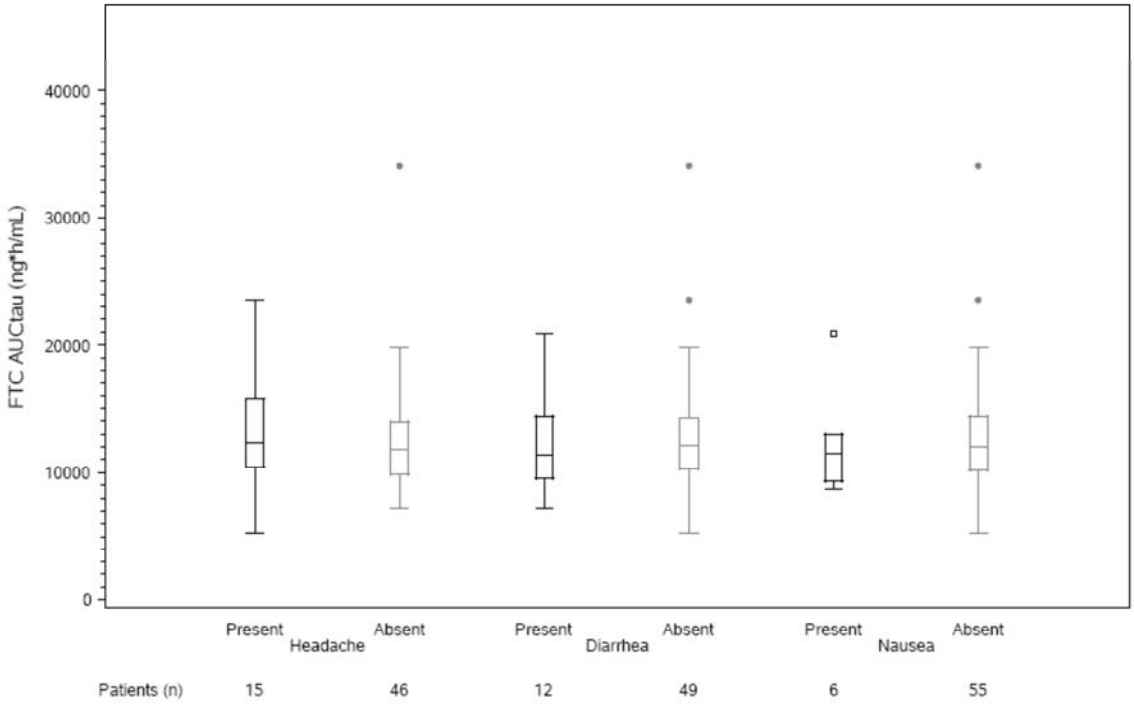


IQR = interquartile range
Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Subject *AB with a maximum increase from baseline in serum creatinine of 2.95 mg/dL in the Quartile 4 subgroup was excluded from the figure for better visualization purposes.
Numbers presented in the square brackets were the sample size, minimum, median, and maximum of COBI 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 7.1

3.3.2.4. FTC

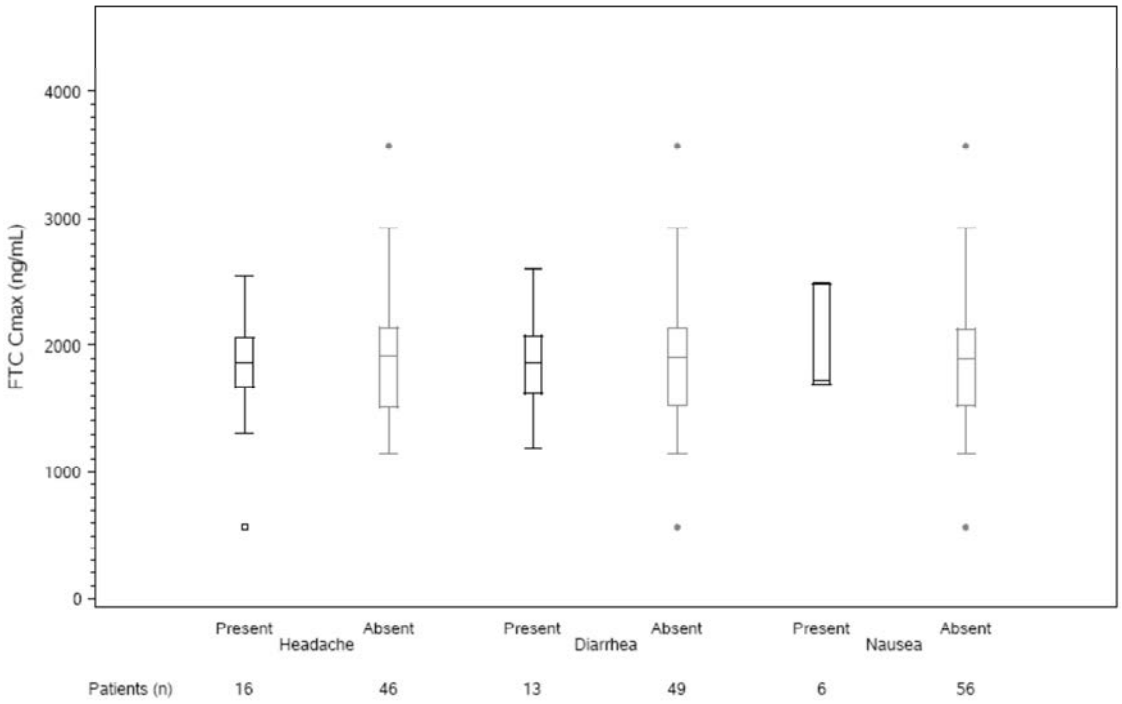
Pharmacokinetic-pharmacodynamic analyses of the FTC exposure-safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2/3 studies using FTC exposures derived from intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea. The relationships between FTC exposure (AUC_{tau} or C_{max}) and incidence of AEs (present/absent) are shown in Figure 37 and Figure 38. The relationship between FTC exposure quartiles and changes in renal laboratory parameters was also evaluated; exposure versus serum creatinine change is shown in Figure 39.

Figure 37. Box Plot of FTC AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set)



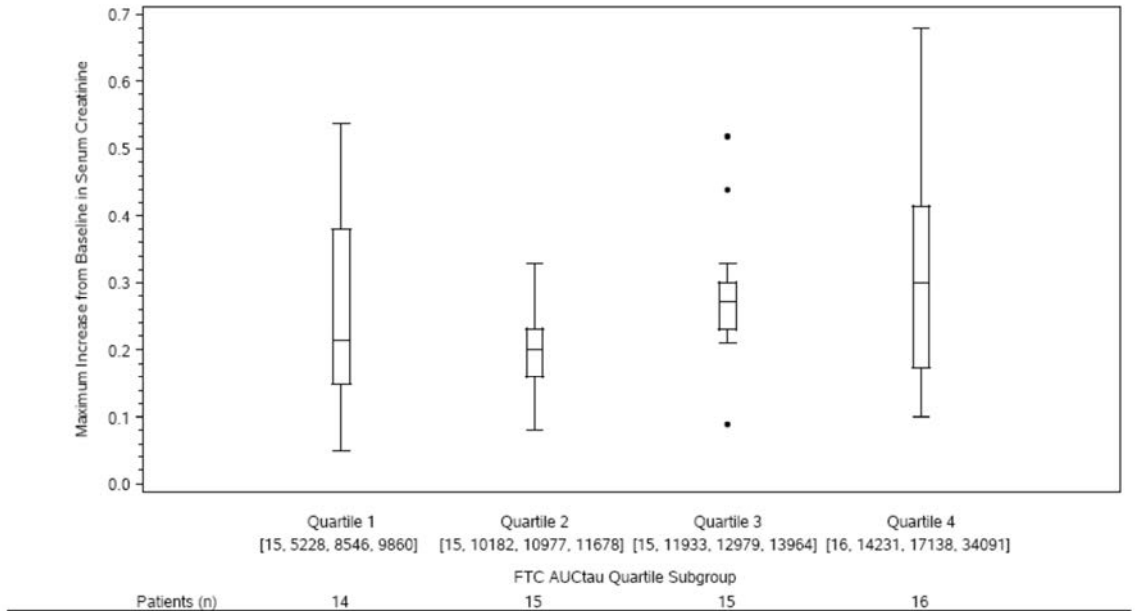
IQR = interquartile range
Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Source: STB PK/PD Figure 4.1

Figure 38. Box Plot of FTC C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set)



IQR = interquartile range
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

Figure 39. 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)



IQR = interquartile range
Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Subject *AB 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

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 two groups.

4. VIROLOGY SUMMARY

Nonclinical and clinical studies are discussed in the following sections.

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 RT

4.1.1.1.1.1. Intracellular Metabolism

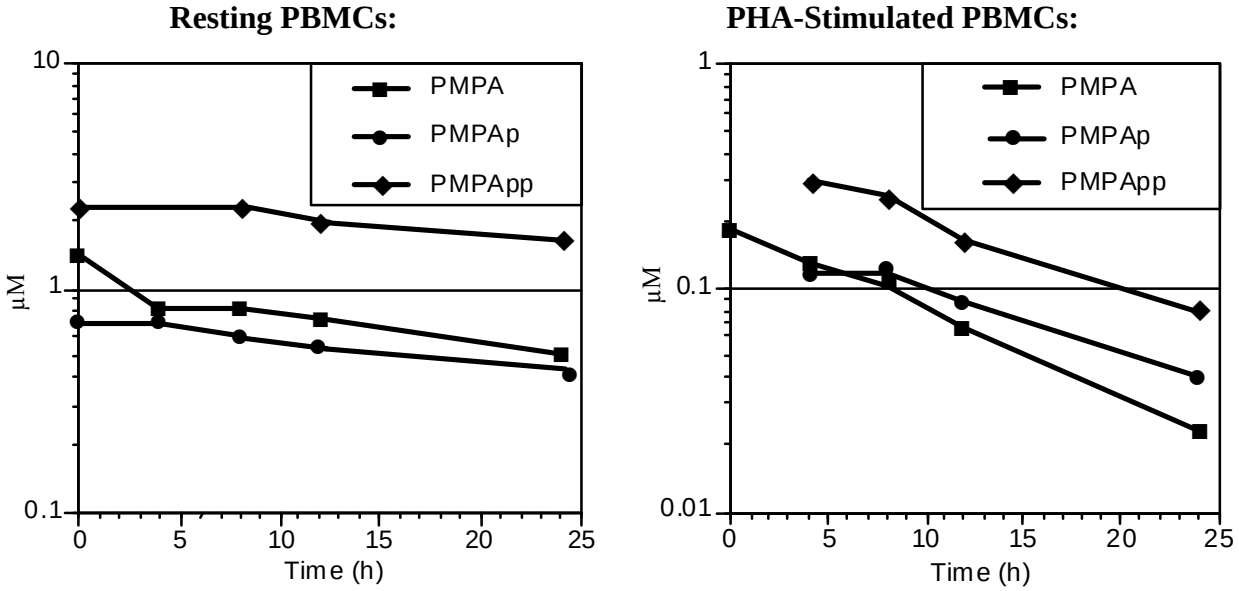
In Vitro

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 isozymes, 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 40. 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 71 and Table 72). 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 40. TFV Intracellular Metabolism in Human PBMCs



PBMC = peripheral blood mononuclear cell; PHA = phytohemagglutinin; TFV or PMPA = tenofovir; PMPAp = tenofovir monophosphate; PMPApp = tenofovir diphosphate
Source: {1574}

Table 71. Metabolism of 10 μM TFV Either Alone or in Combination with 10 μM ABC

Time	TFV Alone (pmol/million cells)[a]			TFV With 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

ABC = abacavir; TFV-DP = tenofovir diphophosphate; TFV-MP = tenofovir monophophosphate
a Values determined by liquid chromatography/tandem mass spectrometry.
Source: PC-104-2008

Table 72. Metabolism of 10 μM ABC Either Alone or in Combination with 10 μM TFV

Time	ABC Alone (pmol/million cells)[a]	ABC With TFV (pmol/million cells)[a]
(h)	CBV-TP[b]	CBV-TP
2	0.03 ± 0.01	0.05 ± 0.02
24	0.17 ± 0.01	0.24 ± 0.03

ABC = abacavir; CBV-TP = carbovir triphosphate
a Values determined by liquid chromatography/tandem mass spectrometry.
b Carbovir triphosphate is the active anabolite of ABC.
Source: PC-104-2008

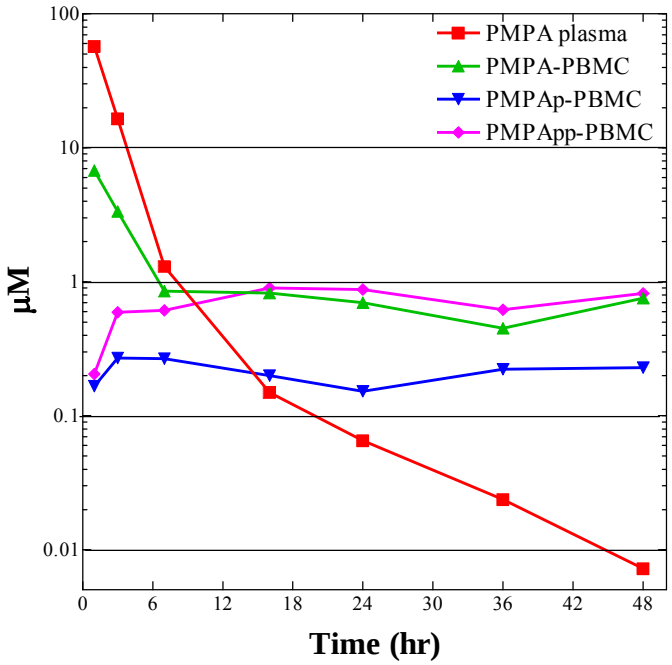
Coadministration of TDF and didanosine (ddI) has been clinically associated with increased plasma concentrations of ddI. In vitro studies showed that TFV-MP and TFV-DP can inhibit purine nucleoside phosphorylase (PNP), which is involved in the metabolic degradation of ddI {6054}. Thus, the clinical observation 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 intraceullar dNTP or rNTP pool concentrations. Zidovudine was the only tested NRTI that significantly altered dNTP pools. Incubation of 10 μM zidovudine (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 41).

Figure 41. **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**



PBMC = peripheral blood mononuclear cell; TFV or PMPA = tenofovir; TFV-MP or PMPAp = tenofovir monophosphate; TFV-DP or PMPApp = tenofovir diphosphate
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 73).

Table 73. **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

TFV-DP = tenofovir diphophosphate; TFV-MP = tenofovir monophophosphate
ND = not determined
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 74). 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 74. 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

dATP = deoxyadenosine triphosphate; K_i = kinetic inhibition constant; K_m = Michaelis-Menten constant
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 (m5.3.5.4, 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 75). TAF concentrations that inhibited virus replication by 50% (EC_{50}) 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 75. 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

EC_{50} = concentration inhibiting viral replication by 50%; NA = not applicable; ZDV = zidovudine
Source: m5.3.5.4, 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 2.4.2.1] and GS-US-120-0114 [Section 2.4.2.2]). The protein binding of TFV was studied in the presence or absence of human plasma and human serum (HS) (P0504-00039.1). The percentages of TFV that remained unbound in human plasma and HS 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 stavudine (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 (m5.3.5.4, 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 76). 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 76. Characteristics and Drug Susceptibilities of Selected Viruses

Selected Viruses				EC_{50} FC From WT Control (HIV-1_{IIIB})[a]				
Drug	Concentration (FC over EC_{50})	Time Point	Genotype	TAF	TFV	FTC	EFV	EVG
TAF	224 nM (16X)	Day 148	K65R	6.5*	5.5*	8.5*	1.4	1.7
TFV	56 µM (16X)	Day 154	K65R S68S/N/R/K	6.5*	5.1*	6.7*	1.5	1.4

EFV = efavirenz; FC = fold change; WT = wild-type

a EC_{50} values against HIV-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.

* Student t-test p-value < 0.05 as compared with wild-type control.

Source: m5.3.5.4, 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 mutations [TAMs], 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 (m5.3.5.4, PC-120-2012). Lymphoid (MT-2) cells infected with wild-type (HIV-1_{LAI}) and TFV-resistant (HIV-$1_{LAI\ -K65R}$, HIV-$1_{LAI\text{-}3TAM}$, and HIV-$1_{LAI\text{-}Q151M}$) 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 77). 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 77. Initial Drug Concentrations Used in Selection Experiments

Viral Isolate	Starting Concentration ($2 \times EC_{50}$)		
	TAF (nM)	TFV (µM)	RAL (nM)
HIV-1_{LAI}	30	7	20
HIV-$1_{LAI-K65R}$	90	21	20
HIV-$1_{LAI-3TAM}$	90	21	20
HIV-$1_{LAI-Q151M}$	390	91	20

Source: m5.3.5.4, 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 78). 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 78. 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 (8X)	RT: **K65R**	3.5*	3.7*	1.0	0.7	0.6
WT-F3	TFV	28 μM (8X)	RT: **K65R, S68N**	5.2*	5.4*	1.6	1.2	0.6
WT-R6	RAL	640 nM (64X)	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 (12X)	RT: K65R, **S68N**	5.9*	6.3*	1.9	2.8*	1.3
K65R-A2.5	TAF	270 nM (18X)	RT: K65R, **S68N**	6.8*	6.3*	1.5	2.3*	1.0
K65R-F2	TFV	42 μM (12X)	RT: K65R, **S68N**	6.1*	5.9*	1.2	2.2	1.4
K65R-R6	RAL	640 nM (64X)	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 (12X)	RT: "3TAM" + **L429I**	8.5*	6.1*	2.2*	> 90*	> 54*
3TAM-A2.5	TAF	270 nM (18X)	RT: "3TAM" + **L429I**	8.6*	6.1*	1.9	> 90*	> 54*
3TAM-F2	TFV	42 μM (12X)	RT: "3TAM" + **L429I**	9*	6.1*	1.7	> 90*	> 54*
3TAM-F2.5	TFV	63 μM (18X)	RT: "3TAM" + **L429I**	ND	ND	ND	ND	ND
3TAM-R6	RAL	640 nM (64X)	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 (39X)	RT: "Q151M" + **T69I**	26.1*	22.1*	1.5	> 90*	3.4*
Q151M-F1.5	TFV	137 µM (39X)	RT: "Q151M" + **T69I**	32.5*	34.5*	2.2*	> 90*	2.7*
Q151M-R6	RAL	640 nM (64X)	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*

3TAM = 3 thymidine analog mutations; EFV = efavirenz; FC = fold change; IN = integrase; NA = not applicable; ND = not determined; RAL = raltegravir; RT = reverse transcriptase; WT = wild-type; ZDV = zidovudine

a Concentrations based on previously defined EC_{50}s 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}s 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}s with wild-type EC_{50}s)

Source: m5.3.5.4, 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 79 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 79. 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 80, 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 80. 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

3TC = lamivudine; ABC = abacavir; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; ND = not determined; RT = reverse transcriptase; ZDV = zidovudine
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 (m5.3.5.4, 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 81). 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 $R^2 = 0.97$ as shown in Figure 42, indicating that TAF and TFV show the same resistance profile against NRTI-resistant HIV-1 mutants in this assay.

Table 81. 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*
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*

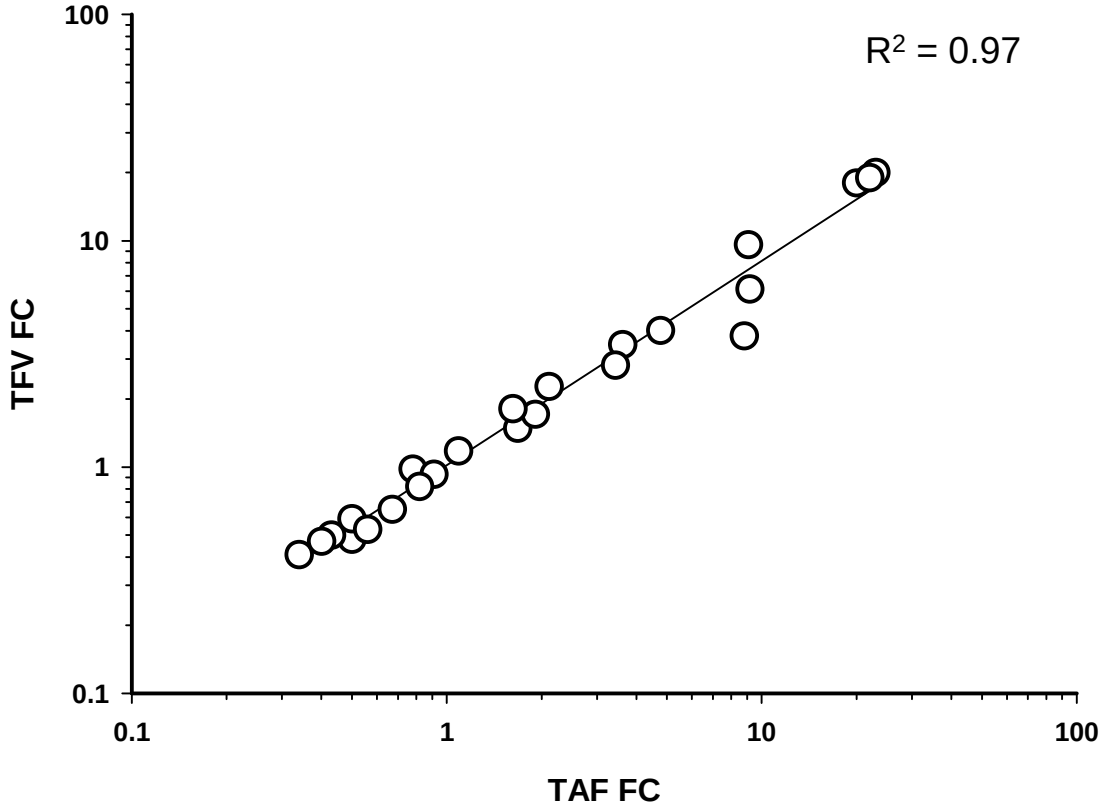
ID = identification; FC = fold change; TAM = thymidine analog mutation

a Susceptibilities are expressed as fold changes (FC) 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 resistance mutations (not shown).

Source: m5.3.5.4, PC-120-2014

Figure 42. Resistance Profile Comparison Between TAF and TFV in the Monogram PhenoSense Assay



Fold changes (FC) for the panel of 24 recombinant HIV-1 isolates (Table 81) for TAF and TFV were plotted. Linear regression was calculated using SigmaPlot.
Source: m5.3.5.4, 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 81). 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 82 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 82. 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

3TC = lamivudine; ABC = abacavir; ID = identification; RT = reverse transcriptase; ZDV = zidovudine

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 Nucleoside-associated RT mutations 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 [redacted] 19[redacted] and [redacted] 20[redacted] 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 (m5.3.5.4, 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 83). 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 83. 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

EC_{50} = concentration inhibiting viral replication by 50%; NA = not applicable; ZDV = zidovudine
Source: m5.3.5.4, 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 2.3.1.1]). Therefore, viral breakthrough experiments were conducted using previously defined TDF-resistant HIV-1 isolates (Table 84) 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 (m5.3.5.4, 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 $10 \times EC_{50}$) 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 84. 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

FC = fold change; ID = identification; ins = insertion; NA = not available; PD = patient-derived; RT = reverse transcriptase; TAM = thymidine analog-associated mutations; WT = wild-type
a Thymidine analog-associated mutations (TAMs): M41L, D67N, K70R, L210W, T215Y/F, K219E/N/Q/R.
b Nucleoside analog mutation (NAM) 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: m5.3.5.4, PC-120-2013 and PC-120-2015

The results of this experiment (Table 85) 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 85. 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

ID = identification; PD = patient-derived; TAM = thymidine analog-associated mutations; WT = wild type
a TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/N/Q/R
b Drug concentrations were 1X the EC_{95}.
Source: m5.3.5.4, 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 (m5.3.5.4, 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 86).

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, nevirapine (NVP) and enfuvirtide (T-20) for NRTI-R and NNRTI-R isolates, indinavir (IDV) 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 86). 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 86. 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, NNRT-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; ID = identification; IDV = indinavir; IN = integrase; NVP = nevirapine; -R = resistant; RAL = raltegravir; RT = reverse transcriptase; PR = protease; T-20 = enfuvirtide; ZDV = zidovudine

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: m5.3.5.4, 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 (m5.3.5.4, 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 (m5.3.5.4, 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 (m5.3.5.4, 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) (m5.3.5.4, 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 87). 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 87; m5.3.5.4, PC-120-2007). The SIs for TAF were also higher compared with TFV and TDF in all cell types tested (Table 87; m5.3.5.4, 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 (m5.3.5.4, 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 (m5.3.5.4, 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 87; m5.3.5.4, PC-120-2017).

Table 87. 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	—

— = not determined; PBMC = peripheral blood mononuclear cell; SI = selectivity index
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: m5.3.5.4, 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}.

4.1.1.2. TAF: In Vivo Pharmacodynamics

No primary PD studies in animals were conducted.

4.1.1.3. EVG: In Vitro Pharmacodynamics

EVG is a low molecular weight, HIV-1 INSTI that prevents integration of the HIV-1 genetic material into the host-cell genome. The primary PD of EVG are described in detail in the following sections.

In this application, the comparator INSTIs used were L-870,810, a Merck investigational INSTI, and the approved INSTI, RAL. At the time of many of these studies, the structure of RAL was not published and RAL was not available for use by Gilead and, therefore, was not consistently used as a comparator in the PD studies.

4.1.1.3.1. Mechanism of Action and Inhibition of HIV-1 Viral Integrase

Activity Against HIV-1 Integrase In Vitro

The inhibitory effect of EVG on the HIV-1 IN was determined by an enzymatic assay using HIV-1 recombinant IN produced in *Escherichia coli* and purified by column chromatography (JTK303-PH-001).

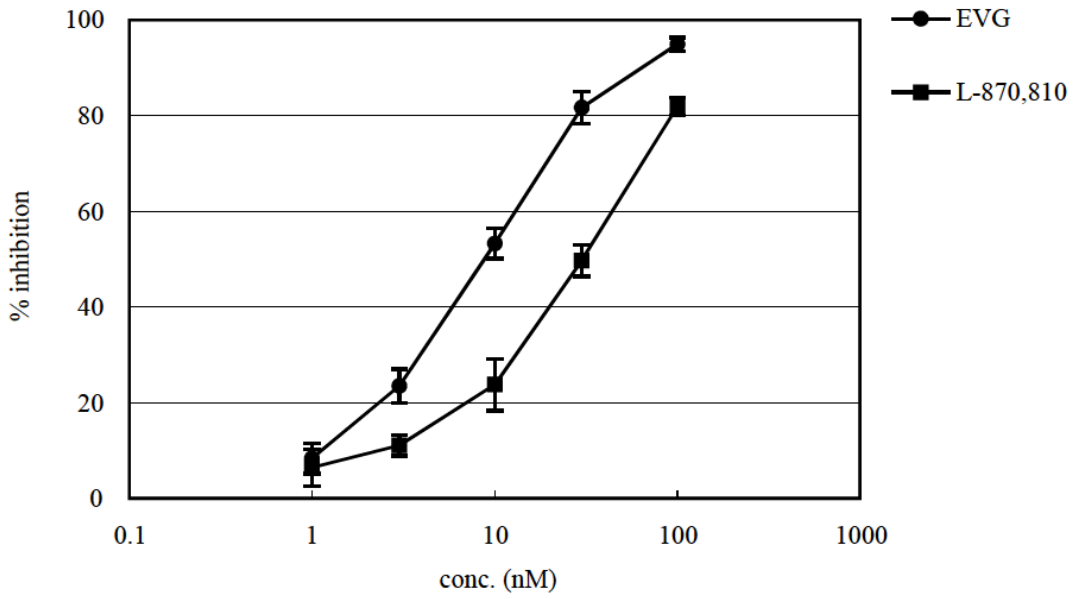
During HIV-1 infection, IN catalyzes the following 2 activities: (1) removal of the 2 terminal nucleotides from the 3'-ends of the viral DNA (3'-processing) and (2) insertion of the processed viral DNA ends into the host cell DNA (strand-transfer reaction). The biochemical mechanism of action of EVG against IN was assessed both on the overall integration reaction (assembly, 3'-processing, and strand transfer) and a specific strand-transfer reaction (JTK303-PH-002). In the overall integration assay, HIV-1 IN and EVG were incubated with unprocessed donor DNA, representing the HIV-1 U5 long terminal repeat (LTR), and the assembly and 3'-end processing reactions were performed. Subsequently, the DNA strand-transfer reaction was initiated by the addition of target DNA. In the strand-transfer specific assay, HIV-1 IN was incubated with the 3'-end processed donor DNA, and the DNA strand-transfer reaction was initiated by the addition of target DNA and EVG. EVG showed potent inhibitory activity against the DNA strand-transfer reaction with an IC_{50} value of 8.8 nM (Table 88 and Figure 43). This IC_{50} value was similar to that for the overall integration reaction (5.3 nM), and therefore EVG is a specific strand-transfer inhibitor. The control IN inhibitor used in many of these studies was the Merck investigational INSTI, L-870,810, which exhibited approximately 3-fold less inhibitory activity on IN in both test systems as compared with EVG.

Table 88. Inhibitory Activity of EVG Against Recombinant HIV-1 Integrase

	IC_{50} (nM)[a]	
Compound	**Overall Integration[b]**	**Strand Transfer**
EVG	5.3 ± 0.2	8.8 ± 0.9
L-870,810	15.9 ± 1.4	30.2 ± 4.0

L-870,810 = Merck investigational INSTI control
a Mean ± SD from 3 separate experiments
b Assembly, 3'-end processing, and strand-transfer reactions
Source: JTK303-PH-002

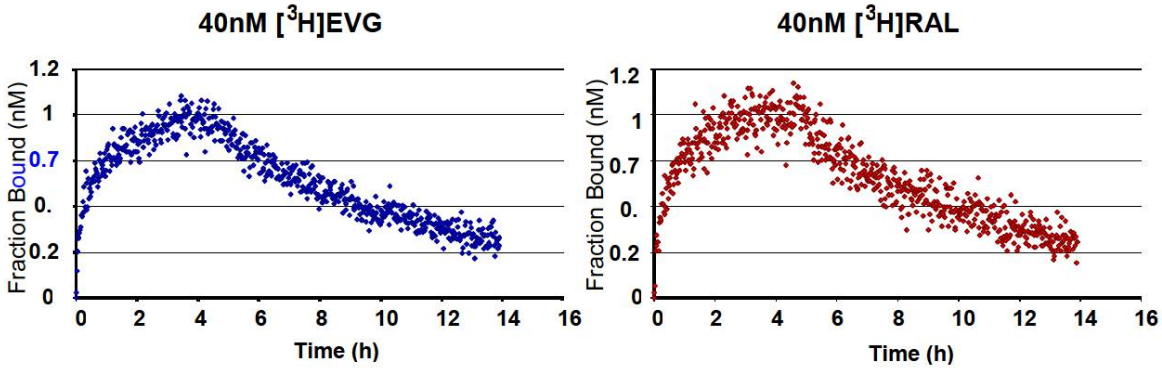
Figure 43. Inhibition of the Strand-Transfer Reaction by EVG



EVG = elvitegravir; L-870,810 = Merck investigational INSTI control
Error bars indicate SDs of mean values of 3 separate experiments. Concentrations of the compounds are expressed on a logarithmic scale.
Source: JTK303-PH-002

The binding and dissociation kinetics of EVG and RAL were determined using purified HIV-1 IN and a scintillation proximity assay (PC-183-2027). The binding of [^{3}H]EVG or [^{3}H]RAL to IN was measured over time, and the overall binding and dissociation profiles were similar (Figure 44). The kinetic constants were similar for both INSTIs, including notable slow dissociation rates (K_{off}) from the IN-DNA complexes (Table 89). The $t_{1/2}$ values for the EVG and RAL association with IN-DNA were 11.1 and 11.0 hours, respectively.

Figure 44. Binding and Dissociation of EVG and RAL from Integrase-DNA Complexes

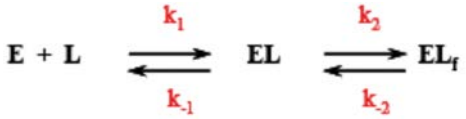


Source: PC-183-2027

Table 89. Kinetic Constants for EVG and RAL Binding and Dissociation with Integrase-DNA Complexes

Compound	Kinetic Constant[a]						
	k_1, $\mu M^{-1}s^{-1}$ ($\times 10^{-3}$)	k_{-1}, s^{-1} ($\times 10^{-4}$)	k_2, s^{-1} ($\times 10^{-4}$)	k_{-2}, s^{-1} ($\times 10^{-4}$)	K_{on}, $\mu M^{-1}s^{-1}$ ($\times 10^{-3}$)	K_{off}, s^{-1} ($\times 10^{-4}$)	Calculated $t_{1/2}$, h
EVG	8.2[b]	6.7	0.8	0.2	1.1	0.17	11.1
RAL	5.5	9.2	1.1	0.2	0.7	0.18	11.0

a



b Mean from 3 separate experiments
Source: PC-183-2027

Activity Against HIV-1 Integrase in Cells

Under standard HIV infection conditions in cells, approximately 90% of the linear viral DNA migrates to the nucleus: approximately 55% integrates into host DNA to form a provirus, approximately 35% circularizes to form 1-LTR, and < 5% circularizes to form 2-LTR circles {8441}. The effect of EVG on the production of full-length viral DNA, integrated provirus, and 2-LTR circles was quantified in HIV-1 infected T-cell lines, MT-4 or SupT1 (JTK303-PH-005 and PC-186-2006).

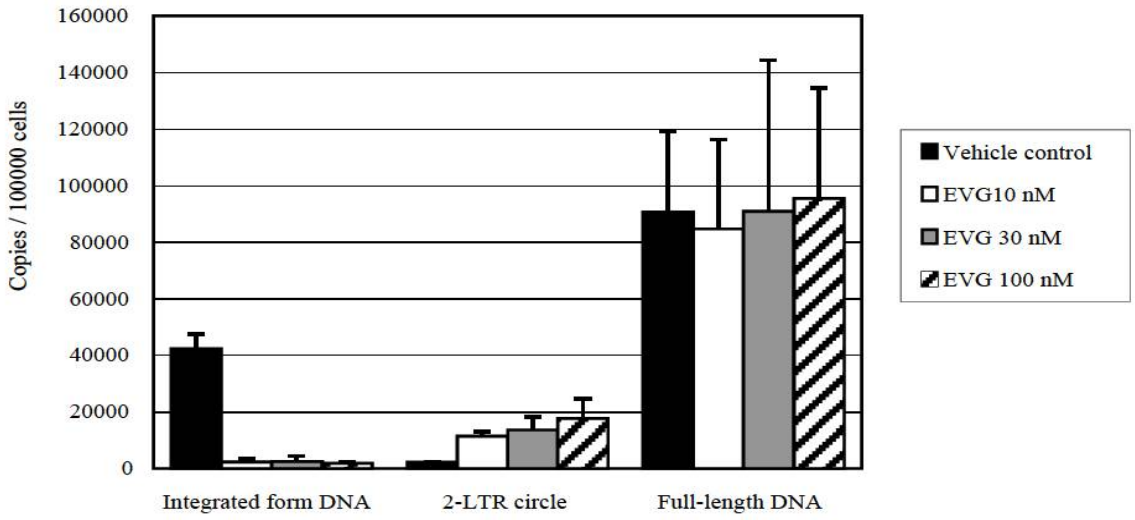
EVG inhibited the integration of HIV-1 DNA into the host chromosomal DNA in HIV-1 infected MT-4 cells, as assessed using an Alu-polymerase chain reaction (PCR) assay at 18 hours after infection, and showed a 94.6% reduction in integrated provirus at 10 nM (Figure 45 and Table 90). A dose-dependent increase in the accumulation of 2-LTR circles of 5-fold was also observed at 10 nM EVG (JTK303-PH-005).

EVG, at 10 nM, had no effect on the generation of full-length viral DNA synthesized by RT. EFV, a representative NNRTI, suppressed the level of full-length DNA because of its strong inhibitory activity against RT (Table 90). An HIV-1 PI, nelfinavir (NFV), did not significantly influence the level of any forms of HIV-1 DNA (Table 90).

Similar findings were observed for EVG in HIV-1 infected SupT1 cells, where EVG did not inhibit the production of full-length viral DNA (late RT signal; $IC_{50} \geq 1000$ nM), but inhibited the integration of viral DNA with an EC_{50} of 0.3 nM (Alu-PCR signal; Table 91; PC-186-2006). The control IN inhibitor L-870,810 similarly showed no inhibition of the production of full-length viral DNA ($IC_{50} \geq 1000$ nM), but inhibited integration of viral DNA with a 4-fold higher IC_{50} (1.3 nM).

Therefore, EVG acts as an HIV-1 INSTI and does not alter the reverse transcription of the viral DNA.

Figure 45. Effects of EVG on the Generation of 3 Different Forms of HIV-1 DNA in Infected Cells



Error bars indicate the SD of the mean values of 3 separate experiments.
Source: JTK303-PH-005

Table 90. Effects of EVG on the Generation of Full-Length, Integrated, and 2-LTR Circle Forms of HIV-1 DNA in Infected MT-4 Cells

	Number of DNA copies (copies/10^5 cells)[a]			
HIV-1 DNA	**Vehicle Control**	**EVG (10 nM)**	**EFV (10 nM)**	**NFV (100 nM)**
Integrated Form DNA (% Inhibition)	42,382 ± 5282 (0.0)	2301 ± 1121 (94.6)	1477 ± 362 (96.5)	33,279 ± 10,134 (21.5)
2-LTR Circles (Fold Change)	2233 ± 368 (1.0)	11,415 ± 1548 (5.1)	658 ± 673 (0.3)	2098 ± 89 (0.9)
Full-Length DNA (Fold Change)	90,623 ± 28,423 (1.0)	84,642 ± 31,574 (0.9)	31,933 ± 8000 (0.4)	82,912 ± 16,286 (0.9)

NFV = nelfinavir
a Mean ± SD from 3 separate experiments
Source: JTK303-PH-005

Table 91. Effects of EVG on the Accumulation of Late-RT and Alu-PCR Products in Single-Cycle HIV-1 Vector-Infected SupT1 Cells

	EC_{50} (nM)[a]			
HIV-1 DNA	**EVG**	**L-870,810**	**EFV**	**APV**
Late-RT Signal 12 h Postinfection	> 1000	> 1000	5.0	> 1000
Alu-PCR Signal 48 h Postinfection	0.3	1.3	0.5	> 1000

APV = amprenavir
a Mean from 2 separate experiments
Source: PC-186-2006

4.1.1.3.2. In Vitro Evaluation of EVG on Laboratory Strains of HIV-1

EVG was evaluated for antiviral activity (EC_{50}) and cytotoxicity (CC_{50}) against wild-type laboratory strains of HIV-1 (JTK303-PH-016 and PC-186-2002). EVG showed an EC_{50} value of 0.38 nM against HIV-1_{NL4-3} in MT-4 cells (Table 92). The SI for EVG was > 14,000. Against HIV-1_{IIIB}, EVG showed EC_{50} values of 0.17 nM in MT-4 cells and 0.6 nM in MT-2 cells, and SI values of > 23,000 and > 13,000, respectively. The overall mean EC_{50} for wild-type HIV-1 in T-cell lines was 0.38 nM. The control inhibitor L-870,810 inhibited HIV with 3- to 24-fold higher EC_{50} values and had a lower SI than EVG.

Table 92. Antiviral Activity of EVG and Control Compounds Against Wild-Type HIV-1 in T-Lymphocytoid Cell Lines

HIV-1 Strain	**Cell Line**	**EVG**			**L-870,810**		
		EC_{50} (nM)[a]	**CC_{50} (nM)**	**SI[b]**	**EC_{50} (nM)**	**CC_{50} (nM)**	**SI**
NL4-3	MT-4	0.38[c]	5623[c]	14,797	—	—	—
III_B	MT-4	0.17 ± 0.03	4000 ± 2000	23,529	4 ± 3	1600 ± 400	400
III_B	MT-2	0.6 ± 0.1	8000 ± 1000	13,333	2 ± 1	3000 ± 2000	1500
Mean	—	0.38 ± 0.22	5900 ± 2000	15,500	3 ± 1.3	2300 ± 990	750

a Mean ± SD of 3 separate experiments unless otherwise indicated
b Selectivity index = CC_{50}/EC_{50}
c Value determined from a single experiment
Source: JTK303-PH-016 and PC-186-2002

EVG was also evaluated against 3 HIV-1 macrophage-tropic viruses. Assays for these viruses (Ba-L, ADA, and JR-CSF strains) were performed using a human monocyte/macrophage culture and analysis for the p24 antigen after 7 days (JTK303-PH-010). Following removal of the supernatant samples, cytotoxicity was measured by tetrazolium-based (XTT) staining for determination of cell viability. The mean EC_{50} for EVG was 0.35 nM in macrophage cultures, and the minimum SI was > 323 (Table 93).

Table 93. Anti-HIV-1 Activity of EVG and Control Compounds Against HIV-1 M-tropic Laboratory Strains in Monocyte/Macrophage Cells

	EVG			ZDV			EFV		
Virus	EC_{50} (nM)	CC_{50}[a] (μM)	SI[b]	EC_{50} (nM)	CC_{50}[a] (μM)	SI[b]	EC_{50} (nM)	CC_{50}[a] (μM)	SI[b]
Ba-L	0.67	> 0.5	> 746	0.20	> 1.0	> 5000	2.12	> 10	> 4717
ADA	0.07	> 0.5	> 7143	0.18	> 1.0	> 5556	3.58	> 10	> 2793
JR-CSF	0.31	> 0.1	> 323	3.82	> 1.0	> 262	—	—	—

a CC_{50} values that were higher than the maximum concentrations of these compounds in each assay are listed as greater than the highest concentration tested.
b Selective index = CC_{50}/EC_{50}
Source: JTK303-PH-010

4.1.1.3.3. Effects of EVG on Clinical Isolates of HIV In Vitro

EVG activity was evaluated in PBMCs infected with HIV-1 clinical isolates from 8 subtypes and a single HIV-2 isolate (JTK303-PH-010). Phytohemagglutinin A-activated PBMCs from at least 2 normal donors were infected with HIV isolates and cultured with EVG for 7 days. After cultivation, cell-free supernatant samples were collected for analysis of p24 antigen (HIV-1) or RT activity (HIV-2).

EVG showed broad anti-HIV activity against all HIV-1 and HIV-2 isolates tested in this study. Against these viruses, EVG was highly potent with average EC_{50} values ranging from 0.1 to 1.26 nM in PBMCs (8 subtypes, 12 viruses; Table 94). A similar antiviral potency (EC_{50} = 0.53 nM) was also observed against a single HIV-2 isolate. Compared with the RT and PIs ZDV, EFV, and NFV, EVG was highly active against the range of viruses used in this study.

Table 94. Anti-HIV Activity of EVG and Control Compounds Against 8 Subtypes of HIV-1 Clinical Isolates and an HIV-2 Isolate in PBMCs

Subtype	Isolate	EC_{50} (nM)			
		EVG	ZDV	EFV	NFV
HIV-1					
A	RW/92/016	0.41	7.91	0.61	13.4
B	96USHIPS7	0.26	8.41	0.65	25.8
	BR/92/014	0.53	0.60	30.9	32.5
	BR/92/021	0.76	2.13	47.0	70.5
	BR/93/017	0.18	1.10	0.58	2.05
	BR/93/022	1.13	11.7	0.62	20.1
C	BR/92/025	0.10	2.84	0.30	< 0.10
D	UG/92/046	0.50	7.26	1.19	27.7
E	CMU02	1.26	9.07	1.82	22.7
F	BR/93/020	0.74	25.3	0.32	16.4
G	JV1083	0.35	11.1	0.65	14.0
O	BCF01	1.17	1.52	0.69	0.99
HIV-2					
	CDC 310319	0.53	1.14	> 1000	16.1

Source: JTK303-PH-010

4.1.1.3.4. Time of Addition Studies of EVG

Time of drug addition studies showed that EVG inhibited HIV-1 replication consistent with the time of integration of the viral DNA into the host chromosome (PC-183-2027). These experiments were conducted in MT-2 cells infected with HIV-1_{IIIB} for 2 hours and then the virus was removed. Infected cells were exposed to EVG (250 nM) or RAL (1.25 μM) at 2, 6, 8, 10, 12, 15, or 24 hours after infection, and then continuously until the 48-hour time point. Supernatant was harvested 48 hours after infection, and p24 was measured. Both EVG and RAL inhibited the viral life cycle when added to cells up to 12 to 15 hours after infection, consistent with the time of integration of the viral DNA into the host genome. After the time of integration (at 24 hours after infection), the addition of the INSTIs did not show antiviral inhibition.

The intracellular antiviral persistence of EVG and RAL was determined in MT-2 cells using HIV-1_{IIIB} (PC-183-2027). Cells were pre-exposed to high concentrations of EVG, RAL, lopinavir (LPV), or TFV for 8 hours prior to infection. The cells were then washed to remove extracellular drugs, infected by HIV-1, and inhibition of replication was measured by p24 at 48 hours (Table 95). The INSTIs EVG and RAL and the PI LPV did not show significant intracellular persistence, as shown by the > 20-fold decrease in antiviral activity after cell washing compared with cells that were unwashed. In contrast, TFV retained antiviral potency

after cell washing, which is consistent with the persistence of the TFV-DP active metabolite within cells.

Table 95. Intracellular Antiviral Persistence of EVG, RAL, TFV, and LPV

	HIV Growth (% p24 vs No Drug)[a]			
Virus	**EVG**	**RAL**	**TFV**	**LPV**
Constant Drug	3.23 ± 1.33	3.10 ± 0.82	4.71 ± 0.40	3.80 ± 1.11
Persistence Assay	83.8 ± 3.72	92.9 ± 6.6	2.43 ± 0.83	90.9 ± 15.7

a Mean ± SD for 3 experiments. The concentrations of drugs used were 500-times above the EC_{50} for EVG, RAL, and LPV, and 100 times above the EC_{50} for TFV.
Source: PC-183-2027

4.1.1.3.5. Effects of Human Serum Albumin and Human α_1-Acid Glycoprotein on the Anti-HIV-1 Activity of EVG

The effect of HS on the antiviral activity of EVG was evaluated with HS and the major components of human plasma (JTK303-PH-006 and PC-186-2004). EVG showed potent, dose-dependent anti-HIV-1 activity in the absence of HS in human PBMC cultures, with an EC_{50} value of 0.2 nM in these experiments against HIV-1_{IIIB}. Anti-HIV activity of EVG was moderately reduced with the addition of 50% HS to the culture medium, resulting in a 7.5-fold increase in the EC_{50} value to 1.5 nM (0.67 ng/mL). The EC_{90} value for EVG shifted 8.2-fold to 9.8 nM (4.4 ng/mL) in the presence of 50% HS, which was similar to that of EFV (10.8 nM). EVG also showed dose-dependent cytotoxicity in PBMC cultures (CC_{50}, 9.7 μM) that was similarly affected by 50% HS (170 μM; Table 96). The SIs in the absence and presence of 50% HS were 48,500 and > 100,000, respectively, based on the CC_{50}/EC_{50} values ratio.

The effect of HS components, human serum albumin (HSA) and AAG, on EVG antiviral activity was also tested in MT-4 cells and freshly isolated primary human T-cells infected with HIV-1_{IIIB} (JTK303-PH-007 and PC-186-2004). EVG showed potent dose-dependent anti-HIV-1 activity in the absence of human plasma components in MT-4 cells, with an EC_{50} value of 1.7 nM in these experiments (Table 97). The anti-HIV activity of EVG was reduced 14.1-fold by the addition of 40 mg/mL HSA and was not changed by the addition of 1.2 mg/mL AAG. The EC_{50} shift for EFV was similar to that of EVG in 40 mg/mL HSA and was also not changed by the addition of 1.2 mg/mL AAG. Nelfinavir (PI) did not show any anti-HIV-1 activity at concentrations up to 100 nM in the presence of 0.8 or 1.2 mg/mL AAG.

The effect of HS components on the activity of EVG was also tested in PBMCs. In these experiments, the EC_{50} value for EVG in the absence of HS components was 0.2 nM (Table 98). In the presence of 35 mg/mL HSA, the EC_{50} for EVG was shifted 80-fold to 16 nM. In the presence of 1.5 mg/mL AAG, the EC_{50} for EVG was shifted 3-fold to 0.6 nM. The percentage of protein binding for EVG was calculated from these values as 99.0% and 74.5% for HSA and AAG, respectively. The combined protein binding of EVG was calculated as 99.0%, resulting in a combined protein-adjusted EC_{95} of 100 nM (45 ng/mL) and an 80-fold shift in the antiviral potency of EVG.

Table 96. Effects of Human Serum on the Anti-HIV-1 Activity and Cytotoxicity of EVG and EFV in Human PBMC Cultures

	EVG			EFV		
	EC_{50} (nM)	EC_{90} (nM)	CC_{50} (μM)	EC_{50} (nM)	EC_{90} (nM)	CC_{50} (μM)
0% HS[a]	0.2 ± 0.1[b]	1.2 ± 0.4	9.7 ± 2.5	0.2 ± 0.1	1.2 ± 0.4	24.4 ± 11.4
50% HS	1.5 ± 0.4 (7.5)[c]	9.8 ± 4.6 (8.2)	170 ± 12	2.2 ± 1.0 (11.0)[c]	10.8 ± 5.2 (9.0)	> 300

a Cells were maintained in media complemented with 15% fetal bovine serum (FBS) for all studies, and human serum (HS) was added to 0% or 50%.
b Mean ± SD from 5 to 6 donors
c Fold reduction (EC_{50} 50% HS/EC_{50} 0% HS)
Source: JTK303-PH-006

Table 97. Effects of Human Plasma Components on the Anti-HIV-1 Activity of EVG and Control Compounds in MT-4 and MT-2 Cells

	EC_{50} (nM)[a] (Fold Reduction)[b]		
Plasma Component	EVG	EFV	NFV
MT-4 Cells			
None	1.7 ± 0.2	1.6 ± 0.1	14.9 ± 1.2
+ 40 mg/mL HSA	23.9 ± 3.2 (14.1)	16.8 ± 2.3 (10.5)	55.2 ± 9.2 (3.7)
+ 0.8 mg/mL AAG	3.2 ± 0.3 (1.9)	1.9 ± 0.1 (1.2)	> 100 (> 6.7)
+ 1.2 mg/mL AAG	3.9 ± 0.4 (2.3)	2.9 ± 0.3 (1.8)	> 100 (> 6.7)

a Mean ± SD, 3 separate experiments. All experiments were performed in the presence of 10% FBS.
b EC_{50} with plasma component/EC_{50} without plasma component
Source: JTK303-PH-007

Table 98. Human Serum-Adjusted Antiviral EC_{50} and EC_{95} of EVG in Human T Cells

Compound	Control EC_{50} (nM)[a]	HSA EC_{50} (nM)[a]	HSA Protein Binding (%)	AAG EC_{50} (nM)[a]	AAG Protein Binding (%)	Combined Protein Binding (%)	Combined Protein-Adjusted EC_{50} (nM)	Combined Protein-Adjusted EC_{95} (nM)
EVG[b]	0.2 ± 0.1	16 ± 17	99.0	0.6 ± 0.3	74.5	99.0	16 ± 18	100 ± 117
L-870,810[c]	3 ± 2	54 ± 55	93.7	9 ± 10	62.2	94.3	60 ± 76	372 ± 477

a The EC_{50} for Control (10% FBS), (10% FBS + HSA 35 mg/mL), and (10% FBS + AAG 1.5 mg/mL) were run in parallel.
b The data are given as the mean ± SD of at least 4 independent donors.
c The data are given as the mean ± SD of at least 3 independent donors
Source: PC-186-2004

For the purpose of determining the in vivo IQ, the combined protein-adjusted EC_{95} value for EVG in PBMCs of 100 nM (44.8 ng/mL) is the most relevant value.

4.1.1.3.6. In Vitro Resistance Selection Experiments

The development of resistance to EVG was examined using dose escalation and high MOI viral breakthrough experiments. The use of multiple approaches, replicates, and viral strains in resistance selection experiments helps to find multiple patterns of resistance (if they exist) that may be found in patients. It is difficult to predict which approach is most clinically relevant.

Dose-Escalation Resistance Selections

To determine the pattern of resistance that develops to EVG in culture, 3 independent dose-escalation resistance selection experiments were conducted using HIV-1_{IIIB} or HIV-1_{HXB2} in MT-2 cells and increasing concentrations of EVG (JTK303-PH-012 [EVG selection 1]; PC-183-2007 [EVG selections 2 and 3]). Selection 1 was continued until the concentration of EVG reached an approximately 50% CC_{50}. The nucleotide sequences of the IN-coding region were determined for the viruses at various times during the selection and at the final passage (Table 99). Population-based sequencing on the IN coding region derived from the cellular proviral DNA showed the E92Q IN mutation emerged at passage 30, S147G emerged at passages 60 and 70, and H51Y emerged along with E157Q as a mixture through passage 90 and at an EVG concentration of 2560 nM. The resulting final virus from the first selection had the mutations H51Y, E92Q, S147G, and E157E/Q.

For EVG selections 2 and 3, the selected virus genotypes were determined from supernatant virus (PC-183-2007). Both experiments led to the development of viruses that carried the primary EVG IN resistance mutation T66I. In the second selection, virus with T66I was selected by passage 7. In addition, a genetic variant in the C-terminal domain of IN, R263K, initially present at a frequency of 4%, was enriched to 100% by passage 11. The final virus had the mutations D10E, S17N, T66I, and R263K at an EVG concentration of 1640 nM. The D10E and S17N substitutions were present in the initial HIV-1_{IIIB} population and are likely not involved in resistance to EVG.

The third EVG selection experiment confirmed the selection of the T66I mutation, and the F121Y and S153Y IN mutations emerged. The final virus had the mutations D10E, S17N, T66I, F121F/Y, and D232N at an EVG concentration of 3072 nM. The D232N substitution is a naturally occurring variant in some wild-type strains of HIV and is likely not involved in resistance to EVG.

Table 99. Genotypic Analysis of the Integrase Genes from HIV-1_{IIIB} Variants Selected in the Presence of EVG

HIV-1_{IIIB} Selection Details[a]	Integrase Amino Acid Mutation
EVG Selection 1	
P10, 0.5 nM	—
P22, 2.5 nM	—
P30, 10 nM	**E92Q**
P38, 20 nM	**E92Q**
P50, 160 nM	**E92Q**
P60, 640 nM	**E92Q** **S147G**
P70, 1280 nM	**H51Y** **E92Q** **S147G** **E157E/Q**
P80, 1280 nM	**H51Y** **E92Q** **S147G** **E157Q/E**
P90, 2560 nM	**H51Y** **E92Q** **S147G** **E157E/Q**
EVG Selection 2	
P8, 103 nM	*D10E* *S17N* **T66I**
P11, 820 nM	*D10E* *S17N* **T66I**
P12, 1640 nM	*D10E* *S17N* **T66I** **R263K**
EVG Selection 3	
P3, 5 nM	**T66I/T**
P4, 10 nM	**T66I**
P6, 40.5 nM	**T66I** *D232D/N*
P7, 81 nM	**T66I** *D232N*
P9, 384 nM	**T66I** **S153Y/S** *D232N*
P11, 1536 nM	*D10D/E* **T66I** **S153Y/S** *D232N*
P12, 3072 nM	*D10E* *S17N* **T66I** **F121Y/F** *D232N*

P = passage

a HIV-1_{IIIB} variants selected in MT-2 cells in the presence of increasing concentrations of EVG after the indicated number of passages (P10, P22, etc). A passage was defined as each time new cells were infected with or without a step up in drug concentration. Amino acid changes from the wild-type starting virus are shown in bold. Polymorphic or preexisting substitutions not thought to contribute to EVG resistance are shown in italics.

Source: JTK303-PH-012 and PC-183-2007

The drug susceptibilities of the EVG-selected mutant viruses were evaluated (Table 100). In all selections studied, the level of phenotypic resistance to EVG increased with increasing passage number and EVG concentration. In the first selection, the EVG EC_{50} values increased 8.7-, 63.3-, 212-, and 449-fold against viruses from passages 30, 60, 70, and 80, respectively. In MT-4 cells, the EC_{50} values for EVG increased, but to generally lower levels than in MT-2 cells. Cross-resistance to the HIV-1 INSTI L-870,810 was also observed for each of the mutants, but with a lower fold change compared with EVG. No cross-resistance to ZDV, EFV, or NFV was

observed for any of the above mutants selected by EVG (maximum mean fold change in EC_{50} was 1.1-fold). The selected pools from the second EVG selection were not phenotyped. The viruses obtained from the third EVG selection showed increasing resistance of 7.8-, 42-, and 585-fold for passages 3, 6, and 12, respectively. These viruses did not show cross-resistance to RAL or TFV.

Table 100. Phenotypic Analysis for EVG Against Wild-Type HIV-1_{IIIB} or EVG-Resistant Mutant HIV-1

Selection No-HIV-1_{IIIB} Variant Passage Number[a]	Resistance (Fold Change in EC_{50})[b]							
	EVG		L-870,810	RAL	ZDV	EFV	TFV	NFV
Assay	MT-2	MT-4	MT-4	MT-2	MT-4	MT-4	MT-2	MT-4
Wild-Type HIV-1_{IIIB} Starting Virus (P0)	1.0	1.0	1.0	—	1.0	1.0	—	1.0
EVG Selection 1 (JTK303-PH-012)								
P30, 10 nM	8.7	**14.9**	5.2	—	0.5	1.1	—	0.6
P60, 640 nM	**63.3**	**30.5**	7.9	—	0.5	0.8	—	0.6
P70, 1280 nM	**212**	**63.8**	**11.7**	—	0.7	0.8	—	0.8
P80, 1280 nM	**449**	**96.8**	**11.1**	—	0.5	0.6	—	0.8
EVG Selection 3 (PC-183-2007)								
P3, 5 nM	7.8	—	—	0.9	—	—	0.9	—
P6, 40.5 nM	**41.9**	—	—	3.0	—	—	1.0	—
P12, 3072 nM	**585**	—	—	—	—	—	0.9	—

P = passage
Phenotypic analysis in MT-2 cells used a p24 antigen ELISA. Phenotypic analysis in MT-4 cells used an XTT assay.
Fold-change values > 10 are shown in **bold**.
a Passage number of EVG resistant variants, final concentration of EVG
b Mean and SD of 3 separate experiments. Ratio of EC_{50} value against EVG resistant variants/EC_{50} value against wild-type virus.
Source: JTK303-PH-012 and PC-183-2007

Breakthrough Resistance Selections

The development of EVG resistance in cell culture was also studied using a viral breakthrough method that uses a high MOI of HIV-1_{HXB2} in MT-2 cells and constant concentrations of EVG for up to 45 days until extensive cytopathic effects were observed (PC-183-2007). Five concentrations of EVG and the comparator RAL were investigated based on multiples of the selecting drug EC_{50}: 5-, 10-, 20-, 40-, and 80-fold. Viral breakthrough was observed among all 5 drug concentrations for EVG and RAL (Table 101). Viruses with IN resistance mutations were observed at EVG concentrations corresponding to 10-fold the EC_{50} (T66I/T), and 40- and 80-fold the EC_{50} (Q148R). Viruses with emergent IN-resistance mutations were also observed for RAL at concentrations corresponding to 5-fold the EC_{50} (N155H) and 40-fold the EC_{50} (Q148K).

Wild-type virus by population sequencing was associated with viral breakthrough for EVG and RAL at the other drug concentrations. The observed wild-type breakthrough viruses may be due to incomplete integration inhibition relating to the high MOIs or low levels of resistance not detected by standard population sequencing.

Table 101. Genotypic Analysis of the Integrase Genes from HIV-1_{HXB2} Variants Selected in the Presence of EVG or RAL During Breakthrough Selections

Selecting Compound[a]	Drug Concentrations (fold over EC_{50}[b])				
	5	10	20	40	80
EVG	None	T66I/T	None	Q148R	Q148R
RAL	N155H	None	None	Q148K	None

a Changes in the IN gene compared with wild-type HXB2 are shown for EVG and RAL.
b The EC_{50} for EVG and RAL against HIV-1_{HXB2} were 1.2 nM and 5.6 nM, respectively.
Source: PC-183-2007

Characterization of EVG-Selected Integrase Mutations

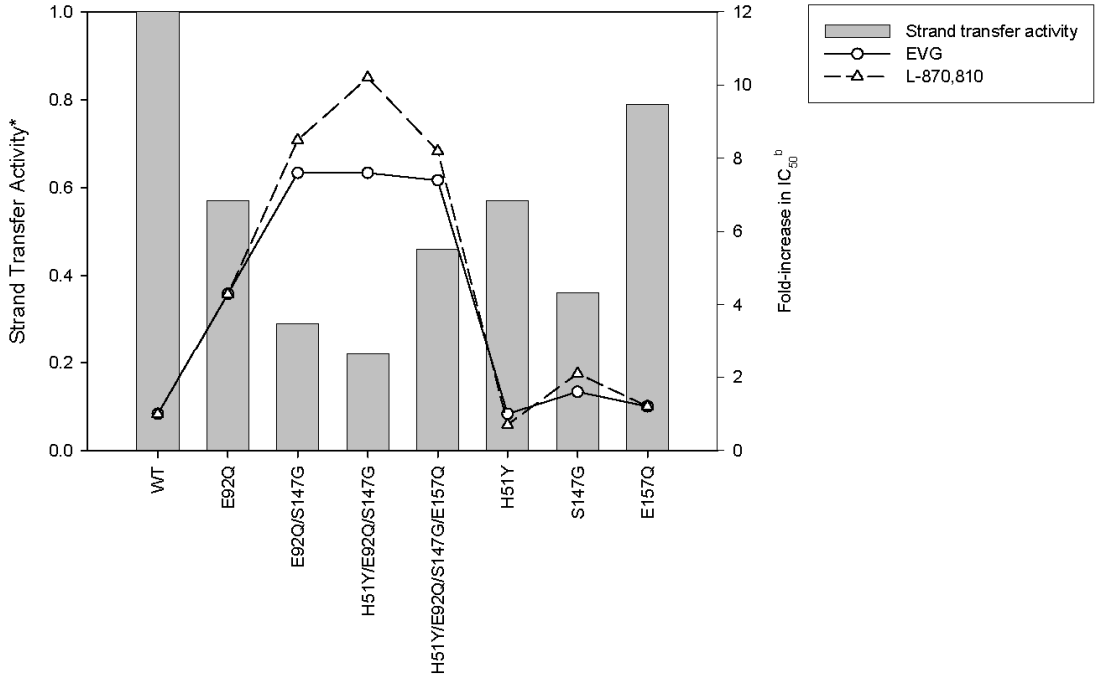
To evaluate the role of each mutation in resistance to EVG, site-directed mutant viruses in a background of HIV-1_{HXB2} and/or IN enzymes carrying each major mutation and combinations of mutations were evaluated (JTK303-PH-015, PC-183-2002, and PC-183-2007).

EVG-Selected Mutant Integrase Enzyme Analyses

The EVG resistance mutations E92Q, H51Y, S147G, E157Q, the double mutant E92Q+S147G, the triple mutant H51Y+E92Q+S147G, and the quadruple mutant H51Y+E92Q+S147G+E157Q from the first EVG selection were characterized for their activity and inhibition by EVG using purified recombinant IN enzymes in the 3'-processing and strand-transfer assays (Figure 46; JTK303-PH-015). All of the 7 mutant enzyme activities were weaker than wild-type IN. The IN with E92Q, double, and triple mutations showed 57%, 29%, and 22% activity, respectively, compared with wild-type IN in the strand-transfer assay. The activity of the quadruple IN was slightly better than the triple mutant, but still had only 46% of the wild-type activity. Other INs with single mutations (H51Y, S147G, or E157Q) also showed decreased activity (57%, 36%, or 79%, respectively). The 3'-processing activity of the mutant IN enzymes showed decreases similar to that measured in the strand-transfer assay.

In the strand-transfer assay, susceptibility of INSTIs with E92Q and E92Q+S147G to EVG decreased by 4.3- and 7.6-fold, respectively (Figure 46, open circles). The addition of H51Y and E157Q to E92Q+S147G did not cause further decreases in the susceptibility to EVG (7.6- and 7.4-fold, respectively). Susceptibility to the control INSTI (L-870,810) also had decreased susceptibility to 4.3- and 8.5-fold for IN with E92Q and E92Q+S147G, respectively. The third and fourth mutations also had little influence on the susceptibility to L-870,810 (10.2- and 8.2-fold, respectively). Except for E92Q, the single mutations showed little effect on drug susceptibility.

Figure 46. Effect of EVG-Selected Mutations on HIV-1 Strand-Transfer Activity and Inhibition by EVG and L-870,810



a Mean strand-transfer activity of each mutant IN/mean strand-transfer activity of wild-type IN (3 experiments)
b Mean IC_{50} of each mutant IN/mean IC_{50} of wild-type IN; 4 experiments for EVG and 3 experiments for L-870,810
Source: JTK303-PH-015

EVG-Selected Site-Directed Mutant Virus Analyses

To understand the phenotypic pattern of resistance to EVG in cells, viruses with single and multiple IN mutations were also studied in multiple HIV backgrounds and assays. The EVG-selected IN mutations were engineered into HIV-1_{NL4-3} or HIV-1_{HXB2} and phenotyped for EVG, RAL, and inhibitors from other drug classes (JTK303-PH-016, PC-183-2002, PC-183-2007, and PC-183-2025).

Viruses with single mutations were constructed and studied for their phenotypic resistance to EVG and other inhibitors (Table 102). Overall, the T66K, E92Q, F121Y, Q148R, Q148K, and N155H (RAL-selected) mutations reduced EVG susceptibility from 11.8-fold to 107.6-fold. Viruses with single mutations at H51Y, S147G, E157Q, S153Y, and R263K showed low-level reduced susceptibility (< 10-fold) to EVG.

The pattern of resistance mutations that emerged in the first dose-escalation selection were studied as site-directed mutant viruses. The E92Q mutation conferred 33- to 79-fold reduced susceptibility to EVG. The addition of S147G, H51Y, and E157Q to the E92Q mutation as double, triple, or quadruple mutants further reduced EVG susceptibility (70- to 358-fold, 143- to 405-fold, and 154- to 437-fold compared with wild type, respectively).

To study the T66I-based EVG resistance pattern observed from the EVG second and third selections, as well as Q148R from the breakthrough selections, additional site-directed mutant viruses were assessed. Viruses carrying the T66I mutation alone showed 15-fold reduced susceptibility to EVG, but remained susceptible to the control ARV compounds RAL and TFV. R263K alone reduced EVG susceptibility 6-fold; its addition to T66I further reduced EVG susceptibility (94-fold reduced) relative to T66I alone. Site-directed mutant viruses carrying T66I+F121Y or T66I+S153Y mutations had 37- and 41-fold reduced susceptibility to EVG, respectively. F121Y or S153Y mutations alone had 12- and 5-fold reduced susceptibility to EVG, respectively. The RAL breakthrough selection showed virus with N155H and Q148K, with 24- and 26-fold resistance to RAL, respectively, and high-level cross-resistance to EVG (35- and 50-fold, respectively). All of the IN mutant viruses tested remained susceptible to TFV, EFV, and LPV where tested.

Table 102. Antiviral Activity of EVG and Control Compounds Against Emergent HIV-1 NL4-3 Site-Directed Integrase Mutations

Integrase Genotype	Resistance (Fold Change in EC_{50})						
	EVG	**RAL**	**TFV**	**ZDV**	**EFV**	**LPV**	**Report No.**
EVG Selection 1							
H51Y	1.53	—	—	1.32	1.01	1.81	JTK303-PH-016
	3.6	0.8	1.0	—	0.75	1.2	PC-183-2002
	2.9	1.2	1.5	—	—	—	PC-183-2007
E92Q	**79.2**	—	—	1.70	0.84	1.58	JTK303-PH-016
	32.7	5.3	0.9	0.9	1.0	1.0	PC-183-2002
S147G	2.08	—	—	1.30	0.82	1.36	JTK303-PH-016
	7.6	1.0	0.8	—	1.0	0.75	PC-183-2002
	9.7	1.3	1.6	—	—	—	PC-183-2025
H51Y + S147G	**33**	2.1	2.5	—	—	—	PC-183-2007
E157Q	0.55	—	—	1.09	0.40	1.04	JTK303-PH-016
	2.3	1.6	1.0	—	1.0	1.0	PC-183-2002
E92Q + S147G	**358**	—	—	1.48	0.99	0.88	JTK303-PH-016
	69.6	8.4	0.7	0.6	1.2	0.8	PC-183-2002
E92Q + S147G + H51Y	**405**	—	—	1.33	0.75	0.77	JTK303-PH-016
	143	7.0	0.8	0.7	1.1	0.9	PC-183-2002
E92Q + S147G + H51Y + E157Q	**437**	—	—	0.54	0.29	0.28	JTK303-PH-016
	154	6.2	1.0	0.75	1.3	0.9	PC-183-2002
EVG Selection 2							
T66I	**14.5**	1.3	1.0	—	—	—	PC-183-2007
R263K	6.3	1.4	1.2	—	—	—	PC-183-2007
T66I + R263K	**105**	1.0	0.5	—	—	—	PC-183-2007
EVG Selection 3							
F121Y	**11.8**	7.2	1.0	—	—	—	PC-183-2007
S153Y	4.9	1.7	1.1	—	—	—	PC-183-2007
T66I + F121Y	**37.2**	**10.2**	0.6	—	—	—	PC-183-2007
T66I + S153Y	**41.3**	0.9	0.6	—	—	—	PC-183-2007
T66K	**39.9**	**19.1**	1.2	—	—	—	PC-183-2007

Integrase Genotype	Resistance (Fold Change in EC_{50})						
	EVG	**RAL**	**TFV**	**ZDV**	**EFV**	**LPV**	**Report No.**
Breakthrough Selections							
Q148R	**107.6**	**34.0**	0.7	—	—	—	PC-183-2025
Q148K	**49.6**	**26.1**	0.7	—	—	—	PC-183-2007
N155H	**35.2**	**21.0**	1.1	—	—	—	PC-183-2025

Fold-change values > 10 are shown in **bold**.
Source: JTK303-PH-016, PC-183-2002, PC-183-2007, and PC-183-2025

In vitro resistance selection experiments with EVG demonstrated that EVG can select 3 primary resistance mutations in HIV-1 IN, the T66I, E92Q, or Q148R mutations. The T66I, E92Q, and Q148R mutations resulted in HIV-1 that had 15-, 36-, and 109-fold reduced susceptibility to EVG, respectively. The other IN mutations H51Y, F121Y, S147G, S153Y, E157Q, and R263K were also selected by EVG and further decreased susceptibility to EVG when added to either the T66I or E92Q mutations.

EVG Cross-Resistance to HIV with Other Integrase Mutations

Additional cross-resistance analyses of HIV-1 with mutations in other IN positions than those that were selected by EVG in culture were investigated (Table 103; PC-183-2025). This study identified additional IN mutations T66A/K and E92G with > 10-fold reduced susceptibility to EVG. In addition, the study showed that susceptibility of the mutants to the EVG metabolites GS-9202 (M1) and GS-9200 (M4) were similar to EVG, with the exception of H51Y, which showed a 6.1- to 22.2-fold change toward GS-9200 as further described in Section 4.1.1.3.8.

Table 103. Antiviral Activity of EVG, M1, M4, and Control Compounds Against HIV-1 NL4-3 Site-Directed Integrase Mutant Viruses

Integrase Genotype[a]	EVG	GS-9200 (M4)	GS-9202 (M1)	RAL	TFV	LPV
H51Y	3.0	0.8	17.8	1.2	1.5	—
T66A	8.4	—	—	1.2	1.1	—
	33.9	**14.1**	**28.8**	3.9	1.8	—
T66I	**14.9**	**10.7**	**23.1**	1.3	1.0	—
	30.8	9.2	**19.9**	2.3	3.8	—
T66K	**40.8**	—	—	**19.4**	1.2	—
L68I	0.8	—	—	0.8	0.9	0.9
L68V	1.5	—	—	1.0	1.1	—
V72I	1.6	—	—	1.6	1.0	1.1
E92G	**39.3**	6.5	**22.1**	1.7	2.0	—
E92Q	**39.4**	—	—	5.8	0.9	1.0
	78.1	**22.2**	**48.5**	**11.2**	3.3	—
T97A	2.1	—	—	2.4	0.7	0.9
F121Y	**12.1**	**12.5**	**19.1**	7.3	1.0	—
E138A	0.8	—	—	1.1	0.8	0.8
E138K	0.6	—	—	0.9	1.1	1.1
G140S	3.1	—	—	1.6	0.9	1.0
Y143H	1.6	—	—	3.4	1.0	0.8
Y143R	5.4	—	—	**37.7**	1.0	1.0
P145S	**31.2**	—	—	0.6	0.7	0.6
Q146I	**134**	—	—	3.5	0.9	1.0
Q146K	2.0	—	—	1.0	0.9	0.8
Q146L	**20.8**	—	—	1.4	0.9	0.9
Q146P	6.0	—	—	1.2	1.0	0.9
Q146R	4.8	—	—	1.9	0.9	1.0
S147G	9.7	2.7	6.8	1.3	1.6	—
Q148H	4.8	—	—	**18.8**	0.9	0.9
Q148K	**49.6**	—	—	**26.1**	0.7	0.7
Q148R	**108**	—	—	**34.0**	0.7	0.9
S153F	5.3	2.2	3.4	2.0	2.5	—
S153Y	5.0	1.6	2.1	1.7	1.0	—

Integrase Genotype[a]	EVG	GS-9200 (M4)	GS-9202 (M1)	RAL	TFV	LPV
N155H	**35.2**	—	—	**21.0**	1.1	0.9
	67.3	**18.8**	**41.4**	**25.9**	2.8	—
N155S	**64.9**	—	—	**10.9**	0.7	0.6
G163K	1.2	—	—	1.4	0.9	0.8
G163R	1.3	—	—	1.6	0.9	0.8
S230R	1.0	—	—	1.6	1.0	—
N232D	1.8	—	—	0.8	—	1.0
R263K	6.4	3.3	—	1.0	0.5	1.6
H51Y + S147G	**33.7**	**12.9**	**144.6**	2.1	2.5	—
T66A + S153F	**55.3**	**19.3**	**29.4**	1.1	1.7	—
T66I + F121Y	**38.0**	**22.6**	**41.3**	**10.4**	0.6	—
T66I + S147G	**34.4**	—	—	1.9	1.0	0.9
T66I + S153Y	**42.2**	**24.8**	**43.7**	0.9	0.6	—
T66I + R263K	**108**	**58.3**	**297**	1.0	0.5	0.9
E92G + S153F	**30.7**	8.0	**15.5**	1.5	1.8	—
E92Q + T66I	**107**	—	—	**25.2**	0.9	0.9
E92Q + L68I	**42.7**	—	—	7.4	0.8	0.8
E92Q + L68V	**66.2**	—	—	**13.6**	1.1	1.0
E92Q + S147G	**69.5**	**52.9**	**81.7**	**6.5**	0.8	0.9
E92Q + N155H	**123**	—	—	**103**	0.8	0.6
Q148H + G140S	**> 869**	—	—	**756**	1.0	1.1
Q148K + E138A + G140A	**372**	—	—	**354**	0.9	0.8
Q148R + L68V	**137**	—	—	**71.4**	0.6	0.6
Q148R + N155H	**112**	—	—	**81.3**	0.3	0.4
Q148R + E138K + S147G	**153**	—	—	**33.3**	0.9	0.9
N155H + L68V	**50.4**	—	—	**23.4**	0.7	0.6
E92Q + H51Y + S147G	**144**	**85.0**	**399**	6.8	0.9	1.0
E92Q + H51Y + S147G + E157Q	**171**	**106**	**399**	6.1	0.9	1.0

M1 = hydroxide of the chlorofluorophenyl group; M4 = glucuronide conjugate of the carboxylic acid
Fold-change values > 10 are shown in **bold**.
Source: PC-183-2025

4.1.1.3.7. Activity of EVG on Recombinant HIV-1 with HIV Drug Resistance Mutations in RT and Protease

The anti-HIV-1 activity of EVG against a panel (n = 120) of patient-derived RT and protease drug-resistant recombinant clones of HIV-1 was evaluated using the PhenoSense HIV drug resistance assay (JTK303-PH-009; Table 104). All of the tested clones with resistance to RT and protease remained susceptible to EVG (mean EC_{50} value was 1.06 nM), with EC_{50} values comparable with the wild-type reference clone NL4-3 (1.11 nM). For this panel, mean susceptibility to the NRTIs ZDV, 3TC, ddI, d4T, ABC, and TFV was ≥ 12.2-fold reduced relative to wild type. For recombinant clones with NNRTI-R, mean susceptibility was ≥ 86.9-fold reduced for delavirdine (DLV), EFV, and NVP. For recombinant clones with PI-R, mean susceptibility for amprenavir (APV), IDV, NFV, RTV, saquinavir (SQV), LPV, and ATV was ≥ 32.0-fold reduced relative to wild type.

Table 104. EVG Susceptibility of Reverse Transcriptase and Protease Resistant Patient-Derived Recombinant HIV-1 Molecular Clones

	Recombinant Clone	Reference Clone (NL4-3)
Mean EC_{50} (nM)	1.06	1.11[a]

a Ten replicates, 1 experiment
Source: JTK303-PH-009

EVG remained active in PBMCs (EC_{50} values ≤ 1.13 nM) against patient isolates with multiple drug resistance mutations in protease and RT (Table 105; JTK303-PH-010). Several HIV-1 viruses with RT and protease mutations introduced by site-directed mutagenesis were also evaluated in 293T or MT-2 cells (RT: K65R, M184V, K103N, and Y181C; protease: D30N, M46I/L/V, V82A/F/S/T, I84A/C/V, and L90M), and these also showed sensitivity to EVG (Table 106, Table 107, and Table 108; JTK303-PH-009 and PC-186-2008). Based on the comparison of resistance mutations, EVG exhibited potent inhibitory activity against many types of resistant clones, such as resistant clones against NRTIs, NNRTIs, and PIs. In contrast, most of the 16 examined anti-HIV drugs showed significant decreases in antiviral susceptibility of recombinant clones expressing genetic mutations conferring resistance to the corresponding drugs (Table 106, Table 107, and Table 108).

Table 105. Anti-HIV Activity of EVG and Control Compounds Against Drug-Resistant HIV-1 Clinical Isolates in PBMCs

Isolate	Resistance Mutations[a]		EC_{50} (nM)			
			EVG	ZDV	EFV	NFV
Protease Inhibitor-Resistant Isolates						
1064–52	Protease[b]	L10I, I54V, L63P, A71T, V82F, L90M	0.63	13.6	0.29	838.5
1002–60	Protease	L10I, M46I, I54V, L63P, V82F, L90M	0.13	6.72	0.21	> 1000
052–52	Protease	L10R, M46I, L63P, A71V, V82T, I84V	0.17	63.9	< 0.10	95.0
144–44	Protease	V32I, M46I, L63P, L90M	0.72	7.24	0.60	165.3
Multidrug-Resistant Isolates						
MDR 769	RT[c]	M41L, K65R, D67N, V75I, F116Y, Q151M, Y181I, L210W, T215Y	0.18	720.7	0.54	> 1000
	Protease	L10I, M36M or V, M46I, I54V, L63P, A71V, V82A, I84V, L90M				
MDR 807	RT	M41L, D67N, M184V, L210W, T215Y, K219N	1.13	159.4	0.71	135.0
	Protease	L10I, G48V, I54T, L63Q, A71V, V82A				
MDR 1385	Protease	L10I, M36I, M46I, I54I or V, L63P, A71V, V82T, L90M	0.02	> 1000	> 1000	> 1000
MDR 3761	Protease	L10I, M46I, I84V, L63P, A71I, L90M	0.73	> 1000	> 1000	> 1000

a Mutation sites are represented as the position number in the RT- or protease-coding region and the amino acid residue in the wild-type and drug-resistant viruses.
b Protease gene
c Reverse transcriptase gene
Source: JTK303-PH-010

Table 106. Drug Susceptibility of Recombinant HIV-1 Molecular Clones Containing Mutations Associated with NRTI Resistance

RT Mutation[a]	N[b]	Fold Increase in EC_{50}[c]						
			NRTIs					
		EVG	ZDV	3TC	ddI	d4T	ABC	TFV
Wild-type	8	0.9	0.8	1.1	1.1	1.0	0.9	0.8
K65R[d]	1	2.0	—	—	—	—	—	4.4
M184V[d]	1	1.0	—	—	—	—	—	0.9
6 TAMs[e]	5	0.9	**531.6**	6.7	2.2	6.2	6.9	5.0
6 TAMs, M184I or V	7	1.0	**92.1**	**98.0**	2.1	2.7	7.4	1.6
2-5 TAMs[f]	16	1.0	**271.3**	6.1	2.5	4.8	6.6	3.5
2-5 TAMs, T69ins	4	1.2	**506.4**	**19.5**	6.0	**17.0**	**19.3**	**12.2**
2-5 TAMs, K65R and/or Q151M	4	1.1	**437.8**	**57.3**	**17.2**	**21.0**	**19.8**	8.5
M184I or V	12	0.9	0.4	**102.4**	1.4	0.8	3.1	0.6
K65R and/or Q151M	7	0.9	**181.6**	**40.1**	9.6	**10.3**	**13.3**	4.0
K65R and/or Q151M, M184I or V	12	0.9	**262.6**	**108.0**	**13.2**	9.0	**24.1**	2.2

TAM = thymidine analog mutation
Fold-change values > 10 are shown in bold.
a Mutation sites are represented as the position number in the RT-coding region and the amino acid residue in the wild-type virus.
b Number of clones
c Mean EC_{50} fold increase above reference clone (NL4-3 or III_B)
d Mean EC_{50} from one site-directed mutant virus in MT-2 cells
e Six thymidine analog mutations (at RT positions M41, D67, K70, L210, T215, K219)
f Two to 5 thymidine analog mutations (at RT positions M41, D67, K70, L210, T215, K219)
Source: JTK303-PH-009 and PC-186-2008

Table 107. Drug Susceptibility of Recombinant HIV-1 Molecular Clones Containing Mutations Associated with NNRTI Resistance

RT Mutation[a]	N[b]	Fold Increase in EC_{50}[c]				
		EVG	L-870,810	NVP	DLV	EFV
Wild-type (nM)	8	0.9	4.2	1.2	1.9	1.3
K103N	46	0.9	—	**127.3**	**86.9**	**128.6**
	1[d]	0.6	0.6	—	—	71
Y181C	1[d]	0.5	0.8	—	—	3.1
K103N, Y181C	14	1.0	—	**187.1**	**122.1**	**154.7**
K103N, Y188C/H/L	6	0.8	—	**197.0**	**109.2**	**218.0**

Fold-change values > 10 are shown in bold.
a Mutation sites are represented as the position number in the RT-coding region and the amino acid residue in the wild-type virus
b Number of clones
c Mean EC_{50} fold increase above reference clone (NL4-3)
d Mean EC_{50} from one site-directed mutant virus in MT-2 cells
Source: JTK303-PH-009 and PC-186-2008

Table 108. Drug Susceptibility of Recombinant HIV-1 Molecular Clones Containing Mutations Associated with Protease Inhibitor Resistance

Protease Mutation[a]	N[b]	Fold Increase in EC_{50}[c]							
		EVG	PIs						
			APV	IDV	NFV	RTV	SQV	LPV	ATV
Wild-Type	8	0.9	0.6	0.7	0.9	0.8	0.7	0.7	0.7
M46I/L/V, V82A/F/S/T	14	0.9	**27.6**	**31.3**	**34.6**	**59.5**	**42.8**	**76.8**	**32.2**
M46I/L/V, V82A/F/S/T, I84A/C/V, or L90M	14	1.0	**62.3**	**29.1**	**41.7**	**130.6**	**45.4**	**112.0**	**34.7**
M46I/L/V, V82A/F/S/T, I84A/C/V, L90M	3	1.0	**34.0**	**32.0**	**64.0**	**163.3**	**108.0**	**82.3**	**45.0**
D30N	8	1.0	1.1	1.6	**37.8**	1.3	1.3	1.1	3.7
D30N, L90M	5	1.0	9.6	**11.3**	**209.2**	**29.2**	**114.4**	**11.6**	**41.4**

Fold-change values > 10 are shown in bold.
a Mutation sites are represented as the position number in the protease-coding region and the amino acid residue in the wild-type virus.
b Number of clones
c Mean EC_{50} fold increase above reference clone (NL4-3).
Source: JTK303-PH-009

4.1.1.3.8. Activity of EVG Metabolites

In a clinical study in which subjects were dosed orally with [^{14}C]EVG and RTV, the parent compound EVG was the most abundant radiolabeled component in plasma (93%; GS-US-183-0126). The key human metabolites identified in vitro and in vivo were M1 (0% to 1% for nonboosted EVG and below the limits of detection in humans dosed with EVG and boosted with RTV or COBI; M1 is the hydroxylation of the chlorofluorophenyl group, GS-9202 as standard), M4 (3.5%, M4 is the glucuronide conjugate of the carboxylic acid, GS-9200 as standard), and M7 (glucuronide conjugate of M1, JTP-74488 as standard). In rabbit microsomal fractions fortified with the cofactor for sulfation, HM1 (sulfate conjugate of M1, standard JTP-74492) was also detected (60N-0508) {11201}. The effects of these EVG metabolites on DNA strand-transfer activity were evaluated using recombinant wild-type HIV-1 IN and synthetic metabolite standards (JTK303-PH-013).

Activity of EVG Metabolites GS-9202 (M1) and GS-9200 (M4) Against Recombinant HIV-1 Integrase Enzyme

Of the 4 EVG metabolites, GS-9202 (M1) retained the highest inhibitory potency against HIV-1 IN with an IC_{50} of 38.8 nM (5.2-fold decrease in potency compared with EVG). Other metabolites were 38- to 426-fold less than the parent drug (Table 109; JTK303-PH-013).

Table 109. IC_{50} Values for EVG, its Metabolites, and L-870,810 against Strand-Transfer Activity of Wild-Type HIV-1 Integrase

Compound	Identity	IC_{50} (nM)	
		Mean ± SD	Fold Change vs EVG[a]
EVG	Parent	7.4 ± 1.2	1.0
GS-9202	M1	38.8 ± 4.9	5.2
GS-9200	M4	281 ± 16.5	38
JTP-74488	M7	3150 ± 1364	426
JTP-74492	HM1	2689 ± 567	363
L-870,810	Control	18.0 ± 1.1	—

GS-9202 (M1); GS-9200 (M4); JTP-74488 (M7), and JTP-74492 (HM1) = chemically synthesized standards of EVG metabolites; L-870,810 = Merck investigational INSTI control; "—" = not calculated

a Mean IC_{50} of metabolite/mean IC_{50} of EVG generated from 3 experiments.

Source: JTK303-PH-013

Antiviral Activity of EVG Metabolites GS-9202 (M1) and GS-9200 (M4) Against HIV-1_{IIIB} and EVG-Resistant Variants

In order to investigate whether the EVG oxidative metabolite M1 and the glucuronidated metabolite M4 show antiviral activity in cells, the effect on replication of wild-type HIV-1_{IIIB} was evaluated in an antiviral assay in MT-4 or MT-2 cells using the synthetic standards GS-9202

(M1) and GS-9200 (M4). Additionally, cross-resistance of EVG-resistant viruses to GS-9202 and GS-9200 was evaluated (Table 103; PC-183-2025).

The EC_{50} value for EVG and GS-9202 (M1) against HIV-1_{IIIB} in MT-4 cells was 42.5 nM (6.1-fold less than the parent drug EVG; JTK303-PH-014). The difference in potency between GS-9202 and EVG is comparable with that for inhibition of HIV-1 IN observed in the enzyme assay of 5.2-fold reduced activity of GS-9202 compared with EVG (JTK303-PH-013). The EC_{50} values for EVG, GS-9202, and GS-9200 (M4) were also determined using HIV-1_{IIIB} or HIV-1_{HXB2} in MT-2 cells (PC-183-2007). In this study, the EC_{50} values using HIV-1_{IIIB} for EVG, GS-9202, and GS-9200 were 0.6, 5.6, and 4 nM, respectively, resulting in 9.3- and 6.7-fold lower activity for GS-9202 and GS-9200, respectively, than the parent drug EVG. Using HIV-1_{HXB2}, the EC_{50} values were 1.2, 12.5, and 10.5 nM for EVG, GS-9202, and GS-9200, respectively. The increased potency of GS-9200 in these experiments compared with the enzymatic IC_{50} may be due to EVG-contaminating GS-9200, or generated chemically or enzymatically by hydrolysis.

EVG-resistant viruses were evaluated for the phenotypic profiles of GS-9202 (M1) and GS-9200 (M4) (Table 103). GS-9202 and GS-9200 had phenotypic profiles that were similar to EVG, and susceptibilities to GS-9202 and GS-9200 decreased with the accumulation of EVG-associated mutations. GS-9202 appeared more impacted by the H51Y mutation, and consistently showed greater resistance to viruses containing H51Y compared with EVG. These EVG-resistant viruses retained susceptibility to the NNRTI EFV (PC-183-2025).

HIV-1 resistance selection experiments using GS-9202 and GS-9200 led to the development of previously reported EVG resistance mutations H51Y, T66A, E92G, S147G, and a novel variant at S153 (S153F; PC-183-2008 and PC-183-2021). Population sequencing results showed that the GS-9202 selection led to the emergence of detectable H51Y at passage 2, which became the full H51Y mutant by passage 8, and was H51Y+S14G at passage 10. The GS-9200 selection led to the emergence of S153F at passage 4, T66A+S153F+D232N at passage 7, then started to switch resistance patterns to T66T/A+E92E/G+S153F+D232N at passage 8, and finally was E92G+S153F+D232N at passage 9. The magnitude of resistance to selected pools and site-directed mutant viruses representing these mutations for GS-9202 and GS-9200 was overall similar to that for EVG, with the exception of H51Y, which showed a higher magnitude of resistance to GS-9202 than EVG or GS-9200.

These results demonstrate that GS-9202 and GS-9200 retained antiviral activity against wild-type HIV-1_{IIIB} in MT-2 cells with ≥ 7-fold less activity than the parent drug EVG. The resistance profiles of EVG and its metabolites GS-9202 and GS-9200 were overlapping. EVG itself is the dominant plasma species among EVG and its metabolic products; therefore, INSTI-R mutations selected by EVG itself will likely predominate if virologic failure occurs on boosted EVG.

4.1.1.4. EVG: In Vivo Pharmacodynamics

No primary PD studies in animals were conducted. A primary PD study in humans (Study GS-US-183-0101) was conducted.

4.1.1.5. FTC: In Vitro Pharmacodynamics

4.1.1.5.1. Mechanism of Action

4.1.1.5.1.1. 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.

4.1.1.5.1.2. 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 47. 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}.

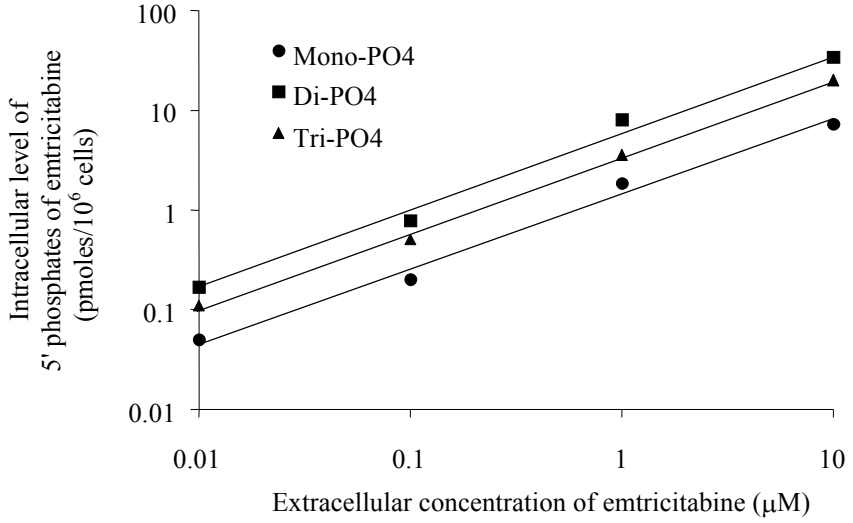
In studies to determine which enzymes were responsible for phosphorylating FTC to the 5'-triphosphate, 2'-deoxycytidine kinase was identified as the enzyme that catalyzes the phosphorylation of FTC to the corresponding 5'-monophosphate. An apparent K_m (Michaelis-Menton constant) value of 11.8 μM and an apparent relative maximum velocity (V_{max}) of 9.3 $nmol \bullet mL^{-1} \bullet h^{-1}$ 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 $nmol \bullet mL^{-1} \bullet h^{-1}$ 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 47. Intracellular Levels of FTC-TP as a Function of Extracellular FTC Concentration



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.

4.1.1.5.2. Inhibition of Viral and Human DNA Polymerases

4.1.1.5.2.1. 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 110. 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 110. 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

Source: {4545}

4.1.1.5.2.2. 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.

4.1.1.5.3. In Vitro Evaluation of Antiretroviral Activity

4.1.1.5.3.1. 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 111. 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 112. 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 111. Inhibitory Effect of FTC on the Replication of Laboratory Strains of HIV-1 and HIV-2

Virus	Cell Type	Assay	EC_{50} (μM)
HIV-1_{IIIB}	CEM	RT	0.1 [a,b]
	MT-4	cytoprotection	0.5 [a,b]
	PBMC	RT	0.01 [b]
HIV-1_{LAV}	CEM	RT	0.009 [a]
	HT4-6C	RT	0.02 [a]
	PBMC	p24	0.009 [b]
	PBMC	RT	0.001 [d]
HIV-1_{LAI}	CEM	cytoprotection	0.04 [c]
	MT-2	cytoprotection	0.62 [c]
	PBMC	p24	0.03 [c]
	PBMC	p24	0.0014 [e]
HIV-2_{ZY}	MT-4	RT	1.5 [a]
	CEM	RT	0.1 [a]
HIV-2_{ROD2}	PBMC	p24	0.007 [b]

a Source: {4534}
b Source: {4541}
c Source: TPI 462 v2
d Source: {4526}
e Source: TPI 10498 v2

Table 112. 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 113). 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 113. 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[c]
WT – pre-ZDV[b]	0.008	ND[c]
WT – MKC09-day 29[b]	0.02	ND[c]

a Source: {4534}
b Source: TPI 462 v2
c ND = not determined

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 TIBO 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 114. 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 114. 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}

4.1.1.5.3.2. 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-chemokine receptor type 5 (CCR5) and PBMCs. Within each model, EC_{50} values were comparable for all subtypes of HIV-1. Results are presented in Table 115. 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 than in PBMCs (TPI 10498 v2 and TPI 11419 v2).

Table 115. EC_{50} Values of NRTIs Against HIV-1 Group M and Group O Isolates in PBMCs and MAGI-CCR5 Cells

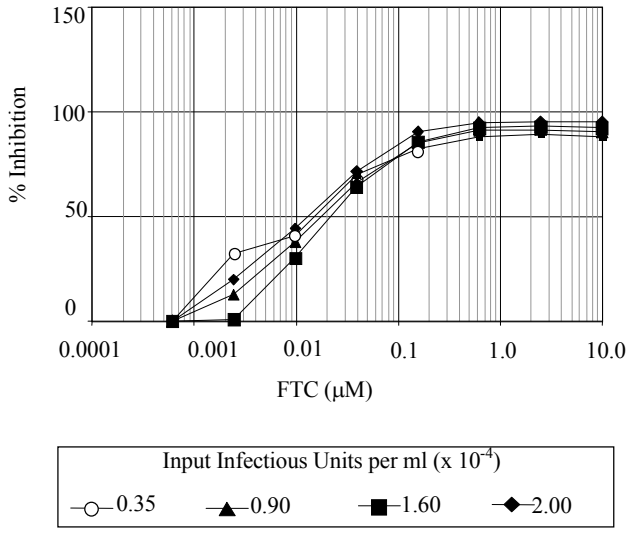
Isolate	Subtype	Host Cell	ZDV (μM)	3TC (μM)	ddI (μM)	FTC (μM)
Group M						
RW/92/008	A	PBMCs[a]	0.008	0.054	0.26	0.012
		MAGI-CCR5[b]	0.085	0.20	3.0	0.055
BR/92/025	C	PBMCs[a]	0.035	0.027	0.49	0.017
		MAGI-CCR5[b]	0.033	0.17	0.95	0.032
UG/92/024	D	PBMCs[a]	0.003	0.026	0.21	0.007
		MAGI-CCR5[b]	0.035	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

4.1.1.5.3.3. Effect of Multiplicity of Infection

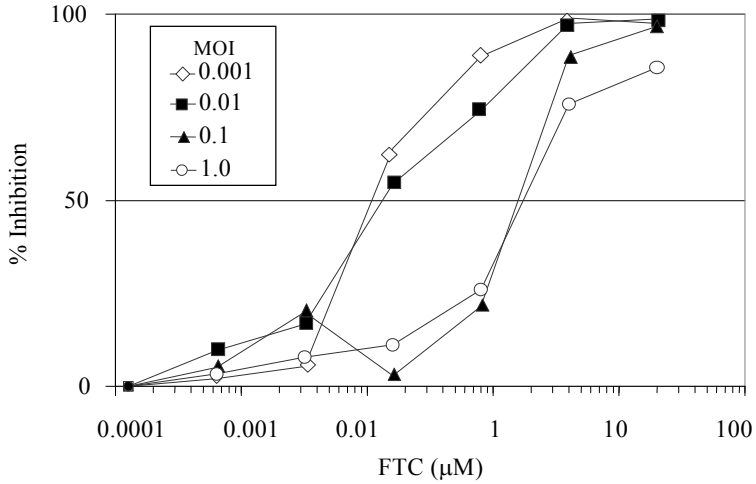
The effect of MOI on the antiviral activity of FTC was assessed in 2 cell lines using 2 different assay methods and was found to be minimal. In MAGI-CCR5 cells (Figure 48), an increase of 5.7-fold in infectious titer resulted in no change in EC_{50} (10518 v2). In PBMCs (Figure 49), using p24 ELISA, 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 48. Effect of Multiplicity of Infection on the EC_{50} of FTC in MAGI-CCR5 Cells



Source: 10518 v2

Figure 49. Effect of Multiplicity of Infection on the EC_{50} of FTC in PBMCs

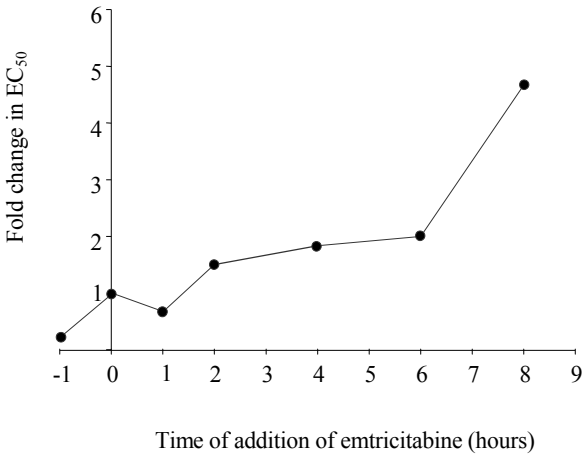


Source: 11773

4.1.1.5.3.4. Effect of Time of Addition

Various concentrations of FTC were added to MAGI 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 50 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 50. Fold Change in FTC EC_{50} as a Function of Time of Addition



Source: 10247

4.1.1.5.3.5. 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 (FBS)-containing media, or in modified media where FBS was replaced with 25% HSA or 25% HSA plus 1-mg/mL AAG. Neither the medium containing 25% HSA alone or in combination with 1-mg/mL AAG affected the antiviral activity of FTC (463), indicating that FTC activity is not affected by binding to serum proteins.

4.1.1.5.4. In Vitro HIV-1 Resistance

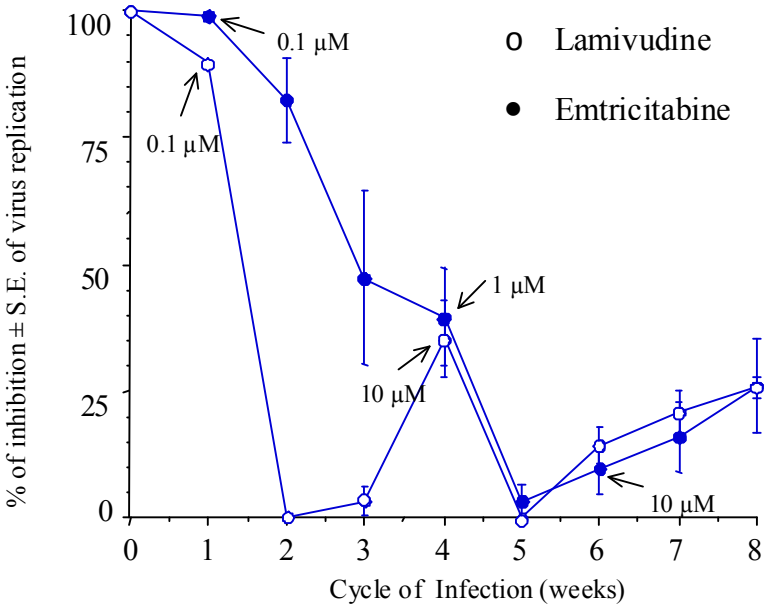
The development of resistance to FTC was examined by passaging virus in vitro in the presence of drug. In a study reported by Tisdale and colleagues, the wild-type virus HIV-1_{HXB2} or the ZDV-resistant mutant virus HIV-1_{RTMC} (contains D67N, K70R, T215Y, and K219Q RT mutations) was passaged in MT-4 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 51 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 derivative U-87201E {1777}.

Figure 51. HIV-1 Breakthrough in the Presence of FTC and 3TC



Source: {1777}

4.1.1.5.4.1. 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 k_{cat} (enzyme catalytic constant) 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 117 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.

4.1.1.5.4.2. Activity Against Drug-Resistant Variants of HIV-1

FTC activity has been evaluated extensively against a panel of clinical isolates (Table 116 and Table 117). 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 116. 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 117. 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.

4.1.1.6. 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.N-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 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.

4.1.1.7. FTC/TDF

4.1.1.7.1. 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 118). Similarly, FTC-TP was also readily observed to form over the same time period when incubated alone (Table 119).

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 52, Table 118, and Table 119). 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 118. Metabolism of 10 μM TFV Either Alone or in Combination with 10 μM FTC

Time	TFV Alone (pmol/million cells)[a]			PMPA With 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

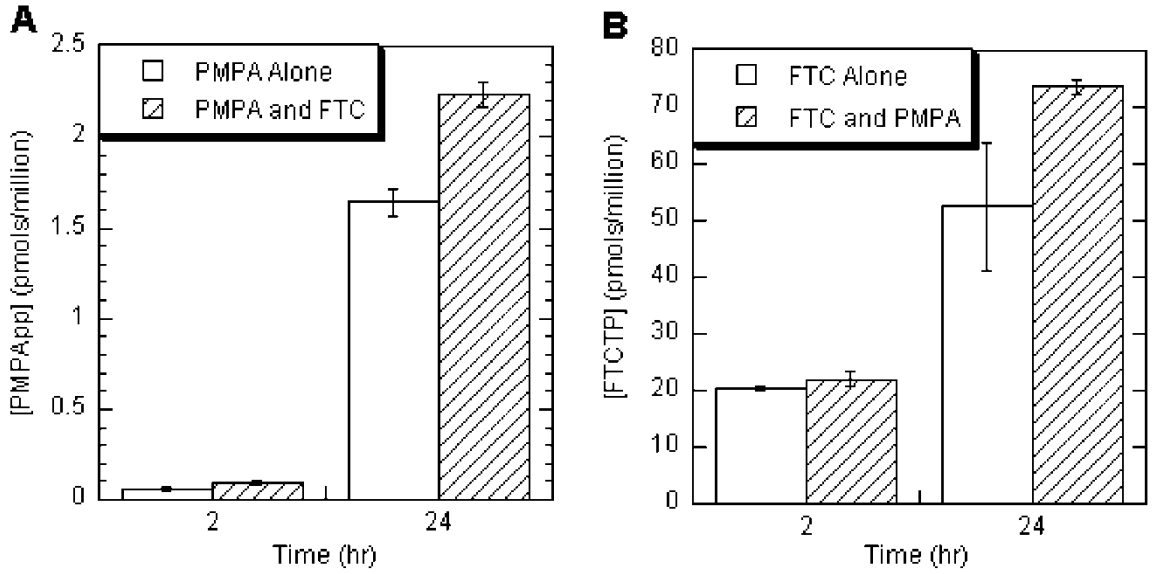
TFV or PMPA = tenofovir; TFV-DP = tenofovir disphophosphate; TFV-MP = tenofovir monophophosphate
a Values determined by LC/MS/MS.
Source: PC-164-2001

Table 119. Metabolism of 10 μM FTC Either Alone or in Combination with 10 μM TFV

Time	FTC Alone (pmol/million cells)[a]	FTC With TFV (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

FTC-TP = emtricitabine 5'-triphosphate
a Values determined by LC/MS/MS.
Source: PC-164-2001

Figure 52. Formation of the Active Metabolites of TFV and FTC



FTC-TP = emtricitabine 5′-triphosphate; PMPA = tenofovir; PMPApp = tenofovir diphosphate
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.

4.1.1.7.2. 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 120). 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 4.1.3).

Table 120. 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

MOI = multiplicity of infection
Source: PC-164-2002

4.1.1.7.3. 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 single drug selections and one-half the EC_{50} values for the 2 drug selections to allow for adequate virus replication. As summarized in Table 121, 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 121. 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)

RT = reverse transcriptase
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 122 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 122. 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

dATP = deoxyadenosine triphosphate; K_i = kinetic inhibition constant; K_m = Michaelis-Menten constant; Pol = polymerase
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 123). 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 123. 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

3TC-TP = lamivudine 5'-triphosphate; d4T-TP = stavudine triphosphate; ddATP = dideoxyadenosine triphosphate; ddCTP = dideoxycytidine triphosphate; dNTP = 2'-deoxynucleoside triphosphate; Pol = polymerase; TFV-DP = tenofovir diphophosphate
a f inc (%) = $100 \times [V_{max}(\text{dNTP analog})/K_m(\text{dNTP analog})]/[V_{max}(\text{dNTP})/K_m(\text{dNTP})]$.
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 pol {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 (m5.3.5.4, 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 124). 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 124. TAF and TFV Antiviral Activity Against Human Viruses and SIV

Viruses	TAF (nM)		TFV[a] (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[b]	> 1000[c]	> 1000[b]	enviroxime
RSV	> 1000	> 1000	> 1000	> 1000	RBV
VZV	> 1000	> 1000	> 1000	> 1000	acyclovir
HCMV	> 1000	> 1000	> 1000	> 1000	ganciclovir
HSV-1	> 1000	> 1000	> 1000[c]	> 1000	acyclovir
HSV-2_{KW}	424	> 1000	146	> 1000	acyclovir
HSV-2_{MS}	697	> 1000	278	> 1000	acyclovir

CC_{50} = concentration resulting in 50% cytotoxicity; EC_{50} = concentration inhibiting viral replication by 50%; HCMV = human cytomegalovirus; HCV = hepatitis C virus; HSV-1/HSV-2 = herpes simplex virus type 1/type 2; RBV = ribavirin; rIFN-α = recombinant interferon α; RSV = respiratory syncytial virus; SIV = simian immunodeficiency virus; VZV = varicella zoster virus; ZDV = zidovudine

a Also referred to as GS-1278 in PC-120-2003.
b Cell growth inhibition observed at the highest concentration.
c Viral inhibition observed at the highest concentration.
Source: m5.3.5.4, PC-120-2003

4.1.2.3. EVG: Activity Against the Other HIV-1 Enzyme Reverse Transcriptase and Protease

EVG did not inhibit HIV-1 RT DNA polymerase activity in vitro up to a concentration of 50 μM, whereas ZDV-5'-triphosphate (ZDV-TP), an NRTI, inhibited RT activity with an IC_{50} value of 0.01 μM (Table 125; JTK303-PH-003). EVG did not show significant activity against HIV-1 protease (IC_{50} values of > 50 μM), while pepstatin A, an aspartic PI, inhibited activity with an IC_{50} value of 1.2 μM (Table 125; JTK303-PH-008).

Table 125. Effect of EVG Against HIV-1 Reverse Transcriptase and HIV-1 Protease

	HIV-1 RT	HIV-1 Protease
Compound	**IC_{50} (μM)[a]**	**IC_{50} (μM)**
EVG	> 50 (3.9 ± 1.4%)[b]	> 50 (29%)[b]
ZDV-TP	0.0104 ± 0.0013	—
Pepstatin A	—	1.2

a Mean ± SD from 3 separate experiments
b % inhibition at 50 μM
Source: JTK303-PH-003, JTK303-PH-008

4.1.2.4. EVG: Activity Against Other Viruses

4.1.2.4.1. Antiviral Activity Against Hepatitis B Virus

EVG was found to have no antiviral activity against HBV in stably transfected HepG2 cells in vitro (EC_{50} > 6 μM; the CC_{50} was also > 6 μM; PC-183-2024).

4.1.2.4.2. Antiviral Activity Against Hepatitis C Virus

EVG was found to have no specific antiviral activity against HCV 1b replicon in Huh-7 cells (EC_{50} = 22 μM); the EC_{50} was higher than the CC_{50} of 16 μM (PC-183-2024).

4.1.2.5. COBI: Inhibition of HIV-1 and Host Proteases

Secondary PD properties of COBI were evaluated in a number of in vitro assays in order to ensure that COBI lacked HIV, HBV, or HCV antiviral activity; and to evaluate whether COBI had the potential for reduced metabolic adverse effects frequently associated with RTV treatment (eg, lipid disorders and insulin resistance).

COBI did not exhibit HBV or HCV antiviral activity in vitro. Unlike RTV, COBI did not inhibit HIV-1 protease in vitro and showed no HIV-1 antiviral activity both in the presence and absence of HS proteins. Furthermore, COBI exhibited no effect on lipid accumulation and had a less pronounced effect on glucose uptake compared with RTV in vitro.

COBI and RTV were evaluated in an in vitro enzymatic assay for their inhibitory effect on HIV-1 protease enzymatic activity (PC-216-2001). COBI did not have any effect on the HIV-1 protease enzymatic activity at concentrations up to 30 μM. In comparison, the IC_{50} for RTV was 0.6 nM when tested in parallel under the same assay conditions. These enzyme inhibition data indicate that COBI does not bind to the active site of the HIV-1 protease and inhibit its activity.

4.1.2.6. COBI: Anti-HIV Activity in MT-2 Cells

The ARV activity of COBI was evaluated in a standard 5-day in vitro HIV-1 cytopathic assay in MT-2 cells (PC-216-2002). There was no inhibition of HIV-1 replication observed in the

presence of 30 μM COBI relative to untreated control in the absence of HS (Table 126). Under the same assay conditions, RTV inhibited HIV-1 replication with an EC_{50} of 0.0133 μM (Table 126).

As the majority of PIs bind extensively to HS proteins, the effect of HS on the ARV activity of COBI and RTV was also evaluated in MT-2 cells by determining the anti-HIV EC_{50} values in the presence of 40% HS. In addition, anti-HIV EC_{50} values in the presence of physiological concentrations of HSA (35 mg/mL) combined with AAG (1.0 mg/mL), the 2 major HS components responsible for binding of PIs, were determined. The EC_{50} values of COBI in the presence of 40% HS or HSA combined with AAG were both > 90 μM (Table 126). In the presence of HS or HSA + AAG, RTV retained significant ARV activity (EC_{50} = 60 and 400 nM, respectively), although much reduced compared with the activity without HS (Table 126). These observations are consistent with the lack of inhibition of the HIV-1 protease enzymatic activity by COBI, and indicate that, even at concentrations exceeding maximal unbound clinical exposure levels by over 300-fold (0.09 μM free COBI concentration; using a maximal plasma concentration of approximately 1.4 μM [C_{max} 1150 ng/mL]) and a fraction unbound of 6.3%, COBI does not exert any ARV activity.

Table 126. Anti-HIV Activity of COBI and RTV

	EC_{50} ± SD (μM)[a]		
Compounds	**No HS**	**40% HS**	**HSA + AAG**
COBI	> 30	> 90	> 90
RTV	0.0133 ± 0.0047	0.060 ± 0.010	0.400 ± 0.000

a Data shown represent the mean and SD from at least 2 independent experiments.
Source: PC-216-2002

4.1.2.7. COBI: Anti-HIV Activity in Peripheral Blood Mononuclear Cells

The antiviral activity of COBI was tested in PBMCs against a panel of 17 HIV-1 and 2 HIV-2 primary isolates (PC-216-2011). Different groups of HIV-1 (M, N, O), as well as the most prevalent group M (subtypes A, B, C, D, E, F, and G), were represented among the tested isolates (Table 127).

As observed in T-cell lines, there was no inhibition of HIV-1 replication in the presence of COBI. Ritonavir was used as a control and exhibited the expected level of antiviral activity across all tested isolates. The mean EC_{50} of RTV against the 17 tested HIV-1 isolates was 0.068 μM (range of 0.005 to 0.406 μM; median 0.043 μM), resulting in a mean SI of > 328. Two HIV-2 isolates were also evaluated; no selective antiviral activity of COBI was observed against the tested isolates.

Consistent with in vitro studies on the HIV-1 protease enzymatic activity, and in immortalized T-cell lines, these findings further support the conclusion that COBI is devoid of HIV antiviral activity.

Table 127. Activity of COBI and RTV Against Primary HIV Isolates in Human PBMCs

Viral Isolate				COBI			RTV		
Type	Group	Subtype	Name	EC_{50} (nM)[a]	CC_{50} (nM)	SI	EC_{50} (nM)[a]	CC_{50} (nM)	SI
HIV-1	M	A	92UG029	17,526	12,901	< 1	42.4	> 10,000	> 236
			92UG037	14,595	12,901	< 1	81.1	> 10,000	> 123
		B	93BR021	15,745	12,901	< 1	40.6	> 10,000	> 246
			JR-CSF	15,344	12,901	< 1	15.9	> 10,000	> 629
		C	92BR025	12,074	12,901	< 1	52.5	> 10,000	> 190
			93IN101	22,514	12,901	< 1	45.8	> 10,000	> 218
		D	92UG001	26,906	12,901	< 1	23.9	> 10,000	> 419
			92UG024	11,812	12,901	1.09	16.2	> 10,000	> 616
		E	93TH073	18,314	12,901	< 1	5.5	> 10,000	> 1804
			CMU08	24,028	12,901	< 1	19.7	> 10,000	> 507
		F	93BR019	14,975	> 30,000	> 2.00	73.9	> 5000	> 67.7
			93BR020	20,705	12,901	< 1	43.2	> 10,000	> 231
		G	G3	12,523	12,901	1.05	24.7	> 10,000	> 405
			JV1083	15,971	> 30,000	> 1.88	73.5	> 5000	> 68.1
	N	NA	YBF30	12,380	12,901	1.04	57.3	> 10,000	> 174
	O	NA	BCF02	23,693	12,901	< 1	406	> 10,000	> 24.6
			BCF03	14,217	12,901	< 1	136	> 10,000	> 73.4
HIV-2	NA	NA	CDC310319	6471	> 30,000	> 4.64	108	> 5000	> 46.4
			CDC310342	11,921	12,901	1.08	58.6	> 10,000	> 171

NA = not applicable; SI = selectivity index (CC_{50}/EC_{50})
a EC_{50} values were determined by HIV-1 p24 ELISA, except for HIV-1 group O and HIV-2 (activity determined by virion-associated RT assay).
Source: PC-216-2011

4.1.2.8. COBI: Anti-HIV Activity of COBI Metabolites

Preliminary identification of COBI metabolites was performed using hepatic microsomal fractions and primary hepatocytes (AD-216-2038 and AD-216-2074). The predominant metabolites identified in mouse, rat, dog, monkey, and human were denoted E1 (synthetic standard GS-342006 or GS-9454, or M21), E3 (synthetic standard GS-364751 or GS-9612, or M31), and E5 (synthetic standard GS-341842). More comprehensive metabolite identification was performed subsequently using plasma and excreta samples from mouse, rat, and human following oral administration of [^{14}C]COBI (AD-216-2073 and AD-216-2082; and GS-US-216-0111). In those studies, the notations for E1, E3, and E5 were M21, M31, and M26,

respectively; this numbering system is used below, and in other text and tabulated summaries. No unique human metabolites were identified in GS-US-216-0111.

Authentic standards of M21 (GS-9454), M31 (GS-9612), and M26 (GS-341842) were tested for their ARV activity in a standard 5-day HIV-1 cytopathic assay in MT-2 cells (EC_{50} as described in Section 4.1.2.6; PC-216-2002). None of the tested metabolites were found to have HIV-1 antiviral activity, up to a concentration of 30 μM (Table 128).

Table 128. Antiviral Activity of COBI Metabolites Identified In Vitro

Compounds	HIV Antiviral Activity EC_{50} (μM)[a]
COBI	> 30
GS-9454 (M21)	> 30
GS-9612 (M31)	> 30
GS-341842 (M26)	> 30

a Data shown represent the mean from at least 2 independent experiments.
Source: PC-216-2002

4.1.2.9. COBI: Activity Against Other Viruses

The anti-HBV activity of COBI was tested in WT-42 cells, a clone of HepG2 cells stably transfected with wild-type HBV (PC-216-2006). In contrast to TFV, a compound with demonstrated anti-HBV activity {8381}, COBI had no antiviral activity against HBV or cytotoxicity at the tested concentrations up to 12.5 μM (Table 129). As expected, TFV showed potent antiviral activity in this assay (EC_{50} = 0.63 μM).

Table 129. Anti-HBV Activity of COBI in WT-42 Cells

Compounds	EC_{50} ± SD (μM)[a]	CC_{50} ± SD (μM)[a]
COBI	> 12.5	> 12.5
TFV	0.63 ± 0.02	> 50

Source: PC-216-2006

The anti-HCV activity of COBI was tested in Huh-Luc cells, a clone of Huh-7, which stably replicates a subgenomic HCV genotype 1b replicon encoding a luciferase reporter gene (PC-216-2006). No anti-HCV activity or cytotoxicity was detected after a 3-day treatment with COBI at concentrations up to 30 μM (Table 130). Boehringer-Ingelheim's investigational PI BILN-2061 (ciluprevir) was tested as an experimental control in the same assay and exhibited the expected antiviral activity {5838}, with an EC_{50} of 0.6 nM.

Table 130. Anti-HCV Activity and Cytotoxicity of COBI in Huh-Luc Replicon Cells

Compounds	EC_{50} ± SD (μM)[a]	CC_{50} ± SD (μM)[a]
COBI	> 30	> 30
BILN-2061	0.0006 ± 0.0001	> 30

a Data shown represent the mean and SD from at least 2 independent experiments.
Source: PC-216-2006

4.1.2.10. FTC: Anti-Hepatitis B Virus Activity

4.1.2.10.1. 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 131) {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 131).

Table 131. 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.

4.1.2.10.2. 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 anti-tumor 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 (WHcAg) 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: 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 (m5.3.5.4, 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 with itself 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 scores from 41 to 131) when combined with any of the N(t)RTIs or NNRTIs (Table 132). The combination of TAF with INSTIs resulted in the highest level of synergy (synergy scores of 271, 205, and 179 for EVG, RAL, and dolutegravir [DTG], respectively). The combination of TAF with PIs resulted in moderate synergy (synergy scores of 96 and 56 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 132. 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

ATV = atazanavir; d4T = stavudine; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; NVP = nevirapine; RAL = raltegravir; RBV = ribavirin

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.

4.1.3.2. EVG: Drug Interactions

4.1.3.2.1. EVG in Combination with the Pharmacoenhancers COBI or RTV

The effect of COBI on EVG antiviral activity was investigated in a 5-day HIV-1 antiviral assay in MT-2 cells (PC-216-2005). The EC_{50} of EVG was 1.4 nM and was similar to historical values when determined in the absence of COBI, and was unchanged in the presence of 5 μM COBI (1.5 nM). These results are consistent with the lack of HIV-1 antiviral activity of COBI (Sections 4.1.2.5, 4.1.2.6, and 4.1.2.7). Therefore, the combination of EVG and COBI did not show any antagonism on the anti-HIV-1 activity of EVG.

Ritonavir is an inhibitor of HIV-1 protease and has also been used as a pharmacoenhancer of several HIV ARVs. The anti-HIV-1 activity of EVG in combination with RTV was further evaluated in HIV-1_{IIIB} infected MT-2 cells using the Prichard and Shipman MacSynergy II 3-dimensional model for statistical evaluation of combination anti-HIV assays. Results from this 2-drug combination study are presented in Table 133 (PC-183-2006). Viral growth/inhibition was evaluated by measuring virus-induced cytopathic effects at the experimental endpoint. The antiviral combination of EVG with RTV showed minor synergy and no evidence of antagonism.

4.1.3.2.2. Two-Drug Anti-HIV Activity Studies of EVG in Combination with Other Anti-HIV Drugs

The anti-HIV-1 activity of EVG in combination with a broad panel of representatives from all classes of approved anti-HIV agents (NRTIs, NNRTIs, PIs, fusion inhibitor, entry inhibitors, and INSTIs) was evaluated in HIV-1_{IIIB} infected MT-2 cells, or HIV-1_{Ba-L} infected PM-1 cells. Results from the 2-drug combination studies are presented in Table 133 (PC-183-2004, PC-183-2006, and PC-183-2017). This study was performed using the Prichard and Shipman MacSynergy II 3-dimensional model for statistical evaluation of combination anti-HIV assays {4177} or by the combination index method using CalcuSyn software. Viral growth/inhibition was evaluated by measuring virus-induced cytopathic effects at the experimental endpoint.

As summarized in Table 133, the antiviral activity of EVG with ARV drugs in 2-drug combination studies was not antagonistic when combined with the NRTIs ABC, ddI, FTC, 3TC, d4T, TFV, or ZDV; the NNRTIs EFV, etravirine (ETV), or NVP; the PIs APV, ATV, DRV, IDV, LPV, NFV, RTV, SQV, or TPV; the fusion inhibitor T-20; the CCR5 coreceptor antagonist maraviroc (MVC), or the INSTI RAL. For all these combinations, additive to synergistic anti-HIV activity was observed.

There was no evidence of synergistic cytotoxicity within the drug concentrations examined for EVG. Although not unexpected, because none of the drugs are cytotoxic within the concentration ranges evaluated, it is worthwhile to note that no synergistic cytotoxicities were observed at concentrations where the drugs display potent antiviral activities.

Table 133. Two-Drug Combination Anti-HIV Activity of EVG with Other Anti-HIV Antiretroviral Compounds

Drug Combination	Cell Type	Volume ($\mu M^2\%$)[a]		Combined Effect[b]	Report No.
		Synergy	Antagonism		
EVG + Nucleoside Reverse Transcriptase Inhibitors (NRTIs)					
EVG + ABC	MT-2	17.6 ± 14.0	-17.9 ± 12.8	Additive	PC-183-2006
EVG + ddI	MT-2	66.0 ± 73.6	-3.5 ± 4.4	Moderate Synergy	PC-183-2006
EVG + FTC	MT-2	167.5	-7.84	Strong Synergy	PC-183-2004
	MT-2	80.1 ± 58.6	-7.0 ± 4.5	Moderate Synergy	PC-183-2006
EVG + 3TC					
	MT-2	52.7 ± 47.9	-4.6 ± 23.6	Moderate Synergy	PC-183-2006
EVG + d4T	MT-2	12.1 ± 15.7	-6.5 ± 3.9	Additive	PC-183-2006
EVG + TFV					
	MT-2	133.2	-4.0	Strong Synergy	PC-183-2004
	MT-2	61.5 ± 49.1	-2.2 ± 3.6	Moderate Synergy	PC-183-2006
EVG + ZDV					
	MT-2	59.4 ± 64.5	-3.1 ± 6.1	Moderate Synergy	PC-183-2006
EVG + Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
EVG + EFV					
	MT-2	80.3 ± 46.4	-3.9 ± 5.0	Moderate Synergy	PC-183-2006
EVG + ETV	MT-2	35.9 ± 27.0	-16.0 ± 15.2	Minor Synergy	PC-183-2006
EVG + NVP	MT-2	63.3 ± 20.0	-22.1 ± 20.5	Moderate Synergy	PC-183-2006
EVG + Protease Inhibitors (PIs)					
EVG + APV	MT-2	29.3 ± 10.2	-13.3 ± 2.0	Minor Synergy	PC-183-2006
EVG + ATV	MT-2	32.2 ± 6.6	-13.9 ± 14.2	Minor Synergy	PC-183-2006
EVG + DRV	MT-2	49.0 ± 8.9	-1.6 ± 2.7	Minor Synergy	PC-183-2006
EVG + IDV					
	MT-2	31.7 ± 9.1	-7.7 ± 5.4	Minor Synergy	PC-183-2006
EVG + LPV	MT-2	29.3 ± 30.2	-18.2 ± 14.4	Minor Synergy	PC-183-2006
EVG + NFV					
	MT-2	33.1 ± 7.6	-1.9 ± 5.9	Minor Synergy	PC-183-2006
EVG + RTV	MT-2	35.7 ± 43.2	-4.8 ± 7.2	Minor Synergy	PC-183-2006
EVG + SQV	MT-2	15.1 ± 14.3	-11.4 ± 10.3	Additive	PC-183-2006
EVG + TPV	MT-2	23.2 ± 20.4	-6.5 ± 6.9	Additive	PC-183-2006

Drug Combination	Cell Type	Volume ($\mu M^2\%$)[a]		Combined Effect[b]	Report No.
		Synergy	Antagonism		
EVG + Fusion or Entry Inhibitor					
EVG + T-20	MT-2	26.3 ±14.5	-2.6 ± 3.3	Minor Synergy	PC-183-2006
EVG + MVC	PM-1	7.8 ± 15.1	-2.6 ± 3.3	Additive	PC-183-2017
EVG + Integrase Inhibitor					
EVG + RAL	MT-2	9.0 ± 5.9	-19.7 ± 12.8	Additive	PC-183-2006
Antagonism and Synergy Controls					
EVG + EVG	MT-2	14.5 ± 14.2	-2.3 ± 2.9	Additive	PC-183-2006
TFV + FTC	MT-2	114.9	-0.5	Strong Synergy	PC-183-2004
d4T + RBV	MT-2	37.1	-468.8	Strong Antagonism	PC-183-2004
	MT-2	13.2 ± 27.8	-481 ± 197	Strong Antagonism	PC-183-2006
	PM-1	0.2 ± 0.4	-180 ± 92.6	Strong Antagonism	PC-183-2017

a Synergy/antagonism volumes were calculated at the 95% CI with the MacSynergy II™ program. Synergy/antagonism volumes represent the mean and SD of at least 3 independent experiments.

b The combined effect was determined by the mean synergy and antagonism volumes. As defined by the MacSynergy II program, volumes of < 25 $\mu M^2\%$ indicate insignificant synergy (additive); ≥ 25 and < 50 $\mu M^2\%$ indicate minor synergy/antagonism; ≥ 50 and < 100 $\mu M^2\%$ indicate moderate synergy/antagonism; and ≥ 100 $\mu M^2\%$ indicate strong synergy/antagonism. The combined effect terms from PC-183-2004 and PC-183-2006 were updated using these definitions.

Source: PC-183-2004, PC-183-2006, and PC-183-2017

4.1.3.2.3. Antiviral Activity of EVG in the Presence of Anti-HBV Drugs

The anti-HIV activity of EVG was evaluated in the presence of approved anti-HBV drugs in a 5-day cytopathic assay in MT-2 cells infected with HIV-1_{IIIB} using the MacSynergy method (PC-183-2023; Table 134). The HIV-1 antiviral activity of EVG with anti-HBV drugs in 2-drug combination studies was not antagonistic when combined with adefovir, clevudine, entecavir, or telbivudine. For all these combinations, additive to synergistic anti-HIV activity was observed.

Table 134. Two-Drug Combination Anti-HIV Activity of EVG with Other Anti-HBV Antiretroviral Compounds

MacSynergy Analysis[a]					
			Volume ($\mu M^2\%$)[a]		
Drug Combination	Conc. of Second Drug[b]	Cell Type	Synergy	Antagonism	Combined Effect[b]
EVG + Adefovir	8 × EC_{50}	MT-2	44.1 ± 10.8	-4.1 ± 4.05	Minor Synergy
EVG + Clevudine	8 × EC_{50}	MT-2	7.9 ± 10.9	-21.6 ± 2.5	Additive
	10 μM	MT-2	5.6	-2.01	Additive
EVG + Entecavir	8 × EC_{50}	MT-2	14.8 ± 22.6	-10.0 ± 16.8	Additive
	5 μM	MT-2	76.7 ± 56.2	-4.8 ± 8.0	Moderate Synergy
EVG + Telbivudine	8 × EC_{50}	MT-2	15.2 ± 9.1	-12.3 ± 8.3	Additive

a Synergy/antagonism volumes were calculated at the 95% CI with the MacSynergy II program. Synergy/antagonism volumes represent the mean and SD of at least 3 independent experiments.

b The combined effect is determined by the mean synergy and antagonism volumes. As defined by the MacSynergy II program, volumes of < 25 $\mu M^2\%$ indicate insignificant synergy (additive); ≥ 25 and < 50 $\mu M^2\%$ indicate minor synergy/antagonism; ≥ 50 and < 100 $\mu M^2\%$ indicate moderate synergy/antagonism; and ≥ 100 $\mu M^2\%$ indicate strong synergy/antagonism. The combined effect terms from PC-183-2004 and PC-183-2006 were updated using these definitions.

Source: PC-183-2023

4.1.3.3. COBI: Drug Interactions

The potential for DDIs with clinically approved or investigational ARV drugs was evaluated, as COBI is proposed to be coadministered with some of these agents. The selected HIV drugs included several representatives of each class, namely NRTI/NtRTIs (TFV, FTC, ABC, 3TC, ZDV); NNRTIs (EFV, NVP); INSTIs (RAL, EVG); and PIs (ATV, DRV).

Drugs were tested in MT-2 cells infected with HIV-1 (as described in Section 4.1.2.6), in the presence or absence of 5 μM COBI, and the fold change of EC_{50} value for each drug in the presence of COBI was calculated (PC-216-2005). In the absence of COBI, the expected range of ARV activities was observed for all tested ARVs (Table 135). Overall, no significant changes were observed in the activity of any of the tested ARVs in the presence of 5 μM COBI, as the minimum and maximum fold change with all drugs tested was 0.7 and 1.9, respectively.

Table 135. Antiviral Activity of Several Antiretroviral Drugs in the Presence of COBI

Drug	Class	EC_{50} ± SD (nM)[a] Without COBI	Fold Change in EC_{50} ± SD[a] with 5 μM COBI
3TC	NRTI	5117 ± 1147	1.0 ± 0.7
ABC	NRTI	927 ± 79	1.5 ± 1.1
FTC	NRTI	903 ± 359	1.9 ± 0.3
TFV	NRTI	5467 ± 661	1.0 ± 0.5
ZDV	NRTI	82 ± 52	1.7 ± 0.4
EFV	NNRTI	0.5 ± 0.4	1.0 ± 0.0
NVP	NNRTI	44 ± 18	1.1 ± 0.3
ATV	PI	8.8 ± 3.3	0.9 ± 0.8
DRV	PI	8.1 ± 5.0	0.7 ± 0.6
EVG	INSTI	1.4 ± 1.4	1.1 ± 0.2
RAL	INSTI	5.6 ± 2.9	1.3 ± 0.3

a Data shown represent the mean and SD from 3 independent experiments.
Source: PC-216-2005

4.1.3.4. FTC: 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 136.

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 136. Synergistic Activity of FTC with Other Antiretroviral Agents

Compounds	Class	Cell line	HIV Strain	Results	References
DLV	NNRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
EFV	NNRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
Emivirine	NNRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
NVP	NNRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
ABC	NRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
Adefovir	NRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
Amdoxovir	NRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
ddI	NRTI	MT-4	IIIB	Strongly Synergistic	{4541}
ddI	NRTI	MT-2	IIIB	Additive	{4543}
ddI	NRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
EVG	INSTI	MT-2	IIIB	Synergistic	(Report No. 183-2004)
3TC	NRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
RPV	NNRTI	MT-2	IIIB	Strongly Synergistic	(Report No. PC-264-2001)
d4T	NRTI	MT-2	IIIB	Additive	{4543}
d4T	NRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
ddC	NRTI	MT-4	IIIB	Strongly Synergistic	{4541}
ddC	NRTI	MT-2	IIIB	Additive	{4543}
ZDV	NRTI	MT-4	IIIB	Strongly Synergistic	{4541}
ZDV	NRTI	MT-2	IIIB	Additive	{4543}
ZDV	NRTI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
APV	PI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
IDV	PI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
NFV	PI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)
RTV	PI	MT-2	LAI	Additive to Synergistic	(Report No. 470), (Report No. 10804)

Source: 470; 10804; PC-183-2004; PC-264-2001

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 2.3.1.1]). 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. EVG

EVG showed potent inhibitory activity against the DNA strand-transfer reaction with an IC_{50} value of 8.8 nM. This IC_{50} value was similar to that for the overall integration reaction (5.3 nM), and therefore EVG is a specific strand-transfer inhibitor. EVG inhibited the integration of HIV-1 DNA into the host chromosomal DNA in HIV-1 infected MT-4 cells using an Alu-PCR assay at 18 hours after infection (94.6% reduction at 10 nM) and caused a dose-dependent increase in the accumulation of 2-LTR circles (5-fold for 10 nM EVG). The association and dissociation kinetics of EVG and RAL to IN were similar, and both had slow dissociation rates. EVG at 10 nM had no effect on the generation of full-length viral DNA synthesized by RT. Similar findings were observed for EVG in HIV-1 infected SupT1 cells, where EVG did not inhibit the production of full-length viral DNA but inhibited the integration of viral DNA with an EC_{50} of 0.3 nM. EVG lacks activity against other HIV-1 enzymes; EVG up to a concentration of 50 μM did not specifically inhibit HIV-1 RT DNA polymerase activity or HIV-1 protease activity in vitro.

EVG inhibited laboratory strains and various clinical isolates (wild-type and drug-resistant clones) of HIV-1 with a median EC_{50} value of 0.38 nM (range 0.02 to 1.3 nM) in human PBMCs in vitro. The EVG CC_{50} under the same conditions was 170 μM (SI of > 100,000). There was no difference in the cytotoxicity of EVG in stimulated versus unstimulated PBMCs. EVG showed activity against multiple subtypes of HIV-1 and HIV-2. EVG showed broad anti-HIV activity

against HIV-1 subtypes A, B, C, D, E, F, G, and O with average EC_{50} values ranging from 0.1 to 1.26 nM in PBMCs, and HIV-2 with an EC_{50} of 0.53 nM.

EVG showed an EC_{50} value of 0.38 nM against the laboratory strain HIV-1_{NL4-3} in MT-4 cells. The SI (CC_{50}/EC_{50}) for EVG was > 14,000. Against HIV-1_{IIIB}, EVG showed EC_{50} values of 0.17 nM in MT-4 cells and 0.6 nM in MT-2 cells. The overall mean EC_{50} for wild-type HIV-1 in cell lines was 0.38 nM.

Anti-HIV activity of EVG was moderately reduced with the addition of 50% HS to the culture medium, resulting in an increase in the EC_{90} value to 9.8 nM (4.4 ng/mL). Consistent with the protein shift in the activity assay, EVG showed decreased cytotoxicity in PBMC cultures in the presence of 50% HS (CC_{50} values of 9.7 and 170 μM without and with 50% HS, respectively). EVG showed potent dose-dependent anti-HIV-1 activity in the absence of human plasma components in MT-4 cells, with an EC_{50} value of 1.7 nM. The EC_{95} value for EVG in the presence of the HS components HSA and AAG was 100 nM (44.8 ng/mL) in HIV-1 infected human PBMC cultures, representing an 80-fold loss in antiviral activity.

In vitro resistance selection experiments with EVG demonstrated that EVG can select 3 primary resistance mutations in HIV-1 IN, the T66I, E92Q, and Q148R mutations. The T66I, E92Q, and Q148R mutations resulted in HIV-1 that had 15-, 36-, and 109-fold reduced susceptibility to EVG, respectively. Additional secondary IN mutations, including H51Y, F121Y, S147G, S153Y, E157Q, and R263K, were also selected by EVG and further decreased susceptibility to EVG when added to either the T66I or E92Q mutations. In the enzymatic activity assays, IN with INSTI-R mutations show decreased activity compared with wild type. Decreased replication capacity of HIV-1 with INSTI-R mutations is also observed in subjects with virologic failure and INSTI mutations in vivo.

Antiviral susceptibility to EVG and to 16 approved anti-HIV drugs was evaluated for 120 subject-derived recombinant clones resistant to NRTIs, NNRTIs, and PIs. EVG showed potent inhibitory activity against 120 recombinant clones with a mean EC_{50} value of 1.06 nM, comparable with the EC_{50} value of EVG on the wild-type reference clone NL4-3 (1.11 nM). In addition, EVG showed full activity against a panel of site-directed recombinant viruses and a panel of primary clinical isolates showing resistance to NRTIs, NNRTIs, and PIs.

The combination antiviral activity of EVG with other anti-HIV drugs did not show any antagonism. In contrast, EVG exhibited additive to synergistic interactions with the NRTIs FTC, TFV, FTC/TDF, ZDV, 3TC, 3TC/ZDV, ABC, ddI, and d4T; the NNRTIs EFV, NVP, and ETV; and the PIs ATV, LPV, NFV, IDV, RTV, TPV, and DRV. In vitro combination assays with the fusion inhibitor T-20, the IN inhibitor RAL, and the entry inhibitor MVC demonstrated additive interactions with EVG. The antiviral activity of EVG in combination with TFV and FTC was synergistic, and the same level of synergy was observed in the presence of the pharmacoenhancer COBI.

EVG had no detectable activity against human HBV or HCV. When EVG was combined with a panel of inhibitors of HBV, there was no antagonism in the anti-HIV activity of EVG.

In a clinical study in which subjects were dosed orally with [^{14}C]EVG and RTV, the parent compound was the most abundant radiolabeled component in plasma. The predominant human metabolites identified in vitro and in vivo were M1 (hydroxylation of the chlorofluorophenyl group, GS-9202, 0%–1%), M4 (glucuronide conjugate of the carboxylic acid, GS-9200, 3.5%), and M7 (glucuronide conjugate of M1, JTP-74488, < 1%). In a rabbit microsomal fraction fortified with the cofactor for sulfation, HM1 (sulfate conjugate of M1, JTP-74492) was also detected. Using a recombinant wild-type HIV-1 IN, EVG showed potent inhibition of DNA strand transfer with an IC_{50} of 7.4 nM. All 4 human metabolites of EVG inhibited the strand-transfer reaction with lower potency than the parent drug, EVG. Of the 4 EVG metabolites, GS-9202 (M1) retained highest inhibitory potency against HIV-1 IN with an IC_{50} of 38.8 nM (5.2-fold decrease in potency) and other metabolites had potencies 38- to 426-fold less than the parent drug. The effects of GS-9202 (M1) and GS-9200 (M4) on replication of wild-type HIV-1_{IIIB} was evaluated in MT-2 cells and showed 9.3- and 6.7-fold less potency than the parent drug EVG, respectively.

The HIV-1 IN mutations selected by GS-9202 (M1) and GS-9200 (M4) were similar to those previously selected in vitro by the parent molecule, EVG, and were the T66I, E92Q, and S153Y mutations. The mutations selected by GS-9200 (M4) also produced similar reductions in susceptibility to both GS-9200 (M4) and EVG when selected viral pools were analyzed phenotypically. The results indicate that the resistance profile of EVG and its M1 and M4 metabolites are overlapping and that mutations selected by either EVG, GS-9202, or GS-9200 (M4) will affect both compounds to a similar degree. EVG itself is the dominant plasma species among EVG and its metabolic products; therefore, INSTI-R mutations selected by EVG itself will likely predominate if virologic failure occurs on boosted EVG.

4.1.4.3. COBI

The potential for pharmacologic DDIs with COBI was evaluated and showed that none of the tested ARV drugs had its EC_{50} significantly changed in the presence of supratherapeutic levels of COBI (> 50-fold over unbound clinical concentrations), making COBI suitable for coadministration with the tested drugs from all major classes of ARVs. In addition, the 3 most prevalent human metabolites of COBI were also shown to be inactive in the HIV-1 antiviral assay. Finally, COBI lacks in vitro antiviral activity against hepatitis viruses, HBV and HCV, indicating that it would be suitable for ARV PK boosting in HIV-infected patients coinfected with HBV and/or HCV.

4.1.4.4. 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.

4.1.4.5. 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). An integrated virology analysis was performed for HIV-infected subjects with clinical virology data from 1 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, and GS-US-292-0106. Genotyping of PR/RT only was performed at screening for all subjects enrolled in Study GS-US-292-0102. For all subjects in Study GS-US-292-0109 and select subjects in 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 137.

Table 137. Resistance Mutations by Antiretroviral Class

Resistance Mutations[a]		
Drug Class	**Codon Mutations**	
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	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	
Thymidine Analogue Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F[b], K219Q/N/E/R	
Nucleoside-Associated Mutations (NAMs)	TAMs plus E44D[c], K65R, T69D/N[c], K70E, L74V/I, Y115F, V118I[c], M184V/I	
Multi-NRTI Resistance Mutations	Q151M Complex: A62V, V75I, F77L, F116Y, Q151M	
Multi-NRTI Resistance Mutations	T69 Insertion Complex: T69S-SS, -SA, -SG, or others	
Nonnucleoside Reverse Transcriptase Inhibitors (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	
Protease Inhibitors (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
Entry Inhibitors	—	G36D/S, I37V, V38A/E/M, Q39R, Q40H, N42T, N43D
Integrase Strand Transfer Inhibitors (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 Adapted from the current International Antiviral Society-USA (IAS-USA) Guidelines lists with some modifications.
b 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.
c 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.
d Primary and secondary IN mutations observed in clinical studies of INSTIs.

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 (m5.3.5.4, 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 can be found in the Virology Study Report (m5.3.5.4, 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. GS-US-292-0104

4.2.1.1.1. 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 the E/C/F/TAF FDC compared with the STB STR in HIV-infected, ART-naive adults.

4.2.1.1.2. 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 138). 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 138).

Table 138. 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)

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
a Drug resistance mutations are defined in Table 137.
b In the E/C/F/TAF group, 3 subjects (Subjects *AC , *AD , and *AE) were IN assay failures. One subject (Subject *AD) was a PR/RT assay failure.
c In the STB group, 2 subjects (Subjects *AF and *AG) were IN assay failures.
Source: m5.3.5.4, PC-120-2020: GS-US-292-0104 Virology Listings 1 and 2

4.2.1.1.3. 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 53, Table 139; results for individual subjects are presented in Table 140).

All 5 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48, with ongoing analysis for 1 subject (Subject *AH). 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, with ongoing analysis for 1 subject (Subject *AJ). Two subjects (Subjects *AK and *AL) 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.

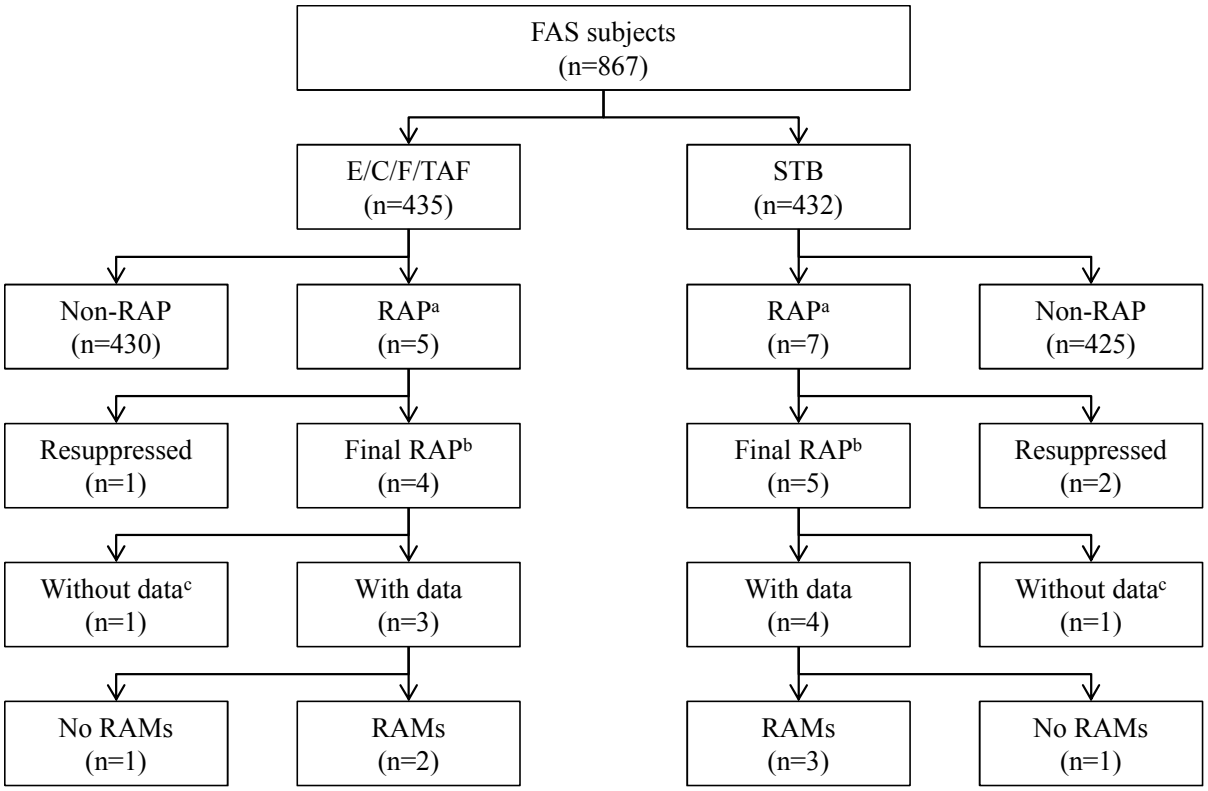
Final Resistance Analysis Population

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 3 subjects with available data included in the Final RAP, 2 had resistance mutations emerge while on E/C/F/TAF and 1 had no emergent resistance. Subject *AM 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 *AN 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 *AO did not have emergent resistance to any study drug at Week 48.

In the STB group, of the 4 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 had no genotypic or phenotypic resistance to FTC and TFV; and IN assay failure.

Figure 53. GS-US-292-0104: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



FAS = full analysis set; RAM = resistance-associated mutation; RAP = resistance analysis population
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: m5.3.5.4, PC-120-2020: GS-US-292-0104 Virology Listings 3 and 4; m5.3.5.1, GS-US-292-0104, Appendix 16.2, Listing 16.1

Table 139. 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[c]	3 (0.7)	6 (1.4)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	1 (0.2)	2 (0.5)	
Final RAP[d]	4 (0.9)	5 (1.2)	0.75
Subjects with Data[c]	3 (0.7)	4 (0.9)	
Developed Resistance Mutations to Study Drugs	2 (0.5)	3 (0.7)	0.69
No Resistance Mutations Observed	1 (0.2)	1 (0.2)	
Developed Any NRTI-R	2 (0.5)	3 (0.7)	
E44D	0	1 (0.2)	
K65R	1 (0.2)	1 (0.2)	
M184V	2 (0.5)	3 (0.7)	
Developed Any INSTI-R	2 (0.5)	2 (0.5)	
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	1 (0.2)	
E138K	0	1 (0.2)	
Developed Any NNRTI-R	0	0	
Developed Any Primary PI-R	0	1 (0.2)	
V32I	0	1 (0.2)	

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistant; RAP = resistance analysis population

a Drug resistance mutations are defined in Table 137.

b Fisher exact test comparing the proportions in each group using the whole population as the denominator.

c Subjects *AH (E/C/F/TAF group) and *AJ (STB group) have pending data.

d Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.

Source: m5.3.5.4, PC-120-2020: GS-US-292-0104 Virology Listings 3 and 4; m5.3.5.1, GS-US-292-0104, Appendix 16.2, Listing 16.1

Table 140. 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 (Fold Change 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
*AN	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
*AM	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
*AH	E/C/F/TAF	138000	B	ESDD	Data pending				
*AJ	STB	62800	B	ESDD	Data pending				
*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
*AK[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
*AL[d]	STB	17200	B	Week 16	None	S24N	0.66	0.98	2.0
*AS	STB	647000	AG	Week 36	None	AF	0.95	1.1	AF

* = stop codon; AF = assay failure; BL = baseline; ESDD = early study drug discontinuation; IN = integrase; RT = reverse transcriptase; WT = wild-type

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: m5.3.5.4, PC-120-2020: GS-US-292-0104 Virology Listings 3 and 4; m5.3.5.1, GS-US-292-0104, Appendix 16.2, Listing 16.1

4.2.1.1.4. 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, with data available for 3 and 4 subjects, respectively. Two subjects (0.5%) from the E/C/F/TAF group showed emergence of resistance to study drugs while 3 subjects (0.7%) from the STB group showed emergence of resistance to study drugs. All 5 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.

4.2.1.2. GS-US-292-0111

4.2.1.2.1. 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 the E/C/F/TAF FDC compared with the STB STR in HIV-infected, ART-naive adults.

4.2.1.2.2. 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 141). 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 141).

Table 141. 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)

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
a Drug resistance mutations are defined in Table 137.
Source: m5.3.5.4, PC-120-2020: GS-US-292-0111 Virology Listings 1 and 2

4.2.1.2.3. 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%) subjects in the STB group analyzed (Figure 54, Table 142; results for individual subjects are presented Table 143).

All 11 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48, with ongoing analyses for 3 subjects (Subjects *AT , *AU , and *AV). Subject *AW 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, with ongoing analysis for 1 subject (Subject *AX). Three subjects (Subjects *AY , *AZ , and *BA) 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 *AY and *BA) had no genotypic or phenotypic resistance to any study drug, and 1 subject (Subject *AZ) had PR/RT and IN assay failure.

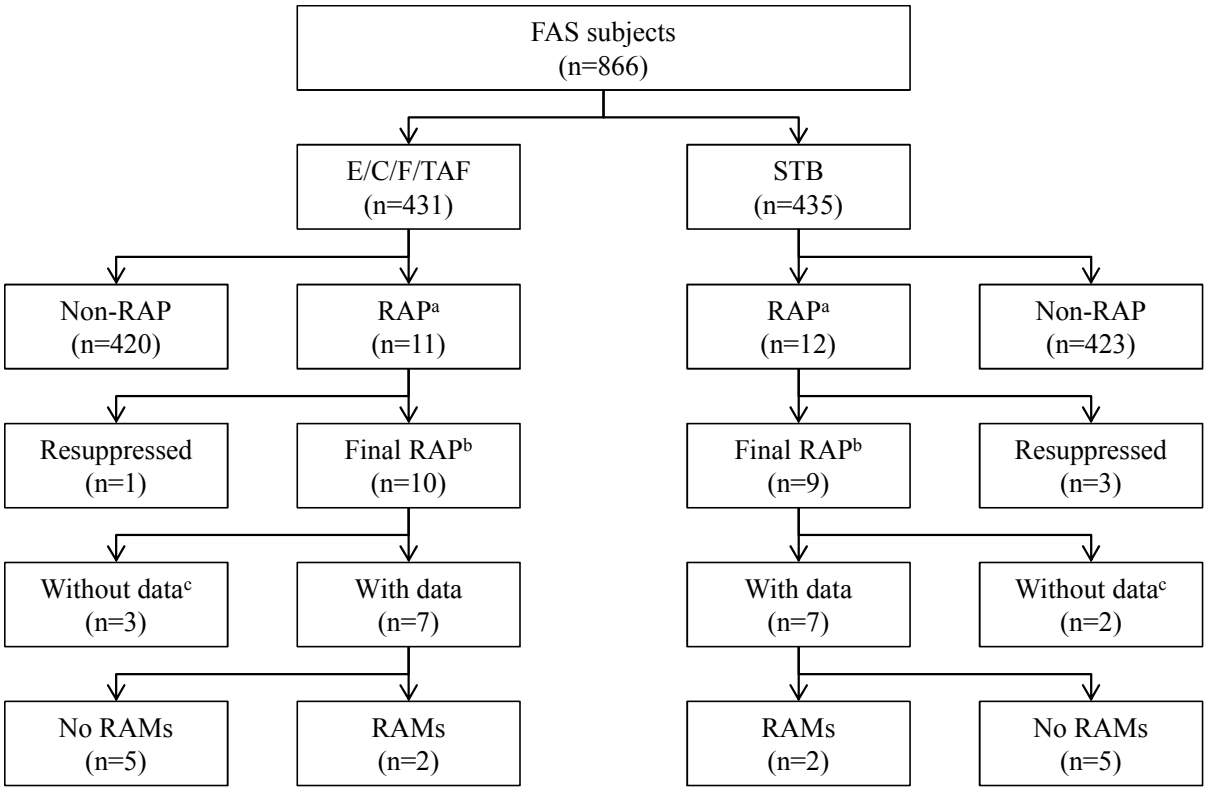
Final Resistance Analysis Population

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 7 subjects with available data included in the Final RAP, 2 subjects had resistance mutations emerge while on E/C/F/TAF. Subject *BB 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 *BC developed genotypic and phenotypic resistance to both FTC (M184V; FTC FC > 89) and EVG (T66A; EVG FC = 12.3). For the remaining 5 subjects with data in the Final RAP, no genotypic or phenotypic resistance to any study drug was observed.

In the STB group, of the 7 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 *BD 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 *BE developed genotypic and phenotypic resistance to FTC (M184V; FTC FC > 64). For the remaining 5 subjects, no genotypic or phenotypic resistance to any study drug was observed.

Figure 54. GS-US-292-0111: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



FAS = full analysis set; RAM = resistance-associated mutation; RAP = resistance analysis population
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: m5.3.5.4, PC-120-2020: GS-US-292-0111 Virology Listings 3 and 4; m5.3.5.1, GS-US-292-0111, Appendix 16.2, Listing 16.1

Table 142. 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	7 (1.6)	9 (2.1)	
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[d]	7 (1.6)	7 (1.6)	
Developed Resistance Mutations to Study Drugs	2 (0.5)	2 (0.5)	1.0
No Resistance Mutations Observed	5 (1.2)	5 (1.1)	
Developed Any NRTI-R	2 (0.5)	2 (0.5)	
K65R	0	1 (0.2)	
M184V	2 (0.5)	2 (0.5)	
Developed Any INSTI-R	2 (0.5)	1 (0.2)	
Primary INSTI-R	2 (0.5)	1 (0.2)	
T66I/A	1 (0.2)	0	
E92Q	1 (0.2)	0	
Q148R	0	1 (0.2)	
Secondary INSTI-R	1 (0.2)	1 (0.2)	
L68V	1 (0.2)	0	
E138K	0	1 (0.2)	
Developed Any NNRTI-R	0	0	
Developed Any Primary PI-R	0	0	

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistant; RAP = resistance analysis population

a Drug resistance mutations are defined in Table 137.

b Fisher exact test comparing the proportions 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.

d Subjects *AT , *AU , and *AV in the E/C/F/TAF group and Subject *AX in the STB group have pending data

Source: m5.3.5.4, PC-120-2020: GS-US-292-0111 Virology Listings 3 and 4; m5.3.5.1, GS-US-292-0111, Appendix 16.2, Listing 16.1

Table 143. 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
*AT	E/C/F/TAF	115000	B	Week 16	Data pending				
*BB	E/C/F/TAF	384000	B	Week 24	P170P/L, V179V/I, **M184V**	L68V, **E92Q**	0.49	> 84	AF
*AU	E/C/F/TAF	1610000	B	Week 12	Data pending				
*BF	E/C/F/TAF	150000	B	Week 36	W71P, T139T/A, E204E/K	AF	0.98	1.3	AF
*BC	E/C/F/TAF	463000	B	Week 16	**M184V**, H208Y, E248K	**T66A**	0.48	> 89	12.3
*BG	E/C/F/TAF	8120	B	Week 48	V276V/I	A21A/T	0.96	0.95	1.6
*BH	E/C/F/TAF	36800	B	Week 36	None	I208I/L	0.79	0.99	1.1
*AW$_d$	E/C/F/TAF	31700	B	Week 16	AF	AF	AF	AF	AF
*AV	E/C/F/TAF	9470	B	Week 24	Data pending				
*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, V245E, G273G/E, R277K, V292I, E297A	AF	0.87	1.1	AF
*AY$_d$	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
*BD	STB	239000	B	Week 36	**K65R**, I135M, **M184V**	E138K, **Q148R**	1.3	> 82	> 95

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
*BE	STB	88300	B	Week 48	**M184V**	None	0.42	> 64	1.9
*AX	STB	51000	B	Week 48	Data pending				
*BL	STB	130000	B	Retest	None	ND	0.95	1.2	ND
*BM	STB	8420	B	Week 36	AF	AF	AF	AF	AF
*BN	STB	87800	B	Week 48	None	S17S/N, V31V/I, L101L/I, K127K/R, L172L/F, I208I/L, K211R, T218T/S, S230S/N	0.91	1.1	1.1
*AZ[d]	STB	1650000	B	Week 36	AF	AF	AF	AF	AF
*BO	STB	94100	B	Week 24	None	None	0.81	1.1	1.7
*BP	STB	42100	B	Week 48	None	None	0.89	0.98	AF
*BA[d]	STB	1910	B	Week 36	K238K/R	T112T/I	0.85	1.1	1.0

AF = assay failure; BL = baseline; IN = integrase; ND = not done; RT = reverse transcriptase; WT = wild-type
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: m5.3.5.4, PC-120-2020: GS-US-292-0111 Virology Listings 3 and 4; m5.3.5.1, GS-US-292-0111, Appendix 16.2, Listing 16.1

4.2.1.2.4. 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, with data available for 7 subjects from each group. Two subjects (0.5%) 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 3 of 4 subjects (2 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.

4.2.1.3. GS-US-292-0102

4.2.1.3.1. 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 the E/C/F/TAF FDC compared with the STB STR in HIV-infected, ART-naive adult subjects.

4.2.1.3.2. 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 144).

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 144).

Table 144. GS-US-292-0102: Summary of Pretreatment HIV-1 Subtype and PR and RT Resistance Mutations Detected

	Number of Subjects n (%)		
HIV-1 Subtype and Mutation Class[a]	**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)

NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
a Drug resistance mutations are defined in Table 137.
Source: m5.3.5.4, PC-120-2020: GS-US-292-0102 Virology Listing 1

4.2.1.3.3. 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 55, Table 145; results for individual subjects are presented in Table 146).

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 145). 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 146).

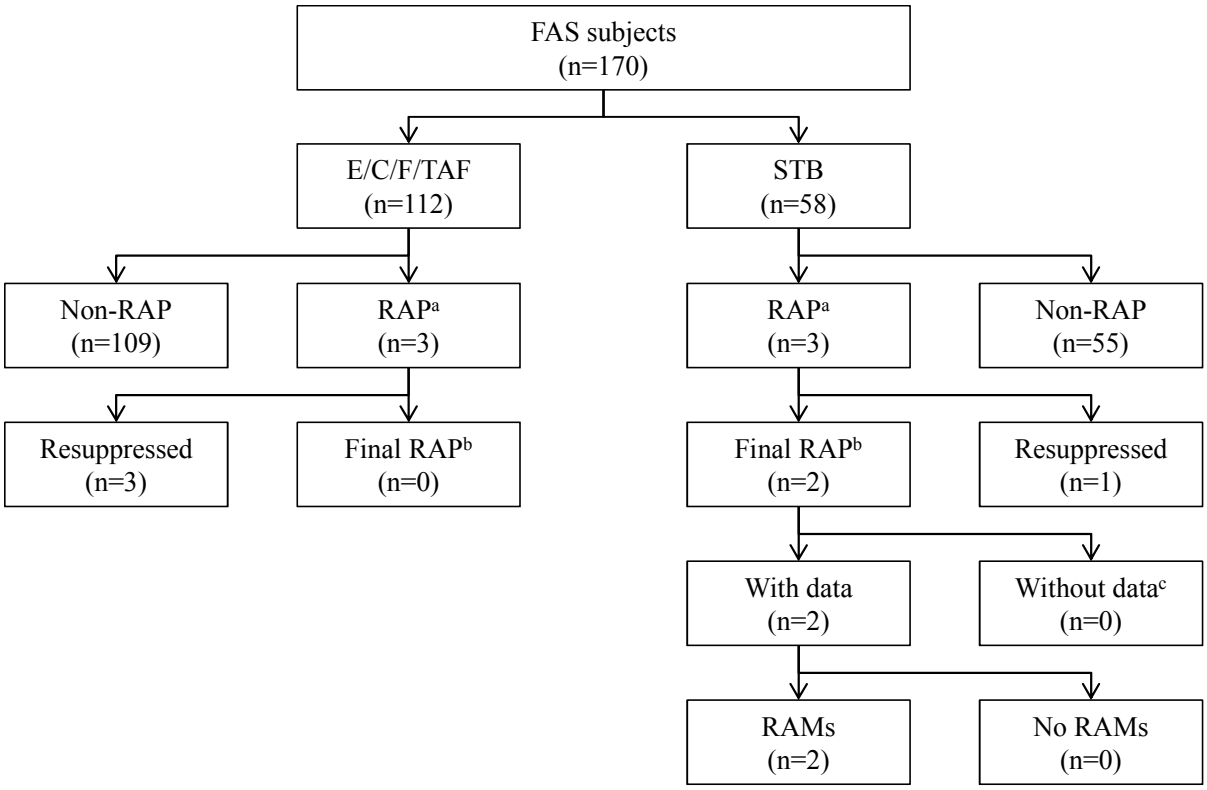
All 3 subjects in the STB group were evaluated for the development of resistance at Week 48. Subject *BQ , who did not have emergent resistance, had HIV-1 RNA subsequently resuppress to < 50 copies/mL upon further treatment with STB, which was maintained with open-label E/C/F/TAF, and was therefore not 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 145). Subject *BR developed genotypic and phenotypic resistance to both EVG (E92Q; FC = 12.8) and FTC (M184M/I/V; FTC FC > 73), and Subject *BS developed genotypic resistance to FTC (M184M/V) and TFV (K70K/E) (Table 146). 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 55. GS-US-292-0102: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



FAS = full analysis set; RAM = resistance-associated mutation; RAP = resistance analysis population
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: m5.3.5.4, PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3; m5.3.5.1, GS-US-292-0102, Appendix 16.2, Listing 17.1

Table 145. 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	

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistant; RAP = resistance analysis population

a Drug resistance mutations are defined in Table 137.

b Fisher exact test comparing the proportions 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: m5.3.5.4, PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3; m5.3.5.1, GS-US-292-0102, Appendix 16.2, Listing 17.1

Table 146. 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
[redacted][d]	E/C/F/TAF	34700	B	Week 24	Q207D, K259K/N	None	0.83	0.89	1.4
[redacted][d]	E/C/F/TAF	15200	B	Week 40	K11K/R	None	0.83	1.0	1.1
[redacted][d]	E/C/F/TAF	25600	B	Week 48	K122K/E, I135A/V, V292M	V31M, I203I/M	1.1	1.2	1.7
*BQ[d]	STB	22500	B	Week 24	None	None	1.1	0.95	1.0
*BR	STB	38700	B	Week 32	K32K/E, I63I/M, Q174Q/K, **M184M/I/V**	**E92Q**	0.57	> 73	12.8
*BS	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

BL = baseline; IN = integrase gene; RT = reverse transcriptase gene; WT = wild-type
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: m5.3.5.4, PC-120-2020: GS-US-292-0102 Virology Listings 2 and 3; m5.3.5.1, GS-US-292-0102, Appendix 16.2, Listing 17.1

4.2.1.3.4. 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.

4.2.1.4. GS-US-292-0109

4.2.1.4.1. 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/r+FTC/TDF.

4.2.1.4.2. 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 147).

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 147).

Table 147. GS-US-292-0109: Summary of Pretreatment HIV-1 Subtype and PR and RT Resistance Mutations Detected

	Number of Subjects n (%)		
HIV-1 Subtype and Mutation Class[a]	**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)

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
a Drug resistance mutations are defined in Table 137.
Source: m5.3.5.4, PC-120-2020: GS-US-292-0109 Virology Listing 1

4.2.1.4.3. Virology Analyses in Subjects in the Resistance Analysis Population

Resistance Analysis Population

Of the 1196 subjects comprising the Week 48 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 56, Table 148; results for individual subjects are presented in Table 149).

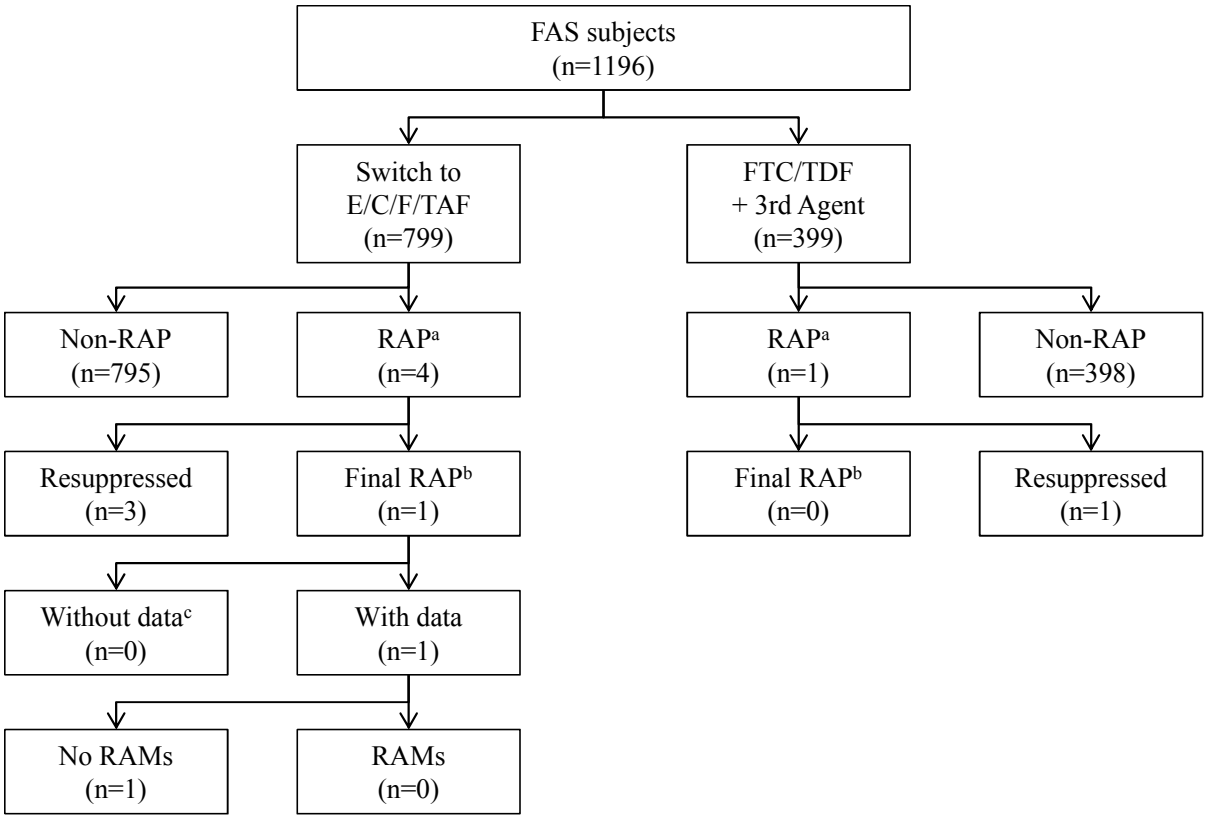
All 4 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48. Three subjects (Subjects *BT , *BU , and *BV) achieved HIV-1 RNA resuppression to < 50 copies/mL with further E/C/F/TAF treatment and were therefore not included in the Final RAP. Subject *BT demonstrated 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 *BU and *BV 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 *BW 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 *BX) in the E/C/F/TAF group that was included in the Final RAP had no detectable resistance to any study drug.

Figure 56. GS-US-292-0109: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



FAS = full analysis set; RAM = resistance-associated mutation; RAP = resistance analysis population
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: m5.3.5.4, PC-120-2020: GS-US-292-0109 Virology Listings 2 and 3; m5.3.5.1, GS-US-292-0109, Appendix 16.2, Listing 14.1

Table 148. 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	

RAP = Resistance Analysis Population
a Drug resistance mutations are defined in Table 137.
b Fisher exact test comparing the proportions in each group using the whole population as the denominator.
c Subject *BT had M184M/I detected prior to HIV-1 RNA resuppression (Table 149).
d Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
Source: m5.3.5.4, PC-120-2020: GS-US-292-0109 Virology Listings 2 and 3; m5.3.5.1, GS-US-292-0109, Appendix 16.2, Listing 14.1

Table 149. 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
*BU[d]	E/C/F/TAF	< 50	B	Week 12	Q179Q/R, E224E/D, V292V/I	AF	1.2	1.0	AF
*BV[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
*BW[d]	FTC/TDF+3rd Agent (STB)	< 50	B	Week 12	AF	AF	AF	AF	AF
*BT[d]	E/C/F/TAF	< 50	B	Week 8	**M184M/I**	None	0.77	3.8	1.1
*BX	E/C/F/TAF	< 50	B	Week 24	None	None	0.84	0.91	0.97

AF = assay failure; BL = baseline; IN = integrase; RT = reverse transcriptase; WT = wild-type
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: m5.3.5.4, PC-120-2020: GS-US-292-0109 Virology Listings 2 and 3; m5.3.5.1, GS-US-292-0109, Appendix 16.2, Listing 14.1

4.2.1.4.4. 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.

4.2.1.5. GS-US-292-0112

4.2.1.5.1. 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 the E/C/F/TAF FDC in

HIV-infected adult subjects with stable, mild to moderate renal impairment (subjects with $eGFR_{CG}$ 30 to 69 mL/min, inclusive).

4.2.1.5.2. 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 150).

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 150).

Table 150. GS-US-292-0112: Summary of Pretreatment HIV-1 Subtype and PR, RT, and IN Resistance Mutations Detected

Mutation Class[a]	Number of Subjects n (%)	
	Cohort 1[b]: Switch (N = 242)	Cohort 2: ART-Naive (N = 6)
Subtype B	Not done	5 (83.3)
Non-B Subtype	Not done	1 (16.7)
NRTI-Associated	Not done	0
INSTI-Associated (Primary)	Not done	0
INSTI-Associated (Secondary)	Not done	2 (40)[c]
NNRTI-Associated	Not done	2 (33.3)
PI-Associated (Primary)	Not done	0

INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
a Drug resistance mutations are defined in Table 137.
b Subjects in Cohort 1 were HIV-1 suppressed at study enrollment.
c Subject [redacted] was an IN assay failure.
Source: m5.3.5.4, PC-120-2020: GS-US-292-0112 Virology Listing 1 and Listing 2

4.2.1.5.3. 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-defined 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 57, Table 151; results for individual subjects are presented in Table 152).

All 2 subjects in the Cohort 1 switch group were evaluated for the development of resistance at Week 24. Subject *BY 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.

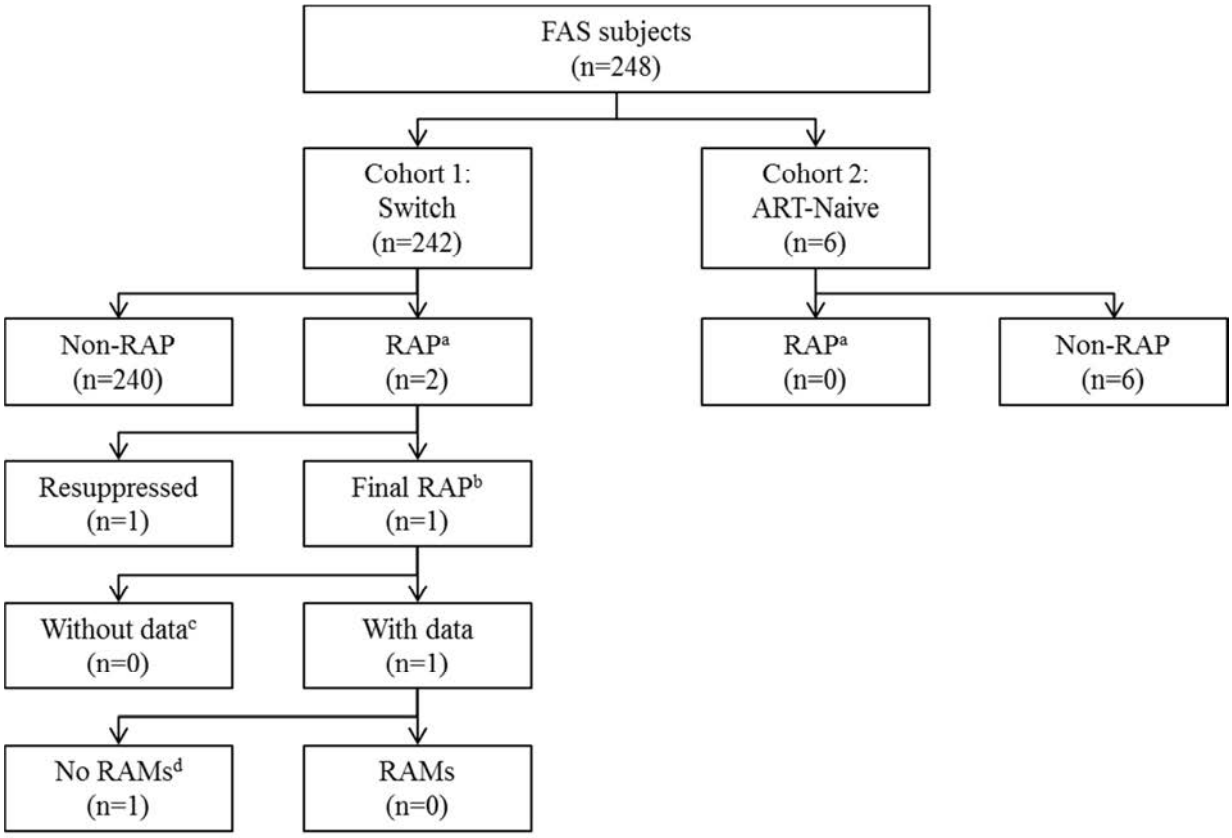
Resistance testing results for Subject *BY are presented in Table 152 and a detailed narrative is provided in the Virology Study Report (m5.3.5.4, PC-120-2020). Briefly, this subject had an ARV history that included LPV/r+FTC/TDF, LPV/r+ABC/3TC, and RAL+ABC/3TC. Following switch to E/C/F/TAF, the subject 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 *BZ 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 152 and a detailed narrative is provided in the Virology Study Report (m5.3.5.4, PC-120-2020). Briefly, this subject had an ARV history that included NFV+ABC+ZDV, ATV+ABC/3TC, and ATV/r+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 57. GS-US-292-0112: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 24



E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FAS = full analysis set; RAM = resistance-associated mutation; RAP = resistance analysis population

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 *BZ had RAMs detected on treatment; however, all were present prior to initiating E/C/F/TAF.

Source: m5.3.5.4, PC-120-2020: GS-US-292-0112 Virology Listings 3 and 4; m5.3.5.2, GS-US-292-0112, Appendix 16.2, Listing 18

Table 151. 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

RAM = resistance-associated mutation; RAP = resistance analysis population
a Drug resistance mutations are defined in Table 137.
b Subject *BY had both NRTI-R and INSTI-R detected prior to HIV-1 RNA resuppression (Table 152).
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.
d Subject *BZ had RAMs detected on treatment; however, all were present prior to initiating E/C/F/TAF.
Source: m5.3.5.4, PC-120-2020: GS-US-292-0112 Virology Listings 3 and 4; m5.3.5.2, GS-US-292-0112, Appendix 16.2, Listing 18

Table 152. 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
*BY [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
*BZ	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					

BL = baseline; IN = integrase; ND = not done; RT = reverse transcriptase; PR = protease; R = resistant; WT = wild-type

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: m5.3.5.4, PC-120-2020: GS-US-292-0112 Virology Listings 3 and 4; m5.3.5.2, GS-US-292-0112, Appendix 16.2, Listing 18

4.2.1.5.4. 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 non-study 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).

4.2.1.6. GS-US-292-0106

4.2.1.6.1. 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 the E/C/F/TAF FDC in HIV-infected, ART-naive adolescents.

4.2.1.6.2. 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 153).

The HIV-1 subtype was determined for each subject using the screening genotype. Overall, non-B HIV-1 subtypes were predominant (Table 153).

Table 153. 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

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

a HIV-1 subtypes reported as Complex by the Monogram assay were resolved using the REGA subtyping tool whenever possible {30531}.

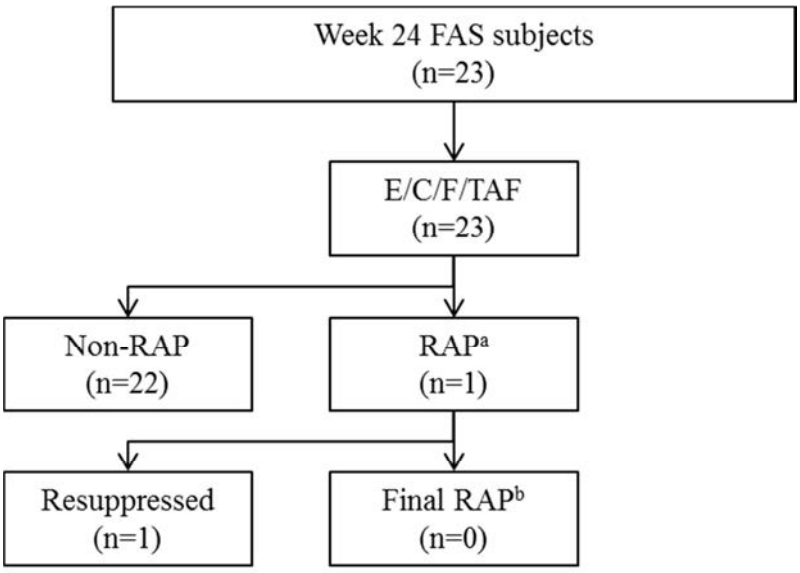
b Drug resistance mutations are defined in Table 137.

Source: m5.3.5.4, PC-120-2020: GS-US-292-0106 Virology Listings 1 and 2

4.2.1.6.3. 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 58, Table 154). Subject [redacted] 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 58. GS-US-292-0106: Resistance Analysis Population Inclusion Criteria Through Week 24



FAS = full analysis set; RAM = resistance-associated mutation; RAP = resistance analysis population
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: m5.3.5.2, GS-US-292-0106, Appendix 16.2, Listing 15.1

Table 154. 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

RAP = resistance analysis population
a Drug resistance mutations are defined in Table 137.
b Does not include subjects who resuppressed HIV-1 RNA < 50 copies/mL while continuing study drugs.
Source: m5.3.5.2, GS-US-292-0106, Appendix 16.2, Listing 15.1

4.2.1.6.4. 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.

4.2.2. 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 are 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 are 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 were to have 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 were also to have 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 155. The distribution of baseline RAMs was comparable between treatment groups.

Table 155. E/C/F/TAF Integrated Analysis: Summary of PR and RT Resistance Mutations Detected Pretreatment

Drug Class[a]	Number of Subjects n (%)		
	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)

NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
a Drug resistance mutations are defined in Table 137.
b Subject *AD had PR/RT assay failure
c Subjects *AC , *AD , and *AE were IN assay failures.
d Subjects *AF and *AG were IN assay failures.
Source: m5.3.5.4, 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 156). 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 156. 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 *AD had no subtype information available due to assay failure.
Source: m5.3.5.4, 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 157).

Table 157. E/C/F/TAF Integrated Analyses: Proportion 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

NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistant; TAM = thymidine analogue mutation

a Proportion of subjects in the FDA snapshot algorithm category "Virologic Success at Week 48" are shown.

b Subject *AD 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 137.

Source: m5.3.5.4, 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 59, Table 158).

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 159).

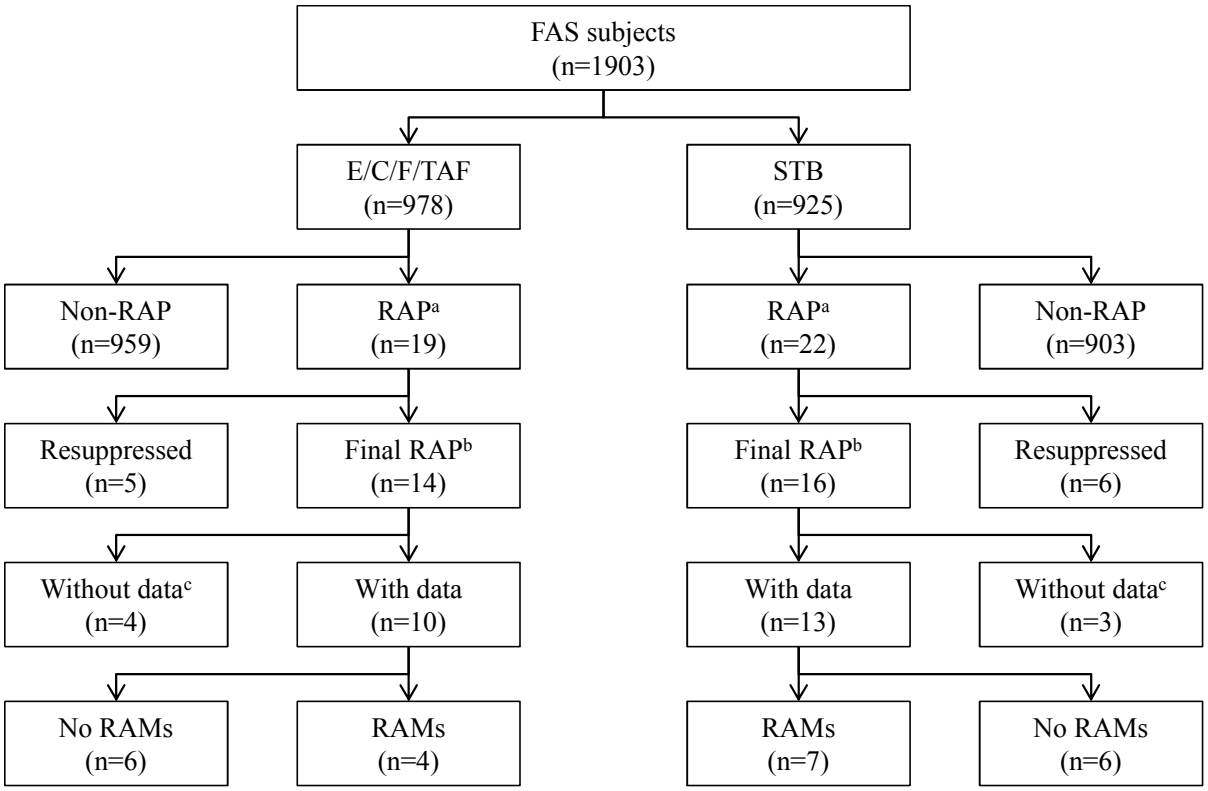
All 14 subjects in the E/C/F/TAF group were evaluated for the development of resistance at Week 48, with ongoing analyses for 4 subjects. Of the 10 subjects with available data included in the Final RAP, 4 subjects (0.4%, 4 of 978 subjects in the E/C/F/TAF group) had resistance mutations emerge while on E/C/F/TAF and 6 subjects (0.6%) had no emergent resistance. All 4 subjects with emergent resistance mutations (Subjects *AN , *AM , *BB , and *BC) had M184V detected, which was associated with phenotypic resistance to FTC (FC ≥ 63 to > 89). In addition, all 4 subjects had emergent primary INSTI-R, with 2 subjects (Subjects *AM and *BB) harboring E92Q and 1 subject each harboring N155H (Subject *AN) and T66A (Subject *BC). Phenotypic resistance to EVG was observed in 3 subjects (FC = 12.3-60), with Subject *BB having assay failure. One subject (Subject *AN) developed K65R; however, no phenotypic resistance to TFV was observed (FC = 1.0).

For the remaining 6 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 ongoing analyses for 2 subjects and 1 subject had assay failure. Of the 13 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 6 subjects (0.7%) had no emergent resistance. All 7 subjects with emergent resistance (Subjects *BR , *BS , *AP , *AR , *AQ , *BD , and *BE) had M184V/I detected, with phenotypic resistance to FTC observed in 5 subjects. Four subjects had emergent primary INSTI-R, with 2 subjects (Subjects *BR and *AP) harboring E92Q, 1 subject (Subject *BD) 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 *BD) harboring K65R, 1 subject (Subject *BS) harboring K70K/E, and 1 subject (Subject *AR) harboring E44E/D. All subjects with additional NRTI-R remained sensitive to TFV (FC = 0.5to 1.3) except Subject *AP , who was not determined due to assay failure.

For the remaining 6 subjects in the STB group, no genotypic or phenotypic resistance to any study drug was observed.

Figure 59. E/C/F/TAF Integrated Analysis: Resistance Analysis Population Inclusion Criteria and Genotypic Results Through Week 48



FAS = full analysis set; RAM = resistance-associated mutation; RAP = resistance analysis population

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: m5.3.5.4, 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 158. 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[c]	13 (1.3)	18 (1.9)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	5 (0.5)	6 (0.7)	
Final RAP[d]	14 (1.4)	16 (1.7)	0.71
Subjects with Data[c]	10 (1.0)	13 (1.4)	
Developed Resistance Mutations to Study Drugs	4 (0.4)	7 (0.8)	0.38
No Resistance Mutations Observed	6 (0.6)	6 (0.7)	
Developed Any NRTI-R	4 (0.4)	7 (0.8)	
E44E/D	0	1 (0.1)	
K65R	1 (0.1)	2 (0.2)	
K70K/E	0	1 (0.1)	
M184V/I	4 (0.4)	7 (0.8)	
Developed Any INSTI-R	4 (0.4)	4 (0.4)	
Primary INSTI-R	4 (0.4)	4 (0.4)	
T66A	1 (0.1)	0	
E92Q	2 (0.2)	3 (0.3)	
Q148R	0	2 (0.2)	
N155H	1 (0.1)	0	
Secondary INSTI-R	0	2 (0.2)	
E138K	0	2 (0.2)	
Developed Any NNRTI-R	0	0	
Developed Any Primary PI-R	0	0	

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistant; RAP = Resistance Analysis Population

a Drug resistance mutations are defined in Table 137.

b Fisher exact test comparing the proportions in each group using the whole population as the denominator.

c Subjects *AH , *AT , *AU , and *AV (E/C/F/TAF group) and Subjects *AJ and *AX (STB group) have pending data. Subject *BM had assay failure for PR, RT, and IN.

d Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drugs.

Source: m5.3.5.4, 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 159. 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	INSTI	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
*AN	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
*AM	GS-US-292-0104	E/C/F/TAF	367000	1	B	Week 48	**M184V**, T286T/I	**E92Q**	0.65	> 70	56
*BB	GS-US-292-0111	E/C/F/TAF	384000	137	B	Week 24	P170P/L, V179V/I, **M184V**	L68V, **E92Q**	0.49	> 84	AF
*BF	GS-US-292-0111	E/C/F/TAF	150000	283	B	Week 36	W71P, T139T/A, E204E/K	AF	0.98	1.3	AF
*BC	GS-US-292-0111	E/C/F/TAF	463000	21	B	Week 16	**M184V**, H208Y, E248K	**T66A**	0.48	> 89	12.3
*BG	GS-US-292-0111	E/C/F/TAF	8120	468	B	Week 48	V276V/I	A21A/T	0.96	0.95	1.6
*BH	GS-US-292-0111	E/C/F/TAF	36800	244	B	Week 36	None	I208I/L	0.79	0.99	1.1

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	INSTI	TFV[c]	FTC	EVG
*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
*BJ	GS-US-292-0111	E/C/F/TAF	31100	395	B	Week 36	K122Q, D177E, Q207E, V245E, G273G/E, R277K, V292I, E297A	AF	0.87	1.1	AF
*BR	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
*BS	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
*AP	GS-US-292-0104	STB	127000	20	B	Week 16	V60I, **K65R**, **M184V**	**E92Q**, T124S, K264K/*	AF	AF	21

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	INSTI	TFV[c]	FTC	EVG
*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
*AS	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
*BD	GS-US-292-0111	STB	239000	2	B	Week 36	**K65R**, I135M, **M184V**	E138K, **Q148R**	1.3	> 82	> 95
*BE	GS-US-292-0111	STB	88300	348	B	Week 48	**M184V**	None	0.42	> 64	1.9
*BL	GS-US-292-0111	STB	130000	395	B	Retest	None	ND	0.95	1.2	ND

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	INSTI	TFV[c]	FTC	EVG
*BN	GS-US-292-0111	STB	87800	513	B	Week 48	None	S17S/N, V31V/I, L101L/I, K127K/R, L172L/F, I208I/L, K211R, T218T/S, S230S/N	0.91	1.1	1.1
*BO	GS-US-292-0111	STB	94100	750	B	Week 24	None	None	0.81	1.1	1.7
*BP	GS-US-292-0111	STB	42100	287	B	Week 48	None	None	0.89	0.98	AF

* = stop codon; AF = assay failure; BL = baseline; ESDD = Early Study Drug Discontinuation; IN = integrase; INSTI = integrase strand-transfer inhibitor; RT = reverse transcriptase; WT = wild-type

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.

Source: m5.3.5.4, 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; m5.3.5.1, GS-US-292-0102, Appendix 16.2, Listing 17.1; m5.3.5.1, GS-US-292-0104, Appendix 16.2, Listing 16.1; m5.3.5.1, 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 amino acid substitutions 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. There were no additional substitutions in the RT or IN genes 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 9 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 7 virologic failure subjects with emergent primary INSTI-R and phenotypic resistance to EVG, six 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. Three of the 7 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 3 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 11 subjects who developed any treatment-emergent genotypic resistance, 4 of 978 subjects (0.4%) 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 4 subjects (1 with T66A, 2 with E92Q, and 1 with N155H), with 1 subject also developing K65R. All 4 subjects had baseline HIV-1 RNA levels of > 350,000 copies/mL and 3 of 4 subjects had baseline CD4 counts < 50 cells/μL. Furthermore, no additional 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 were similar with the STB group, although with less frequent development of M184V and K65R. Overall, the emergence of resistance was numerically lower for the E/C/F/TAF group (0.4%) compared with the STB group (0.8%); however, the difference did not achieve statistical significance ($p = 0.38$). No other 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 numerically lower for the E/C/F/TAF group (0.4%) compared with the STB group (0.8%); however, the difference did not achieve statistical significance.

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

6.1. Tabular Summary of Clinical Pharmacology Studies

6.1.1. 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 treatment: 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; 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
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 treatment: <u>Cohort 1:</u> • Formulation 1 E/C/F/TAF (150/150/200/25 mg) QD PO (A) • 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)	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; m5.3.3.1, 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	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) Multiple-dose phase: 18 (10 Japanese; 8 Caucasian)	Healthy adult Japanese (first generation Japanese descent) or Caucasian (not of Japanese or Asian descent) subjects	Study completed; m5.3.3.1, Final CSR
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; 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
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; m5.3.3.4, 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 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	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: 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)	Cohort 4: 24 days	Randomized to Cohort 4: 24 Completed: 23 Safety Analysis Set: 24	Healthy adult subjects	Study completed; Final CSR

6.1.2. 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
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 coadministration of TAF+COBI relative to the administration of TAF alone	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) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 11-22, fed) (F) Cohort 4: • TAF 8 mg QD PO (Days 1-12, fed) (G) • TAF 8 mg + COBI 150 mg QD PO (Days 13-22, fed) (H)	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; m5.3.3.4, Final CSR

6.1.3. 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; m5.3.3.1, 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; m5.3.3.3, 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: Subjects with	Cohort 1: Adult subjects with mild hepatic impairment (CPT Class A) and healthy matched control subjects Cohort 2: Adult subjects with moderate hepatic impairment (CPT Class B) and healthy matched control subjects	Study completed; m5.3.3.3, 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
						moderate hepatic impairment: 10 Matched controls: 10		
Healthy Subject PD 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 treatment: • 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; m5.3.4.1, 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; m5.3.4.2, Final CSR

6.1.4. EVG

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-183-0102 (synopsis)	Determine effect of RTV on steady-state PK of EVG	Phase 1, open-label, fixed-sequence, single-center, multiple-dose, crossover study	• EVG 100 mg BID PO (A) • EVG 100 mg + RTV 100 mg BID PO (B)	20 days (10 days per treatment)	Enrolled: 12 Completed: 12 Safety Analysis Set: A: 12 B: 12	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-183-0113 (synopsis)	Examine effect of a range of RTV doses on the PK of EVG and on hepatic CYP3A activity using a CYP3A substrate (MDZ)	Phase 1, randomized, open-label, single-center, multiple-dose, 2-group study	Group 1: • EVG 125 mg + RTV 20 mg QD PO (Days 2−11) (A) • EVG 125 mg + RTV 100 mg QD PO (Days 12−21) (C) Group 2: • EVG 125 mg + RTV 50 mg QD PO (Days 2−11) (B) • EVG 125 mg + RTV 200 mg QD PO (Days 12−21) (D) MDZ 1 mg IV (Days 11 and 21)	21 days A: 10 days B: 10 days C: 10 days D: 10 days	Randomized: 24 Completed: 21 Safety Analysis Set: A: 12 B: 12 C: 11 D: 11 MDZ: 24	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-183-0126 (synopsis)	Determine the mass balance of EVG following administration of a single oral dose of RTV-boosted [^{14}C]EVG	Phase 1, open-label, single-center, single-dose, mass-balance study	• EVG 50 mg (mixture of unlabeled EVG and [^{14}C]EVG) + RTV 100 mg PO	Single dose	Enrolled: 8 Completed: 8	Healthy adult male 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	GS-US-183-0140 (synopsis)	Evaluate the relative BA of the Phase 3 formulation of EVG boosted with RTV	Phase 1, randomized, open-label, single-center, multiple-dose, 2-sequence, 2-way crossover study	• EVG 125 mg + RTV 100 mg QD PO (Reference) (A) • EVG 150 mg + RTV 100 mg QD PO (Phase 3 Formulation 2, Test) (B)	20 days (10 days per treatment)	Randomized: 26 Completed: 24 Safety Analysis Set: A: 25 B: 26	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-183-0103 (synopsis)	Evaluate if PK parameters of EVG, FTC, or TFV are affected after coadministration of EVG+RTV and FTC/TDF compared with their administration alone Investigate effect of antacids on EVG+RTV PK	Phase 1, randomized, open-label, single-center, multiple-dose study	• FTC/TDF (200/300 mg) QD PO (A) • FTC/TDF (200/300 mg) + EVG 50 mg + RTV 100 mg QD PO (B) • EVG 50 mg + RTV 100 mg QD PO (C) • EVG 50 mg + RTV 100 mg + 20 mL magnesium/ aluminum-containing antacid suspension QD PO (D)	28 days A: 7 days B: 10 days C: 10 days D: 1 day	Randomized: 26 Completed: 24 Safety Analysis Set: A: 26 B: 24 C: 26 D: 13	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-183-0119 (synopsis)	Evaluate if PK parameters of EVG are affected after staggered administration of EVG+RTV and antacid or after coadministration of EVG+RTV and omeprazole compared to administration of EVG+RTV alone	Phase 1, randomized, open-label, single-center, multiple-dose study	• EVG 50 mg + RTV 100 mg QD PO (Days 1−10) (A) • EVG 50 mg + RTV 100 mg PO 4 h after 20 mL Maalox Max (Day 11) (B) • EVG 50 mg + RTV 100 mg PO 4 h before 20 mL Maalox Max (Day 11) (C) • EVG 50 mg + RTV 100 mg PO 2 h after 20 mL Maalox Max (Day 11) (D) • EVG 50 mg + RTV 100 mg 2 h before 20 mL Maalox Max (Day 11) (E) • EVG 50 mg + RTV 100 mg QD PO 2 h after omeprazole 40 mg QD (Days 11−15) (F)	15 days A: 10 days B: 1 day C: 1 day D: 1 day E: 1 day F: 5 days	Randomized: 60 Completed: 49 Safety Analysis Set: A: 60 B: 9 C: 10 D: 11 E: 10 F: 10	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-183-0146 (synopsis)	Examine effect of KTZ on PK of EVG+RTV and determine additional effect of KTZ on CYP3A enzyme activity using MDZ as CYP3A probe substrate when administered with EVG+RTV	Phase 1, non-randomized, open-label, single-center, multiple-dose study	• EVG 150 mg + RTV 100 mg QD PO (Days 2−11) (A) • EVG 150 mg + RTV 100 mg QD + KTZ 200 mg BID, PO (Days 12−15) (B) MDZ 5-mg syrup PO on Days 1, 11, and 15	15 days	Enrolled: 18 Completed: 18 Safety Analysis Set: A: 18 B: 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
Healthy Subject PD and PK/PD	GS-US-183-0128 (synopsis)	Evaluate effect of steady-state EVG+RTV exposures at therapeutic and supratherapeutic doses on the QTcF interval compared to placebo	Phase 1, single-center, 2-part study Part 1: Randomized, partially double-blind, parallel-group comparison of placebo vs moxifloxacin (positive control) Part 2: Randomized, double-blind, placebo-controlled, parallel-group comparison of 2 EVG+RTV doses vs placebo	Part 1: • Moxifloxacin 400 mg PO (single dose on Day 1) (A) • Moxifloxacin placebo PO (single dose on Day 1) (B) Part 2: • EVG 125 mg + RTV 100 mg QD PO (Days 6−15) (C) • EVG 250 mg + RTV 100 mg QD PO (Days 6−15) D) • EVG+RTV placebos QD PO (Days 6−15) (E)	15 days	Part 1: Randomized: 126 Completed: 126 Part 2: Continued from Part 1: 124 Completed: 122 Safety Analysis Set: A: 42 B: 42 C: 41 D: 42 E: 41	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-183-0101 (synopsis)	Investigate safety, tolerability, antiviral activity, and PK/PD of EVG	Phase 1/2, randomized, double-blind, multicenter, multiple-dose, placebo-controlled, proof-of-concept, sequential-cohort, dose-ranging study	• EVG 200 mg BID PO (A) • EVG 400 mg BID PO (B) • EVG 800 mg QD PO (C) • EVG 800 mg BID PO (D) • EVG 50 mg + RTV 100 mg QD PO (E) • Placebo, BID or QD PO (F) • Placebo + RTV 100 mg QD PO (G)	10 days per cohort	Randomized: 48 Treated: 40 Completed: 40 Safety Analysis Set: A: 6 B: 6 C: 6 D: 6 E: 6 F: 8 G: 2	HIV infected, ART-naive or ART-experienced adult subjects who were not currently receiving ARV therapy	Study completed; Final CSR

6.1.5. COBI

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-216-0101 (synopsis)	Evaluate the safety and tolerability of escalating single and multiple oral doses of COBI Characterize the single-dose PK and steady-state PK and PD (anti-CYP3A activity) of COBI	Phase 1, randomized, double-blind, single-center, placebo- and active-controlled, single and multiple dose-ranging study	4:1:1 randomization for each cohort • Part A, Cohort 1, Periods 1 and 2: COBI 50 mg, RTV 100 mg, or matching placebo(s) PO • Part A, Cohort 2, Periods 1 and 2: COBI 100 mg, RTV 100 mg, or matching placebo(s) PO • Part B, Cohort 3: COBI 200 mg, RTV 100 mg, or matching placebo(s) PO	Part A, Period 1: 1 day Part A, Period 2: 14 days Part B: 14 days	Randomized: 60 Completed: 48 Safety Analysis Set: • COBI 50 mg: 12 • COBI 100 mg: 15 • COBI 200 mg: 15 • RTV 100 mg: 9 • Placebo: 9	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-216-0111 (synopsis)	Determine the mass-balance of COBI at steady-state using a tracer dose of [^{14}C]COBI	Phase 1, open-label, single-center, multiple-dose, mass-balance study	• COBI 150 mg QD PO (Days 1−6) • COBI 150 mg (capsule containing nonradiolabeled COBI + [^{14}C]COBI) PO (Day 7)	7 days	Enrolled: 8 Completed: 8	Healthy adult male subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-216-0113 (synopsis)	Evaluate the PK of COBI following oral administration at single and multiple doses	Phase 1, open-label, single-center, single- and multiple-dose, staggered dose-escalation cohort study	<u>Cohort 1:</u> • COBI 300 mg QD PO <u>Cohort 2:</u> • COBI 400 mg QD PO	Cohort 1: 7 days Cohort 2: Single dose	Enrolled: 24 Completed: 24 Safety Analysis Set: Cohort 1: 12 Cohort 2: 12	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
Intrinsic Factor PK	GS-US-216-0121 (synopsis)	Cohort 1: Evaluate renal function and renal creatinine handling before, during, and following completion of administration of COBI or RTV in healthy subjects. Cohort 2: Evaluate renal function and renal creatinine handling in stable mild/moderate renal impairment before, during, and following completion of administration of COBI, and assess the PK and safety of COBI in stable mild/moderate renal impairment	Phase 1, 2-cohort study. Cohort 1 was a randomized, double-blind, placebo (negative)-controlled, single-center, multiple-dose, parallel-group cohort. Cohort 2 was a single-treatment, open-label, multicenter, multiple-dose cohort.	All treatments were administered PO each morning following consumption of a standardized meal. Cohort 1 • COBI 150 mg + RTV 100 mg placebo OR RTV 100 mg + COBI 150 mg placebo OR COBI 150 mg placebo + RTV 100 mg placebo (Days 1-7) • Probe drug (IV iohexol) (Days 0, 7, and 14) Cohort 2 • COBI 150 mg (Days 1-7) • Probe drug (IV iohexol) (Days 0, 7, and 14)	Cohort 1: 7 days Cohort 2: 7 days	Enrolled: 54 Cohort 1: 36 Cohort 2: 18 Completed: 54 Cohort 1: 36 Cohort 2: 18 Note: One subject in Cohort 2 completed COBI treatment but did not receive the Day 14 iohexol dose due to an AE of maculo-papular rash	Cohort 1: Healthy adult subjects with normal renal function ($eGFR_{CG}$ ≥ 80 mL/min) Cohort 2: Adult subjects with stable mild/ moderate renal 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
Extrinsic Factor PK	GS-US-216-0134 (synopsis)	Evaluate the PK of COBI and TFV following multiple-dose administration of COBI and TDF alone or in combination	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatment: Cohort 1: • COBI 150 mg QD PO (A) • COBI 150 mg + TDF 300 mg QD PO (B) Cohort 2: • COBI 150 mg + TDF 300 mg QD PO (B) • TDF 300 mg QD PO (C)	19 days (7 days of each treatment with a 5-day washout period in between)	Enrolled: 46 Completed: 45 Safety Analysis Set: 46 A: 32 B: 45 C: 14	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PD and PK/PD	GS-US-216-0107 (synopsis)	Evaluate the effects of COBI on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, randomized, partially blinded, single-center, single-dose, placebo- and positive (moxifloxacin)-controlled, 8-sequence, 4-period crossover, thorough QT/QTc study	• COBI 250 mg PO (A) • COBI 400 mg PO (B) • Placebo PO (C) • Moxifloxacin 400 mg PO (D)	22 days (single dose on Days 1, 8, 15, and 22)	Randomized: 48 Completed: 48 Safety Analysis Set: A: 48 B: 48 C: 48 D: 48	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 PD and PK/PD	GS-US-216-0112 (synopsis)	Evaluate the effects of COBI on CYP enzymes 2B6 and 2D6, and on the drug efflux transporter Pgp using validated phenotyping probes	Phase 1, open-label, single-center, multiple-cohort, crossover study	Cohort 1 (CYP2D6) • Desipramine 50 mg PO, single dose (A) • COBI 150 mg QD PO for 10 days, + desipramine 50 mg PO, single dose on 10th day (B) Cohort 2 (Pgp) • Digoxin 0.5 mg PO, single dose (C) • COBI 150 mg QD PO for 10 days, + digoxin 0.5 mg PO, single dose on 10th day (D) Cohort 3 (CYP2B6) • EFV 600 mg PO, single dose (E) • COBI 150 mg QD PO for 10 days, + EFV 600 mg PO, single dose on 10th day (F)	Cohorts 1 and 2: 25 days (including washout) Cohort 3: 31 days (including washout)	Enrolled: 53 Completed: 48 Safety Analysis Set: A: 10 B: 9 C: 24 D: 22 E: 18 F: 17	Healthy adult subjects: Cohort 1 was limited to individuals who were intermediate, extensive, or ultra-rapid CYP2D metabolizers; Cohort 3 was limited to individuals who were intermediate or extensive CYP2B6 metabolizers	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 PD and PK/PD	GS-US-216-0116 (synopsis)	Evaluate multiple-dose PK of a new formulation of COBI, administered alone; evaluate multiple-dose PK of EVG as a stand-alone tablet administered with a new formulation of COBI tablet	Phase 1, 2-cohort, randomized, open-label, multiple-dose, crossover study	Cohort 1: • COBI 150 mg Formulation 2 (new formulation) QD PO (A) • COBI 150 mg Formulation 1 (original formulation) QD PO (B) Single PO dose of MDZ 5 mg on Days 10 and 20 (metabolic probe) Cohort 2: • EVG 150 mg + COBI 150 mg Formulation 2 (new formulation) QD PO (C) • EVG 150 mg + RTV 100 mg QD PO (D)	20 days (10 days for each treatment within a cohort)	Randomized: 62 Cohort 1: 38 Cohort 2: 24 Completed: 57 Cohort 1: 35 Cohort 2: 22 Safety Analysis Set: A: 36 B: 38 C: 24 D: 24	Healthy adult subjects	Study completed; Final CSR

6.1.6. EVG+COBI

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	GS-US-183-0133 (synopsis)	Evaluate any differences in the PK and safety of EVG+COBI by evaluating subjects with moderate impairment of hepatic function (CPT Classification B) compared to matched subjects with normal hepatic function	Phase 1, open-label, parallel-group, multiple-dose study	• EVG 150 mg + COBI 150 mg QD PO, immediately following consumption of a standard meal	10 days followed by an 11-day follow-up period	Enrolled: 20 Completed: 20 (10 subjects with moderate hepatic impairment, and 10 matched control subjects)	Adult subjects with moderate hepatic impairment (CPT Classification B) and healthy matched control subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-183-1004 (synopsis)	Evaluate the PK of EVG and its metabolite GS-9200 following the administration of EVG+COBI in subjects with decreased UGT1A1 activity (UGT1A1*28 genotype) and wild-type (UGT1A1*1) matched control subjects	Phase 1, nonrandomized, open-label, parallel, multiple-dose study	• EVG 150 mg + COBI 150 mg QD PO in the AM with a standard moderate-fat meal	10 days	Enrolled: 36 Completed: 36 Safety Analysis Set: Subjects with decreased UGT1A1 activity: 18 Wild-type matched controls: 18	Healthy adult subjects with decreased UGT1A1 activity (UGT1A1*28) or wild-type matched controls (UGT1A1*1)	Study completed; m5.3.3.3, 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	GS-US-216-0124 (synopsis)	Evaluate the PK, safety, and renal function prior to, during, and after dosing with EVG+COBI in subjects with severe renal impairment	Phase 1, open-label, parallel-group, multiple-dose study	• EVG 150 mg + COBI 150 mg QD PO, immediately following consumption of standard meal	7 days followed by a 7-day follow-up period	Enrolled: 24 (13 renally impaired and 11 matched controls) Completed: 23 (12 renally impaired and 11 matched controls)	Adult subjects with severe renal impairment and matched control subjects with normal renal function	Study completed; Final CSR
Extrinsic Factor PK	GS-US-216-0120 (synopsis)	Evaluate the relative BA and PK of EVG+COBI after coadministration with a representative H_2-receptor antagonist or a representative proton pump inhibitor	Phase 1, randomized, open-label, single-center, multiple-dose, 3-sequence, 4-treatment, 2-period crossover study	• EVG 150 mg + COBI 150 mg QD PO in the AM with food (A) • EVG 150 mg + COBI 150 mg QD PO in the AM with food + famotidine 40 mg QD PO in the PM with food 12 h after EVG+COBI (B) • EVG 150 mg + COBI 150 mg QD PO in the AM with food + omeprazole 20 mg QD PO in the AM in a fasted state 2 h before EVG+COBI (C) • EVG 150 mg + COBI 150 mg QD PO in the AM with food + omeprazole 20 mg QD PO in the PM in a fasted state 12 h after EVG+COBI (D)	16 days (8 days per treatment)	Randomized: 33 Completed: 32 Safety Analysis Set: A: 33 B: 11 C: 11 D: 11	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-216-0122 (synopsis)	Determine whether simultaneous coadministration of EVG+COBI with a representative H_2-receptor antagonist reduces the relative BA of EVG+COBI	Phase 1, randomized, open-label, single-center, multiple-dose, 2-way crossover study	• EVG 150 mg + COBI 150 mg QD PO in the AM with food (A) • EVG 150 mg + COBI 150 mg + famotidine 40 mg QD PO in the AM with food (B)	16 days (8 days per treatment)	Randomized: 16 Completed: 16 Safety Analysis Set: A: 16 B: 16	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-216-0123 (synopsis)	Evaluate the PK and safety of EVG+COBI coadministered once daily with ATV, rosuvastatin, or RFB vs once-daily administration of EVG+COBI, ATV+RTV, single dose of rosuvastatin alone, or once-daily administration of RFB alone	Phase 1, partially randomized, open-label, single-center, single- and multiple-dose, multiple-cohort, crossover study	Cohort 1: • Rosuvastatin 10 mg, single dose PO on Day 1 (A) • EVG 85 mg + COBI 150 mg + ATV 300 mg QD PO (Days 4−13) (B) • EVG 150 mg + COBI 150 mg QD PO (Days 15−24) (C) • EVG 150 mg + COBI 150 mg + rosuvastatin 10 mg single dose PO on Day 25 (D) Cohort 2: • EVG 85 mg + COBI 150 mg + ATV 300 mg QD PO (Days 4−13) (B) • ATV 300 mg + RTV 100 mg QD PO (Days 15−24) (E)	Cohort 1: 22 days Cohort 2: 20 days Cohort 3: 36 days	Enrolled: 34 Cohort 1: 12 Cohort 2: 10 Cohort 3: 12 Completed: 29 Cohort 1: 10 Cohort 2: 7 Cohort 3: 12	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
				Cohort 3: • EVG 150 mg + COBI 150 mg QD PO (Days 1−10) (C) • EVG 150 mg + COBI 150 mg QD PO, + RFB 150 mg, QOD PO (Days 11−23) (F) • RFB 300 mg QD PO (Days 35−46) (G)				
Extrinsic Factor PK	GS-US-216-0125 (synopsis)	Evaluate the drug interaction potential between EVG+COBI and methadone or BUP/NLX	Phase 1, open-label, crossover, 2-cohort, 2-center, multiple-dose study	Cohort 1: • Methadone (80 to 120 mg) once daily (Reference) (A) • Methadone (80 to 120 mg) + EVG 150 mg + COBI 150 mg once daily (Test) (B) Cohort 2: • BUP/NLX (16 mg/4 mg to 24 mg/6 mg) once daily (Reference) (C) • BUP/NLX (16/4 mg to 24/6 mg) + EVG 150 mg + COBI 150 mg once daily (Test) (D)	11 days (1 day for reference)	Enrolled: 30 Completed: 28 Analyzed (PK, PD, Safety): Cohort 1: 11 Cohort 2: 17	Healthy adult subjects on stable doses of methadone or BUP/NLX (at least 2 weeks prior to screening)	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-216-0137 (synopsis)	Evaluate the PK of CBZ, CBZE, EVG, and COBI following the coadministration of EVG+COBI+CBZ relative to the administration of CBZ alone or EVG+COBI alone	Phase 1, open-label, fixed-sequence, single-cohort, multiple-dose, DDI study	• EVG 150 mg + COBI 150 mg QD PO in the AM with a standard meal (Days 1-10) (A) • CBZ 100 mg BID PO (in the AM and PM) with a standard meal for 3 days, then CBZ 200 mg BID PO (in the AM and PM) with a standard meal for 18 days (Days 11-31) (B) • EVG 150 mg + COBI 150 mg QD PO (in the AM) + CBZ 200 mg BID (in the AM and PM) with a standard meal (Days 32-41) (C)	41 days	Enrolled: 14 Completed: 12 Safety Analysis Set: 14	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
Extrinsic Factor PK	GS-US-344-0102 (synopsis)	Evaluate the PK of LDV on coadministration with ATR, DRV+RTV, RPV, and RAL relative to administration of LDV alone; evaluate the PK of ATR, DRV, RTV, RPV, and RAL on coadministration with LDV relative to the administration of ATR, DRV, RTV, RPV, or RAL alone; Evaluate the PK of SOF, metabolites GS-566500 and GS-331007, LDV, EVG, and COBI on coadministration of LDV/SOF with EVG+COBI relative to LDV/SOF or EVG+COBI alone; evaluate the PK of SOF, GS-566500, GS-331007, LDV, ATV, and RTV on coadministration of LDV/SOF with	Phase 1, open-label, multiple-dose, multicohort, single- center study	Cohort 1: • LDV 90 mg QD or ATR (600/200/300 mg) QD on Days 1–14 followed by LDV 90 mg QD + ATR (600/200/300 mg) QD on Days 16–29 For Cohorts 2 through 6, subjects are randomized to 1 of 6 sequences and received each of the 3 treatments in that cohort for 10 days. Cohort 2: • LDV 90 mg QD (A) • DRV 800 mg QD + RTV 100 mg QD (D) • LDV 90 mg QD + DRV 800 mg QD + RTV 100 mg QD (E) Cohort 3: • LDV 90 mg QD (A) • RPV 25 mg QD (F) • LDV 90 mg QD + RPV 25 mg QD (G) Cohort 4: • LDV 90 mg QD (A) • RAL 400 mg BID (H) • LDV 90 mg QD + RAL 400 mg BID (I) Cohort 5:	Cohort 1: 28 days Cohorts 2 through 6: 30 days	Overall: 168 treated 159 completed Cohort 1: 30 treated 26 completed Cohort 2: 24 treated 23 completed Cohort 3: 24 treated 23 completed Cohort 4: 30 treated 28 completed Cohort 5: 30 treated 29 completed Cohort 6: 30 treated 30 completed	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
		ATV+RTV relative to LDV/SOF or ATV+RTV alone; evaluate the safety and tolerability of coadministration of LDV and ATR, DRV+RTV, RPV, or RAL; and evaluate the safety and tolerability of coadministration of LDV/SOF and EVG+COBI or ATV+RTV		• LDV/SOF FDC (90/400 mg) QD (J) • EVG 150 mg QD + COBI 150 mg QD (K) • LDV/SOF FDC (90/400 mg) QD + EVG 150 mg QD + COBI 150 mg QD (L) <u>Cohort 6:</u> • LDV/SOF FDC (90/400 mg) QD (J) • ATV 300 mg QD + RTV 100 mg QD (M) • LDV/SOF FDC (90/400 mg) QD + ATV 300 mg QD + RTV 100 mg QD (N)				

6.1.7. 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

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	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
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 and PK food effect on PK for 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

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 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 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

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	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 h before the start of a 3-h 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-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

6.1.8. STB

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-236-0110 (synopsis)	Evaluate the relative BA of 2 formulations of STB STR	Phase 1, randomized, open-label, single-center, multiple-dose, 6-sequence, 3-treatment, 3-period crossover study	• New STB STR Formulation 2 (150/150/200/300 mg) QD PO (A) • STB STR original tablet Formulation 1 (150/150/200/300 mg) QD PO (B) • FTC 200 mg + TDF 300 mg, QD PO (C)	30 days (10 days per treatment)	Randomized: 42 Completed: 36 Safety Analysis Set: A: 39 B: 40 C: 39	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-236-0105 (synopsis)	Evaluate the effect of food (a high-calorie/high-fat meal or a light meal) on the PK of EVG, FTC, TFV, and COBI when administered as a STB STR	Phase 1, randomized, open-label, single-center, single-dose, 6-sequence, 3-treatment, 3-period crossover study	STB STR (150/150/200/300 mg), single dose PO administered under the following meal conditions: • Fasted (A) • Light meal (B) • High-calorie/ high-fat meal (C)	Single dose under each meal condition	Randomized: 24 Completed: 24 Safety Analysis Set: A: 24 B: 24 C: 24	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-236-0106 (synopsis)	Determine effect of the STB STR on the PK of a representative hormonal contraceptive medication, Ortho Tri-Cyclen® Lo (NGM/EE)	Phase 1, fixed-sequence, open-label, single-center, multiple-dose study	Part A (Lead-In) (1 menstrual cycle): • NGM/EE QD PO for 28 days (21 days active + 7 days inert) Part B (2 menstrual cycles): • NGM/EE QD PO for 39 days (21 days active, 7 days inert,	56 days (up to 84 days if Part A was required)	Enrolled: 21 Completed: 15 Safety Analysis Set: Part A: 19 Part B: 18 NGM/EE: 18 STB STR: 16	Healthy adult women of childbearing potential	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
				11 days active) • STB STR (150/150/200/300 mg) + NGM/EE (active) QD PO for 10 days • NGM/EE (inert) QD PO for 7 days				
Extrinsic Factor PK	GS-US-236-0120 (synopsis)	Evaluate the PK of COBI-boosted EVG administered as STB STR before and after treatment with the ATR STR	Phase 1, open-label, single-center, multiple-dose study	• Period 1: STB STR (150/150/200/300 mg) QD PO (Days 1-7) • Period 2: ATR STR (600/200/300 mg) QD PO (Days 15-28) • Period 3: STB STR (150/150/200/300 mg) QD PO (Days 29-62)	62 days	Enrolled: 32 Completed: 29 Safety Analysis Set: Period 1: 32 Period 2: 31 Period 3: 30	Healthy adults subjects; approximately 25% of subjects had decreased metabolic activity affecting EFV clearance (CYP2B6 genotype)	Study completed; Final CSR
Extrinsic Factor PK	GS-US-236-0135 (synopsis)	Part 1: Evaluate the PK of TVR and EVG following the coadministration of TVR and STB STR relative to the administration of TVR or STB STR alone Part 2: Cohort 1: Evaluate the PK of TVR and ATV following the coadministration of TVR and	Phase 1, randomized, open-label, multiple-dose, 2-part, multiple-cohort study	Part 1: • TVR+STB STR (Test) • STB STR(Reference) • TVR (Reference) Part 2: Cohort 1: • TVR+ATV+RTV + EVG 85 mg (Test) • TVR (Reference) • ATV+RTV (Reference) Cohort 2: • TVR+ATV+RTV + EVG 85 mg (Test) • EVG 150 mg + RTV	10 days	Enrolled: 54 Completed: 48 Analyzed (Safety/PK): Part 1: 16/16 Part 2, Cohort 1, Sequence 1: 13/12 Part 2, Cohort 2, Sequence 2: 13/11 Part 2 Cohort 2: 12/12	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
		ATV+RTV plus EVG 85 mg relative to the administration of TVR or ATV+RTV alone Cohort 2: Evaluate the PK of EVG following the coadministration of TVR and ATV+RTV plus EVG 85 mg relative to the administration of ATV+RTV plus EVG 85 mg or EVG 150 mg + RTV alone		(Reference) • ATV+RTV + EVG 85 mg (Reference)				

3TC = lamivudine; AM = before noon; ART = antiretroviral therapy; ARV = antiretroviral; ATR = efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®); ATV = atazanavir; BID = twice daily; BA = bioavailability; BE = bioequivalence; BUP = buprenorphine; ^{14}C = radiolabeled carbon 14; CBZ = carbamazepine; CBZE = carbamazepine-10,11-epoxide; COBI = cobicistat (Tybost®); CPA = emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®); CPT = Child-Pugh-Turcotte; CSR = clinical study report; CYP = cytochrome P450 enzyme; DDI = drug-drug interaction; DTG = dolutegravir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated); FCV = famciclovir; EFV = efavirenz; $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; EVG = elvitegravir (Vitekta®); FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); FTC = emtricitabine (Emtriva); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada); HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; IV = intravenous; KTZ = ketoconazole; LDV = ledipasvir; LPV = lopinavir; LPV/r = lopinavir boosted with ritonavir; MDZ = midazolam; NLX = naloxone; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamics(s); PI = protease inhibitor; PK = pharmacokinetic(s); PO = orally; PM = after noon; QD = once daily; QOD = every other day; 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; QTcF = QT interval corrected for heart rate using the Fridericia formula; RAL = raltegravir; RFB = rifabutin; RPV = rilpivirine; RTV = ritonavir; SER = sertraline; SOF = sofosbuvir; STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild); STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate (Viread®); TFV = tenofovir; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1

6.2. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

The following outputs present data from E/C/F/TAF PK/PD analyses. These outputs are included in m5.3.4.2.

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. These outputs are included in m5.3.4.2.

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

The following outputs present data from STB PK/PD analyses.

STB PK/PD Table 1	Plasma EVG PK Parameters from Population PK Modeling by Subject with Summary Statistics for Each Parameter, EVG PK/PD Analysis Set
STB PK/PD Table 2.2	Plasma COBI PK Parameters from PK Substudies by Subject with Summary Statistics for Each Parameter, Subjects in PK Substudies
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 Table 3.1	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) by EVG Ctau (ng/mL) Quartile Subgroup, EVG PK/PD Analysis Set

STB PK/PD Table 3.2	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) by EVG Ctau (ng/mL) Quintile Subgroup, EVG PK/PD Analysis Set
STB PK/PD Table 3.3	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) by EVG Ctau (ng/mL) Octile Subgroup, EVG PK/PD Analysis Set
STB PK/PD Table 3.4	Percentage of Pure Virologic Responders at Week 48 (HIV-1 RNA < 50 copies/mL) by EVG Ctau (ng/mL) Quartile Subgroups, EVG PK/PD Analysis Set
STB PK/PD Figure 1.1	Percentage of Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) by EVG Ctau (ng/mL) Quartile Subgroup, EVG PK/PD Analysis Set
STB PK/PD Figure 2.1	Box Plot of EVG AUCtau (ng*h/mL) by Selected Adverse Events Subgroup, EVG PK/PD Analysis Set
STB PK/PD Figure 2.2	Box Plot of EVG Cmax (ng/mL) by Selected Adverse Events Subgroup, EVG PK/PD Analysis Set
STB PK/PD Figure 3.1	Box Plot of COBI AUCtau (ng*h/mL) by Selected Adverse Events Subgroup, COBI PK/PD Analysis Set
STB PK/PD Figure 3.2	Box Plot of COBI Cmax (ng/mL) by Selected Adverse Events Subgroup, COBI PK/PD Analysis Set
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 6.1	Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by EVG AUCtau (ng*h/mL) Quartile Subgroup, EVG PK/PD Analysis Set
STB PK/PD Figure 6.3	Box Plot of Maximum Decrease from Baseline in eGFR(CG) (mL/min) by EVG AUCtau (ng*h/mL) Quartile Subgroup, EVG PK/PD Analysis Set
STB PK/PD Figure 7.1	Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by COBI AUCtau (ng*h/mL) Quartile Subgroup, COBI PK/PD Analysis Set

STB PK/PD Figure 7.3	Box Plot of Maximum Decrease from Baseline in eGFR(CG) (mL/min) by COBI AUCtau (ng*h/mL) Quartile Subgroup, COBI 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 Nonclinical Virology Studies

6.3.1. TAF Tabular Summary of Nonclinical Virology Studies

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.	Location in CTD
Primary Pharmacodynamics						
Drug Combination Studies with TAF	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2002	m5.3.5.4
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	m5.3.5.4
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	m5.3.5.4
Cytotoxicity Assay with TAF	No	MT-2, MT-4, and HepG2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2007	m5.3.5.4
Cytotoxic Effect of TAF on PBMCs	No	PBMCs	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2009	m5.3.5.4
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	m5.3.5.4
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	m5.3.5.4
In Vitro Evaluation of TAF Resistance Barrier	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2013	m5.3.5.4
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	m5.3.5.4

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.	Location in CTD
Comparison of TAF Resistance Profile in Multiple In Vitro Assays	No	In Vitro	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2015	m5.3.5.4
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	m5.3.5.4

a An entry of "Yes" indicates that the study includes a Good Laboratory Practice (GLP) compliance statement.

6.3.2. EVG, COBI, and STB Tabular Summary of Nonclinical Virology Studies

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Primary Pharmacodynamics					
Production and Purification of Human Immunodeficiency Virus Type 1 Integrase	No	In Vitro	In Vitro	Japan Tobacco Inc. Osaka, Japan	JTK303-PH-001
EVG Inhibitory Activity Against Recombinant Human Immunodeficiency Virus Type 1 Integrase	No	In Vitro	In Vitro	Japan Tobacco Inc. Osaka, Japan	JTK303-PH-002
HIV Integrase Inhibitors Do Not Exert a Postantibiotic Effect Despite Binding with High Affinity to the Integrase-DNA Complex	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2027
Inhibitory Activity of EVG on Integration of Human Immunodeficiency Virus Type 1 Viral DNA into Host DNA	No	MT-4 cells	In Vitro	Japan Tobacco Inc. Osaka, Japan and [redacted] Japan	JTK303-PH-005
Effect of GS-9160 on the Integration of Viral DNA in Infected Cells	No	SupT1 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-186-2006
Antiviral Activity of EVG Against HIV-1 NL4 3 Integrase Mutant Viruses in MT-4 Cells	No	MT-4 cells	In Vitro	[redacted], USA	JTK303-PH-016
Antiviral Activity of GS-9160 and EVG	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-186-2002
Anti-HIV Activity and Cytotoxicity of One Coded Compound (EVG) Tested Against a Panel of HIV Viruses in Fresh Human PBMC and Macrophage Cultures	No	PBMC and Macrophage cells	In Vitro	[redacted], USA	JTK303-PH-010

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Anti-Human Immunodeficiency Virus Type 1 Activity and Cytotoxicity of EVG in the Absence or Presence of Human Serum in Human PBMC Culture	No	PBMCs	In Vitro	Japan Tobacco Inc. Osaka, Japan and [redacted] Japan	JTK303-PH-006
Antiviral Activity of GS-9160 in Primary Human T-Lymphocytes and Macrophages	No	PBMC and Macrophages	In Vitro	Gilead Sciences Foster City, CA USA	PC-186-2004
Effects of Human Serum Albumin and Human α1-Acid Glycoprotein on the Anti Human Immunodeficiency Virus Type 1 Activity of EVG	No	MT-4 cells	In Vitro	Japan Tobacco Inc. Osaka, Japan and [redacted] Japan	JTK303-PH-007
Selection of EVG-resistant Human Immunodeficiency Virus Type 1 Variants	No	MT-4 cells	In Vitro	Japan Tobacco Inc. Osaka and Kanagawa, Japan and [redacted] Japan	JTK303-PH-012
In Vitro Selection of HIV-1 Resistant to EVG	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2007
Characterization of Human Immunodeficiency Virus Type 1 Integrase with EVG-selected Mutation	No	In Vitro	In Vitro	Japan Tobacco Inc. Osaka, Japan	JTK303-PH-015
Resistance and Cross-Resistance Profile of HIV-1 Carrying the EVG-selected E92Q, S147G, H51Y, and E157Q Mutations in Integrase	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2002
Antiviral Activity of EVG and Control Compounds Against HIV-1 HXB2 Site Directed Integrase Mutant Viruses in MT-2 cells	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2025
Activity of GS-9160 [and EVG] Against Drug-resistant Mutants of HIV-1	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-186-2008

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Activity of a Novel HIV-1 Integrase Inhibitor, EVG, Against HIV-1 Resistant to Protease and Reverse Transcriptase Inhibitors	No	HEK293 cells	In Vitro	[redacted] USA	JTK303-PH-009
Effect of EVG Metabolites on Recombinant Human Immunodeficiency Virus Type I Integrase Activity	No	In Vitro	In Vitro	Japan Tobacco Inc. Osaka, Japan	JTK303-PH-013
Antiviral Activity of EVG Metabolite M1 Against Human Immunodeficiency Virus Type 1 IIIB and EVG-resistant Variants	No	MT-4 cells	In Vitro	Japan Tobacco Inc. Osaka, Japan and [redacted] Japan	JTK303-PH-014
In Vitro Selection of HIV-1 Resistant to the EVG Metabolite, GS-9200 (M4)	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2008
In Vitro Selection of HIV-1 Resistant to the EVG Metabolite, GS-9202 (M1)	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2021
Resistance analysis in clinical study subjects with virologic failure after receiving FTC/RPV/TDF	No	Clinical isolates	In Vitro	Gilead Sciences Foster City, CA USA	PC-264-2005
Secondary Pharmacodynamics					
Effect of EVG on Human Immunodeficiency Virus Type 1 Reverse Transcriptase Activity	No	In Vitro	In Vitro	Japan Tobacco Inc. Osaka, Japan	JTK303-PH-003
In Vitro Receptor Binding of EVG	No	In Vitro	In Vitro	[redacted] France	JTK303-PH-008
Activity of EVG Against HBV and HCV	No	AD38 and Huh-Luc cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2024
Metabolite Profiling and Identification of [14C]EVG/EVG in Pooled Female New Zealand Rabbit Liver Microsomes	No	Microsomes	In Vitro	[redacted] USA	60N-0508

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Activity of COBI Against HIV-1 and Host Proteases	No	HIV-1 protease enzyme, cathepsin D enzyme, 26S proteasome	In Vitro	Gilead Sciences Foster City, CA USA	PC-216-2001
Anti-HIV-1 Activity of COBI in MT-2 Cells	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-216-2002
Activity of COBI against HBV and HCV	No	HepG2 and Huh-7 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-216-2006
Evaluation of COBI Antiviral Activity Against HIV Primary Isolates	No	PBMCs	In Vitro	[redacted] USA	PC-216-2011
Identification of Major Metabolites of COBI In Vitro (Rat, Dog, Human)	No	Hepatocytes	In Vitro	Gilead Sciences Foster City, CA USA	AD-216-2038
Identification of Major Metabolites of COBI in CD-1 Mouse Microsomes In Vitro	No	Microsomes	In Vitro	Gilead Sciences Foster City, CA USA	AD-216-2074
Pharmacokinetics, Metabolism, and Excretion of [14C]COBI Following Oral Administration to Mice	No	Mouse	Oral	[redacted]	AD-216-2073
Radioprofiling and Metabolite Identification	No	Rat	Oral	[redacted]	AD-216-2082
Pharmacodynamic Drug Interactions					
Antiviral Activity of HIV Inhibitors in Combination with COBI	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-216-2005
Combination Studies of EVG with Other Antiretroviral Drug Classes (NRTI, NNRTI, PI)	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2006
Combination Study of EVG with Emtricitabine and Tenofovir	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2004

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Combination Studies of EVG with the CCR5 Inhibitor, Maraviroc	No	PM-1 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2017
Combination Study of the Anti-HIV-1 Activity of EVG with Anti-HBV Antivirals	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-183-2023

a An entry of "Yes" indicates that the study includes a Good Laboratory Practice (GLP) compliance statement.

6.3.3. FTC Tabular Summary of Nonclinical Virology 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] Georgia	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

6.3.4. TDF Tabular Summary of Nonclinical Virology 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] Canada	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 thymidine analogue mutations 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 thymidine analogue mutations in HIV-1 reverse transcriptase	In vitro	In vitro	[redacted] USA	AIDS 2007;21:1405–1414 {11306}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
The K65R mutation in HIV-1 reverse transcriptase exhibits bidirectional phenotypic antagonism with thymidine analogue mutations	In vitro	In vitro	[redacted] USA	J Virol 2006,80:4971–4977 {9037}
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}

Type of Study/Description	Test System	Method of Administration	Testing Facility	Study No and Reference
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}
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] 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] Australia	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

6.3.5. FTC/TDF Tabular Summary of Nonclinical Virology 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

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.3 — SUMMARY OF CLINICAL EFFICACY

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (E/C/F/TAF FDC)

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.3 — SUMMARY OF CLINICAL EFFICACY 1
TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 3
LIST OF IN-TEXT FIGURES 3
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 5
PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS 8
1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY 9
2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES 15
2.1. ART-Naive Subjects: Studies GS-US-292-0104, GS--US-292-0111, and GS-US-292-0102 15
2.1.1. Study GS-US-292-0104 (Phase 3) 15
2.1.2. Study GS-US-292-0111 (Phase 3) 24
2.1.3. Study GS-US-292-0102 (Phase 2) 33
2.2. Virologically Suppressed Subjects: Study GS-US-292-0109 43
3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES 54
3.1. Study Populations 54
3.1.1. Subject Disposition 54
3.1.2. Demographic and Other Baseline Characteristics 56
3.1.3. Analysis Populations 63
3.2. Comparison of Efficacy Results of All Studies 65
3.2.1. ART-Naive Subjects: Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102 65
3.2.2. Virologically Suppressed Subjects: Studies GS-US-292-0109 and GS-US-292-0102 78
3.2.3. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112 80
3.2.4. ART-Naive Adolescent Subjects: Study GS-US-292-0106 83
3.3. Comparison of Results in Subpopulations 85
3.3.1. ART-Naive Subjects: Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102 86
3.3.2. Virologically Suppressed Subjects: Study GS-US-292-0109 93
3.3.3. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112 96
3.3.4. Results of Ad Hoc Analyses in Subjects of Age ≥ 65 years 96
4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS 97
4.1. Choice of Dose 97
4.2. Food Effect on Dose of E/C/F/TAF FDC 98
5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS 99
6. REFERENCES 100
7. APPENDIX 102
7.1. Tabular Summary of Studies Relevant for Efficacy 103
7.2. Additional Efficacy Analysis 106

LIST OF IN-TEXT TABLES

Table 1. Studies Supporting Clinical Efficacy for the E/C/F/TAF Marketing Application 10
Table 2. Number of Subjects Enrolled or Randomized Who Received E/C/F/TAF in Studies Included in the Submission by Region 12
Table 3. Efficacy Endpoints Included in this Summary by Study 13
Table 4. 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) 55
Table 5. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Demographic and Baseline Characteristics (Safety Analysis Set) 57
Table 6. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Baseline Disease Characteristics (Safety Analysis Set) 60
Table 7. 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 64
Table 8. 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) 66
Table 9. 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) 67
Table 10. GS-US-292-0102: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) 68
Table 11 GS-US-292-0109: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) 79
Table 12. GS-US-292-0112: Virologic Outcome at Week 24 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) 81
Table 13. GS-US-292-0112: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) 82
Table 14. GS-US-292-0106: Virologic Outcome at Week 24 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) 84
Table 15. 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) 89
Table 16. 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) 91
Table 17. 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) 95

LIST OF IN-TEXT FIGURES

Figure 1. GS-US-292-0104: Mean and 95% CIs of Change from Baseline by Visit in HIV-1 RNA (log_{10} copies/mL) (FAS) 72
Figure 2. GS-US-292-0111: Mean and 95% CIs of Change from Baseline by Visit in HIV-1 RNA (log_{10} copies/mL) (FAS) 73
Figure 3. GS-US-292-0104: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS) 75
Figure 4. GS-US-292-0111: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS) 76
Figure 5. GS-US-292-0102: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS) 77

Figure 6. 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) 87
Figure 7. 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) 94

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV	atazanavir
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
BHIVA	British HIV Association
BL	baseline
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
CMH	Cochran-Mantel-Haenszel
COBI, C	cobicistat (Tybost®)
CSR	clinical study report
C-telopeptide	type I collagen C-telopeptide
CV	coefficient of variation
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
DHHS	Department of Health and Human Services
DRV, D	darunavir
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 creatinine method
$eGFR_{CKD\text{-}EPI,\ cysC}$	estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C method
E_{max}	Maximum (pharmacodynamics) effect
EQ VAS	EQ visual analogue scale
EVG, E	elvitegravir (Vitekta®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

$FEPO_4$	fractional excretion of phosphate
FEUA	fractional excretion of uric acid
FTC, F	emtricitabine (Emtriva®)
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®/Eviplera®)
GFR	glomerular filtration rate
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HDL	high-density lipoprotein
IC_{95}	Concentration that results in 955% inhibition
HIV, HIV-1	human immunodeficiency virus, type 1
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INSTI	integrase strand-transfer inhibitor
IQ_{95}	95% inhibitory quotient
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	intravenous
LDL	low-density lipoprotein
LOCF	last observation carried forward
LSM	least-squares mean
m	Module
M = E	missing = excluded
M = F	missing = failure
M = LOCF	missing = last observation carried forward
MH	Mantel-Haenszel
N or n	number of subjects in a population (N) or subset (n)
N/A	not applicable
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PEP	postexposure prophylaxis
P-gp	P-glycoprotein
PI	protease inhibitor
PINP	procollagen type 1 N-terminal propeptide
PK	pharmacokinetic(s)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

PO	orally
PP	per protocol
PrEP	pre-exposure prophylaxis
PT	preferred term
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QD	once daily
RBP	retinol binding protein
RNA	ribonucleic acid
ROW	Rest of World
RPV	rilpivirine
RTV	ritonanvir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
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
USPI	United States prescribing information
vs	versus

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_{tau}	area under the plasma/PBMC 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
PBMC	peripheral blood mononuclear cell
T_{max}	time (observed time point) of C_{max}
$t_{1/2}$	estimate of the terminal elimination half-life of the drug

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 (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 the optimization of tolerability, long-term safety, and adherence of potent ART regimens {29705}. In addition, there remains a significant medical need for new, effective therapies that take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, non-HIV comorbidities, and regimen simplification.

For ART-naive HIV- infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI) {28776, 27621}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {21053}, {29702}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. 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}. Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF.

Gilead Sciences (Gilead) has coformulated TAF with the HIV-1 INSTI elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), and the NRTI emtricitabine (FTC; F) into an FDC tablet that is suitable for once-daily use. This E/C/F/TAF FDC may provide a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients infected with HIV.

This document is a summary of clinical efficacy data from 6 clinical studies (Table 1) relevant to the proposed indication.

Table 1. Studies Supporting Clinical Efficacy for the E/C/F/TAF Marketing Application

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	CSR and Narrative Locations
HIV-Infected, ART-Naive Adult Subjects				
GS-US-292-0104	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 435) STB + placebo-to-match E/C/F/TAF FDC (N = 432)	Week 48 efficacy, PK, and safety	**CSR:** m5.3.5.1, GS-US-292-0104 **Narrative:** Section 2.1.1
GS-US-292-0111	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 431) STB + placebo-to-match E/C/F/TAF FDC (N = 435)	Week 48 efficacy, PK, and safety	**CSR:** m5.3.5.1, GS-US-292-0111 **Narrative:** Section 2.1.2
GS-US-292-0102	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB Open-label extension phase allowed crossover from STB to E/C/F/TAF after the Week 48 visit and enrollment of virologically suppressed adult subjects who had received a DRV+COBI-containing regimen in Study GS-US-299-0102	Randomized phase: E/C/F/TAF FDC + placebo-to-match STB (N = 112) STB + placebo-to-match E/C/F/TAF FDC (N = 58) Open-label extension phase: Continued on E/C/F/TAF FDC (N = 105) Switch to E/C/F/TAF FDC (N = 161) from STB to E/C/F/TAF FDC (N = 53) from D/C/F/TAF to E/C/F/TAF FDC (N = 70) from DRV+COBI+TVD to E/C/F/TAF FDC (N = 38)	Week 48[b] efficacy, PK, and safety	**CSR:** m5.3.5.1, GS-US-292-0102 **Narrative:** Section 2.1.3
HIV-Infected, Virologically Suppressed Adult Subjects				
GS-US-292-0109	Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to E/C/F/TAF FDC	Switch to E/C/F/TAF FDC (N = 959) Stay on FTC/TDF+3rd Agent (N = 477)	Week 48 efficacy and safety	**CSR:** m5.3.5.1, GS-US-292-0109 **Narrative:** Section 2.2
HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment				
GS-US-292-0112	Phase 3, open-label, multicenter, multiple cohort study evaluated the safety, efficacy, and tolerability of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 248)	Week 24 efficacy and safety	**CSR:** m5.3.5.2, GS-US-292-0112 **Narrative:** m2.7.4, Section 1.1.4.1
HIV-Infected, ART-Naive, Adolescent Subjects				
GS-US-292-0106	Phase 2/3, open-label, multicenter, 2-part, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 48) PK substudy: N = 24	Week 24 efficacy, PK, and safety	**CSR:** m5.3.5.2, GS-US-292-0106 **Narrative:** m2.7.4, Section 1.1.4.2

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

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.

The following is the proposed indication for E/C/F/TAF:

E/C/F/TAF is indicated for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of E/C/F/TAF.

The efficacy of E/C/F/TAF for the treatment of HIV-1 infection in ART-naive subjects is supported by data from the randomized, double-blind, active-controlled studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102. 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 Stribild® (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 (United States [US] versus ex-US) at screening.

The Phase 2, randomized, double-blind, active-controlled study in ART-naive subjects (Study GS-US-292-0102) 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.

Stribild was chosen as the comparator in the 3 double-blind studies in ART-naive subjects (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102) because it allowed for a direct and exclusive comparison between TAF and TDF (as the other components of the regimens are identical). Stribild is now a preferred standard of care regimen for initial therapy in the United States (US) Department of Health and Human Services (DHHS) guidelines and the British HIV Association (BHIVA) guidelines, and an alternative initial ARV regimen in the European AIDS Clinical Society (EACS) guidelines {26961}, {27621}, {27094}.

The efficacy of E/C/F/TAF in virologically suppressed adult subjects who switched to E/C/F/TAF is supported by data from Study GS-US-292-0109 and the extension phase of 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, Atripla® (ATR), COBI-boosted atazanavir (ATV/co)+FTC/TDF (Truvada®; TVD), or ritonavir-boosted atazanavir (ATV/r)+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 + a 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 darunavir (DRV; D) +COBI-containing regimen in Study GS-US-299-0102 who switch to E/C/F/TAF. All of these subjects were required to have an $eGFR_{CG}$ of > 50 mL/min at study entry.

The efficacy of E/C/F/TAF in adult subjects with mild to moderate renal impairment is supported by data from 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.

Data from the Phase 2/3, open-label study GS-US-292-0106 support the efficacy of E/C/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.

Across these 6 studies, a total of 2394 subjects were enrolled or randomized and received at least 1 dose of E/C/F/TAF in the US, Europe, and Rest of World (including Asia, Africa, Australia, Canada, and Central and South America) (Table 2), 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).

Table 2. Number of Subjects Enrolled or Randomized Who Received E/C/F/TAF in Studies Included in the Submission by Region

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

a Phase 3 studies: GS-US-292-0104 (US:252; Europe: 74; ROW: 109), GS-US-292-0111 (US:280; Europe: 86; ROW: 65); GS-US-292-0109 (US:648; Europe: 125; ROW: 186); GS-US-292-0112 (US:171; Europe: 26; ROW: 51); GS-US-292-0106 (US:9; Europe: 0; ROW: 39)

b Phase 2 study: Study GS-US-292-0102

Source: m5.3.5.1, GS-US-292-0104, Section 15.2, Table 1; m5.3.5.1, GS-US-292-0111, Section 15.2, Table 1; m5.3.5.1, GS-US-292-0102, Section 15.2, Table 1.1 and 1.2; m5.3.5.1, GS-US-292-0109, Section 15.2, Table 1; m5.3.5.2, GS-US-292-0112, Section 15.2, Table 1; m5.3.5.2, GS-US-292-0106, Section 15.2, Table 1

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 Phase 2 study in ART-naive subjects (Study GS-US-292-0102), and for subjects with mild to moderate renal impairment (Study GS-US-292-0112). For adolescents (Study GS-US-292-0106), for subjects with mild to moderate renal impairment (Study GS-US-292-0112), and for the switch subjects in Study GS-US-292-0102, the proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 24 as defined by the FDA snapshot algorithm was evaluated.

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-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	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	Weeks 24 & 48	Week 24
HIV-1 RNA < 50 copies/mL using M = F	Week 48	Week 48	Week 48	Week 24	Week 24
Change from baseline in HIV-1 RNA	Week 48	Week 48	—	—	—
Change from baseline in CD4 cell count	Week 48	Week 48	Week 48	Weeks 24 & 48	Week 24

M = E = missing = exluded; 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 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 studies are presented in m5.3.5.4, PC-120-2020.

Statistical methods are presented in the statistical analysis plans (SAPs) for the individual studies (m5.3.5.1, GS-US-292-0104, Appendix 16.1.9, SAP; m5.3.5.1, GS-US-292-0111, Appendix 16.1.9, SAP; m5.3.5.1, GS-US-292-0102, Appendix 16.1.9, SAP; m5.3.5.1, GS-US-292-0109, Appendix 16.1.9, SAP; m5.3.5.2, GS-US-292-0106, Appendix 16.1.9, SAP; m5.3.5.2, GS-US-292-0112, Appendix 16.1.9, SAP) and in the Integrated Summary of Efficacy (ISE) SAP for the pooled studies (m5.3.5.3). A tabular summary of study designs for Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, and GS-US-292-0109 is provided in Appendix 7.1

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. ART-Naive Subjects: Studies GS-US-292-0104, GS--US-292-0111, and GS-US-292-0102

2.1.1. 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) (m5.3.5.1, GS-US-292-0104) 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 event (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 (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 ≤ 100,000 copies/mL, 17.4% had > 100,000 to ≤ 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-defined 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% confidence interval [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-defined 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 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 (standard deviation [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 similar for each treatment group through Week 48 (observed data) using the FAS, 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 rate of virologic success by FDA-defined 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 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.

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 the table below.

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; Q1, Q3 = first, third quartile

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 the table below.

	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

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 the table below.

	GLSMs by Treatment			
TFV PK Parameter	E/C/F/TAF (N = 15)	STB (N = 15)	GLSM Ratio (%)	90% CI (%)
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

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 the table below.

TFV-DP PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 10)	STB (N = 10)		
AUC_{tau} (µmol•h/L)	7.13	2.11	338.22	(163.78, 698.45)

GLSM = geometric least-squares mean

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 United States prescribing information [USPI]). The TFV exposure following E/C/F/TAF was also lower than the exposure seen after coadministration of TDF with or without boosted protease inhibitors.

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 adverse event (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 AEs 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 serious adverse events (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 (PINP) (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%); PINP: 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 (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-defined 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
  - Proteinuria
- Increases from baseline in fasting lipid parameters were higher in the E/C/F/TAF group than the STB group.

2.1.2. Study GS-US-292-0111 (Phase 3)

A complete study description and results for Study GS-US-292-0111 are available in the CSR (m5.3.5.1, GS-US-292-0111) 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 $eGFR_{CG}$ ≥ 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 ($eGFR_{CKD\text{-}EPI,\ cysC}$) 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-defined 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-defined 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) log10 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 rate of virologic success by FDA-defined 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 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 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 the table below.

Treatment E/C/F/TAF	AUC_{last} (ng·h/mL) Mean (%CV) (N = 20)	C_{max} (ng/mL) Mean (%CV) (N = 20)	T_{max} (h) Median (Q1, Q3) (N = 21)	$t_{1/2}$ (h) Median (Q1, Q3) (N = 19)
TAF	259.0 (71.6)	201.6 (72.6)	1.00 (0.50, 2.05)	0.48 (0.39, 0.68)

CV = coefficient of variation; Q1, Q3 = first, third quartile

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 the table below.

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)

NC = not calculated
a Values are listed as mean (%CV) except T_{max} and $t_{1/2}$, which are listed as median (Q1, Q3).

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 the table below.

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)

GLSM = geometric least-squares mean

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 the table below.

TFV-DP PK Parameter	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	E/C/F/TAF (N = 11)	STB (N = 4)		
AUC_{tau} (µmol•h/L)	21.02	7.76	270.90	(164.29, 446.71)

GLSM = geometric least-squares mean

Overall, the steady-state plasma exposure 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 exposure 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}. 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).

Serious AEs 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 PINP (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) percent 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%); PINP 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 proximal renal tubulopathy (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 ≥ 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). Elven 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-defined 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
- Increases from baseline in fasting lipid parameters were higher in the E/C/F/TAF group than the STB group.

2.1.3. Study GS-US-292-0102 (Phase 2)

A complete study description and results for Study GS-US-292-0102 are available in the CSR (m5.3.5.1, GS-US-292-0102) and a brief narrative of this study is presented below.

Title

A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of 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 darunavir (DRV, D)+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-defined 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-defined 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-defined 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 protease inhibitors.

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 the table below:

	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

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 proximal renal tubulopathy 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 percent 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-defined 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/T/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

  — 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.

2.2. Virologically Suppressed Subjects: Study GS-US-292-0109

A complete study description and results for Study GS-US-292-0109 are available in the CSR (m5.3.5.1, GS-US-292-0109) 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 is 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-defined 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

Diagnosis and Main Criteria for Inclusion

Subjects enrolled in this study were HIV-infected adults receiving ART regimens consisting of STB, ATR, ATV/r+TVD, or ATV/co+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 remaining 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%) prematurely 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 9 subjects (0.9%) in the E/C/F/TAF group and 7 subjects (1.5%) in the FTC/TDF+3rd Agent group.

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 (m5.3.5.1, GS-US-292-0109, Appendix 16.2, Listing 44).

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 the table below:

	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

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: 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: 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 proximal renal tubulopathy (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 changes from baseline in serum creatinine were: 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: 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 efavirenz (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 were: 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.

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

  — Decreases in proteinuria and albuminuria

  — Decreases in several markers of proximal renal tubular 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.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Study Populations

3.1.1. Subject Disposition

Across the 6 clinical studies summarized in this document, 2394 subjects were randomized or enrolled and received at least 1 dose of E/C/F/TAF (Table 4). 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 total of 1032 ART-naive subjects across 5 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 the 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 the Phase 3 study GS-US-292-0109, 161 subjects in the extension phase of the Phase 2 study GS-US-292-0102, and 242 subjects with mild to moderate renal impairment in the Phase 3 study GS-US-292-0112.

Subject disposition for Studies GS-US-292-0104 and GS-US-292-0111 combined is summarized in m5.3.5.3, E/C/F/TAF Integrated Summary of Safety (ISS), Table 1 and Figure 1.

Table 4. 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 m5.3.5.1, 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 1).

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 entering the open-label extension phase.

The denominator for percentages was based on the number of subjects in the Safety Analysis Set

Source: m5.3.5.3, E/C/F/TAF, Integrated Summary of Safety [ISS], Table 1; m5.3.5.1, GS-US-292-0102, Section 15.1, Table 3.1; m5.3.5.1, GS-US-292-0109, Section 15.1, Table 3; m5.3.5.2, GS-US-292-0112, Section 15.1, Table 2; m5.3.5.2, GS-US-292-0106, Section 15.1, Table 2

3.1.2. Demographic and Other Baseline Characteristics

3.1.2.1. Demographic and General Baseline Characteristics

Demographic and general baseline characteristics were generally similar between treatment groups within each randomized study (Table 5). 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 87 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 pivotal studies (GS-US-292-0104 and GS-US-292-0111), approximately 10% 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 (GS-US-292-0106) included 28 female subjects (58.3%). Across studies of adult subjects, the most common races were white (approximately 55% to 70%) and black (approximately 20% to 30%), and approximately 15% to 25% subjects were Hispanic or Latino. Of the adolescent subjects (Study GS-US-292-0106), 87.5% were black and 12.5% were Asian, and none were Hispanic or Latino.

Table 5. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: 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 m5.3.5.1, 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: m5.3.5.3 E/C/F/TAF ISS Table 2; m5.3.5.1, GS-US-292-0102, Section 15.1, Tables 1.1 and 5.1; m5.3.5.1, GS-US-292-0109, Section 15.1, Tables1 and 5.1; m5.3.5.2, GS-US-292-0112, Section 15.1, Tables 1 and 4.1; m5.3.5.2, GS-US-292-0106, Section 15.1, Tables 1, 4.1 and 5

3.1.2.2. Baseline Disease Characteristics

Baseline disease characteristics were generally similar between treatment groups within each randomized study (Table 6). The median baseline HIV-1 RNA value in ART-naive subjects (across all 5 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 425 cells/μL in ART-naive subjects (across all 5 studies) and approximately 675 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 (83.3%) 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 values of subjects who were ART-naive (Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, and GS-US-292-0106) or virologically suppressed (Study GS-US-292-0109) ranged from 105.7 to 117.0 mL/min ($eGFR_{CG}$ in adult subjects or calculated using the modified Schwartz formula in adolescent subjects), and proteinuria by urinalysis (dipstick) of any grade was observed in approximately 10% or less of these subjects.

In contrast, 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 30 to 59 mL/min; 63.3% [157 of 248 subjects]) at baseline.

Table 6. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: 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%)
Missing	1	0	0	0	0	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)
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	N/A[h]
Hypertension[g]									
Yes	118 (13.6%)	146 (16.8%)	14 (12.5%)	6 (10.3%)	—[e]	—[e]	95 (39.3%)	3 (50%)	N/A[h]
Cardiovascular disease[g]									
Yes	11 (1.3%)	14 (1.6%)	4 (3.6%)	1 (1.7%)	—[e]	—[e]	—	—	N/A[h]
Hyperlipidemia[g]									
Yes	92 (10.6%)	100 (11.5%)	15 (13.4%)	6 (10.3%)	—[e]	—[e]	—	—	N/A[h]

N/A = 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 m5.3.5.1, 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: m5.3.5.3, E/C/F/TAF ISS, Table 3; m5.3.5.1, GS-US-292-0102, Section 15.1, Table 6.1; m5.3.5.1, GS-US-292-0109, Section 15.1, Table 6.1 and Appendix 16.2, Listing 7; m5.3.5.2, GS-US-292-0112, Section 15.1, Tables 5.1, 20.2, 21.2, and Ad Hoc Table req6756.14; m5.3.5.2, GS-US-292-0106, Section 15.1, Tables 4.1 and 5

3.1.3. Analysis Populations

For 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 7). 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 7. 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: m5.3.5.1, GS-US-292-0104, Section 15.1, Table 4; m5.3.5.1, GS-US-292-0111, Section 15.1, Table 4; m5.3.5.1, GS-US-292-0102, Section 15.1, Tables 4.1 and 4.2; m5.3.5.1, GS-US-292-0109, Section 15.1, Table 4; m5.3.5.2, GS-US-292-0112, Section 15.1, Table 3; m5.3.5.2, GS-US-292-0106, Section 15.1, Table 3

3.2. Comparison of Efficacy Results of All Studies

3.2.1. ART-Naive Subjects: 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 (m5.3.5.1, GS-US-292-0104, Section 9; GS-US-292-0111, Section 9; GS-US-292-0102, Section 9).

3.2.1.1. 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 8). 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 8). 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 8. 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 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: m5.3.5.3, 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 9). 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 9. 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: m5.3.5.3, 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 10). 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 10. 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: 5.3.5.1, GS-US-292-0102, Section 15.1, Table 10.3

3.2.1.2. 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-defined 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-defined 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-defined snapshot algorithm (HIV-1 RNA < 20 copies/mL) based on the FAS (m5.3.5.3, 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-defined 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%.

3.2.1.3. 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% (m5.3.5.3, 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% (m5.3.5.3, 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%.

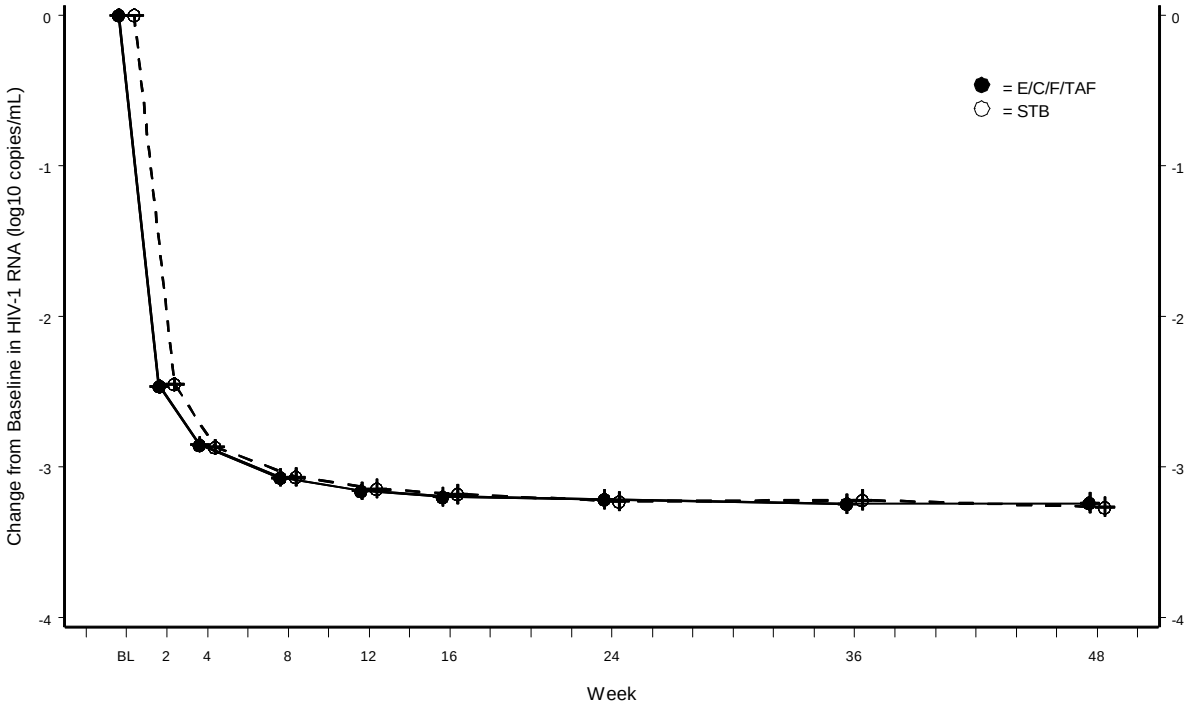
High and similar rates of virologic suppression were achieved in the 2 treatment groups at Weeks 24 and 48 using the Week 48 PP Analysis Set. The percentages of subjects with virologic suppression at Week 48 were as follows: M = F: E/C/F/TAF 95.0%, 96 of 101 subjects; STB 90.7%, 49 of 54 subjects; M = E: E/C/F/TAF 95.0%, 96 of 101 subjects; STB 92.5%, 49 of 53 subjects.

3.2.1.4. 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. 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.

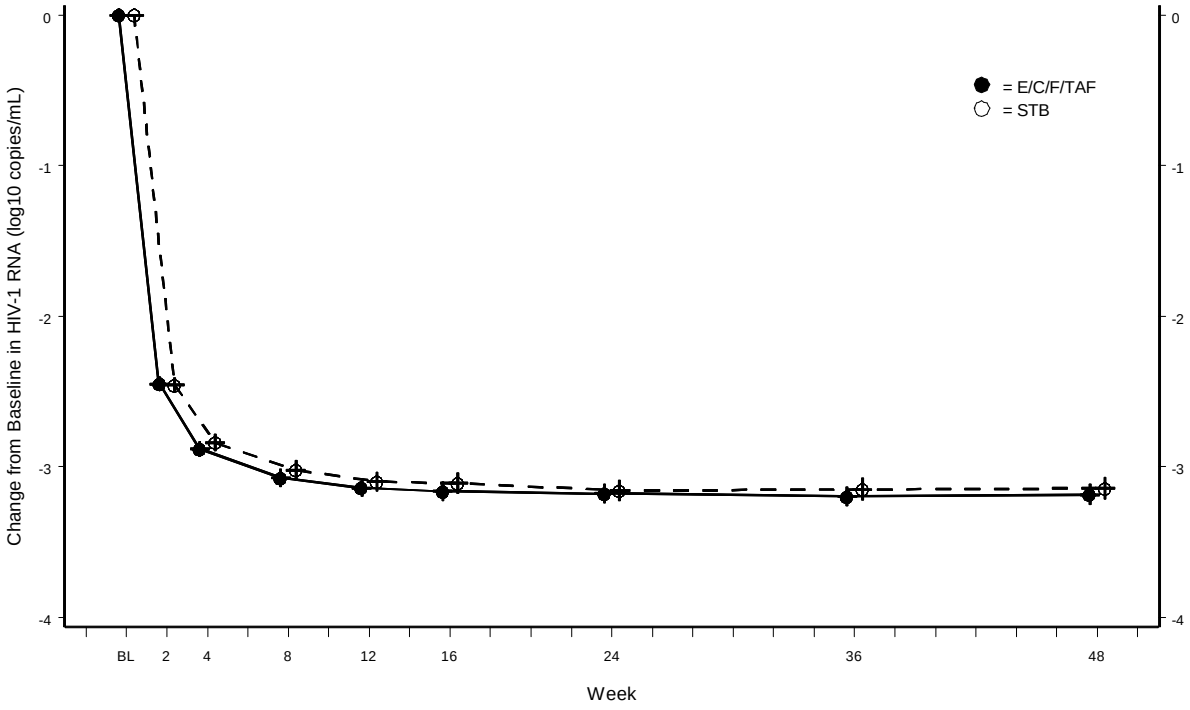
Data Extracted: CRF Data: [redacted]20[redacted], Lab Data: [redacted]20[redacted], DXA Data: [redacted]20[redacted], PK Data: [redacted]20[redacted]
Source: .../version1/prog/t-effchg.sas v9.2 Output file: g-effchg-rna.out [redacted]20[redacted]:10:17

Source: m5.3.5.1, GS-US-292-0104, 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. 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: m5.3.5.1, GS-US-292-0111, 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 (m5.3.5.3, 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.

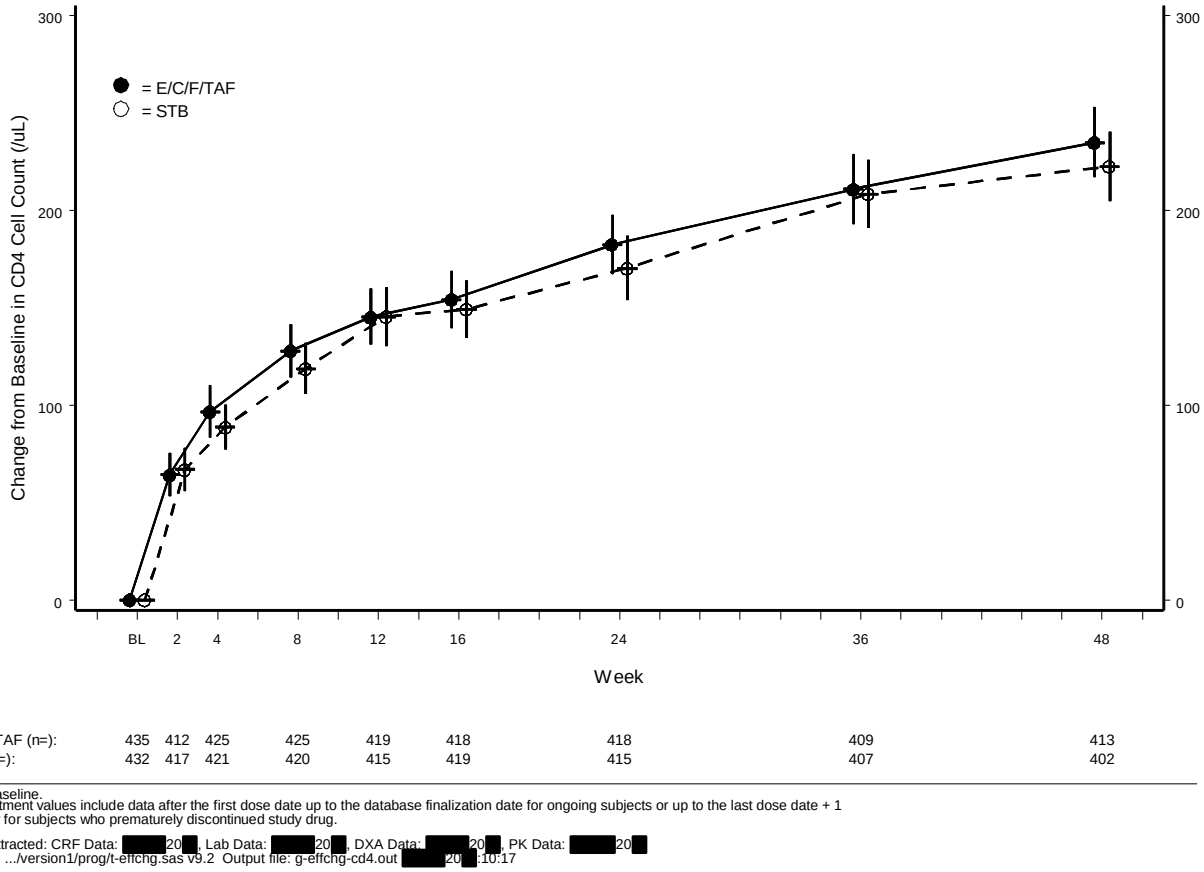
3.2.1.5. Change from Baseline in CD4 Cell Counts

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 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. GS-US-292-0104: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS)



Source: m5.3.5.1, GS-US-292-0104, Section 15.1, Figure 7.1

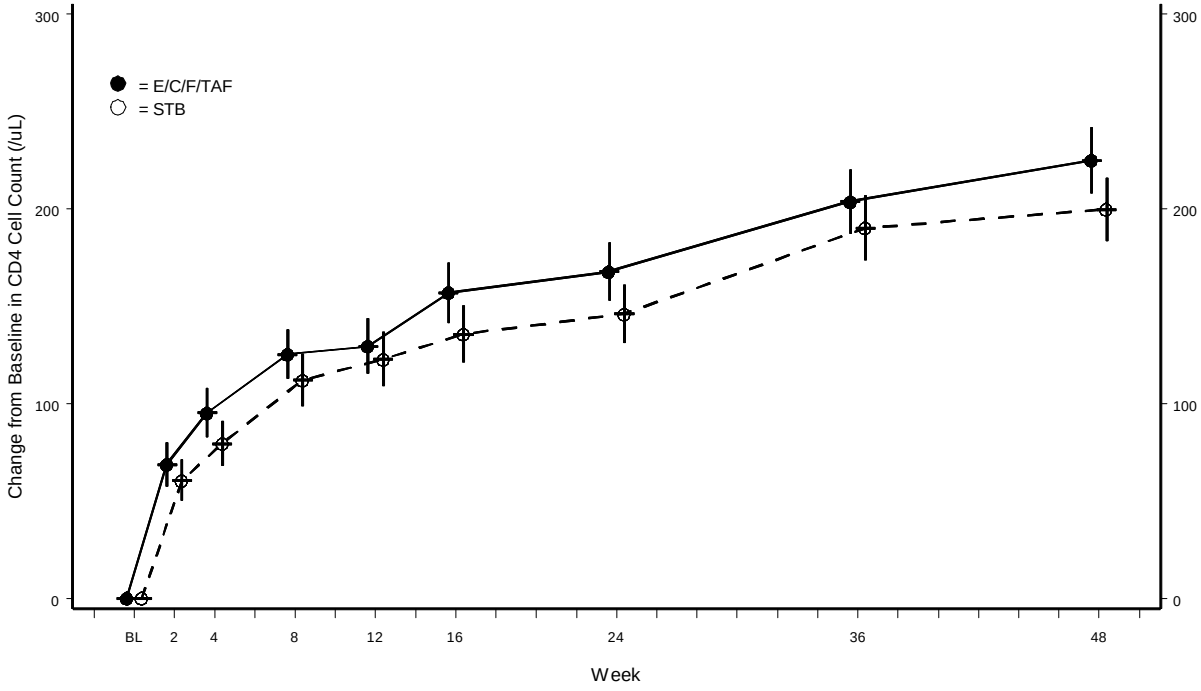
Study GS-US-292-0111

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. 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: m5.3.5.1, GS-US-292-0111, 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 (m5.3.5.3, 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

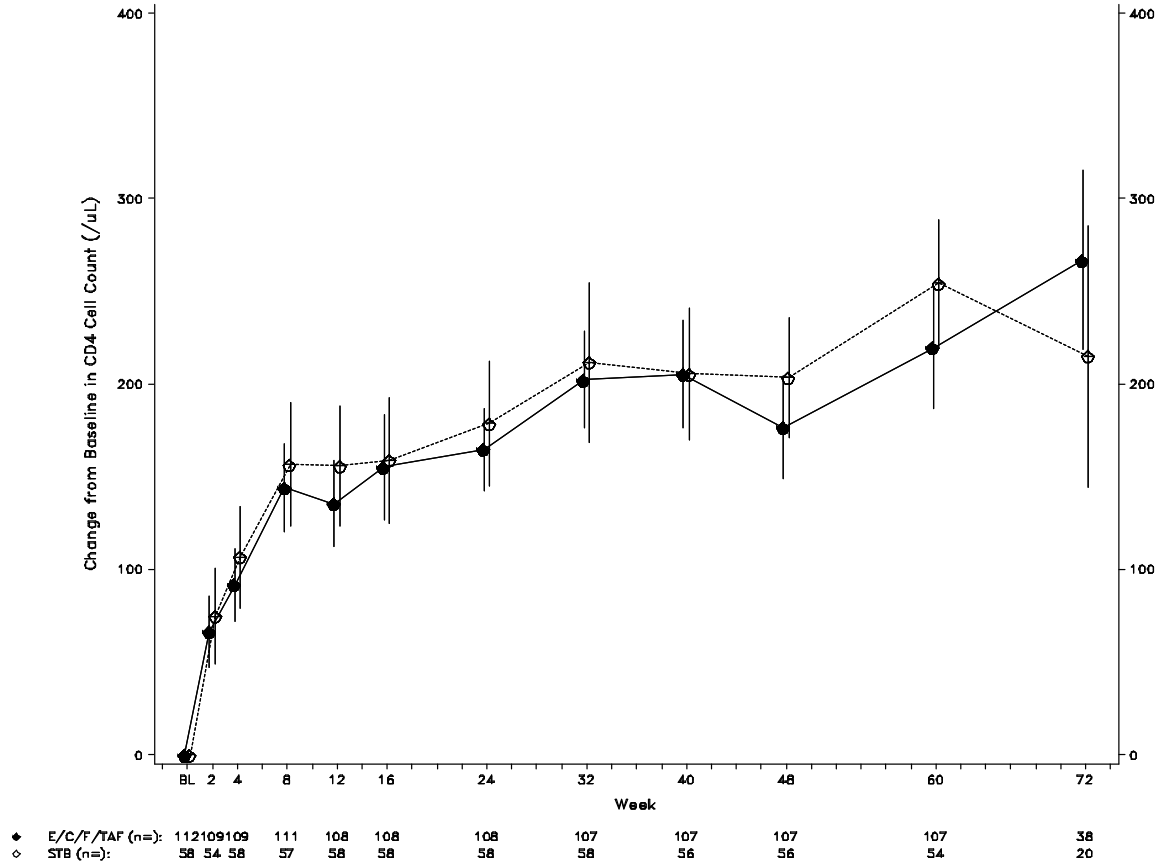
were as follows: E/C/F/TAF 228 (178.9) cells/μL; STB 207 (171.5) cells/μL; difference in LSM: 20 cells/μL, 95% CI: 4 to 37 cells/μL (m5.3.5.3, Ad Hoc Table Req6854.1).

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. GS-US-292-0102: Mean and 95% CIs of Change from Baseline by Visit in CD4 Cell Count (cells/μL) (FAS)



Source: m5.3.5.1, GS-US-292-0102, Section 15.1, Figure 4.1

3.2.2. Virologically Suppressed Subjects: 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.

3.2.2.1. Study GS-US-292-0109 (Phase 3)

Detailed efficacy results are presented in the CSR (m5.3.5.1, GS-US-292-0109, 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 11). 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 11 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: m5.3.5.1, GS-US-292-0109, 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.

3.2.2.2. Study GS-US-292-0102 (Phase 2)

Detailed efficacy results are presented in the CSR (m5.3.5.1, GS-US-292-0102, 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 subjects) 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.

3.2.3. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

Detailed efficacy results are presented in the CSR (m5.3.5.2, GS-US-292-0112, Section 9).

3.2.3.1. 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 12). 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 12. 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: m5.3.5.2, GS-US-292-0112, Section 15.1, Table 26.1

3.2.3.2. 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.

3.2.3.3. 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 13). 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 13. 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: m5.3.5.2, GS-US-292-0112, Section 15.1, Table 26.2

3.2.3.4. 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).

3.2.3.5. 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.

3.2.4. ART-Naive Adolescent Subjects: Study GS-US-292-0106

Detailed efficacy results are presented in the CSR (m5.3.5.2, GS-US-292-0106, Section 9).

3.2.4.1. 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 14). 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 14. 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: m5.3.5.2, GS-US-292-0106, Section 15.1, Table 9.1

3.2.4.2. 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).

3.2.4.3. 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) log10 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.

3.2.4.4. 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.

3.3. Comparison of Results in Subpopulations

Subgroups Analyzed

In ART-naive subjects from 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: United States (US) and ex-US
- Study drug adherence (%): < 95 and ≥ 95

In ART-naive subjects from 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 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 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 (ICH) 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.

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). Additionally, 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. A forest plot was used to present the overall and within subgroup treatment differences with the corresponding 95% CIs.

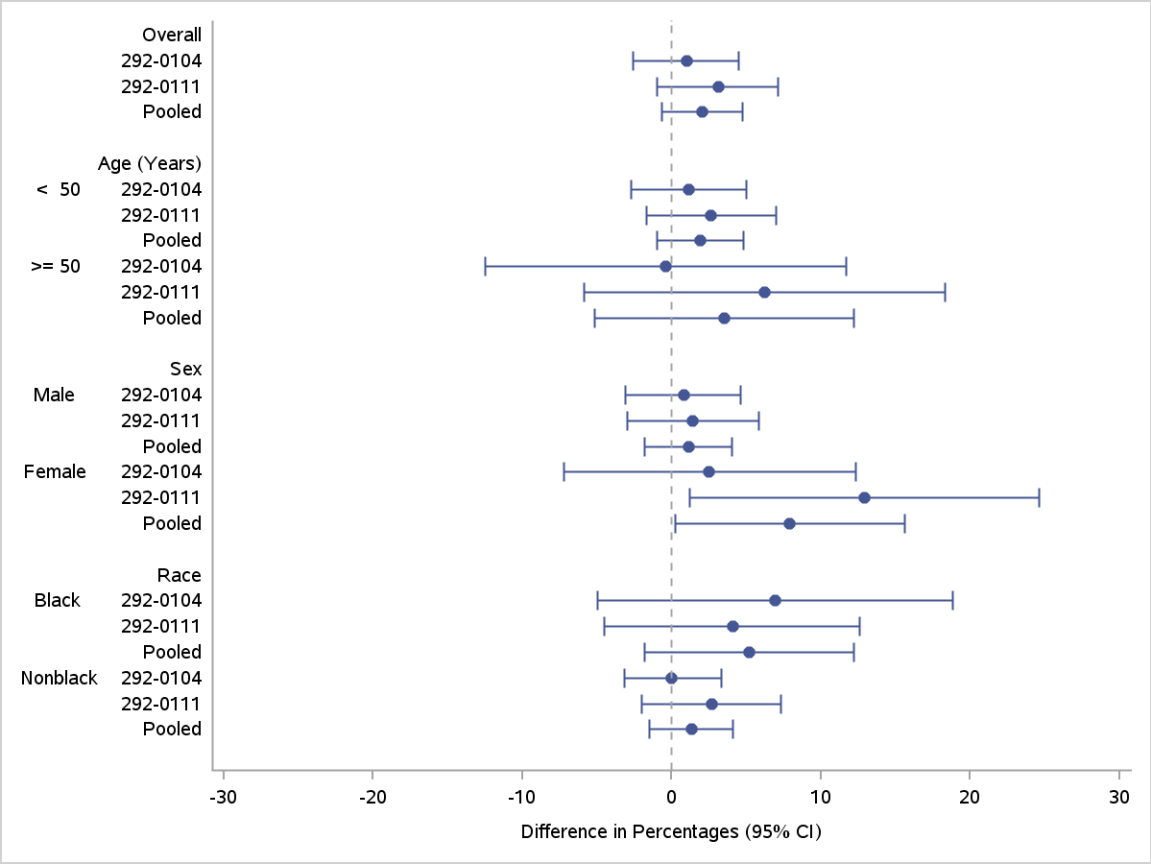
3.3.1. ART-Naive Subjects: Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102

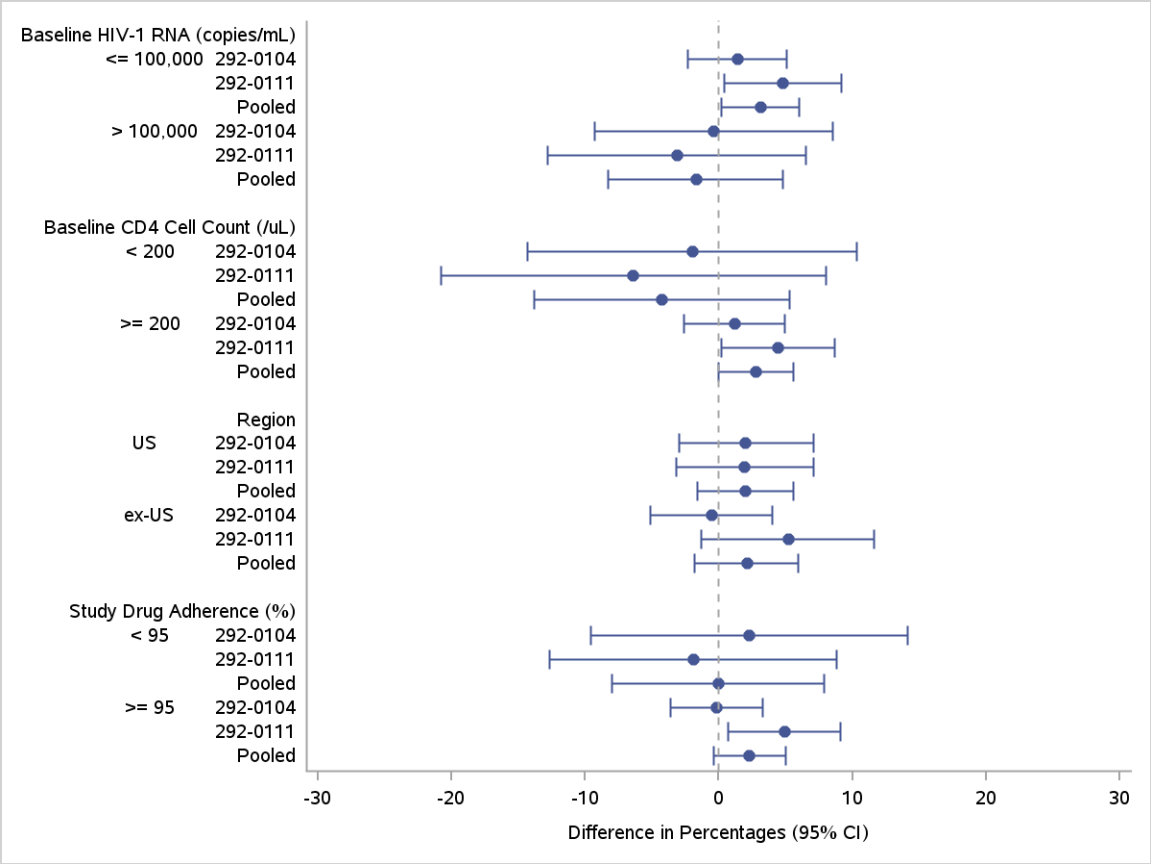
Pooled Data from Studies GS-US-292-0104 and GS-US-292-0111

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-defined 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 6 and Table 15).

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 16).

Figure 6. **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 (BL) 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.
BL 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]20[redacted], Lab Data: [redacted]20[redacted], s292-0111: CRF,DXA Data: [redacted]20[redacted], Lab Data: [redacted]20[redacted]
Source: .../version1/prog/t-snapshot-trtdiff.sas v9.2 Output file: g-snapshot-forest-wk48.out [redacted]20[redacted]:15:52
Source: m5.3.5.3, E/C/F/TAF ISE, Figure 1

Table 15. 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%)

				E/C/F/TAF vs. STB
		E/C/F/TAF (N=866)	STB (N=867)	Difference in Percentages (95% CI)[a]
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%)
> 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 (BL) HIV-1 RNA and region (if not the subgroup factor), and study (for pooled analysis) stratum.

b BL 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: m5.3.5.3, E/C/F/TAF ISE, Table 3

Table 16. 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)
	> 100,000	171/196 (87.2%)	174/195 (89.2%)		0.82 (0.44 to 1.53)

				E/C/F/TAF vs. STB	
		E/C/F/TAF (N=866)	STB (N=867)	p-value[a]	Odds Ratio (95% CI)[b]
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 (BL) 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 BL 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: m5.3.5.3, E/C/F/TAF ISE, Table 4

Study GS-US-292-0102

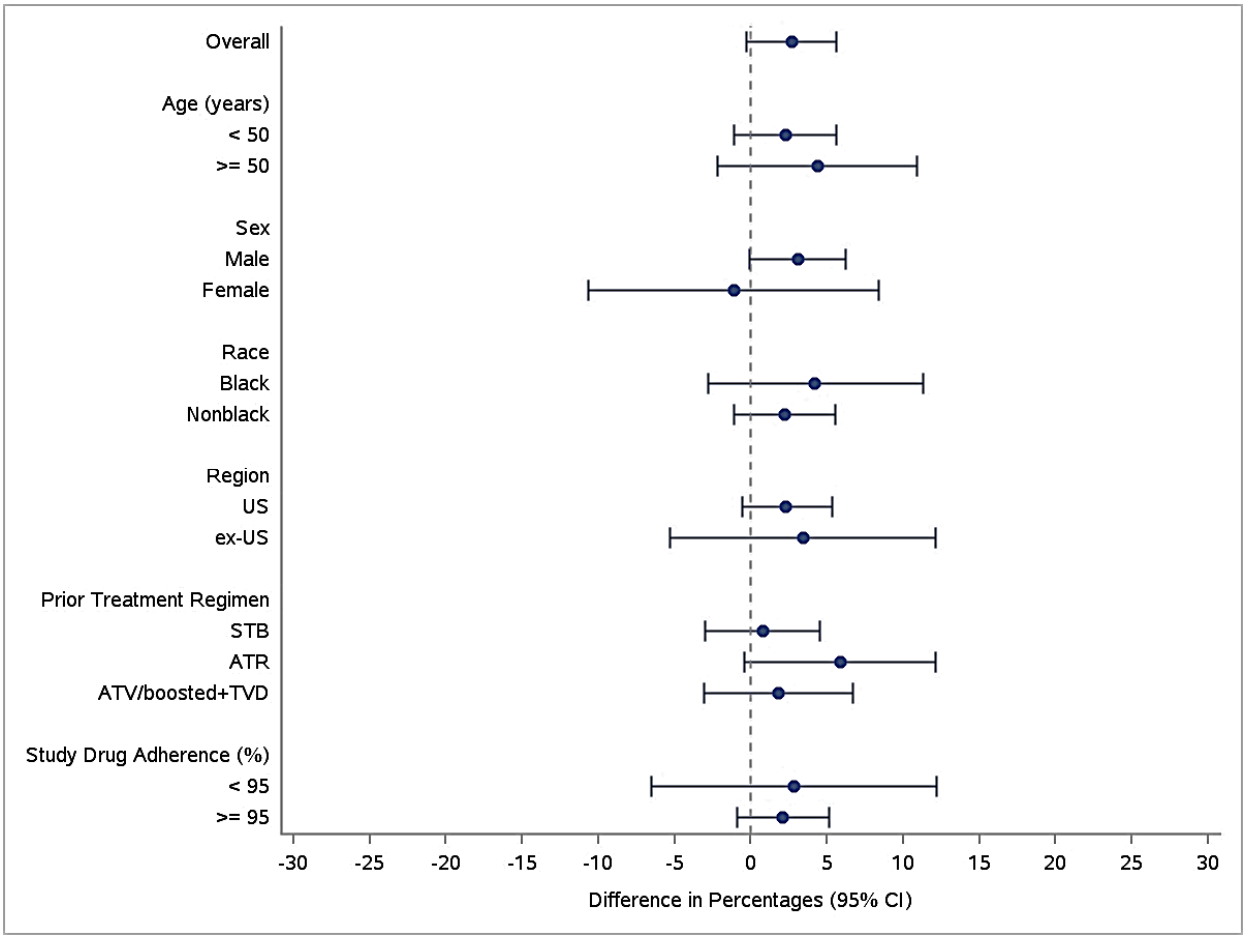
In Study GS-US-292-0102, the rate of virologic success rate at Week 24 was similar between the 2 treatment groups when assessed using the FDA-defined snapshot algorithm (HIV-1 RNA < 50 copies/mL) for all prespecified subgroups. The 95% CIs for differences in virologic success between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments. Data for Week 48 were consistent with results for Week 24 (m5.3.5.1, GS-US-292-0102, Section 9.3).

3.3.2. Virologically Suppressed Subjects: 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 7 and Table 17) (m5.3.5.1, 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+FTC/TDF [Week 48 FAS, observed data]; m5.3.5.1, 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 (m5.3.5.1, GS-US-292-0109, Section 15.1, Table 19.3).

Figure 7. **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: m5.3.5.1, GS-US-292-0109, Section 15.1, Figure 3

Table 17. 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: m5.3.5.1, GS-US-292-0109, Section 15.1, Table 12.1

3.3.3. Subjects with Mild to Moderate Renal Impairment: 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) (m5.3.5.2, GS-US-292-0112, Section 9.3).

3.3.4. Results of Ad Hoc Analyses in Subjects of Age ≥ 65 years

In addition to the discussed prespecified analyses in Section 3.3, 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-defined 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 (m5.3.5.3, 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-defined 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 (m5.3.5.3, 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-defined 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 (m5.3.5.3, Ad Hoc Table Req6756.9).

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

4.1. Choice of Dose

Three components of the E/C/F/TAF FDC, EVG 150 mg, COBI 150 mg, and FTC 200 mg, are ARV agents that were developed by Gilead and are approved as single agents and as components of the STB FDC for the treatment of HIV-1 infection in the US, the European Union, and other markets worldwide. FTC 200 mg is also part of the approved FDCs TVD, ATR, and FTC/RPV/TDF ([Complera®/Eviplera®]) for the treatment of HIV-1 infection.

Each E/C/F/TAF tablet contains EVG, COBI, and FTC at the same dosages as in STB.

The selected dose of TAF single agent is 25 mg. Following an administration of TAF 8 mg, the mean viral load decline was similar to 300 mg TDF. Notably, TAF doses of 25 and 40 mg demonstrated significantly greater antiviral effect than 8-mg TAF, whereas TAF 25 mg did not show a significant difference from TAF 40 mg. Pharmacokinetic/pharmacodynamic (PK/PD) analysis showed that TAF AUC fits well with a maximum response achievable with a drug (E_{max}) model, with an E_{max} for decreases in HIV-1 RNA of approximately 1.7 to 1.8 $\log_{10}$ copies/mL decline from baseline. Upon comparison of antiviral activity with 40 mg and previous data with 120 mg (GS-US-120-1101), TAF 25 mg is expected to provide near-maximal activity (HIV-1 RNA decreases of approximately 1.7 to 1.8 $\log_{10}$ copies/mL) (Study GS-US-120-0104).

When coadministered with COBI, TAF exposures are increased. Tenofovir is transported by P-glycoprotein (P-gp) and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by COBI reduces P-gp-mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed (Studies GS-US-292-0101 and GS-US-311-0101). Results from Study GS-US-292-0103 confirmed that TAF and TFV exposure following a dose of TAF 10 mg given with COBI is comparable with the exposure achieved following administration of TAF 25 mg alone. Therefore, the dose of TAF in the E/C/F/TAF FDC is 10 mg, which yields TAF exposures similar to those of TAF 25 mg alone.

Phase 2 data in Study GS-US-292-0102 with TAF 10 mg in the E/C/F/TAF FDC demonstrated efficacy, based on high proportions of subjects with plasma HIV-1 RNA < 50 copies/mL; the E/C/F/TAF FDC was generally well tolerated. Accordingly, cumulative results from Studies GS-US-120-0104, GS-US-292-0101, GS-US-311-0101, GS-US-292-0103, and GS-US-292-0102 were used in selecting a 10 mg TAF dose for the Phase 3 clinical development of the E/C/F/TAF FDC.

The E/C/F/TAF FDC (EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg) was shown to be effective with a favorable safety and tolerability profile in Phase 2/3 and Phase 3 studies (GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106). Moreover, TAF PK/PD analyses evaluating TAF exposure versus response in the 2 pivotal studies (GS-US-292-0104, GS-US-292-0111) using results from the FDA snapshot

algorithm showed uniformly high virologic success across the quartile categories of TAF AUC_{tau} with no trends in exposure-response relationship observed, confirming the dose selection of TAF 10 mg for the E/C/F/TAF FDC that provides equivalent exposure as TAF 25 mg single agent.

4.2. Food Effect on Dose of E/C/F/TAF FDC

The effect of food on the absorption/bioavailability of TAF was evaluated when given as part of E/C/F/TAF (Study GS-US-292-0110).

Administration of E/C/F/TAF under fed versus fasting conditions did not affect overall exposure of TAF, but resulted in a modestly lower C_{max} and delayed T_{max}. The GLSM ratios (90% CIs) of the AUC_{last} of TAF when administered with a light/low-fat or high-calorie/high-fat meal were 114.95% (106.82% to 123.69%) and 116.65% (108.40% to 125.52%), respectively, and were within the predefined no effect boundary. The GLSM ratios (90% CIs) of the C_{max} of TAF were 68.04% (58.96% to 78.52%) and 63.20% (54.76% to 72.93%) when administered under light/low-fat or high calorie/high-fat conditions, respectively. These modest changes in TAF PK parameters upon E/C/F/TAF administration with food (versus fasted) were not considered clinically relevant (m2.7.2, Section 2.5.1.1).

Although TAF (when administered as E/C/F/TAF) is unaffected by food and does not require a food restriction, it is recommended that boosted EVG be administered with food to achieve EVG exposure that provides a high mean 95% inhibitory quotient (IQ_{95}) (EVG trough concentration [C_{tau}]/concentration that results in 95% inhibition [IC_{95}]) (m2.7.2, Section 3.2.3.1).

As such, E/C/F/TAF was administered with food in the clinical development program to align with the dosing recommendations for EVG and for STB, the comparator in the pivotal Phase 3 studies.

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

In 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.

Of a total of 112 subjects treated with E/C/F/TAF during the randomized phase, 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 (m5.3.5.1, 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 (m5.3.5.1, GS-US-292-0102, Section 9).

All Phase 3 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 for Efficacy
7.2	Additional Efficacy Analyses

7.1. Tabular Summary of Studies Relevant for Efficacy

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; m5.3.5.1, 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
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; m5.3.5.1, 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, 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; m5.3.5.1, 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-292-0111 (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; m5.3.5.1, Week 48 Interim CSR

ART = antiretroviral therapy; ARV = antiretroviral; ATR = efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®); ATV = atazanavir; COBI = cobicistat (Tybost®); CSR = clinical study report; DVR = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; PO = orally; QD = once daily; RNA = ribonucleic acid; RTV = ritonavir; STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®); STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate (Viread®)

7.2. Additional Efficacy Analysis

The following outputs for GS-US-292-0104 and GS-US-292-011 are described in the ISE SAP and are included in m5.3.5.3:

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
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 and are included in m5.3.5.3.

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 2.7.4 — SUMMARY OF CLINICAL SAFETY

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (E/C/F/TAF FDC)

Gilead Sciences

[redacted] **20**[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.4 — SUMMARY OF CLINICAL SAFETY 1
TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 4
LIST OF IN-TEXT FIGURES 5
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 6
PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS 10
INTRODUCTION 11
EXECUTIVE SUMMARY 13
1. EXPOSURE TO DRUG 19
1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies 19
1.1.1. Primary Safety Populations for E/C/F/TAF 19
1.1.2. Other Safety Populations Supportive of E/C/F/TAF 24
1.1.3. Safety Assessments 25
1.1.4. Summary of Results of Individual Studies 26
1.2. Overall Extent of Exposure 45
1.3. Demographic and Other Characteristics of Study Population 49
1.3.1. Summary of Demographic and General Baseline Characteristics 49
1.3.2. Summary of Baseline Disease Characteristics 54
1.4. Analysis Sets 60
2. ADVERSE EVENTS 64
2.1. Analysis of Adverse Events 64
2.1.1. Common Adverse Events 68
2.1.2. Deaths 85
2.1.3. Other Serious Adverse Events 85
2.1.4. Other Significant Adverse Events 88
2.1.5. Analysis of Adverse Events by Organ System or Syndrome 90
2.2. Narratives 147
3. CLINICAL LABORATORY EVALUATIONS 148
3.1. Laboratory Abnormalities 154
3.1.1. ART-Naive Subjects 154
3.1.2. Virologically Suppressed Subjects 161
3.1.3. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112 165
3.1.4. ART-Naive Adolescent Subjects: Study GS-US-292-0106 171
4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY 173
4.1.1. ECG Findings 173
5. SAFETY IN SPECIAL GROUPS AND SITUATIONS 175
5.1. Intrinsic Factors 175
5.1.1. Summary of Intrinsic Factors 175
5.1.2. Sex 175
5.1.3. Age 176
5.1.4. Race 177
5.1.5. HIV-1 RNA Stratum at Baseline 178

5.1.6. CD4 Cell Count at Baseline 178
5.1.7. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters 178
5.1.8. Renal Impairment 180
5.1.9. Hepatic Impairment 182
5.1.10. Coinfection with HIV-1 and Hepatitis B and/or Hepatitis C Virus 183
5.2. Extrinsic Factors 184
5.2.1. Summary of Extrinsic Factors 184
5.2.2. Prior Treatment Regimen 184
5.2.3. Effect of Food 184
5.2.4. Region 185
5.3. Drug Interactions 185
5.4. Use in Pregnancy and Lactation 187
5.4.1. E/C/F/TAF FDC 187
5.4.2. TAF 188
5.4.3. EVG, COBI, and FTC 188
5.5. Overdose 189
5.6. Drug Abuse 191
5.7. Withdrawal and Rebound 191
5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability 191
6. POSTMARKETING DATA 192
7. APPENDICES 193
7.1. List of Appendices 193
7.2. Tabular Summary of E/C/F/TAF Studies Relevant for Safety 194
7.3. Tabular Summary of TAF Studies Relevant for Safety 196
7.4. Tabular Summary of EVG Studies Relevant for Safety 199
7.5. Tabular Summary of COBI Studies Relevant for Safety 200
7.6. Tabular Summary of FTC Studies Relevant for Safety 201
7.7. E/C/F/TAF FDC: Integrated Safety Analyses 204
8. REFERENCES 213

LIST OF IN-TEXT TABLES

Table 1. Studies Supporting Clinical Safety for the E/C/F/TAF Fixed-Dose Combination Marketing Application 22
Table 2. Studies Providing Supporting Clinical Safety for the E/C/F/TAF Fixed-Dose Combination 24
Table 3. Other Completed Studies of TAF 24
Table 4. Studies for Other Components of E/C/F/TAF 25
Table 5. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Duration of Exposure to Study Drug (Safety Analysis Set) 46
Table 6. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Demographic and Baseline Characteristics (Safety Analysis Set) 50
Table 7. 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) 55
Table 8. 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 62
Table 9. 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) 66
Table 10. GS-US-292-0104 and GS-US-292-0111: Adverse Events Reported for ≥ 5% of Subjects in Either Treatment Group (Safety Analysis Set) 69
Table 11. 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) 71
Table 12. GS-US-292-0102: Treatment Emergent Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set) 73
Table 13. 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) 75
Table 14. GS-US-292-0109: Treatment Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group (Safety Analysis Set) 77
Table 15. GS-US-292-0109: Study Drug-Related Adverse Events Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set) 78
Table 16. GS-US-292-0112: Adverse Events Reported for at Least 5% of Subjects in Cohort 1 (Safety Analysis Set) 80
Table 17. GS-US-292-0112: Study Drug Related, Treatment Emergent Adverse Events Reported for at Least 1% of Subjects in Cohort 1 (Safety Analysis Set) 82
Table 18. GS-US-292-0106: Adverse Events Occurring in at Least 5% of Subjects (Safety Analysis Set) 83
Table 19. GS-US-292-0106: Study Drug-Related Adverse Events (Safety Analysis Set) 84
Table 20. Phase 1 TAF Safety Population: Discontinuations Due to Adverse Events 90
Table 21. GS-US-292-0104 and GS-US-292-0111: Clinical Hip BMD Status at Baseline and Week 48 (Hip DXA Analysis Set) 98
Table 22. GS-US-292-0104 and GS-US-292-0111: Clinical Spine BMD Status at Baseline and Week 48 (Spine DXA Analysis Set) 99
Table 23. GS-US-292-0109: Percentage of Subjects with > 3% Change in Hip and Spine BMD by Visit (Hip and Spine DXA Analysis Sets) 108
Table 24. 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) 110
Table 25. 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) 110

Table 26. 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) 115
Table 27. GS-US-292-0104 and GS-US-292-0111: Changes from Baseline in $eGFR_{CG}$ at Weeks 24 and 48 (Safety Analysis Set) 124
Table 28. GS-US-292-0104 and GS-US-292-0111: Renal Biomarkers at Week 48 126
Table 29. GS-US-292-0104 and GS-US-292-0111: Summary of Adverse Events: Eye Disorders (Safety Analysis Set) 140
Table 30. GS-US-292-0102: Summary of Adverse Events: Eye Disorders (Safety Analysis Set) 142
Table 31. GS-US-292-0109: Summary of Adverse Events in the SOC of Eye Disorders (Safety Analysis Set) 144
Table 32. 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) 150
Table 33. 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) 156
Table 34. GS-US-292-0102: Summary of Fasting Metabolic Assessments Change from Baseline at Week 24 and Week 48 (Safety Analysis Set) 159
Table 35. GS-US-292-0109: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set) 164
Table 36. GS-US-292-0112: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set) 166
Table 37. 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) 169
Table 38. GS-US-292-0106: Summary of Fasting Glucose and Lipid Parameters at Week 24 (Safety Analysis Set) 171

LIST OF IN-TEXT FIGURES

Figure 1. 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) 95
Figure 2. 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) 96
Figure 3. 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) 102
Figure 4. 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) 103
Figure 5. 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) 105
Figure 6. 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) 106
Figure 7. 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) 112
Figure 8. 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) 113
Figure 9. 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) 122
Figure 10. 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) 125

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
ART	antiretroviral therapy/treatment
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
ATV	atazanavir
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
AV	atrioventricular
BID	twice daily
BL	baseline
BMD	bone mineral density
BMI	body mass index
BR	background regimen
/co	boosted with cobicistat
CD4	cluster determinant 4
CI	confidence interval
CK	creatine kinase
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®)
CPK	creatine phosphokinase
CPT	Child-Pugh-Turcotte
CSR	clinical study report
C-telopeptide	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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

DDI	drug-drug interaction
DRV, D	darunavir
DTG	dolutegravir
DXA	dual-energy x-ray absorptiometry
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
$eGFR_{MDRD}$	estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation
EVG, E	elvitegravir (Vitekta®)
EVG/r	ritonavir-boosted elvitegravir
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
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
IDV	indinavir
INSTI	integrase strand-transfer inhibitor
INSTI-R	integrase strand-transfer inhibitor resistant
INR	international normalized ratio

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

IQ_{95}	95% inhibitory quotient
ISS	Integrated Summary of Safety
ITT	intent-to-treat
IV	intravenous
KM	Kaplan-Meier
LDL	low-density lipoprotein
LFT	liver function test
LLT	lower-level term
LOCF	last observation carried forward
LPV	lopinavir
LPV/r	ritonavir boosted lopinavir
LSM	least-squares mean
m	Module
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
NFV	nelfinavir
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)
PEP	postexposure prophylaxis
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PO	orally
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PSUR	periodic safety update report
PT	preferred term
PTH	parathyroid hormone

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

PVF	pure virologic failure
QD	once daily
/r	boosted with ritonavir
RAL	raltegravir
RBC	red blood cell
RBP	retinol binding protein
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SER	sertraline
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SMQ	Standardized MedDRA Query
SOC	system organ class
ST segment	period when the ventricles are depolarized
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
STR	single-tablet regimen
tQT	thorough QT
TAF	tenofovir alafenamide
TBLH	total body less head
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir (Viread®)
TFV-DP	tenofovir diphosphate
TG	treatment group
TmP/GFR	renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
TLOVR	time to loss of virologic response
TVD	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
UACR	urine albumin to creatinine ratio
UGT	uridine glucuronosyltransferase
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
UK	United Kingdom
US	United States
vs	versus
ZDV	zidovudine

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

AUC	area under the plasma/serum/PBMC concentration versus time curve
AUC_{inf}	area under the plasma/serum/PBMC concentration versus time curve extrapolated to infinite time
AUC_{last}	area under the plasma/serum/PBMC concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma/serum/PBMC concentration versus time curve over the dosing interval
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{max}	maximum observed plasma/serum/PBMC concentration of drug
C_{min}	minimum observed plasma/serum concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
C_{trough}	plasma/serum/PBMC concentration at the end of the dosing interval
PBMC	peripheral blood mononuclear cell
T_{max}	time (observed time point) of C_{max}
$t_{1/2}$	estimate of the terminal elimination half-life of the drug

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 the optimization of tolerability, long-term safety, and adherence of potent ART regimens {29705}. In addition, there remains a significant medical need for new, effective therapies that take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, non-HIV comorbidities, and regimen simplification.

For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI) {28776}, {27621}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {21053}, {29702}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. 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}. Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF.

Gilead Sciences (Gilead) has coformulated TAF with the HIV-1 INSTI elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), and the NRTI emtricitabine (FTC; F) into an FDC tablet that is suitable for once-daily use. The E/C/F/TAF FDC may provide a potent, convenient, well-tolerated, and practical regimen for the long-term treatment of patients infected with HIV-1.

This document is a summary of the clinical safety data that support the proposed prescribing information for the E/C/F/TAF FDC tablet. The proposed indication for the E/C/F/TAF FDC tablet is the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of E/C/F/TAF. Each E/C/F/TAF FDC tablet contains TAF 10 mg, and EVG, COBI, and FTC at the same doses as included in the approved Stribild® (STB) FDC, ie, 150 mg of EVG, 150 mg of COBI, and 200 mg of FTC.

To support a direct comparison of TAF versus TDF, 2 identical Phase 3 studies differing only in geographic regions were conducted with STB as the comparator to support the registration of E/C/F/TAF. Accordingly, the safety of E/C/F/TAF has been established by these 2 pivotal Phase 3 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, 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 Phase 2 study that enrolled ART-naive subjects who have received E/C/F/TAF for more than 96 weeks and 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. Supportive safety data are provided by Phase 1 studies of TAF (E/C/F/TAF, F/TAF, and TAF) as well as Phase 2 and Phase 3 studies of EVG, COBI, and FTC.

EXECUTIVE SUMMARY

Exposure to Drug

Across the Phase 2 and 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).

Demographic and Other Characteristics of the Study Population

Demographic and general baseline characteristics were generally similar between treatment groups within each study. 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 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).

Approximately 15% of subjects in the pivotal ART-naive studies were women. With the exception of Study GS-US-292-0106, the most subjects across studies were white or black. Subjects in GS-US-292-0106 were black (87.5%) or Asian (12.5%). 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] body mass index [BMI] 20.0 kg/m^2 [18.1, 23.2]).

Baseline disease characteristics were generally similar between treatment groups within each 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 (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 mL/min (45.7, 62.4) 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 mL/min/1.73 m^2.

Across the Phase 3 studies in adults with normal renal function, 10% or less of subjects had any Grade 1, 2, or 3 proteinuria at baseline. In subjects with mild to moderate renal impairment, 9.5% of virologically suppressed subjects had Grade 2 proteinuria by urinalysis (dipstick), and 23.1% of subjects had Grade 1 proteinuria at baseline. Among adolescent subjects, < 5% had proteinuria at baseline.

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. 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. 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 studies (Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109) and < 10% in the E/C/F/TAF group in each study. 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, less off-target TFV-associated toxicity was anticipated in subjects receiving E/C/F/TAF in the Phase 3 randomized studies, including less impact on the nephrotoxicity and reduced BMD. Results from the Phase 2 Study GS-US-292-0102 provided supportive evidence, demonstrating that subjects receiving E/C/F/TAF relative to STB 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).

Significant differences between E/C/F/TAF and STB in renal and bone safety were anticipated in the Phase 3 program, and, after the primary hypothesis of noninferior efficacy of E/C/F/TAF relative to STB was achieved, 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 efavirenz (EFV)-related symptom assessment composite score (virologically suppressed subjects; $p < 0.001$).

<u>Bone Safety</u>

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 studies in ART-naive subjects, subjects receiving E/C/F/TAF experienced significantly less BMD reduction than those receiving STB.

In 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 percent 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 and GS-US-292-0112 confirmed the results in 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.

Renal Safety

Renal Events

There were no cases of proximal renal tubulopathy reported (including Fanconi syndrome) in subjects receiving E/C/F/TAF.

Renal Laboratory Parameters

Across all 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 generally 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.

Across all ART-naive studies, fewer subjects receiving E/C/F/TAF developed treatment-emergent proteinuria than subjects receiving STB. Conversely, 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 change from baseline in UPCR and UACR was 0.1% and -19.5%, respectively.

Across the 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 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 COBI-boosted atazanavir [ATV/co]+ Truvada® TVD) had all 4 confirmed renal laboratory abnormalities as well as a renal AE of Fanconi syndrome.

Ocular Safety

Across all 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.

Clinical Laboratory Evaluations

Laboratory Abnormalities

In the 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, 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-arm 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.

The differences in metabolic laboratory parameters observed between treatment with E/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 in the E/C/F/TAF group compared with the STB group.

Safety in Special Groups and Situations

The 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.

Safety in Subjects with Renal Impairment

The totality of efficacy, safety, and pharmacokinetic (PK) data from 249 HIV-infected subjects with mild to moderate renal impairment in Study GS-US-292-0112 confirm that treatment with E/C/F/TAF may be initiated and continued with no dose adjustment in patients with mild to moderate renal impairment (eGFR > 30 mL/min). As expected due to the renal elimination, FTC PK was higher in subjects with mild to moderate renal impairment compared with those having normal renal function. 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}. 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

The PK of the E/C/F/TAF FDC itself has not been studied in subjects with hepatic impairment. The safety and efficacy of E/C/F/TAF have not been established in patients with significant underlying liver disorders. Regarding the separate components of the FDC, the PK of EVG, COBI, TAF, and 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.

Based on these data, the E/C/F/TAF FDC may be used without dose adjustment in patients with mild or moderate hepatic impairment. Treatment with E/C/F/TAF is not recommended for use in patients with severe hepatic impairment, because no data are available regarding the use of EVG or COBI in this population.

1. EXPOSURE TO DRUG

1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

The principal sources of safety data for the E/C/F/TAF FDC are presented in Table 1 and consist of 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 3 study in ART-naive adolescent subjects (Study GS-US-292-0106). Supportive safety information is provided by 1 Phase 2 study (Study GS-US-292-0102) that included ART-naive subjects and subjects who switched to E/C/F/TAF from another regimen during the open-label extension phase. Studies providing supportive safety data are presented in Table 2 and include Phase 1 studies of TAF (E/C/F/TAF, F/TAF, and TAF) as well as key studies of EVG, COBI, and FTC.

1.1.1. Primary Safety Populations for E/C/F/TAF

ART-Naive Adult Subjects

The 2 pivotal Phase 3 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 [PrEP] or postexposure prophylaxis [PEP] up to 6 months prior to screening), HIV-infected adults with plasma HIV-1 RNA ≥ 1000 copies/mL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and an $eGFR_{CG}$ ≥ 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, 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 ≥ 5000 copies/mL, no prior use of any approved or experimental anti-HIV drug for any length of time, and an $eGFR_{CG}$ ≥ 70 mL/min at screening. The randomized phase of the study was 48 weeks, and most subjects who continued on E/C/F/TAF in the open-label extension completed a total of 96 weeks of treatment with E/C/F/TAF.

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, Atripla® (ATR), ATV/co+ TVD, or ritonavir-boosted ATV (ATV/r)+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 [redacted] 20[redacted]) or had discontinued study treatment before this time. The rationale for performing the interim Week 48 analysis was to include the most current Week 48 data from a virologically suppressed population along with Week 48 data from the 2 pivotal studies in the treatment naive population (GS-US-292-0104 and GS-US-292-0111) in the initial marketing applications for E/C/F/TAF.

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. Most subjects in the open-label extension completed 48 weeks of treatment with 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). 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.

ART-Naive Adolescent Subjects

The safety of E/C/F/TAF in adolescent subjects is supported by data from the Phase 3 open-label Study GS-US-292-0106 (summary information in Section 1.1.4.2). 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.

Table 1. Studies Supporting Clinical Safety for the E/C/F/TAF Fixed-Dose Combination Marketing Application

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	CSR & Narrative Locations
HIV-Infected, ART-Naive Adult Subjects				
GS-US-292-0104	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 435) STB + placebo-to-match E/C/F/TAF FDC (N = 432)	Week 48 efficacy, PK, and safety	**CSR:** m5.3.5.1, GS-US-292-0104 CSR **Narrative:** m2.7.3, Section 2.1.1
GS-US-292-0111	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + placebo-to-match STB (N = 431) STB + placebo-to-match E/C/F/TAF FDC (N = 435)	Week 48 efficacy, PK, and safety	**CSR:** m5.3.5.1, GS-US-292-0111 CSR **Narrative:** m2.7.3, Section 2.1.2
GS-US-292-0102	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB Open-label extension phase allowed crossover from STB to E/C/F/TAF after the Week 48 visit and enrollment of virologically suppressed adult subjects who had received a DRV+COBI-containing regimen in Study GS-US-299-0102	Randomized phase: E/C/F/TAF FDC + placebo-to-match STB (N = 112) STB + placebo-to-match E/C/F/TAF FDC (N = 58) Open-label extension phase: Continued on E/C/F/TAF FDC (N = 105) Switch to E/C/F/TAF FDC (N = 161) from STB to E/C/F/TAF (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:** m5.3.5.1, GS-US-292-0102 CSR **Narrative:** m2.7.3, Section 2.1.3
HIV-Infected, Virologically Suppressed Adult Subjects				
GS-US-292-0109	Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to E/C/F/TAF FDC	Switch to E/C/F/TAF FDC (N = 959) Stay on FTC/TDF+3rd Agent (N = 477)	Week 48 efficacy and safety	**CSR:** m5.3.5.1, GS-US-292-0109 CSR **Narrative:** m2.7.3, Section 2.2
HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment				
GS-US-292-0112	Phase 3, open-label, multicenter, multiple cohort study evaluated the safety, efficacy, and tolerability of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 248)	Week 24 efficacy and safety	**CSR:** m5.3.5.2, GS-US-292-0112 CSR **Narrative:** Section 1.1.4.1
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:** m5.3.5.2, GS-US-292-0106 CSR **Narrative:** m2.7.4, Section 1.1.4.2

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

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 E/C/F/TAF

Supportive safety data are also provided by Phase 1 studies (including E/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 Phase 1 studies. Further details on the TAF Phase 1 studies are provided in the individual clinical study reports (CSRs) located as specified in Table 2. Other completed studies of TAF not included with this application are listed in Table 3.

Studies for other components of E/C/F/TAF (ie, EVG, COBI, and FTC) are also included with this application as supportive safety information, listed in Table 4.

Table 2. Studies Providing Supporting Clinical Safety for the E/C/F/TAF Fixed-Dose Combination

Safety Population	Studies Included in Population	N Receiving TAF	Location
E/C/F/TAF Phase 1	GS-US-292-0101	38	m5.3.3.1, GS-US-292-0101
	GS-US-292-0103	34	m5.3.1.2, GS-US-292-0103
	GS-US-292-0108	20	m5.3.3.1, GS-US-292-0108
	GS-US-292-0110	43	m5.3.3.4, GS-US-292-0110
	GS-US-292-1316	20	m5.3.3.4, GS-US-292-1316
	GS-US-342-1167	24	GS-US-342-1167
TAF Phase 1	GS-120-1101 (first in human)	20	m5.3.4.2, GS-120-1101
	GS-US-120-0104 (dose ranging)	25	m5.3.4.2, GS-US-120-0104
	GS-US-120-0107 (tQT)	58	m5.3.4.1, GS-US-120-0107
	GS-US-120-0108 (renal impairment)	27	m5.3.3.3, GS-US-120-0108
	GS-US-120-0109 (ADME)	8	m5.3.3.1, GS-US-120-0109
	GS-US-120-0114 (hepatic impairment)	40	m5.3.3.3, GS-US-120-0114
F/TAF Phase 1	311-0101 (DDI)	50	m5.3.3.4, GS-US-311-0101

Table 3. Other Completed Studies of TAF

Studies Included in Population	N Receiving TAF	Location
GS-US-120-0117 (DDI)	36	Appendix 7.3
GS-US-120-0118 (DDI)	40	Appendix 7.3

Table 4. Studies for Other Components of E/C/F/TAF

Safety Population	Studies Included in Population	Location
EVG Phase 3	GS-US-183-0145	Appendix 7.4
EVG Phase 1	GS-US-183-1004	m5.3.3.3, GS-US-183-1004
COBI Phase 3	GS-US-216-0114	Appendix 7.5
COBI Phase 1	GS-US-216-0137	m5.3.3.4, GS-US-216-0137
FTC Phase 2 and Phase 3	FTC-301A	Appendix 7.6
	FTC-302	
	FTC-303	
	FTC-203	

1.1.3. Safety Assessments

Primary safety data were pooled for the 2 pivotal Phase 3 registration 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 prespecified primary endpoint analysis was at 48 weeks for all studies except Studies GS-US-292-0112 and GS-US-292-0106 (24 weeks). The Phase 3 studies in ART-naive adults were double-blind, randomized studies, whereas the other Phase 3 studies were open-label studies. 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 of E/C/F/TAF 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 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 Food and Drug Administration [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 m5.3.5.3, 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 biopharmaceutic, clinical pharmacology, and efficacy studies of E/C/F/TAF are presented in m2.7.1, m2.7.2, and m2.7.3, respectively.

Narrative safety data are provided in this section for subjects with mild to moderate renal impairment (GS-US-292-0112, Section 1.1.4.1) and for ART-naive adolescent subjects (GS-US-292-0106, Section 1.1.4.2).

1.1.4.1. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

A complete study description and results for Study GS-US-292-0112 are available in the CSR (m5.3.5.2, 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, 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 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.

Comparison	aGFR (GLSM)				GLSM Ratio (%)	90% CI
	n	Test Treatment	n	Reference Treatment		
Week 2/4/8 aGFR vs Baseline aGFR (mL/min)	32	56.59	32	57.20	98.94	(93.71,104.46)
Week 24 aGFR vs Baseline aGFR (mL/min)	30	58.72	32	57.20	102.66	(97.11,108.53)

aGFR = actual glomerular filtration rate; 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.

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 $eGFR_{CG}$ ≥ 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:

	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)

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 [redacted] (BL $eGFR_{CG}$ < 50 mL/min) was excluded for sensitivity analysis as TAF PK parameter estimates are unreliable due to an unusual PK profile.

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.

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 (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. There were no AEs of proximal renal tubulopathy (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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 50 mL/min group), and hypercholesterolemia (baseline $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 50 mL/min); of these, 3 subjects (2 with baseline $eGFR_{CG}$ < 50 mL/min and 1 with baseline $eGFR_{CG}$ ≥ 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 considered 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 proximal renal tubulopathy (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 $eGFR_{CG}$ ≥ 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 adverse events was low, and no AEs of proximal renal tubulopathy (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.

1.1.4.2. ART-Naive Adolescent Subjects: Study GS-US-292-0106

A complete study description and results for Study GS-US-292-0106 are available in the CSR (m5.3.5.2, 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 (STR) 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.

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

GLSM = geometric least-squares mean
a N = 23 for the Test group
b N = 15 for the Test group
c N = 51 for the Reference group

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 was 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 proximal renal tubulopathy.

Mean and median baseline values and percentage changes from baseline at Week 24 in spine and TBLH BMD are shown in the following table.

	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)

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.

	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)

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

A total of 2573 subjects have received at least 1 dose of E/C/F/TAF (150/150/200/10 mg) in the E/C/F/TAF clinical program, 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).

Disposition for subjects in the E/C/F/TAF Phase 2 and Phase 3 studies is described in m2.7.3, Section 3.1.1.

Table 5 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 5. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: 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 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: m5.3.5.3, E/C/F/TAF ISS, Tables 4 and Req6863.5; m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 7.1; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Table 7; m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 15.1, Table 7; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 15.1, Table 6

1.3. Demographic and Other Characteristics of Study Population

1.3.1. Summary of Demographic and General Baseline Characteristics

Demographic and general baseline characteristics were generally similar between treatment groups within each randomized study (Table 6). 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 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 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 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 6. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: 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 m5.3.5.1, Study GS-US-292-0102 Week 96 CSR, Section 8.

Source: m5.3.5.3, E/C/F/TAF ISS, Table 2; m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Tables 1.1 and 5.1; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 1 and 5.1; m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 15.1, Tables 1 and 4.1; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 15.1, Tables 1 and 4.1

1.3.2. Summary of Baseline Disease Characteristics

Baseline disease characteristics were generally similar between treatment groups within each randomized study (Table 7). The median baseline HIV-1 RNA value in ART-naive subjects (across all 5 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 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 80%) 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 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 (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 mL/min (45.7, 62.4) 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 mL/min/1.73 m^2.

Across the Phase 3 studies in adults with normal renal function, 10% or less of subjects had any Grade 1, 2, or 3 proteinuria at baseline. In subjects with mild to moderate renal impairment, 9.5% of virologically suppressed subjects had Grade 2 proteinuria by urinalysis (dipstick), and 23.1% of subjects had Grade 1 proteinuria at baseline. Among adolescent subjects, < 5% had proteinuria at baseline.

In contrast, 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 30 to 59 mL/min; 63.3% [157 of 248 subjects]) at baseline.

Table 7. 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
$eGFR_{CG}$ (mL/min)									

	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	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]
Hypertension[e]									

	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)
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 m5.3.5.1, 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: m5.3.5.3, E/C/F/TAF ISS, Table 3; m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 6.1; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Table 6.1; m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 15.1, Table 5.1; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 15.1, Table 5.1

1.4. Analysis Sets

Safety Analysis Set

For studies in ART-naive subjects (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 8). 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 8. 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%)	—	—	—

	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 Analysis Set	—	—	112	53[b]	—	—	—	—	—
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]	—	—	—	—	—

DXA = dual-energy x-ray absorptiometry; TBLH = total body less head
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 (m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 4.1)
Source: m5.3.5.3, E/C/F/TAF ISS, Tables 1, 20.1.2, and 20.2.2; m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 4.1; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Table 4; m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 15.1, Table 3; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 15.1, Table 3

2. ADVERSE EVENTS

This section provides an overall summary of AEs in the E/C/F/TAF development program, with the main focus on the 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. Adverse events from the Phase 1 TAF studies are not described in detail in this summary as they are generally consistent with the results from the Phase 2 and Phase 3 studies; deaths, SAEs, and AEs leading to discontinuation are summarized for the Phase 1 studies.

2.1. Analysis of Adverse Events

Table 9 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. 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 9. 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%)

	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 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: m5.3.5.3, E/C/F/TAF ISS, Table 6; m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 20.1; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Table 21; m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 15.1, Table 32; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 15.1, Table 14

2.1.1. Common Adverse Events

2.1.1.1. Summary of Common Adverse Events

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 study.

2.1.1.2. ART-Naive Subjects

2.1.1.2.1. Studies GS-US-292-0104 and GS-US-292-0111

Detailed AE results for Studies GS-US-292-0104 and GS-US-292-0111 may be found in the respective CSRs (m5.3.5.1, GS-US-292-0104 Week 48 CSR, Section 11.2; m5.3.5.1, 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 10.

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 10. 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 preferred term was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: m5.3.5.3, 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) (m5.3.5.3, 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 (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 (E/C/F/TAF 1.4%, 12 subjects; STB 1.0%, 9 subjects; Table 9 and Table 11). 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 11. 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 preferred term was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: m5.3.5.3, E/C/F/TAF ISS, Table 11

2.1.1.2.2. Study GS-US-292-0102

Detailed AE results for Study GS-US-292-0102 may be found in m5.3.5.1, 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 12. 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 12. 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 system organ class, high level term, and preferred term, respectively.
Source: m5.3.5.1, 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 [redacted] 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 [redacted] and [redacted]). 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 13). 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 13. 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 system organ class, high level term, and preferred term, respectively.
Source: m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 25.1

2.1.1.3. Virologically Suppressed Subjects

2.1.1.3.1. Study GS-US-292-0109

Detailed AE results for Study GS-US-292-0109 may be found in m5.3.5.1, 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 14. 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 14. 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 preferred term was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: m5.3.5.1, 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 9). 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 15).

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)

Among the common study drug-related AEs, there were no notable differences between treatment groups. All reports of study drug-related jaundice and ocular icterus were for subjects taking ATV/boosted+TVD regimens.

Table 15. 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 preferred term was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Table 26

2.1.1.3.2. Study GS-US-292-0102 Open-Label Extension

In the open-label extension of 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

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.

2.1.1.4. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

Detailed AE results for Study GS-US-292-0112 may be found in m5.3.5.2, 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 16. 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 $eGFR_{CG}$ ≥ 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 16. 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 Version 17.0.
b Multiple AEs were counted only once per subject for each system organ class, high level term, and preferred term, respectively.
Source: m5.3.5.2, 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 considered serious and not related to study drug by the investigator. Three subjects had a single nonserious Grade 3 AE considered related to study drug: blood creatine phosphokinase increased (baseline $eGFR_{CG}$ < 50 mL/min group), gastroesophageal reflux disease (baseline $eGFR_{CG}$ ≥ 50 mL/min group), and hypercholesterolemia (baseline $eGFR_{CG}$ ≥ 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 17. 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 17. 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 Version 17.0.
b Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 15.1, Table 37

2.1.1.5. ART-Naive Adolescent Subjects: Study GS-US-292-0106

Detailed AE results for Study GS-US-292-0106 may be found in m5.3.5.2, GS-US-292-0106 Interim CSR, Section 11.2.

Adverse events that occurred in at least 5% of subjects in Study GS-US-292-0106 are summarized in Table 18. 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 18. GS-US-292-0106: Adverse Events Occurring in at Least 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 system organ class and preferred term, respectively. System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies.
Source: m5.3.5.2, 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 9). 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 19). 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 19. GS-US-292-0106: Study Drug-Related Adverse Events (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 system organ class and preferred term, respectively. System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies.
Source: m5.3.5.2, GS-US-292-0106 Interim CSR, Section 15.1, Table 19

2.1.2. 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 9). None of the events that resulted in death was considered related to study drug by the investigator.

ART-Naive Subjects

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 (m5.3.5.3, 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 [redacted] 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 [redacted] in the STB group in Study GS-US-292-0104 died as a result of cardiac arrest (reported as vagally mediated bradycardic/asystole). Subject [redacted] 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 [redacted] in the STB group in Study GS-US-292-0111 died on Day 62 of acute ethanol and multiple drug toxicity (reported as an SAE of recreational drug and alcohol overdose on Day 62). Subject [redacted] 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).

Virologically Suppressed Subjects

Study GS-US-292-0109

Two subjects in the E/C/F/TAF group died during Study GS-US-292-0109 (Table 9; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 11.3). Subject [redacted] died on Day 148 of septic shock and Subject *CA 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.

2.1.2.1. Phase 1 TAF Safety Population

No deaths were reported in Phase 1 studies with TAF.

2.1.3. Other Serious Adverse Events

2.1.3.1. Summary of Other Serious Adverse Events

Serious AEs were reported for a similar percentage of subjects in both treatment groups in the comparative 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 $eGFR_{CG}$ ≥ 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 AEs and SAEs was low and generally similar across all studies; few of these were reported as related to study drugs. 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).

2.1.3.2. ART-Naive Subjects

2.1.3.2.1. 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 9). 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 (m5.3.5.3, 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; m5.3.5.3, 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 2.1.5.3.3.1.1.

2.1.3.2.2. 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 9; m5.3.5.1, 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.

2.1.3.3. Virologically Suppressed Subjects

2.1.3.3.1. 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 9; m5.3.5.1, 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.

2.1.3.3.2. 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.

2.1.3.4. Subjects with Mild to Moderate Renal Impairment: 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) (m5.3.5.2, 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.

2.1.3.5. ART-Naive Adolescent Subjects: Study GS-US-292-0106

The SAEs were reported for 4 subjects (8.3%) in Study GS-US-292-0106 (Table 9; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 11.4). With the exception of visual impairment and intermediate uveitis in Subject *CB , 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 *CB are noted as ocular events and described in more detail in Section 2.1.5.4.6.

2.1.3.6. Phase 1 TAF Safety Population

One SAE was reported in Phase 1 studies with TAF. In Study GS-US-120-0104, 1 subject (Subject [redacted]) experienced chest pain, which was considered to be not related to study drug (m5.3.4.2, GS-US-120-0104).

2.1.4. Other Significant Adverse Events

2.1.4.1. Summary of Other Significant Adverse Events

Adverse events that led to discontinuation of study drug are described in this section. 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 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.

2.1.4.2. ART-Naive Subjects

2.1.4.2.1. 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 9). 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; m5.3.5.3, 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 2.1.5.3.3.1.1, 4 subjects had renal AEs that resulted in discontinuation of study drugs.

2.1.4.2.2. 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 [redacted]) 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.

2.1.4.3. Virologically Suppressed Subjects

2.1.4.3.1. 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 9). 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.

2.1.4.3.2. 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.

2.1.4.4. Subjects with Mild to Moderate Renal Impairment: 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 2.1.5.3.5.1).

No AEs leading to discontinuation of study drug were reported for Cohort 2 ART-naive subjects.

2.1.4.5. ART-Naive Adolescent Subjects: Study GS-US-292-0106

No subject in Study GS-US-292-0106 discontinued study drug due to an AE (Table 9).

2.1.4.6. Phase 1 TAF Safety Population

Discontinuations due to AEs in the TAF Phase 1 studies are summarized in Table 20. No treatment-related trends were observed regarding discontinuations due to AEs in these studies.

Table 20. Phase 1 TAF Safety Population: Discontinuations Due to Adverse Events

Study No.	No. of Subjects Who Discontinued Due to an AE	AEs Leading to Discontinuation (No. of Subjects)	Associated Treatment and Relationship
GS-US-292-0101	1	Elevated CPK (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
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-311-0101	2	Anxiety (1) Joint abscess (1)	F/TAF+EVG, related FTC/TAF, unrelated

Source: m5.3.3.1, GS-US-292-0101; m5.3.1.2, GS-US-292-0103; m5.3.3.1, GS-US-292-0108; m5.3.3.4, GS-US-292-0110; m5.3.3.4, GS-US-292-1316; GS-US-342-1167; m5.3.4.2, GS-120-1101; m5.3.4.2, GS-US-120-0104; m5.3.4.1, GS-US-120-0107; m5.3.3.3, GS-US-120-0108; m5.3.3.1, GS-US-120-0109; m5.3.3.3, GS-US-120-0114; and m5.3.3.4, GS-US-311-0101

2.1.5. Analysis of Adverse Events by Organ System or Syndrome

2.1.5.1. Summary of Analysis of Adverse Events by Organ System or Syndrome

As TAF is associated with 90% lower systemic tenofovir exposure, less off-target tenofovir-associated toxicity was anticipated in subjects receiving E/C/F/TAF in the Phase 3 randomized studies, including less impact on proximal renal tubular function and prespecified bone parameters. Results from the Phase 2 Study GS-US-292-0102 provided supportive evidence, demonstrating that subjects receiving E/C/F/TAF relative to STB 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). Significant differences between E/C/F/TAF and STB in renal and bone safety were anticipated in the Phase 3 program, and after the primary hypothesis of noninferior efficacy of E/C/F/TAF relative to STB was achieved, 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; $p < 0.001$).

2.1.5.2. Bone Safety

2.1.5.2.1. Summary of Bone Safety

Bone safety was assessed in the E/C/F/TAF Phase 2 and Phase 3 studies 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 effect some degree of recovery. The decrease in BMD appears to be greater with TDF than with other NRTIs {11882}, {17735}, {29368}, {18854}.

Summary of 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.

In Studies GS-US-292-0104 and GS-US-292-0111, the incidence of fracture events was low and similar in both treatment groups (E/C/F/TAF 1.3%, 11 subjects; STB 1.7%, 15 subjects). 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. 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). In Study GS-US-292-0112 in patients with renal impairment, 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. No fracture events occurred in Cohort 2 ART-naive subjects. No fractures were reported in Study GS-US-292-0106.

Summary of Bone Mineral Density

Across all studies in ART-naive subjects, subjects receiving E/C/F/TAF experienced significantly less BMD reduction than those receiving STB.

In Studies GS-US-292-0104 and GS-US-292-0111, statistical analysis using the fallback procedure confirmed significance using adjusted alphas. At Week 48, approximately one-third as many 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%; STB 50.1%), and approximately half as many subjects in the E/C/F/TAF group compared with the STB group had a > 3% decrease from baseline 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. 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. 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).

In patients with renal impairment (Study GS-US-292-0112), hip and spine BMD increased for Cohort 1 subjects after switching to E/C/F/TAF. 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.

In ART-naive adolescent subjects (Study GS-US-292-0106), mean changes from baseline of approximately 1.7% and 0.8% in spine and 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. 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.

Summary of Fracture Probability

Across ART-naive Studies GS-US-292-0104 and GS-US-292-0111, for subjects aged ≥ 40 years, baseline fracture risk was low, but subjects experienced less of an increase in fracture risk by FRAX analysis in the E/C/F/TAF group than in the STB group. Baseline 10-year probability of a major osteoporotic fracture was (mean [SD]) E/C/F/TAF: 2.82% [2.029%]; STB: 3.21% [2.344%]. Mean (SD) increase from baseline at Week 48 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 least-squares mean [LSM] -0.12%, 95% CI: -0.22% to -0.02%; $p = 0.014$).

In the virologically suppressed Study GS-US-292-0109, for subjects aged ≥ 40 years, baseline fracture risk was low, but after switching to E/C/F/TAF, subjects experienced less of an increase in fracture risk by FRAX analysis than subjects who retained their TDF-based regimen. 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).

In patients with renal impairment (Study GS-US-292-0112), for subjects aged ≥ 40 years, fracture risk was higher in subjects without pre-switch TDF use than in subjects with pre-switch TDF use. Subjects switching to E/C/F/TAF with pre-switch TDF use experienced a decrease in or less of an increase in fracture risk by FRAX analysis.

Summary of Bone Laboratory Parameters

Across ART-naive Studies GS-US-292-0104 and GS-US-292-0111, increases from baseline in the bone turnover biomarkers C-telopeptide (bone resorption biomarker) and P1NP (bone formation), as well as PTH (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%).

In the virologically suppressed Study GS-US-292-0109, subjects who switched to E/C/F/TAF experienced a decrease from baseline in serum levels of P1NP and PTH 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 C-telopeptide in the E/C/F/TAF group compared with an increase from baseline in the FTC/TDF+3rd Agent group at Week 48 ($p = 0.007$ for the difference between groups).

In patients with renal impairment (Study GS-US-292-0112), for subjects who switched to E/C/F/TAF (Cohort 1), median percentage decreases from baseline at Weeks 24 and 48 were observed in C-telopeptide, PINP, and PTH. For each of the bone laboratory parameters, Cohort 1 switch subjects with TDF use at baseline had median percentage decreases from baseline at Week 24, whereas those without TDF use at baseline had median percentage increases from baseline at Week 24.

2.1.5.2.2. Methodology

The PTs included in the analysis of fracture events were defined by the Gilead medical monitor in a blinded fashion prior to database lock, based on both the Standardized MedDRA Query (SMQ) 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 2.1.5.2.6.2.2.

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.

2.1.5.2.3. ART-Naive Subjects

2.1.5.2.3.1. 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 (m5.3.5.1, GS-US-292-0104 Week 48 CSR, Section 11.2.4.1; m5.3.5.1, GS-US-292-0111 Week 48 CSR, Section 11.2.4.1).

2.1.5.2.3.1.1. 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; m5.3.5.3, 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) (m5.3.5.3, 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.

2.1.5.2.3.1.2. Bone Mineral Density

2.1.5.2.3.1.2.1. 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 (Section 1.1.3). 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; m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Tables 20.1.1 and 20.2.1).

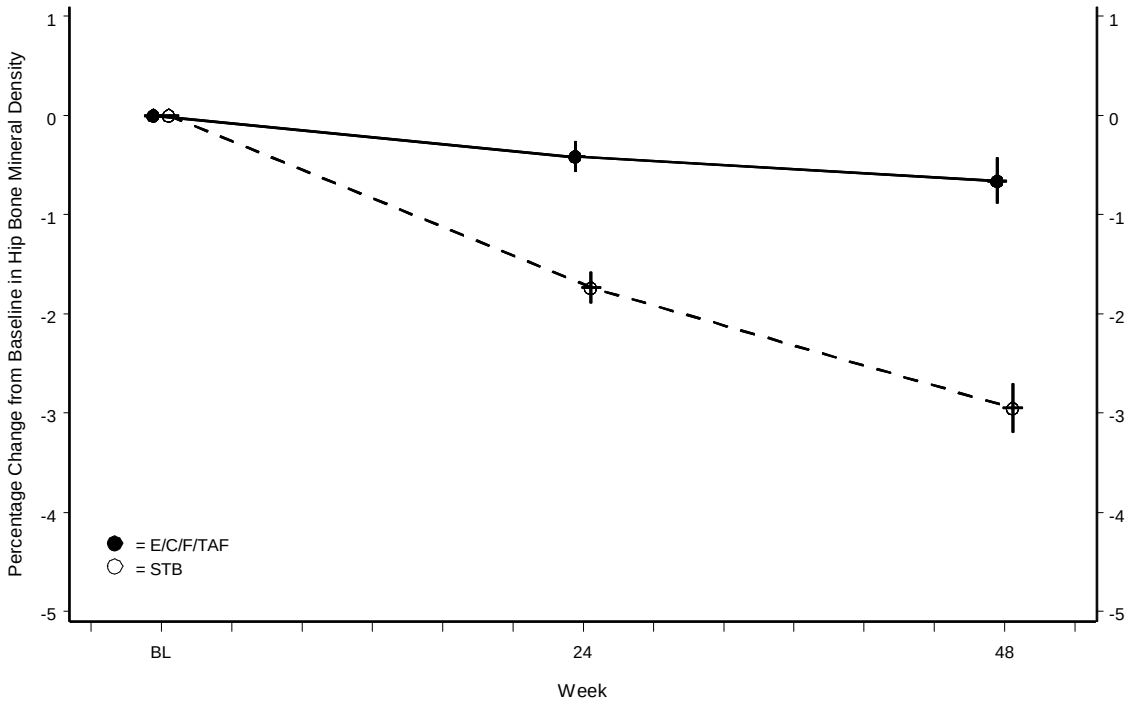
Sensitivity analyses of percentage changes from baseline in BMD at the hip or at the spine were performed to exclude subjects who took osteoporosis medications during the study. Results were similar to those observed for all subjects in the Hip and Spine DXA Analysis Sets (m5.3.5.1, GS-US-292-0104 Week 48 CSR, Section 11.2.4.1.2.1; m5.3.5.1, 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; m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Tables 7 and 14). Decreased bone density was considered related to study drugs for 2 subjects (0.2%) in each treatment group (m5.3.5.3, E/C/F/TAF ISS, Table 11). No AEs of decreased bone density resulted in discontinuation of study drugs.

Figure 1. 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)



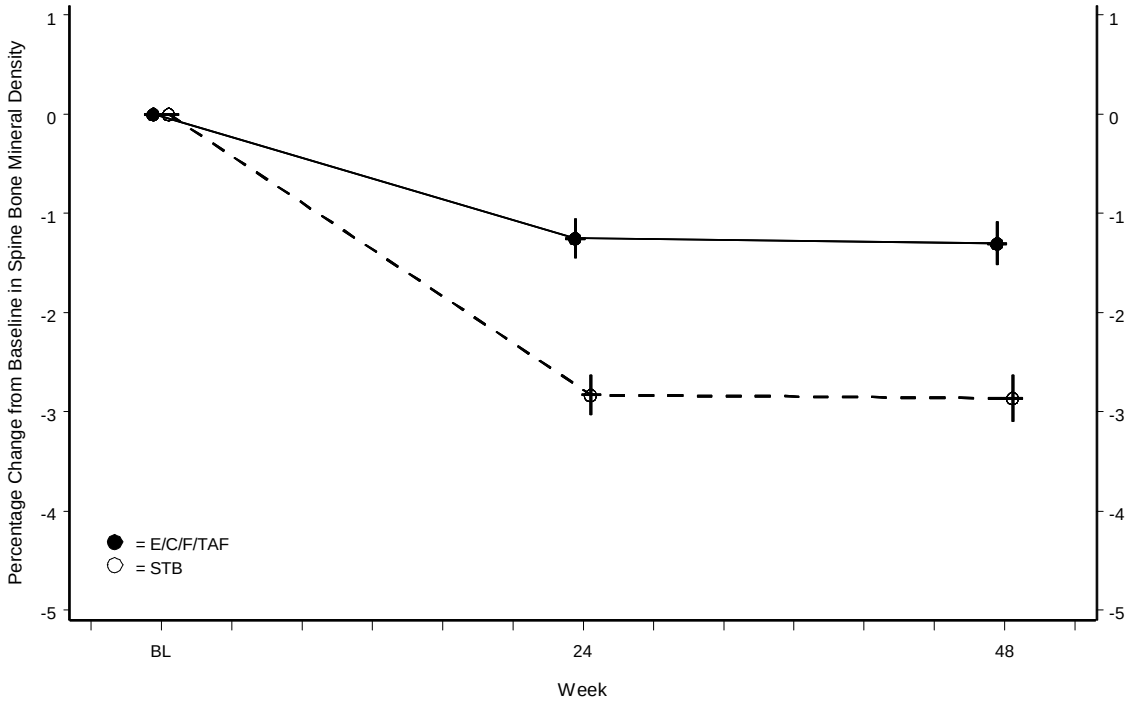
E/C/F/TAF (n=):	836	789	780
STB (n=):	848	815	767

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] 17:41

Source: m5.3.5.3, E/C/F/TAF ISS, Figure 3.2.1

Figure 2. 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: m5.3.5.3, 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; m5.3.5.3, 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.

2.1.5.2.3.1.2.2. 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 21 and Table 22). 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 21. 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: m5.3.5.3, E/C/F/TAF ISS, Table 21.1

Table 22. 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: m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Table 7). Osteopenia was considered related to study drugs for 25 subjects: E/C/F/TAF 8 subjects (0.9%), STB 17 subjects (2.0%); osteoporosis was considered related to study drugs for 7 subjects: E/C/F/TAF 3 subject (0.3%), STB 4 subjects (0.5%) (m5.3.5.3, 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 (m5.3.5.1, GS-US-292-0104 Week 48 CSR, Appendix 16.2, Listing 17; m5.3.5.1, 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 (m5.3.5.3, E/C/F/TAF ISS, Tables 14 and 16).

2.1.5.2.3.1.3. 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; m5.3.5.3, 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 least-squares mean (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; m5.3.5.3, 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).

2.1.5.2.3.1.4. 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; m5.3.5.3, 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%).

2.1.5.2.3.2. Study GS-US-292-0102

Bone safety for Study GS-US-292-0102 is described in detail in m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 11.2.4.1.

2.1.5.2.3.2.1. 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.

2.1.5.2.3.2.2. Bone Mineral Density

2.1.5.2.3.2.2.1. 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)

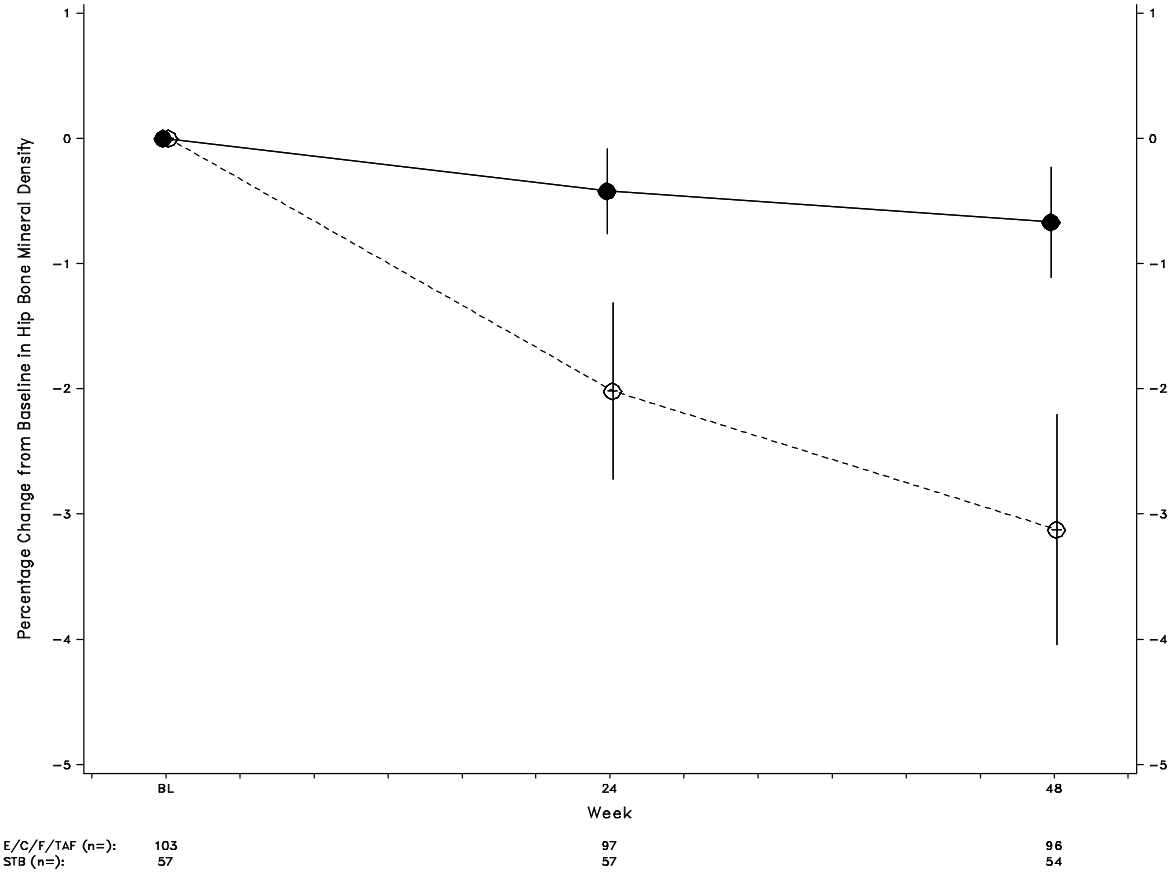
Analysis using LOCF to replace missing values showed similar results to the observed data for the randomized phase.

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%).

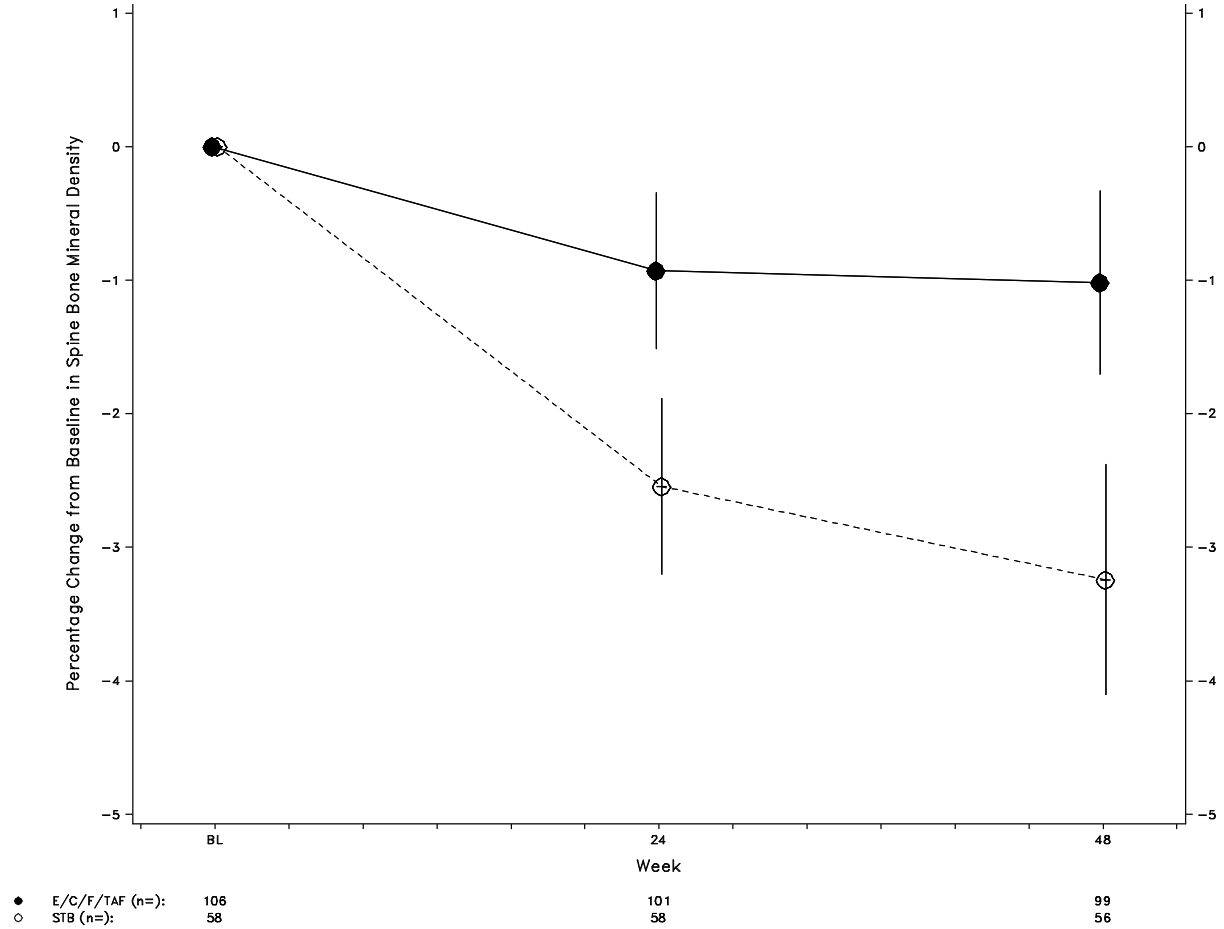
In the E/C/F/TAF group at Week 96, the categorical distributions of percentage change from baseline in hip or spine BMD were consistent with results at Week 48.

Figure 3. 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: m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Figure Req6660.1.1

Figure 4. 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: m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Figure Req6660.2.1

2.1.5.2.3.2.2.2. 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.

2.1.5.2.3.2.3. 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.

2.1.5.2.4. Virologically Suppressed Subjects

2.1.5.2.4.1. Study GS-US-292-0109

Bone safety for Study GS-US-292-0109 is described in detail in m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 11.2.4.1.

2.1.5.2.4.1.1. 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 [redacted]), radius fracture (Subject [redacted]), and hip fracture (Subject [redacted]). 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.

2.1.5.2.4.1.2. Bone Mineral Density

2.1.5.2.4.1.2.1. Percentage Change from Baseline in Hip and Spine BMD

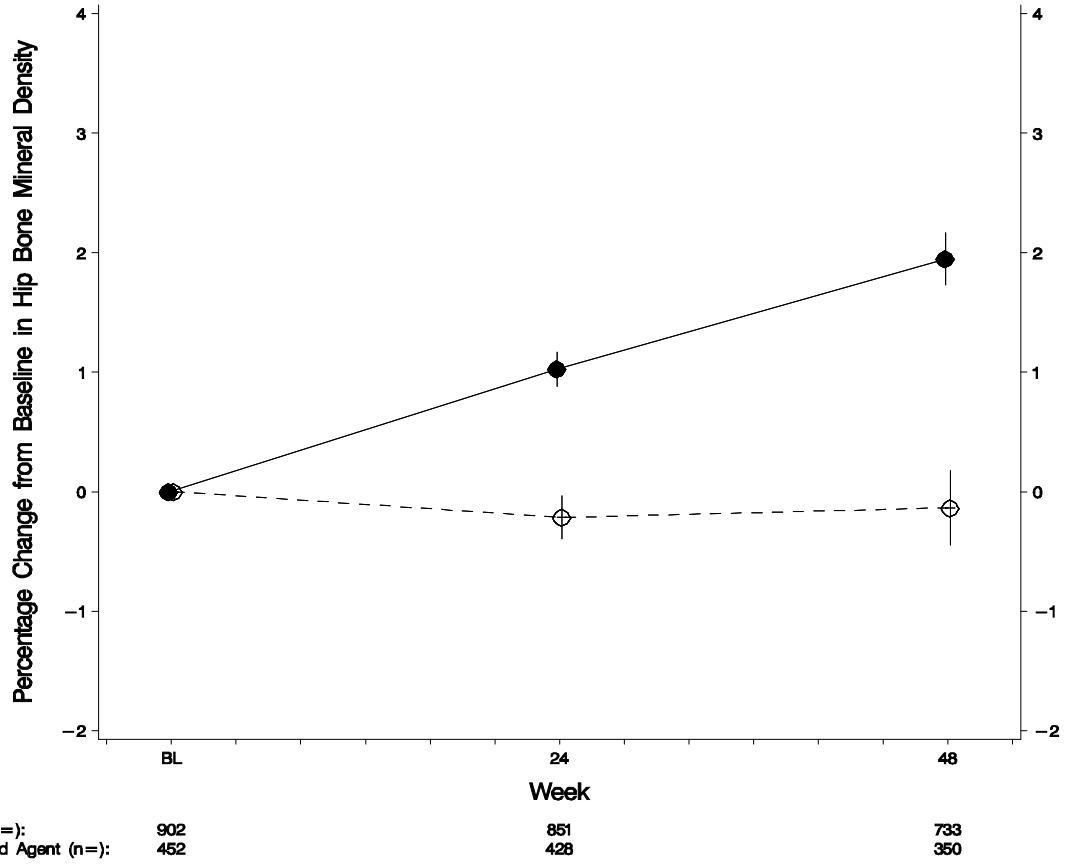
The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for Study GS-US-292-0109, respectively (Section 1.1.3). Statistical analysis using the fallback procedure confirmed significance using adjusted alphas, which 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)

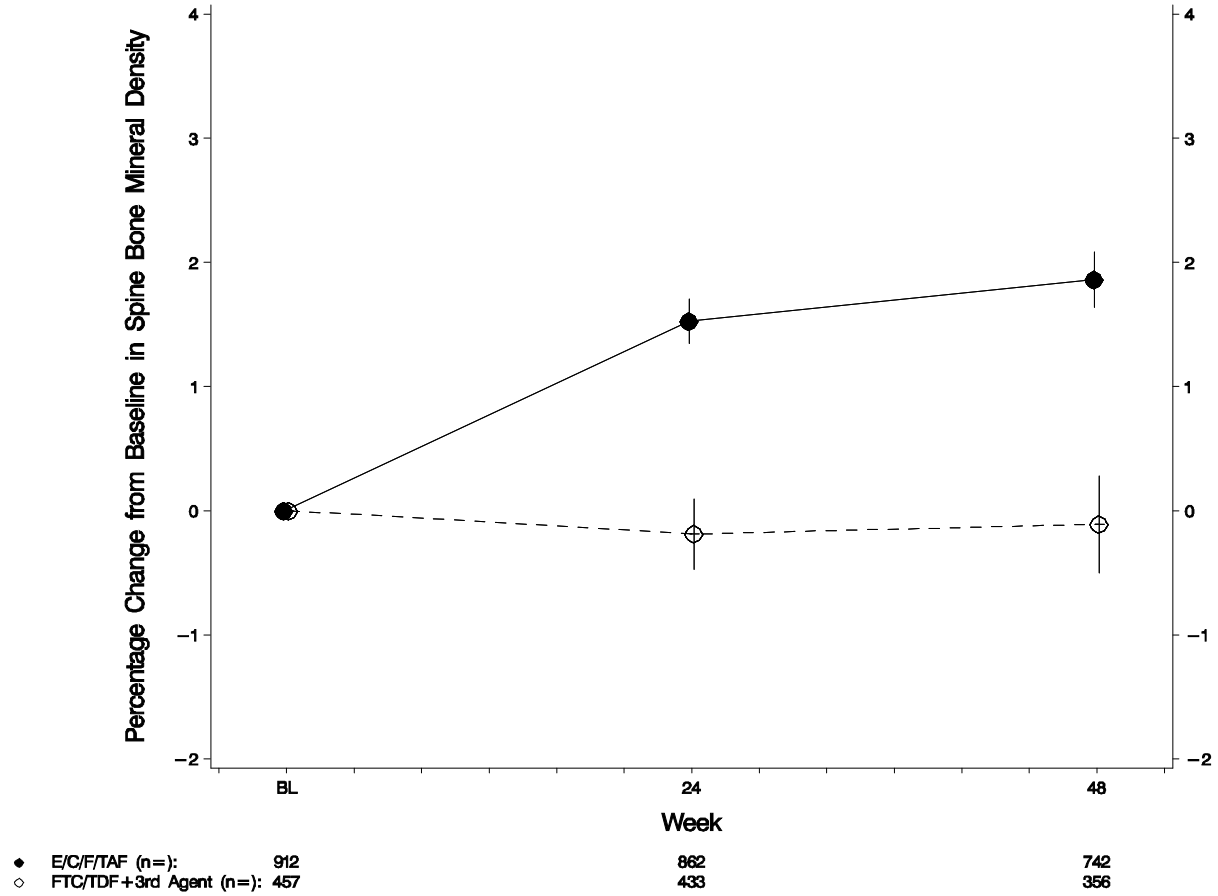
Similar results were obtained when the data were analyzed using the LOCF approach for the Week 48 Hip and Spine DXA Analysis Sets.

Figure 5. **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: m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Figure 8.2.1

Figure 6. **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: m5.3.5.1, 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 23).

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 23. 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: m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 43.1 and 43.2

2.1.5.2.4.1.2.2. 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).

2.1.5.2.4.1.3. 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).

2.1.5.2.4.1.4. 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)

2.1.5.2.4.2. Study GS-US-292-0102 Open-Label Extension

2.1.5.2.4.2.1. 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 [redacted]) was nonserious while the ankle fracture (Subject [redacted]) 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.

2.1.5.2.4.2.2. Bone Mineral Density

2.1.5.2.4.2.2.1. 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 24 and Table 25). Few subjects in this switch group had > 3% decrease from baseline in hip BMD (1.6%) or spine BMD (7.5%).

Table 24. 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: m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 37.3.1.2

Table 25. 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: m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 37.3.2.2

2.1.5.2.4.2.2.2. 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.

2.1.5.2.4.2.3. 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.

2.1.5.2.5. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

Bone safety for Study GS-US-292-0112 is described in detail in m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 11.3.4.1.

2.1.5.2.5.1. 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 considered serious. All fracture events were the result of trauma, and none were reported as fragility fractures.

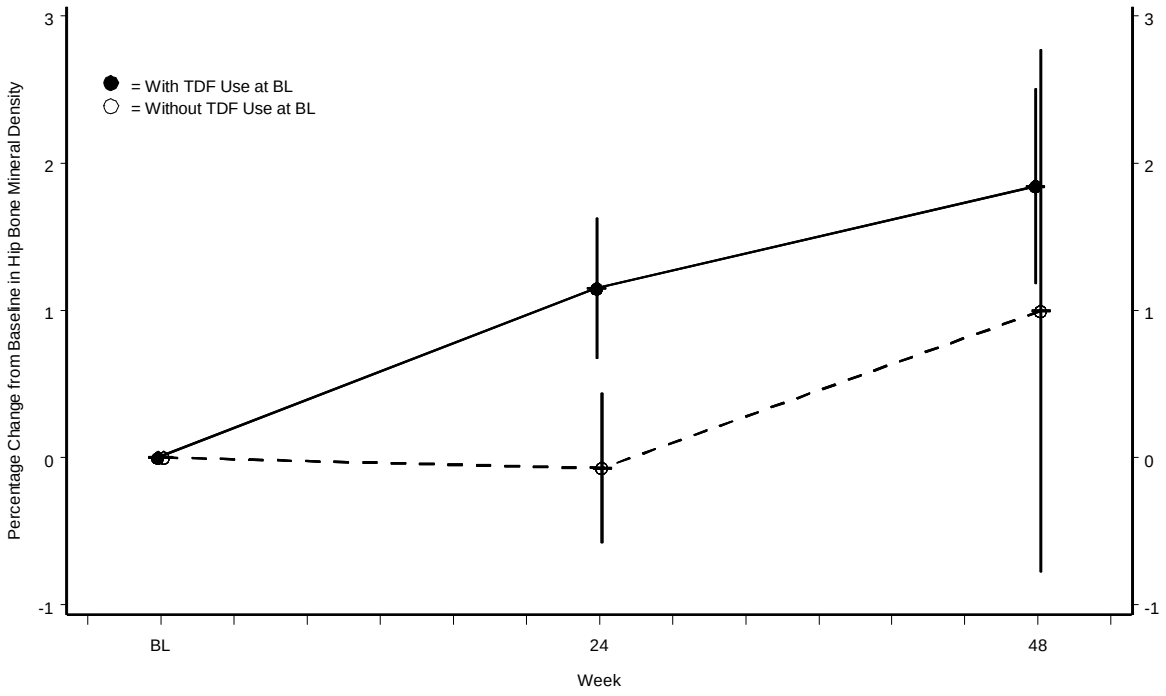
No fracture events occurred in Cohort 2 ART-naive subjects.

2.1.5.2.5.2. Bone Mineral Density

2.1.5.2.5.2.1. 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. 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)



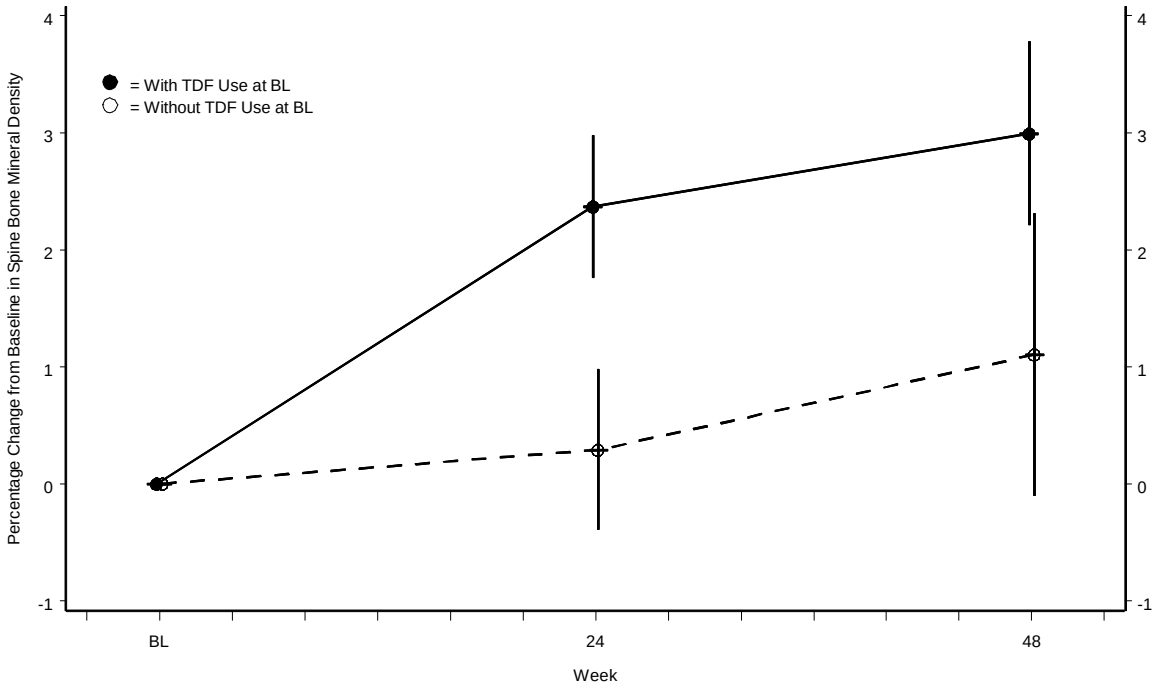
With TDF Use at BL (n=):	154	148	110
Without TDF Use at BL (n=):	82	77	51

BL = Baseline.
Only subjects with nonmissing baseline hip BMD value were included in hip DXA analysis set.

Data Extracted: CRF Data: [redacted]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-hip-bmd-mean.out [redacted]20[redacted]:10:37

Source: m5.3.5.1, GS-US-292-0112 Week 24 CSR, Section 15.1, Figure 22.1.2

Figure 8. 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], Lab Data: [redacted], Dexa Data: [redacted]
Source: .../version1/prog/t-dexa-bmd.sas v9.2 Output file: g-dexa-spine-bmd-mean.out [redacted]:10:37

Source: m5.3.5.1, 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.

2.1.5.2.5.2.2. 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.

2.1.5.2.5.3. 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).

2.1.5.2.5.4. 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.

2.1.5.2.6. ART-Naive Adolescent Subjects: Study GS-US-292-0106

Bone safety for Study GS-US-292-0106 is described in detail in m5.3.5.2, GS-US-292-0106 Interim CSR, Section 11.2.4.1.

2.1.5.2.6.1. Fracture Events

No fractures were reported in Study GS-US-292-0106.

2.1.5.2.6.2. Bone Mineral Density

2.1.5.2.6.2.1. 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 26.

Table 26. 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: m5.3.5.2, 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.

2.1.5.2.6.2.2. 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).

2.1.5.2.6.2.3. 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.

2.1.5.3. Renal Safety

2.1.5.3.1. Summary of 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.

Summary of Renal Events

There were no cases of proximal renal tubulopathy reported (including Fanconi syndrome) in either treatment group in Studies GS-US-292-0104 and GS-US-292-0111, or GS-US-292-0102 (randomized phase and open-label extension), and in either cohort in GS-US-292-0112. In the virologically suppressed Study GS-US-292-0109, there were no AEs of proximal renal tubulopathy (including Fanconi Syndrome) 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.

Across ART-naive Studies GS-US-292-0104 and GS-US-292-0111, renal adverse events were uncommon and balanced between treatment arms. 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. 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. Three subjects in Study GS-US-292-0104, all in the STB group, had renal AEs that resulted in discontinuation of study drugs. One subject in the STB group in Study GS-US-292-0111 had a renal AE that resulted in discontinuation of study drugs.

In the randomized phase of the Phase 2 Study GS-US-292-0102, no subject discontinued study drugs due to a renal AE. There were no cases of renal failure, and no subject discontinued study drug due to renal AEs in the switch groups during the extension phase of Study GS-US-292-0102.

In the virologically suppressed Study GS-US-292-0109, 1 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 (linked to Hodgkin's disease) that resulted in discontinuation of the study drug; both events were considered by the investigator as not related to study drugs.

In subjects with renal impairment (Study GS-US-292-0112), 1 subject (0.4%) in Cohort 1 had an SAE of acute renal failure in the setting of increased diuretic use that resolved 2 days after onset. Two of the 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.

Summary of Renal Laboratory Parameters

Summary of Serum Creatinine

Across all ART-naive studies (GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), 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 generally remained stable.

Across all studies in which subjects switched from a TDF-based regimen to E/C/F/TAF (GS-US-292-0109 and GS-US-292-0112), 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.

Summary of Estimate Glomerular Filtration Rate

Across all ART-naive studies (GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), decreases from baseline in median $eGFR_{CG}$ values were smaller in the E/C/F/TAF group compared with the STB group. Consistent results were observed using $eGFR_{CKD-EPI}$ serum creatinine. A consistent effect on eGFR was observed in subjects receiving E/C/F/TAF in these ART-naive adult studies, as well as the adolescent study (GS-US-292-0106): median decrease from baseline of approximately 7 mL/min (range: -5.1 to -7.2 mg/dL). Decreases were observed by Week 2, and remained stable.

Conversely, across all studies in which subjects switched from a TDF-based regimen to E/C/F/TAF (GS-US-292-0109 and GS-US-292-0112), minimal changes in $eGFR_{CG}$ were observed in subjects receiving E/C/F/TAF, and varied depending on prior regimen (range of median change from baseline: -0.4 to 5.8 mg/dL).

Summary of Proteinuria by Urinalysis (Dipstick)

Across all ART-naive studies (GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), fewer subjects receiving E/C/F/TAF developed treatment-emergent proteinuria than subjects receiving STB.

In 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%; STB 36.7%; p = 0.022).

Conversely, across all studies in which subjects switched from a TDF-based regimen to E/C/F/TAF (GS-US-292-0109 and GS-US-292-0112), decreases in proteinuria were observed.

In Study GS-US-292-0109, 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%; FTC/TDF+3rd Agent 5.6%), 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%; FTC/TDF+3rd Agent 7.0%).

In Study GS-US-292-0112, 32.3% of subjects in Cohort 1 had Grade 1 or 2 baseline proteinuria. Most subjects had either no change or an improvement from the baseline proteinuria toxicity grade at Week 24. For 75.0% of subjects, the proteinuria grade improved from baseline at Week 24.

In Study GS-US-292-0106, 2 of 48 subjects (4.2%) had Grade 1 or Grade 2 proteinuria at baseline. Postbaseline, treatment-emergent Grade 1 or Grade 2 proteinuria, generally isolated and transient, was reported for 20.9% (10 of 48 subjects).

Summary of Proteinuria by Quantitative Assessment

In the ART-naive Phase 3 studies (GS-US-292-0104 and GS-US-292-0111), there was a decrease from baseline in proteinuria, quantified by UPCR, and a decrease from baseline in albuminuria, quantified by UACR, in 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 and UACR in the STB group.

Across studies in which subjects switched from a TDF-based regimen to E/C/F/TAF (Studies GS-US-292-0109 and GS-US-292-0112), 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. In Study GS-US-292-0112, in Cohort 1 (switch subjects; baseline median UPCR of 160.6 mg/g, median UACR of 28.8 mg/g), median percentage decreases were 35.3% and 38.8% for UPCR and UACR, respectively, at Week 24. The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42.2% at baseline to 21.2% at Week 24 and 48.9% at baseline to 27.0% at Week 24, respectively. In subjects with mild to moderate renal impairment (GS-US-292-0112) who switched from a non-TDF containing regimen, median percentage change from baseline in UPCR and UACR was 0.1% and -19.5%, respectively.

In Study GS-US-292-0106, 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%]).

Summary of Tubular Proteinuria (Urine Retinol Binding Protein to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio)

Across the ART-naive studies (GS-US-292-0104, GS-US-292-0111, and GS-US-292-0102), 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.

In the ART-naive Phase 3 studies (GS-US-292-0104 and GS-US-292-0111), 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 change from baseline at Week 48: E/C/F/TAF 9.2% [-23.0%, 48.6%]; STB 51.2% [2.9%, 132.9%]).

Across studies in which subjects switched from a TDF-based regimen to E/C/F/TAF (GS-US-292-0109 and GS-US-292-0112), 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. 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 Study GS-US-292-0106, a reduction from baseline was observed at Week 24 in the urine beta-2-microglobulin to creatinine ratio (median [Q1, Q3] 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.

Summary of Other Renal Biomarkers

Other renal biomarkers assessed included FEUA, the marker of proximal renal tubular function, and specific measures of renal phosphate handling, TmP/GFR and $FEPO_4$, each using unadjusted and adjusted serum creatinine values.

In the ART-naive Phase 3 studies (GS-US-292-0104 and GS-US-292-0111), 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%]). 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 TmP/GFR between treatment groups Median (Q1, Q3) $FEPO_4$ using adjusted serum creatinine was significantly greater in the STB group relative to the E/C/F/TAF group through Week 48 (E/C/F/TAF 0.9% [–2.0%, 4.5%]; STB 1.7% [–1.6%, 5.3%]($p = 0.005$ at Week 48).

In Study GS-US-292-0109, 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). A decrease from baseline in FEUA was observed in the E/C/F/TAF group regardless of prior treatment regimen.

In Study 292-0112, in Cohort 1 (switch subjects), 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).

In Study GS-US-292-0106, No clinically meaningful change from baseline in TmP/GFR, $FEPO_4$, or FEUA was observed through Week 24.

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 and GS-US-292-0111, or Study GS-US-292-0102 (randomized phase and open-label extension), or in subjects with renal impairment in Study GS-US-292-0112. In virologically suppressed subjects (Study GS-US-292-0109), no subject in the E/C/F/TAF group had subclinical renal tubulopathy, while 1 subject in the FTC/TDF+3rd Agent group (taking ATV/co+TVD) had all 4 confirmed renal laboratory abnormalities as well as a renal AE of Fanconi syndrome.

2.1.5.3.2. Methodology

In order to ensure a comprehensive assessment of renal safety, a thorough review was performed of all relevant data 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 proximal renal tubulopathy 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 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 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 {26955}, 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.

2.1.5.3.3. ART-Naive Subjects

2.1.5.3.3.1. 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 (m5.3.5.1, GS-US-292-0104 Week 48 CSR, Section 11.2.4.2; m5.3.5.1, GS-US-292-0111 Week 48 CSR, Section 11.2.4.2).

2.1.5.3.3.1.1. 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.

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) (m5.3.5.3, E/C/F/TAF ISS, Table 7).

2.1.5.3.3.1.2. Renal Laboratory Parameters

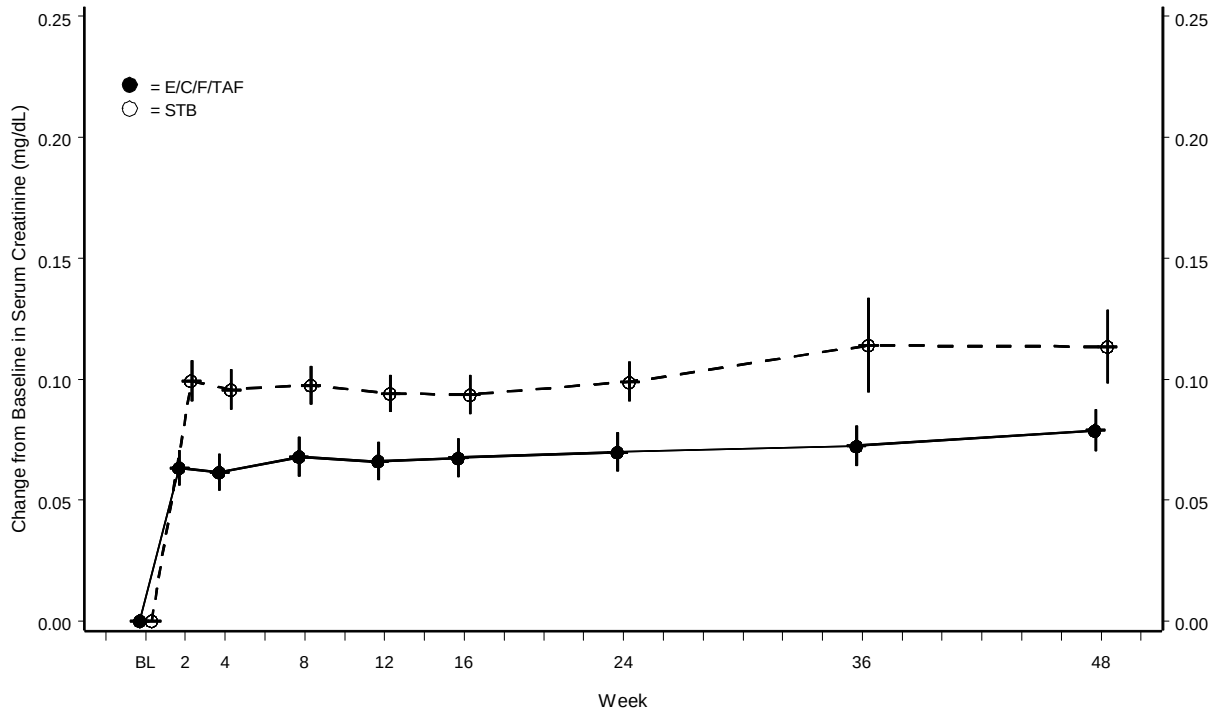
2.1.5.3.3.1.2.1. Serum Creatinine

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

(Section 1.1.3). 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 9). 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 (m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Table 26.1).

Figure 9. 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: m5.3.5.3, 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 (m5.3.5.3, 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.

2.1.5.3.3.1.2.2. 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 27 and Figure 10). 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.

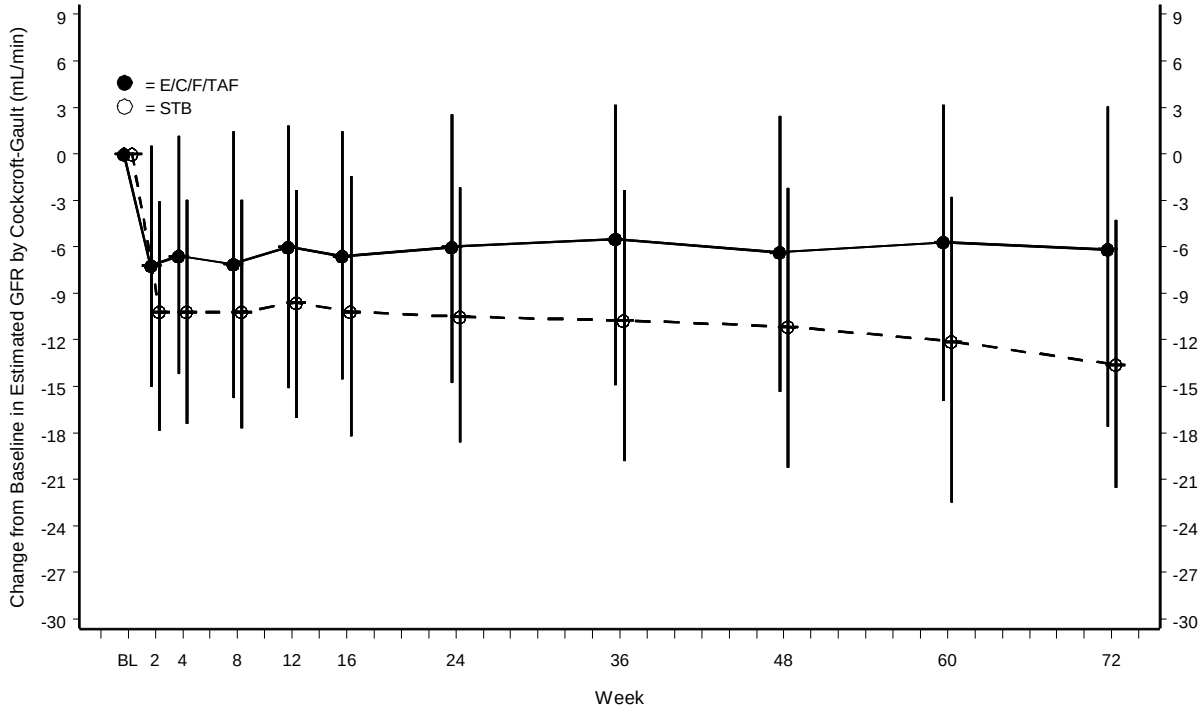
Observations for changes from baseline in $eGFR_{CKD\text{-}EPI,\ creatinine}$ support those seen for $eGFR_{CG}$ (m5.3.5.3, E/C/F/TAF ISS, Table 27.2).

Table 27. 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: m5.3.5.3, E/C/F/TAF ISS, Table 27.1

Figure 10. 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: m5.3.5.3, E/C/F/TAF ISS, Figure 6.1

2.1.5.3.3.1.2.3. 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 (Section 1.1.3). 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; m5.3.5.3, 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 (m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Table 11).

2.1.5.3.3.1.2.4. 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 28). 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 28).

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 28. 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: m5.3.5.3, E/C/F/TAF ISS, Tables 29.1 to 29.4

2.1.5.3.3.1.2.5. 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 percent change from baseline at Week 48: E/C/F/TAF 9.2% [-23.0%, 48.6%]; STB 51.2% [2.9%, 132.9%]; Table 28). 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 percent change from baseline at Week 48: E/C/F/TAF −31.7% [–57.3%, 3.7%], STB 24.1% [-33.8%, 167.9%]; Table 28). The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

2.1.5.3.3.1.2.6. 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%]; m5.3.5.3, 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%]; $p = 0.18$; m5.3.5.3, 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%]; m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Tables 31.1, 32.1, and 33.1).

2.1.5.3.3.1.2.7. Markers of Subclinical Proximal Renal Tubulopathy

No subjects in the E/C/F/TAF group met the criteria for proximal renal tubulopathy.

2.1.5.3.3.2. Study GS-US-292-0102

Renal safety for Study GS-US-292-0102 is described in detail in m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 11.2.4.2.

2.1.5.3.3.2.1. 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 [redacted] 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 [redacted] 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 proximal renal tubulopathy reported (including Fanconi syndrome) in either treatment group.

2.1.5.3.3.2.2. Renal Laboratory Parameters

2.1.5.3.3.2.2.1. 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 ($p = 0.011$).

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.

2.1.5.3.3.2.2.2. 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.

2.1.5.3.3.2.2.3. 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, 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.

2.1.5.3.3.2.2.4. 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.

2.1.5.3.3.2.2.5. 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.

2.1.5.3.3.2.2.6. 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.

2.1.5.3.4. Virologically Suppressed Subjects

2.1.5.3.4.1. Study GS-US-292-0109

Renal safety for Study GS-US-292-0109 is described in detail in m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 11.2.4.2.

2.1.5.3.4.1.1. 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 proximal renal tubulopathy (including Fanconi Syndrome) 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 drug.

2.1.5.3.4.1.2. Renal Laboratory Parameters

2.1.5.3.4.1.2.1. 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.

2.1.5.3.4.1.2.2. 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.

2.1.5.3.4.1.2.3. 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.

2.1.5.3.4.1.2.4. 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.

2.1.5.3.4.1.2.5. 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).

2.1.5.3.4.1.2.6. 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.

2.1.5.3.4.1.2.7. Markers of Subclinical Renal Tubulopathy

No subjects in the E/C/F/TAF group had laboratory findings consistent with subclinical renal tubulopathy. One subject ([redacted]) in the FTC/TDF+3rd Agent (taking ATV/co+TVD) had all 4 confirmed renal laboratory abnormalities as well as a renal AE of Fanconi syndrome.

2.1.5.3.4.2. Study GS-US-292-0102 Open-Label Extension

2.1.5.3.4.2.1. 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 proximal renal tubulopathy (including Fanconi Syndrome).

2.1.5.3.4.2.2. Renal Laboratory Parameters

2.1.5.3.4.2.2.1. 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).

2.1.5.3.4.2.2.2. 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.

2.1.5.3.4.2.2.3. 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.

2.1.5.3.4.2.2.4. 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.

2.1.5.3.4.2.2.5. 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%.

2.1.5.3.4.2.2.6. Other Renal Biomarkers

In the switch groups, there were no changes from baseline in median values for the other renal biomarkers.

2.1.5.3.4.2.2.7. Markers of Subclinical Proximal Renal Tubulopathy

There were no laboratory findings consistent with subclinical renal tubulopathy.

2.1.5.3.5. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

Renal safety for Study GS-US-292-0112 is described in detail in m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 11.2.

2.1.5.3.5.1. Renal Events

One subject (0.4%) in Cohort 1 had an SAE in the renal and urinary disorders SOC. Subject [redacted] (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).

2.1.5.3.5.2. Renal Laboratory Parameters

2.1.5.3.5.2.1. 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%.

2.1.5.3.5.2.2. 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 (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.

2.1.5.3.5.2.3. 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 $eGFR_{CKD\text{-}EPI, cysC}$.

2.1.5.3.5.2.4. 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 (Table Req6756.16).

No changes from the baseline proteinuria toxicity grade were observed for Cohort 2 ART-naive subjects.

2.1.5.3.5.2.5. 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 (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.

2.1.5.3.5.2.6. 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 (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.

2.1.5.3.5.2.7. 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 $eGFR_{CG}$ ≥ 50 mL/min groups; similar results were observed for Cohort 2 (ART-naive).

2.1.5.3.5.2.8. Markers of Subclinical Proximal Renal Tubulopathy

There were no laboratory findings consistent with subclinical renal tubulopathy.

2.1.5.3.6. ART-Naive Adolescent Subjects: Study GS-US-292-0106

Renal safety for Study GS-US-292-0106 is described in detail in m5.3.5.2, GS-US-292-0106 Interim CSR, Section 11.2.4.2.

2.1.5.3.6.1. 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 proximal renal tubulopathy (including Fanconi syndrome) were reported.

2.1.5.3.6.2. Renal Laboratory Parameters

2.1.5.3.6.2.1. 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.

2.1.5.3.6.2.2. 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.

2.1.5.3.6.2.3. 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).

2.1.5.3.6.2.4. 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%]).

2.1.5.3.6.2.5. 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.

2.1.5.3.6.2.6. Other Renal Biomarkers

No clinically meaningful change from baseline in TmP/GFR, $FEPO_4$, or FEUA was observed through Week 24.

2.1.5.3.6.2.7. Markers of Subclinical Proximal Renal Tubulopathy

No subject had laboratory findings consistent with proximal renal tubulopathy.

2.1.5.4. Ocular Safety

2.1.5.4.1. 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 studies, eye disorders were uncommon, balanced between treatment arms, 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.

2.1.5.4.2. Methodology

Any ophthalmic AE reported by subjects who received at least 1 dose of study drug 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

preferred terms, and this list of terms was reviewed and edited by an external ophthalmologist for comprehensiveness.

2.1.5.4.3. ART-Naive Subjects

2.1.5.4.3.1. 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 29).

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 (m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Table 16). Subject [redacted], 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 [redacted], in the STB group, had an SAE of Grade 2 iridocyclitis considered unrelated to study drugs. Subject [redacted], in the STB group, also had an SAE of Grade 2 retinal detachment considered unrelated to study drugs; treatment with study drugs continued. Additionally, Subject [redacted] 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.

There were no AEs of uveitis in the E/C/F/TAF group in either study (m5.3.5.3, 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 (m5.3.5.3, 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 (m5.3.5.3, 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 (m5.3.5.3, 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 29. 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 preferred term was presented by decreasing order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: m5.3.5.3, E/C/F/TAF ISS Table 7

2.1.5.4.3.2. 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 30). No AE in the eye disorders SOC was reported in the STB group.

One nonserious AE of photophobia reported for Subject *CC 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 30. 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 preferred terms 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: m5.3.5.1, 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.

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 [redacted]: 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 [redacted]: 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 *CC : 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 [redacted]: 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.

2.1.5.4.4. Virologically Suppressed Subjects

2.1.5.4.4.1. 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 31).

Subject [redacted] 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 *CD had two Grade 1 AEs of visual acuity reduced and vision blurred, with exact onset dates unknown; and Subject *CE 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 [redacted] (Grade 1, onset Day 252), [redacted] (Grade 1, onset Day 85), [redacted] (Grade 1, onset Day 174), [redacted] (Grade 1, onset Day 295), and [redacted] (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 31. 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 Version 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 preferred terms with at least 1 subject having the event in any treatment group are presented in this table.
Source: m5.3.5.1, 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 *CD [visual acuity reduced and vision blurred] and *CE [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 [redacted] 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.

2.1.5.4.4.2. 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.

2.1.5.4.5. Subjects with Mild to Moderate Renal Impairment: 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 $eGFR_{CG}$ ≥ 50 mL/min) and no subjects in Cohort 2 (ART-naive). None of the AEs in the eye disorders SOC were considered serious or resulted in discontinuation of study drug. Two ocular AEs reported for 1 subject (vitreous floaters and photopsia; Subject [redacted]) 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 $eGFR_{CG}$ ≥ 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.

2.1.5.4.6. ART-Naive Adolescent Subjects: Study GS-US-292-0106

In Study GS-US-292-0106, Subject *CB , 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.

2.1.5.5. Efavirenz-Related Symptom Assessment

2.1.5.5.1. Virologically Suppressed Subjects: Study GS-US-292-0109

The change from baseline in the EFV-related symptom composite score at Week 48, analyzed for the EFV-Related Symptom Analysis Set, was the fourth key alpha-protected safety endpoint for Study GS-US-292-0109 (Section 1.1.3). Statistical analysis using the fallback procedure confirmed significance using an adjusted alpha, which was dependent on the results from preceding tests.

At baseline, the EFV-related symptom composite score was comparable between treatment groups (median score of 1.0 for each group [p = 0.58]). The decrease (ie, improvement) from baseline in the EFV-related symptom composite score was greater in the E/C/F/TAF group than the FTC/TDF+3rd Agent group at Week 48 (median [mean] changes from baseline were: E/C/F/TAF 0.0 [-1.6]; FTC/TDF+3rd Agent 0.0 [-0.1]; p < 0.001 for the difference between treatment groups at Week 48).

The individual median scores for trouble sleeping, impaired concentration, and sleepiness were comparable between treatment groups at baseline and Week 48. There were statistically significant differences between groups for the changes from baseline in individual symptom scores for dizziness (median [mean] changes from baseline were: E/C/F/TAF 0.0 [-0.3]; FTC/TDF+3rd Agent 0.0 [-0.1]; p = 0.007) and abnormal or vivid dreams (mean [median] changes from baseline were: E/C/F/TAF 0.0 [-0.6]; FTC/TDF+3rd Agent 0.0 [0.1]; p < 0.001).

For subjects who switched to E/C/F/TAF from ATR, there was an increase from baseline at Week 48 in the percentage of subjects who reported having no symptoms (ie, score of 0) of dizziness, trouble sleeping, impaired concentration, sleepiness, and abnormal or vivid dreams. In contrast, for subjects who continued to take ATR, there were no significant changes from baseline in the percentages of subjects reporting no symptoms for any of the 5 EFV-related symptoms.

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.

E/C/F/TAF is being administered in 4 ongoing studies that were not included with this application. Narratives for deaths, SAEs, discontinuations due to AEs, pregnancies, and fractures reported to date for these studies that are not included in this application, as appropriate, are provided in m5.3.5.1 (Studies GS-US-292-0117 and GS-US-292-0119), m5.3.3.3 (Study GS-US-292-1249), and m5.3.5.4 (GS-US-236-0128).

3. CLINICAL LABORATORY EVALUATIONS

In the following sections, a summary of the clinical laboratory evaluations for the E/C/F/TAF FDC for the E/C/F/TAF Phase 2 and Phase 3 studies is presented. All laboratory abnormalities discussed in the following sections were treatment emergent and are referred to as laboratory abnormalities in this document.

Table 32 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 studies had a Grade 3 or 4 laboratory abnormality, with the exception of adolescent subjects in Study GS-US-292-0106 (4 subjects, 8.3%). Among the most common Grade 3 or 4 laboratory abnormalities across studies were creatinine kinase, 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 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, Grade 3 or 4 lipase abnormalities were reported less frequently in the E/C/F/TAF arms than in the comparator arms.

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 32. 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 (CK)	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

	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)
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
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 upper limit of normal.

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: m5.3.5.3, E/C/F/TAF ISS, Table 19; m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 15.1, Table 32.1; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Table 33; m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 15.1, Table 45; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 15.1, Table 27

3.1. Laboratory Abnormalities

3.1.1. ART-Naive Subjects

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 (m5.3.5.1, GS-US-292-0104 Week 48 CSR, Section 11.6; m5.3.5.1, 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 33). 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 (m5.3.5.3, 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 (m5.3.5.3, 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, stavudine, 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; m5.3.5.3, 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; m5.3.5.3, 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 (m5.3.5.3, 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) (m5.3.5.3, 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 (m5.3.5.3, E/C/F/TAF ISS, Tables Req6742.3.1 and Req6742.3.2). In the STB group, 5.0% of subjects (n = 43) were taking lipid modifying medications at study entry, and 2.9% of subjects (n = 25) initiated treatment during the study.

One subject in Study GS-US-292-0104 (Subject [redacted] 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 [redacted] 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 33. 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: m5.3.5.3, E/C/F/TAF ISS, Tables 34.1.1, 34.2.1, 34.3.1, 34.4.1, and 34.5

3.1.1.2. Study GS-US-292-0102

Detailed clinical laboratory evaluation results for Study GS-US-292-0102 may be found in m5.3.5.1, 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 34). 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, 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 34. 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	

Metabolic Assessment	E/C/F/TAF (N=112)	STB (N=58)	p-value[a]
Fasting HDL Cholesterol (mg/dL)			
Baseline			
N	111	58	0.66
Median	42	43	
Q1, Q3	35, 51	36, 53	
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	

Metabolic Assessment	E/C/F/TAF (N=112)	STB (N=58)	p-value[a]
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	
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: m5.3.5.1, 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

3.1.2. Virologically Suppressed Subjects

3.1.2.1. Study GS-US-292-0109

Detailed clinical laboratory evaluation results for Study GS-US-292-0109 may be found in m5.3.5.1, 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 35).

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 32).

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 35. GS-US-292-0109: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set)

	E/C/F/TAF (N = 959)		FTC/TDF+3rd Agent (N = 477)		
Metabolic Assessment	**N**	**Median (Q1, Q3)**	**N**	**Median (Q1, Q3)**	**P-Value[a]**
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: m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 15.1, Tables 38.1 to 38.6

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 m5.3.5.1, 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 [redacted] 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.

3.1.3. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

Detailed clinical laboratory evaluation results for Study GS-US-292-0112 may be found in m5.3.5.2, 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 36).

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 $eGFR_{CG}$

≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 50 mL/min group had AEs of hypercholesterolemia and 1 subject in the baseline $eGFR_{CG}$ ≥ 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 $eGFR_{CG}$ ≥ 50 mL/min group).

Table 36. 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

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min	**Baseline $eGFR_{CG}$ ≥ 50 mL/min**	**Total**
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
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

	Cohort 1: Switch		
	Baseline $eGFR_{CG}$ < 50 mL/min	**Baseline $eGFR_{CG}$ ≥ 50 mL/min**	**Total**
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			
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: m5.3.5.2, 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 37). 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 37. 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

	With TDF Use at Baseline[a] N=158	Without TDF Use at Baseline N=84
Change at Week 48		
N	110	52
Median	1	-3
Q1, Q3	-5, 7	-9, 3
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, Truvada, and Viread) immediately prior to the first dose date of study drug.

Source: m5.3.5.2, 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).

3.1.4. ART-Naive Adolescent Subjects: Study GS-US-292-0106

Detailed clinical laboratory evaluation results for Study GS-US-292-0106 may be found in m5.3.5.2, 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 38.

Table 38. 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: m5.3.5.2, 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

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 (m5.3.5.1, GS-US-292-0104 Week 48 CSR, Section 11.7; m5.3.5.1, GS-US-292-0111 Week 48 CSR, Section 11.7; m5.3.5.1, GS-US-292-0102 Week 96 CSR, Section 11.7; m5.3.5.1, GS-US-292-0109 Week 48 CSR, Section 11.8; m5.3.5.2, GS-US-292-0112 Week 24 CSR, Section 11.8; m5.3.5.2, GS-US-292-0106 Interim CSR, Section 11.7).

4.1.1. ECG Findings

4.1.1.1. ART-Naive Subjects

4.1.1.1.1. 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 [redacted], who had a normal ECG at baseline, had clinically significant abnormal sinus rhythm with sinus arrhythmia and first degree atrioventricular (AV) 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 [redacted], 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.

4.1.1.1.2. 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 [redacted] had a nonserious ST segment elevation concurrent with pericarditis, sinus bradycardia, and upper respiratory tract infection; Subject [redacted] 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.

4.1.1.2. Virologically Suppressed Subjects

4.1.1.2.1. 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 [redacted] 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 [redacted] 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 *CF), sinus tachycardia (Subject [redacted]), tachycardia (Subject *CA), and sinus bradycardia (reported for Subjects [redacted] and [redacted]). In the FTC/TDF+3rd Agent group, the reported AEs were extrasystoles (Subject [redacted]), arrhythmia (Subject [redacted]), and sinus bradycardia (Subject [redacted]). 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 *CF in the E/C/F/TAF group were assessed as related to study drug by the investigator.

4.1.1.2.2. 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.

4.1.1.3. Subjects with Mild to Moderate Renal Impairment: 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 not considered serious and resolved within 4 days of onset).

4.1.1.4. ART-Naive Adolescent Subjects: 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.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

5.1.1. Summary of Intrinsic Factors

The safety of E/C/F/TAF was not affected by sex, age, race, HIV-1 RNA level, or CD4 count.

Renal impairment has an effect on E/C/F/TAF, but does not require dose adjustment above an eGFR of 30 mL/min. Baseline eGFR does not have an effect on EVG or COBI exposure.

eGFR does have an effect of FTC exposures, but subjects with $eGFR_{CG} < 50$ mL/min 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 has been evaluated, and no dose adjustment is necessary for patients. The effect of severe hepatic impairment on the PK of TAF has not been studied.

The effect of mild to moderate hepatic impairment (Child Pugh Class A or B) on EVG and COBI has been evaluated, and no dose adjustment is necessary for patients. The effect of severe hepatic impairment on the PK of EVG and COBI 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 in man 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

Sex did not have an effect on EVG, COBI, TAF, and TFV exposures in subjects and was not a statistically or clinically relevant covariate based on population PK analyses (m2.7.2, Section 3.2.2.6).

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

Based on 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.

In ART-naive subjects in 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) (m5.3.5.3, 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 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).

5.1.3. Age

Age did not have an effect on EVG, COBI, and TAF exposures in subjects and was not a statistically or clinically relevant covariate based on population PK analyses (m2.7.2, Section 3.2.2.2).

For FTC PK, there were no relevant differences with respect to range and distribution of AUC values between age groups examined. 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%.

As age is often correlated with renal function and TFV is primarily renally eliminated, there was a modest dependence of TFV exposure on age, but this 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 was still at least 80% lower versus STB.

In adolescent subjects, TAF and TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF (PK substudy in Study GS-US-292-0102 [m2.7.3, Section 2.1.3]), indicating no relevant effects of pediatrics (age ≥ 12 years) on the exposure of TAF (m2.7.2, Section 3.2.2.5). Additionally, in the pooled Phase 2 and Phase 3 study populations used for population PK analyses, HIV-infected adolescent subjects had comparable TAF and TFV exposures versus HIV-infected adult subjects, respectively, again confirming that age was not a clinically relevant covariate.

In ART-naive subjects in 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) (m5.3.5.3, 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 (m5.3.5.3,

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 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 (m5.3.5.3, 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 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) (m5.3.5.3, E/C/F/TAF ISS, Table Req6756.11).

In the adolescent Study GS-US-292-0106, at least 1 AE was reported in 81.3% of subjects (39 of 48 subjects).

5.1.4. Race

Race did not have an effect on EVG, COBI, and TAF exposures in subjects and was not a statistically or clinically relevant covariate based on population PK analyses (m2.7.2, Section 3.2.2.4).

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 > 80% lower versus STB. As such, the observed relationship between race and TFV exposure is not considered to be clinically relevant.

In ART-naive subjects in 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) (m5.3.5.3, E/C/F/TAF ISS, Table 8.3).

In virologically suppressed subjects in 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 Study GS-US-292-0108, the PK of EVG, COBI, FTC, TAF, and 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. No significant differences in safety parameters between Japanese and white subjects were noted. Six Japanese subjects (60.0%) and 9 white subjects (90.0%) experienced at least 1 AE.

5.1.5. HIV-1 RNA Stratum at Baseline

In in ART-naive subjects in 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) (m5.3.5.3, E/C/F/TAF ISS, Table 8.4).

5.1.6. CD4 Cell Count at Baseline

In ART-naive subjects in 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) (m5.3.5.3, E/C/F/TAF ISS, Table 8.5).

5.1.7. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

TAF and TFV

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%) (m2.7.2, Section 3.3.2.1).

Both the TAF and TFV 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. Additionally, the TFV exposure was comparable regardless of the presence or absence of nausea and/or vomiting with no exposure-AE trends noted.

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 groups in the pivotal Phase 3 studies (m5.3.5.3, E/C/F/TAF ISS, Table 7).

The percentage change from baseline in BMD at the hip or spine at Week 48 was also a key safety endpoint of Studies GS-US-292-0104 and GS-US-292-0111. Accordingly, the relationship between TAF and TFV exposure quartiles and changes in BMD at the hip and spine was evaluated. Across all TAF and TFV AUC_{tau} quartiles, the percentage change from baseline at Week 48 in BMD was 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 and TFV exposure quartiles and maximum increase from baseline in serum creatinine was also evaluated. Across all TAF and TFV AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable; no trends in exposure-changes in serum creatinine were noted.

EVG

The PK-PD analyses of the EVG exposure-safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2 and Phase 3 studies using EVG exposures derived from population PK modeling versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea. EVG exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed.

The relationship between EVG exposure quartiles and changes in renal laboratory parameters was also evaluated. Across all EVG AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable; no trends in exposure-changes in laboratory parameters were noted.

COBI

The PK of COBI was evaluated in HIV-uninfected subjects with mild/moderate renal impairment (placebo-controlled study evaluating COBI only, $eGFR_{CG}$ 50-79 mL/min, with an additional cohort of subjects with normal renal function, $eGFR_{CG} \geq 80$ mL/min) in Study GS-US-216-0121. COBI exposures were increased in subjects with mild/moderate renal impairment, which may be due to reductions in COBI clearance with or without a change in its bioavailability.

The PK-PD analyses of the COBI exposure-safety relationship were performed in ART-naive HIV-infected subjects in STB Phase 2 and Phase 3 studies using COBI exposures derived from intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea. COBI exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed.

The relationship between COBI exposure quartiles and changes in renal laboratory parameters was evaluated. Across all COBI AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine was comparable with overlapping values and greater variability in the fourth quartile (for serum creatinine changes), and no trends in exposure-changes in laboratory parameters were noted.

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 $eGFR_{CG}$ ≥ 50 mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

5.1.8. Renal Impairment

The totality of efficacy, safety, and PK data from 249 HIV-infected subjects with mild to moderate renal impairment in Study GS-US-292-0112 confirm that treatment with E/C/F/TAF may be initiated and continued with no dose adjustment in patients with mild to moderate renal impairment (eGFR > 30 mL/min) (m2.7.2, Section 3.2.2.1.1). As expected due to the renal elimination, FTC PK was higher subjects with mild to moderate renal impairment compared with those having normal renal function. 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}. Moreover, subjects with $eGFR_{CG}$ < 50 mL/min did not have a different safety profile compared with subjects with $eGFR_{CG}$ ≥ 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.

TAF and TFV

A substudy of Study GS-US-292-0112 (n = 32) evaluated the PK of TAF and TFV following administration of E/C/F/TAF in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min and showed mean (%CV) TAF and TFV exposures (AUC) of 254.2 (54.1) ng*h/mL and 552.7 (32.0), respectively.

In Study GS-US-120-0108, the PK of TAF and TFV was analyzed in subjects with severe renal impairment ($eGFR_{CG}$ < 30 mL/min, not on dialysis) and matched healthy adult controls. 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. This difference is unlikely to be clinically relevant. Subjects with severe renal impairment had a 6.05-fold mean increase in systemic TFV exposure as assessed by AUC_{inf} relative to age- and sex-matched

subjects with normal renal function. The mean (%CV) TFV exposure observed in subjects with severe renal impairment in this study after a single dose of TAF 25 mg (2073.8 [47.1] ng*h/mL) was within or below the range of TFV plasma exposure measured in historical studies after administration of TDF 300 mg in both healthy, HIV-negative subjects and in HIV-infected patients with normal renal function.

In population PK analyses of TAF and TFV, baseline eGFR was not a statistically or clinically relevant covariate influencing TAF PK. The TAF exposure was higher in subjects with lower $eGFR_{CG}$ relative to normal renal function (> 90 mL/min) but less than a 50% change was shown between moderate renal impairment versus normal renal function. As expected with TFV being primarily renally eliminated, a statistically significant effect of baseline $eGFR_{CG}$ on TFV exposure was observed based on covariate analyses. TFV exposure was higher in subjects with lower $eGFR_{CG}$ relative to normal renal function. However, the TFV exposure observed in subjects with $eGFR_{CG} \geq 30$ and < 50 mL/min was below the range of TFV plasma exposure measured in subjects with severe renal impairment in Phase 1 Study GS-US-120-0108 and historical studies after administration of TDF 300 mg in HIV-infected patients with normal renal function {26885}.

EVG and COBI

The PK of EVG and COBI were evaluated in HIV-uninfected subjects with severe renal impairment (EVG and COBI, baseline $eGFR_{CG} < 30$ mL/min) and a matching cohort of subjects with normal renal function (baseline $eGFR_{CG} \geq 90$ mL/min) in Study GS-US-216-0124. Clinically meaningful differences in the PK of EVG and COBI were not observed at the extremes of renal function.

Baseline eGFR did not have an effect on EVG or COBI exposure and was not a statistically or clinically relevant covariate based on population PK analyses

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]). 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, from the Emtriva prescribing information for subjects with $eGFR_{CG}$ of 50 to 80 mL/min who do not require dose adjustment. Subjects with $eGFR_{CG}$ < 50 mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG}$ ≥ 50 mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

The totality of these data confirm the safety of E/C/F/TAF may be safely administered once daily without dose adjustment in patients with renal impairment ($eGFR_{CG}$ > 30 mL/min).

5.1.9. Hepatic Impairment

TAF and TFV

The PK of TAF and TFV in HIV-uninfected subjects were evaluated in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) versus matched healthy adult subjects (control) in Study GS-US-120-0114 (m2.7.2, Section 3.2.2.1.2). 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 the subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function, which was not considered to be clinically relevant. 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 the subjects with mild hepatic impairment relative to matched control subjects with normal hepatic function; the observed decreases are 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 the subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function which was not considered to be clinically relevant. The effect of severe hepatic impairment on the PK of TAF has not been studied.

EVG and COBI

The PK of EVG and COBI in HIV-uninfected subjects were evaluated in subjects with moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Class B, with an additional cohort of matched subjects [age, sex, and BMI] with normal hepatic function) in Study GS-US-183-0133. The steady-state plasma exposure parameters of EVG were modestly higher (AUC_{tau}, C_{tau}, and C_{max}

were 34.99%, 79.63%, and 41.28% higher, respectively) in subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function but were not considered to be clinically relevant. The AUC_{tau} and C_{max} of COBI were generally comparable in subjects with moderate hepatic impairment relative to normal matched control subjects; COBI C_{tau} was higher (GLSM ratio 207.70%) although not considered to be clinically relevant.

Exploratory analyses indicated no clinically relevant correlations between EVG or COBI exposures versus CPT scores or individual liver function laboratory parameters (ie, albumin, total bilirubin, prothrombin time, and international normalized ratio [INR]) for subjects with moderate hepatic impairment. The mean (SD) percentages for free fraction (unbound concentration) EVG in the normal matched control subjects and moderate hepatic impairment subjects were 1.15% (0.14) and 1.22% (0.23), respectively. These findings are consistent with historical data (GS-US-183-0101) and indicate the lack of effect of hepatic impairment on EVG protein binding. Similar results were observed for COBI (corresponding values were 2.71% [0.56] and 3.23% [0.63], respectively).

The PK of COBI in subjects with severe hepatic impairment have not been evaluated.

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 who were hepatitis C antibody positive were excluded from all Phase 2 and 3 studies of E/C/F/TAF. The exclusion criteria for Study GS-US-292-0104 were updated in Amendment 1 of the protocol to exclude subjects with positive HBV surface antigen. All of the other Phase 2 and Phase 3 studies of E/C/F/TAF excluded subjects with positive HBV surface antigen. In Study GS-US-292-0104, Subject [redacted] 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 [redacted] 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.

Study GS-US-292-1249 is a Phase 3b, open-label study of E/C/F/TAF FDC in adult subjects who are coinfected with HIV-1 and hepatitis B. The study is ongoing.

No dose adjustment of E/C/F/TAF is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B).

5.2. Extrinsic Factors

5.2.1. Summary of Extrinsic Factors

Data pertinent to drug interactions are described in Section 5.3.

The safety of E/C/F/TAF was not affected by prior treatment regimen or region.

Although boosted TAF is unaffected by food, it is recommended that boosted EVG be administered with food to achieve the desired EVG exposure that provides a high mean 95% inhibitory quotient (IQ_{95}) (EVG trough concentrations [C_{tau}]/IC_{95}). As such, E/C/F/TAF was administered with food in its clinical development program to align with the dosing recommendations of STB, the comparator in the pivotal Phase 3 studies.

5.2.2. Prior Treatment Regimen

In virologically suppressed subjects in 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

Following oral administration with food in HIV-1 infected patients, peak plasma concentrations were observed approximately 4 hours postdose for EVG, 3 hours postdose for COBI, 3 hours postdose for FTC, and 1 hour postdose for TAF. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) in HIV-1 infected patients, respectively, were 1.7 ± 0.39 µg/mL, 23 ± 7.5 µg*hr/mL, and 0.45 ± 0.26 µg/mL for EVG, which provides inhibitory quotient of ~ 10 (ratio of C_{trough}: protein binding-adjusted IC_{95} for wild-type HIV-1 virus). Corresponding steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) were 1.1 ± 0.40 µg/mL, 8.3 ± 3.8 µg*hr/mL, and 0.05 ± 0.13 µg/mL for COBI; 1.9 ± 0.5 µg/mL, 13 ± 4.5 µg*hr/mL, and 0.14 ± .25 µg/mL for FTC. Steady-state mean C_{max} and AUC_{tau} for TAF were 0.17 ± 0.09 µg/mL and 0.23 ± 0.22µg*hr/mL, respectively.

For EVG, C_{max} and AUC increased 22% and 36% with a light meal, and 56% and 91% with a high-fat meal, relative to fasting conditions. COBI exposures were unaffected by a light meal, and although there was a modest decrease of 24% and 18% in C_{max} and AUC, respectively, with a high-fat meal, no difference was observed in its pharmacoenhancing effect on EVG. FTC exposures were unaffected by a light or high-fat meal.

Relative to fasting conditions, the administration of E/C/F/TAF with a light meal (~400 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) did not affect overall exposures of TAF to a clinically meaningful extent (approximately 13% higher AUC with light or high-fat meal versus fasted).

5.2.4. Region

In ART-naive subjects in 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; m5.3.5.3, E/C/F/TAF ISS, Table 8.6).

In virologically suppressed subjects in 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 with each component as individual agents have been conducted and pertinent findings and/or recommendations are as follows.

EVG and COBI

Boosted-EVG is metabolized by uridine glucuronosyltransferase (UGT) 1A1/3, and its plasma exposure will increase when coadministered with potent UGT1A1 inhibitors, eg, ATV, lopinavir (LPV). Since dose adjustment is not possible with a FDC tablet, coadministration is not recommended.

COBI exposures, and subsequently those of EVG may be decreased upon coadministration with moderate-to-strong cytochrome P450 enzyme (CYP) 3A inducers. As such, the following agents are contraindicated or not recommended for coadministration with the E/C/F/TAF FDC: rifampin, rifabutin, rifapentine, St. John’s wort, systemic dexamethasone, carbamazepine, oxcarbazepine, phenobarbital, phenytoin as it may result in loss of therapeutic activity of the EVG component of E/C/F/TAF.

No effect of acid reducing agents is expected on EVG or COBI PK; however, administration with antacids should be separated from the E/C/F/TAF FDC by at least 2 hours to prevent lower absorption of EVG.

Cobicistat will substantially increase systemic exposure of CYP3A substrates.

FTC

There are no clinically significant interactions when FTC is coadministered with indinavir (IDV), zidovudine (ZDV), stavudine (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.

TAF

The potential for TAF and TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities (m2.7.2, Section 3.2.3.2.1). TAF weakly inhibited CYP3A-mediated oxidation of midazolam (MDZ) or testosterone with IC_{50} values of 7.6 and 7.4 µM, respectively. TFV at 100 µM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, was assessed at TAF concentration at 50 µM (m4.2.2.6, AD-120-2040). There was no evidence for time- or cofactor-dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control.

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

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

Administration of E/C/F/TAF with a modest CYP3A inducer may result in lower TAF exposure. However, the magnitude of change in TAF and TFV would be expected to be less following E/C/F/TAF due to the presence of the potent CYP3A inhibitor COBI.

F/TAF

Administration of F/TAF FDC plus EFV resulted in no clinically relevant changes in FTC, TFV, TAF, or EFV exposure, as compared with F/TAF FDC dosed alone (m2.7.2, Section 2.5.2.1). Administration of F/TAF FDC plus DRV+COBI resulted in comparable exposures of TAF and FTC, but substantially higher TFV exposure, relative to F/TAF FDC dosed alone. Administration of F/TAF FDC plus DRV+COBI resulted in comparable exposures of DRV and COBI, relative to DRV+COBI dosed alone. Administration of TAF plus COBI resulted in substantially higher TAF and TFV exposures relative to TAF dosed alone, with COBI exposure in the range of historical data.

E/C/F/TAF FDC

Following the coadministration of E/C/F/TAF and sertraline (SER), no clinically relevant alterations in the PK of EVG, COBI, FTC, TAF, TFV, or SER were observed relative to the administration of E/C/F/TAF or SER alone (m2.7.2, Section 2.5.1.2). A lack of CYP-mediated drug interaction was observed upon coadministration of E/C/F/TAF and SER. Overall, the exposures of all analytes following E/C/F/TAF and/or SER were consistent with historical data.

5.4. Use in Pregnancy and Lactation

No adequate and well-controlled studies of E/C/F/TAF or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of EVG, COBI, FTC, or TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. The E/C/F/TAF 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 EVG, COBI, and TFV are excreted into milk. It is not known whether EVG or COBI are excreted in human milk. In humans, samples of breast milk obtained from 5 HIV-infected mothers given TVD 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 E/C/F/TAF FDC.

5.4.1. E/C/F/TAF FDC

5.4.1.1. Phase 1 Studies

No pregnancies were reported in Phase 1 studies with the E/C/F/TAF FDC.

5.4.1.2. Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106

Six pregnancies were reported in 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 (*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 [redacted], 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 [redacted], [redacted], [redacted], STB) were reported as ongoing at the time of report in all 3 cases.

Pregnancy in 1 subject enrolled in Study GS-US-292-0109 (Subject [redacted], E/C/F/TAF) was terminated by an elective abortion.

No pregnancies were reported in Studies GS-US-292-0112 and GS-US-292-0106.

5.4.2. TAF

No pregnancies were reported in clinical studies for TAF single agent.

5.4.3. EVG, COBI, and FTC

Pregnancies in clinical studies are described in individual CSRs. The safety of the use of EVG, COBI, and FTC during pregnancy or breast-feeding are reflected in the respective approved drug labels for Vitekta®, Tybost®, and Emtriva. These products 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 EVG, COBI, and FTC are provided below.

There was no prospective case of live births involving exposure to COBI. There were 2 prospective cases of live births involving first trimester exposure to EVG; no birth defects were detected in these 2 infants. A total of 1543 first trimester exposure and 729 second/third trimester exposure prospective cases of live births involving exposure to FTC were presented. There were 35 cases of birth defects following first trimester exposure and 15 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 for "early diagnoses" in population-based birth defects surveillance systems or with rates among those with earliest exposure in the second or third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis with the exception of didanosine (ddI) and nelfinavir (NFV), 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

Separate review of the available information from the clinical studies remains inconclusive. The registry will continue to examine the data as available from further studies.

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 E/C/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 EVG, COBI, FTC, or TAF. No severe adverse reactions were reported at supratherapeutic doses in studies of EVG (Study GS-US-183-0128), COBI (Studies GS-US-216-0113 and GS-US-216-0107), or FTC.

As EVG and COBI are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. 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 (PSURs) for this product. No new safety issues have been identified regarding overdose.

Study GS-US-292-0104

In Study GS-US-292-0104, 23 subjects reported at least 1 overdose during the study (E/C/F/TAF 1.6%, 7 subjects, STB 3.7%, 16 subjects). In the E/C/F/TAF group, 6 subjects were classified as overdose of study drug, while 1 additional subject who reported an overdose was classified as a procedural deviation. In the STB group, 12 cases were classified as overdose of study drug in 11 subjects, while 3 additional subjects who reported an overdose were classified as procedural deviations and 2 were classified as nonadherence of study drug.

Most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of blinded study medication and not associated with clinical symptoms or sequelae. Adverse events possibly associated with overdoses were observed in 2 of the subjects: (E/C/F/TAF: mild headache [Subject [redacted]], and event not specified [Subject [redacted]]).

Study GS-US-292-0111

In study GS-US-292-0111, 19 subjects reported at least 1 overdose during the study (E/C/F/TAF: 1.8%, 8 subjects, STB 2.5%, 11 subjects). In the E/C/F/TAF group, 7 subjects were classified as overdose of study drug, while 1 additional subject who reported an overdose was classified as a procedural deviation. In the STB group, 10 subjects were classified as overdose of study drug, while 1 additional subject who reported an overdose was classified as a procedural deviation.

Most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of blinded study medication. Two subjects reported AEs associated with the overdose (E/C/F/TAF: dizziness [Subject [redacted]], STB: vomiting [Subject [redacted]]).

Study GS-US-292-0109

In Study GS-US-292-0109, 27 subjects reported at least 1 overdose during the study (E/C/F/TAF: 2.4%, 23 subjects, FTC/TDF + 3rd Agent: 0.8%, 4 subjects). One subject reported an AE associated with overdose (E/C/F/TAF: drowsiness [Subject [redacted]]). Most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of blinded study medication. Subject [redacted] randomized to 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.

Study GS-US-292-0112

In Study GS-US-292-0112, 2 subjects (0.8%) reported at least 1 overdose during the study. Most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of blinded study medication. No AEs were reported with the overdoses.

Study GS-US-292-0106

In Study GS-US-292-0106, 2 subjects (4.2%) reported at least 1 overdose during the study. They were characterized by isolated, inadvertent administrations of single extra daily doses of blinded study medication, and no AEs associated with the overdoses were reported.

5.6. Drug Abuse

No safety issues concerning the abuse or misuse of E/C/F/TAF tablets are anticipated from the available data.

5.7. Withdrawal and Rebound

The safety and efficacy of E/C/F/TAF have not been established in patients coinfected with HIV-1 and HBV. Discontinuation of E/C/F/TAF therapy in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC or TAF components of E/C/F/TAF. Patients coinfected with HIV-1 and HBV who discontinue E/C/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 EVG, COBI, FTC, or TAF on the ability to drive or operate machinery.

6. POSTMARKETING DATA

E/C/F/TAF has not been marketed in any country at the time of this application.

7. APPENDICES

7.1. List of Appendices

Appendix Number	Appendix Title
7.2	Tabular Summary of E/C/F/TAF Studies Relevant for Safety
7.3	Tabular Summary of TAF Studies Relevant for Safety
7.4	Tabular Summary of EVG Studies Relevant for Safety
7.5	Tabular Summary of COBI Studies Relevant for Safety
7.6	Tabular Summary of FTC Studies Relevant for Safety
7.7	E/C/F/TAF FDC: Integrated Safety Analyses

7.2. Tabular Summary of E/C/F/TAF Studies Relevant for Safety

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; m5.3.5.2, 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; m5.3.5.2, Week 24 Interim CSR

7.3. Tabular Summary of TAF Studies Relevant for Safety

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: 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 (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; m5.3.4.2, Final CSR

7.4. Tabular Summary of EVG Studies Relevant for Safety

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-183-0145 (synopsis)	Assess the noninferiority of EVG vs RAL, each administered with a BR containing a fully active PI+RTV and a second agent in HIV-infected, ART-experienced adults Additionally, the efficacy, safety, and tolerability of the 2 treatment regimens, EVG and RAL, are being evaluated	Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled study	• EVG 150 mg QD PO (EVG 85 mg QD for subjects taking ATV+RTV or LPV/r as part of their BR) + RAL placebo BID PO + BR (A) • RAL 400 mg BID PO + EVG placebo QD PO + BR (B)	Blinded Phase: 144 weeks until unblinding Open-Label Extension Phase: 144 weeks, 144 weeks + 30 days or until EVG development is terminated (UK), or until commercially available	Randomized: 724 A: 361 B: 363 Received study drug: 712 A: 354 B: 358 Continuing study drug at Week 96: A: 208 B: 208 Continuing in study at Week 96: A: 216 B: 223	HIV-infected, ART-experienced adult subjects	Study ongoing; Week 96 Interim CSR and Amendment 1

7.5. Tabular Summary of COBI Studies Relevant for Safety

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-216-0114 (synopsis)	Evaluate the efficacy and safety of a regimen containing ATV+COBI+ TVD vs ATV+RTV+ TVD in HIV-infected ART-naive adult subjects	Phase 3, double-blind, multicenter, randomized, active-controlled study	Study drug administered once daily, orally, with food: • COBI 150 mg + ATV 300 mg + TVD (single tablet FTC/TDF, 200/300 mg) + RTV placebo (A) • RTV 100 mg + ATV 300 mg + TVD (single tablet FTC/TDF, 200/300 mg) + COBI placebo (B)	192 weeks	Randomized: 698 A: 349 B: 349 Treated: 692 A: 344 B: 348 Week 144 Per-Protocol Analysis Set: A: 250 B: 257	HIV-infected, ART-naive adults with plasma HIV-1 RNA levels ≥ 5000 copies/mL at screening	Study ongoing; m5.3.5.1, Interim Week 144 CSR

7.6. Tabular Summary of FTC Studies Relevant for Safety

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 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
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) 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; ATV = atazanavir; BID = twice daily; BR = background regimen; COBI = cobicistat (Tybost®); CSR = clinical study report; d4T = stavudine; ddI = didanosine; DRV = darunavir; 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®); FDC = fixed-dose combination; FTC = emtricitabine (Emtriva®); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; INSTI = integrase strand-transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir boosted with ritonavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NVP = nevirapine; PD = pharmacodynamics(s); PI = protease inhibitor; PK = pharmacokinetic(s); PO = orally; QD = once daily; RAL = raltegravir; RNA = ribonucleic acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate (Viread®);UK = United Kingdom; ZDV = zidovudine

7.7. E/C/F/TAF FDC: Integrated Safety Analyses

Table 1	Subject Disposition, Studies GS-US-292-0104 and GS-US-292-0111, All Randomized Subjects
Table 2	Demographics and Baseline Characteristics, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 3	Baseline Disease Characteristics, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 4	Duration of Exposure to Study Drug, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 5	Time to Premature Discontinuation of Study Drug (Kaplan-Meier Estimate), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 5.1	Supporting Table for Table 5: Percentiles of Time to Premature Discontinuation of Study Drug (Kaplan-Meier Estimate), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 5.2	Supporting Table for Table 5: Listing of Time and Censoring Status of Premature Discontinuation of Study Drug (Kaplan-Meier Estimate), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 6	Treatment-Emergent Adverse Events: Overall Summary, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 7	Treatment-Emergent Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 8.1	Treatment-Emergent Adverse Events by Age Group (< 50 Years or ≥ 50 Years), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 8.2	Treatment-Emergent Adverse Events by Sex (Male or Female), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 8.3	Treatment-Emergent Adverse Events by Race (Black or Nonblack), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 8.4	Treatment-Emergent Adverse Events by Baseline HIV-1 RNA Level (≤ 100,000 copies/mL or > 100,000 copies/mL), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 8.5	Treatment-Emergent Adverse Events by Baseline CD4 Cell Count (< 200 /uL or ≥ 200 /uL), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 8.6	Treatment-Emergent Adverse Events by Region (US or ex-US), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 9	Grade 2, 3, or 4 Treatment-Emergent Adverse Events, Studies GS-US-292--0104 and GS-US-292-0111, Safety Analysis Set
Table 10	Grade 3 or 4 Treatment-Emergent Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 11	Treatment-Emergent Study-Drug-Related Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 12	Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 13	Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 14	Treatment-Emergent Serious Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 15	Treatment-Emergent Study-Drug-Related Serious Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 16	Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 17	Treatment-Emergent Potential Uveitis Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 18	Treatment-Emergent Laboratory Abnormalities, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 19	Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 20.1.1	Percentage Change from Baseline in Hip Bone Mineral Density by Visit (LOCF Imputation), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set

Table 20.1.2	Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set
Table 20.2.1	Percentage Change from Baseline in Spine Bone Mineral Density by Visit (LOCF Imputation), Studies GS-US-292-0104 and GS-US-292-0111, Spine DXA Analysis Set
Table 20.2.2	Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Spine DXA Analysis Set
Table 21.1	Clinical Hip Bone Mineral Density Status by Baseline Status and Visit, Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set
Table 21.2	Clinical Spine Bone Mineral Density Status by Baseline Status and Visit, Studies GS-US-292-0104 and GS-US-292-0111, Spine DXA Analysis Set
Table 22.1	Gradation of the Percentage Change in Hip Bone Mineral Density by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set
Table 22.2	Gradation of the Percentage Change in Spine Bone Mineral Density by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Spine DXA Analysis Set
Table 23.1	Bone Biomarkers: Summary of Serum C-type Collagen Sequence (CTx, ng/mL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 23.2	Bone Biomarkers: Summary of Serum Bone Procollagen Type 1 N-terminal Propeptide (P1NP, ng/mL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 23.3	Bone Biomarkers: Summary of Serum Parathyroid Hormone (PTH, pg/mL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 24	Treatment-Emergent Fracture Events, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 25.1.1	Summary of 10 Year Probability of Hip Fracture (%) by Visit (Age ≥ 40 Years), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set

Table 25.1.2	Summary of 10 Year Probability of Hip Fracture (%) by Visit (All Subjects), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set
Table 25.2.1	Summary of 10 Year Probability of Major Osteoporotic Fracture (%) by Visit (Age ≥ 40 Years), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set
Table 25.2.2	Summary of 10 Year Probability of Major Osteoporotic Fracture (%) by Visit (All Subjects), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set
Table 26.1	Summary of Serum Creatinine (mg/dL) by Visit (LOCF Imputation), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 26.2	Summary of Serum Creatinine (mg/dL) by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 27.1	Summary of Estimated GFR by Cockcroft-Gault (mL/min) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 27.2	Summary of Estimated GFR by CKD-EPI Creatinine (mL/min/1.73m^2) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 28	Treatment-Emergent Proteinuria by Urinalysis (Dipstick), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 29.1	Renal Biomarkers: Summary of Urine RBP to Creatinine Ratio (ug/g) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 29.2	Renal Biomarkers: Summary of Urine Beta-2-Microglobulin to Creatinine Ratio (ug/g) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 29.3	Renal Biomarkers: Summary of Urine Protein to Creatinine Ratio (UPCR, mg/g) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 29.4	Renal Biomarkers: Summary of Urine Albumin to Creatinine Ratio (UACR, mg/g) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 30.1	Shift Table of Urine Protein to Creatinine Ratio (UPCR) Category (≤ 200 vs > 200 mg/g) by Baseline Category, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 30.2	Shift Table of Urine Albumin to Creatinine Ratio (UACR) Category (< 30 vs ≥ 30 mg/g) by Baseline Category, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 31.1	Summary of TmP/GFR Ratio (Using Unadjusted SCr, mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 31.2	Summary of TmP/GFR Ratio (Using Adjusted SCr, mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 32.1	Summary of Urine Fractional Excretion of Phosphate (FEPO4 Using Unadjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 32.2	Summary of Urine Fractional Excretion of Phosphate (FEPO4 Using Adjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 33.1	Summary of Urine Fractional Excretion of Uric Acid (FEUA Using Unadjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 33.2	Summary of Urine Fractional Excretion of Uric Acid (FEUA Using Adjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.1.1	Metabolic Assessments: Summary of Fasting Total Cholesterol (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.1.2	Metabolic Assessments: Shift Table of Fasting Total Cholesterol (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.2.1	Metabolic Assessments: Summary of Fasting Direct LDL (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.2.2	Metabolic Assessments: Shift Table of Fasting Direct LDL (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.3.1	Metabolic Assessments: Summary of Fasting HDL (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.3.2	Metabolic Assessments: Shift Table of Fasting HDL (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.4.1	Metabolic Assessments: Summary of Fasting Triglycerides (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Table 34.4.2	Metabolic Assessments: Shift Table of Fasting Triglycerides (mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 34.5	Metabolic Assessments: Summary of Fasting Total Cholesterol to HDL Ratio by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table 35	Summary of Statistical Testing for Key Safety Endpoints Using Fallback Procedure, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table Req6742.3.1	Number and Percentage of Subjects Taking Lipid Modifying Medications at Study Entry, Studies GS-US-292-0104 and GS-US-292-0111,Safety Analysis Set
Table Req6742.3.2	Number and Percentage of Subjects Initiating Lipid Modifying Medications During the Study, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table Req6744.2	Treatment-Emergent Adverse Events: Overall Summary (Age >= 65 Years), Studies GS-US-292-0102, GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set
Table Req6756.11	Treatment-Emergent Adverse Events: Overall Summary, Study GS-US-292-0112, Safety Analysis Set, Subjects with Age >= 65 Years Only
Table Req6756.16	Shift Table of Postbaseline Proteinuria Toxicity Grade by Baseline Proteinuria Toxicity Grade, Safety Analysis Set (Cohort 1 Subjects Only), By TDF Use at Baseline (With vs. Without)
Table Req6758.2.2	Treatment-Emergent Adverse Events: Overall Summary, Study GS-US-292-0109, Subjects with Age >= 65 Years Only, Safety Analysis Set
Table Req6799.1.1	Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Age: 18 - 25 Years, Observed Data), Studies GS-US-292-0102, GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set
Table Req6799.1.2	Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Age: 18 - 25 Years, Observed Data), Studies GS-US-292-0102, GS-US-292-0104 and GS-US-292-0111, Spine DXA Analysis Set
Table Req6863.5	Duration of Exposure to E/C/F/TAF, Subjects Received E/C/F/TAF

Table Req6909.4 Non-parametric Comparisons for Change from Baseline in Serum Creatinine (mg/dL), Safety Analysis Set (Cohort 1 Subjects Only), By TDF Use at Baseline (With vs. Without)

Table Req6909.6 Non-parametric Comparisons for Percentage Change from Baseline in Urine RBP to Creatinine Ratio, Safety Analysis Set (Cohort 1 Subjects Only), By TDF Use at Baseline (With vs. Without)

Table Req6909.7 Non-parametric Comparisons for Percentage Change from Baseline in Urine Beta-2-microglobulin to Creatinine Ratio, Safety Analysis Set (Cohort 1 Subjects Only), By TDF Use at Baseline (With vs. Without)

Table Req6909.8 Non-parametric Comparisons for Percentage Change from Baseline in Urine Protein to Creatinine Ratio, Safety Analysis Set (Cohort 1 Subjects Only), By TDF Use at Baseline (With vs. Without)

Table Req6909.9 Non-parametric Comparisons for Percentage Change from Baseline in Urine Albumin to Creatinine Ratio, Safety Analysis Set (Cohort 1 Subjects Only), By TDF Use at Baseline (With vs. Without)

Figure 1 Subject Disposition, Studies GS-US-292-0104 and GS-US-292-0111, All Randomized Subjects

Figure 2 Time to Premature Discontinuation of Study Drug (Kaplan-Meier Estimate), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 3.1.1 Median (Q1, Q3) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set

Figure 3.1.2 Median (Q1, Q3) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Spine DXA Analysis Set

Figure 3.2.1 Mean and 95% CIs of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Hip DXA Analysis Set

Figure 3.2.2 Mean and 95% CIs of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Spine DXA Analysis Set

Figure 4.1 Median (Q1, Q3) of Percentage Change from Baseline in Serum C-type Collagen Sequence (CTx) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 4.2 Median (Q1, Q3) of Percentage Change from Baseline in Serum Bone Procollagen Type 1 N-terminal Propeptide (P1NP) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 4.3 Median (Q1, Q3) of Percentage Change from Baseline in Serum Parathyroid Hormone (PTH) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 5.1 Median (Q1, Q3) of Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 5.2 Mean and 95% CIs of Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data), Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 6.1 Median (Q1, Q3) of Change from Baseline in Estimated GFR by Cockcroft-Gault (mL/min) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 6.2 Median (Q1, Q3) of Change from Baseline in Estimated GFR by CKD-EPI Creatinine (mL/min/1.73m^2) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 7.1 Median (Q1, Q3) of Percentage Change from Baseline in Urine RBP to Creatinine Ratio by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 7.2 Median (Q1, Q3) of Percentage Change from Baseline in Urine Beta-2-Microglobulin to Creatinine Ratio by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 8.1 Median (Q1, Q3) of Percentage Change from Baseline in Urine Protein to Creatinine Ratio (UPCR) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 8.2 Median (Q1, Q3) of Percentage Change from Baseline in Urine Albumin to Creatinine Ratio (UACR) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 9.1 Median (Q1, Q3) of Change from Baseline in TmP/GFR Ratio (Using Unadjusted SCr, mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 9.2 Median (Q1, Q3) of Change from Baseline in TmP/GFR Ratio (Using Adjusted SCr, mg/dL) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 10.1 Median (Q1, Q3) of Change from Baseline in Urine Fractional Excretion of Phosphate (FEPO4 Using Unadjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 10.2 Median (Q1, Q3) of Change from Baseline in Urine Fractional Excretion of Phosphate (FEPO4 Using Adjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 11.1 Median (Q1, Q3) of Change from Baseline in Urine Fractional Excretion of Uric Acid (FEUA Using Unadjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Figure 11.2 Median (Q1, Q3) of Change from Baseline in Urine Fractional Excretion of Uric Acid (FEUA Using Adjusted SCr, %) by Visit, Studies GS-US-292-0104 and GS-US-292-0111, Safety Analysis Set

Listing 1 Serious Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Randomized Analysis Set

Listing 2 Study-Drug-Related Serious Adverse Events, Studies GS-US-292-0104 and GS-US-292-0111, Randomized Analysis Set

Listing 3 Adverse Events Leading to Premature Study Drug Discontinuation, Studies GS-US-292-0104 and GS-US-292-0111, Randomized Analysis Set

Listing 4 Death Report, Studies GS-US-292-0104 and GS-US-292-0111, Randomized Analysis Set

Listing 5 Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR), Studies GS-US-292-0104 and GS-US-292-0111, Randomized Analysis Set

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SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.5—LITERATURE REFERENCES

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (E/C/F/TAF FDC)

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (E/C/F/TAF FDC)

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES....1
TABLE OF CONTENTS....2
1. TABULAR LISTING OF CLINICAL STUDIES....3

1. TABULAR LISTING OF CLINICAL STUDIES

1.1. 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 treatment: 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; 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
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 treatment: Cohort 1: • Formulation 1 E/C/F/TAF (150/150/200/25 mg) QD PO (A) • 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)	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; m5.3.3.1, 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	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) Multiple-dose phase: 18 (10 Japanese; 8 Caucasian)	Healthy adult Japanese (first generation Japanese descent) or Caucasian (not of Japanese or Asian descent) subjects	Study completed; m5.3.3.1, Final CSR
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; 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
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; m5.3.3.4, 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 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	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: 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)	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
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; m5.3.5.1, 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, 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; m5.3.5.1, 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, 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; m5.3.5.1, 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; m5.3.5.1, 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
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; m5.3.5.2, 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
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; m5.3.5.2, Week 24 Interim CSR

1.2. 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
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 coadministration of TAF+COBI relative to the administration of TAF alone	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) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 11-22, fed) (F) Cohort 4: • TAF 8 mg QD PO (Days 1-12, fed) (G) • TAF 8 mg + COBI 150 mg QD PO (Days 13-22, fed) (H)	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; m5.3.3.4, Final CSR

1.3. 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; m5.3.3.1, 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; m5.3.3.3, 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 (CPT Class B) and	Study completed; m5.3.3.3, 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	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 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
Healthy Subject PD 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 treatment: • 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; m5.3.4.1, 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; m5.3.4.2, 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
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 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: <u>Cohort 1:</u> • TAF 50 mg (2 × 25 mg) + placebo-to-match TDF QD PO (A) • Placebo-to-match TAF + TDF 300 mg QD PO (B) <u>Cohort 2:</u> • 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; m5.3.4.2, Final CSR

1.4. EVG

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-183-0102 (synopsis)	Determine effect of RTV on steady-state PK of EVG	Phase 1, open-label, fixed-sequence, single-center, multiple-dose, crossover study	• EVG 100 mg BID PO (A) • EVG 100 mg + RTV 100 mg BID PO (B)	20 days (10 days per treatment)	Enrolled: 12 Completed: 12 Safety Analysis Set: A: 12 B: 12	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-183-0113 (synopsis)	Examine effect of a range of RTV doses on the PK of EVG and on hepatic CYP3A activity using a CYP3A substrate (MDZ)	Phase 1, randomized, open-label, single-center, multiple-dose, 2-group study	Group 1: • EVG 125 mg + RTV 20 mg QD PO (Days 2−11) (A) • EVG 125 mg + RTV 100 mg QD PO (Days 12−21) (C) Group 2: • EVG 125 mg + RTV 50 mg QD PO (Days 2−11) (B) • EVG 125 mg + RTV 200 mg QD PO (Days 12−21) (D) MDZ 1 mg IV (Days 11 and 21)	21 days A: 10 days B: 10 days C: 10 days D: 10 days	Randomized: 24 Completed: 21 Safety Analysis Set: A: 12 B: 12 C: 11 D: 11 MDZ: 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	GS-US-183-0126 (synopsis)	Determine the mass balance of EVG following administration of a single oral dose of RTV-boosted [^{14}C]EVG	Phase 1, open-label, single-center, single-dose, mass-balance study	• EVG 50 mg (mixture of unlabeled EVG and [^{14}C]EVG) + RTV 100 mg PO	Single dose	Enrolled: 8 Completed: 8	Healthy adult male subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-183-0140 (synopsis)	Evaluate the relative BA of the Phase 3 formulation of EVG boosted with RTV	Phase 1, randomized, open-label, single-center, multiple-dose, 2-sequence, 2-way crossover study	• EVG 125 mg + RTV 100 mg QD PO (Reference) (A) • EVG 150 mg + RTV 100 mg QD PO (Phase 3 Formulation 2, Test) (B)	20 days (10 days per treatment)	Randomized: 26 Completed: 24 Safety Analysis Set: A: 25 B: 26	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-183-0103 (synopsis)	Evaluate if PK parameters of EVG, FTC, or TFV are affected after coadministration of EVG+RTV and FTC/TDF compared with their administration alone Investigate effect of antacids on EVG+RTV PK	Phase 1, randomized, open-label, single-center, multiple-dose study	• FTC/TDF (200/300 mg) QD PO (A) • FTC/TDF (200/300 mg) + EVG 50 mg + RTV 100 mg QD PO (B) • EVG 50 mg + RTV 100 mg QD PO (C) • EVG 50 mg + RTV 100 mg + 20 mL magnesium/ aluminum-containing antacid suspension QD PO (D)	28 days A: 7 days B: 10 days C: 10 days D: 1 day	Randomized: 26 Completed: 24 Safety Analysis Set: A: 26 B: 24 C: 26 D: 13	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-183-0119 (synopsis)	Evaluate if PK parameters of EVG are affected after staggered administration of EVG+RTV and antacid or after coadministration of EVG+RTV and omeprazole compared to administration of EVG+RTV alone	Phase 1, randomized, open-label, single-center, multiple-dose study	• EVG 50 mg + RTV 100 mg QD PO (Days 1−10) (A) • EVG 50 mg + RTV 100 mg PO 4 h after 20 mL Maalox Max (Day 11) (B) • EVG 50 mg + RTV 100 mg PO 4 h before 20 mL Maalox Max (Day 11) (C) • EVG 50 mg + RTV 100 mg PO 2 h after 20 mL Maalox Max (Day 11) (D) • EVG 50 mg + RTV 100 mg 2 h before 20 mL Maalox Max (Day 11) (E) • EVG 50 mg + RTV 100 mg QD PO 2 h after omeprazole 40 mg QD (Days 11−15) (F)	15 days A: 10 days B: 1 day C: 1 day D: 1 day E: 1 day F: 5 days	Randomized: 60 Completed: 49 Safety Analysis Set: A: 60 B: 9 C: 10 D: 11 E: 10 F: 10	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-183-0146 (synopsis)	Examine effect of KTZ on PK of EVG+RTV and determine additional effect of KTZ on CYP3A enzyme activity using MDZ as CYP3A probe	Phase 1, non-randomized, open-label, single-center, multiple-dose study	• EVG 150 mg + RTV 100 mg QD PO (Days 2−11) (A) • EVG 150 mg + RTV 100 mg QD + KTZ 200 mg BID, PO (Days 12−15) (B) MDZ 5-mg syrup PO on	15 days	Enrolled: 18 Completed: 18 Safety Analysis Set: A: 18 B: 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
		substrate when administered with EVG+RTV		Days 1, 11, and 15				
Healthy Subject PD and PK/PD	GS-US-183-0128 (synopsis)	Evaluate effect of steady-state EVG+RTV exposures at therapeutic and supratherapeutic doses on the QTcF interval compared to placebo	Phase 1, single-center, 2-part study Part 1: Randomized, partially double-blind, parallel-group comparison of placebo vs moxifloxacin (positive control) Part 2: Randomized, double-blind, placebo-controlled, parallel-group comparison of 2 EVG+RTV doses vs placebo	Part 1: • Moxifloxacin 400 mg PO (single dose on Day 1) (A) • Moxifloxacin placebo PO (single dose on Day 1) (B) Part 2: • EVG 125 mg + RTV 100 mg QD PO (Days 6−15) (C) • EVG 250 mg + RTV 100 mg QD PO (Days 6−15) D) • EVG+RTV placebos QD PO (Days 6−15) (E)	15 days	Part 1: Randomized: 126 Completed: 126 Part 2: Continued from Part 1: 124 Completed: 122 Safety Analysis Set: A: 42 B: 42 C: 41 D: 42 E: 41	Healthy adult subjects	Study completed; Final CSR
Patient PD and PK/PD	GS-US-183-0101 (synopsis)	Investigate safety, tolerability, antiviral activity, and PK/PD of EVG	Phase 1/2, randomized, double-blind, multicenter, multiple-dose, placebo-controlled,	• EVG 200 mg BID PO (A) • EVG 400 mg BID PO (B) • EVG 800 mg QD PO (C)	10 days per cohort	Randomized: 48 Treated: 40 Completed: 40 Safety Analysis Set: A: 6	HIV infected, ART-naive or ART-experienced adult subjects who were not currently receiving ARV	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
			proof-of-concept, sequential-cohort, dose-ranging study	• EVG 800 mg BID PO (D) • EVG 50 mg + RTV 100 mg QD PO (E) • Placebo, BID or QD PO (F) • Placebo + RTV 100 mg QD PO (G)		B: 6 C: 6 D: 6 E: 6 F: 8 G: 2	therapy	
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-183-0145 (synopsis)	Assess the noninferiority of EVG vs RAL, each administered with a BR containing a fully active PI+RTV and a second agent in HIV infected, ART-experienced adults Additionally, the efficacy, safety, and tolerability of the 2 treatment regimens, EVG and RAL, are being evaluated	Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled study	• EVG 150 mg QD PO (EVG 85 mg QD for subjects taking ATV+RTV or LPV/r as part of their BR) + RAL placebo BID PO + BR (A) • RAL 400 mg BID PO + EVG placebo QD PO + BR (B)	Blinded Phase: 144 weeks until unblinding Open-Label Extension Phase: 144 weeks, 144 weeks + 30 days or until EVG development is terminated (UK), or until commercially available	Randomized: 724 A: 361 B: 363 Received study drug: 712 A: 354 B: 358 Continuing study drug at Week 96: A: 208 B: 208 Continuing in study at Week 96: A: 216 B: 223	HIV infected, ART-experienced adult subjects	Study ongoing; Week 96 Interim CSR and Amendment 1

1.5. COBI

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-216-0101 (synopsis)	Evaluate the safety and tolerability of escalating single and multiple oral doses of COBI Characterize the single-dose PK and steady-state PK and PD (anti-CYP3A activity) of COBI	Phase 1, randomized, double-blind, single-center, placebo- and active-controlled, single and multiple dose-ranging study	4:1:1 randomization for each cohort • Part A, Cohort 1, Periods 1 and 2: COBI 50 mg, RTV 100 mg, or matching placebo(s) PO • Part A, Cohort 2, Periods 1 and 2: COBI 100 mg, RTV 100 mg, or matching placebo(s) PO • Part B, Cohort 3: COBI 200 mg, RTV 100 mg, or matching placebo(s) PO	Part A, Period 1: 1 day Part A, Period 2: 14 days Part B: 14 days	Randomized: 60 Completed: 48 Safety Analysis Set: • COBI 50 mg: 12 • COBI 100 mg: 15 • COBI 200 mg: 15 • RTV 100 mg: 9 • Placebo: 9	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-216-0111 (synopsis)	Determine the mass-balance of COBI at steady-state using a tracer dose of [^{14}C]COBI	Phase 1, open-label, single-center, multiple-dose, mass-balance study	• COBI 150 mg QD PO (Days 1−6) • COBI 150 mg (capsule containing nonradiolabeled COBI + [^{14}C]COBI) PO (Day 7)	7 days	Enrolled: 8 Completed: 8	Healthy adult male subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	GS-US-216-0113 (synopsis)	Evaluate the PK of COBI following oral administration at single and multiple doses	Phase 1, open-label, single-center, single- and multiple-dose, staggered dose-	<u>Cohort 1:</u> • COBI 300 mg QD PO <u>Cohort 2:</u> • COBI 400 mg QD PO	Cohort 1: 7 days Cohort 2: Single dose	Enrolled: 24 Completed: 24 Safety Analysis Set: Cohort 1: 12	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
			escalation cohort study			Cohort 2: 12		
Intrinsic Factor PK	GS-US-216-0121 (synopsis)	Cohort 1: Evaluate renal function and renal creatinine handling before, during, and following completion of administration of COBI or RTV in healthy subjects. Cohort 2: Evaluate renal function and renal creatinine handling in stable mild/moderate renal impairment before, during, and following completion of administration of COBI, and assess the PK and safety of COBI in stable mild/moderate renal impairment	Phase 1, 2-cohort study. Cohort 1 was a randomized, double-blind, placebo (negative)-controlled, single-center, multiple-dose, parallel-group cohort. Cohort 2 was a single-treatment, open-label, multicenter, multiple-dose cohort.	All treatments were administered PO each morning following consumption of a standardized meal. Cohort 1 • COBI 150 mg + RTV 100 mg placebo OR RTV 100 mg + COBI 150 mg placebo OR COBI 150 mg placebo + RTV 100 mg placebo (Days 1-7) • Probe drug (IV iohexol) (Days 0, 7, and 14) Cohort 2 • COBI 150 mg (Days 1-7) • Probe drug (IV iohexol) (Days 0, 7, and 14)	Cohort 1: 7 days Cohort 2: 7 days	Enrolled: 54 Cohort 1: 36 Cohort 2: 18 Completed: 54 Cohort 1: 36 Cohort 2: 18 Note: One subject in Cohort 2 completed COBI treatment but did not receive the Day 14 iohexol dose due to an AE of maculo-papular rash	Cohort 1: Healthy adult subjects with normal renal function ($eGFR_{CG}$ ≥ 80 mL/min) Cohort 2: Adult subjects with stable mild/ moderate renal 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
Extrinsic Factor PK	GS-US-216-0134 (synopsis)	Evaluate the PK of COBI and TFV following multiple-dose administration of COBI and TDF alone or in combination	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatment: Cohort 1: • COBI 150 mg QD PO (A) • COBI 150 mg + TDF 300 mg QD PO (B) Cohort 2: • COBI 150 mg + TDF 300 mg QD PO (B) • TDF 300 mg QD PO (C)	19 days (7 days of each treatment with a 5-day washout period in between)	Enrolled: 46 Completed: 45 Safety Analysis Set: 46 A: 32 B: 45 C: 14	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PD and PK/PD	GS-US-216-0107 (synopsis)	Evaluate the effects of COBI on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, randomized, partially blinded, single-center, single-dose, placebo- and positive (moxifloxacin)-controlled, 8-sequence, 4-period crossover, thorough QT/QTc study	• COBI 250 mg PO (A) • COBI 400 mg PO (B) • Placebo PO (C) • Moxifloxacin 400 mg PO (D)	22 days (single dose on Days 1, 8, 15, and 22)	Randomized: 48 Completed: 48 Safety Analysis Set: A: 48 B: 48 C: 48 D: 48	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 PD and PK/PD	GS-US-216-0112 (synopsis)	Evaluate the effects of COBI on CYP enzymes 2B6 and 2D6, and on the drug efflux transporter Pgp using validated phenotyping probes	Phase 1, open-label, single-center, multiple-cohort, crossover study	Cohort 1 (CYP2D6) • Desipramine 50 mg PO, single dose (A) • COBI 150 mg QD PO for 10 days, + desipramine 50 mg PO, single dose on 10th day (B) Cohort 2 (Pgp) • Digoxin 0.5 mg PO, single dose (C) • COBI 150 mg QD PO for 10 days, + digoxin 0.5 mg PO, single dose on 10th day (D) Cohort 3 (CYP2B6) • EFV 600 mg PO, single dose (E) • COBI 150 mg QD PO for 10 days, + EFV 600 mg PO, single dose on 10th day (F)	Cohorts 1 and 2: 25 days (including washout) Cohort 3: 31 days (including washout)	Enrolled: 53 Completed: 48 Safety Analysis Set: A: 10 B: 9 C: 24 D: 22 E: 18 F: 17	Healthy adult subjects: Cohort 1 was limited to individuals who were intermediate, extensive, or ultra-rapid CYP2D metabolizers; Cohort 3 was limited to individuals who were intermediate or extensive CYP2B6 metabolizers	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 PD and PK/PD	GS-US-216-0116 (synopsis)	Evaluate multiple-dose PK of a new formulation of COBI, administered alone; evaluate multiple-dose PK of EVG as a stand-alone tablet administered with a new formulation of COBI tablet	Phase 1, 2-cohort, randomized, open-label, multiple-dose, crossover study	Cohort 1: • COBI 150 mg Formulation 2 (new formulation) QD PO (A) • COBI 150 mg Formulation 1 (original formulation) QD PO (B) Single PO dose of MDZ 5 mg on Days 10 and 20 (metabolic probe) Cohort 2: • EVG 150 mg + COBI 150 mg Formulation 2 (new formulation) QD PO (C) • EVG 150 mg + RTV 100 mg QD PO (D)	20 days (10 days for each treatment within a cohort)	Randomized: 62 Cohort 1: 38 Cohort 2: 24 Completed: 57 Cohort 1: 35 Cohort 2: 22 Safety Analysis Set: A: 36 B: 38 C: 24 D: 24	Healthy adult subjects	Study completed; Final CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-216-0114 (synopsis)	Evaluate the efficacy and safety of a regimen containing ATV+COBI+ TVD vs ATV+RTV+ TVD in HIV infected ART-naive adult subjects	Phase 3, double-blind, multicenter, randomized, active-controlled study	Study drug administered once daily, orally, with food: • COBI 150 mg + ATV 300 mg + TVD (single tablet FTC/TDF, 200/300 mg) + RTV placebo (A) • RTV 100 mg + ATV 300 mg + TVD (single tablet FTC/TDF, 200/300 mg) + COBI placebo (B)	192 weeks	Randomized: 698 A: 349 B: 349 Treated: 692 A: 344 B: 348 Week 144 Per-Protocol Analysis Set: A: 250 B: 257	HIV infected, ART-naive adults with plasma HIV-1 RNA levels ≥ 5000 copies/mL at screening	Study ongoing; m5.3.5.1, Interim Week 144 CSR

1.6. EVG+COBI

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	GS-US-183-0133 (synopsis)	Evaluate any differences in the PK and safety of EVG+COBI by evaluating subjects with moderate impairment of hepatic function (CPT Classification B) compared to matched subjects with normal hepatic function	Phase 1, open-label, parallel-group, multiple-dose study	• EVG 150 mg + COBI 150 mg QD PO, immediately following consumption of a standard meal	10 days followed by an 11-day follow-up period	Enrolled: 20 Completed: 20 (10 subjects with moderate hepatic impairment, and 10 matched control subjects)	Adult subjects with moderate hepatic impairment (CPT Classification B) and healthy matched control subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-183-1004 (synopsis)	Evaluate the PK of EVG and its metabolite GS-9200 following the administration of EVG+COBI in subjects with decreased UGT1A1 activity (UGT1A1*28 genotype) and wild-type (UGT1A1*1) matched control subjects	Phase 1, nonrandomized, open-label, parallel, multiple-dose study	• EVG 150 mg + COBI 150 mg QD PO in the AM with a standard moderate-fat meal	10 days	Enrolled: 36 Completed: 36 Safety Analysis Set: Subjects with decreased UGT1A1 activity: 18 Wild-type matched controls: 18	Healthy adult subjects with decreased UGT1A1 activity (UGT1A1*28) or wild-type matched controls (UGT1A1*1)	Study completed; m5.3.3.3, 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	GS-US-216-0124 (synopsis)	Evaluate the PK, safety, and renal function prior to, during, and after dosing with EVG+COBI in subjects with severe renal impairment	Phase 1, open-label, parallel-group, multiple-dose study	• EVG 150 mg + COBI 150 mg QD PO, immediately following consumption of standard meal	7 days followed by a 7-day follow-up period	Enrolled: 24 (13 renally impaired and 11 matched controls) Completed: 23 (12 renally impaired and 11 matched controls)	Adult subjects with severe renal impairment and matched control subjects with normal renal function	Study completed; Final CSR
Extrinsic Factor PK	GS-US-216-0120 (synopsis)	Evaluate the relative BA and PK of EVG+COBI after coadministration with a representative H_2-receptor antagonist or a representative proton pump inhibitor	Phase 1, randomized, open-label, single-center, multiple-dose, 3-sequence, 4-treatment, 2-period crossover study	• EVG 150 mg + COBI 150 mg QD PO in the AM with food (A) • EVG 150 mg + COBI 150 mg QD PO in the AM with food + famotidine 40 mg QD PO in the PM with food 12 h after EVG+COBI (B) • EVG 150 mg + COBI 150 mg QD PO in the AM with food + omeprazole 20 mg QD PO in the AM in a fasted state 2 h before EVG+COBI (C) • EVG 150 mg + COBI 150 mg QD PO in the AM with food + omeprazole 20 mg QD PO in the PM in a fasted state 12 h after EVG+COBI (D)	16 days (8 days per treatment)	Randomized: 33 Completed: 32 Safety Analysis Set: A: 33 B: 11 C: 11 D: 11	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-216-0122 (synopsis)	Determine whether simultaneous coadministration of EVG+COBI with a representative H_2-receptor antagonist reduces the relative BA of EVG+COBI	Phase 1, randomized, open-label, single-center, multiple-dose, 2-way crossover study	• EVG 150 mg + COBI 150 mg QD PO in the AM with food (A) • EVG 150 mg + COBI 150 mg + famotidine 40 mg QD PO in the AM with food (B)	16 days (8 days per treatment)	Randomized: 16 Completed: 16 Safety Analysis Set: A: 16 B: 16	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-216-0123 (synopsis)	Evaluate the PK and safety of EVG+COBI coadministered once daily with ATV, rosuvastatin, or RFB vs once-daily administration of EVG+COBI, ATV+RTV, single dose of rosuvastatin alone, or once-daily administration of RFB alone	Phase 1, partially randomized, open-label, single-center, single- and multiple-dose, multiple-cohort, crossover study	Cohort 1: • Rosuvastatin 10 mg, single dose PO on Day 1 (A) • EVG 85 mg + COBI 150 mg + ATV 300 mg QD PO (Days 4−13) (B) • EVG 150 mg + COBI 150 mg QD PO (Days 15−24) (C) • EVG 150 mg + COBI 150 mg + rosuvastatin 10 mg single dose PO on Day 25 (D) Cohort 2: • EVG 85 mg + COBI 150 mg + ATV 300 mg QD PO (Days 4−13) (B) • ATV 300 mg + RTV	Cohort 1: 22 days Cohort 2: 20 days Cohort 3: 36 days	Enrolled: 34 Cohort 1: 12 Cohort 2: 10 Cohort 3: 12 Completed: 29 Cohort 1: 10 Cohort 2: 7 Cohort 3: 12	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
				100 mg QD PO (Days 15−24) (E) Cohort 3: • EVG 150 mg + COBI 150 mg QD PO (Days 1−10) (C) • EVG 150 mg + COBI 150 mg QD PO, + RFB 150 mg, QOD PO (Days 11−23) (F) • RFB 300 mg QD PO (Days 35−46) (G)				
Extrinsic Factor PK	GS-US-216-0125 (synopsis)	Evaluate the drug interaction potential between EVG+COBI and methadone or BUP/NLX	Phase 1, open-label, crossover, 2-cohort, 2-center, multiple-dose study	Cohort 1: • Methadone (80 to 120 mg) once daily (Reference) (A) • Methadone (80 to 120 mg) + EVG 150 mg + COBI 150 mg once daily (Test) (B) Cohort 2: • BUP/NLX (16 mg/4 mg to 24 mg/6 mg) once daily (Reference) (C) • BUP/NLX (16/4 mg to 24/6 mg) + EVG 150 mg + COBI 150 mg once daily (Test) (D)	11 days (1 day for reference)	Enrolled: 30 Completed: 28 Analyzed (PK, PD, Safety): Cohort 1: 11 Cohort 2: 17	Healthy adult subjects on stable doses of methadone or BUP/NLX (at least 2 weeks prior to screening)	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-216-0137 (synopsis)	Evaluate the PK of CBZ, CBZE, EVG, and COBI following the coadministration of EVG+COBI+CBZ relative to the administration of CBZ alone or EVG+COBI alone	Phase 1, open-label, fixed-sequence, single-cohort, multiple-dose, DDI study	• EVG 150 mg + COBI 150 mg QD PO in the AM with a standard meal (Days 1-10) (A) • CBZ 100 mg BID PO (in the AM and PM) with a standard meal for 3 days, then CBZ 200 mg BID PO (in the AM and PM) with a standard meal for 18 days (Days 11-31) (B) • EVG 150 mg + COBI 150 mg QD PO (in the AM) + CBZ 200 mg BID (in the AM and PM) with a standard meal (Days 32-41) (C)	41 days	Enrolled: 14 Completed: 12 Safety Analysis Set: 14	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
Extrinsic Factor PK	GS-US-344-0102 (synopsis)	Evaluate the PK of LDV on coadministration with ATR, DRV+RTV, RPV, and RAL relative to administration of LDV alone; evaluate the PK of ATR, DRV, RTV, RPV, and RAL on coadministration with LDV relative to the administration of ATR, DRV, RTV, RPV, or RAL alone; Evaluate the PK of SOF, metabolites GS-566500 and GS-331007, LDV, EVG, and COBI on coadministration of LDV/SOF with EVG+COBI relative to LDV/SOF or EVG+COBI alone; evaluate the PK of SOF, GS-566500, GS-331007, LDV, ATV, and RTV on coadministration	Phase 1, open-label, multiple-dose, multicohort, single- center study	Cohort 1: • LDV 90 mg QD or ATR (600/200/300 mg) QD on Days 1–14 followed by LDV 90 mg QD + ATR (600/200/300 mg) QD on Days 16–29 For Cohorts 2 through 6, subjects are randomized to 1 of 6 sequences and received each of the 3 treatments in that cohort for 10 days. Cohort 2: • LDV 90 mg QD (A) • DRV 800 mg QD + RTV 100 mg QD (D) • LDV 90 mg QD + DRV 800 mg QD + RTV 100 mg QD (E) Cohort 3: • LDV 90 mg QD (A) • RPV 25 mg QD (F) • LDV 90 mg QD + RPV 25 mg QD (G) Cohort 4: • LDV 90 mg QD (A) • RAL 400 mg BID (H) • LDV 90 mg QD + RAL 400 mg BID (I)	Cohort 1: 28 days Cohorts 2 through 6: 30 days	Overall: 168 treated 159 completed Cohort 1: 30 treated 26 completed Cohort 2: 24 treated 23 completed Cohort 3: 24 treated 23 completed Cohort 4: 30 treated 28 completed Cohort 5: 30 treated 29 completed Cohort 6: 30 treated 30 completed	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
		of LDV/SOF with ATV+RTV relative to LDV/SOF or ATV+RTV alone; evaluate the safety and tolerability of coadministration of LDV and ATR, DRV+RTV, RPV, or RAL; and evaluate the safety and tolerability of coadministration of LDV/SOF and EVG+COBI or ATV+RTV		Cohort 5: • LDV/SOF FDC (90/400 mg) QD (J) • EVG 150 mg QD + COBI 150 mg QD (K) • LDV/SOF FDC (90/400 mg) QD + EVG 150 mg QD + COBI 150 mg QD (L) Cohort 6: • LDV/SOF FDC (90/400 mg) QD (J) • ATV 300 mg QD + RTV 100 mg QD (M) • LDV/SOF FDC (90/400 mg) QD + ATV 300 mg QD + RTV 100 mg QD (N)				

1.7. 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

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	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
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 and PK food effect on PK for 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

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 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 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

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	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 h before the start of a 3-h hemodialysis	1−2 single doses	Enrolled: 29 Completed: 29	Adult subjects with varying degrees of renal insuff-iciency 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-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
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 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) 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

1.8. STB

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-236-0110 (synopsis)	Evaluate the relative BA of 2 formulations of STB STR	Phase 1, randomized, open-label, single-center, multiple-dose, 6-sequence, 3-treatment, 3-period crossover study	• New STB STR Formulation 2 (150/150/200/300 mg) QD PO (A) • STB STR original tablet Formulation 1 (150/150/200/300 mg) QD PO (B) • FTC 200 mg + TDF 300 mg, QD PO (C)	30 days (10 days per treatment)	Randomized: 42 Completed: 36 Safety Analysis Set: A: 39 B: 40 C: 39	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-236-0105 (synopsis)	Evaluate the effect of food (a high-calorie/high-fat meal or a light meal) on the PK of EVG, FTC, TFV, and COBI when administered as a STB STR	Phase 1, randomized, open-label, single-center, single-dose, 6-sequence, 3-treatment, 3-period crossover study	STB STR (150/150/200/300 mg), single dose PO administered under the following meal conditions: • Fasted (A) • Light meal (B) • High-calorie/ high-fat meal (C)	Single dose under each meal condition	Randomized: 24 Completed: 24 Safety Analysis Set: A: 24 B: 24 C: 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
Extrinsic Factor PK	GS-US-236-0106 (synopsis)	Determine effect of the STB STR on the PK of a representative hormonal contraceptive medication, Ortho Tri-Cyclen® Lo (NGM/EE)	Phase 1, fixed-sequence, open-label, single-center, multiple-dose study	Part A (Lead-In) (1 menstrual cycle): • NGM/EE QD PO for 28 days (21 days active + 7 days inert) Part B (2 menstrual cycles): • NGM/EE QD PO for 39 days (21 days active, 7 days inert, 11 days active) • STB STR (150/150/200/300 mg) + NGM/EE (active) QD PO for 10 days • NGM/EE (inert) QD PO for 7 days	56 days (up to 84 days if Part A was required)	Enrolled: 21 Completed: 15 Safety Analysis Set: Part A: 19 Part B: 18 NGM/EE: 18 STB STR: 16	Healthy adult women of childbearing potential	Study completed; Final CSR
Extrinsic Factor PK	GS-US-236-0120 (synopsis)	Evaluate the PK of COBI-boosted EVG administered as STB STR before and after treatment with the ATR STR	Phase 1, open-label, single-center, multiple-dose study	• Period 1: STB STR (150/150/200/300 mg) QD PO (Days 1-7) • Period 2: ATR STR (600/200/300 mg) QD PO (Days 15-28) • Period 3: STB STR (150/150/200/300 mg) QD PO (Days 29-62)	62 days	Enrolled: 32 Completed: 29 Safety Analysis Set: Period 1: 32 Period 2: 31 Period 3: 30	Healthy adults subjects; approximately 25% of subjects had decreased metabolic activity affecting EFV clearance (CYP2B6 genotype)	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-236-0135 (synopsis)	Part 1: Evaluate the PK of TVR and EVG following the coadministration of TVR and STB STR relative to the administration of TVR or STB STR alone Part 2: Cohort 1: Evaluate the PK of TVR and ATV following the coadministration of TVR and ATV+RTV plus EVG 85 mg relative to the administration of TVR or ATV+RTV alone Cohort 2: Evaluate the PK of EVG following the coadministration of TVR and ATV+RTV plus EVG 85 mg relative to the administration of ATV+RTV plus	Phase 1, randomized, open-label, multiple-dose, 2-part, multiple-cohort study	Part 1: • TVR+STB STR (Test) • STB STR(Reference) • TVR (Reference) Part 2: Cohort 1: • TVR+ATV+RTV + EVG 85 mg (Test) • TVR (Reference) • ATV+RTV (Reference) Cohort 2: • TVR+ATV+RTV + EVG 85 mg (Test) • EVG 150 mg + RTV (Reference) • ATV+RTV + EVG 85 mg (Reference)	10 days	Enrolled: 54 Completed: 48 Analyzed (Safety/PK): Part 1: 16/16 Part 2, Cohort 1, Sequence 1: 13/12 Part 2, Cohort 2, Sequence 2: 13/11 Part 2 Cohort 2: 12/12	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
		EVG 85 mg or EVG 150 mg + RTV alone						

3TC = lamivudine; ABC = abacavir; AM = before noon; APV = amprenavir; ART = antiretroviral therapy; ARV = antiretroviral; ATR = efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®); ATV = atazanavir; BID = twice daily; BA = bioavailability; BE = bioequivalence; BR = background regimen; BUP = buprenorphine; ^{14}C = radiolabeled carbon 14; CBZ = carbamazepine; CBZE = carbamazepine-10,11-epoxide; COBI = cobicistat (Tybost®); CPA = emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Complera®); CPT = Child-Pugh-Turcotte; CSR = clinical study report; CYP = cytochrome P450 enzyme; d4T = stavudine; ddI = didanosine; DDI = drug-drug interaction; DVR = darunavir; DTG = dolutegravir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated); FCV = famciclovir; EFV = efavirenz; $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; ETV = etravirine; EVG = elvitegravir (Vitekta®); FDC = fixed-dose combination; FPV = fosamprenavir; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); FTC = emtricitabine (Emtriva®); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; INSTI = integrase strand-transfer inhibitor; IV = intravenous; KTZ = ketoconazole; LDV = ledipasvir; LPV = lopinavir; LPV/r = lopinavir boosted with ritonavir; MDZ = midazolam; NGM/EE = norgestimate/EE = ethinyl estradiol; NLX = naloxone; NNRTI = nonnucleoside reverse transcriptase inhibitor; NVP = nevirapine; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamics(s); PI = protease inhibitor; PK = pharmacokinetic(s); PO = orally; PM = after noon; QD = once daily; QOD = every other day; 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; QTcF = QT interval corrected for heart rate using the Fridericia formula; RAL = raltegravir; RFB = rifabutin; 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; TDF = tenofovir disoproxil fumarate (Viread®); TFV = tenofovir; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1; UK = United Kingdom; ZDV = zidovudine

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-236-0112 (synopsis)	Part A: Evaluate the steady-state PK and confirm the dose of STB STR Part B: Evaluate the safety and tolerability of STB STR	Phase 2/3, open-label, multicenter, 2-part, single-group study	• STB STR (150/150/200/300 mg) QD PO	48 weeks Extension Phase: Subjects have option to continue study drug until subject turns 18 and STB is commercially available for adults in country of enrollment, STB becomes commercially available for adolescents in country of enrollment, or STB development is terminated in country of enrollment	Enrolled: 33 Part A: 14 Part B: 19 Safety Analysis Set: 33 Continuing study drug at Week 24: Main study: 26 Extension: 2	HIV infected, ART-naive adolescents (12 to < 18 years of age)	Study ongoing; m5.3.5.2, Week 24 Interim CSR