SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.1—SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Gilead Sciences

[redacted] 20[redacted]

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

1′-OH MDZ	midazolam metabolite (1′-hydroxymidazolam)
ATV	atazanavir
BCS	Biopharmaceutics Classification System
BIC	bictegravir (GS-9883)
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Vemlidy®)
CBZ	carbamazepine
CBZE	carbamazepine-10,11-epoxide
COBI	cobicistat
CSR	clinical study report
DRV	darunavir
DTG	dolutegravir
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
EFV	efavirenz
ETV	entecavir
EVG	elvitegravir
FDC	fixed-dose combination
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FTC	emtricitabine
GS-566500	sofosbuvir metabolite
GS-331007	sofosbuvir metabolite
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
LDV	ledipasvir
LPV	lopinavir
LTSS	long-term storage stability
m	Module
MDZ	midazolam
N[t]RTI	nucleos(t)ide reverse transcriptase inhibitor
PK	pharmacokinetic(s)
[redacted]	[redacted]
RPV	rilpivirine
RTV	ritonavir
SOF	sofosbuvir
SPE	solid-phase extraction
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)

TFV	tenofovir
TFV-DP	tenofovir-diphosphate
US, USA	United States, United States of America
VEL	velpatasvir
VOX	voxilaprevir

1. BACKGROUND AND OVERVIEW

HIV-1 infection is a life-threatening and serious disease of major public health interest, with approximately 37 million people infected worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. Standard of care for the treatment of HIV-1 infection uses combination antiretroviral (ARV) therapy (ART) to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either an integrase strand-transfer inhibitor (INSTI), the nonnucleoside reverse transcriptase, rilpivirine, or the boosted protease inhibitor, darunavir {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}.

Bictegravir (BIC; B [previously referred to as GS-9883]) is a potent INSTI that is being evaluated for the treatment of HIV-1 infection {Gallant 2016} and that has demonstrated a terminal half-life suitable for once-daily administration without a boosting agent. In a Phase 2 study of ART-naive HIV-infected subjects, BIC was compared with the guideline-recommended INSTI, dolutegravir (DTG) {Sax 2017}. When coadministered with the guideline-recommended N(t)RTI backbone, emtricitabine (FTC; F) and tenofovir alafenamide (TAF), each INSTI demonstrated high ARV activity, with no virologic failures due to resistance, and both treatments were safe and well tolerated. Gilead Sciences (Gilead) has coformulated BIC with FTC and TAF into a fixed-dose combination (FDC) tablet. The B/F/TAF FDC may provide a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV infection.

This Summary of Biopharmaceutical Studies and Associated Analytical Methods is being submitted in support of the marketing application for bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) fixed-dose combination (FDC) for the treatment of HIV-1 infection.

1.1. Formulation Development

The designated commercial drug product is an immediate-release fixed-dose combination (FDC) tablet containing 50 mg of bictegravir (BIC, B), 200 mg of emtricitabine (FTC, F), and 25 mg of tenofovir alafenamide (TAF) (B/F/TAF tablet). BIC is incorporated into the drug product as BIC sodium, and TAF is incorporated into the drug product as the hemifumarate form (referred to as TAF fumarate).

The B/F/TAF tablet is a [redacted] tablet with [redacted] containing BIC and [redacted] containing FTC and TAF. BIC sodium is [redacted] granulated with [redacted] excipients to produce BIC granules, which are subsequently [redacted] with [redacted] excipients to produce the [redacted]. FTC and TAF fumarate are [redacted] granulated with [redacted] excipients and [redacted] with [redacted] magnesium stearate to produce the [redacted]. The [redacted] and the [redacted] are compressed into [redacted] tablet cores that are then film-coated for appearance.

B/F/TAF tablets are capsule-shaped, film-coated purplish-brown, debossed with “GSI” on one side of the tablet and “9883” on the other side. B/F/TAF tablets are approximately 15 mm in length and 8 mm in width.

BIC single-agent tablet strengths of [redacted] mg, [redacted] mg, and [redacted] mg were initially developed and manufactured to support Phase 1 studies. Based on the results of these studies, a BIC dose of [redacted] mg was chosen for Phase 2 studies.

The BIC single-agent tablet formulation was subsequently modified to incorporate FTC and TAF fumarate. The resulting B/F/TAF [redacted] mg FDC tablets containing [redacted] mg of BIC were compared to BIC [redacted] mg single-agent co-administered with F/TAF [redacted] mg tablets in a relative bioavailability study (GS-US-141-1233). Based on higher than expected BIC exposures when administered as the B/F/TAF [redacted] mg FDC, the dose of BIC was reduced from [redacted] mg to [redacted] mg and a new B/F/TAF [redacted] mg FDC tablet was developed. When B/F/TAF tablets containing [redacted] mg of BIC were then administered in Study GS-US-141-1233, similar [redacted] of BIC, FTC and TAF were observed, as compared with subjects that received co-administered BIC [redacted] mg single-agent and F/TAF [redacted] mg tablets. As such, the B/F/TAF 50/200/25 mg tablets were used to initiate Phase 3 studies.

The B/F/TAF 50/200/25 mg tablet formulation was then modified during Phase 3 studies to [redacted] tablet properties and compression process performance by [redacted] the [redacted] content in the F/TAF [redacted] from [redacted]% to [redacted]% w/w. This formulation was used in all further development, clinical, and stability studies, and is identical to the designated commercial tablet formulation.

Table 1 presents an overview of BIC single-agent tablet development and the B/F/TAF FDC tablet development. Detailed description of B/F/TAF formulation development can be found in Section 3.2.P.2.2.

Table 1. Formulation Summary for Key Studies with BIC Single-Agent Tablets and B/F/TAF FDC Tablets Used in Clinical Studies

Product Description	Formulation/Strength	Study Number	Study Results Location
Single Agent Tablets	BIC [redacted] mg, [redacted] mg, [redacted] mg	GS-US-141-1218 Phase 1 (FIH)	m2.7.2, Section 2.2.2.1
		GS-US-141-1219 Phase 1 (POC)	m2.7.2, Section 2.3.1.1
Single Agent Tablet	BIC [redacted] mg	GS-US-141-1475[a] Phase 2 (Safety and Efficacy)	m2.7.3, Section 2.1.3
Fixed Dose Combination Tablet	B/F/TAF [redacted] mg	GS-US-141-1233 (rBA and food effect)	m2.7.2, Section 2.2.1.1
Fixed Dose Combination Tablet Original formulation	B/F/TAF 50/200/25 mg	GS-US-141-1233 (rBA and food effect) and Phase 3 (Safety and Efficacy)[b]	m2.7.2, Section 2.2.1.1
Fixed Dose Combination Tablet Designated Commercial Formulation	B/F/TAF 50/200/25mg	GS-US-380-1489 Phase 3 (Safety and Efficacy)	m2.7.3, Section 2.1.1
		GS-US-380-1490 Phase 3 (Safety and Efficacy)	m2.7.3, Section 2.1.2
		GS-US-380-1844 Phase 3 (Safety and Efficacy)	m2.7.3, Section 2.2.1
		GS-US-380-1878 Phase 3 (Safety and Efficacy)	m2.7.3, Section 2.2.2

FIH = first in human; POC = proof of concept; rBA = relative bioavailability

a [redacted].

b The original formulation of the FDC tablet was used in the following Phase 3 studies: GS-US-141-1233, GS-US-141-1475, GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878.

1.2. Dissolution Profile

According to the Biopharmaceutics Classification System (BCS), BIC is low solubility, high permeability (BCS class 2) compound. FTC is a high solubility, high permeability (BCS 1) compound. TAF is a high solubility, low permeability (BCS 3) compound.

Dissolution of the designated commercial product was performed using a United States Pharmacopeia (USP)/European Pharmacopeia (Ph. Eur.) Type 2 (Paddle) apparatus operated at 75 rpm. The dissolution medium was 900 mL of 0.05 M sodium citrate buffer pH 5.5 containing 0.25% sodium dodecyl sulfate (SDS) maintained at 37°C. The amount of each active ingredient dissolved was determined by [redacted] liquid chromatography using ultraviolet (UV) detection by external standard analysis.

Dissolution profiles for the drug product Lot [redacted], [redacted], and [redacted] are summarized in Table 2, Table 3, and Table 4, respectively. Lot [redacted] was used in the rBA Study GS-US-141-1233. Provided for comparison is Lot [redacted] and Lot [redacted], which are representative of the designated commercial tablet manufacturing process. B/F/TAF tablet

Lot [redacted] was manufactured at [redacted] ([redacted], Germany) and Lot [redacted] was manufactured at [redacted] ([redacted], Ireland). Both sites are proposed commercial manufacturing sites for B/F/TAF tablets. Dissolution data are comparable between the tablet lots, and at not less than 90% of BIC, FTC and TAF were dissolved by 30 minutes, consistent with the dissolution profile expected for an immediate-release formulation.

Detailed information on the dissolution profiles of B/F/TAF tablets is provided in Section 3.2.P.5.4.

Table 2. In Vitro Dissolution Profile for B/F/TAF Tablet Lot [redacted]

	Mean % Dissolved (N = 12)		
Time (minutes)	**BIC**	**FTC**	**TAF**
5	73	36	32
10	84	76	72
15	91	93	91
20	93	96	96
30	95	98	97
45	96	98	98
60	97	99	98

Source: m3.2.P.5.4, Table 9

Table 3. In Vitro Dissolution Profile for B/F/TAF Tablet Lot [redacted]

	Mean % Dissolved (N = 12)		
Time (minutes)	**BIC**	**FTC**	**TAF**
5	46	21	20
10	82	53	52
15	91	75	75
20	94	86	86
30	96	96	97
45	97	99	99
60	98	100	100

Source: m3.2.P.5.4, Table 19

Table 4. In Vitro Dissolution Profile for B/F/TAF Tablet Lot [redacted]

Time (minutes)	Mean % Dissolved (N = 12)		
	BIC	FTC	TAF
5	59	31	28
10	89	70	67
15	96	86	84
20	98	95	93
30	99	98	96
45	100	99	97
60	100	100	98

Source: m3.2.P.5.4, Table 20

1.3. Bioanalytical Methods

Validation methods for B/F/TAF and the TAF metabolites tenofovir (TFV) and tenofovir diphosphate (TFV-DP) are presented in this section. Descriptions of validated methods for any coadministered drugs are provided in Appendix 5.4. For all analytes, the current versions of validation reports are listed. The method validation reports are cumulative of all previous versions, with the exception of the validation reports for Studies 143-001, FTC-101, FTC-102, FTC-106, FTC-107, FTC-108, and FTC-110. For all studies, validation reports and sample analysis reports cited in the corresponding clinical study reports (CSRs) were those in effect at the time of CSR completion.

A tabular summary of the analytical methods, method validation reports, and sample analysis reports for individual studies is provided in Appendix 5.2. A tabular summary of long-term storage stability (LTSS) data, 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) for individual studies is provided in Appendix 5.3.

All samples were analyzed within the time frame supported by LTSS data. Study samples collected in longer-duration clinical studies were analyzed in batches within the established LTSS time frame.

1.3.1. Determination of Bictegravir in Plasma

The BIC bioanalytical method for the determination of BIC in K_2EDTA human plasma was validated at [redacted] ([redacted], United States of America [USA]). The method involved [redacted] of BIC and its internal standard (GS-697140) from human plasma, followed by liquid chromatography/tandem mass spectrometry (LC-MS/MS) with positive ionization. Bioanalytical method validation parameters are summarized in Table 5.

Table 5. Bioanalytical Method Validation for Determination of BIC in Human Plasma ([redacted] 60-1421)

	BIC
Calibrated Range (ng/mL)	1 to 1,000
Interassay Precision Range (%CV)	1.6 to 3.1
Interassay Accuracy Range (%RE)	0.0 to 10.5
Studies Supported	GS-US-141-1218, GS-US-141-1219

Source: [redacted] 60-1421 Amendment 2

A high-range calibration curve BIC bioanalytical method was validated at [redacted] for the determination of BIC in K_2EDTA human plasma. The method involved [redacted] of BIC and its internal standard (GS-697140) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 6.

Table 6. Bioanalytical Method Validation for Determination of BIC in Human Plasma ([redacted] 60-1511)

	BIC
Calibrated Range (ng/mL)	20 to 20,000
Interassay Precision Range (%CV)	3.9 to 5.7
Interassay Accuracy Range (%RE)	2.4 to 5.8
Studies Supported	GS-US-141-1233, GS-US-141-1475, GS-US-141-1478, GS-US-141-1479, GS-US-141-1480, GS-US-141-1481, GS-US-141-1485, GS-US-141-1487, GS-US-311-1790, GS-US-380-1489, GS-US-380-1490, GS-US-380-1761, GS-US-380-1844, GS-US-380-1878, GS-US-380-1991, GS-US-380-1999, GS-US-380-3908, GS-US-380-3909

Source: [redacted] 60-1511 Amendment 3

1.3.2. Determination of Bictegravir in Urine

The BIC bioanalytical method was validated at [redacted] for the determination of BIC in human urine. The method involved [redacted] of BIC and its internal standard (GS-697140) from human urine, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 7.

Table 7. Bioanalytical Method Validation for Determination of BIC in Human Urine ([redacted] 60-1422)

	BIC
Calibrated Range (ng/mL)	1 to 1,000
Interassay Precision Range (%CV)	2.4 to 6.1
Interassay Accuracy Range (%RE)	−1.8 to 3.5
Studies Supported	GS-US-141-1218, GS-US-141-1479, GS-US-141-1481

Source: [redacted] 60-1422 Amendment 1

1.3.3. Determination of FTC in Human Plasma

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

The initial Gilead ([redacted]) FTC plasma method involved [redacted] of FTC and its internal standard (lamivudine) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 8.

Table 8. Bioanalytical Method Validation for Determination of FTC in Human Plasma ([redacted] 7536)

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

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

A combined FTC and emivirine bioanalytical method was developed and validated at Gilead for the determination of FTC and emivirine in human plasma. The method involved [redacted] of FTC, emivirine, and internal standards (lamivudine and GCA-174, respectively) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 9. The studies supported by this method validation assessed FTC concentrations; none assessed emivirine concentrations.

Table 9. Bioanalytical Method Validation for Determination of FTC in Human Plasma ([redacted] 6879)

	FTC
Calibrated Range (ng/mL)	10 to 2500
Interassay Precision Range (%CV)	3.7 to 9.2
Interassay Accuracy Range (%RE)	−0.4 to 1.8
Studies Supported	FTC-102, FTC-303, FTCB-101

Source: [redacted] 6879v4

1.3.4. Determination of FTC in Human Urine

The initial FTC human urine bioanalytical method was developed and validated at Gilead for the analysis of all FTC clinical study samples except for the samples for 1 study (Study 143-001) conducted by [redacted] in 19[redacted]. The proprietary method used by [redacted] to analyze urine samples collected from Study 143-001 was an HPLC-UV method 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 [redacted] of FTC and its internal standard (lamivudine) from human urine, followed by liquid chromatography–mass spectrometry (LC-MS) with positive ionization. Bioanalytical method validation parameters are summarized in Table 10.

Table 10. Bioanalytical Method Validation for Determination of FTC in Human Urine ([redacted] 2638)

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

Source: [redacted] 2638v1

A bioanalytical method using the LC-MS/MS method was developed for the determination of FTC in human urine. The method involved [redacted] of FTC and its internal standard (lamivudine) from human urine, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 11.

Table 11. Bioanalytical Method Validation for Determination of FTC in Human Urine ([redacted] 8361)

	FTC
Calibrated Range (ng/mL)	2500 to 250,000
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, FTC-110

Source: [redacted] 8361v2

1.3.5. 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 [redacted] of TAF and its internal standard (TAF-d_7) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 12.

Table 12. Bioanalytical Method Validation for Determination of TAF in Human Plasma ([redacted] 60-1115)

	TAF
Calibrated Range (ng/mL)	1 to 1000
Interassay Precision Range (%CV)	1.8 to 7.3
Interassay Accuracy Range (%RE)	−3.7 to 6.5
Studies Supported	GS-US-120-0104, GS-US-120-0107, GS-US-120-0108, GS-US-120-0109, GS-US-120-0114, GS-US-120-0117, GS-US-120-0118, GS-US-120-1538, GS-US-120-1554, GS-US-141-1218, GS-US-141-1233, GS-US-141-1475, GS-US-292-0103, GS-US-292-0112, GS-US-292-1316, GS-US-311-0101, GS-US-311-1387, GS-US-311-1388, GS-US-311-1473, GS-US-311-1790, GS-US-320-0101, GS-US-320-0108, GS-US-320-0110, GS-US-320-1615, GS-US-380-1761

Source: [redacted] 60-1115 Amendment 6

A bioanalytical method for the determination of TAF in K_2EDTA human plasma was developed and validated at [redacted]. The method involved [redacted] of TAF and its internal standard ([$^2H_7$]-GS-7171) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 13.

Table 13. Bioanalytical Method Validation for Determination of TAF in Human Plasma ([redacted] 60-1578)

	TAF
Calibrated Range (ng/mL)	1 to 1,000
Interassay Precision Range (%CV)	3.8 to 6.3
Interassay Accuracy Range (%RE)	−7.3 to −5.6
Studies Supported	GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878, GS-US-380-1991, GS-US-380-1999

Source: [redacted] 60-1578 Amendment 1

1.3.6. 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 [redacted] of TAF, TFV, and internal standards (TAF-d_7 and TFV-d_6, respectively) from human urine, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 14.

Table 14. Bioanalytical Method Validation for Determination of TAF and TFV in Human Urine ([redacted] 60-1220)

	TAF	TFV
Calibrated Range (ng/mL)	2 to 1000	10 to 5000
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, GS-US-120-0109	

Source: [redacted] 60-1220 Amendment 1

1.3.7. Determination of TFV and FTC in Human Plasma

The TFV and FTC bioanalytical method was developed and validated at Gilead for the determination of TFV and FTC in human plasma. The method involved the [redacted] of TFV, FTC, and internal standards (adefovir and lamivudine) from human plasma using [redacted], followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 15.

Table 15. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma (Gilead 15401)

	TFV	FTC
Calibrated Range (ng/mL)	10 to 1000	5 to 2000
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-174-0105	

Source: Gilead 15401v9

A combined TFV and FTC bioanalytical method was developed and validated at [redacted] for the determination of TFV and FTC in human plasma. The method involved the [redacted] of TFV, FTC, and [redacted] internal standards (TFV-d_6 and [^{13}C,$^{15}N_2$]FTC, respectively) from human plasma using [redacted], followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 16.

Table 16. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma ([redacted] 42-0831)

	TFV	FTC
Calibrated Range (ng/mL)	5 to 3000	5 to 3000
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	**FTC only:** GS-US-292-0103, GS-US-292-0112, GS-US-292-1316, GS-US-311-0101, GS-US-311-1473, GS-US-320-0101	
	TFV only: GS-US-120-0104	

Source: [redacted] 42-0831 Amendment 6

A combined TFV and FTC bioanalytical method was developed and validated at [redacted] for the determination of TFV and FTC in human plasma. The method involved the [redacted] of TFV, FTC, and [redacted] internal standards (TFV-d_6 and [^{13}C,$^{15}N_2$]FTC, respectively) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 17.

Table 17. Bioanalytical Method Validation for Determination of TFV and FTC in Human Plasma ([redacted] 42-1410)

Parameters	TFV	FTC
Calibrated Range (ng/mL)	5 to 3000	5 to 3000
Interassay Precision Range (%CV)	2.7 to 8.0	2.1 to 8.1
Interassay Accuracy Range (%RE)	–3.3 to 2.3	–1.3 to 3.7
Studies Supported	**FTC only:** GS-US-141-1218, GS-US-141-1233, GS-US-141-1475, GS-US-311-1388, GS-US-380-1489, GS-US-380-1490, GS-US-380-1761, GS-US-311-1790, GS-US-380-1844, GS-US-380-1878, GS-US-380-1991, GS-US-380-1999	
	TFV only: GS-US-320-0108, GS-US-320-0110	

Source: [redacted] 42-1410 Amendment 1

A bioanalytical method for the determination of TFV in human plasma low calibration range was developed and validated at [redacted]. The method involved [redacted] of TFV and its internal standard (TFV-d_6) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 18.

Table 18. Bioanalytical Method Validation for Determination of TFV in Human Plasma ([redacted] 60-1116)

Parameters	TFV
Calibrated Range (ng/mL)	0.3 to 300
Interassay Precision Range (%CV)	2.7 to 8.4
Interassay Accuracy Range (%RE)	0.0 to 3.0
Studies Supported	GS-US-120-0104, GS-US-120-0107, GS-US-120-0108, GS-US-120-0109, GS-US-120-0117, GS-US-292-0103, GS-US-311-0101, GS-US-320-0101

Source: [redacted] 60-1116 Amendment 3

A bioanalytical method for the determination of TFV in human plasma was developed and validated at [redacted] using the liquid chromatographic separation method. The method involved [redacted] of TFV and its internal standard (TFV-d_6) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 19.

Table 19. Bioanalytical Method Validation for Determination of TFV in Human Plasma ([redacted] 60-1352)

Parameters	TFV
Calibrated Range (ng/mL)	0.3 to 300
Interassay Precision Range (%CV)	1.7 to 7.9
Interassay Accuracy Range (%RE)	−2.7 to 2.7
Studies Supported	GS-US-120-0114, GS-US-120-0118

Source: [redacted] 60-1352

A bioanalytical method for the determination of TFV in human plasma was developed and validated at [redacted] using a small sample volume and a liquid chromatographic separation method. This method involved [redacted] of TFV and its internal standard (TFV-d_6) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 20.

Table 20. Bioanalytical Method Validation for Determination of TFV in Human Plasma ([redacted] 60-1368)

Parameters	TFV
Calibrated Range (ng/mL)	0.3 to 300
Interassay Precision Range (%CV)	1.8 to 4.8
Interassay Accuracy Range (%RE)	−2.7 to 2.7
Studies Supported	GS-US-120-1538, GS-US-120-1554, GS-US-141-1218, GS-US-141-1475, GS-US-292-0112, GS-US-292-1316, GS-US-320-0108, GS-US-320-0110, GS-US-320-1615

Source: [redacted] 60-1368 Amendment 2

A bioanalytical method for the determination of TFV in acid-treated human plasma was developed and validated at [redacted] using a small sample volume and liquid chromatographic separation method. This method involved [redacted] of TFV and its internal standard (TFV-d_6) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Table 21.

Table 21. Bioanalytical Method Validation for Determination of TFV in Human Plasma ([redacted] 60-1435)

Parameters	TFV
Calibrated Range (ng/mL)	0.3 to 300
Interassay Precision Range (%CV)	1.1 to 5.9
Interassay Accuracy Range (%RE)	−3.3 to 6.2
Studies Supported	GS-US-311-1387, GS-US-311-1388, GS-US-311-1790, GS-US-380-1761, GS-US-380-1991, GS-US-380-1999

Source: [redacted] 60-1435 Amendment 4

1.3.8. Determination of TFV-DP in PBMCs

Concentrations of tenofovir diphosphate (TFV-DP) in human peripheral blood mononuclear cells (PBMCs) were determined at [redacted] using an LC-MS/MS method with positive ionization which was qualified as [redacted] 60N-1419 and then later validated as [redacted] 60-1574. This method involved [redacted] of TFV-DP and its internal standard ($^{13}C_5$-TFV-DP) from human PBMCs. Bioanalytical method validation parameters are summarized in Table 22.

Table 22. Bioanalytical Method Validation for Determination of TFV-DP in Human PBMCs ([redacted] 60-1574)

Parameter	TFV-DP
Calibrated Range (ng/mL)	1.8 to 900
Interassay precision range (%CV)	1.8 to 7.1
Interassay accuracy range (%RE)	0.2 to 2.4
Studies Supported	GS-US-120-0104, GS-US-292-0112, GS-US-320-0108, GS-US-320-0110

Source: [redacted] 60-1574 Amendment 4

1.3.9. Determination of Coadministered Drugs in Human Plasma, Blood, and Urine

Any interference testing performed for fixed dose combination and/or coadministered drugs is described in each bioanalytical report. Bioanalytical methods used to determine coadministered drugs and corresponding validation data are presented in Appendix 5.4.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Summaries of clinical pharmacology studies of B/F/TAF and its components as single agents or in fixed-dose components are presented in m2.7.2, including the following key studies of relative bioavailability and food effect:

- Study GS-US-141-1233: a Phase 1 relative bioavailability and food effect study which assessed the relative bioavailability of two B/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets versus a BIC (75 mg) single-agent tablet and an F/TAF FDC tablet (200/25 mg), as well as the effect of food on PK of BIC, FTC, and TAF when administered as B/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets (m2.7.2, Section 2.2.1.1)

- Study GS-US-141-1218: a Phase 1 study primarily concerning safety and PK of single- and multiple-ascending doses of BIC in healthy subjects. This study also evaluated the effect of food with a BIC (100 mg) single-agent tablet (m2.7.2, Section 2.2.2.1).

Summaries of clinical efficacy studies are presented in m2.7.3 and summaries of clinical safety studies in m2.7.4.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Bioavailability

3.1.1. BIC

The absolute bioavailability of BIC has not been evaluated in humans. The absorption of BIC in humans is expected to be > 60% based on the results of a human ADME study and evaluation of BIC PK in healthy subjects (Study GS-US-141-1481, m2.7.2, Section 2.2.2.2). Following a single oral dose of 100-mg [^{14}C]BIC under fed conditions in the human ADME study, a minimum of 60% of the administered dose was absorbed, as evidenced by the total radioactivity (35% of dose) and excreted in the feces as intact metabolites (25% to 28% of dose).

3.1.2. TAF

The absolute bioavailability of TAF has not been evaluated in humans. TAF absorption is expected to be modest (approximately 40%) in the context of B/F/TAF under fed conditions based on the results of a human ADME study (Study GS-US-120-0109) and evaluation of TAF PK in healthy subjects with inhibitors of efflux transporters P-gp and/or BCRP, for which TAF is a substrate (Study GS-US-311-0101) {Inoue 1980, Williams 1985}.

3.1.3. FTC

In Study FTC-110, a high absolute bioavailability of FTC was achieved (93%) in healthy subjects by comparing the exposure from oral administration of the commercial capsule formulation (200 mg) with that of an intravenous solution. Emtricitabine is not extensively metabolized; therefore, its bioavailability is likely to be governed only by absorption, with minimum first-pass metabolism in the intestinal wall or liver.

3.1.4. B/F/TAF

An FDC formulation containing BIC 75 mg, FTC 200 mg, and TAF 25 mg was developed and evaluated for relative bioavailability compared with BIC 75 mg + F/TAF (200/25 mg), each administered under fasted conditions (Study GS-US-141-1233). Bictegravir AUC_{inf} and C_{max} for single-dose administration of the B/F/TAF (75/200/25 mg) FDC were approximately 27% and 31% higher, respectively, relative to BIC 75 mg + F/TAF (200/25 mg). Therefore, another FDC formulation was developed that contained BIC 50 mg, FTC 200 mg, and TAF 25 mg. Upon single-dose administration of the B/F/TAF (50/200/25 mg) FDC or BIC 75 mg + F/TAF (200/25 mg) under fasted conditions, the GLSM ratios and their 90% CIs for the BIC primary PK parameters of AUC_{last}, AUC_{inf}, and C_{max} were 78.46% (73.38, 83.89), 78.56% (73.44, 84.04), and 78.07% (73.41, 83.01), respectively, and were within the protocol-defined boundary of PK equivalence (70% to 143%). Based on these data, the B/F/TAF 50/200/25 mg FDC was chosen for further evaluation in Phase 3 studies.

3.2. Effect of Food

3.2.1. B/F/TAF

The effect of food on the components of the B/F/TAF FDC was evaluated with a high or moderate fat meal relative to fasted conditions (Study GS-US-141-1233, m2.7.2, Section 2.2.1.1).

Bictegravir AUC_{inf} and C_{max} were approximately 24% higher, following a high-fat meal, as compared with fasted conditions (Table 23). Similarly, a moderate-fat meal increased BIC AUC_{inf} and C_{max} by 24% and 20%, respectively, as compared with fasted conditions (Table 24).

Table 23. GS-US-141-1233: Statistical Comparisons of Bictegravir Plasma Pharmacokinetic Parameters Between Treatments for Food Effect: Fasted Versus High Fat (Cohort 2, BIC PK Analysis Set)

	GLSM		
BIC PK Parameter	**50-mg B/F/TAF FDC, High Fat (Test) (N = 27)**	**50-mg B/F/TAF FDC, Fasted (Reference) (N = 27)**	**%GLSM Ratio (90% CI) (Test/Reference)**
AUC_{last} (hr•ng/mL)	131,962.22	106,453.17	123.96 (115.91, 132.57)
AUC_{inf} (hr•ng/mL)	136,547.35	109,756.73	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5815.57	5136.15	113.23 (106.45, 120.43)

Source: GS-US-141-1233 Final CSR, Section 15.1, Table 5.1.2

Table 24. GS-US-141-1233: Statistical Comparisons of Bictegravir Plasma Pharmacokinetic Parameters Between Treatments for Food Effect: Fasted Versus Moderate Fat (Cohort 2, BIC PK Analysis Set)

	GLSM		
BIC PK Parameter	**50-mg B/F/TAF FDC, Moderate Fat (Test) (N = 27)**	**50-mg B/F/TAF FDC, Fasted (Reference) (N = 27)**	**%GLSM Ratio (90% CI) (Test/Reference)**
AUC_{last} (hr•ng/mL)	131,530.35	106,453.17	123.56 (115.53, 132.14)
AUC_{inf} (hr•ng/mL)	136,166.18	109,756.73	124.06 (115.95, 132.74)
C_{max} (ng/mL)	6158.13	5136.15	119.90 (112.72, 127.53)

Source: GS-US-141-1233 Final CSR, Section 15.1, Table 5.1.2

Food had no effect on FTC AUC_{inf} following administration of the B/F/TAF FDC, however, a small, 14% decrease in FTC C_{max} was observed following administration with a high-fat meal, as compared with fasted conditions (Table 25 and Table 26).

Table 25. GS-US-141-1233: Statistical Comparisons of FTC Plasma Pharmacokinetic Parameters Between Treatments for Food Effect: Fasted Versus High Fat (Cohort 2, FTC PK Analysis Set)

	GLSM		
FTC PK Parameter	50-mg B/F/TAF FDC, High Fat (Test) (N = 27)	50-mg B/F/TAF FDC, Fasted (Reference) (N = 27)	%GLSM Ratio (90% CI) (Test/Reference)
AUC_{last} (hr•ng/mL)	10,127.57	10,546.87	96.02 (93.47, 98.65)
AUC_{inf} (hr•ng/mL)	10,380.51	10,766.50	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1831.14	2141.20	85.52 (78.37, 93.31)

Source: GS-US-141-1233 Final CSR, Section 15.1, Table 5.1.2

Table 26. GS-US-141-1233: Statistical Comparisons of FTC Plasma Pharmacokinetic Parameters Between Treatments for Food Effect: Fasted Versus Moderate Fat (Cohort 2, FTC PK Analysis Set)

	GLSM		
FTC PK Parameter	50-mg B/F/TAF FDC, Moderate Fat (Test) (N = 27)	50-mg B/F/TAF FDC, Fasted (Reference) (N = 27)	%GLSM Ratio (90% CI) (Test/Reference)
AUC_{last} (hr•ng/mL)	10,670.45	10,546.87	101.17 (98.48, 103.94)
AUC_{inf} (hr•ng/mL)	10,909.48	10,766.50	101.33 (98.66, 104.06)
C_{max} (ng/mL)	1966.45	2141.20	91.84 (84.17, 100.21)

Source: GS-US-141-1233 Final CSR, Section 15.1, Table 5.1.2

Tenofovir alafenamide AUC_{last} was approximately 63% higher following a high-fat meal, as compared with fasted conditions (Table 27). A moderate-fat meal increased TAF AUC_{last} 48%, as compared with fasted conditions (Table 28). Food had no effect on TAF C_{max} following administration of the B/F/TAF FDC.

Table 27. GS-US-141-1233: Statistical Comparisons of TAF Plasma Pharmacokinetic Parameters Between Treatments for Food Effect: Fasted Versus High Fat (Cohort 2, TAF PK Analysis Set)

	GLSM		
TAF PK Parameter	50-mg B/F/TAF FDC, (Test) High Fat (N = 27)	50-mg B/F/TAF FDC, Fasted (Reference) (N = 28)	%GLSM Ratio (90% CI) (Test/Reference)
AUC_{last} (hr•ng/mL)	297.23	182.77	162.62 (143.10, 184.80)
AUC_{inf} (hr•ng/mL)	307.40	184.57	166.55 (146.54, 189.29)
C_{max} (ng/mL)	195.69	213.39	91.71 (73.46, 114.49)

Source: GS-US-141-1233 Final CSR, Section 15.1, Table 5.1.2

Table 28. GS-US-141-1233: Statistical Comparisons of TAF Plasma Pharmacokinetic Parameters Between Treatments for Food Effect: Fasted Versus Moderate Fat (Cohort 2, TAF PK Analysis Set)

TAF PK Parameter	GLSM		%GLSM Ratio (90% CI) (Test/Reference)
	50-mg B/F/TAF FDC, Moderate Fat (Test) (N = 27)	50-mg B/F/TAF FDC, Fasted (Reference) (N = 28)	
AUC_{last} (hr•ng/mL)	270.87	182.77	148.20 (130.41, 168.41)
AUC_{inf} (hr•ng/mL)	273.58	184.57	148.23 (130.42, 168.47)
C_{max} (ng/mL)	211.35	213.39	99.04 (79.33, 123.65)

Source: GS-US-141-1233 Final CSR, Section 15.1, Table 5.1.2

The changes in exposures of the components of the B/F/TAF FDC are not considered clinically meaningful based on the lack of exposure-safety relationship for BIC and TAF (m2.7.2, Section 3.3.2). B/F/TAF was administered without regard to food in Phase 2 and 3 studies. Collectively, safety, efficacy, and PK, and PKPD data support administration of B/F/TAF without regard to food.

3.3. Discussion and Conclusions

Administration of the B/F/TAF (50/200/25 mg) FDC and BIC 75 mg + F/TAF (200/25 mg), resulted in similar exposures of BIC, TAF and FTC. Administration of B/F/TAF with or without food does not result in clinically meaningful changes in the PK of its components. B/F/TAF was administered without regard to food in Phase 2 and 3 studies. Collectively, safety, efficacy, and PK-PD data support administration of B/F/TAF without regard to food.

4. REFERENCES

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5. APPENDICES

5.1. List of Appendices

Appendix Number	Appendix Title
5.2	Tabular Summary of Bioanalytical Methods for Individual Studies
5.3	Long-Term Storage Stability
5.4	Determination of Coadministered Drugs in Human Plasma, Whole Blood, and Urine

5.2. Tabular Summary of Bioanalytical Methods for Individual Studies

A tabular summary of bioanalytical methods, method validation reports, and sample analysis reports for individual studies is provided below for studies conducted to support the B/F/TAF clinical development program. Study numbers shown in **bold** have not been previously reported to regulatory agencies. The current versions of the validation reports and sample analysis reports are listed. The listed method validation reports are cumulative of all previous versions, with the exception of the validation reports for Studies 143-001, FTC-101, FTC-102, FTC-106, FTC-107, FTC-108, and FTC-110. Validation reports and sample analysis reports cited in the corresponding CSRs were those in effect at the time of CSR completion.

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
143-001	Human Plasma	FTC	Method documents not available (property of [redacted])	HPLC-UV	80 ng/mL (LLOQ)	Sample analysis reports not available (property of [redacted])
	Human Urine	FTC	Method documents not available (property of [redacted])	HPLC-UV	1000 ng/mL (LLOQ)	Sample analysis reports not available (property of [redacted])
FTC-101	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 8200v4
	Human Urine	FTC	[redacted] 2638v1	LC/MS (SIM)	250-5000 ng/mL	[redacted] 8200v4
FTC-102	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS	10-2500 ng/mL	[redacted] 7027v3
FTC-106	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 8603v2
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS	2.5-250 µg/mL	[redacted] 8603v2
FTC-107	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 10824v1
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS	2.5-250 µg/mL	[redacted] 10824v1
	Human Dialysate	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 10824v1
FTC-108	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 11088v1
		Penciclovir	[redacted] V-01-BIO-TP0260-01	LC-MS/MS	25-2000 ng/mL	[redacted] 11088v1
	Human Urine	FTC	[redacted] 8361v2	LC-MS/MS	2500-250,000 ng/mL	[redacted] 11088v1
		Penciclovir	[redacted] V-01-BIO-TP0260-01	LC-MS/MS	2500-250,000 ng/mL	[redacted] 11088v1

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
FTC-110	Human Plasma	FTC	[redacted] 7536v6	LC-MS/MS	5-5000 ng/mL	[redacted] 11694v1
	Human Urine	FTC	[redacted] 8361v2	LC/MS-MS	2500-250,000 ng/mL	[redacted] 11694v1
FTC-303	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS	10-2500 ng/mL	[redacted] 6564v3
FTCB-101	Human Plasma	FTC	[redacted] 6879v4	LC-MS/MS	10-2500 ng/mL	[redacted] 6525v2
GS-US-120-0104	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1128A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1128B
		TFV	[redacted] 42-0831 Amendment 6	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1128C
	Human PBMC	TFV-DP[b]	[redacted] 60-1574 Amendment 4	LC-MS/MS	1.8-900 ng/mL	[redacted] 60N-1128F
GS-US-120-0107	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1230A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1230B
GS-US-120-0108	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1269A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1269B
	Human Urine	TAF	[redacted] 60-1220 Amendment 1	LC-MS/MS	2-1000 ng/mL	[redacted] 60-1269C
		TFV			10-5000 ng/mL	
GS-US-120-0109	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1245A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1245B
	Human Urine	TAF	[redacted] 60-1220 Amendment 1	LC-MS/MS	2-1000 ng/mL	[redacted] 60-1245C
		TFV			10-5000 ng/mL	
GS-US-120-0114	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1344A
		TFV	[redacted] 60-1352	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1344B Amendment 1
GS-US-120-0117	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1330A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1330B Amendment 1
		RPV	[redacted] 42-1102 Amendment 3	LC-MS/MS	1-500 ng/mL	[redacted] 60-1330C

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
GS-US-120-0118	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1–1000 ng/mL	[redacted] 60-1369A Amendment 1
		TFV	[redacted] 60-1352	LC-MS/MS	0.3–300 ng/mL	[redacted] 60-1369B Amendment 1
		ATV	[redacted] 42-0830 Amendment 5	LC-MS/MS	10–5000 ng/mL	[redacted] 60-1369C
		DRV	[redacted] 42-0902 Amendment 4	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1369D
		LPV	[redacted] 42-1359 Amendment 1	LC-MS/MS	100-20,000 ng/mL	[redacted] 60-1369E
		DTG	[redacted] 42-1369 Amendment 2	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1369F
GS-US-120-1538	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1463A
		TFV	[redacted] 60-1368 Amendment 2	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1463B
		MDZ	[redacted] 42-0624 Amendment 1	LC-MS/MS	0.1-100 ng/mL	[redacted] 60-1463C
		1'-OH MDZ				
GS-US-120-1554	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1460A
		TFV	[redacted] 60-1368 Amendment 2	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1460B
		RPV	[redacted] 42-1408	LC-MS/MS	1-500 ng/mL	[redacted] 60-1460C
GS-US-141-1218	**Human Plasma**	**BIC**	[redacted] **60-1421 Amendment 2**	**LC-MS/MS**	**1-1,000 ng/mL**	[redacted] **60-1430A Amendment 1**
		TAF	[redacted] **60-1115 Amendment 6**	**LC-MS/MS**	**1-1000 ng/mL**	[redacted] **60-1430C**
		TFV	[redacted] **60-1368 Amendment 2**	**LC-MS/MS**	**0.3-300 ng/mL**	[redacted] **60-1430D**
		FTC	[redacted] **42-1410 Amendment 1**	**LC-MS/MS**	**5-3000 ng/mL**	[redacted] **60-1430E**
	Human Urine	**BIC**	[redacted] **60-1422 Amendment 1**	**LC-MS/MS**	**1-1,000 ng/mL**	[redacted] **60-1430B**
GS-US-141-1219	**Human Plasma**	**BIC**	[redacted] **60-1421 Amendment 2**	**LC-MS/MS**	**1-1,000 ng/mL**	[redacted] **60-1480**
GS-US-141-1233	**Human Plasma**	**TAF**	[redacted] **60-1115 Amendment 6**	**LC-MS/MS**	**1-1000 ng/mL**	[redacted] **60-1530A**
		FTC	[redacted] **42-1410 Amendment 1**	**LC-MS/MS**	**5-3000 ng/mL**	[redacted] **60-1530B**
		BIC	[redacted] **60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	[redacted] **60-1530C**

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
GS-US-141-1475	**Human Plasma**	**BIC**	**[redacted] 60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-1519A**
		TAF	**[redacted] 60-1115 Amendment 6**	**LC-MS/MS**	**1-1000 ng/mL**	**[redacted] 60-1519B**
		TFV	**[redacted] 60-1368 Amendment 2**	**LC-MS/MS**	**0.3-300 ng/mL**	**[redacted] 60-1519C**
		FTC	**[redacted] 42-1410 Amendment 1**	**LC-MS/MS**	**5-3000 ng/mL**	**[redacted] 60-1519D**
GS-US-141-1478	**Human Plasma**	**BIC**	**[redacted] 60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-15125**
GS-US-141-1479	**Human Plasma**	**BIC**	**[redacted] 60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-1522A**
	Human Urine	**BIC**	**[redacted] 60-1422 Amendment 1**	**LC-MS/MS**	**1-1,000 ng/mL**	**[redacted] 60-1522B**
GS-US-141-1480	**Human Plasma**	**BIC**	**[redacted] 60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-1524**
GS-US-141-1481	**Human Plasma**	**BIC**	**[redacted] 60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-1518A**
	Human Urine	**BIC**	**[redacted] 60-1422 Amendment 1**	**LC-MS/MS**	**1-1,000 ng/mL**	**[redacted] 60-1518B**
GS-US-141-1485	**Human Plasma**	**BIC**	**[redacted] 60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-1515A**
		ATV	**[redacted] 42-0830 Amendment 5**	**LC-MS/MS**	**10-5000 ng/mL**	**[redacted] 60-1515B**
		COBI	**[redacted] 60-1343 Amendment 2**	**LC-MS/MS**	**5-2500 ng/mL**	**[redacted] 60-1515C**
		Rifampicin	**[redacted] 42-1219**	**LC-MS/MS**	**20-10,000 ng/mL**	**[redacted] 60-1515D**
		Voriconazole	**[redacted] 42-0725 Amendment 1**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-1515E**
		DRV	**[redacted] 42-0902 Amendment 4**	**LC-MS/MS**	**20-10,000 ng/mL**	**[redacted] 60-1515F**
GS-US-141-1487	**Human Plasma**	**BIC**	**[redacted] 60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	**[redacted] 60-1564**
		Iohexol	**[redacted] 2100-775 Addendum 9**	**LC-MS/MS**	**1000-500,000 ng/mL**	**[redacted] 8328011**
GS-US-174-0105	Human Plasma	FTC	Gilead 15401v9	LC-MS/MS	5-2000 ng/mL	Gilead Sciences S-174-01
		TFV			10-1000 ng/mL	
	Human Whole Blood	Tacrolimus	[redacted] 6332-138 Amendment 1	LC-MS/MS	0.1-10 ng/mL	[redacted] 6511-218
GS-US-292-0103	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1142A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1142B
		COBI	[redacted] 60-0949 Amendment 6	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1142C
		EVG			20-10,000 ng/mL	
		FTC	[redacted] 42-0831 Amendment 6	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1142D

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
GS-US-292-0112	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1316A
		TFV	[redacted] 60-1368 Amendment 2	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1316B
		FTC	[redacted] 42-0831 Amendment 6	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1316C
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1316D
		COBI			5-2500 ng/mL	
		Iohexol	[redacted] 2100-775 Addendum 9	LC-MS/MS	1000-500,000 ng/mL	[redacted] 8283389
GS-US-292-1316	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1411A
		TFV	[redacted] 60-1368 Amendment 2	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1411B
		FTC	[redacted] 42-0831 Amendment 6	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1411C
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1411D
		COBI			5-2500 ng/mL	
		Sertraline	[redacted] 42-1402	LC-MS/MS	0.2-200 ng/mL	[redacted] 60-1411E
GS-US-311-0101	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1125A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1125B
		FTC	[redacted] 42-0831 Amendment 6	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1125C
		DRV	[redacted] 42-0902 Amendment 4	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1125D
		EFV	[redacted] 42-0827 Amendment 3	LC-MS/MS	5-5000 ng/mL	[redacted] 60-1125E
		COBI	[redacted] 60-0949 Amendment 6	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1125F
GS-US-311-1387	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1557A
		TFV	[redacted] 60-1435 Amendment 4	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1557B
		CBZ	[redacted] 42-1371	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1557D
		CBZE			5-5000 ng/mL	

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
GS-US-311-1388	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1531A
		TFV	[redacted] 60-1435 Amendment 4	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1531B
		FTC	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1531C
		ATV	[redacted] 42-0830 Amendment 5	LC-MS/MS	10-5000 ng/mL	[redacted] 60-1531D
		COBI	[redacted] 60-1343 Amendment 2	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1531E
GS-US-311-1473	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1443A Amendment 1
		FTC	[redacted] 42-0831 Amendment 6	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1443B Amendment 1
		EVG	[redacted] 60-1343 Amendment 2	LC-MS/MS	20-10,000 ng/mL	[redacted] 60-1443C Amendment 1
		COBI			5-2500 ng/mL	
GS-US-311-1790	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1526A
		TFV	[redacted] 60-1435 Amendment 4	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1526B
		FTC	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1526C
		BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1526D
		Norgestrel	[redacted] 42-1226 Amendment 1	LC-MS/MS	0.02-20 ng/mL	[redacted] 60-1526E
		Norgestimate			0.05-50 ng/mL	
		17-Desacetyl Norgestimate	[redacted] 42-1502 Amendment 1	LC-MS/MS	0.02-10 ng/mL	[redacted] 60-1526F
		Ethinyl Estradiol	[redacted] 42-0931 Amendment 1	LC-MS/MS	0.0025-0.5 ng/mL	[redacted] 60-1526G
GS-US-320-0101	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1152A
		TFV	[redacted] 60-1116 Amendment 3	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1152B
		TFV	[redacted] 42-0831 Amendment 6	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1152C Amendment 1

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
GS-US-320-0108	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1356A Amendment 1
		TFV	[redacted] 60-1368 Amendment 2	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1356B Amendment 2
		TFV	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1356C Amendment 2
	Human PBMCs	TFV-DP[b]	[redacted] 60-1574 Amendment 4	LC-MS/MS	1.8 to 900 ng/mL	[redacted] 60N-1356D Amendment 1
GS-US-320-0110	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1357A Amendment 1
		TFV	[redacted] 60-1368 Amendment 2	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1357B Amendment 2
		TFV	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1357C Amendment 2
	Human PBMCs	TFV-DP[b]	[redacted] 60-1574 Amendment 4	LC-MS/MS	1.8 to 900 ng/mL	[redacted] 60N-1357D Amendment 1
GS-US-320-1615	Human Plasma	TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1489A
		TFV	[redacted] 60-1368 Amendment 2	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1489B
GS-US-380-1489	**Human Plasma**	**BIC**	[redacted] **60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	[redacted] **60-1599**
		TAF	[redacted] **60-1578 Amendment 1**	**LC-MS/MS**	**1-1,000 ng/mL**	[redacted] **60-1599B**
		FTC	[redacted] **42-1410 Amendment 1**	**LC-MS/MS**	**5-3000 ng/mL**	[redacted] **60-1599C**
GS-US-380-1490	**Human Plasma**	**BIC**	[redacted] **60-1511 Amendment 3**	**LC-MS/MS**	**20-20,000 ng/mL**	[redacted] **60-15101**
		TAF	[redacted] **60-1578 Amendment 1**	**LC-MS/MS**	**1-1,000 ng/mL**	[redacted] **60-15101B**
		FTC	[redacted] **42-1410 Amendment 1**	**LC-MS/MS**	**5-3000 ng/mL**	[redacted] **60-15101C**

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
GS-US-380-1761	Human Plasma	SOF	[redacted] 60-1323 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1550A
		GS-566500			10-5000 ng/mL	
		GS-331007			10-5000 ng/mL	
		LDV	[redacted] 60-1433 Amendment 3	LC-MS/MS	1-2000 ng/mL	[redacted] 60-1550B
		TAF	[redacted] 60-1115 Amendment 6	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1550C
		TFV	[redacted] 60-1435 Amendment 4	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1550D
		BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1550E
		FTC	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1550F
GS-US-380-1844	Human Plasma	BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-15103
		TAF	[redacted] 60-1578 Amendment 1	LC-MS/MS	1-1,000 ng/mL	[redacted] 60-15103B
		FTC	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-15103C
GS-US-380-1878	Human Plasma	BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-15104
		TAF	[redacted] 60-1578 Amendment 1	LC-MS/MS	1-1,000 ng/mL	[redacted] 60-15104B
		FTC	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-15104C
GS-US-380-1991	Human Plasma	BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1645A
		TAF	[redacted] 60-1578 Amendment 1	LC-MS/MS	1-1,000 ng/mL	[redacted] 60-1645B
		TFV	[redacted] 60-1435 Amendment 4	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1645C
		FTC	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1645D
GS-US-380-1999	Human Plasma	SOF	[redacted] 60-1323 Amendment 5	LC-MS/MS	5-2500 ng/mL	[redacted] 60-1609A
		GS-566500			10-5000 ng/mL	
		GS-331007			10-5000 ng/mL	
		VEL	[redacted] 60-1393 Amendment 2	LC-MS/MS	1-1000 ng/mL	[redacted] 60-1609B
		BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1609C
		TAF	[redacted] 60-1578 Amendment 1	LC-MS/MS	1-1,000 ng/mL	[redacted] 60-1609D
		TFV	[redacted] 60-1435 Amendment 4	LC-MS/MS	0.3-300 ng/mL	[redacted] 60-1609E
		FTC	[redacted] 42-1410 Amendment 1	LC-MS/MS	5-3000 ng/mL	[redacted] 60-1609F
		VOX	[redacted] 8109.123113.1	LC-MS/MS	0.5-1000 ng/mL	[redacted] 10527.043016.1

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range	Sample Analysis Report[a]
GS-US-380-3908	Human Plasma	BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1647
		Metformin	[redacted] ARMET1 ARMET1.A1 ARMET1.A2 ARMET1.A3 ARMET1.A4 ARMET1.A5	LC-MS/MS	10-2500 ng/mL	[redacted] 32531-1
	Human Whole Blood	Metformin	[redacted] ARMET3	LC-MS/MS	10-2500 ng/mL	[redacted] 32531-3
	Human Urine	Metformin	[redacted] ARMET2 ARMET2.A1 ARMET2.A2	LC-MS/MS	30-6000 ng/mL	[redacted] 32531-2
GS-US-380-3909	Human Plasma	BIC	[redacted] 60-1511 Amendment 3	LC-MS/MS	20-20,000 ng/mL	[redacted] 60-1627
GS-US-380-4270	Human Plasma	MDZ	[redacted] 42-0624 Amendment 1	LC-MS/MS	0.1-100 ng/mL	[redacted] 60-16131

1′-OH MDZ = midazolam metabolite (1′-hydroxymidazolam); ATV = atazanavir; BIC= bictegravir; CBZ = carbamazepine; CBZE = carbamazepine-10,11-epoxide; COBI = cobicistat; CSR = clinical study report; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LC-MS/MS = liquid chromatography-tandem mass spectrometry; LDV = ledipasvir; LPV = lopinavir; MDZ = midazolam; [redacted]; RPV = rilpivirine; SOF = sofosbuvir; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir diphosphate; VEL = velpatasvir; VOX = voxilaprevir

a Current validation and sample analysis reports are listed. Validation and sample analysis reports listed in the corresponding CSRs were those in effect at the time of CSR completion.

b The method was qualified as [redacted] 60N-1419 and validated as [redacted] 60-1574.

5.3. Long-Term Storage Stability

Appendix Table 1. Long-Term Storage Stability of BIC, TAF, TFV, TFV-DP, and FTC in Human Matrices

Analyte	Matrix	Current LTSS Data	Current Validation Report
BIC	Plasma (concentration range 20 - 20000 ng/mL)	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3
BIC	Plasma (concentration range 1 - 1000 ng/mL)	206 days at –20°C and –70°C	[redacted] 60-1421 Amendment 2
FTC	Plasma	190 days at –20°C, 340 days at –70°C, and 1426 days at –80°C	[redacted] 42-1410 Amendment 1
TAF	Plasma	520 days at −70°C	[redacted] 60-1578 Amendment 1
TFV	Plasma (concentration range 0.3 - 300 ng/mL)	366 days at –20°C and 1092 days at –70°C	[redacted] 60-1368 Amendment 2
TFV	Acidified Plasma (concentration range 0.3 - 300 ng/mL)	464 days at –20°C and –70°C	[redacted] 60-1435 Amendment 4
TFV	Plasma (concentration range 5 - 3000 ng/mL)	190 days at –20°C, 340 days at –70°C, and 1426 days at -80°C	[redacted] 42-1410 Amendment 1
BIC	Urine	194 days at -20°C and 376 days at −70°C	[redacted] 60-1422 Amendment 1
FTC	Urine	664 days at −70°C	[redacted] 42-1236 Amendment 2
TAF	Urine	103 days at –20°C and –70°C	[redacted] 60-1220 Amendment 1
TFV	Urine	103 days at –20°C and –70°C	[redacted] 60-1220 Amendment 1
TFV-DP	PBMCs	345 days at −70°C	[redacted] 60-1574 Amendment 4

LTSS = long-term storage stability; PBMC = peripheral blood mononuclear cell; [redacted]; BIC= bictegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TFV = tenofovir

Appendix Table 2. Combination Long-Term Storage Stability of BIC, TAF, and FTC in Human Plasma

Primary Analyte	Primary Analyte in the Presence of:	Matrix	Current LTSS Data (days)	Current Validation Report
BIC	TAF, TFV, FTC	Human Plasma	90 days at −20°C and 371days at −70°C	[redacted] 60-1602 A-D
TAF	BIC, TFV, FTC	Human Plasma	61 days at −20°C and 384 days at −70°C	[redacted] 60-1602 A-D
FTC	BIC, TAF, TFV	Human Plasma	109 days at −20°C and 395 days at −70°C	[redacted] 60-1602 A-D

BIC= bictegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TFV = tenofovir

Appendix Table 3. Tabular Summary of Long-Term Storage Stability Data for Individual Studies

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
143-001	Human Plasma	FTC	[redacted] 19 through [redacted] 19	Not reported	Not reported	1426 days at -80°C	Gilead 15401v9	Not reported
	Human Urine	FTC	[redacted] 19 through [redacted] 19	Not reported	Not reported	664 days at -70°C	[redacted] 42-1236 Amendment 2	Not reported
FTC-101	Human Plasma	FTC	[redacted] 19 through [redacted] 19	[redacted] 19 through [redacted] 20	548 days at −80°C	1426 days at −80°C	[redacted] 7536v6	[redacted] 8200v4
	Human Urine	FTC	[redacted] 19 through [redacted] 19	[redacted] 19 through [redacted] 20	548 days at −70°C	664 days at −70°C	[redacted] 2638v1	[redacted] 8200v4
FTC-102	Human Plasma	FTC	[redacted] 19 through [redacted] 19	[redacted] 19 through [redacted] 19	249 days at −80°C	1426 days at −80°C	[redacted] 6879v4	[redacted] 7027v3
FTC-106	Human Plasma	FTC	[redacted] 19 through [redacted] 19	[redacted] 19 through [redacted] 20	325 days at -80°C	1426 days at -80°C	Gilead 15401v9	[redacted] 8603v2
	Human Urine	FTC	[redacted] 19 through [redacted] 19	[redacted] 19 through [redacted] 20	325 days at -70°C	664 days at -70°C	[redacted] 42-1236 Amendment 2	
FTC-107	Human Plasma	FTC	[redacted] 19 through [redacted] 20	[redacted] 20 through [redacted] 20	373 days at −80°C	1426 days at −80°C	Gilead 15401v9	
	Human Urine	FTC	[redacted] 19 through [redacted] 20	[redacted] 20 through [redacted] 20	373 days at −80°C	664 days at −70°C	[redacted] 42-1236 Amendment 2	[redacted] S-01-TP0006-01
	Human Dialysate	FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	275 days at −80°C	460 days at −80°C	[redacted] 20050v1	

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
FTC-108	Human Plasma	FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	154 days at −80°C	1426 days at −80°C	Gilead 15401v9	[redacted] S-01-TP0006-03
		Penciclovir	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	236 days at −80°C	Not reported	[redacted] V-01-BIO-TP0260-01	
	Human Urine	FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	222 days at −80°C	294 days at −80°C	[redacted] 8361v2	
		Penciclovir	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	258 days at −80°C	Not reported	[redacted] V-01-BIO-TP0260-01	
FTC-110	Human Plasma	FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	38 days at -80°C	1426 days at -80°C	Gilead 15401v9	[redacted] S-01-BIO-TP0006-07
	Human Urine	FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	45 days at -80°C	664 days at -70°C	[redacted] 42-1236 Amendment 2	
FTC-303	Human Plasma	FTC	[redacted] 19 through [redacted] 19	[redacted] 19 through [redacted] 19	334 days at −80°C	1426 days at −80°C	Gilead 15401v9	[redacted] 6564v3
FTCB-101	Human Plasma	FTC	[redacted] 19 through [redacted] 19	[redacted] 19 through [redacted] 19	346 days at -80°C	1426 days at -80°C	Gilead 15401v9	[redacted] 6525v2
GS-US-120-0104	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	228 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1128A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	258 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1128B
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	251 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1128C
	Human PBMCs	TFV-DP[c]	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	290 days at −70°C	345 days at −70°C	[redacted] 60-1574 Amendment 4	[redacted] 60N-1128F

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-120-0107	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	102 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1230A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	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 through [redacted] 20	[redacted] 20 through [redacted] 20	95 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1269A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	98 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1269B
	Human Urine	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	103 days at −70°C	103 days at −70°C	[redacted] 60-1220 Amendment 1	[redacted] 60-1269C
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	103 days at −70°C	103 days at −70°C	[redacted] 60-1220 Amendment 1	
GS-US-120-0109	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	43 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1245A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	30 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1245B
	Human Urine	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	29 days at −70°C	103 days at −70°C	[redacted] 60-1220 Amendment 1	[redacted] 60-1245C
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	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	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-120-0114	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	87 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1344A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	106 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1344B Amendment 1
GS-US-120-0117	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	30 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1330A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	41 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1330B Amendment 1
		RPV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	41 days at −70°C	783 days at −70°C	[redacted] 42-1102 Amendment 3	[redacted] 60-1330C
GS-US-120-0118	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	51 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1369A Amendment 1
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	46 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1369B Amendment 1
		ATV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	24 days at −70°C	721 days at −70°C	[redacted] 42-0830 Amendment 5	[redacted] 60-1369C
		DRV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	23 days at −70°C	1635 days at −70°C	[redacted] 42-0902 Amendment 4	[redacted] 60-1369D
		LPV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	12 days at −70°C	43 days at −70°C	[redacted] 42-1359 Amendment 1	[redacted] 60-1369E
		DTG	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	20 days at −70°C	77 days at −70°C	[redacted] 42-1369 Amendment 2	[redacted] 60-1369F

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-120-1538	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	29 days at –70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1463A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	26 days at –70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1463B
		MDZ	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	35 days at –70°C	135 days at −70°C	[redacted] 42-0624 Amendment 1	[redacted] 60-1463C
		1'-OH MDZ	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	35 days at –70°C	135 days at −70°C	[redacted] 42-0624 Amendment 1	[redacted] 60-1463C
GS-US-120-1554	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	29 days at –70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1460A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	438 days at –70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1460B
		RPV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	35 days at –70°C	783 days at −70°C	[redacted] 42-1408	[redacted] 60-1460C
GS-US-141-1218	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	154 days at –70°C	206 days at –20°C and –70°C	[redacted] 60-1421 Amendment 2	[redacted] 60-1430A Amendment 1
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	53 days at –70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1430C
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	35 days at –70°C	366 days at –20°C and 1092 days at –70°C	[redacted] 60-1368 Amendment 2	[redacted] 60-1430D
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	37 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-1430E
	Human Urine	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	134 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 60-1422 Amendment 1	[redacted] 60-1430B

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-141-1219	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	70 days at –70°C	206 days at –20°C and –70°C	[redacted] 60-1421 Amendment 2	[redacted] 60-1480
GS-US-141-1233	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	169 days at –70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1530A
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	155 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-1530B
		BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	149 days at –70°C[b]	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1530C
GS-US-141-1475	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	150 days at –70°C[a]	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1519A
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	154 days at –70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1519B
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	149 days at –70°C	366 days at –20°C and 1092 days at –70°C	[redacted] 60-1368 Amendment 2	[redacted] 60-1519C
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	154 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-1519D
GS-US-141-1478	Human Plasma	BIC	[redacted] 20 through [redacted] 20.	[redacted] 20 through [redacted] 20	90 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-15125
GS-US-141-1479	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	81 days at –70°C[a]	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1522A
	Human Urine	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	100 days at –70°C[a]	194 days at -20°C and 376 days at -70°C	[redacted] 60-1422 Amendment 1	[redacted] 60-1522B

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-141-1480	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	37 days at –70°C[a]	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1524
GS-US-141-1481	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	15 days at –70°C[a]	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1518A
	Human Urine	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	15 days at –70°C[a]	194 days at -20°C and 376 days at -70°C	[redacted] 60-1422 Amendment 1	[redacted] 60-1518B
GS-US-141-1485	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	182 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1515A
		ATV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	58 days at –70°C	721 days at –70°C	[redacted] 42-0830 Amendment 5	[redacted] 60-1515B
		COBI	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	10 days at –70°C	121 days at -10°C to -30°C 1297 days at -60°C to -80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1515C
		Rifampicin	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	11 days at –70°C	99 days at –20°C and –70°C	[redacted] 42-1219	[redacted] 60-1515D
		Voriconazole	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	15 days at –70°C	80 days at –70°C	[redacted] 42-0725 Amendment 1	[redacted] 60-1515E
		DRV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	47 days at –70°C	1635 days at –20°C and –70°C	[redacted] 42-0902 Amendment 4	[redacted] 60-1515F

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-141-1487	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	39 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1564
		Iohexol	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	46 days at –70°C	725 days at –10°C to –30°C and 1260 days at –60°C to –80°C	[redacted] 2100-775 Addendum 9	[redacted] 8328011
GS-US-174-0105	Human Plasma	FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	151 days at −80°C	1426 days at −80°C	Gilead 15401v9	Gilead S-174-01
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	151 days at −80°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	
	Human Whole Blood	Tacrolimus	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	168 days at −80°C	1369 days at −60°C to −80°C	[redacted] 6332-138 Amendment 1	[redacted] 6511-218
GS-US-292-0103	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	45 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1142A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	292 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1142B
		COBI	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	70 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1142C
		EVG	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	70 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 6	[redacted] 60-1142C
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	45 days at −70°C	1297 days at −60°C to −80°C	Gilead 15401v9	[redacted] 60-1142D

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-292-0112	Human Plasma	TAF	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	434 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1316A
		TFV	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	438 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1316B
		FTC	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	441 days at −70°C	1297 days at −60°C to −80°C	Gilead 15401v9	[redacted] 60-1316C
		EVG	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	497 days at −70°C	585 days at −70°C	[redacted] 60-0949 Amendment 6	[redacted] 60-1316D
		COBI	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	497 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	
		Iohexol	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	458 days at −70°C	1260 days at −60°C to −80°C	[redacted] 2100-775 Addendum 9	[redacted] 8283389
	Human PBMCs	TFV-DP[c]	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	273 days at−70°C	345 days at −70°C	[redacted] 60-1574 Amendment 4	[redacted] 60N-1316E
GS-US-292-1316	Human Plasma	TAF	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	63 days at -70°C	520 days at -70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1411A
		TFV	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	66 days at -70°C	1092 days at -70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1411B
		FTC	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	32 days at -70°C	1297 days at -60°C to -80°C	Gilead 15401v9	[redacted] 60-1411C
		COBI	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	15 days at -70°C	1297 days at -60°C to -80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1411D
		EVG	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	15 days at -70°C	585 days at -70°C	[redacted] 60-0949 Amendment 6	
		Sertraline	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	27 days at -70°C	74 days at -70°C	[redacted] 42-1402	[redacted] 60-1411E

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-311-0101	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	63 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1125A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	62 days at −70°C	1092 days at −70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1125B
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	73 days at −70°C	1297 days at −60°C to −80°C	Gilead 15401v9	[redacted] 60-1125C
		DRV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	40 days at −70°C	301 days at −70°C	[redacted] 42-0902 Amendment 4	[redacted] 60-1125D
		EFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	40 days at −70°C	1301 days at −70°C	[redacted] 42-0827 Amendment 3	[redacted] 60-1125E
		COBI	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	48 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1125F
GS-US-311-1387	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	42 days at −70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1557A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	39 days at −70°C	1092 days at –70°C	[redacted] 60-1368 Amendment 2	[redacted] 60-1557B
		CBZ	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	38 days at −70°C	96 days at –70°C	[redacted] 42-1371	[redacted] 60-1557D
		CBZE	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	38 days at −70°C	96 days at –70°C	[redacted] 42-1371	[redacted] 60-1557D

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-311-1388	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	21 days at −70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1531A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	23 days at −70°C	344 days at –70°C	[redacted] 60-1435 Amendment 4	[redacted] 60-1531B
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	23 days at −70°C	340 days at –70°C	[redacted] 42-0831 Amendment 6	[redacted] 60-1531C
		ATV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	22 days at −70°C	721 days at –70°C	[redacted] 42-0830 Amendment 5	[redacted] 60-1531D
		COBI	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	19 days at −70°C	1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1531E
GS-US-311-1473	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	48 days at −70°C	520 days at −70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1443A Amendment 1
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	46 days at −70°C	190 days at −20°C, 340 days at −70°C, and 1426 days at −80°C	[redacted] 42-0831 Amendment 6	[redacted] 60-1443B Amendment 1
		EVG	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	48 days at −70°C	585 days at -70°C and 1297 days at −60°C to −80°C	[redacted] 60-1343 Amendment 2	[redacted] 60-1443C Amendment 1

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-311-1790	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	18 days at −70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1526A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	16 days at −70°C	344 days at –70°C	[redacted] 60-1435 Amendment 4	[redacted] 60-1526B
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	15 days at −70°C	340 days at –70°C	[redacted] 42-0831 Amendment 6	[redacted] 60-1526C
		BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	15 days at −70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1526D
		Norgestrel/ Norgestimate	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	63 days at −70°C	618 days at –70°C	[redacted] 42-1226 Amendment 1	[redacted] 60-1526E
		17-Desacetyl Norgestimate	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	49 days at −70°C	153 days at –70°C	[redacted] 42-1502 Amendment 1	[redacted] 60-1526F
		Ethinyl Estradiol	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	66 days at −70°C	182 days at –70°C	[redacted] 42-0931 Amendment 1	[redacted] 60-1526G
GS-US-320-0101	Human Plasma	TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	161 days at −70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1152A
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	255 days at −70°C	1092 days at –70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1152B
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	356 days at −70°C	340 days at −70°C	[redacted] 42-0831 Amendment 6	[redacted] 60-1152C Amendment 1

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-320-0108	Human Plasma	TAF	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	480 days at −70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1356A Amendment 1
		TFV	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	557 days at −70°C	1092 days at –70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1356B Amendment 2
		TFV	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	543 days at −70°C	340 days at −70°C	[redacted] 42-0831 Amendment 6	[redacted] 60-1356C Amendment 2
	Human PBMCs	TFV-DP[c]	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	528 days at −70°C	345 days at −70°C	[redacted] 60-1574 Amendment 4	[redacted] 60N-1356D Amendment 1
GS-US-320-0110	Human Plasma	TAF	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	506 days at −70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1357A Amendment 1
		TFV	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	576 days at −70°C	1092 days at –70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1357B Amendment 2
		TFV	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	573 days at −70°C	340 days at −70°C	[redacted] 42-0831 Amendment 6	[redacted] 60-1357C Amendment 2
	Human PBMCs	TFV-DP[c]	[redacted]20 Through [redacted]20	[redacted]20 Through [redacted]20	447 days at −70°C	345 days at −70°C	[redacted] 60-1574 Amendment 4	[redacted] 60N-1357D Amendment 1
GS-US-320-1615	Human Plasma	TAF	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	119 days at −70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1489A
		TFV	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	126 days at −70°C	1092 days at –70°C	[redacted] 60-1116 Amendment 3	[redacted] 60-1489B
GS-US-380-1489	Human Plasma	BIC	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	305 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1599
		TAF	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	348 days at –70°C	520 days at –70°C	[redacted] 60-1578 Amendment 1	[redacted] 60-1599B
		FTC	[redacted]20 through [redacted]20	[redacted]20 through [redacted]20	285 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-1599C

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-380-1490	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	309 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-15101
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	352 days at –70°C	520 days at –70°C	[redacted] 60-1578 Amendment 1	[redacted] 60-15101B
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	295 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-15101C
GS-US-380-1761	Human Plasma	SOF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	37 days at –70°C	174 Days at -20°C and 813 days at -70°C	[redacted] 60-1323 Amendment 5	[redacted] 60-1550A
		GS-566500				174 Days at -20°C and 747 days at -70°C		
		GS-331007				174 Days at -20°C and 813 days at -70°C		
		LDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	35 days at –70°C	623 days at –20°C and –70°C	[redacted] 60-1433 Amendment 3	[redacted] 60-1550B
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	22 days at –70°C	520 days at –70°C	[redacted] 60-1115 Amendment 6	[redacted] 60-1550C
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	27 days at –70°C	464 days at –20°C and –70°C	[redacted] 60-1435 Amendment 4	[redacted] 60-1550D
		BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	25days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1550E
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	25 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-1550F

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-380-1844	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	316 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-15103
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	281 days at –70°C	520 days at –70°C	[redacted] 60-1578 Amendment 1	[redacted] 60-15103B
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	294 days at –70°C	190 days at -20°C and 340 days at -70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-15103C
GS-US-380-1878	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	299 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-15104
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	289 days at –70°C	520 days at –70°C	[redacted] 60-1578 Amendment 1	[redacted] 60-15104B
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	281 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-15104C
GS-US-380-1991	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	70 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1645A
		TAF	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	77 days at –70°C	520 days at –70°C	[redacted] 60-1578 Amendment 1	[redacted] 60-1645B
		TFV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	69 days at –70°C	21 Days at -20°C and 745 Days at -70°C	[redacted] 60-1435 Amendment 4	[redacted] 60-1645C
		FTC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	71 days at –70°C	190 days at –20°C and 340 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-1645D

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-380-1999	Human Plasma	SOF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	35-days at –70°C	174 Days at -20°C and 813 days at -70°C	[redacted] 60-1323 Amendment 5	[redacted] 60-1609A
		GS-566500				174 Days at -20°C and 747 days at -70°C		
		GS-331007				174 Days at -20°C and 813 days at -70°C		
		VEL	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	34 days at –70°C	1302 days at –20°C and 1315 days at –70°C	[redacted] 60-1393 Amendment 2	[redacted] 60-1609B
		BIC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	33 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1609C
		TAF	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	33 days at –70°C	520 days at –70°C	[redacted] 60-1578 Amendment 1	[redacted] 60-1609D
		TFV	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	31 days at –70°C	464 days at –20°C and –70°C	[redacted] 60-1435 Amendment 4	[redacted] 60-1609E
		FTC	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	28 days at –70°C	161 days at –20°C and 570 days at –70°C	[redacted] 42-1410 Amendment 1	[redacted] 60-1609F
		VOX	[redacted] 20[redacted] through [redacted] 20[redacted]	[redacted] 20[redacted] through [redacted] 20[redacted]	33 days at –70°C	420 days at –20°C and –70°C	[redacted] 8109.123113.1	[redacted] 10527.043016.1

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a]	Supporting LTSS Data	Current Validation/ LTSS Report[b]	Sample Analysis Report[b]
GS-US-380-3908	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	30 days at –70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1647
		Metformin	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	42 days at –70°C	367 days at –20°C and –70°C	[redacted] ARMET1 ARMET1.A1 ARMET1.A2 ARMET1.A3 ARMET1.A4 ARMET1.A5	[redacted] 32531-1
	Human Whole Blood	Metformin	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	68 days at –70°C	87 days at –20°C and 127 days at –70°C	[redacted] ARMET3	[redacted] 32531-3
	Human Urine	Metformin	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	49 days at –70°C	589 days at –20°C and –70°C	[redacted] ARMET2 ARMET2.A1 ARMET2.A2	[redacted] 32531-2
GS-US-380-3909	Human Plasma	BIC	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	91days at -70°C	731 days at –20°C and –70°C	[redacted] 60-1511 Amendment 3	[redacted] 60-1627
GS-US-380-4270	Human Plasma	MDZ	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	15 days at –70°C	63 days at -20°C and 135 days at –70°C	[redacted] 42-0624 Amendment 1	[redacted] 60-16131

1′-OH MDZ = midazolam metabolite (1′-hydroxymidazolam); ATV = atazanavir; BIC= bictegravir; CBZ = carbamazepine; CBZE = carbamazepine-10,11-epoxide; COBI = cobicistat; CSR = clinical study report; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; LDV = ledipasvir; LPV = lopinavir; LTSS = long-term storage stability; MDZ = midazolam; PBMC = peripheral blood mononuclear cell; [redacted]; RPV = rilpivirine; SOF = sofosbuvir; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir diphosphate; VEL = velpatasvir; VOX = voxilaprevir

a Sample maximum transpired time is the calculated maximum time between the date of the first sample collection and the date of the last sample analysis.

b Current validation/LTSS and sample analysis reports are listed. Validation and sample analysis reports listed in the corresponding CSRs were those in effect at the time of CSR completion.

c The method was qualified as [redacted] 60N-1419 and validated as [redacted] 60-1574.

5.4. Determination of Coadministered Drugs

This section describes the bioanalytical methods used to determine the concentration of administered drugs in human plasma, urine, and whole blood and the corresponding validation data that support B/F/TAF clinical studies. The current versions of the validation reports are listed and are cumulative of all previous versions, with the exception of the validation report for Study FTC-108 ([redacted] V-01-BIO-TP0260-01). Validation reports cited in the corresponding CSRs were those in effect at the time of CSR completion.

Bioanalytical methods are described here in alphabetical order.

5.4.1. Determination of 17-Desacetyl Norgestimate in Human Plasma

A commercial bioanalytical method for determination of 17-desacetyl norgestimate in human plasma was developed and validated at [redacted]. This method involved the liquid-liquid extraction of 17-desacetyl norgestimate and its internal standard (17-desacetyl norgestimate-d_6) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 4.

Appendix Table 4. Bioanalytical Method Validation for Determination of 17-Desacetyl Norgestimate in Human Plasma ([redacted] 42-1502)

	17-Desacetyl Norgestimate
Calibrated Range (ng/mL)	0.02 to 10
Interassay Precision Range (%CV)	2.1 to 3.6
Interassay Accuracy Range (%RE)	–3.3 to 1.8
Studies Supported	GS-US-311-1790

Source: [redacted] 42-1502 Amendment 1

5.4.2. Determination of Atazanavir in Human Plasma

A commercially available atazanavir (ATV) bioanalytical method was developed at [redacted] for the simultaneous determination of ATV and ritonavir (RTV) in human plasma. RTV was not analyzed in the supported studies. The method involved the extraction of ATV and its internal standard (ATV-d_5) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 5.

Appendix Table 5. Bioanalytical Method Validation for Determination of ATV in Human Plasma ([redacted] 42-0830)

	ATV
Calibrated Range (ng/mL)	10 to 5000
Interassay Precision Range (%CV)	3.8 to 5.5
Interassay Accuracy Range (%RE)	−2.4 to −0.1
Studies Supported	GS-US-120-0118, GS-US-141-1485, GS-US-311-1388

Source: [redacted] 42-0830 Amendment 5

5.4.3. Determination of Carbamazepine in Human Plasma

A commercial bioanalytical method for determination of CBZ and carbamazepine-10,11-epoxide (CBZE) in human plasma was developed and validated at [redacted]. This method involved protein precipitation extraction of CBZ and CBZE and internal standards (CBZ-d_{10} and CBZE-d_{10}, respectively) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 6.

Appendix Table 6. Bioanalytical Method Validation for Determination of Carbamazepine and Carbamazepine-10,11-epoxide in Human Plasma ([redacted] 42-1371)

	Carbamazepine (CBZ)	Carbamazepine-10,11-epoxide (CBZE)
Assay Range (ng/mL)	20 to 20,000	5 to 5000
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-311-1387	

Source: [redacted] 42-1371

5.4.4. Determination of Darunavir in Human Plasma

A commercial bioanalytical method for determination of darunavir (DRV) in human plasma was developed and validated at [redacted]. This method involved protein precipitation extraction of DRV and its internal standard (DRV-d_9) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 7.

Appendix Table 7. Bioanalytical Method Validation for Determination of DRV in Human Plasma ([redacted] 42-0902)

	DRV
Calibrated Range (ng/mL)	20 to 10,000
Interassay Precision Range (%CV)	2.8 to 10.6
Interassay Accuracy Range (%RE)	−3.9 to −1.0
Studies Supported	GS-US-120-0118, GS-US-141-1485, GS-US-311-0101

Source: [redacted] 42-0902 Amendment 4

5.4.5. Determination of Dolutegravir in Human Plasma

A commercial bioanalytical method for the determination of dolutegravir (DTG) in human plasma was validated at [redacted]. This method involved the protein precipitation extraction of DTG and internal standard ([^{13}C,$^{2}H_5$]DTG) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 8.

Appendix Table 8. Bioanalytical Method Validation for Determination of DTG in Human Plasma ([redacted] 42-1369)

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

Source: [redacted] 42-1369 Amendment 2

5.4.6. Determination of Efavirenz in Human Plasma

A 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 ($^{13}C_6$-efavirenz) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 9.

Appendix Table 9. Bioanalytical Method Validation for Determination of EFV in Human Plasma ([redacted] 42-0827)

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

Source: [redacted] 42-0827 Amendment 3

5.4.7. Determination of Ethinyl Estradiol in Human Plasma

A commercial bioanalytical method for determination of ethinyl estradiol in human plasma was developed and validated at [redacted]. This method involved the liquid-liquid extraction of ethinyl estradiol and its internal standard (ethinyl estradiol-d_4) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 10.

Appendix Table 10. Bioanalytical Method Validation for Determination of Ethinyl Estradiol in Human Plasma ([redacted] 42-0931)

	Ethinyl Estradiol
Calibrated Range (ng/mL)	0.0025 to 0.5
Interassay Precision Range (%CV)	3.8 to 7.9
Interassay Accuracy Range (%RE)	–4.1 to 1.2
Studies Supported	GS-US-311-1790

Source: [redacted] 42-0931 Amendment 1

5.4.8. Determination of Elvitegravir and Cobicistat in Human Plasma

A combined elvitegravir (EVG) and cobicistat (COBI) bioanalytical method was developed and validated at [redacted] for the determination of EVG and COBI in human plasma. The method involved the extraction of EVG, COBI, and stable isotope internal standards (EVG-d_8 and COBI-d_8, respectively) from human plasma using SPE, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 11.

Appendix Table 11. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma ([redacted] 60-0949)

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

Source: [redacted] 60-0949 Amendment 6

A combined EVG and COBI bioanalytical method was developed and validated at [redacted] using an improved liquid chromatographic separation method to support the F/TAF program. This method involved protein precipitation extraction of EVG, COBI, and stable isotope internal standards (EVG-d_8 and COBI-d_8, respectively) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 12.

Appendix Table 12. Bioanalytical Method Validation for Determination of EVG and COBI in Human Plasma ([redacted] 60-1343)

	EVG	COBI
Calibrated Range (ng/mL)	20 to 10,000	5 to 2500
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-141-1485 (COBI only), GS-US-292-0112, GS-US-292-1316, GS-US-311-1388 (COBI only), GS-US-311-1473	

Source: [redacted] 60-1343 Amendment 2

5.4.9. Determination of Iohexol in Human Plasma

The commercial iohexol bioanalytical method involving the extraction of iohexol and its internal standard iohexol- d_{10}) from human plasma using protein precipitation extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted] ([redacted], USA). Bioanalytical validation parameters are summarized in Appendix Table 13.

Appendix Table 13. Bioanalytical Method Validation for Determination of Iohexol in Human Plasma ([redacted] 2100-775)

	Iohexol
Calibrated Range (ng/mL)	1,000 to 500,000
Interassay Precision Range (%CV)	4.2 to 8.3
Interassay Accuracy Range (%RE)	−5.5 to 5.0
Studies Supported	GS-US-141-1487, GS-US-292-0112

Source: [redacted] 2100-775 Addendum 9

5.4.10. Determination of Ledipasvir in Human Plasma

The ledipasvir (LDV) bioanalytical method was developed and validated at [redacted]. The method involved protein precipitation extraction of LDV and internal standard (LDV-d_{16}) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 14.

Appendix Table 14. Bioanalytical Method Validation for Determination of LDV in Human Plasma ([redacted] 60-1433)

	LDV
Calibrated Range (ng/mL)	1 to 2000
Interassay Precision Range (%CV)	3.2 to 9.2
Interassay Accuracy Range (%RE)	−6.9 to 0.4
Studies Supported	GS-US-380-1761

Source: [redacted] 60-1433 Amendment 3

5.4.11. Determination of Lopinavir in Human Plasma

A lopinavir (LPV) bioanalytical method was developed and validated at [redacted] for the simultaneous determination of LPV and RTV in human plasma. RTV was not analyzed in the supported study. The method involved the protein precipitation extraction of LPV and internal standard (LPV-d_8) from human plasma followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 15.

Appendix Table 15. Bioanalytical Method Validation for Determination of LPV in Human Plasma ([redacted] 42-1359)

	LPV
Calibrated Range (ng/mL)	100 to 20,000
Interassay Precision Range (%CV)	1.2 to 1.4
Interassay Accuracy Range (%RE)	–6.3 to –3.3
Studies Supported	GS-US-120-0118

Source: [redacted] 42-1359 Amendment 1

5.4.12. Determination of Metformin in Plasma, Urine, and Whole Blood

Bioanalytical methods for determination of metformin in plasma, whole blood, and urine were developed and validated by [redacted] ([redacted], USA). Bioanalytical method validation parameters are summarized in Appendix Table 16.

The method for quantification of metformin in plasma (ARMET1) involved protein precipitation extraction of metformin and internal standard metformin-d_6 from human plasma (K_2EDTA), followed by LC-MS/MS.

The method for quantification of metformin in urine (ARMET2) involved liquid-liquid extraction of metformin and internal standard metformin-d_6 from human urine, followed by LC-MS/MS.

The method for quantification of metformin in whole blood (ARMET3) involved protein precipitation extraction of metformin and internal standard metformin-d_6 from human whole blood (K_2EDTA), followed by LC-MS/MS.

Appendix Table 16. Bioanalytical Method Validation for Determination of Metformin in Human Plasma, Urine, and Whole Blood ([redacted] ARMET1, ARMET2, and ARMET3)

	Metformin		
Parameter	**Plasma**	**Whole Blood**	**Urine**
Calibrated Range (ng/mL)	10.0 to 2500	10.0 to 2500	30.0 to 6000
Interassay Precision (%CV)	≤ 4.19	≤ 8.55	≤ 2.54
Interassay Accuracy Range (%RE)	−6.21 to −0.521	1.38 to 6.84	0.847 to 1.63
Studies Supported	GS-US-380-3908		

Source: [redacted] ARMET1, [redacted] ARMET1.A1, [redacted] ARMET1.A2, [redacted] ARMET1.A3, [redacted] ARMET1.A4, [redacted] ARMET1.A5, ARMET3, [redacted] ARMET2, [redacted] ARMET2.A1, [redacted] ARMET2.A2

5.4.13. Determination of Midazolam and 1'-Hydroxymidazolam 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 (MDZ-d_4 and 1′-OH MDZ-d_4, respectively) from human plasma using liquid-liquid extraction followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Appendix Table 17.

Appendix Table 17. Bioanalytical Method Validation for Determination of MDZ and 1'-OH MDZ in Human Plasma ([redacted] 42-0624)

	MDZ	**1′-OH MDZ**
Calibrated Range (ng/mL)	0.1 to 100	0.1 to 100
Interassay Precision Range (%CV)	2.4 to 7.1	3.0 to 8.2
Interassay Accuracy Range (%RE)	−2.7 to −1.0	−3.0 to −1.3
Studies Supported	GS-US-120-1538, GS-US-380-4270 (MDZ only)	

Source: [redacted] 42-0624 Amendment 1

5.4.14. Determination of Norgestrel and Norgestimate in Human Plasma

A commercial bioanalytical method for determination of norgestrel and norgestimate in human plasma was developed and validated at [redacted]. This method involved the liquid-liquid extraction of norgestrel and norgestimate and internal standards norgestrel-d_6 and norgestimate-d_6 from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 18.

Appendix Table 18. Bioanalytical Method Validation for Determination of Norgestrel and Norgestimate in Human Plasma ([redacted] 42-1226)

	Norgestrel	Norgestimate
Calibrated Range (ng/mL)	0.02 to 20	0.05 to 50
Interassay Precision Range (%CV)	1.3 to 5.6	1.8 to 3.8
Interassay Accuracy Range (%RE)	–2.3 to 4.3	–10.8 to 5.8
Studies Supported	GS-US-311-1790	

Source: [redacted] 42-1226 Amendment 1

5.4.15. Determination of Penciclovir in Human Plasma and Urine

The bioanalytical method for the determination of penciclovir in human plasma and urine was developed and validated at Gilead. The method involved protein precipitation extraction of penciclovir and its internal standard (acyclovir) from human plasma and urine followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 19.

Appendix Table 19. Bioanalytical Method Validation for Determination of Penciclovir in Human Plasma and Urine ([redacted] V-01-BIO-TP0260-01)

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

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

5.4.16. Determination of Rifampicin in Human Plasma

A commercial bioanalytical method for determination of rifampicin in human plasma was developed and validated at [redacted]. This method involved liquid-liquid extraction of rifampicin and its internal standard (rifampicin-d_8) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 20.

Appendix Table 20. Bioanalytical Method Validation for Determination of Rifampicin in Human Plasma (42-1219)

	Rifampicin
Calibrated Range (ng/mL)	20 to 10,000
Interassay Precision Range (%CV)	1.5 to 3.5
Interassay Accuracy Range (%RE)	–4.4 to 1.6
Studies Supported	GS-US-141-1485

Source: 42-1219

5.4.17. Determination of Rilpivirine in Human Plasma

A commercial bioanalytical method for determination of rilpivirine (RPV) in human plasma was developed and validated at . This method involved liquid-liquid extraction of RPV and its internal standard (RPV-d_6) from human plasma, followed by LC-MS/MS with positive ionization Bioanalytical method validation parameters are summarized in Appendix Table 21.

Appendix Table 21. Bioanalytical Method Validation for Determination of RPV in Human Plasma (42-1102)

	RPV
Calibrated Range (ng/mL)	1 to 500
Interassay Precision Range (%CV)	2.8 to 5.7
Interassay Accuracy Range (%RE)	–7.2 to 2.2
Studies Supported	GS-US-120-0117

Source: 42-1102 Amendment 3

A commercial bioanalytical method for determination of RPV in human plasma was developed and validated at . This method involved liquid-liquid extraction of RPV and its internal standard (RPV-d_6) from human plasma, followed by LC/MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 22.

Appendix Table 22. Bioanalytical Method Validation for Determination of RPV in Human Plasma (42-1408)

	RPV
Assay Range (ng/mL)	1 to 500
Interassay Precision Range (%CV)	3.4 to 4.9
Interassay Accuracy Range (%RE)	–3.5 to -2.3
Studies Supported	GS-US-120-1554

Source: 42-1408

5.4.18. Determination of Sertraline in Human Plasma

A commercially available sertraline bioanalytical method involving the extraction of sertraline and its internal standard (sertraline-d_3) from human plasma using protein precipitation followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Appendix Table 23.

Appendix Table 23. Bioanalytical Method Validation for Determination of Sertraline in Human Plasma ([redacted] 42-1402)

	Sertraline
Calibrated Range (ng/mL)	0.2 to 200
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

5.4.19. Determination of Sofosbuvir, GS-566500, and GS-331007 in Human Plasma

The bioanalytical method for determination of sofosbuvir (SOF) and its 2 predominant human metabolites, GS-566500 and GS-331007, in human plasma was later improved and validated at [redacted]. This method involved protein precipitation extraction of SOF, GS-566500, and GS-331007 and internal standards (SOF-d_4, GS-566500-d_4, and GS-331007-d_4) from human plasma, followed by LC/MS/MS with negative ionization. Bioanalytical method validation parameters are summarized in Appendix Table 24.

Appendix Table 24. Bioanalytical Assay Validation for SOF, GS-566500 and GS-331007 in Human Plasma ([redacted] 60-1323)

	SOF	GS-566500	GS-331007
Calibrated range (ng/mL)	5 to 2500	10 to 5000	10 to 5000
Interday precision range (%CV)	2.4 to 9.7	5.1 to 7.7	2.5 to 7.2
Interday accuracy range (%RE)	−5.1 to 3.4	−2.2 to 2.9	−1.0 to 2.5
Studies Supported	GS-US-380-1761, GS-US-380-1999		

Source: [redacted] 60-1323 Amendment 5

5.4.20. Determination of Tacrolimus in Human Whole Blood

A commercially available tacrolimus bioanalytical method involving the extraction of tacrolimus and its internal standard (FR900520) from human whole blood using protein precipitation, followed by LC-MS/MS with positive ionization was developed and validated at [redacted]. Bioanalytical method validation parameters are summarized in Appendix Table 25.

Appendix Table 25. Bioanalytical Method Validation for Determination of Tacrolimus in Human Whole Blood (6332-138 Original and Amendment 1)

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

Source: 6332-138 Amendment 1

5.4.21. Determination of Velpatasvir in Human Plasma

A bioanalytical method for determination of velpatasvir (VEL) in human plasma was developed and validated at . This method involved the liquid-liquid extraction of VEL and its internal standard (VEL-$^{13}C_6$) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 26

Appendix Table 26. Bioanalytical Method Validation for Determination of VEL in Human Plasma (60-1393)

	VEL
Calibrated Range (ng/mL)	1 to 1000
Interassay Precision Range (%CV)	1.6 to 3.8
Interassay Accuracy Range (%RE)	−2.0 to 4.5
Studies Supported	GS-US-380-1999

Source: 60-1393 Amendment 2

5.4.22. Determination of Voriconazole and Voriconazole N-oxide in Human Plasma

A bioanalytical method for quantitation of voriconazole and voriconazole N-oxide in human K_2EDTA plasma was initially developed and validated at . Voriconazole N-oxide was not analyzed in the supported study. The method involved liquid-liquid extraction of voriconazole and voriconazole N-oxide and their internal standards (ketoconazole and fluconazole, respectively) from human plasma, followed by LC-MS/MS with positive ionization. Bioanalytical method validation parameters are summarized in Appendix Table 27.

Appendix Table 27. Bioanalytical Method Validation for Determination of Voriconazole in Human Plasma (42-0725)

	Voriconazole
Calibrated Range (ng/mL)	20 to 20,000
Interassay Precision Range (%CV)	5.7 to 11.8
Interassay Accuracy Range (%RE)	–4.9 to 6.1
Studies Supported	GS-US-141-1485

Source: 42-0725 Amendment 1

5.4.23. Determination of Voxilaprevir in Human Plasma

A bioanalytical method for quantitation of voxilaprevir (VOX) in human plasma was initially developed and validated at [redacted]. The method involved protein precipitation extraction of VOX and internal standard GS-646906 (D_9-VOX) from human plasma, followed by LC-MS/MS with negative ionization. Bioanalytical method validation parameters are summarized in Appendix Table 28.

Appendix Table 28. Bioanalytical Method Validation for Determination of VOX in Human Plasma (InVentiv 8109.123113.1)

	VOX
Calibrated Range (ng/mL)	0.5 to 1000
Interassay Precision Range (%CV)	5.10 to 9.29
Interassay Accuracy Range (%RE)	4.00 to 5.33
Studies Supported	GS-US-380-1999

Source: [redacted] 8109.123113.1

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.2—SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ΔΔQTc	time-matched, baseline-adjusted, placebo-corrected QT interval corrected for heart rate
ΔΔQTcF	time-matched, baseline-adjusted, placebo-corrected QT interval corrected for heart rate using the Fridericia formula
$\Delta Glucose_{60}$	mean glucose level at 60 minutes post-glucose ingestion
ΔQTcF	time-matched and baseline-adjusted QT interval corrected for heart rate using the Fridericia formula
µCi	microcurie(s)
3TC or LAM	lamivudine
AAUCMB	average area under the curve minus baseline
ABC	abacavir
ABC/3TC	abacavir/lamivudine (coformulated)
ADME	absorption, distribution, metabolism, and excretion
ADV-R	adefovir dipivoxil resistance
AE	adverse event
AF	assay failure
aGFR	actual glomerular filtration rate
AIDS	acquired immunodeficiency syndrome
ANOVA	analysis of variance
AR_AUC	accumulation ratio of AUC
AR_C_{max}	accumulation ratio of C_{max}
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AUC	area under the plasma concentration versus time curve
AUC_{gluc}	area under the serum glucose concentration-time curve
AUC_{inf}	area under the plasma concentration versus time curve extrapolated to infinite time
AUC_{last}	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval
$AUC_{x\text{-}xx}$	partial area under the concentration versus time curve from time “x” to time “xx”
AUC_{XX}	area under the plasma concentration versus time curve from time zero to time XX
BA	bioavailability
BCRP	breast cancer resistance protein
BE	bioequivalence
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated)
BID	twice daily
BL	baseline
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
BSA	body surface area

/co	boosted with cobicistat
CatA	cathepsin A
CBZ	carbamazepine
CCR5	chemokine (C-C motif) receptor 5
CC_{XX}	concentration that resulted in XX% cytotoxicity
CD4	cluster determinant 4
CES1	carboxylesterase 1
CHB	chronic hepatitis B
CI	confidence interval
CL_{cr}	creatinine clearance
CL/F	apparent oral clearance after administration of the drug
$CL_{iohexol}$	plasma clearance of iohexol
CL_R	renal clearance
CL_{ss}/F	apparent oral clearance at steady state after administration of the drug
C_{max}	maximum observed concentration of drug
$C_{max, ss}$	maximum observed concentration of drug at steady state
$C_{max, ss}$	minimum observed concentration of drug at steady state
COBI; C	cobicistat (GS-9350; Tybost®)
CPT	Child-Pugh-Turcotte
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval
CV	coefficient of variation
CYP	cytochrome P450
D_1	sequential zero-order
$DAVG_{11}$	time-weighted averaged change from baseline at Day 11
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir
EC_{50}	half-maximal effective concentration
EC_{95}	95% effective concentration
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
ECG	electrocardiogram
ED_{50}	dose that produced a therapeutic response in 50% of subjects
EE	ethinyl estradiol
EFV	efavirenz
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
E_{max}	concentration for maximum antiviral/pharmacodynamic effect
ETV	entecavir
ETV-R	entecavir resistance
EVG; E	elvitegravir (Vitekta®)
FAS	Full Analysis Set

FDA	Food and Drug Administration
FDC	fixed-dose combination
f_{eXX}	fraction of dose recovered in urine during the XX hours postdose
FSH	follicle-stimulating hormone
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FTC; F	emtricitabine (Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
FTC-TP	emtricitabine 5′-triphosphate
F_u	percent unbound
GFR	glomerular filtration rate
Gilead	Gilead Sciences
GLP-1	glucagon-like peptide 1
GLSM	geometric least-squares mean
G_{max}	maximum glucose concentration
G_{mean60}	mean blood glucose level during the first 60 minutes after glucose ingestion
GS-331007	metabolite of sofosbuvir
GS-566500	metabolite of sofosbuvir
H2RA	H2-receptor antagonist
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV, HIV-1, HIV-2	human immunodeficiency virus, type 1, type 2
IAS-USA	International Antiviral Society-USA
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IC_{XX}	concentration that resulted in XX% inhibition
IN	integrase
INSTI	integrase strand-transfer inhibitor
INSTI-R	integrase strand-transfer inhibitor resistance
IQ	inhibitory quotient
IQR	interquartile range
ISS	Integrated Summary of Safety
IV	intravenous
k_a	first order absorption rate constant
LAM-R	lamivudine resistance
LDV	ledipasvir
LDV/SOF	ledipasvir/sofosbuvir (coformulated; Harvoni®)
LH	luteinizing hormone
LPV/r	ritonavir-boosted lopinavir
m	module
MATE1	multidrug and toxin extrusion protein 1
MDZ	midazolam
mGFR	measured glomerular filtration rate

mtDNA	mitochondrial DNA
N or n	number of subjects in a population (N) or subset (n)
NA	not applicable
ND	not determined; no data available; or not done
NG	norgestrel
NGM	norgestimate
NGMN	norelgestromin (17-desacetyl norgestimate)
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OAT	organic anion transporter
OATP	organic anion transporter protein
OAV	oral antiviral
OC	oral contraceptive
OCT2	organic cation transporter 2
OGTT	oral glucose tolerance test
$paEC_{95}$	protein-adjusted 95% effective concentration
$paIC_{95}$	protein-adjusted concentration that results in 95% inhibition
$paIQ_{95}$	protein-adjusted inhibitory quotient of 95%
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PMPA	tenofovir (see TFV)
pol/RT	polymerase/reverse transcriptase
PPI	proton pump inhibitor
PR	protease
PXR	pregnane X receptor
Q1, Q2, Q3, Q4	first quartile, second quartile, third quartile, fourth quartile
QD	once daily
Q/F	intercompartmental clearance
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
QTcI	QT interval corrected for heart rate using the individual correction formula
QTcN	QT interval corrected for heart rate using population-specific correction factor
-R	resistant
RAL	raltegravir
RAM	resistance-associated mutation

RAP	Resistance Analysis Population
rBA	relative bioavailability
RBT	rifabutin
R/F/TAF	emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®)
RIF	rifampin
RNA	ribonucleic acid
RPV	rilpivirine
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SBR	stay on baseline regimen
SD	standard deviation
SDM	site-directed mutant, site-directed mutagenesis
SOF	sofosbuvir
SOF/VEL	sofosbuvir/velpatasvir (coformulated)
SOF/VEL/VOX	sofosbuvir/velpatasvir/voxilaprevir (coformulated)
$SrCL_R$	renal clearance by tubular secretion, estimated as the difference between CL_R of the drug and mGFR
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
$t_{1/2}$	estimated terminal elimination half-life of the drug in plasma
TAF	tenofovir alafenamide (Vemlidy®)
TAM	thymidine analog mutation
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
T_{lag}	absorption lag time
T_{max}	time (observed time point) of C_{max}
$T_{max, ss}$	time (observed time point) of C_{max} at steady-state
UGT	uridine diphosphate glucuronosyltransferase
US, USA	United States, United States of America
V_c/F	apparent volume of central compartment
VEL	velpatasvir
VF	virologic failure
VORI	voriconazole
VOX	voxilaprevir (GS-9857)
V_p/F	apparent volume of peripheral compartment
V_{ss}	steady-state volume of distribution
V_z/F	apparent volume of distribution of the drug
ZDV	zidovudine

1. BACKGROUND AND OVERVIEW

1.1. Background

HIV-1 infection is a life-threatening and serious disease of major public health interest, with approximately 37 million people infected worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. Standard of care for the treatment of HIV-1 infection uses combination antiretroviral (ARV) therapy (ART) to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either an integrase strand-transfer inhibitor (INSTI), the nonnucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine (RPV), or the boosted protease inhibitor (PI), darunavir (DRV) {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}.

Bictegravir (BIC; B [previously referred to as GS-9883]) is a potent INSTI that is being evaluated for the treatment of HIV-1 infection {Gallant 2016} and that has demonstrated a terminal half-life suitable for once daily administration without a boosting agent. In a Phase 2 study of ART-naive HIV-infected subjects, BIC was compared with the guideline-recommended INSTI, dolutegravir (DTG) {Sax 2017}. When coadministered with the guideline-recommended N(t)RTI backbone, emtricitabine (FTC; F) and tenofovir alafenamide (TAF), each INSTI demonstrated high ARV activity, with no virologic failures due to resistance and both treatments were safe and well tolerated. Gilead Sciences (Gilead) has coformulated BIC with FTC and TAF into a fixed-dose combination (FDC) tablet. The bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) FDC may provide a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV infection.

Clinical studies of B/F/TAF and its components as single agents or in FDCs considered pertinent to describe the pharmacokinetics (PK), pharmacodynamics (PD), and virology within the context of B/F/TAF are discussed in this Summary of Clinical Pharmacology.

This document includes new data that has not been previously submitted as part of a marketing application in any region, including studies conducted with BIC and studies conducted with B/F/TAF. These studies are further described in Section 1.2.3.1.

Data are also provided from previous marketing applications, including studies conducted with TAF, emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF; Genvoya®); FTC; and emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; Truvada®). Data from these studies have been previously reviewed by regulatory authorities in the context of a marketing application in at least 1 region. These studies are further described in Section 1.2.3.2.

This document is organized as follows:

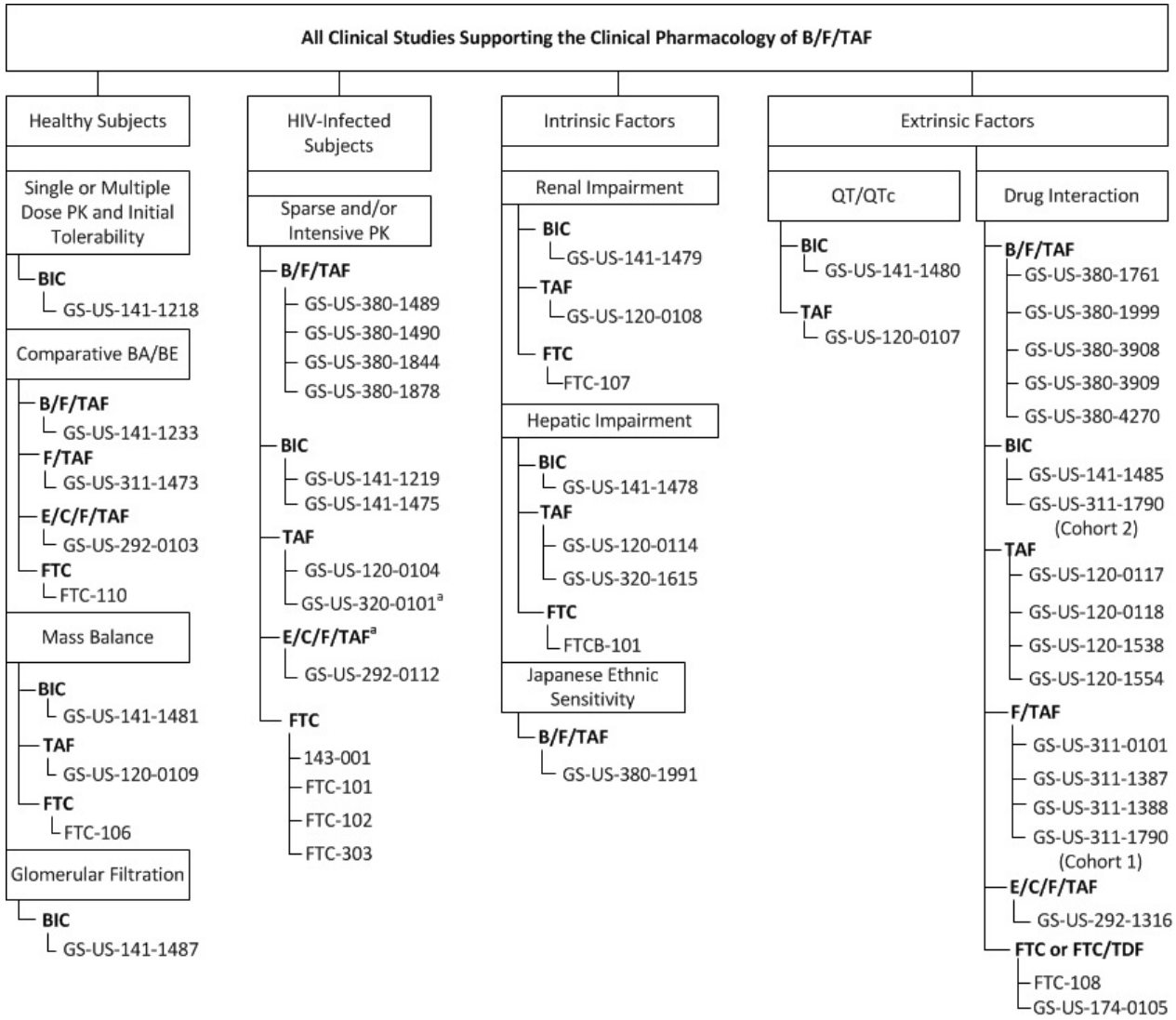
- An overview of the data presented in this module supporting the clinical pharmacology and virology of B/F/TAF in the remainder of Section 1.
- Summaries of individual clinical studies are provided in Section 2.
- The clinical pharmacology of B/F/TAF and its components is characterized in Section 3.
  - Section 3.1 presents the absorption, metabolism, distribution, and elimination (ADME) characteristics of BIC, TAF, and FTC as single agents as determined through in vitro or nonclinical and clinical studies.
  - Section 3.2 presents PK across various populations and the effects of intrinsic and extrinsic factors, including the following:
    - Section 3.2.3.3 describes the effect of renal impairment on the PK of BIC, TAF, and FTC.
    - Section 3.2.3.4 describes the effect of hepatic impairment on the PK of BIC, TAF, and FTC.
    - Section 3.2.4.1 describes the effect of food on B/F/TAF exposure.
    - Section 3.2.4.2 describes known and potential drug-drug interactions (DDIs) for B/F/TAF.
  - Section 3.3 describes the PK/PD relationships, with efficacy and safety parameters discussed in Sections 3.3.2 and 3.3.3, respectively.
- The nonclinical and clinical virology of B/F/TAF and its components are characterized in Sections 4.1 and 4.1.1, respectively.

Pharmacokinetic studies related to biopharmaceutics are referenced in this summary and are discussed in detail in the Summary of Biopharmaceutic Studies (m2.7.1).

1.2. Clinical Pharmacology Introduction

A comprehensive program of 49 clinical studies characterized the PK of B/F/TAF and its components BIC, FTC, and TAF. Figure 1 shows the studies conducted to evaluate the PK of B/F/TAF and studies conducted with BIC, TAF, F/TAF, E/C/F/TAF, FTC, and FTC/TDF to evaluate their contribution to the clinical pharmacology profile of B/F/TAF.

Figure 1. Clinical Studies Supporting the Clinical Pharmacology of B/F/TAF by Study Type and Study Drug



a Intensive PK sampling was conducted in PK substudies.

1.2.1. Human Biomaterials Studies

Studies pertinent to the PK of B/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.

1.2.2. Bioanalytical Methods

The bioanalytical methods used for the determination of plasma or urine concentrations of BIC, TAF, tenofovir (TFV), and FTC during the clinical development programs for B/F/TAF, BIC, TAF, and FTC are described in m2.7.1, Section 1.3. An overview of the validated bioanalytical methods used for the determination of plasma or urine concentrations of BIC, TAF, TFV, and FTC, as well as all other relevant analytes, as applicable, in the individual clinical studies is provided in m2.7.1, Appendix 5.2.

1.2.3. Clinical Studies with BIC, B/F/TAF, TAF, F/TAF, E/C/F/TAF, FTC, and FTC/TDF Contributing Information to the Summary of Clinical Pharmacology of B/F/TAF

1.2.3.1. Studies Supporting the Clinical Pharmacology of BIC and B/F/TAF

Figure 2 and Table 1 summarize the 21 studies conducted with BIC or B/F/TAF to characterize the clinical pharmacology of BIC and B/F/TAF. Additional information on these studies is available in the study narratives in Section 2 and in tabular summaries of clinical pharmacology studies in Appendix 6.1. Information regarding BIC, B/F/TAF, and F/TAF formulations used throughout clinical development is provided in m2.7.1.

Figure 2. Summary of BIC and B/F/TAF Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of B/F/TAF by Study Type

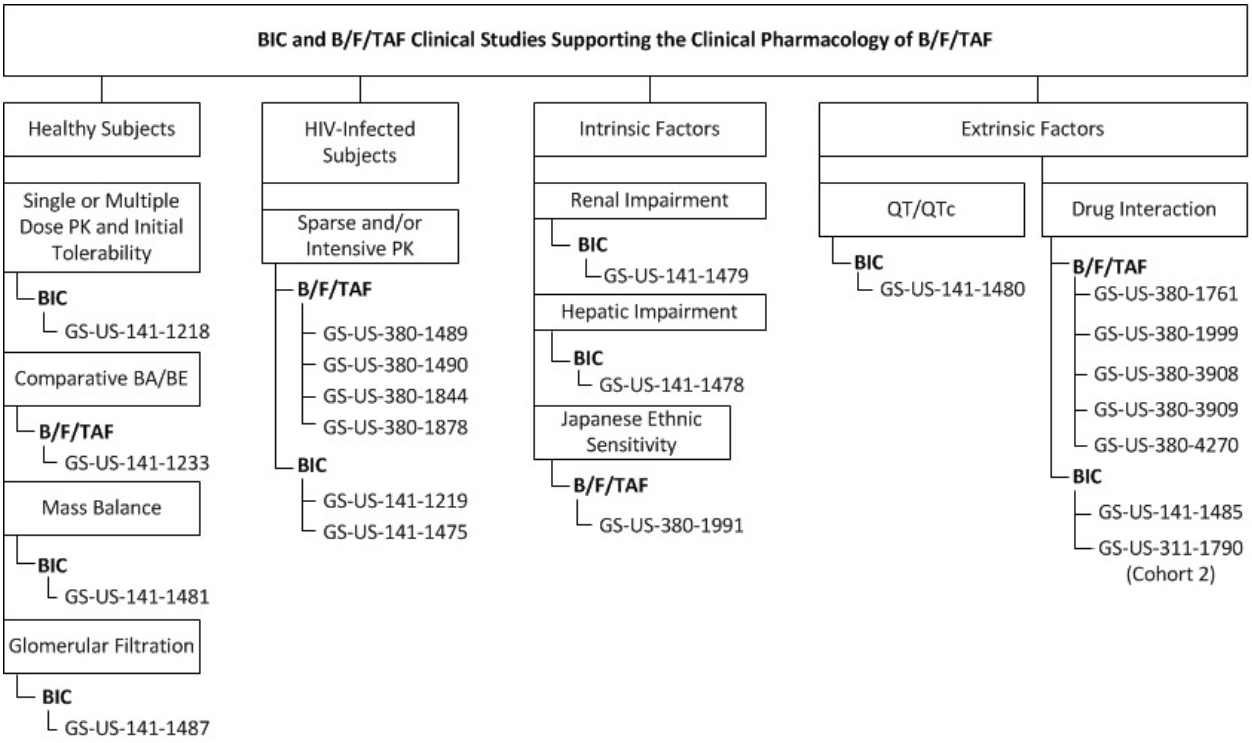


Table 1. Overview of BIC and B/F/TAF Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of B/F/TAF

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-141-1218, Section 2.2.2.1	Phase 1 placebo-controlled study to evaluate the safety, tolerability, and PK of single- and multiple-ascending doses of BIC and the DDI potential between BIC and F/TAF in healthy subjects	**BIC** 5-mg tablet ([redacted]), 25-mg tablet ([redacted]), 50 mg (2 × 25-mg tablets), 100-mg tablet ([redacted]), 300 mg (3 × 100-mg tablets), 600 mg (6 × 100-mg tablets) **F/TAF** 200/25-mg tablet ([redacted])	130	**Placebo-to-match BIC**
GS-US-141-1219, Section 2.3.1.1	Phase 1b placebo-controlled study to evaluate the safety, PK, and short-term antiviral activity of BIC compared with placebo-to-match in HIV-infected subjects	**BIC** 5-mg tablet ([redacted]), 25-mg tablet ([redacted]), 50 mg (2 × 25-mg tablets), 100-mg tablet ([redacted])	20	**Placebo-to-match BIC**
GS-US-141-1475, m2.7.3, Section 2.1.3	Phase 2, randomized, double-blinded study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF	**BIC** 75-mg tablet ([redacted]) + **F/TAF** 200/25-mg tablet ([redacted]) **B/F/TAF** 50/200/25-mg tablet ([redacted])	98	**DTG** 50-mg tablet + **F/TAF** 200/25-mg tablet **Placebo-to-match BIC**
GS-US-141-1478, Section 2.4.2.1	Phase 1 study to evaluate the PK of single-dose BIC in subjects with normal or impaired hepatic function	**BIC** 75-mg tablet ([redacted])	20	Not applicable
GS-US-141-1479, Section 2.4.2.2	Phase 1 study to evaluate the PK of single-dose BIC in subjects with normal or impaired renal function	**BIC** 75-mg tablet ([redacted])	18	Not applicable
GS-US-141-1480, Section 2.2.2.2	Phase 1 placebo- and positive-controlled study to evaluate the effects of BIC (at therapeutic and supratherapeutic doses) on ΔΔQTcF in healthy subjects	**BIC** 75-tablet ([redacted]) and 300 mg (4 × 75-mg tablets)	48	**Placebo-to-match BIC** **Moxifloxacin** 400-mg tablet

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-141-1481, Section 2.2.2.3	Phase 1 mass balance study to evaluate the PK, metabolism, and excretion of a single oral dose of radiolabeled [^{14}C]BIC in healthy male subjects	**BIC** 100 mg (99 mg of nonradiolabeled BIC [as GS-9883-01] plus approximately 100 µCi [1 mg] radiolabeled [^{14}C]GS-9883 administered orally as an approximately 40-mL ethanolic solution) ([redacted] and [redacted], [redacted], and [redacted])	8	Not applicable
GS-US-141-1485, Section 2.5.2.1	Phase 1 study to evaluate the effects of the probe drugs, ATV +COBI (a mixed inhibitor of UGT1A1/CYP3A4/P-gp), RIF (a CYP3A4/P-gp/UGT1A1 inducer), ATV (a UGT1A1/CYP3A4 inhibitor), VORI (a CYP3A4 inhibitor), RBT (a CYP3A4/P-gp inducer), and DRV/co (a CYP3A4 inhibitor) on the PK and safety of BIC in healthy subjects	**BIC** 75 mg (3 × 25-mg tablets) ([redacted]) + **ATV** 300-mg capsule + **COBI** 150-mg tablet **BIC** 75 mg (3 × 25-mg tablets) ([redacted]) + **RIF** 600 mg (2 × 300-mg capsules) **BIC** 75 mg (3 × 25-mg tablets) ([redacted]) + **ATV** 400 mg (2 × 200-mg capsules) **BIC** 75 mg (3 × 25-mg tablets) ([redacted]) + **VORI** 300 mg (2 × 50-mg tablets + 1 × 200-mg tablet) **BIC** 75-mg tablet ([redacted]) or 3 × 25-mg tablets ([redacted]) + **RBT** 300 mg (2 × 150-mg capsules) **BIC** 75-mg tablet ([redacted]) or 3 × 25-mg tablets ([redacted]) + **DRV/co** 800/150-mg tablet	90	**BIC** 75-mg tablet or 3 × 25-mg tablets
GS-US-141-1487, Section 2.2.2.4	Phase 1 placebo-controlled study to evaluate the effect of BIC on renal function as assessed by markers of GFR in healthy subjects	**BIC** 75-mg tablet ([redacted])	40	**Placebo-to-match BIC**
GS-US-311-1790 (Cohort 2)[c], Section 2.5.2.2	Phase 1 study to evaluate the effect of BIC on the PK of a representative hormonal contraceptive medication, NGM/EE (Ortho Tri-Cyclen® Lo), in healthy women of childbearing age	**BIC** 75-mg tablet ([redacted]) + **Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/EE 0.025 mg	16	**Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/EE 0.025 mg

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-141-1233, Section 2.2.1.1	Phase 1 study to evaluate the relative bioavailability of 2 B/F/TAF FDC tablets (75/200/25 mg and 50/200/25 mg) compared with BIC 75-mg + F/TAF 200/25 mg administered simultaneously under fasted conditions and of the effect of food on the PK of BIC, FTC, and TAF when administered as the B/F/TAF FDC in healthy subjects	**B/F/TAF** 75/200/25-mg tablet ([redacted]) **B/F/TAF** 50/200/25-mg tablet ([redacted])	56	**F/TAF** 200/25-mg tablet **BIC** 75-mg tablet
GS-US-380-1489, m2.7.3, Section 2.1.1	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs ABC/DTG/3TC	**B/F/TAF** 50/200/25-mg tablet ([redacted]) **Placebo-to-match ABC/DTG/3TG** ([redacted])	308	**ABC/DTG/3TG** 600/50/300-mg tablet **Placebo-to-match B/F/TAF**
GS-US-380-1490, m2.7.3, Section 2.1.2	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	**B/F/TAF** 50/200/25-mg tablet ([redacted]) **Placebo-to-match DTG** ([redacted]) **Placebo-to-match F/TAF** ([redacted])	98	**DTG** 50-mg tablet + **F/TAF** 200/25-mg tablet **Placebo-to-match B/F/TAF**
GS-US-380-1844, m2.7.3, Section 2.2.1	Phase 3, randomized, double-blinded study to evaluate the safety and efficacy of switching to B/F/TAF from DTG+ABC/3TC or ABC/DTG/3TC vs continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC	**B/F/TAF** 50/200/25-mg tablet ([redacted]) **Placebo-to-match ABC/DTG/3TG** ([redacted])	563	**ABC/DTG/3TG** 600/50/300-mg tablet **Placebo-to-match B/F/TAF**

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-380-1878, m2.7.3, Section 2.2.2	Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching to B/F/TAF vs continuing on boosted ATV or DRV plus either FTC/TDF or ABC/3TC	**B/F/TAF** 50/200/25-mg tablet ([redacted])	577	Current ARV drug regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally once daily with food. Investigators provided a prescription for the ARV treatment, and subjects were responsible for obtaining the medication
GS-US-380-1991, Section 2.4.1.1	Phase 1 study to investigate the steady-state PK of B/F/TAF in healthy Japanese and Caucasian subjects	**B/F/TAF** 50/200/25-mg tablet ([redacted])	50	Not applicable
GS-US-380-1761, Section 2.5.1.1	Phase 1 study to evaluate the steady-state PK of BIC, FTC, TAF, its metabolite TFV, and to evaluate the steady-state PK of SOF, its metabolites GS-566500 and GS-331007, and LDV after administration of LDV/SOF+B/F/TAF in healthy subjects	**LDV/SOF** 90/400-mg tablet + **BIC/F/TAF** 75/200/25-mg tablet ([redacted])	30	**LDV/SOF** 90/400-mg tablet **B/F/TAF** 75/200/25-mg tablet
GS-US-380-1999, Section 2.5.1.2	Phase 1 study to evaluate the DDI potential between B/F/TAF and SOF/VEL/VOX in healthy subjects	**B/F/TAF** 50/200/25-mg tablet ([redacted]) + **SOF/VEL/VOX** 400/100/100-mg tablet + **VOX** 100-mg tablet	30	**B/F/TAF** 50/200/25-mg tablet **SOF/VEL/VOX** 400/100/100-mg tablet + **VOX** 100-mg tablet
GS-US-380-3908, Section 2.5.1.3	Phase 1 placebo-controlled study to assess the effect of B/F/TAF on metformin PK and PD in healthy subjects	**B/F/TAF** 50/200/25-mg tablet ([redacted]) **Metformin** 500-mg tablet and 850-mg tablet	32	**B/F/TAF placebo-to-match** **Metformin** 500-mg tablet and 850-mg tablet

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-380-3909, Section 2.5.1.4	Phase 1 study to evaluate the effect on BIC PK of simultaneous administration of antacid, calcium, or iron supplements with B/F/TAF compared with administration of B/F/TAF alone under fasted and fed conditions and evaluate the effect on BIC PK of staggered administration of B/F/TAF and antacid, calcium, or iron supplements compared with administration of B/F/TAF alone in healthy subjects	**B/F/TAF** 50/200/25-mg tablet ([redacted]) + **Maximum strength antacid** 20 mL oral suspension **B/F/TAF** 50/200/25-mg tablet ([redacted]) + **Calcium carbonate** 2 × 600-mg tablets **B/F/TAF** 50/200/25-mg tablet ([redacted]) + **Ferrous fumarate** 324-mg tablet	42	**B/F/TAF** 50/200/25-mg tablet
GS-US-380-4270, Section 2.5.1.5	Phase 1 study to evaluate the effect of BIC when administered as the B/F/TAF on the PK of the CYP3A probe MDZ in healthy subjects	**B/F/TAF** 50/200/25-mg tablet ([redacted]) **MDZ** 2-mg oral syrup	14	**MDZ** 2-mg oral syrup

a Lot number provided only for BIC, FTC, or TAF-containing products.
b Number of subjects who were administered any test treatment.
c The study information for Study GS-US-311-1790 (Cohort 2) is provided in this table. The study information for Study GS-US-311-1790 (Cohort 1) is provided in Table 2.

1.2.3.2. Studies Supporting the Clinical Pharmacology of TAF and FTC

The clinical pharmacology of FTC and TAF is characterized using data from 28 clinical studies conducted with TAF, F/TAF, E/C/F/TAF, FTC, and FTC/TDF as presented in the following sections.

Table 2 summarizes the clinical studies conducted with TAF, F/TAF, E/C/F/TAF, FTC, and FTC/TDF contributing information to this Summary of Clinical Pharmacology.

Table 2. Overview of TAF, F/TAF, E/C/F/TAF, FTC, and FTC/TDF Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of B/F/TAF

Study Number	Study Description	Test Treatment(s)		Reference Treatment(s)
		Dose and Formulation (Lot Number[a])	n[b]	Dose and Formulation
TAF				
GS-US-120-0104	Phase 1 proof-of-concept study to evaluate the short-term antiviral potency, safety, and tolerability of TAF versus TDF in HIV-infected subjects who had not received ART within 90 days prior to screening	**TAF** 8-mg tablet ([redacted]) **TAF** 25-mg tablet ([redacted]) **TAF** 40-mg tablet ([redacted])	25	**TDF** 300-mg tablet Placebo-to-match TAF tablet
GS-US-120-0107	Phase 1 study to evaluate the effect of TAF on QT/QTc interval in healthy subjects	**TAF** 25-mg tablet ([redacted]) 5 × **TAF** 25-mg tablet ([redacted])	58	5 × placebo-to-match TAF **Moxifloxacin** 400-mg tablet
GS-US-120-0108	Phase 1 study to evaluate the PK and safety of TAF in subjects with or without renal impairment	**TAF** 25-mg tablet ([redacted], [redacted], [redacted])	27	Not applicable
GS-US-120-0109	Phase 1 mass balance study to evaluate TAF ADME in healthy subjects	**TAF** [^{14}C]-labeled, 25-mg capsule (each containing a mixture of unlabeled TAF and 100 µCi [^{14}C]TAF) ([^{14}C]TAF: [redacted]; TAF: [redacted]; Capsules: [redacted])	8	Not applicable
GS-US-120-0114	Phase 1 study to evaluate the PK and safety of TAF in subjects with or without impaired hepatic function	**TAF** 25-mg tablet ([redacted])	40	Not applicable
GS-US-120-0117	Phase 1 single-dose study to evaluate the DDI potential between RPV and TAF in healthy subjects	**TAF** 25-mg tablet ([redacted]) + **RPV** 25-mg tablet	36	**TAF** 25-mg tablet **RPV** 25-mg tablet

Study Number	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-120-0118	Phase 1 study to evaluate the DDI potential between TAF and boosted PIs or unboosted INSTI in healthy subjects	**TAF** 10-mg tablet ([redacted]) + **FTC** 200-mg capsule **ATV** 300-mg capsule + **RTV** 100-mg tablet 2 × **DRV** 400-mg tablet + **RTV** 100-mg tablet **LPV/r** 4 × 200/50-mg tablet **DTG** 50-mg tablet	40	**TAF** 10-mg tablet + **FTC** 200-mg capsule **ATV** 300-mg capsule + **RTV** 100-mg tablet 2 × **DRV** 400-mg tablet + **RTV** 100-mg tablet **LPV/r** 4 × 200/50-mg tablet **DTG** 50-mg tablet
GS-US-120-1538	Phase 1 study to evaluate the DDI potential between MDZ and TAF in healthy subjects	**TAF** 25-mg tablet ([redacted]) + **MDZ** 2.5-mg oral syrup **TAF** 25-mg tablet ([redacted]) + **MDZ** 1-mg solution for injection	18	**TAF** 25-mg tablet **MDZ** 1-mg solution
GS-US-120-1554	Phase 1 study to evaluate the DDI potential between RPV and TAF in healthy subjects	**TAF** 25-mg tablet ([redacted]) + **RPV** 25-mg tablet	34	**TAF** 25-mg tablet **RPV** 25-mg tablet
GS-US-320-0101	Phase 1b study to evaluate the safety, viral kinetics, and anti-HBV activity of TAF in subjects with CHB infection	**TAF** 8-mg tablet ([redacted], [redacted], [redacted], [redacted]) **TAF** 25-mg tablet ([redacted], [redacted], [redacted], [redacted]) 1 × **TAF** 40-mg tablet and 3 × **TAF** 40-mg tablet ([redacted], [redacted], [redacted] and [redacted])	41	**TDF** 300-mg tablet
GS-US-320-1615	Phase 1 study to evaluate the PK and safety of TAF in subjects without CHB infection, with or without severe hepatic impairment	**TAF** 25-mg tablet ([redacted])	20	Not applicable

Study Number	Study Description	Test Treatment(s)		Reference Treatment(s)
		Dose and Formulation (Lot Number[a])	n[b]	Dose and Formulation
F/TAF				
GS-US-311-0101	Phase 1 study to evaluate the DDI potential between various ARVs (including EFV) and F/TAF in healthy subjects	**F/TAF** 200/40-mg tablet ([redacted]) + **EFV** 600-mg tablet **F/TAF** 200/25-mg tablet ([redacted]) + 2 × **DRV** 400-mg tablet **+ COBI** 150-mg tablet **TAF** 8-mg tablet ([redacted]) + **COBI** 150-mg tablet	50	**F/TAF** 200/40-mg tablet **F/TAF** 200/25-mg tablet 2 × **DRV** 400-mg tablet + **COBI** 150-mg tablet **TAF** 8-mg tablet
GS-US-311-1387	Phase 1 study to evaluate the DDI potential between CBZ and TAF administered as F/TAF in healthy subjects (Part A)	**F/TAF** 200/25-mg tablet ([redacted]) + **CBZ** 3 × 100 mg tablets BID	22	**F/TAF** 200/25-mg tablet **CBZ** 1 × 100 mg tablet BID **CBZ** 2 × 100 mg tablets BID **CBZ** 3 × 100 mg tablets BID
GS-US-311-1388	Phase 1 study to evaluate the DDI potential between F/TAF and ATV+COBI in healthy subjects	**ATV** 300-mg tablet + **COBI** 150-mg tablet + **F/TAF** 200/10-mg tablet ([redacted])	20	**F/TAF** 200/10-mg tablet ATV 300-mg tablet COBI 150-mg tablet
GS-US-311-1473	Phase 1 study to evaluate the bioequivalence of FTC and TAF administered as F/TAF FDC tablet or as E/C/F/TAF FDC tablet in healthy subjects	**F/TAF** 200/25-mg tablet ([redacted])	116	**E/C/F/TAF** 150/150/200/10-mg tablet
GS-US-311-1790 (Cohort 1)[c]	Phase 1 study to evaluate the effect of F/TAF on the PK of a representative hormonal contraceptive medication, NGM/EE (Ortho Tri-Cyclen Lo), in healthy women of childbearing age	**F/TAF** 200/25-mg tablet ([redacted]) + **Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/ EE 0.025 mg	15	**Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/EE 0.025 mg

Study Number	Study Description	Test Treatment(s)		Reference Treatment(s)
		Dose and Formulation (Lot Number[a])	n[b]	Dose and Formulation
E/C/F/TAF				
GS-US-292-0103	Phase 1 study to evaluate the rBA of EVG, COBI, FTC, TAF, and TFV between E/C/F/TAF and FTC+TAF or EVG+COBI in healthy subjects	**E/C/F/TAF** 150/150/200/10-mg tablet ([redacted])	33	EVG 150-mg tablet + COBI 150-mg tablet FTC 200-mg capsule + TAF 25-mg tablet
GS-US-292-0112	Phase 3 study to evaluate the safety and efficacy of E/C/F/TAF in HIV-infected subjects with mild to moderate renal impairment	**E/C/F/TAF** 150/150/200/10-mg tablet ([redacted])	248	Not applicable
GS-US-292-1316	Phase 1 study to evaluate the DDI potential between sertraline and E/C/F/TAF in healthy subjects	**Sertraline** 50-mg tablet + **E/C/F/TAF** 150/150/200/10-mg tablet ([redacted])	19	**Sertraline** 50-mg tablet **E/C/F/TAF** 150/150/200/10-mg tablet
FTC or FTC/TDF				
143-001	Phase 1 study to evaluate the safety, tolerability, and PK of single-ascending doses of FTC in HIV-infected subjects	**FTC** 100-mg capsule ([redacted]) 2 × **FTC** 100-mg capsule ([redacted]) 4 × **FTC** 100-mg capsule ([redacted]) 8 × **FTC** 100-mg capsule ([redacted]) 12 × **FTC** 100-mg capsule ([redacted])	12	Placebo-to-match FTC
FTC-101	Phase 1 study to evaluate the safety, tolerability, PK and antiviral activity of multiple-ascending doses of FTC in HIV-infected subjects	**FTC** 25-mg capsule ([redacted]) **FTC** 100-mg capsule ([redacted]) 2 × **FTC** 100-mg capsule ([redacted])	41	Not applicable
FTC-102	Phase 1 study to evaluate the safety and antiviral activity of FTC versus 3TC in HIV-infected subjects	**FTC** 25-mg capsule ([redacted]) **FTC** 100-mg capsule ([redacted]) 2 × **FTC** 100-mg capsule ([redacted])	60	**3TC** 150-mg tablet
FTC-106	Phase 1 mass balance study to evaluate FTC ADME in healthy subjects	**FTC** 200-mg in oral solution containing 250 µCi [14C]FTC ([redacted])	6	2 × **FTC** 100-mg capsule

Study Number	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
FTC-110	Phase 1 study to evaluate the absolute bioavailability of FTC in healthy subjects	**FTC** 200-mg capsule ([redacted]) **FTC** 10-mg/mL oral solution ([redacted]) **FTC** 10-mg/mL IV solution ([redacted])	12	Not applicable
FTC-303	Phase 3 study to evaluate the efficacy and safety of FTC versus 3TC in virologically suppressed, HIV-infected subjects	2 × **FTC** 100-mg capsule ([redacted]) + background ARV regimen	294	**3TC** 150-mg tablet + background ARV regimen
FTC-107	Phase 1 study to evaluate the PK of FTC in non-HIV-infected subjects with various degrees of renal insufficiency	2 × **FTC** 100-mg capsule ([redacted])	29	Not applicable
FTCB-101	Phase 1 study to evaluate the safety, tolerability, antiviral activity, and PK of FTC in HBV-infected, non-HIV-infected subjects	**FTC** 25-mg capsule ([redacted]) 2 × **FTC** 25-mg capsule ([redacted]) **FTC** 100-mg capsule ([redacted]) 2 × **FTC** 100-mg capsule ([redacted]) 3 × **FTC** 100-mg capsule ([redacted])	49	Not applicable
FTC-108	Phase 1 study to evaluate the DDI potential between FTC and famciclovir	**FTC** 2 × 100-mg capsule ([redacted]) **Famciclovir** 500-mg tablet **FTC** 2 × 100-mg capsule ([redacted]) + **Famciclovir** 500-mg tablet	12	Not applicable
GS-US-174-0105	Phase 1 study to evaluate the DDI potential between FTC and tacrolimus	**FTC/TDF** 200/300-mg tablet ([redacted]) + **Tacrolimus** 0.5-mg or 1.0-mg capsules	27	**FTC/TDF** 200/300-mg tablet **Tacrolimus** 0.5-mg or 1.0-mg capsules

Study-level data for TAF, F/TAF, E/C/F/TAF, FTC, and FTC/TDF are provided separately.
a Lot number provided only for TAF-containing products.
b Number of subjects who were administered any test treatment.
c The study information for Study GS-US-311-1790 (Cohort 1) is provided in this table. The study information for Study GS-US-311-1790 (Cohort 2) is provided in Table 1.

1.2.4. Absorption, Distribution, Metabolism, and Elimination

Results from pertinent in vitro or in vivo nonclinical studies and clinical studies for the ADME, including DDI liability, of B/F/TAF and its components are described in Section 3.1.

1.2.5. Pharmacokinetics

A comprehensive program of Phase 1 clinical studies characterized the PK of B/F/TAF and its components. The results of the intensive PK analyses in healthy and HIV-infected subjects are discussed in Section 3.2.1.

Results of the population PK analyses of BIC, TAF, and FTC are discussed in Section 3.2.2. Population PK modeling was conducted using nonlinear mixed-effects modeling (NONMEM) to establish population PK models that describe the plasma PK for BIC and TAF in HIV-infected subjects receiving B/F/TAF, including identification of covariates influencing their PK.

Table 3 presents the 18 clinical studies providing data for population PK analyses. These analyses used intensive and/or sparse plasma concentration data from 11 Phase 1 studies in healthy subjects or HIV-infected subjects and 7 Phase 3 studies in HIV-infected subjects.

Table 3. Studies Used in the Population PK Analysis of BIC and TAF in Healthy Subjects and HIV-Infected Subjects

Study	Population	Formulation	Phase	Sampling	Included in Population PK Analysis
GS-US-120-0104	Treatment-Naive, HIV-Infected Subjects	TAF	1	Intense	TAF
GS-US-120-0107	Healthy Subjects	TAF	1	Intense	TAF
GS-US-120-0108	Healthy Subjects	TAF	1	Intense	TAF
GS-US-120-0117	Healthy Subjects	TAF	1	Intense	TAF
GS-US-120-0118	Healthy Subjects	TAF	1	Intense	TAF
GS-US-292-0101	Healthy Subjects	TAF	1	Intense	TAF
GS-US-311-1089	Virologically Suppressed, HIV-Infected Subjects	F/TAF	3	Sparse	TAF
GS-US-320-1228	Healthy Subjects	TAF	1	Intense	TAF
GS-US-366-1160	Virologically Suppressed, HIV-Infected Subjects	R/F/TAF	3	Sparse	TAF
GS-US-366-1216	Virologically Suppressed, HIV-Infected Subjects	R/F/TAF	3	Sparse	TAF
GS-US-380-1489	Treatment-Naive, HIV-Infected Subjects	B/F/TAF	3	Intense + Sparse	BIC+TAF
GS-US-380-1490	Treatment-Naive, HIV-Infected Subjects	B/F/TAF	3	Intense + Sparse	BIC+TAF
GS-US-141-1233	Healthy Subjects	B/F/TAF	1	Intense	BIC
GS-US-380-1844	Virologically Suppressed, HIV-Infected Subjects	B/F/TAF	3	Intense + Sparse	BIC
GS-US-380-1878	Virologically Suppressed, HIV-Infected Subjects	B/F/TAF	3	Intense + Sparse	BIC
GS-US-380-1991	Healthy Subjects	B/F/TAF	1	Intense	BIC
GS-US-380-1999	Healthy Subjects	B/F/TAF	1	Intense	BIC
GS-US-380-3909	Healthy Subjects	B/F/TAF	1	Intense	BIC

In the population PK model-building processes, various structural and error models were tested to determine base models. Subsequently, individual estimates of model parameters were obtained by Bayesian estimation and evaluated for correlations with potential covariates, including, but not limited to age, sex, body weight, body mass index (BMI), race, creatinine clearance (CL_{cr}), HIV infection status, prior HIV treatment experience, fasting/fed administration status, HBV coinfection, HCV coinfection, and usage of potential concomitant medications (eg, proton pump inhibitor [PPI], H2-receptor antagonist [H2RA]). Covariates that showed a significant ($p < 0.01$) effect on model parameters and could be meaningfully explained from a clinical or scientific perspective were examined further using NONMEM by a forward addition ($p < 0.01$) and backward deletion ($p < 0.001$) methodology to create final models with the retention of statistically significant covariates. Further details on the identification and evaluation of covariates are discussed in the respective population PK reports, BIC Population PK Report and TAF Population PK Report. Using the final models, sensitivity analyses were performed to determine the magnitude and thus clinical relevance of the model-identified statistically significant covariates on the AUC_{tau} and C_{max} of BIC and TAF and C_{tau} of BIC. The potential effect of intrinsic and extrinsic factors on PK is discussed in Sections 3.2.3 and 3.2.4, respectively.

1.2.6. Pharmacokinetics/Pharmacodynamics

The PK/PD relationships between the individual components BIC, TAF, and FTC, and various efficacy and safety parameters were evaluated in HIV-infected subjects. These PK/PD analyses for efficacy and safety are presented in Sections 3.3.2 and 3.3.3, respectively.

1.3. Virology Introduction

A comprehensive program of nonclinical experiments and clinical studies characterized the antiviral activity of B/F/TAF and its individual components.

1.3.1. Nonclinical Virology

Nonclinical virology studies characterized the antiviral activity of the B/F/TAF components, BIC, TAF, and FTC, as well as TFV and/or tenofovir disoproxil fumarate (TDF) against laboratory strains and 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:

- **Primary Pharmacodynamics:** mechanism of action, antiviral activity against HIV (wild-type and drug-resistant strains), including drug-resistance selections, and antiviral activity of TAF against hepatitis B virus (HBV) (Section 4.1.1)

- **Secondary Pharmacodynamics:** cytotoxicity and effect against host enzymes (eg, DNA polymerases and proteases) and non-HIV viruses (Section 4.1.2)

- **Pharmacodynamic drug interactions** (Section 4.1.3)

The detailed characterization of nonclinical virology is presented in the m2.6.3.

1.3.2. Clinical Virology

Clinical virology analyses were performed for subjects with HIV infection with data from 4 Phase 3 studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878). Integrated virology analyses were performed for HIV-infected subjects with clinical virology data from the 2 Phase 3 studies in ART-naive subjects (Studies GS-US-380-1489 and GS-US-380-1490). Resistance analyses were performed on plasma HIV-1 isolates from all subjects who met prespecified criteria. Results from these analyses are provided in Section 4.2.1.

Clinical virology analyses were performed for subjects with HBV monoinfection with data from 2 Phase 3 studies (Studies GS-US-320-0108 and GS-US-320-0110) and subjects with HIV/HBV coinfection with data from Study GS-US-292-1249. Results from these analyses are provided in Section 4.2.2.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

A tabular summary of clinical pharmacology studies is provided in Appendix 6.1.

Narratives summarizing clinical pharmacology results for studies that contribute information to this Summary of Clinical Pharmacology and were conducted using BIC or B/F/TAF are provided in Sections 2.2 to 2.5.

2.1. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Studies pertinent to the PK of B/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).

2.2. Studies in Healthy Subjects

2.2.1. B/F/TAF Study

2.2.1.1. Study GS-US-141-1233

Location:	GS-US-141-1233
Title:	A Phase 1, Open-label, Two-Cohort, Multiple-Period, Fixed-Sequence, Crossover Study to Evaluate 1) the Relative Bioavailability of Two GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets Versus a GS-9883 (75 mg) Tablet and a Emtricitabine/Tenofovir Alafenamide (200/25 mg) Fixed-Dose Combination Tablet Administered Simultaneously and 2) the Effect of Food on the Pharmacokinetics of GS-9883, Emtricitabine and Tenofovir Alafenamide When Administered as GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets
Primary Objective(s):	To evaluate the relative bioavailability of 2 FDC tablets containing BIC (75 mg or 50 mg), FTC 200 mg, and TAF 25 mg, compared with a 75-mg strength tablet of BIC and a 200/25-mg strength FDC tablet of F/TAF administered simultaneously under fasted conditions
Study Design and Subject Population:	This Phase 1, open-label, 2-cohort, fixed-sequence, single-dose, single-center study evaluated the relative bioavailability of the B/F/TAF 75/200/25 mg and 50/200/25 mg FDC tablets compared with the BIC 75 mg tablet and F/TAF 200/25 mg FDC tablet administered simultaneously under fasted conditions and the effect of food on the PK of BIC, FTC, and TAF when administered as the B/F/TAF FDC in healthy subjects. In Cohort 1, B/F/TAF 75/200/25 mg FDC was evaluated using a 3-period fixed treatment sequence. Subjects received single doses of BIC 75 mg + F/TAF 200/25 mg under fasted conditions on Day 1(Treatment A); B/F/TAF 75/200/25 mg FDC under fasted conditions on Day 9 (Treatment B); and B/F/TAF 75/200/25 mg FDC under fed conditions on Day 17 (high-fat meal; Treatment C), with 7-day washout periods between treatments. In Cohort 2, B/F/TAF 50/200/25 mg FDC was evaluated using a 4-period fixed treatment sequence. Subjects received single doses of BIC 75 mg + F/TAF 200/25 mg under fasted conditions on Day 1 (Treatment A); B/F/TAF 50/200/25 mg FDC under fasted conditions on Day 9 (Treatment D); B/F/TAF 50/200/25 mg FDC under fed conditions on Day 17 (high-fat meal; Treatment E); and B/F/TAF 50/200/25 mg FDC under fed conditions on Day 25 (moderate-fat meal; Treatment F), with 7-day washout periods between treatments. Eligible subjects were healthy male and nonpregnant, nonlactating female adults, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 90 mL/min, and had no significant medical history. A total of 56 subjects (28 per cohort) were enrolled in the study. All, but 1 subject received all doses of study drug and completed the study; 1 subject in Cohort 2 discontinued study drug due to withdrawal of consent.

Summary of Results and Conclusions:

Pharmacokinetic Results:

Plasma PK parameters for BIC, FTC, and TAF and the statistical comparisons for relative bioavailability between the B/F/TAF 75/200/25 FDC or B/F/TAF 50/200/25 mg FDC (referred to as the 75- or 50-mg B/F/TAF FDC in this study narrative) and BIC 75 mg + F/TAF, each administered in the fasted state, are presented in the table below. Under fasted conditions, BIC AUC_{inf} and C_{max} for the 75-mg B/F/TAF FDC were approximately 27% and 31% higher, respectively, than those observed for BIC 75 mg + F/TAF. FTC and TAF exposures were similar between the 75-mg B/F/TAF FDC and BIC 75 mg + F/TAF under fasted conditions.

The geometric least-squares mean (GLSM) ratios and their 90% CIs comparing the primary PK parameters for BIC, FTC, and TAF between the 50-mg B/F/TAF FDC and BIC 75 mg + F/TAF under fasted conditions were within the protocol-defined boundaries of equivalence (70% to 143%), with the exception of TAF C_{max}, for which the GLSM ratio (90% CI) was 84.17% (67.59%, 104.81%).

BIC exposure (AUC_{inf} and C_{max}) from the 75-mg and 50-mg B/F/TAF FDCs was approximately dose proportional when administered under fasted conditions.

The variability associated with BIC exposure following administration of the 50-mg B/F/TAF FDC was lower, irrespective of fasted or fed condition, relative to BIC 75 mg + F/TAF administered under fasted conditions.

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF 75/200/25 mg, fasted (Test) (N = 28) vs BIC 75 mg + F/TAF 200/25 mg, fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (h*ng/mL)	151,844.0 (26.9)	119,619.4 (26.6)	126.76 (117.82,136.37)
AUC_{inf} (h*ng/mL)	156,637.5 (27.5)	123,174.0 (26.6)	126.82 (117.87,136.45)
C_{max} (ng/mL)	7123.9 (21.6)	5593.9 (31.0)	130.72 (119.95,142.45)
FTC PK Parameter			
AUC_{last} (h*ng/mL)	11,412.3 (13.5)	11,199.3 (13.7)	101.89 (99.50, 104.33)
AUC_{inf} (h*ng/mL)	11,642.8 (13.2)	11,436.4 (13.2)	101.78 (99.45, 104.16)
C_{max} (ng/mL)	2264.3 (22.7)	2153.6 (21.5)	104.86 (97.73, 112.50)
TAF PK Parameter			
AUC_{last} (h*ng/mL)	205.5 (45.5)	223.6 (45.2)	91.62 (82.13, 102.21)
AUC_{inf} (h*ng/mL)	206.8 (45.2)	225.1 (45.0)	91.56 (82.27, 101.91)
C_{max} (ng/mL)	253.3 (44.2)	276.7 (51.7)	95.47 (79.88, 114.10)
B/F/TAF 50/200/25 mg, fasted (Test) (N = 27) vs BIC 75 mg + F/TAF 200/25 mg, fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (h*ng/mL)	109,061.4 (21.0)	142,396.6 (30.5)	78.46 (73.38, 83.89)
AUC_{inf} (h*ng/mL)	112,619.6 (21.9)	146,931.6 (31.1)	78.56 (73.44, 84.04)
C_{max} (ng/mL)	5228.1 (16.9)	6791.1 (26.4)	78.07 (73.41, 83.01)
FTC PK Parameter			
AUC_{last} (h*ng/mL)	10,652.9 (13.6)	11,035.5 (14.4)	96.52 (93.95, 99.15)
AUC_{inf} (h*ng/mL)	10,873.9 (13.6)	11,234.6 (14.2)	96.76 (94.22, 99.37)
C_{max} (ng/mL)	2220.4 (30.1)	2166.4 (27.0)	102.36 (93.85, 111.64)
TAF PK Parameter[a]			
AUC_{last} (h*ng/mL)	207.1 (46.5)	236.7 (45.3)	85.37 (75.24, 96.85)
AUC_{inf} (h*ng/mL)	208.8 (46.3)	238.3 (45.0)	85.48 (75.33, 97.00)
C_{max} (ng/mL)	249.2 (51.6)	291.9 (55.4)	84.17 (67.59, 104.81)

a N = 28 for both the Test and Reference groups

Plasma PK parameters for BIC, FTC, and TAF and the statistical comparisons for food effect for the 75-mg B/F/TAF FDC comparing fasted conditions to administration following a high-fat meal and for the 50-mg B/F/TAF FDC comparing fasted conditions to administration following a high-fat or moderate-fat meal are presented in the table below. Following a high-fat meal, BIC AUC_{inf} and C_{max} for the 75-mg B/F/TAF FDC were approximately 46% and 27% higher, respectively, than those observed under fasted conditions. In comparison, BIC AUC_{inf} and C_{max} for the 50-mg B/F/TAF FDC were approximately 24% and 13% higher, respectively, following a high-fat meal than under fasted conditions. With a similar food effect as the high-fat meal, the moderate-fat meal increased BIC

AUC_{inf} and C_{max} for the 50-mg B/F/TAF FDC by 24% and 20%, respectively, compared with those observed under fasted conditions. BIC exposure (AUC_{inf} and C_{max}) from the 75-mg and 50-mg B/F/TAF FDCs was approximately dose proportional when administered following a high-fat meal. A high-fat meal increased TAF AUC_{last} by 57% and 63%, respectively, for the 75-mg and 50-mg B/F/TAF FDCs compared with those observed under fasted conditions, and a moderate-fat meal increased TAF AUC_{last} by 48% for the 50-mg B/F/TAF FDC compared with that observed under fasted conditions. Food had no meaningful effect on TAF C_{max} for the 75-mg or 50-mg B/F/TAF FDC. Neither the moderate-fat nor high-fat meal altered FTC AUC, but slight decreases in FTC C_{max} were observed following administration with a high-fat meal (approximately 17% and 14% decreases for the 75-mg and 50-mg B/F/TAF FDCs, respectively).
The effect of food on FTC and TAF exposures was consistent with historical data from Study GS-US-311-1386, which evaluated food effect for F/TAF. Collectively, the observed food effects on BIC, FTC, and TAF exposures were not considered clinically significant.

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF 75/200/25 mg, high fat (Test) (N = 28) vs B/F/TAF 75/200/25 mg, fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (h*ng/mL)	216,733.1 (23.4)	151,844.0 (26.9)	144.45 (134.26, 155.40)
AUC_{inf} (h*ng/mL)	226,142.1 (24.9)	156,637.5 (27.5)	145.88 (135.58, 156.95)
C_{max} (ng/mL)	8941.1 (16.9)	7123.9 (21.6)	126.74 (116.30, 138.12)
FTC PK Parameter			
AUC_{last} (h*ng/mL)	11,483.0 (15.7)	11,412.3 (13.5)	100.34 (97.99, 102.75)
AUC_{inf} (h*ng/mL)	11,706.5 (15.6)	11,642.8 (13.2)	100.24 (97.95, 102.59)
C_{max} (ng/mL)	1872.5 (20.1)	2264.3 (22.7)	83.18 (77.53, 89.25)
TAF PK Parameter			
AUC_{last} (h*ng/mL)	315.3 (44.0)	205.5 (45.5)	156.81 (140.57, 174.94)
AUC_{inf} (h*ng/mL)	319.7 (43.1)	206.8 (45.2)	158.20 (142.14, 176.08)
C_{max} (ng/mL)	212.2 (49.4)	253.3 (44.2)	83.22 (69.63, 99.46)
B/F/TAF 50/200/25 mg, high fat (Test) (N = 27) vs B/F/TAF 50/200/25 mg, fasted (Reference) (N = 27)			
BIC PK Parameter			
AUC_{last} (h*ng/mL)	135,117.3 (21.1)	109,061.4 (21.0)	123.96 (115.91, 132.57)
AUC_{inf} (h*ng/mL)	140,032.4 (21.8)	112,619.6 (21.9)	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5936.3 (18.3)	5228.1 (16.9)	113.23 (106.45, 120.43)
FTC PK Parameter			
AUC_{last} (h*ng/mL)	10,213.0 (12.0)	10,652.9 (13.6)	96.02 (93.47, 98.65)
AUC_{inf} (h*ng/mL)	10,467.0 (11.9)	10,873.9 (13.6)	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1881.1 (24.2)	2220.4 (30.1)	85.52 (78.37, 93.31)
TAF PK Parameter[a]			
AUC_{last} (h*ng/mL)	310.3 (34.9)	207.1 (46.5)	162.62 (143.10, 184.80)
AUC_{inf} (h*ng/mL)	318.4 (32.8)	208.8 (46.3)	166.55 (146.54, 189.29)
C_{max} (ng/mL)	236.6 (65.1)	249.2 (51.6)	91.71 (73.46, 114.49)
B/F/TAF 50/200/25 mg, moderate fat (Test) (N = 27) vs B/F/TAF 50/200/25 mg, fasted (Reference) (N = 27)			
BIC PK Parameter			
AUC_{last} (h*ng/mL)	135,217.3 (22.9)	109,061.4 (21.0)	123.56 (115.53, 132.14)
AUC_{inf} (h*ng/mL)	140,197.7 (23.6)	112,619.6 (21.9)	124.06 (115.95, 132.74)
C_{max} (ng/mL)	6279.6 (18.3)	5228.1 (16.9)	119.90 (112.72, 127.53)
FTC PK Parameter			
AUC_{last} (h*ng/mL)	10,738.3 (9.8)	10,652.9 (13.6)	101.17 (98.48, 103.94)
AUC_{inf} (h*ng/mL)	10,973.3 (9.5)	10,873.9 (13.6)	101.33 (98.66, 104.06)
C_{max} (ng/mL)	1998.9 (18.4)	2220.4 (30.1)	91.84 (84.17, 100.21)
TAF PK Parameter[a]			
AUC_{last} (h*ng/mL)	290.6 (41.3)	207.1 (46.5)	148.20 (130.41, 168.41)
AUC_{inf} (h*ng/mL)	293.1 (40.9)	208.8 (46.3)	148.23 (130.42, 168.47)
C_{max} (ng/mL)	251.1 (66.7)	249.2 (51.6)	99.04 (79.33, 123.65)

a N = 28 for the Reference group

	Conclusions: • For the 75-mg B/F/TAF FDC, BIC AUC_{inf} and C_{max} under fasted conditions were approximately 27% and 31% higher, respectively, than those observed for BIC 75 mg + F/TAF. FTC and TAF exposures were similar between the 75-mg B/F/TAF FDC and BIC 75 mg + F/TAF. • For the 50-mg B/F/TAF FDC, the GLSM ratios and their 90% CIs comparing the primary PK parameters for BIC, FTC, and TAF between the 50-mg B/F/TAF FDC and BIC 75 mg + F/TAF under fasted conditions were within the protocol-defined boundary of equivalence, with the exception of TAF C_{max}, for which the lower bound of the 90% CI was narrowly outside the boundary. These results demonstrate that the 50-mg B/F/TAF FDC will provide safe and efficacious concentrations of BIC, FTC, and TAF. • Compared with fasted conditions, administration of the 75- and 50-mg B/F/TAF FDCs with a high-fat meal resulted in increases in BIC AUC_{inf} of approximately 46% and 24%, respectively, with the moderate-fat meal effecting BIC exposure for the 50-mg B/F/TAF FDC to an extent similar to the high-fat meal. The effect of food on TAF exposure was consistent with historical data, and the effect of food on FTC exposure is minimal. The food effect on BIC and TAF exposures for the 50-mg B/F/TAF FDC was not considered clinically significant. • Single doses of BIC 75 mg + F/TAF, the 75-mg B/F/TAF FDC, or the 50-mg B/F/TAF FDC were well tolerated. No deaths, serious adverse events (SAEs), Grade 3 or 4 adverse events (AEs), AEs leading to premature discontinuation of study drug, or pregnancies were reported during this study.

2.2.2. BIC Studies

2.2.2.1. Study GS-US-141-1218

Location:	GS-US-141-1218
Title:	A Phase 1, Double Blind, Randomized, Placebo-Controlled, First-in-Human, Single- and Multiple-Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Oral GS-9883 in Healthy Subjects and a Randomized, Open-Label, 2-Cohort, 3-Period, Crossover, Pharmacokinetic Study Evaluating the Drug Interaction Potential between Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet and GS-9883 in Healthy Subjects
Primary Objective(s):	• To evaluate the safety and tolerability of single- and multiple-ascending oral doses of BIC compared with placebo in healthy subjects • To evaluate the PK of BIC following single- and multiple-ascending oral doses of BIC in healthy subjects
Study Design and Subject Population:	This Phase 1 study evaluated the safety, tolerability, and PK of BIC; the effect of food on BIC PK; and the PK interaction between BIC and F/TAF and the TAF metabolite, TFV, in healthy subjects. In Part A (single-ascending dose), subjects received single doses of BIC 5, 25, 50, 100, 300, and 600 mg or placebo-to-match (randomized 6:2 in each dose cohort) on Day 1 in a blinded fashion under fasted conditions. In Part B (multiple-ascending dose), subjects received BIC 5, 25, 50, 100, and 300 mg or placebo-to-match (randomized 6:2 in each dose cohort) once daily on Days 1 to 14 in a blinded fashion under fasted conditions. In Part C (food effect), subjects received a single dose of BIC 100 mg under fasted conditions on Day 1 and single dose of BIC 100 mg under fed conditions on Day 9. In Part D (F/TAF DDI), subjects were randomized (1:1) to 1 of 2 treatment sequences (Cohort 1 or 2) and received F/TAF 200/25 mg once daily for 7 days, BIC 100 mg once daily for 7 days, and BIC 100 mg + F/TAF 200/25 mg once daily for 7 days under fed conditions, according to the assigned treatment sequence. Eligible subjects were healthy male and nonpregnant, nonlactating female adults, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ $\geq$ 90 mL/min, and had no significant medical history. A total of 130 subjects were enrolled (Part A: 48 subjects; Part B: 40 subjects; Part C: 8 subjects; Part D: 34 subjects) and received at least 1 dose of study drug. A total of 128 subjects completed study drug dosing and completed the study; 1 subject in the placebo group of Part B discontinued study drug due to AE (hepatitis) and 1 subject in Part D withdrew consent.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The BIC PK parameters following single ascending doses of BIC 5, 25, 50, 100, 300, or 600 mg under fasted conditions are presented in the table below. Maximum plasma concentrations were achieved between 1.25 and 3.50 hours (median T_{max}). The $t_{1/2}$ ranged from 16.72 to 18.90 hours and demonstrated low intersubject variability. The apparent clearance and volume of distribution were very low, consistent with in vitro and nonclinical PK data. BIC exposures were approximately dose proportional over the dose range of 25 to 100 mg, with decreasing dose proportionality at higher doses (up to 600 mg).

BIC PK Parameter, Mean (%CV)[a]	Single Dose BIC					
	5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)	600 mg (N = 6)
AUC_{inf} (h*ng/mL)	13,059.7 (25.1)	35,718.2 (21.3)	78,399.5 (29.7)	163,028.2 (24.3)	355,917.3 (32.9)	454,446.8 (19.9)
CL/F (mL/h)	398.8 (19.5)	727.5 (21.4)	675.6 (23.2)	656.2 (32.9)	936.1 (37.0)	1357.2 (16.6)
C_{max} (ng/mL)	691.2 (22.1)	1618.3 (26.7)	3965.0 (40.1)	6998.3 (36.1)	14,605.0 (27.1)	20,050.0 (7.5)
$t_{1/2}$ (h)	18.51 (16.81, 19.99)	18.08 (16.63, 19.64)	16.72 (15.77, 17.11)	18.90 (17.96, 20.05)	18.14 (17.86, 20.53)	17.89 (16.38, 19.52)
T_{max} (h)	1.25 (1.00, 1.50)	2.00 (1.00, 3.00)	3.00 (1.50, 4.00)	2.25 (1.50, 3.00)	3.50 (2.00, 6.00)	3.50 (2.00, 4.00)
V_z/F (mL)	10,312.6 (20.2)	19,038.8 (27.3)	16,701.5 (26.5)	19,834.7 (57.5)	23,228.3 (26.5)	34,770.6 (10.7)

a Data are presented as mean (%CV), except for T_{max} and $\mathbf{t_{1/2}}$, which are presented as median (Q1, Q3).

The BIC PK parameters following administration of BIC 5, 25, 50, 100, or 300 mg once daily for 7 days are presented in the table below. The PK absorption profile observed on Days 1 and 7 was similar to that observed in Part A. The median T_{max} values ranged from 1.5 to 2.5 hours on Day 1 and 1.5 to 4.0 hours on Day 7. Linearity was observed comparing BIC AUC and C_{max} on Days 1 and 7 over the dose range of 25 to 50 mg. Steady state levels of BIC were achieved between Days 4 to 6 of dosing and maintained through Day 14. Accumulation is approximately 1.6-fold, which is consistent with the observed half-life of the BIC (approximately 18 h).

	BIC PK Parameter, Mean (%CV)[a]	Multiple-Dose BIC				
		5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)
Day 1	AUC_{0-24} (h*ng/mL)	9033.6 (8.2)	27,775.1 (28.3)	58,371.4 (18.9)	79,773.8 (18.9)	180,714.3 (17.6)
	C_{max} (ng/mL)	709.7 (9.5)	2220.0 (35.6)	4648.3 (18.7)	6248.3 (26.8)	13,716.7 (19.1)
	T_{max} (h)	1.50 (1.50, 1.50)	1.75 (1.00, 3.00)	1.50 (1.00, 2.00)	2.50 (2.00, 3.00)	2.50 (2.00, 4.00)
Day 7	AUC_{tau} (h*ng/mL)	14,392.0 (16.7)	50,008.2 (26.6)	89,710.1 (22.7)	126,785.8 (23.7)	277,200.2 (16.7)
	C_{max} (ng/mL)	982.5 (7.9)	3455.0 (24.1)	6538.3 (17.6)	9396.7 (20.8)	19,900.0 (21.2)
	C_{tau} (ng/mL)	400.83 (26.9)	1322.00 (27.8)	2241.67 (28.2)	3145.00 (26.1)	6758.33 (21.6)
	T_{max} (h)	1.50 (1.00, 2.00)	3.00 (2.00, 3.00)	1.75 (1.50, 2.00)	1.75 (1.50, 3.00)	4.00 (2.00, 4.00)
	Accumulation Ratio of AUC (%)	160.5 (19.0)	182.2 (17.1)	154.0 (15.9)	158.5 (12.1)	157.5 (22.6)

a Data are presented as mean (%CV), except for T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3).

The BIC PK parameters after administration of a single dose of BIC 100 mg under fasted and fed conditions are presented in the table below. Administration of a single dose of BIC 100 mg with food (high-calorie/high-fat breakfast) increased the GLSM values of C_{max} and AUC_{inf} 101% (90% CI: 165.93% to 242.74%) and 84% (90% CI: 152.05% to 222.59%), respectively. There were no apparent changes in clearance and $t_{1/2}$ following administration with food, indicating that food enhanced the bioavailability of BIC by improving its solubility and/or absorption.

BIC PK Parameter	GLSM		% GLSM Ratio (Fed/Fasted)	90% CI
	BIC 100 mg Fed (n = 8)	BIC 100 mg Fasted (n = 8)		
AUC_{inf} (h*ng/mL)	211,500.7	114,966.1	183.97	(152.05, 222.59)
AUC_{last} (h*ng/mL)	206,941.8	112,724.6	183.58	(151.91, 221.86)
C_{max} (ng/mL)	111,59.91	5560.75	200.69	(165.93, 242.74)

The statistical comparisons of the primary PK parameters for BIC, FTC, TAF, and TFV after administration of BIC alone and in combination with F/TAF are presented in the table below. Following the administration of BIC+F/TAF, BIC exposure was not notably affected by F/TAF. The 90% CI of the GLSM ratios for each primary PK parameter evaluated were within the predefined equivalence boundaries of 70% to 143%. Similarly, the exposure of FTC and TFV were not notably affected by BIC. The C_{max} and AUC_{last} TAF following BIC+F/TAF were 37% and 30% higher, respectively, than those following F/TAF treatment alone. These differences are not considered clinically significant and F/TAF can be administered with BIC without dose adjustment.

	GLSM		% GLSM Ratio (90% CI)
	Test	Reference	
BIC PK Parameter: BIC+F/TAF (Test) (N = 34) vs BIC (Reference) (N = 34)			
AUC_{tau} (h*ng/mL)	212,852.8	210,816.0	100.97 (98.22, 103.79
C_{max} (ng/mL)	14,693.24	14,761.70	99.54 (96.41, 102.76)
C_{tau} (ng/mL)	5681.53	5553.18	102.31 (98.48, 106.29)
FTC PK Parameter: BIC+F/TAF (Test) (N = 34) vs F/TAF (Reference) (N = 33)			
AUC_{tau} (h*ng/mL)	9545.74	9363.40	101.95 (100.13, 103.80)
C_{max} (ng/mL)	1759.80	1773.33	99.24 (94.19, 104.55)
C_{tau} (ng/mL)	67.04	63.33	105.86 (101.26, 110.67)
TAF PK Parameter: BIC+F/TAF (Test) (N = 34) vs F/TAF (Reference) (N = 33)			
AUC_{last} (h*ng/mL)	352.61	272.28	129.50 (123.67, 135.61)
C_{max} (ng/mL)	277.95	203.10	136.86 (116.99, 160.09)
TFV PK Parameter: BIC+F/TAF (Test) (N = 34) vs F/TAF (Reference) (N = 33)			
AUC_{tau} (h*ng/mL)	299.66	263.52	113.72 (110.07, 117.49)
C_{max} (ng/mL)	17.66	16.01	110.30 (105.27, 115.56)
C_{tau} (ng/mL)	10.46	9.09	115.04 (110.79, 119.46)

Conclusions:

- BIC was safe and well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, or pregnancies were reported during this study; 1 subject in the placebo group prematurely discontinued study drug due to an AE of hepatitis. The safety profile for BIC did not differ with increasing doses of BIC, whether administered as a single or multiple doses, with or without food, or administered alone or coadministered with F/TAF.
- BIC PK behaved in an approximately dose proportional manner across the 25 to 100 mg dose range. There were no time-dependent differences observed in BIC PK.
- Steady state levels of BIC were achieved between Days 4 to 6 of dosing and maintained through Day 14. Accumulation is approximately 1.6-fold, which is consistent with the half-life of the compound.
- There were no apparent changes in clearance and $t_{1/2}$ following administration with food, indicating that food enhanced the bioavailability of BIC by improving its solubility and/or absorption.
- No relevant differences in BIC, FTC, TAF, and TFV PK were observed upon coadministration of BIC (100 mg) with F/TAF 200/25 mg. F/TAF may be coadministered with BIC without dose adjustment.

2.2.2.2. Study GS-US-141-1480

Location:	GS-US-141-1480
Title:	A Phase 1, Partially-Blinded, Randomized, Placebo- and Positive-Controlled Study to Evaluate the Effect of GS-9883 on the QT/QTc Interval in Healthy Subjects
Primary Objective(s):	To evaluate the effects of BIC (at therapeutic and supratherapeutic doses) on time-matched, baseline-adjusted, placebo-corrected QTc using the Fridericia formula (ΔΔQTcF)
Study Design and Subject Population:	This Phase 1, partially-blinded, randomized, placebo- and positive-controlled, 4-period, single-dose, crossover study evaluated the effects of BIC (at therapeutic and supratherapeutic doses) on ΔΔQTcF in healthy subjects. Subjects were randomized to 1 of 2 Williams squares and then 1 of 4 treatment sequences per Williams square (ABCD, BDAC, CADB, DCBA, BCAD, CDBA, ABDC, DACB; 6 subjects planned per sequence) and received the following treatments under fed conditions according to their treatment sequence: • **Therapeutic Exposure (Treatment A):** A single dose of BIC 75 mg (1 × BIC 75-mg tablet plus 3 × placebo-to-match BIC tablets) • **Supratherapeutic Exposure (Treatment B):** A single dose of BIC 300 mg (4 × BIC 75-mg tablets) • **Placebo Control (Treatment C):** A single dose of 4 × placebo-to-match BIC tablets • **Positive Control (Treatment D):** A single dose of moxifloxacin 400 mg (1 × 400-mg tablet) BIC and placebo were administered in a double-blind fashion and moxifloxacin was administered in an open-label fashion. Subjects were male and nonpregnant, nonlactating females, who were aged 18 to 45 years of age (inclusive), had a BMI from 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG} \geq 90$ mL/min, had a normal 12-lead electrocardiogram (ECG), and had no significant medical history. A total of 48 subjects were randomized into this study, and all 48 subjects received study drug and completed the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Overall, the plasma concentration-time profiles, including the median T_{max}, were similar between the 2 BIC dose levels under fed conditions, with higher BIC exposures following the 300-mg dose than following the 75-mg dose, as expected. An approximately 3.4-fold higher BIC AUC_{inf} (581,283.3 vs 171,732.1 h*ng/mL) and C_{max} (24,681.3 vs 7279.6 ng/mL) were observed with the BIC 300 mg relative to BIC 75 mg under fed conditions. The $t_{1/2}$ was similar between the 2 doses (median of approximately 18 h), with low interindividual variability. The PK parameters were consistent with historical data (Study GS-US-141-1485). The statistical analysis of dose proportionality is presented in the table below. BIC exposure was slightly less than proportional to dose under fed conditions when the dose was increased from 75 to 300 mg (4-fold). The GLSM ratios for dose-normalized C_{max} and AUC_{inf} were about 86% (using the 75-mg dose as a reference).

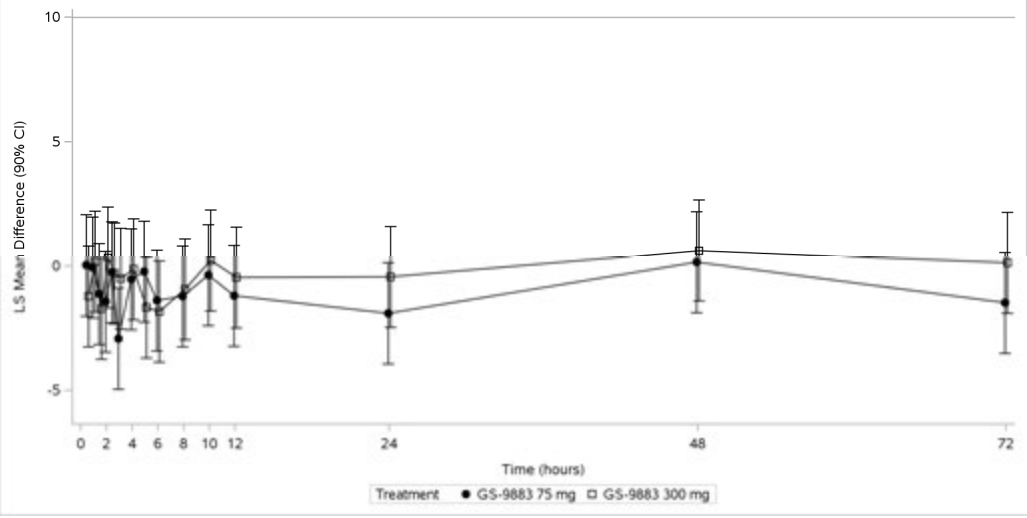
Parameter	GLSM		GLSM Ratio (%) (Test/Reference)	90% CI (%)
	BIC 300 mg (Test) (N = 48)	BIC 75 mg (Reference) (N = 48)		
$AUC_{inf}D$ (h*ng/mL)	142,587.49	166,056.64	85.87	(81.31, 90.68)
$AUC_{last}D$ (h*ng/mL)	138,579.51	161,556.80	85.78	(81.28, 90.52)
$C_{max}D$ (ng/mL)	6114.88	7143.87	85.60	(81.37, 90.05)

$AUC_{inf}D$ (Dose-normalized AUC_{inf} for 75 mg dose) = AUC_{inf} when taking BIC 75 mg or AUC_{inf} / 4 when taking BIC 300 mg; $AUC_{last}D$ (Dose-normalized AUC_{last} for 75 mg dose) = AUC_{last} when taking BIC 75 mg or AUC_{last} / 4 when taking BIC 300 mg; $C_{max}D$ (Dose-normalized C_{max} for 75 mg dose) = C_{max} when taking BIC 75 mg or C_{max} / 4 when taking BIC 300 mg (Note: 4 = 300 mg / 75 mg)
Statistical analysis for dose proportionality was based on the mixed-effect model including sequence, period, and dose as fixed effects; and subject within sequence as a random effect.

Pharmacodynamic Results:

Assay Sensitivity: ΔΔQTcF was evaluated for a single dose of moxifloxacin 400 mg to demonstrate assay sensitivity. In this analysis, the lower bound of the 2-sided 96.67% CI for the mean difference between the positive control and placebo was greater than 5 msec at 2 time points (2.5 and 4 h) after dosing, thereby establishing assay sensitivity.

Noninferiority Analyses: The noninferiority evaluation for ΔΔQTcF is presented in the figure below. For the primary endpoint analysis, BIC was concluded to have no QTcF prolongation effect, as the upper bounds of the 2-sided 90% CIs for the mean differences between therapeutic or supratherapeutic doses of BIC and placebo were less than 10 msec at all time points after dosing. Results from the analyses of secondary endpoints, evaluating changes from predose baseline in QTcB, QTcN, and QTcI, were consistent with those from the primary endpoint analysis.



Least squares means and CIs were based on the mixed-effect model including sequence, period, treatment, time point, treatment by time point interaction, and gender as fixed effects; subject within sequence as a random effect; and the predose baseline QTcF as a continuous covariate.

Categorical Analyses: Results from categorical analyses of QTcF, QTcB, QTcN, and QTcI are summarized in the table below. No subject had an absolute QTc interval > 480 msec at any postdose assessment, or a change from predose baseline QTc > 60 msec following any treatment. Two subjects had an absolute QTcB interval > 450 msec and 3 subjects had a change from predose baseline QTcB > 30 msec following a therapeutic (75 mg) or supratherapeutic (300 mg) dose of BIC.

	BIC 75 mg (N = 48)	BIC 300 mg (N = 48)	Placebo (N = 48)	Moxifloxacin (N = 48)
Observed Value				
> 500 msec	0	0	0	0
> 480 msec	0	0	0	0
> 450 msec	QTcB (n = 1)	QTcB (n = 1)	QTcF (n = 1) QTcB (n = 1) QTcN (n = 1)	QTcB (n = 2) QTcN (n = 1) QTcI (n = 3)
Change from Predose/Baseline				
> 60 msec	0	0	0	0
> 30 msec	QTcB (n = 2)	QTcB (n = 1)	QTcB (n = 1)	QTcB (n = 6)

Only subjects with treatment-emergent QTc interval prolongations (> 450, > 480, and > 500 msec) were counted as events for "Observed Value" and included in the numerator. Treatment-emergent means a subject had a QTc interval prolongation at any postdose assessment that was not present at the predose assessment.

Pharmacokinetic/Pharmacodynamic Results:

There was no consistent, pharmacologically meaningful association between ΔΔQTc and BIC plasma concentrations.

Conclusions:

- An approximately 3.4-fold higher BIC AUC_{inf} (581,283.3 vs 171,732.1 h*ng/mL) and C_{max} (24,681.3 vs 7279.6 ng/mL) were observed with the BIC 300-mg dose relative to the 75-mg dose under fed conditions. The GLSM ratios for dose-normalized C_{max} and AUC_{inf} were about 86% (using the 75-mg dose as a reference). The $t_{1/2}$ was similar between the 2 doses (median of approximately 18 h), with low interindividual variability. The PK parameters were consistent with historical data.
- The expected increase in QTc upon administration of moxifloxacin 400 mg demonstrated assay sensitivity. BIC, administered at doses of 75 and 300 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 Harmonization (ICH) guidance.
- There was no pharmacologically meaningful association between ΔΔQTcF and BIC plasma concentrations.
- Single doses of BIC administered at therapeutic (75 mg) and supratherapeutic (300 mg) doses were generally well tolerated in healthy subjects. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to premature discontinuation of study drug were reported during this study.

2.2.2.3. Study GS-US-141-1481

Location:	GS-US-141-1481
Title:	A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of GS-9883 in Healthy Subjects
Primary Objective(s):	To determine the mass balance of BIC following administration of a single, oral dose of [^{14}C]BIC
Study Design and Subject Population:	This Phase 1, open-label, single-center, mass-balance study evaluated the PK, metabolism, and excretion of BIC following administration of a single, oral dose of radiolabeled [^{14}C]BIC in healthy subjects. Subjects received a single dose of BIC 100 mg (99 mg of nonradiolabeled BIC [as GS-9883-01] plus approximately 100 µCi [1 mg] radiolabeled [^{14}C]BIC). Eligible subjects were healthy males, who were aged 18 to 45 years of age (inclusive), had a BMI from 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG} \geq 90$ mL/min, and had no significant medical history. Eight subjects were enrolled into this study; all subjects received study drug and completed the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** This mass balance study demonstrated that recovery of BIC was primarily from feces relative to urine. The cumulative mean (SD) recovery of [^{14}C]-radioactivity in feces plus urine was 95.3% (1.50%), with 60.3% (5.50%) recovered from feces and 35.0% (4.95%) recovered from urine. Most (90.9%) of the administered [^{14}C]-radioactivity was recovered in the first 120 hours postdose. Renal clearance of the unchanged parent was minimal, with about 1.3% of the BIC dose recovered in urine through 144 hours postdose. Metabolism is the major clearance pathway for BIC in humans. A total of 20 metabolites of BIC were identified by high performance liquid chromatography-mass spectrometry/TopCount method. Direct glucuronidation, hydroxylation, defluorination, dehydrogenation, and Phase II conjugation of oxidized metabolites were the major metabolic pathways for BIC. In human plasma, [^{14}C]BIC was the major circulatory radioactive component and M20 (sulfate of hydroxy-BIC) and M15 (glucuronide of BIC) were the major metabolites in plasma, accounting for approximately 67.9%, 20.1%, and 8.6%, respectively, of the plasma $AUC_{0\text{-}72h}$ of total radioactivity. In human urine, M15 (co-eluted with M58, both direct glucuronides of BIC) was the major metabolite (21.4% of dose). The radioactivity in feces samples pooled by time intervals and for individual subjects was accounted for mainly by BIC (31% to 34% of dose), the cysteine conjugate of desfluoro-hydroxy-BIC (10% to 13% of dose), hydroxy-BIC co-eluted with desfluoro-hydroxy-BIC (7% to 8% of dose for the co-eluted peak), and minor oxidation products. The levels of M21 (hydroxyl-BIC) and M22 (desfluoro-hydroxy-BIC) were similar, each ranging on average from approximately 3% to 4% of the dose in the M21/M22 mixture in feces from humans. **Conclusions:** • The total mean (SD) recovery of ^{14}C-radioactivity in feces plus urine by liquid scintillation counting was 95.3% (1.50%), with 60.3% (5.50%) recovered from feces and 35.0% (4.95%) recovered from urine. Most (90.9%) of the administered ^{14}C-radioactivity was recovered in the first 120 hours postdose. • Metabolism is the major clearance pathway for BIC. Direct glucuronidation, hydroxylation, defluorination, dehydrogenation, and Phase II conjugation of oxidized metabolites were the major metabolic pathways for BIC. • A single oral dose of BIC 100 mg, containing a mixture of unlabeled and radiolabeled [^{14}C]BIC, was well tolerated in healthy male subjects with no clinically significant safety findings in this study. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to premature discontinuation of study drug were reported during this study.

2.2.2.4. Study GS-US-141-1487

Location:	GS-US-141-1487
Title:	A Randomized, Blinded, Placebo-Controlled Phase 1 Study Evaluating the Effect of GS-9883 on Renal Function as Assessed by Markers of Glomerular Filtration Rate
Primary Objective(s):	To assess renal function before, during, and after administration of BIC versus placebo via determination of actual glomerular filtration rate (aGFR) as assessed by iohexol clearance
Study Design and Subject Population:	This Phase 1, randomized, blinded, placebo-controlled, 2-group, multiple-dose, parallel-design study evaluated the effect of BIC on renal function as assessed by markers of glomerular filtration rate (GFR) in healthy subjects. Subjects were randomized 1:1 to receive 1 of the 2 following treatments: • **BIC (Treatment A):** BIC 75 mg administered once daily on Days 1 to 14 under fed conditions • **Placebo (Treatment B):** placebo (BIC 75 mg placebo-to-match tablet) administered once daily on Days 1 to 14 under fed conditions Subjects received iohexol alone on Days -1 and 21 and coadministered with the assigned study treatment on Days 7 and 14. Eligible subjects were healthy males and nonpregnant, nonlactating females, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ ≥ 90 mL/min, and had no significant medical history. A total of 40 subjects (20 per treatment group) were randomized in the study, and all subjects completed study drug dosing and the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** BIC plasma PK parameter values were consistent with historical results and similar on Days 7 and 14, indicating that steady-state exposure to BIC was reached by Day 7. Mean (%CV) BIC PK parameter values on Days 7 and 14, respectively, were as follows: AUC_{tau} 160,084.7 (23.8)and 167,757.2 (24.9) h*ng/mL; C_{max} 12,079.5 (21.4) and 12,356.5 (21.3) ng/mL; and C_{tau} 4179.0 (29.9) and 4373.0 (32.2) ng/mL. Iohexol exposures were similar in the 2 treatment groups in this study and consistent with published values. Mean (%CV) iohexol AUC_{inf} values in the BIC and placebo groups, respectively, were 424.8 (11.3) and 432.2 (8.6) h*µg/mL on Day −1; 425.6 (11.8) and 409.4 (10.4) h*µg/mL on Day 7; 426.2 (10.4) and 417.1 (10.4) h*µg/mL on Day 14; and 431.8 (11.9) and 423.4 (10.7) h*µg/mL on Day 21. Mean (%CV) $CL_{iohexol}$ values indicated no differences in glomerular function between the 2 treatment groups, and were 128.6 (12.1) and 125.6 (8.7) mL/min on Day −1; 128.5 (13.2) and 133.0 (9.7) mL/min on Day 7; 127.9 (11.0) and 130.6 (10.6) mL/min on Day 14; and 126.6 (12.4) and 128.7 (10.8) mL/min on Day 21 in the BIC and placebo groups, respectively. Body surface area (BSA)-adjusted aGFR, $eGFR_{CG}$, and measured glomerular filtration rate (mGFR) and the comparisons with baseline on each study day within each treatment group are shown in the table below (PD Analysis Set).

Treatment	Study Day			
	Day −1[a]	Day 7	Day 14	Day 21
BIC 75 mg (n = 20)				
Mean (95% CI) BSA-Adjusted aGFR (mL/min/1.73 m^2)	119.2 (111.1, 127.3)	119.1 (111.1, 127.0)	118.5 (111.5, 125.6)	117.3 (110.2, 124.4)
GLSM Ratio[b] (90% CI) (%)	—	99.96 (97.47, 102.52)	99.64 (97.15, 102.19)	98.57 (96.12, 101.10)
Placebo (n = 20)				
Mean (95% CI) BSA-Adjusted aGFR (mL/min/1.73 m^2)	114.5 (110.0, 119.1)	120.8 (115.5, 126.0)	118.5 (113.3, 123.6)	116.7 (111.6, 121.8)
GLSM Ratio[b] (90% CI) (%)	—	105.38 (103.06, 107.75)	103.40 (101.12, 105.72)	101.80 (99.56, 104.09)
BIC 75 mg (n = 20)				
Mean (95% CI) BSA-Adjusted $eGFR_{CG}$ (mL/min/1.73 m^2)	93.4 (83.6, 103.1)	81.8 (74.0, 89.6)	88.2 (80.0, 96.4)	91.3 (82.7, 99.8)
GLSM Ratio[b] (90% CI) (%)	—	87.97 (83.96, 92.17)	94.88 (90.56, 99.41)	98.20 (93.72, 102.89)
Placebo (n = 20)				
Mean (95% CI) BSA-Adjusted $eGFR_{CG}$ (mL/min/1.73 m^2)	86.4 (80.6, 92.2)	86.7 (80.9, 92.4)	91.6 (86.9, 96.3)	89.7 (84.3, 95.2)
GLSM Ratio[b] (90% CI) (%)	—	100.33 (95.82, 105.05)	106.45 (101.66, 111.46)	104.05 (99.37, 108.95)
BIC 75 mg (n = 20)				
Mean (95% CI) BSA-Adjusted mGFR (mL/min/1.73 m^2)	121.6 (113.5, 129.6)	119.7 (99.0, 140.4)	119.3 (111.0, 127.7)	125.8 (115.4, 136.2)
GLSM Ratio[b] (90% CI) (%)	—	93.99 (84.52, 104.53)	98.12 (88.23, 109.12)	103.07 (92.68, 114.62)
Placebo (n = 20)				
Mean (95% CI) BSA-Adjusted mGFR (mL/min/1.73 m^2)	129.4 (123.3, 135.5)	138.2 (126.6, 149.9)	138.9 (132.0, 145.8)	126.8 (118.4, 135.2)
GLSM Ratio[b] (90% CI) (%)	—	105.65 (98.54, 113.27)	107.38 (100.15, 115.13)	97.54 (90.97, 104.58)

a The Day −1 (baseline) value was the last available value prior to the start of BIC or placebo dosing.
b Test / Reference. For between-visit comparisons, the Day 7, 14, or 21 value was Test and the Day −1 value was Reference.

Comparisons of BSA-adjusted aGFR, $eGFR_{CG}$, and mGFR between treatment groups on Days 7, 14, and 21 are shown in the table below (PD Analysis Set).

Study Day	GLSM		GLSM Ratio (%) Test / Reference	90% CI (%)
	BIC 75 mg (Test)	Placebo (Reference)		
BSA-Adjusted aGFR Comparisons				
Day 7	116.45	121.88	95.54	91.86, 99.38
Day 14	116.08	119.58	97.07	93.82, 100.44
Day 21	114.91	117.67	97.66	93.84, 101.63
BSA-Adjusted $eGFR_{CG}$ Comparisons				
Day 7	78.99	87.34	90.44	83.85, 97.54
Day 14	85.27	92.59	92.10	86.07, 98.54
Day 21	87.74	91.04	96.38	91.20, 101.85
BSA-Adjusted mGFR Comparisons				
Day 7	112.80	136.19	82.83	70.77, 96.94
Day 14	118.97	137.01	86.83	80.61, 93.53
Day 21	124.49	124.93	99.65	90.93, 109.20

No differences from baseline aGFR, $eGFR_{CG}$, or mGFR were observed within either treatment group on any study day. No differences in aGFR or $eGFR_{CG}$ were observed between the BIC and placebo groups on any study day. No differences in mGFR were observed between treatment groups on Days 14 or 21. The difference in mGFR between treatment groups on Day 7 was likely due to random variations and/or multiple comparisons, as it was not consistent with the overall results observed for aGFR, $eGFR_{CG}$, and mGFR.

Conclusions:

- Treatment with BIC did not result in a change in glomerular filtration, as evidenced by no changes in aGFR measured by iohexol clearance after 14 days of once-daily dosing with BIC 75 mg.
- BIC treatment was well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, AEs leading to premature discontinuation of study drug, or pregnancies were reported during this study. Adverse events were generally mild, and no clinically relevant changes in laboratory values, vital signs, or ECGs occurred.

2.3. Studies in HIV-Infected Subjects

2.3.1. BIC Study

2.3.1.1. Study GS-US-141-1219

Location:	GS-US-141-1219
Title:	A Phase 1b Randomized, Double-Blinded, Sequential Cohort Placebo-Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-9883 in HIV-1 Infected Subjects
Primary Objective:	To evaluate the short-term antiviral potency of BIC at multiple oral doses ranging from 5 mg to 100 mg compared with placebo-to-match BIC each administered once daily as monotherapy for 10 days, with respect to the time-weighted average change from baseline to Day 11 ($DAVG_{11}$) in plasma HIV-1 RNA (log_{10} copies/mL) in ARV-treatment naive adult subjects and subjects who were ART-experienced but INSTI naive.
Study Design and Subject Population:	This Phase 1b, double-blinded, adaptive, sequential cohort, placebo-controlled study evaluated the short-term antiviral potency, safety, and PK of BIC monotherapy in HIV-1 infected subjects. Part 1 enrolled 10 subjects who were randomized 1:1 to Cohort 1 (BIC 25 mg) or 2 (BIC 100 mg). Within each cohort, subjects were assigned in a 4:1 ratio to receive BIC 25 mg or placebo-to-match (Cohort 1) or BIC 100 mg or placebo-to-match (Cohort 2) once daily for 10 days. The safety and viral data from Part 1 were then evaluated in a preliminary interim analysis. Based on the preliminary data from Part 1, Part 2 enrolled 10 subjects who were randomized 1:1 to Cohort 3 (BIC 5 mg) or 4 (BIC 50 mg). Within each cohort, subjects were assigned in a 4:1 ratio to receive BIC 5 mg or placebo-to-match (Cohort 3) or BIC 50 mg or placebo-to-match (Cohort 4) once daily for 10 days. Eligible subjects were subjects with chronic HIV-1 infection and plasma HIV-1 RNA ≥ 10,000 to ≤ 400,000 copies/mL, who had no resistance associated mutations to INSTIs, a CD4 cell count > 200 cells/μL, no use of any ARV drugs within 12 weeks prior to screening, and had not previously taken any INSTI. A total of 20 subjects were randomized and received study drug (5 per cohort), and all subjects completed study drug dosing and completed the study.
Summary of Results and Conclusions:	**Efficacy Results:** A summary of efficacy endpoints following the administration of BIC 5, 25, 50, and 100 mg once daily for 10 days is presented in the table below. Administration of BIC led to a dose dependent decrease in viral load. With increasing doses of BIC, the reduction of $DAVG_{11}$ in plasma HIV-1 RNA increased, the maximum reduction of HIV-1 RNA from baseline increased, the viral decay slope steepened, and the reduction of plasma HIV-1 RNA at Day 11 from baseline increased. For all BIC dose groups, there was a statistically significant difference compared with placebo in $DAVG_{11}$ in plasma HIV-1 RNA, maximum reduction from baseline in plasma HIV-1 RNA, viral decay slope, and change from baseline at Day 11 in plasma HIV-1 RNA.

Efficacy Endpoint	BIC 5 mg[a] (N = 3)	BIC 25 mg (N = 4)	BIC 50 mg (N = 4)	BIC 100 mg (N = 4)	Placebo (N = 4)
$DAVG_{11}$ (log_{10} copies/mL)					
Mean (SD)	−0.92 (0.104)	−1.33 (0.174)	−1.37 (0.310)	−1.61 (0.256)	−0.01 (0.144)
Maximum Reduction of Plasma HIV-1 RNA from Baseline (log_{10} copies/mL)[b]					
Mean (SD)	−1.52 (0.079)	−2.18 (0.241)	−2.31 (0.191)	−2.91 (0.526)	−0.12 (0.177)
Viral Decay Slope[c]					
Mean (SD)	−0.184 (0.0134)	−0.252 (0.0277)	−0.272 (0.0580)	−0.315 (0.0413)	−0.011 (0.0200)
Change of Plasma HIV-1 RNA at Day 11 from Baseline (log_{10} copies/mL)					
Mean (SD)	−1.45 (0.097)	−2.08 (0.209)	−2.06 (0.345)	−2.43 (0.386)	0.08 (0.295)

a A subject in the BIC 5 mg group was excluded from the PP Analysis Set as this subject's baseline HIV-1 RNA value was 173 copies/mL.
b Maximum reduction is defined as the minimum of change from baseline. All available HIV-1 RNA data up to Day 17 were used for this analysis.
c Viral Decay Slope = (log_{10} [HIV-1 RNA on Day x] − log_{10} [HIV-1 RNA on Day 1]) / (x−1), where x is the collection day of the last available on-treatment HIV-1 RNA collected up to Day 7.

Viral suppression (HIV-1 RNA < 50 copies/mL) was achieved at any time through Day 17 by 1 subject (25.0%) in the BIC 50 mg group and 2 subjects (50%) in the BIC 100 mg group.

At baseline, no subject had a primary integrase strand-transfer inhibitor resistance (INSTI-R) substitution in their HIV-1 RNA and all isolates were fully susceptible to BIC. No subject developed a primary INSTI-R substitution. One subject in the BIC 25 mg group had emergent M50M/I at Day 11 with no change in phenotypic susceptibility to BIC. No other INSTI-R substitutions emerged during this study. At Day 11, phenotypic susceptibility data to BIC were available for 13 of the 20 subject isolates and no significant change in susceptibility to BIC was found from baseline.

Pharmacokinetic/Pharmacodynamic Results:

Pharmacokinetic parameters of BIC following single-dose administration on Day 1 are presented in the table below. Following single-dose administration, BIC demonstrated rapid absorption, with a median T_{max} between 1.00 and 1.83 hours postdose for the 4 BIC treatment groups (5, 25, 50, and 100 mg). Mean BIC AUC_{0-24} and C_{max} were approximately dose proportional following single-dose administration of 5 to 50 mg dose administration, with decreasing dose proportionality at the 100 mg dose.

	BIC Single Dose PK (Day 1)			
PK Parameter	**5 mg (n = 4)**	**25 mg (n = 4)**	**50 mg (n = 4)**	**100 mg (n = 4)**
AUC_{0-24} (ng*h/mL)	6262.2 (22.9)	31,291.8 (10.0)	68,476.5 (17.0)	94,588.5 (28.9)
C_{last} (ng/mL)	141.3 (39.9)	609.3 (18.2)	1565.0 (30.6)	1987.5 (43.2)
C_{max} (ng/mL)	493.3 (14.6)	2565.0 (12.9)	4957.5 (13.5)	7367.5 (31.1)
T_{max} (h)	1.00 (1.00, 1.25)	1.83 (1.33, 2.50)	1.75 (1.50, 2.50)	1.50 (1.25, 1.75)

Data are presented as mean (% CV), except for T_{max}, which is presented as median (Q1, Q3).

Pharmacokinetic parameters of BIC following multiple-dose administration are presented in the table below. The plasma concentration versus time profiles observed on Day 10 after multiple-daily doses of BIC (5, 25, 50, and 100 mg) were similar to the plasma concentration versus time profiles observed on Day 1. The median T_{max} values for the BIC treatment groups were between 1.25 and 2.74 hours postdose. The median $t_{1/2}$ ranged from 15.86 to 20.88 hours across BIC treatment groups. The terminal phases across doses were parallel until 96 hours after dosing. Plasma concentrations of BIC reached steady-state by Day 10 of once-daily dosing. Following multiple-dose administration, dose proportionality was observed in AUC_{tau}, C_{max}, and C_{tau} over the dose range of 5 to 100 mg using the 50-mg dose as a reference.

PK Parameter	BIC Multiple Dose PK (Day 10)			
	5 mg (n = 4)	25 mg (n = 4)	50 mg (n = 4)	100 mg (n = 4)
AUC_{tau} (ng*h/mL)	9983.0 (26.7)	48,950.3 (40.0)	87,538.4 (32.7)	178,901.7 (17.8)
AR_AUC (%)	160.2 (16.1)	157.4 (38.0)	125.3 (16.7)	193.3 (11.6)
C_{tau} (ng/mL)	225.3 (37.5)	1052.3 (54.1)	2053.0 (47.6)	4520.0 (21.9)
C_{max} (ng/mL)	741.5 (18.2)	3475.0 (20.5)	6080.0 (21.8)	12,235.0 (24.9)
AR_C_{max} (%)	149.8 (4.4)	138.5 (27.0)	122.0 (10.9)	168.4 (9.6)
T_{max} (h)	1.50 (0.75, 3.00)	1.25 (1.00, 1.50)	1.75 (1.25, 2.50)	2.74 (1.25, 3.99)
T_{last} (h)	168.03 (144.97, 168.69)	111.14 (99.03, 145.03)	169.21 (168.75, 169.52)	169.79 (156.98, 170.08)
$t_{1/2}$ (h)	20.79 (17.15, 23.80)	15.86 (14.07, 19.37)	17.84 (15.50, 20.51)	20.88 (17.91, 24.47)
CL_{ss}/F (mL/h)	523.8 (22.0)	567.3 (34.7)	621.9 (34.0)	570.6 (15.3)
V_z/F (mL)	15,526.6 (38.9)	13,231.5 (32.4)	15,559.1 (20.3)	17,620.6 (31.7)

Data are presented as mean (% CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3). Accumulation ratio of AUC (AR_AUC) = AUC_{tau} on Day 10 / AUC_{0-24} on Day 1; Accumulation ratio of C_{max} (AR_C_{max}) = C_{max} on Day 10 / C_{max} on Day 1.

Inhibitory quotient was estimated by dividing predose concentration on Day 11 (C_{tau}) by the in vitro protein-adjusted concentration that results in 95% inhibition ($paIC_{95}$, 162 ng/mL). BIC doses of 25, 50, and 100 mg once daily yielded median protein-adjusted inhibitory quotient of 95% ($paIQ_{95}$) values of 4.9, 13.4, and 25.9, respectively. Increased BIC exposures were correlated with increased reduction in plasma HIV-1 RNA from baseline to Day 11. The in vivo 50% effective inhibitory concentration demonstrated by a concentration for maximum antiviral/pharmacodynamic effect (E_{max}) model was 0.87 for IQ and 6847 ng*h/mL for AUC_{tau}. Using the E_{max} model, both the steady-state C_{tau} and AUC_{tau} are predictive of plasma viral load reduction from baseline.

Based on PK/PD analyses, exposure associated with a 75 mg dose of single agent BIC is expected to provide near-maximal virologic response, with a predicted $paIQ_{95}$ of approximately 20, providing considerable coverage above the target concentration of 162 ng/mL ($paIC_{95}$).

Conclusions:

- BIC demonstrated a dose-dependent decrease in viral load through 10 days of treatment, as evidenced by the increased reduction in $DAVG_{11}$ in plasma HIV-1 RNA with increasing doses of BIC from 5 to 100 mg.
- All HIV-1 isolates were fully susceptible to BIC at baseline and Day 11. No primary INSTI-R substitutions or phenotypic resistance to BIC were found in this study.
- Increased BIC exposures were correlated with increased reduction in plasma HIV-1 RNA from baseline on Day 11. The PK/PD analyses supported the selection of a dose between 50 and 100 mg as the clinical efficacious dose for later phase studies.
- BIC was well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, AEs leading to premature discontinuation of study drug, or pregnancies were reported during this study. The safety profile of BIC did not differ with increasing doses of BIC when administered as multiple doses.
- BIC doses of 25, 50, and 100 mg once daily for 10 days yielded median $paIQ_{95}$ of 4.9, 13.4, and 25.9, respectively.

2.4. Intrinsic Factor Studies

2.4.1. B/F/TAF Study

2.4.1.1. Study GS-US-380-1991

Location:	GS-US-380-1991
Title:	A Phase 1 Single Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) Fixed-Dose Combination (FDC) Tablets in Healthy Japanese and Caucasian Subjects
Primary Objective(s):	To investigate the single dose PK of BIC, FTC, TAF, and TFV when administered as B/F/TAF 50/200/25 mg FDC in healthy Japanese and Caucasian subjects
Study Design and Subject Population:	This Phase 1, open-label, single-dose study investigated the PK of B/F/TAF in healthy Japanese and Caucasian subjects. Subjects received a single dose of B/F/TAF 50/200/25 mg under fasted conditions on Day 1. Eligible subjects were Japanese and Caucasian males and nonpregnant, nonlactating females, who were 18 to 55 years of age (inclusive), had a BMI of 18.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ ≥ 90 mL/min, and had no significant medical history. A total of 50 subjects were randomized into the study, and all subjects completed study drug dosing. All, but 1 subject completed the study; 1 subject discontinued the study due to AEs.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The primary PK parameters and statistical comparisons of BIC, FTC, TAF, and TFV are presented in the table below. Plasma exposures (AUC_{inf}, AUC_{last}, and C_{max}) of BIC, FTC, TAF, and TFV following single oral administration of B/F/TAF under fasted conditions were comparable between Japanese and Caucasian subjects. The GLSM ratios and 90% CIs for the comparisons of plasma PK parameters between Japanese and Caucasian subjects were within the predefined no-effect boundaries of 70% and 143% for all analytes tested (ie, BIC, FTC, TAF, and TFV).

PK Parameter	Mean (%CV) Japanese (Test) (N = 25)	Mean (%CV) Caucasian (Reference) (N = 25)	GLSM Ratio (%) (90% CI)
BIC			
AUC_{inf} (h*ng/mL)	114,889.7 (21.2)	103,040.2 (31.3)[a]	114.33 (100.36, 130.24)
AUC_{last} (h*ng/mL)	113,636.7 (20.9)	101,533.4 (30.7)[a]	114.70 (100.80, 130.51)
C_{max} (ng/mL)	6556.0 (17.9)	5224.0 (21.0)	126.32 (115.05, 138.70)
FTC			
AUC_{inf} (h*ng/mL)	11,166.9 (18.2)	10,613.2 (14.3)[a]	104.54 (96.63, 113.10)
AUC_{last} (h*ng/mL)	10,965.4 (18.6)	10,359.2 (14.3)[a]	105.08 (97.02, 113.81)
C_{max} (ng/mL)	2679.6 (39.9)	2448.4 (21.7)	103.23 (88.23, 120.79)
TAF			
AUC_{inf} (h*ng/mL)	174.8 (51.6)[b]	170.5 (40.8)[a]	97.41 (78.55, 120.80)
AUC_{last} (h*ng/mL)	169.8 (53.1)	167.1 (41.2)[a]	95.92 (77.31, 119.00)
C_{max} (ng/mL)	300.6 (58.3)	262.4 (41.9)	105.59 (85.37, 130.61)
TFV			
AUC_{inf} (h*ng/mL)	325.4 (24.0)	324.2 (24.3)[a]	100.41 (89.54, 112.59)
AUC_{last} (h*ng/mL)	267.1 (24.3)	267.1 (20.4)[a]	99.33 (89.19, 110.62)
C_{max} (ng/mL)	12.0 (30.3)	11.0 (24.4)	107.17 (93.44, 122.92)

a n = 24; no sample collected past 8 hours for 1 subject
b n = 24; terminal elimination phase could not be reliably estimated for 1 subject

	Conclusions: • The PK of BIC, FTC, TAF, and TFV were comparable between Japanese and Caucasian subjects following administration of the B/F/TAF FDC tablet, supporting the use of the 50/200/25 mg dose of B/F/TAF in HIV-infected Japanese patients. • The single oral dose of B/F/TAF was well tolerated by Japanese and Caucasian subjects. No deaths, SAEs, Grade 3 or 4 AEs, or pregnancies were reported during this study. One Caucasian subject discontinued the study due to AEs (nausea and vomiting). Most AEs were Grade 1 in severity, and no clinically meaningful changes in median laboratory values, vital signs, or ECGs occurred.

2.4.2. BIC Studies

2.4.2.1. Study GS-US-141-1478

Location:	GS-US-141-1478
Title:	A Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Hepatic Function
Primary Objective(s):	To evaluate the PK profile of a single oral dose of BIC in subjects with impaired hepatic function relative to matched, healthy controls with normal hepatic function
Study Design and Subject Population:	This Phase 1, open-label, parallel-group, adaptive, single-dose, multicenter study evaluated the PK profile and safety of a single oral dose of BIC in subjects with normal or impaired hepatic function. Each subject in the moderate hepatic impairment group (Cohort 1) was matched for age (± 10 years), sex, and BMI (± 20% of ≥ 18 and ≤ 36 kg/m^2) with a healthy subject in the control group. Subjects received a single dose of BIC 75 mg under fed conditions on Day 1. Cohort 2 (mild hepatic impairment) was not enrolled based on a review of the preliminary safety and PK data from Cohort 1. Eligible subjects were male and nonpregnant, nonlactating female subjects, who were aged 18 to 70 years of age (inclusive), had a BMI from 18.0 to 36 kg/m^2 (inclusive), and had an estimated $eGFR_{CG}$ ≥ 60 mL/min. Subjects with moderate hepatic impairment were selected from subjects with hepatic impairment at screening caused by nonhepatitis B-induced liver cirrhosis and were categorized based upon the Child-Pugh-Turcotte (CPT) classification system (Class B). Subjects with hepatic impairment also had a diagnosis of chronic (> 6 months), stable hepatic impairment with no clinically significant change in hepatic status within the 3 months (90 days) prior to study drug administration on Day 1. A total of 10 subjects with moderate hepatic impairment and 10 matched healthy control subjects with normal hepatic function received study drug and completed the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The plasma PK parameters for BIC and statistical comparisons are presented in the table below. BIC exposure was lower in the moderate hepatic impairment group compared with normal matched controls, as shown by GLSM ratios for BIC AUC_{inf} and C_{max} of 58.71% and 63.50%, respectively. However, overall BIC exposures overlapped between the 2 groups due to the large variability observed in the hepatic impairment group. Mean (%CV) percentage unbound plasma fraction of BIC was higher in subjects with moderate hepatic impairment (0.809% [21.4%]) than in normal matched control subjects (0.610% [6.2%]). The GLSM ratios for free AUC_{inf} and free C_{max} were 76.54% and 82.78%, respectively. Exploratory linear regression analyses of BIC AUC_{inf} and C_{max} versus individual laboratory components of CPT score (eg, albumin, total bilirubin prothrombin time, or international normalized ratio) indicated no correlation between BIC plasma exposure and hepatic function.

BIC PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Moderate Hepatic Impairment (Test) (N = 10)	Healthy Control (Reference) (N = 10)	
AUC_{inf} (h*ng/mL)	113,086.2 (50.7)	172,883.6 (23.4)	58.71 (41.28,83.50)
C_{max} (ng/mL)	5013.0 (29.1)	7849.0 (27.8)	63.50 (49.80,80.96)
C_{24} (ng/mL)	1643.6 (47.5)	2666.0 (24.9)	51.56 (30.96,85.87)
Free AUC_{inf} (h*ng/mL)	880.9 (55.7)	1054.2 (22.7)	76.54 (56.48,103.71)
Free C_{max} (ng/mL)	39.6 (27.7)	48.1 (28.2)	82.78 (64.98,105.45)

Free PK parameter is calculated as: Mean unbound fraction (%) * PK Parameter / 100 for a single subject.

	Conclusions: • Total (bound and unbound) BIC exposure (AUC_{inf}) was approximately 41% lower in subjects with moderate hepatic impairment relative to normal-matched control subjects; however, due to an increase of free fraction (ie, as percentage unbound BIC) in subjects with moderate hepatic impairment, the free BIC exposure (AUC_{inf}) was only approximately 23% lower in subjects with moderate hepatic impairment relative to normal-matched control subjects. • Differences in exposure to BIC in subjects with moderate hepatic impairment compared with normal matched controls are not clinically significant. • The single dose of BIC 75 mg was well tolerated by subjects with moderate hepatic impairment and normal healthy control subjects. No deaths, SAEs, Grade 3 or 4 AEs, AEs leading to premature discontinuation of study drug, or pregnancies were reported during this study. All AEs were Grade 1 in severity, and no clinically meaningful changes in median laboratory values, vital signs, or ECGs occurred.

2.4.2.2. Study GS-US-141-1479

Location:	GS-US-141-1479
Title:	A Phase 1, Open-Label, Parallel-Group, Adaptive Single-dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Renal Function
Primary Objective(s):	To evaluate the PK profile of oral BIC in subjects with impaired renal function relative to matched, healthy controls with normal renal function
Study Design and Subject Population:	This Phase 1, open-label, parallel-group, adaptive, single-dose study evaluated the PK and safety of BIC in subjects with impaired renal function based on $eGFR_{CG}$. The study was designed to enroll up to 60 subjects using an adaptive design to include up to 3 cohorts of subjects with different levels of renal impairment (severe, moderate, and mild) and matched control subjects with normal renal function ($eGFR_{CG} \geq 90$ mL/min). Each subject in the renal impairment group was matched for age (± 10 years), sex, and BMI (± 20% of ≥ 18 and ≤ 40 kg/m^2) with a healthy subject in the control group. Only subjects with severe renal impairment (Cohort 1) were enrolled in this study, and, based on preliminary safety and PK data, subjects with moderate and mild renal impairment were not enrolled in the adaptive cohorts (Cohorts 2 and 3, respectively). In Cohort 1, subjects received a single dose of BIC 75 mg under fed conditions on Day 1. Eligible subjects were male and nonpregnant, nonlactating female subjects, who were aged 18 to 79 years of age (inclusive) and had a BMI from 18.0 to 40.0 kg/m^2 (inclusive). The subjects with severe renal impairment had an $eGFR_{CG}$ from 15 to 29 mL/min and the matched control subjects had an $eGFR_{CG} \geq 90$ mL/min. A total of 10 subjects with severe renal impairment and 8 matched control subjects with normal renal function received study drug and completed the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Plasma PK parameters for BIC and the statistical comparisons are presented in the table below. Mean AUC_{inf}, AUC_{last}, and C_{max} for total BIC were slightly lower in the severe renal impairment group relative to the normal renal function group, with GLSM ratios of 72.63%, 72.43%, and 80.32%, respectively. The modest reduction in BIC plasma exposure in subjects with severe renal impairment compared with subjects with normal renal function was not clinically relevant.

GS-9883 PK Parameter	Mean (%CV)		GLSM Ratio % (90% CI)
	Severe Renal Impairment (Test) (N = 10)	Normal Renal Function (Reference) (N = 8)	
Total AUC_{inf} (h*ng/mL)	138,169.7 (44.4)	170,105.6 (24.8)	72.63 (48.80, 108.10)
Total AUC_{last} (h*ng/mL)	136,956.4 (44.2)	168,876.8 (24.7)	72.43 (48.54, 108.07)
Total C_{max} (ng/mL)	5977.0 (34.8)	7227.5 (29.5)	80.32 (59.56, 108.30)
Free AUC_{inf} (h*ng/mL)[a]	830.6 (32.1)	824.5 (24.7)	99.29 (79.49, 124.04)
Free AUC_{last} (h*ng/mL)[a]	822.5 (32.0)	818.6 (24.6)	99.02 (79.24, 123.74)
Free C_{max} (ng/mL)[a]	37.7 (21.6)	35.0 (28.4)	109.80 (87.46, 137.85)

a Free AUC_{last}, free AUC_{inf}, and free C_{max} were calculated based on unbound plasma BIC (PK parameter × percentage unbound BIC/100 for each subject).

Mean (%CV) percentage unbound plasma BIC values determined 2 hours after BIC dosing were 0.75% (72.03) for the severe renal impairment group and 0.49% (9.32) for the normal renal function group. Mean free AUC_{inf}, AUC_{last}, and C_{max}, calculated using percentage of unbound plasma BIC, were similar between the 2 groups.

	In individual subjects, the percentages of unbound plasma BIC ranged from 0.43% to 0.63%, except for 1 subject in the severe renal impairment group who had a significantly higher percentage of unbound plasma BIC (2.28%). This subject also had lower plasma BIC exposure, an anomaly not explained by the subject's medical history or concomitant medications. Sensitivity analyses of the primary endpoints were performed excluding this subject's data, and results were similar, with GLSM ratios for total BIC AUC_{inf}, AUC_{last}, and C_{max} of 87.51%, 87.44%, and 90.12%, respectively. The fraction of the BIC dose and the amount of unchanged BIC excreted in the urine were similar between subjects with severe renal impairment and subjects with normal renal function. Linear regression analyses of BIC AUC_{inf}, AUC_{last}, and C_{max} versus screening $eGFR_{CG}$ indicated no correlation between BIC exposure and renal function. **Conclusions:** • The decrease in BIC plasma exposure in subjects in the severe renal impairment group compared with control subjects in the normal renal function group was modest and not considered clinically relevant. Free BIC exposure and the mean amount of unchanged BIC excreted in the urine were comparable between the 2 renal function groups. • Severe renal dysfunction did not significantly alter the BIC PK profile in this study; therefore, no dose adjustment for BIC is warranted in subjects with mild, moderate, or severe renal impairment. • The single dose of BIC 75 mg was well tolerated by subjects in both renal function groups in this study. No deaths, SAEs, Grade 3 or 4 AEs, AEs leading to premature discontinuation of study drug, or pregnancies were reported during this study. All AEs were Grade 1 in severity, and no clinically meaningful changes in median laboratory values, vital signs, or ECGs occurred.

2.5. Extrinsic Factor Studies

2.5.1. B/F/TAF Studies

2.5.1.1. Study GS-US-380-1761

Location:	GS-US-380-1761
Title:	A Phase 1 Study to Evaluate Pharmacokinetic Drug-Drug Interaction Potential between GS-9883/Emtricitabine/Tenofovir Alafenamide Fumarate (GS-9883/F/TAF) and Ledipasvir/Sofosbuvir (LDV/SOF) Fixed-Dose Combination (FDC) Tablets
Primary Objective(s):	• To evaluate the steady-state PK of BIC, FTC, and TAF upon administration of B/F/TAF FDC with ledipasvir/sofosbuvir (LDV/SOF; Harvoni®) FDC • To evaluate the steady-state PK of SOF, its metabolites GS-566500 and GS-331007, and LDV upon administration of LDV/SOF FDC with B/F/TAF FDC
Study Design and Subject Population:	This Phase 1, fixed-sequence, open-label, single-center, multiple-dose, 3-period study evaluated the steady-state PK of BIC, FTC, TAF, its metabolite TFV and the steady-state PK of sofosbuvir (SOF), its metabolites GS-566500 and GS-331007, and ledipasvir (LDV) after administration of LDV/SOF+B/F/TAF in healthy subjects. Subjects received the following 3 study treatments under fed conditions: • **LDV/SOF (Treatment A):** LDV/SOF 90/400 mg once daily on Days 1 to 10 (Treatment A) • **B/F/TAF (Treatment B):** B/F/TAF 75/200/25 mg once daily on Days 11 to 20 (Treatment B) • **LDV/SOF+B/F/TAF (Treatment C):** LDV/SOF 90/400 mg + B/F/TAF 75/200/25 mg once daily on Days 21 to 30 Eligible subjects were healthy males and nonpregnant, nonlactating females, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ ≥ 90 mL/min, and had no significant medical history. A total of 30 subjects were enrolled in the study, and all subjects completed study drug dosing and the study.
Summary of Results and Conclusions:	**Pharmacokinetics Results:** The mean and percentage coefficient of variation (%CV) of the primary PK parameters for BIC, FTC, TAF, TFV, SOF, GS-566500, GS-331007, and LDV following the administration B/F/TAF or LDV/SOF alone or in combination and the results of the statistical analysis are summarized in the tables below. Coadministration of B/F/TAF and LDV/SOF did not result in clinically relevant changes in the PK of LDV or SOF (including its metabolites GS-566500 or GS-331007). Coadministration of LDV/SOF and B/F/TAF did not result in clinically relevant changes in the PK of BIC, FTC, or TAF. Compared with administration of B/F/TAF alone, LDV/SOF+B/F/TAF led to increases in TFV AUC_{tau} of 67%, TFV C_{max} of 43%, and AUC_{tau} of 81%, which was not considered clinically meaningful, as the TFV exposure remained markedly lower as compared with TDF-containing ARV regimens.

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	LDV/SOF+B/F/TAF (Test) (N = 30)	LDV/SOF (Reference) (N = 30)	
SOF			
AUC_{tau} (h*ng/mL)	3166.6 (24.3)	2967.2 (24.6)	106.67 (101.07, 112.58)
C_{max} (ng/mL)	1914.2 (37.4)	1697.1 (38.2)	111.41 (100.45, 123.57)
GS-566500			
AUC_{tau} (h*ng/mL)	2685.4 (17.1)	2727.1 (15.4)	98.19 (94.43, 102.11)
C_{max} (ng/mL)	611.4 (19.1)	616.7 (18.8)	98.96 (95.14, 102.93)
GS-331007			
AUC_{tau} (h*ng/mL)	11,552.3 (17.2)	10,370.7 (14.9)	110.98 (107.94, 114.10)
C_{max} (ng/mL)	903.9 (18.2)	822.1 (17.7)	109.90 (106.78, 113.12)
C_{tau} (ng/mL)	315.7 (20.6)	308.0 (18.4)	102.01 (98.53, 105.61)
LDV			
AUC_{tau} (h*ng/mL)	10,175.1 (35.0)	11,500.0 (28.6)	87.32 (82.61, 92.29)
C_{max} (ng/mL)	567.0 (31.1)	656.4 (25.3)	85.40 (80.74, 90.33)
C_{tau} (ng/mL)	364.5 (38.8)	400.9 (34.3)	89.92 (84.24, 95.99)

PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	LDV/SOF+B/F/TAF (Test) (N = 30)	B/F/TAF (Reference) (N = 30)	
BIC			
AUC_{tau} (h*ng/mL)	188,882.4 (20.8)	188,231.7 (19.3)	100.11 (97.17, 103.14)
C_{max} (ng/mL)	13,306.3 (15.2)	13,570.0 (16.6)	98.25 (94.04, 102.66)
C_{tau} (ng/mL)	5188.0 (29.2)	4992.3 (29.9)	103.99 (99.44, 108.74)
FTC			
AUC_{tau} (h*ng/mL)	11,309.1 (15.0)	11,505.7 (20.4)	98.89 (95.47, 102.43)
C_{max} (ng/mL)	2036.3 (26.6)	2013.3 (15.2)	99.19 (93.51, 105.20)
C_{tau} (ng/mL)	74.9 (19.2)	73.4 (21.6)	102.62 (98.85, 106.54)
TAF			
AUC_{last} (h*ng/mL)	430.0 (29.3)	342.6 (33.6)	126.65 (119.26, 134.49)
C_{max} (ng/mL)	304.8 (46.0)	261.6 (49.7)	117.23 (99.53, 138.08)
TFV			
AUC_{tau} (h*ng/mL)	474.7 (20.8)	284.1 (21.0)	166.97 (160.09, 174.14)
C_{max} (ng/mL)	26.2 (19.6)	18.3 (19.5)	143.36 (137.21, 149.80)
C_{tau} (ng/mL)	16.9 (23.8)	9.3 (21.2)	180.95 (172.75, 189.54)

Conclusions:

- No dose modification of LDV/SOF or B/F/TAF is warranted upon coadministration of these agents.
- LDV/SOF and B/F/TAF were well tolerated when administered alone or in combination. No deaths, SAEs, Grade 3 or 4 AEs, AEs leading to premature discontinuation of study drug, or pregnancies were reported during this study.

2.5.1.2. Study GS-US-380-1999

Location:	GS-US-380-1999, GS-US-380-1999 Amendment 1
Title:	A Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between GS-9883/Emtricitabine/Tenofovir Alafenamide and Sofosbuvir/Velpatasvir/GS-9857 in Healthy Subjects
Primary Objective(s):	• To evaluate the steady-state PK of BIC, FTC, TAF, and TFV upon administration of B/F/TAF FDC with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) • To evaluate the steady-state PK of SOF, its metabolites (GS-566500 and GS-331007), velpatasvir (VEL), and voxilaprevir (VOX) upon administration of B/F/TAF FDC with SOF/VEL/VOX
Study Design and Subject Population:	This Phase 1, randomized, open-label, multiple-dose, single-center, 3-period study evaluated the DDI potential between B/F/TAF and SOF/VEL/VOX in healthy subjects. Subjects were randomized into 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA) to receive the following 3 study treatments under fed conditions beginning on Day 1: • **B/F/TAF (Treatment A):** B/F/TAF 50/200/25 mg once daily for 10 days • **B/F/TAF+SOF/VEL/VOX+VOX (Treatment B):** B/F/TAF 50/200/25 mg + SOF/VEL/VOX 400/100/100 mg + VOX 100 mg once daily for 10 days • **SOF/VEL/VOX (Treatment C):** SOF/VEL/VOX 400/100/100 mg + VOX 100 mg once daily for 10 days Eligible subjects were healthy male and nonpregnant, nonlactating female adults, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ $\geq$ 80 mL/min and had no significant medical history. A total of 30 subjects were enrolled in the study, and all subjects completed study drug dosing and the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Plasma PK parameters and statistical comparisons are presented in the table below for BIC, FTC, TAF, and TFV when administered with or without SOF/VEL/VOX+VOX. Plasma exposures of BIC and FTC were comparable between B/F/TAF coadministered with SOF/VEL/VOX+VOX and B/F/TAF alone, with 90% CIs for the GLSM ratios comparing BIC and FTC AUC_{tau}, C_{max}, and C_{tau} between test and reference treatments within the prespecified lack of DDI boundary of 70% to 143%. Compared with administration of B/F/TAF alone, coadministration with SOF/VEL/VOX+VOX resulted in higher TAF AUC_{tau}, AUC_{last}, and C_{max} (57.3%, 58.0%, and 28.1% higher, respectively) and TFV AUC_{tau}, C_{max}, and C_{tau} (67.4%, 51.4%, and 73.6% higher, respectively). However, these changes are not considered clinically relevant because the TAF exposure in this study was within the wide range of safe and efficacious TAF exposure established in E/C/F/TAF and F/TAF clinical development programs, and TFV exposure in this study was markedly lower than that observed following TDF-containing regimens.

	Mean (%CV)		
	B/F/TAF + SOF/VEL/VOX+VOX (Test) (N = 30)	**B/F/TAF (Reference) (N = 30)**	**%GLSM Ratio (90% CI) (Test/Reference)**
BIC PK Parameter			
AUC_{tau} (h*ng/mL)	128,196.2 (20.1)	120,187.3 (19.5)	106.60 (103.34, 109.96)
C_{max} (ng/mL)	8265.3 (14.7)	8525.0 (20.0)	97.69 (94.39, 101.10)
C_{tau} (ng/mL)	3572.0 (30.5)	3224.0 (29.7)	110.46 (104.61, 116.63)
FTC PK Parameter			
AUC_{tau} (h*ng/mL)	9444.8 (14.3)	9919.9 (12.1)	94.94 (93.05, 96.87)
C_{max} (ng/mL)	1630.0 (25.6)	1829.7 (21.6)	88.55 (83.11, 94.34)
C_{tau} (ng/mL)	70.5 (22.2)	63.9 (20.5)	110.22 (104.80, 115.91)
TAF PK Parameter			
AUC_{tau} (h*ng/mL)	443.4 (38.2)	281.6 (35.5)	157.25 (144.20, 171.48)
AUC_{last} (h*ng/mL)	441.5 (38.3)	279.7 (36.0)	158.02 (144.68, 172.58)
C_{max} (ng/mL)	280.4 (61.0)	217.2 (47.8)	128.05 (108.90, 150.56)
TFV PK Parameter			
AUC_{tau} (h*ng/mL)	480.1 (20.0)	286.8 (20.2)	167.36 (161.55, 173.38)
C_{max} (ng/mL)	26.9 (20.8)	17.8 (21.8)	151.41 (144.85, 158.27)
C_{tau} (ng/mL)	16.7 (22.1)	9.6 (22.6)	173.55 (167.77, 179.53)

Plasma PK parameters and statistical comparisons are presented in the table below for SOF, its metabolites (GS-566500 and GS-331007), VEL, and VOX when administered with or without B/F/TAF. Plasma exposures of SOF, its metabolites (GS-566500 and GS-331007), VEL, and VOX were comparable between SOF/VEL/VOX+VOX coadministered with B/F/TAF and SOF/VEL/VOX+VOX alone, with 90% CIs for the GLSM ratios comparing SOF and GS-566500 AUC_{tau} and C_{max}, and comparing GS-331007, VEL, and VOX AUC_{tau}, C_{max}, and C_{tau} between test and reference treatments within the prespecified lack of DDI boundary of 70% to 143%.

PK Parameters	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	B/F/TAF + SOF/VEL/VOX+VOX (Test) (N = 30)	SOF/VEL/VOX+VOX (Reference) (N = 30)	
SOF			
AUC_{tau} (h*ng/mL)	3450.1 (27.8)	3129.2 (22.6)	108.69 (102.41, 115.35)
C_{max} (ng/mL)	1867.2 (48.0)	1574.3 (33.0)	114.07 (104.02, 125.09)
GS-566500			
AUC_{tau} (h*ng/mL)	2978.5 (22.8)	3056.2 (22.5)	97.50 (95.33, 99.71)
C_{max} (ng/mL)	612.0 (25.1)	629.0 (23.3)	97.15 (92.61, 101.92)
GS-331007			
AUC_{tau} (h*ng/mL)	11,157.2 (16.3)	10,843.3 (17.0)	102.95 (100.44, 105.52)
C_{max} (ng/mL)	851.7 (15.7)	831.5 (17.1)	102.66 (99.45, 105.97)
C_{tau} (ng/mL)	308.3 (21.3)	303.3 (19.7)	101.28 (98.10, 104.56)
VEL			
AUC_{tau} (h*ng/mL)	7708.9 (36.4)	8048.1 (33.9)	95.77 (90.21, 101.67)
C_{max} (ng/mL)	897.6 (31.6)	937.3 (29.9)	96.00 (91.24, 101.00)
C_{tau} (ng/mL)	137.6 (52.9)	144.1 (47.2)	94.42 (88.02, 101.28)
VOX			
AUC_{tau} (h*ng/mL)	4460.3 (66.1)	4818.6 (61.3)	91.01 (80.04, 103.49)
C_{max} (ng/mL)	879.8 (69.1)	929.3 (55.6)	89.84 (76.36, 105.69)
C_{tau} (ng/mL)	27.8 (71.4)	27.6 (56.5)	96.74 (88.31, 105.97)

Conclusions:

- There were no clinically relevant differences in the plasma PK of BIC, FTC, TAF, TFV, SOF, its metabolites (GS-566500 and GS-331007), VEL, or VOX when B/F/TAF or SOF/VEL/VOX+VOX was administered alone or in combination once-daily for 10 days. No dose modification of B/F/TAF or SOF/VEL/VOX is warranted upon coadministration of these agents.
- Once-daily doses of B/F/TAF or SOF/VEL/VOX+VOX, alone or in combination, for 10 days were well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, AEs leading to premature discontinuation of study drug, or pregnancies were reported during this study.

2.5.1.3. Study GS-US-380-3908

Location:	GS-US-380-3908
Title:	A Phase 1, Blinded, Placebo-controlled, Two-period Crossover Drug Interaction Study to Assess the Effect of GS-9883/F/TAF on Metformin Pharmacokinetics in Healthy Subjects
Primary Objective:	To evaluate the effect of BIC on the PK of metformin following the steady-state coadministration of B/F/TAF FDC with metformin in healthy subjects
Study Design and Subject Population:	This Phase 1, blinded, placebo-controlled, multiple-dose, single center, 2- period crossover study assessed the effect of B/F/TAF on metformin PK and PD in healthy subjects. Subjects were randomized into 1 of 2 treatment sequences (AB, BA) to receive each of the following 2 treatments for 9 days, with a 3-day washout period between treatments: • **Metformin (Treatment A):** placebo-to-match B/F/TAF once daily on Days 1 to 9 or 13 to 21 in the morning and metformin 850 mg administered once daily 12 hours postdose of placebo on Day 5 or 17, 500 mg administered twice daily on Days 6 to 8 or 18 to 20 in the morning (coadministered with placebo) and 12 hours postmorning dose, and 500 mg coadministered once daily on Day 9 or 21 with placebo in the morning • **B/F/TAF+Metformin (Treatment B):** B/F/TAF 50/200/25 mg once daily on Days 1 to 9 or 13 to 21 in the morning and metformin 850 mg once daily 12 hours postdose of placebo on Day 5 or 17, 500 mg administered twice daily on Days 6 to 8 or 18 to 20 in the morning (coadministered with B/F/TAF) and 12 hours postmorning dose, and 500 mg coadministered once daily on Day 9 or 21 with placebo in the morning Eligible subjects were healthy males and nonpregnant, nonlactating females, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ ≥ 80 mL/min, and had no significant medical history. A total of 32 subjects were randomized into the study and received at least 1 dose of study drug, and 30 subjects completed dosing with study drugs and the study. One subject discontinued during the placebo dosing period due to AE, and 1 subject discontinued during the B/F/TAF dosing period due to protocol violation.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Metformin plasma, whole blood, and urine PK parameters and statistical comparisons are presented in the table below. Metformin plasma C_{max} was within the lack of DDI boundary of 70% to 143%. However, metformin plasma AUC_{tau} was increased by 39% (%GLSM ratio [90% CI]: 139.48% [131.37%, 148.09%]) when coadministered with B/F/TAF relative to coadministration with placebo. Median plasma $t_{1/2}$ was similar between the 2 treatments, and plasma CL_{ss}/F was decreased approximately 29% upon coadministration with B/F/TAF relative to coadministration with placebo. Evaluation of whole blood metformin exposure (AUC_{tau}) when coadministered with B/F/TAF demonstrated a smaller increase over coadministration with placebo than the observed change in plasma (%GLSM ratio [90% CI]: 134.71% [129.54%, 140.09%]). Metformin CL_R decreased approximately 31% when coadministered with B/F/TAF relative to coadministration with placebo. The fraction of dose recovered as unchanged metformin in urine during the dosing interval (f_{e12}) was comparable between coadministered treatments. Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion; therefore, CL_R represents the total clearance of metformin. As such, these data indicate that the observed increase in plasma metformin exposure (AUC_{tau}) upon coadministration with B/F/TAF was due to an effect on the elimination of metformin and that metformin absorption was unaffected by B/F/TAF. Metformin CL_R (520.9 mL/min) was higher than CL_{cr} (mGFR; 138.6 mL/min), consistent with renal tubular secretion as the known primary route of elimination of metformin. Renal clearance by tubular secretion ($SrCL_R$), estimated as the difference between metformin CL_R and mGFR, decreased approximately 39% when coadministered with B/F/TAF relative to coadministration with placebo, suggesting that the decrease in metformin CLR was likely due to the inhibition of renal secretion, consistent with the known inhibition of organic cation transporter 2 (OCT2) and/or multidrug and toxin extrusion protein 1 (MATE1) by BIC.

PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	B/F/TAF with Metformin (Test) (N = 32)	Placebo with Metformin (Reference) (N = 30)	
Plasma Metformin			
AUC_{tau} (ng*h/mL)	7180.3 (27.3)	5180.0 (24.8)	139.48 (131.37, 148.09)
C_{max} (ng/mL)	1353.4 (27.1)	1059.4 (25.4)	128.10 (120.78, 135.85)
C_{tau} (ng/mL)	157.9 (30.1)	122.5 (44.5)	135.78 (120.62, 152.85)
$t_{1/2}$ (h)[a]	6.36 (5.11, 7.28)	7.06 (4.73, 10.02)	—
CL_{ss}/F (mL/min)	1233.3 (25.3)	1734.9 (34.7)	71.70 (67.53, 76.12)
V_z/F (L)	674.0 (35.9)	1056.5 (45.6)	64.92 (56.66, 74.39)
Whole Blood Metformin			
AUC_{tau} (ng*h/mL)	7159.3 (22.5)	5289.3 (19.3)	134.71 (129.54, 140.09)
C_{max} (ng/mL)	1040.2 (22.1)	813.5 (20.7)	128.18 (122.48, 134.14)
C_{tau} (ng/mL)	326.1 (19.6)	247.9 (24.0)	132.01 (125.49, 138.88)
$t_{1/2}$ (h)[a]	15.82 (14.64, 17.68)	18.61 (16.64, 20.54)	—
Urine Metformin			
f_{e12} (%)	29.7 (20.9)	32.1 (26.1)	95.47 (86.49, 105.38)
CL_R (mL/min)	357.2 (21.5)	520.9 (20.0)	68.53 (63.37, 74.11)
$SrCL_R$ (mL/min)	232.4 (25.8)	382.4 (24.3)	—

a Data are presented as median (Q1, Q3).

To assess whether any apparent change in metformin PK resulted in a change in the PD effects of metformin, PD endpoints specific to metformin were also evaluated by measuring changes in plasma glucose, active glucagon-like peptide 1 (GLP-1), and lactate levels through an oral glucose tolerance test (OGTT) relative to baseline levels (without metformin) following metformin administration with B/F/TAF or placebo. Statistically significant changes relative to baseline in plasma glucose, active GLP-1, and lactate were observed following coadministration of metformin with B/F/TAF or placebo ($p < 0.001$). Importantly, these PD responses were comparable when coadministered with B/F/TAF or placebo, as presented in the table below. In particular, there were no statistically significant differences in mean ΔAUC_{gluc60}, ΔG_{mean60}, $\Delta Glucose_{60}$, or ΔG_{max} values between B/F/TAF and placebo ($p \geq 0.082$).

The totality of the PK and PD data indicate that the 39% increase in metformin plasma exposure (AUC_{tau}) following metformin coadministration with B/F/TAF, relative to placebo, did not result in clinically significant changes in the degree to which metformin decreased glucose levels or increased active GLP-1 and lactate levels.

PD Parameter	Mean (90% CI) Difference Between Before and After Metformin		Statistical Comparison of B/F/TAF vs Placebo p-value[a]
	B/F/TAF (N = 32)	Placebo (N = 30)	
Glucose			
ΔAUC_{gluc60} (mg*min/dL)	−997.2 (−1197.2, −797.2)[b]	−764.6 (−995.5, −533.8)[b]	0.261
$\Delta Glucose_{60}$ (mg/dL)	−19.7 (−26.5, −12.9)[b]	−17.8 (−25.6, −10.0)[b]	0.756
ΔG_{max} (mg/dL)	−22.9 (−28.0, −17.8)[b]	−16.1 (−21.5, −10.8)[b]	0.082
ΔG_{mean60} (mg/dL)	−16.6 (−20.0, −13.3)[b]	−12.7 (−16.6, −8.9)[b]	0.261
Active GLP-1			
Pre-Glucose (pmol/L)	0.6 (0.4, 0.7)[b]	0.8 (0.5, 1.0)[b]	0.342
60 Minutes Post-Glucose (pmol/L)	1.6 (1.2, 2.0)[b]	1.8 (1.1, 2.6)[b]	0.507
120 Minutes Post-Glucose (pmol/L)	1.9 (1.3, 2.5)[b]	2.2 (1.7, 2.6)[b]	0.546
Lactate			
60 Minutes Post-Glucose	1.6 (0.5, 2.6)	0.8 (−0.3, 1.9)	0.369
120 Minutes Post-Glucose (mg/dL)	2.1 (1.1, 3.0)[b]	2.2 (1.2, 3.2)[b]	0.729

a Statistical comparison of B/F/TAF vs placebo p-values were based on 2-sided Wilcoxon signed-rank test comparing difference before and after metformin between treatment groups.
b $p < 0.001$ for the difference between before and after metformin.

Conclusions:

- Metformin plasma exposure was increased approximately 39% following coadministration with B/F/TAF, relative to placebo, likely due to inhibition of renal transporters OCT2 and/or MATE1 by BIC; however, the PD characteristics of metformin with B/F/TAF, such as glucose reduction, and active GLP-1 and lactate increases after OGTT, were unaffected by coadministration with B/F/TAF, relative to placebo. The lack of differences in the observed PD effects following coadministration of metformin with B/F/TAF, relative to coadministration of metformin with placebo, support the conclusion that changes in plasma PK exposure are not clinically significant.
- Coadministration of metformin with B/F/TAF was generally safe and well tolerated in this healthy subject study. No deaths, SAEs, or pregnancies were reported during this study. One subject discontinued study drug due to a Grade 3 AE of nephrolithiasis, which the investigator considered not related to study drug, while receiving placebo with metformin.

2.5.1.4. Study GS-US-380-3909

Location:	GS-US-380-3909
Title:	A Phase 1, Open Label, Multiple-Cohort, Multiple-Period, Fixed-Sequence, Drug Interaction Study to Evaluate the Effect of Antacid and Mineral Supplements on GS-9883 Pharmacokinetics
Primary Objective:	• To evaluate the effect of simultaneous administration of antacid, calcium, or iron supplements with B/F/TAF FDC compared with administration of B/F/TAF FDC alone under fasted and fed conditions on BIC PK • To evaluate the effect of staggered administration of B/F/TAF FDC and antacid compared with administration of B/F/TAF FDC alone on BIC PK
Study Design and Subject Population:	This Phase 1, open-label, single-dose, fixed-sequence, multiple-cohort, multiple-period, single-center, adaptive study evaluated the effect on BIC PK of simultaneous administration of antacid, calcium, or iron supplements with B/F/TAF compared with administration of B/F/TAF alone under fasted and fed conditions and evaluated the effect on BIC PK of staggered administration of B/F/TAF and antacid compared with administration of B/F/TAF alone in healthy subjects. The study was designed to enroll up to 4 cohorts of 14 subjects each. Cohorts 1 through 3 were initiated in parallel. After review of preliminary PK data from Cohorts 1 and 2, Cohort 4 was not conducted. Further details on the study design for Cohort 4 are available in the clinical study report (CSR). In Cohort 1 (Fasted Simultaneous Administration), subjects received a single dose of B/F/TAF 50/200/25 mg on Day 1 (Treatment A); a single dose of B/F/TAF administered simultaneously with a single dose of 20 mL maximum-strength antacid oral suspension on Day 9 (Treatment B); a single dose of B/F/TAF administered simultaneously with a single dose of calcium carbonate (2 × 600 mg tablets) on Day 17 (Treatment C); and a single dose of B/F/TAF administered simultaneously with a single dose of ferrous fumarate (1 × 324-mg tablet) on Day 25 (Treatment D), with 7-day washout periods between treatments. All treatments were administered under fasting conditions. In Cohort 2 (Fasted Staggered [2 h] Administration), subjects received a single dose of B/F/TAF 50/200/25 mg on Day 1 (Treatment A), a single dose of B/F/TAF administered 2 hours before a single dose of 20 mL maximum-strength antacid oral suspension on Day 9 (Treatment E); and a single dose of B/F/TAF administered 2 hours after a single dose of 20 mL maximum-strength antacid oral suspension on Day 17 (Treatment F), with 7-day washout periods between treatments. All treatments were administered under fasting conditions. In Cohort 3 (Fed Simultaneous Administration), subjects received a single dose of B/F/TAF 50/200/25 mg under fasting conditions on Day 1 (Treatment A); a single dose of B/F/TAF administered simultaneously with a single dose of 20 mL maximum-strength antacid oral suspension under fed conditions on Day 9 (Treatment G); a single dose of B/F/TAF administered simultaneously with a single dose of calcium carbonate (2 × 600 mg tablets) under fed conditions on Day 17 (Treatment H); and a single dose of B/F/TAF administered simultaneously with a single dose of ferrous fumarate (1 × 324-mg tablet) under fed conditions on Day 25 (Treatment I), with 7-day washout periods between treatments. Eligible subjects were healthy males and nonpregnant, nonlactating females, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ ≥ 90 mL/min, and had no significant medical history. A total of 42 subjects (14 subjects per cohort) were enrolled in the study, and 41 subjects (97.6%) completed study drug administration and the study. One subject in Cohort 2 discontinued study drug due to AE (urticaria).
Summary of Results and Conclusions:	**Pharmacokinetic Results:** BIC plasma PK parameters and statistical comparisons are presented in the table below. Results from Cohort 1 showed BIC exposure was reduced following simultaneous administration of B/F/TAF with maximum-strength antacid, calcium carbonate, or ferrous fumarate under fasted conditions compared with administration of B/F/TAF alone. The largest reduction in BIC exposure (AUC_{inf}) (approximately 79% lower vs B/F/TAF alone under fasted conditions) was observed upon simultaneous administration with maximum-strength antacid, which contains the maximum strength of magnesium and aluminum ions. In comparison, simultaneous administration with calcium carbonate or ferrous fumarate under fasted conditions reduced BIC exposure by approximately 33% and 63%, respectively, versus B/F/TAF alone under fasted conditions.

Results from Cohort 2 showed that the effect of maximum-strength antacid on BIC exposure was reduced by staggering administration by 2 hours. BIC administration under fasted conditions 2 hours before or after maximum-strength antacid reduced BIC exposure (AUC_{inf} by approximately 13% and 52%, respectively, versus B/F/TAF alone under fasted conditions.

Results from Cohort 3 showed that BIC exposures (AUC_{inf}) were unaffected following simultaneous administration of B/F/TAF with calcium carbonate or ferrous fumarate after a moderate-fat meal versus B/F/TAF alone under fasted conditions. Simultaneous administration of B/F/TAF with maximum-strength antacid after a moderate-fat meal reduced BIC exposure (AUC_{inf}) by approximately 47% versus B/F/TAF alone under fasted conditions.

BIC PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	B/F/TAF Under Test Conditions (N = 14)	B/F/TAF Alone (Fasted) (Reference) (N = 14)	
B/F/TAF (fasted) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng*h/mL)	27,960.7 (52.5)	121,887.9 (24.4)	21.23 (17.57, 25.65)
C_{24} (ng/mL)	427.0 (57.4)	1795.7 (26.3)	21.94 (17.80, 27.04)
C_{max} (ng/mL)	1199.8 (52.0)	5635.0 (18.8)	19.89 (16.46, 24.02)
B/F/TAF (fasted) with calcium carbonate (Test)			
AUC_{inf} (ng*h/mL)	85,037.3 (43.1)	121,887.9 (24.4)	66.67 (56.67, 78.42)
C_{24} (ng/mL)	1222.9 (43.9)	1795.7 (26.3)	64.89 (54.47, 77.31)
C_{max} (ng/mL)	3442.1 (36.9)	5635.0 (18.8)	58.31 (50.72, 67.04)
B/F/TAF (fasted) with ferrous fumarate (Test)			
AUC_{inf} (ng*h/mL)	46,148.7 (32.9)	121,887.9 (24.4)	37.11 (32.95, 41.80)
C_{24} (ng/mL)	674.8 (32.8)	1795.7 (26.3)	36.92 (32.59, 41.83)
C_{max} (ng/mL)	1667.1 (27.1)	5635.0 (18.8)	29.10 (25.87, 32.72)
B/F/TAF (fasted) 2 hours before 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng*h/mL)	115,908.1 (30.3)[a]	132,814.0 (27.0)	86.70 (81.01, 92.78)
C_{24} (ng/mL)	1699.2 (27.9)[a]	2009.3 (28.3)	85.46 (79.92, 91.38)
C_{max} (ng/mL)	5616.2 (22.7)[a]	5920.0 (16.5)	93.40 (87.53, 99.66)
B/F/TAF (fasted) 2 hours after 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng*h/mL)	67,704.6 (47.0)[a]	132,814.0 (27.0)	47.66 (38.26, 59.35)
AUC_{last} (ng*h/mL)	63,447.0 (45.8)[a]	124,721.4 (28.0)	47.34 (37.91, 59.12)
C_{max} (ng/mL)	2735.0 (48.3)[a]	5920.0 (16.5)	41.51 (33.25, 51.83)
B/F/TAF (fed) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng*h/mL)	50,813.5 (34.8)	93,658.3 (27.2)	53.25 (44.21, 64.14)
C_{24} (ng/mL)	803.6 (36.4)	1410.1 (29.7)	56.01 (46.21, 67.88)
C_{max} (ng/mL)	2446.4 (31.4)	4700.7 (23.6)	51.46 (42.69, 62.03)
B/F/TAF (fed) with calcium carbonate (Test)			
AUC_{inf} (ng*h/mL)	94,832.8 (21.2)	93,658.3 (27.2)	103.29 (88.96, 119.93)
AUC_{last} (ng*h/mL)	91,454.0 (20.1)	91,204.9 (26.5)	102.36 (88.07, 118.98)
C_{max} (ng/mL)	4105.0 (13.7)	4700.7 (23.6)	89.58 (77.83, 103.10)
B/F/TAF (fed) with ferrous fumarate (Test)			
AUC_{inf} (ng*h/mL)	77,307.8 (24.8)	93,658.3 (27.2)	83.84 (74.07, 94.89)
C_{24} (ng/mL)	1228.7 (25.0)	1410.1 (29.7)	88.93 (78.12, 101.24)
C_{max} (ng/mL)	3485.0 (23.2)	4700.7 (23.6)	75.12 (64.82, 87.05)

a N = 13 for Test treatment

	Conclusions: • The expected chelating effect of maximum-strength antacid on BIC exposure was reduced by staggering administration by 2 hours. • Administration of B/F/TAF with a meal reduced the expected chelating effect of metal cations on BIC exposure. • Single doses of B/F/TAF alone or in combination with maximum-strength antacid, calcium carbonate, or ferrous fumarate were well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, or pregnancies were reported during the study. One subject discontinued study drug due to an AE of Grade 2 urticaria, which began 1 day after receiving B/F/TAF alone and was considered related to study drug by the investigator. The subject was treated with diphenhydramine, and the event resolved on Day 7; no post-treatment clinical laboratory abnormalities were noted.

2.5.1.5. Study GS-US-380-4270

Location:	GS-US-380-4270
Title:	A Phase 1, Open-Label, Fixed-Sequence Study Evaluating the Drug Interaction Potential of Bictegravir on Midazolam
Primary Objective:	To evaluate the effect of BIC when administered as the B/F/TAF FDC on the PK of the cytochrome P450 (CYP) 3A probe, midazolam (MDZ)
Study Design and Subject Population:	This Phase 1, open-label, fixed-sequence, single- and multiple-dose, single-center study evaluated the effect of BIC when administered as the B/F/TAF FDC on the PK of the CYP3A probe MDZ in healthy subjects. Subjects received a single dose of MDZ 2 mg under fed conditions on Day 1 (Treatment A); B/F/TAF 50/200/25 mg once daily in the morning under fed conditions on Days 3 to 11 (Treatment B); and a single dose of MDZ under fed conditions administered 5 hours after a single dose of B/F/TAF in the morning under fed conditions on Day 12 (Treatment C). Eligible subjects were healthy males and nonpregnant, nonlactating females, who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had an $eGFR_{CG}$ ≥ 90 mL/min), and had no significant medical history. A total of 14 subjects were randomized into the study, and 14 subjects completed dosing with study drugs and the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** MDZ plasma PK parameters and statistical comparisons are presented in the table below. Plasma exposures of MDZ were comparable following administration alone or in combination with steady-state B/F/TAF. Midazolam plasma AUC_{inf}, AUC_{last}, and C_{max} GLSM ratios and 90% CIs were all within the predefined no-effect boundaries of 70% and 143% when administered with steady-state B/F/TAF relative to when administered alone (%GLSM ratio [90%CI]: 114.52 [99.79, 131.42], 115.47 [99.67, 133.78], and 103.44 [87.23, 122.68], respectively). Plasma $t_{1/2}$ for MDZ was also similar when administered with steady-state B/F/TAF relative to when administered alone (median [Q1, Q3] $t_{1/2}$: 4.46 [2.70, 5.31] h and 4.73 [2.91, 5.13] h, respectively). No clinically relevant differences in MDZ exposures were observed when MDZ was administered with steady-state B/F/TAF versus when MDZ was administered alone, confirming that BIC is not an inducer or inhibitor of CYP3A.

MDZ PK Parameter	Mean (%CV) Test Treatment C (B/F/TAF + MDZ) (N = 14)	Mean (%CV) Reference Treatment A MDZ (N = 14)	% GLSM Ratio (90% CI)
AUC_{inf} (h*ng/mL)	38.4 (40.0)	33.3 (45.4)	114.52 (99.79, 131.42)
AUC_{last} (h*ng/mL)	36.6 (38.6)	31.5 (43.8)	115.47 (99.67, 133.78)
C_{max} (ng/mL)	6.2 (32.3)	6.0 (39.1)	103.44 (87.23, 122.68)
$t_{1/2}$ (h)[a]	4.46 (2.70, 5.31)	4.73 (2.91, 5.13)	—

a median (Q1, Q3)

Conclusions:

- Statistical comparisons of the primary PK parameters (AUC_{inf}, AUC_{last}, and C_{max}) of MDZ between steady-state B/F/TAF plus MDZ (test) and MDZ alone (reference), demonstrated that the GLSM ratios and 90% CIs were within the predefined no-effect boundaries of 70% and 143%.
- Following coadministration of MDZ and B/F/TAF relative to MDZ alone, no clinically relevant differences in MDZ exposures were observed, confirming that BIC is not an inducer or inhibitor of CYP3A.
- B/F/TAF and MDZ administered alone and in combination were generally safe and well tolerated in this healthy subject study. No deaths, SAEs, Grade 3 or 4 AEs, AEs that led to premature study drug discontinuation, or pregnancies were reported during the study.

2.5.2. BIC Studies

2.5.2.1. Study GS-US-141-1485

Location:	GS-US-141-1485
Title:	A Phase 1 Adaptive Study to Evaluate Transporter, Cytochrome (CYP) 450-Mediated and UGT1A1 Drug-Drug Interactions Between GS-9883 and Probe Drugs
Primary Objective(s):	• To evaluate the effect of mixed uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1)/ CYP3A4/P-glycoprotein (P-gp) inhibition on the PK of BIC • To evaluate the effect of CYP3A4/P-gp/UGT1A1 induction on the PK of BIC
Study Design and Subject Population:	This Phase 1, open-label, multiple-dose, multiple-cohort, adaptive study evaluated the effects of the probe drugs, atazanavir (ATV) + cobicistat (COBI) (a mixed inhibitor of UGT1A1/CYP3A4/P-gp), rifampin (RIF, a CYP3A4/P-gp/UGT1A1 inducer), ATV (a UGT1A1/CYP3A4 inhibitor), voriconazole (VORI, a CYP3A4 inhibitor), rifabutin (RBT, a CYP3A4/P-gp inducer), and darunavir boosted with cobicistat (DRV/co; a CYP3A4 inhibitor) on the PK and safety of BIC in healthy subjects. Subjects were assigned to the following cohorts and received the following study treatments: • **Cohort 1** (**UGT1A1/CYP3A4/P-gp Inhibitor**)**:** Subjects received a single dose of BIC 75 mg under fed conditions on Day 1; ATV 300 mg + COBI 150 mg once daily under fed conditions on Days 5 to 8 and Days 10 to 12; and single doses of BIC 75 mg + ATV 300 mg + COBI 150 mg under fed conditions on Day 9, with a washout period on Days 2 to 4. • **Cohort 2 (CYP3A4/P-gp/UGT1A1 Inducer):** Subjects received a single dose of BIC 75 mg under fed conditions on Day 1; RIF 600 mg once daily under fed conditions on Days 5 to 14 and Days 16 to 18; and single doses of BIC 75 mg + RIF 600 mg under fed conditions on Day 15, with a washout period on Days 2 to 4. • **Cohort 3 (UGT1A1/CYP3A4 Inhibitor):** Subjects received a single dose of BIC 75 mg under fed conditions on Day 1; ATV 400 mg once daily under fed conditions on Days 5 to 8 and Days 10 to 12; and single doses of BIC 75 mg + ATV 400 mg under fed conditions on Day 9, with a washout period on Days 2 to 4. • **Cohort 4 (CYP3A4 Inhibitor):** Subjects received a single dose of BIC 75 mg under fasted conditions on Day 1; VORI 300 mg twice daily under fasted conditions on Days 5 to 8 and Days 10 to 12; and single dose of BIC 75 mg and doses of VORI 300 mg in the morning and afternoon under fed conditions on Day 9, with a washout period on Days 2 to 4. • **Cohort 5 (CYP3A4/P-gp Inducer):** Subjects received BIC 75 mg once daily under fasted conditions on Days 1 to 6 and BIC 75 mg and RBT 300 mg once daily under fasted conditions on Days 7 to 20. • **Cohort 6 (CYP3A4 Inhibitor):** Subjects received subjects received BIC 75 mg once daily under fed conditions on Days 1 to 6 and BIC 75 mg and DRV/co 800/150 mg once daily under fed conditions on Days 7 to 20. Eligible subjects were healthy male and nonpregnant, nonlactating females who were 18 to 45 years of age (inclusive), had a BMI of 19.0 and 30.0 kg/m^2 (inclusive), had an $eGFR_{CG} \geq 90$ mL/min, and had no significant medical history. A total of 90 subjects (15 subjects per cohort) were enrolled in the study, and 86 subjects (95.6%) completed study drug administration. Four subjects also prematurely discontinued study drug: 2 subjects discontinued due to an AE; 1 subject withdrew consent, and 1 subject discontinued due to a protocol violation. One subject completed study drug treatment, but discontinued the study due to withdrawn consent.

Summary of Results and Conclusions:

Pharmacokinetic Results:

BIC PK parameter estimates are summarized in the table below for each cohort. Coadministration of a single dose of BIC with a UGT1A1/CYP3A4/P-gp inhibitor (ATV+COBI) under fed conditions resulted in increases of 306% in AUC_{inf}, 31% in C_{max}, and 222% in median $t_{1/2}$ relative to those for a single dose of BIC alone. Coadministration of a single dose of BIC with a UGT1A1/CYP3A4 inhibitor (ATV alone) under fed conditions resulted in increases of 315% in AUC_{inf}, 28% in C_{max}, and 225% in median $t_{1/2}$ relative to those for a single dose of BIC alone, similar to the DDI observed when BIC was coadministered with ATV+COBI. However, coadministration of a single dose of BIC with an inhibitor of CYP3A4 only (VORI) under fasted conditions resulted in an increase of only 61% in AUC_{inf} and no significant increase in C_{max} relative to those for a single dose of BIC alone; median $t_{1/2}$ increased by 60% relative to those for a single dose of BIC alone. In addition, coadministration of multiple doses of BIC once daily with a CYP3A4 inhibitor (DRV/COBI) under fed conditions resulted in increases of 74% in AUC_{tau}, 52% in C_{max}, and 111% in C_{tau} relative to those for BIC administered once daily alone.

Coadministration of a single dose of BIC with a CYP3A4/UGT1A1/P-gp inducer (RIF) under fed conditions resulted in decreases of 75% in AUC_{inf}, 28% in C_{max}, and 69% in median $t_{1/2}$ relative to those for a single dose of BIC alone. In addition, coadministration of multiple doses of BIC once daily with a CYP3A4/P-gp inducer (RBT) under fasted conditions resulted in decreases of 38% in AUC_{tau}, 20% in C_{max}, and 56% in C_{tau} compared with those for BIC administered once daily alone.

BIC PK Parameter	Test[a]	Reference[a]	%GLSM Ratio (90% CI) (Test/Reference)
Cohort 1: BIC 75 mg Single Dose + ATV 300 mg QD + COBI 150 mg QD (Test; N = 15) vs BIC 75 mg Single Dose (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	628,290.3 (17.4)	154,433.7 (16.0)	405.62 (376.07, 437.49)
C_{max} (ng/mL)	9033.3 (12.2)	6890.0 (12.3)	131.11 (122.71, 140.08)
$t_{1/2}$ (h)	59.99 (52.94, 63.10)	18.62 (15.87, 20.96)	–
Cohort 2: BIC 75 mg Single Dose + RIF 600 mg QD (Test; N = 15) vs BIC 75 mg Single Dose (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	36,398.0 (21.5)	155,986.3 (41.8)	24.52 (22.00, 27.33)
C_{max} (ng/mL)	5131.3 (15.7)	7118.7 (17.0)	72.21 (67.06, 77.75)
$t_{1/2}$ (h)	5.65 (5.30, 6.18)	18.09 (14.47, 20.75)	–
Cohort 3: BIC 75 mg Single Dose + ATV 400 mg QD (Test; N = 15) vs BIC 75 mg Single Dose (Reference; N = 15); fed			
AUC_{inf} (h*ng/mL)	638,857.0 (20.5)	154,253.8 (21.8)	414.51 (381.02, 450.94)
C_{max} (ng/mL)	9110.7 (16.6)	7078.7 (13.3)	128.10 (122.95, 133.47)
$t_{1/2}$ (h)	56.86 (50.70, 66.90)	17.47 (15.26, 19.81)	
Cohort 4: BIC 75 mg Single Dose + VORI 300 mg BID (Test; N = 15) vs BIC 75 mg Single Dose (Reference; N = 15); fasted			
AUC_{inf} (h*ng/mL)	160,519.3 (26.9)	101,659.4 (37.2)	161.14 (141.07, 184.06)
C_{max} (ng/mL)	5442.7 (33.6)	4844.0 (21.5)	108.94 (96.14, 123.43)
$t_{1/2}$ (h)	25.45 (18.65, 28.08)	15.92 (15.12, 19.76)	
Cohort 5: BIC 75 mg QD + RBT 300 mg QD (Test; N = 13) vs BIC 75 mg QD (Reference; N = 15); fasted			
AUC_{tau} (h*ng/mL)	66,164.3 (37.4)	106,486.2 (37.2)	62.01 (53.06, 72.47)
C_{max} (ng/mL)	6140.0 (36.0)	7624.7 (35.5)	80.37 (66.93, 96.50)
C_{tau} (ng/mL)	1212.2 (43.0)	2732.9 (40.7)	43.98 (37.14, 52.07)
Cohort 6: BIC 75 mg QD + DRV/co 800/150 mg QD (Test; N = 13) vs BIC 75 mg QD (Reference; N = 15); fed			
AUC_{tau} (h*ng/mL)	265,249.0 (19.3)	152,356.1 (16.2)	173.60 (161.55, 186.54)
C_{max} (ng/mL)	17,300.0 (15.0)	11,402.0 (15.2)	151.56 (140.15, 163.90)
C_{tau} (ng/mL)	8486.9 (24.9)	4017.3 (21.6)	211.43 (195.18, 229.03)

a Mean (%CV) for AUC_{last}, AUC_{inf}, AUC_{tau}, C_{max}, and C_{tau}; median (Q1, Q3) for $t_{1/2}$

Conclusions:

- Coadministration of a single dose of BIC with a UGT1A1/CYP3A4/P-gp inhibitor (ATV+COBI) or UGT1A1/CYP3A4 inhibitor (ATV) under fed conditions resulted in increases in AUC_{inf} of 306% and 315%, respectively, and increases in median $t_{1/2}$ of approximately 222% and 225% relative to those for a single dose of BIC alone, respectively, suggesting reduction of UGT1A1- and CYP3A4-mediated clearance of BIC. The similarity in the effect of ATV+COBI and ATV on BIC exposure indicated that P-gp inhibition had a minor impact on BIC absorption.
- Coadministration of a single dose of BIC with a CYP3A4 inhibitor (VORI) under fasted conditions resulted in increases of 61% in AUC_{inf} and 60% in median $t_{1/2}$, and coadministration of multiple once-daily doses of BIC with a CYP3A4 inhibitor (DRV/COBI) under fed conditions resulted in increases of 74% in AUC_{tau}, 52% in C_{max}, and 111% in C_{tau} relative to those for BIC administered once daily alone. These results demonstrated that inhibition of CYP3A4-specific metabolism led to smaller increases in BIC exposure compared with that observed following dual UGT1A1/CYP3A4 inhibition by ATV. Therefore, it is likely that inhibition of either metabolic pathway alone will not lead to large (ie, > 2-fold) increases in BIC exposure.
- Coadministration of a single dose of BIC with a CYP3A4/UGT1A1/P-gp inducer (RIF) resulted in decreases of 75% in AUC_{inf} and 28% in C_{max} relative to those for a single dose of BIC alone. In comparison, coadministration of multiple once-daily doses of BIC with a CYP3A4/P-gp inducer (RBT) led to modest decreases of 38% in AUC_{tau}, 20% in C_{max}, and 56% in C_{tau}.
- Single doses of BIC were well tolerated alone or in combination with ATV+COBI, RIF, ATV, or VORI. In addition, multiple doses of BIC were well tolerated alone or in the presence of RBT or DRV/COBI. No deaths, SAEs, Grade 3 or 4 AEs, or pregnancies were reported during the study. Two subjects had an AE that led to premature discontinuation of study drug. One subject in Cohort 5 prematurely discontinued BIC+RBT due to Grade 2 AE of vomiting, and 1 subject in Cohort 6 prematurely discontinued BIC+DRV/co due to a Grade 2 AE of drug eruption. Both of these AEs have been observed previously for the probe drugs and were considered related to study drug by the investigator.

2.5.2.2. Study GS-US-311-1790 (Cohort 2)

Location:	GS-US-311-1790
Title:	A Phase 1, Randomized, Open Label, Drug Interaction Study Evaluating the Effect of Emtricitabine/ Tenofovir Alafenamide Fixed-Dose Combination Tablet or GS-9883 on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol
Primary Objective:	To determine the effect of FTC and TAF administered as the F/TAF 200/25 mg FDC tablet or BIC 75 mg on the PK of a representative hormonal contraceptive medication, norgestimate (NGM)/ethinyl estradiol (EE) (Ortho Tri-Cyclen® Lo)
Study Design and Subject Population:	This Phase 1, randomized, open-label, single center, fixed-sequence, multiple-dose, multiple-cohort study evaluated the effect of FTC and TAF, administered as F/TAF FDC tablet, or BIC on the PK of a representative hormonal contraceptive medication (Ortho Tri-Cyclen Lo) in healthy women of childbearing age. Subjects participated in a Lead-in period (Part A) of 28 days during which they completed dosing with hormonal NGM/EE oral contraceptive (OC) prior to Day 1 assessments of Cycle 1 (Part B). For Part B, subjects were randomized to 1 of 2 cohorts to receive the following treatments: • **Cohort 1 (F/TAF):** Subjects continued the use of OC once daily for the remainder of the study (2 full 28-day menstrual cycles) until Day 56 and were administered F/TAF 200/25 mg once daily on Days 29 to 42 (Cycle 2). • **Cohort 2 (BIC):** Subjects continued the use of OC once daily for the remainder of the study (2 full 28-day menstrual cycles) until Day 56 and were administered BIC 75 mg once daily on Days 29 to 42 (Cycle 2). Data from Cohort 2 are presented below; data from Cohort 1 are available in the CSR. Eligible subjects were healthy, nonpregnant, nonlactating, premenopausal women who were 18 to 45 years of age (inclusive), had a BMI of 19.0 to 30.0 kg/m^2 (inclusive), had either a normal 12-lead ECG or an ECG with abnormalities that were considered clinically insignificant by the investigator in consultation with the sponsor, and $eGFR_{CG} \geq 90$ mL/min. A total of 16 subjects were enrolled in Cohort 2 and received at least 1 dose of study drug. Fifteen subjects completed Cohort 2. One subject withdrew consent and prematurely discontinued study drug.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Systemic exposures of norelgestromin (NGMN, major metabolite of NGM), norgestrel (NG, minor metabolite of NGM), and EE when OC was coadministered with BIC were similar to those achieved when OC was administered alone. The GLSM ratios and the associated 90% CIs of all primary PK parameters of NGMN, NG, and EE were within the prespecified no-effect bounds of 70% to 143%. The PK of OC was not altered by BIC. The BIC exposures (given with food) were consistent with historical data. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and progesterone median concentrations were generally comparable across all treatment cycles. LH median values were lower than those expected for the ovulatory phase; FSH median values were within or lower than the reference range for the ovulatory phase {Quest Diagnostics 2013}. These results are consistent with a possible decrease in serum LH and FSH by oral hormonal contraceptives. Consistent with absence of ovulation, median progesterone concentrations measured at Day 21 of the OC cycle were substantially lower in all treatment cycles than those expected for the luteal phase. **Conclusions:** • No loss of contraceptive efficacy is expected with coadministration of OC with BIC: — Similar plasma exposures of NGMN, NGM, and EE were achieved when OC was coadministered with BIC. — FSH, LH, and progesterone were generally comparable across all treatment cycles. • When BIC was coadministered with OC, PK exposures of BIC were consistent with historical data. • Taking OC as an oral contraceptive concurrent with BIC treatment is safe and well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, AEs that led to premature study drug discontinuation, or pregnancies were reported during the study.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

The clinical pharmacology of B/F/TAF across all supporting studies is described in the following sections by individual analyte. Unless otherwise specified, BIC 75 mg, FTC 200 mg, and TAF 25 mg administered as single agents and B/F/TAF 50/200/25 mg, F/TAF 200/25 mg, or E/C/F/TAF 150/150/200/10 mg as the FDC were the doses and formulations used in the clinical studies. Figure 1 shows all clinical studies supporting the clinical pharmacology for this marketing application by study type.

3.1. Absorption, Distribution, Metabolism, and Elimination Characteristics

The following sections summarize the results of clinical and nonclinical studies investigating the ADME of BIC, TAF, and FTC as single agents and as components of BIC+F/TAF or B/F/TAF. The results of nonclinical studies investigating absorption are discussed in detail in the Nonclinical Pharmacokinetics Written Summary (m2.6.4).

3.1.1. Absorption

3.1.1.1. BIC

The absolute bioavailability of BIC has not been evaluated in humans. After oral administration of BIC in a solution-based formulation, the oral bioavailability of BIC was moderate to high with 50%, 42%, and 74% in rats, dogs, and monkeys, respectively (m2.6.4, Section 3.2).

The absorption of BIC in humans is expected to be > 60% based on the results of a human ADME study and evaluation of BIC PK in healthy subjects (Study GS-US-141-1481, Section 2.2.2.2). Following a single oral dose of 100-mg [^{14}C]BIC under fed conditions in the human ADME study, a minimum of 60% of the administered dose was absorbed, as evidenced by the total radioactivity recovered in the urine (35% of dose) and excreted in the feces as intact metabolites (25% to 28% of dose). In vitro, BIC is a substrate of P-gp and breast cancer resistance protein (BCRP) (m2.6.4, Section 7.1). Importantly, the trans-epithelial permeability of BIC was high across human colon carcinoma-derived cell (Caco-2) monolayers and, therefore, passive transcellular diffusion is expected to be the primary mechanism for BIC intestinal absorption (m2.6.4, Section 3.1).

Coadministration of BIC and F/TAF demonstrated that BIC exposure was unaffected by F/TAF, indicating that TAF and FTC do not alter BIC absorption (Study GS-US-141-1218, Section 2.2.2.1).

Following oral administration of BIC administered as a single agent, BIC exhibited dose-proportional increases in exposure (AUC and C_{max}) across the dose range of 25 to 100 mg in healthy subjects under fasted conditions (Study GS-US-141-1218, Section 2.2.2.1). Less than dose-proportional increases in BIC exposure were observed at doses greater than 100 mg, presumably limited by solubility.

In the exploratory food effect study with BIC administered as a single agent, food enhanced the availability of BIC. Coadministration of BIC single agent (100 mg) with a high-fat meal increased BIC AUC_{inf} and C_{max} by 84% and 101%, respectively, compared with the exposures achieved under fasted conditions (Study GS-US-141-1218, Section 2.2.2.1). However, in the dedicated food effect study with the B/F/TAF, the effect of food on BIC exposure was significantly less than that observed with the single agent (BIC AUC increased 24% with a moderate- or high-fat meal compared with fasted administration of the B/F/TAF) (Study GS-US-141-1233, Section 2.2.1.1). The difference in the effect of food on BIC exposures between BIC administered as a single agent and BIC administered as part of the B/F/TAF is likely the result of increased bioavailability of BIC in the FDC formulation compared with the single agent formulation. Following administration of the B/F/TAF with or without food, the observed median T_{max} of BIC was 2.0 to 4.0 hours (Study GS-US-141-1233, Section 2.2.1.1).

Consistent with the cation-coordinating pharmacophore of INSTIs and previous reports of INSTI susceptibility to chelation-type drug interactions with divalent and trivalent metal cations {GENVOYA® 2017, GlaxoSmithKline 2015, Patel 2011, Ramanathan 2013}, BIC absorption was impacted by polyvalent cation-containing antacids and supplements. BIC exposure (AUC_{inf}) was reduced following simultaneous administration of B/F/TAF with maximum-strength antacid (ie, maximum chelation interaction scenario), calcium carbonate, or ferrous fumarate under fasted conditions by approximately 79%, 33%, and 63%, respectively, compared with administration of B/F/TAF alone under fasted conditions (Study GS-US-380-3909, Section 2.5.1.4). However, the chelating effect of polyvalent cation-containing drugs on BIC exposure was mitigated by staggering administration ± 2 hours or coadministration with food. The effect of cations on BIC absorption is described further in the context of a DDI in Section 3.2.4.2.2.1.

3.1.1.2. TAF

The absolute bioavailability of TAF was not evaluated in humans. TAF absorption is expected to be modest (approximately 40%) in the context of B/F/TAF under fed conditions based on the results of a human ADME study (Study GS-US-120-0109) and evaluation of TAF PK in healthy subjects with inhibitors of efflux transporters P-gp and/or BCRP, for which TAF is a substrate (Study GS-US-311-0101, {Inoue 1980, Williams 1985}). The impact of P-gp inducers and P-gp/BCRP inhibitors on TAF absorption/exposures is discussed further in the context of a DDI in Section 3.2.4.2.2.2.

Coadministration of BIC and F/TAF demonstrated that TAF exposure was unaffected by BIC, indicating that BIC does not alter TAF absorption (Study GS-US-141-1218, Section 2.2.2.1).

The TAF PK profile following single doses and at steady-state was characterized in healthy subjects and HIV-infected subjects at doses ranging from 8 to 125 mg (Studies GS-US-120-0104 [N = 25], GS-US-292-0103 [N = 19], GS-US-120-0107 [N = 48]). TAF exposure exhibited dose proportionality across the range of doses studied.

The effect of food on TAF absorption following administration of B/F/TAF was evaluated (Study GS-US-141-1233, Section 2.2.1.1). A moderate- and high-fat meal increased TAF AUC_{last} by 48% and 63%, respectively, compared with fasted conditions. These results were

consistent with historical data of TAF as a single agent {Vemlidy 2017, VEMLIDY® 2016} and as the F/TAF {DESCOVY® 2017, Gilead Sciences International Ltd 2016}. Following administration of the B/F/TAF with or without food, the observed median T_{max} of TAF was 0.5 to 2.0 hours (Study GS-US-141-1233, Section 2.2.1.1). The effect of food on TAF absorption as an extrinsic factor is described further in Section 3.2.4.1.

3.1.1.3. FTC

FTC is rapidly and extensively absorbed after oral administration in mice, rats, and cynomolgus monkeys, with oral bioavailability ranging from 58% to 97% (m2.6.4, Section 3.2). Single- and multiple-dose PK studies in humans have confirmed nonclinical data and showed that FTC was rapidly and extensively absorbed after oral administration. Plasma FTC concentrations reached a maximum within 1 to 2 hours of dosing over a dose range of 25 to 1200 mg and then followed an apparent multi-exponential decay (Study 143-001). Greater than 85% of an oral dose of FTC was absorbed with little first-pass elimination prior to reaching the systemic circulation based on a ^{14}C ADME study (Study FTC-106). A high absolute bioavailability (93%) of FTC was achieved by comparing oral and intravenous (IV) exposure (Study FTC-110).

Following both single- and multiple-dose administration of FTC over the dose range of 25 to 200 mg, plasma concentrations of FTC (C_{max}, AUC, and C_{tau}) were approximately dose proportional for once daily or twice daily doses (Study FTC-101).

Coadministration of BIC and F/TAF demonstrated that FTC exposure was unaffected by BIC, indicating that BIC does not alter FTC absorption (Study GS-US-141-1218, Section 2.2.2.1).

The effect of food on FTC absorption following administration of B/F/TAF was evaluated clinically (Study GS-US-141-1233, Section 2.2.1.1). Relative to fasting conditions, FTC AUC_{inf} was similar following administration with a moderate- or high-fat meal. The lack of effect of food on FTC exposure in B/F/TAF was consistent with historical data for FTC as a single agent {Emtriva 2016, EMTRIVA® 2017} and as part of F/TAF {DESCOVY® 2017, Gilead Sciences International Ltd 2016}. Following administration of the B/F/TAF with or without food, the observed median T_{max} of FTC was 1.5 to 2.0 hours (Study GS-US-141-1233, Section 2.2.1.1). The effect of food on FTC absorption is described further as an extrinsic factor in Section 3.2.4.1.

3.1.2. Distribution

3.1.2.1. BIC

In rats, tissue distribution of [^{14}C]BIC and its metabolites after a single dose (2 mg/kg) was rapid and extensive (m2.6.4, Section 4.3). BIC is highly bound to human plasma proteins (> 99%) in vitro (m2.6.4, Section 4.1).

Consistent with in vitro data, BIC protein binding was high (> 99%) in plasma from healthy humans based on ex vivo results. In subjects with severe renal impairment, the percent bound remained > 99%, but the percent unbound was higher (0.75%) compared with healthy matched control subjects (0.49%) (Study GS-US-141-1479, Section 2.4.2.2). Similarly, percent unbound

was also higher in subjects with severe hepatic impairment (0.81%) compared with healthy matched control subjects (0.61%) (Study GS-US-141-1478, Section 2.4.2.1). The effect of renal impairment on BIC PK is further discussed in Section 3.2.3.3.1.

Following a single 100-mg dose of [^{14}C]BIC to healthy male subjects, the blood-to-plasma ratio of [^{14}C]-radioactivity was approximately 0.50 to 0.55 through 120 hours postdose, indicating that BIC was predominantly distributed to plasma rather than the cellular components of blood (Study GS-US-141-1481, Section 2.2.2.2).

3.1.2.2. TAF

Following oral administration of [^{14}C]TAF to rat, mouse, and dog, [^{14}C]TAF-derived radioactivity was widely distributed in all species (m2.6.4, Section 4.3). The in vitro plasma protein binding of TAF was moderate in human plasma with a percentage unbound value of 46.8% (m2.6.4, Section 4.1). Based on ex vivo plasma protein binding studies, the TAF percent unbound ranged from 14% to 23% in subjects with severe renal impairment, subjects with mild and moderate hepatic impairment and healthy matched control subjects. However, the percent unbound TAF was approximately 2-fold higher in subjects with severe hepatic impairment (35% to 40%) (Studies GS-US-120-0108, GS-US-120-0114, and GS-US-320-1615).

Following administration of an oral dose of [^{14}C]TAF in healthy subjects in a human ADME study, the blood to plasma concentration ratio of ^{14}C-radioactivity at 0.25 hours and 216 hours postdose was 0.6 and 2.4, respectively (Study GS-US-120-0109).

3.1.2.3. FTC

The tissue distribution of [^{14}C]FTC was characterized in rats and cynomolgus monkeys after a single oral dose of 200 mg/kg and FTC was widely distributed (m2.6.4, Section 4.3). The protein binding of FTC was < 5% in mouse, rabbit, monkey, and human plasma (m2.6.4, Section 4.1).

The V_{ss} of FTC as determined following IV administration in humans averaged 109 L (Study FTC-110). Emtricitabine and its minor metabolites demonstrate blood-to-plasma concentration ratios of approximate 1.0, indicating similar distribution into the blood cellular components relative to plasma (Study FTC-106). Emtricitabine distributes into white blood cells and semen (Studies FTC-101 and FTC-106). High levels of FTC 5′-triphosphate (FTC-TP; the intracellular anabolite of FTC) were measured in PBMCs.

3.1.3. Metabolism and Elimination

3.1.3.1. BIC

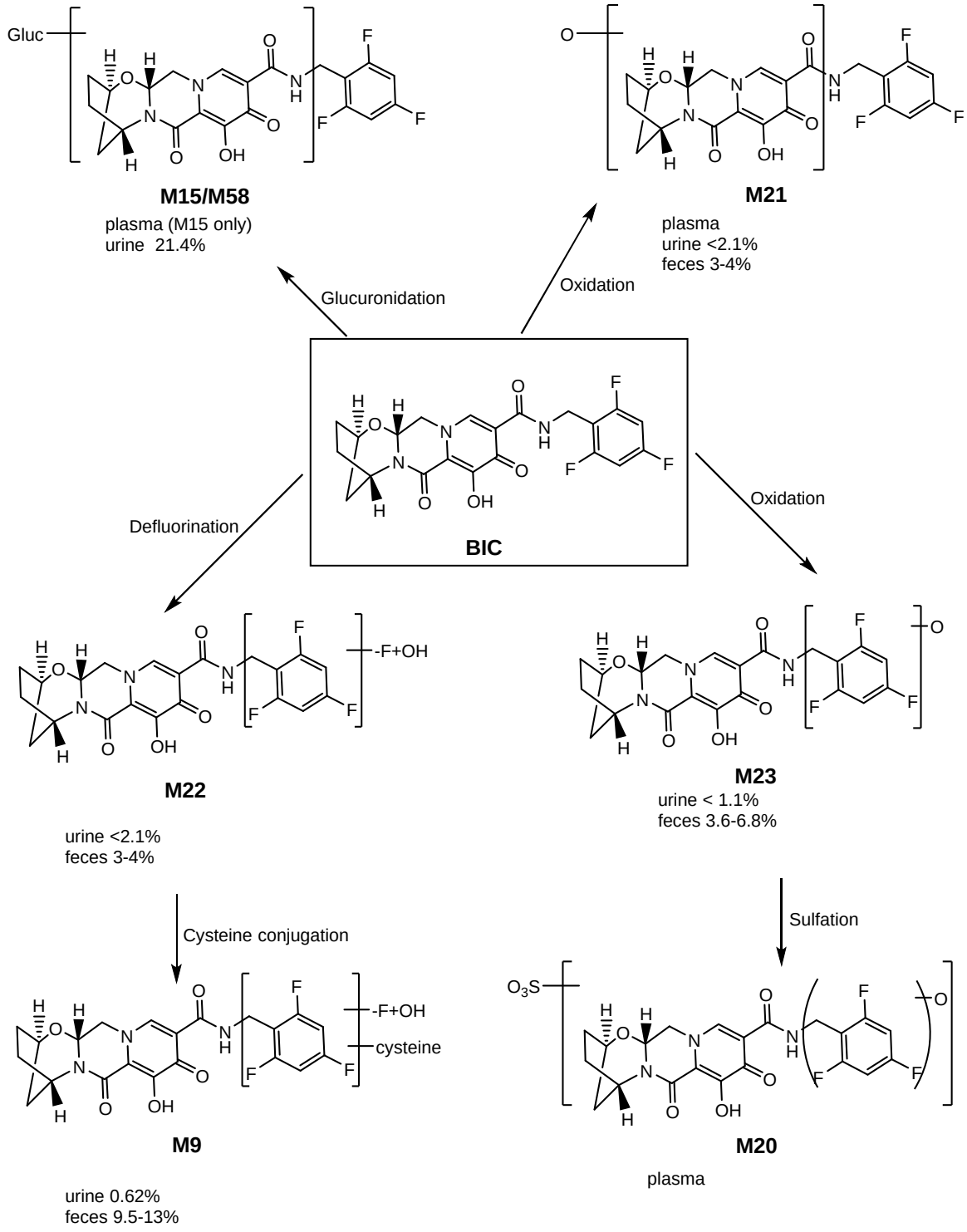
The metabolism of BIC, including metabolic routes leading to elimination, was characterized in vitro in hepatic microsomes and hepatocytes (m2.6.4, Sections 5.1 and 5.2); in vivo in rats and monkeys (m2.6.4, Section 5.3); and in a human mass balance PK study (Study GS-US-141-1481, Section 2.2.2.2). No unique metabolites were identifiable.

In vitro experiments were conducted to determine CYP and UGT reaction phenotyping and demonstrated that BIC is mainly metabolized by CYP3A and UGT1A1 (m2.6.4, Section 7.1).

Following a single oral dose of 100-mg [^{14}C]BIC in healthy male subjects, 95.3% of the [^{14}C]BIC dose was recovered with 60.3% of the dose from feces and 35.0% of the dose from urine (Study GS-US-141-1481, Section 2.2.2.2). Unchanged BIC constituted the majority (67.9%) of circulating total radioactivity in plasma with an observed median $t_{1/2}$ of 17.26 hours. M20 (hydroxy-BIC-sulfate, 20.1%) and M15 (BIC-glucuronide, 8.6%) were the major metabolites identified in plasma. Unchanged drug accounted for 31% to 34% of the radioactive dose in the feces that likely represents a combination of both unabsorbed drug and deconjugated BIC glucuronide. Desfluoro-hydroxy- BIC-cysteine-conjugate (10%−13% of dose) and other minor oxidative metabolites were identified in feces. Radioactivity in urine consisted primarily of M15/M58 (BIC-glucuronide; 21% of dose) and other minor oxidative metabolites and their conjugates. Renal clearance of the unchanged parent was minimal (1.3% of dose).

Figure 3 presents a proposed major biotransformation pathway for [^{14}C]BIC. There were no unique human metabolites; all human metabolites were also found in nonclinical species. Overall, clinical and nonclinical data indicate that metabolism is the primary clearance pathway for BIC. Additionally, results of the human ADME study showing the recoveries of oxidative metabolites and direct glucuronide(s) in total excreta are in agreement with BIC DDI modeling/analyses (QP-2015-1001), which estimated similar contributions by UGT1A1 and CYP3A to BIC metabolism based on probe DDI data with BIC (Study GS-US-141-1485, Section 2.5.2.1).

Figure 3. Proposed Major Biotransformation and Excretion Pathway for BIC in Humans



Metabolites M21 and M22 coeluted in urine. M23 coeluted with M51 in urine.
Modified from Study GS-US-141-1481, Figure 10-10; values reported are % of dose administered

3.1.3.2. TAF

The metabolism of TAF, including metabolic routes leading to elimination, was characterized in vitro in hepatocytes; in vivo in mice, rats, and dogs (m2.6.4, Section 5.3); and in a human mass balance study (Study GS-US-120-0109).

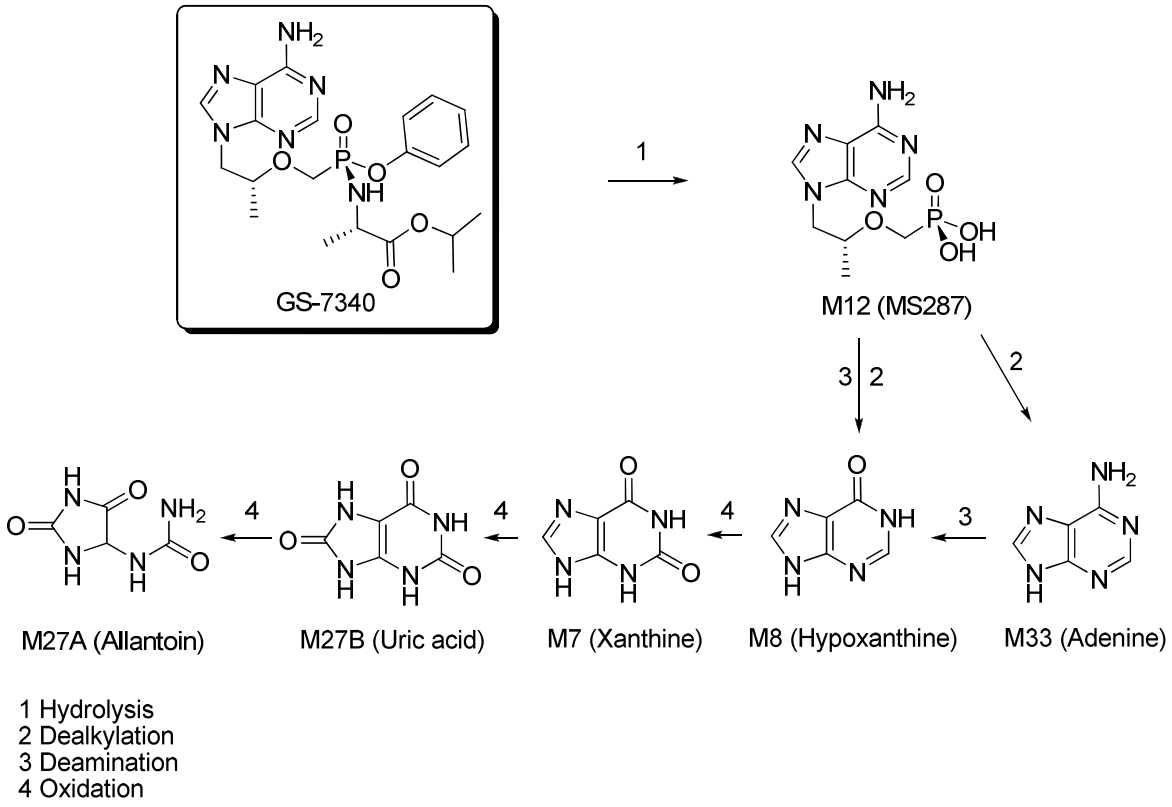
In vitro phenotyping experiments showed that TAF is a poor substrate of CYP3A and not metabolized by other P450s (m2.6.4, Section 5.1). TAF is metabolized primarily via hydrolysis by carboxylesterase 1 (CES1) in primary hepatocytes, while cathepsin A (CatA) is the major enzyme hydrolyzing TAF to TFV in PBMCs or other HIV target cells {Murakami 2015}. TFV is then further phosphorylated to tenofovir diphosphate (TFV-DP) by cellular nucleotide kinases. Due to its plasma stability and intracellular activation by CatA, TAF is efficiently loaded into PBMCs (including lymphocytes and other HIV-target cells) and macrophages, which results in high concentrations of TFV-DP in PBMCs and minimal exposure of TFV to the systemic circulation and off-target tissues, including the kidney and bone (Study GS-US-120-0104, {Lee 2005, Ruane 2012}).

Following a single dose of [^{14}C]TAF in healthy male subjects**,** approximately 84.4% of radioactive dose was recovered, with 47.2% of the dose from feces and 36.2% from urine (Study GS-US-120-0109). Renal excretion of TAF as unchanged parent was minimal (1.4% of dose). TAF was rapidly metabolized to TFV, with a median TAF plasma $t_{1/2}$ of 0.51 hours and the median TFV T_{max} of 3.25 hours postdose. Plasma circulating TFV exhibits a long $t_{1/2}$ (median plasma $t_{1/2}$ of 32.37 hours). ^{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 observed, including xanthine, hypoxanthine, and adenine, which are identical to the endogenous products of purine metabolism and are not associated with safety risk.

The predominant species detected in feces and urine was TFV (22.2% of the dose in urine, and 31.4% of the dose in feces) with other minor metabolites including xanthine, hypoxanthine, and adenine (< 2% of the dose).

Figure 4 presents a proposed biotransformation pathway for [^{14}C]TAF. Overall, results of the human ADME and nonclinical data indicate that TAF is primarily metabolized via the purine catabolic pathway following conversion to TFV (M12).

Figure 4. Proposed Major Biotransformation and Excretion Pathway for TAF in Humans



M12 = TFV
Pathways are proposed based on general knowledge of metabolism and do not imply definitive pathways. Direct experimentation was not performed.
Source: GS-US-120-0109

3.1.3.3. FTC

The elimination pathway and metabolism of FTC was characterized in vitro in hepatic microsomes and hepatocytes; in vivo in mice, rats, and cynomolgus monkeys (m2.6.4, Section 5.3); and in a human mass balance PK study (Study FTC-106).

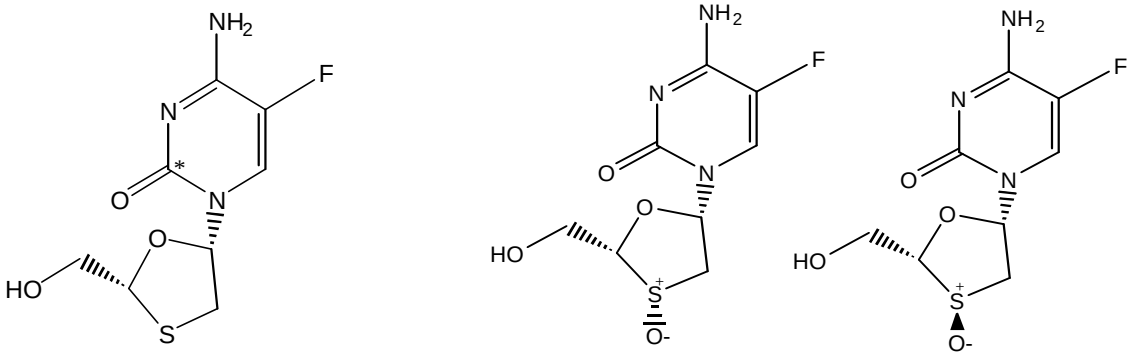
In vitro phenotyping experiments showed that FTC is not subject to significant metabolism by CYP enzymes (m2.6.4, Section 5.1). Formation of a sulfoxide metabolite(s) (M1 and/or M2) by CYP3A4 was low and inhibitor studies suggested that at least 1 other non-P450 enzyme may play a role. A direct glucuronide metabolite, M3, was also detected at low levels {Frick 1993}.

Following a single oral dose of [^{14}C]FTC to healthy male subjects, 99.6% of the total radioactive dose was recovered with 85.8% of the dose from urine and 13.7% of the dose from feces (Study FTC-106). FTC was the predominant species present in plasma with an observed median $t_{1/2}$ of 10.2 hours. Approximately 65.4% and 13.2% of the dose as unchanged parent drug was excreted in urine and feces, respectively. The in vitro identified metabolites of FTC were recovered in low levels in urine (12.9% of dose) and in feces (0.01% of dose).

Figure 5 presents the putative metabolites of FTC. Three metabolites M1, M2, and M3 were identified.

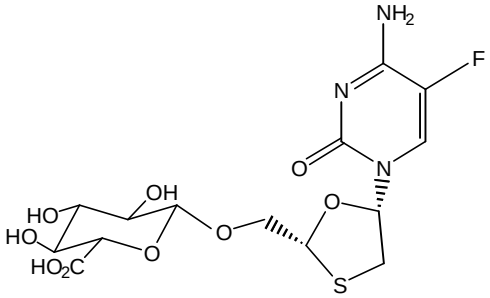
Overall, results of the human ADME and nonclinical data indicate that FTC is eliminated primarily as unchanged drug by renal excretion. Additionally, FTC is effectively metabolized intracellularly in PBMCs (the active site for the anti-HIV action) to form its active metabolite, emtricitabine 5′-triphosphate (FTC-TP) (Studies FTC-101 and FTC-106).

Figure 5. 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: m2.6.4, Section 5.2.2

3.1.3.4. Interaction Potential with Human Drug Metabolizing Enzymes

The potential for B/F/TAF to undergo DDIs based upon the effects on major human drug metabolizing enzymes and the potential clinical implications is discussed further in Section 3.2.4.2.

3.1.3.4.1. BIC

Clinical and nonclinical studies indicated that BIC is primarily metabolized by UGT1A1 and CYP3A (Study GS-US-141-1481, Section 2.2.2.2 and m2.6.4, Section 7.1). Clinical DDI studies were conducted to characterize the effect of inhibitors or inducers of CYP3A and/or UGT1A1 to provide guidance upon coadministration with such agents (Section 3.2.4.2.2.1).

Nonclinical studies indicated that BIC is unlikely to be a clinically relevant inhibitor or inducer of major human drug metabolizing enzymes (m2.6.4, Section 7.1). Lack of CYP3A inhibition or induction in vivo was confirmed by a clinical study, in which B/F/TAF had no effect on MDZ PK (Study GS-US-380-4270, Section 2.5.1.5).

3.1.3.4.2. TAF

Clinical and nonclinical studies indicated that TAF is not metabolized by CYP or UGT enzymes, and drugs that solely inhibit or induce CYP3A or UGT1A1 are not expected to have a relevant effect on TAF PK (Study GS-US-120-0109 and m2.6.4, Section 7.3).

Nonclinical studies indicated that TAF is unlikely to be a clinically relevant inhibitor or inducer of major human drug metabolizing enzymes (m2.6.4, Section 7.3). Lack of CYP3A inhibition or induction in vivo was confirmed by a clinical study, in which TAF had no effect on MDZ PK, either presystemically or systemically (Study GS-US-120-1538).

3.1.3.4.3. FTC

Clinical and nonclinical studies indicated that FTC is not metabolized (Study FTC-106 and m2.6.4, Section 7.2).

Nonclinical studies indicated that FTC is unlikely to be a clinically relevant inhibitor or inducer of major human drug metabolizing enzymes (m2.6.4, Section 7.2). Based on the totality of data, FTC does not have CYP or UGT-mediated interaction potential.

3.1.3.5. Interaction Potential with Human Drug Transporters

The potential for B/F/TAF to undergo human drug transporter-mediated interactions and the potential clinical implications is discussed further in Section 3.2.4.2.2.1.

3.1.3.5.1. BIC

BIC is a substrate of P-gp and BCRP in vitro (m2.6.4, Section 7.1). However, based on nonclinical and clinical data, the liability for P-gp/BCRP-mediated DDI is low due to high permeability/absorption of BIC (Section 3.1.1.1). Lack of a clinically relevant DDI with a strong P-gp inhibitor was confirmed by a clinical study, in which BIC exposures were similarly affected by coadministration of ATV+COBI (CYP/UGT and P-gp inhibition) or ATV alone (CYP/UGT inhibition), indicating that P-gp inhibition did not impact BIC PK (Study GS-US-141-1485, Section 2.5.2.1).

Nonclinical studies demonstrated that BIC did not inhibit any of the transporters evaluated in vitro at clinically relevant concentrations, except MATE1 and OCT2 (m2.6.4, Section 7.1). Accordingly, a clinical DDI study was conducted to characterize the effect of B/F/TAF on the OCT2/MATE1 substrate metformin to provide guidance upon coadministration (Study GS-US-380-3908, Section 2.5.1.3), and the results of this study are further discussed in Section 3.2.4.2.1.

3.1.3.5.2. TAF

Nonclinical studies indicated TAF is a substrate of P-gp, BCRP, organic anion transporter protein (OATP) 1B1, and OATP1B3 (m2.6.4, Section 7.3). Clinical DDI studies were conducted to characterize the effect of inducers and inhibitors of these transporters on TAF exposures to provide guidance upon coadministration with such agents, and the results of these studies are further discussed in Section 3.2.4.2.2.2.

Nonclinical studies demonstrated that clinically relevant concentrations of TAF did not inhibit any of the transporters evaluated vitro, and, as such, TAF is unlikely to be a perpetrator of transporter-mediated drug interactions (m2.6.4, Section 7.3).

3.1.3.5.3. FTC

Nonclinical studies indicated FTC is a substrate of the renal transporter, organic anion transporter (OAT) 3 (AD-236-2010); however, no clinically relevant OAT3-mediated DDI is expected {Stray 2013}.

Nonclinical studies demonstrated that clinically relevant concentrations of FTC did not inhibit any of the transporters evaluated vitro, and as such, FTC is unlikely to be a perpetrator of transporter-mediated drug interactions.

3.2. Pharmacokinetics

3.2.1. Pharmacokinetic Profile

The PK of BIC, TAF, and FTC from intensive PK in healthy and HIV-infected subjects is described in the following sections. Population PK analysis in HIV-infected subjects, including comparisons between healthy and HIV-infected subjects, is summarized in Section 3.2.2.

3.2.1.1. Pharmacokinetics of BIC

3.2.1.1.1. Single- and Multiple-Dose Pharmacokinetics

Table 4 presents the BIC plasma PK parameters following single-dose administration of BIC 5 to 600 mg. BIC AUC and C_{max} were approximately dose proportional over the dose range of 25 to 100 mg, with decreasing dose proportionality at higher doses. The median T_{max} was 1.25 to 3.5 hours postdose over the dose range of 5 to 600 mg. The median $t_{1/2}$ ranged from 16.7 to 18.9 hours, supportive of once daily dosing.

Table 4. GS-US-141-1218: BIC Plasma PK Parameters Following Single-Dose Administration of BIC (5 to 600 mg) in Healthy Subjects

BIC PK Parameter, Mean (%CV)[b]	Single Dose BIC[a]					
	5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)	600 mg (N = 6)
AUC_{inf} (h*ng/mL)	13,059.7 (25.1)	35,718.2 (21.3)	78,399.5 (29.7)	163,028.2 (24.3)	355,917.3 (32.9)	454,446.8 (19.9)
C_{max} (ng/mL)	691.2 (22.1)	1618.3 (26.7)	3965.0 (40.1)	6998.3 (36.1)	14,605.0 (27.1)	20,050.0 (7.5)
$t_{1/2}$ (h)	18.51 (16.81, 19.99)	18.08 (16.63, 19.64)	16.72 (15.77, 17.11)	18.90 (17.96, 20.05)	18.14 (17.86, 20.53)	17.89 (16.38, 19.52)
T_{max} (h)	1.25 (1.00, 1.50)	2.00 (1.00, 3.00)	3.00 (1.50, 4.00)	2.25 (1.50, 3.00)	3.50 (2.00, 6.00)	3.50 (2.00, 4.00)

a Administered under fasting conditions.
b Data are presented as mean (%CV), except for T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3).
Source: GS-US-141-1218, Section 2.2.2.1

Table 5 presents the BIC plasma PK parameters following multiple-dose administration of BIC 5 to 300 mg. The PK profile at steady state was similar to that following single-dose administration with median T_{max} of 1.5 to 4 hours. The accumulation ratios at steady state were approximately 154.0% to 182.2%, consistent with BIC $t_{1/2}$.

Table 5. GS-US-141-1218: BIC Plasma PK Parameters Following Multiple-Dose Administration of BIC (5 to 300 mg) in Healthy Subjects

	BIC PK Parameter, Mean (%CV)[b]	Multiple-Dose BIC[a]				
		5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)
Day 1	AUC_{0-24} (h*ng/mL)	9033.6 (8.2)	27,775.1 (28.3)	58,371.4 (18.9)	79,773.8 (18.9)	180,714.3 (17.6)
	C_{max} (ng/mL)	709.7 (9.5)	2220.0 (35.6)	4648.3 (18.7)	6248.3 (26.8)	13,716.7 (19.1)
	T_{max} (h)	1.50 (1.50, 1.50)	1.75 (1.00, 3.00)	1.50 (1.00, 2.00)	2.50 (2.00, 3.00)	2.50 (2.00, 4.00)
Day 7	AUC_{tau} (h*ng/mL)	14,392.0 (16.7)	50,008.2 (26.6)	89,710.1 (22.7)	126,785.8 (23.7)	277,200.2 (16.7)
	C_{max} (ng/mL)	982.5 (7.9)	3455.0 (24.1)	6538.3 (17.6)	9396.7 (20.8)	19,900.0 (21.2)
	C_{tau} (ng/mL)	400.83 (26.9)	1322.00 (27.8)	2241.67 (28.2)	3145.00 (26.1)	6758.33 (21.6)
	T_{max} (h)	1.50 (1.00, 2.00)	3.00 (2.00, 3.00)	1.75 (1.50, 2.00)	1.75 (1.50, 3.00)	4.00 (2.00, 4.00)
	Accumulation Ratio of AUC (%)	160.5 (19.0)	182.2 (17.1)	154.0 (15.9)	158.5 (12.1)	157.5 (22.6)

a Administered under fasting conditions.
b Data are presented as mean (%CV), except for T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3).
Source: GS-US-141-1218, Section 2.2.2.1

3.2.1.1.2. Pharmacokinetics of BIC in HIV-Infected Subjects

Table 6 presents the steady-state BIC plasma PK parameters following multiple-dose administration of BIC 5, 25, 50, and 100 mg in HIV-infected subjects. BIC AUC_{tau} and C_{max} were dose proportional. Median BIC T_{max} was achieved 1.25 to 2.74 hours postdose. The median BIC $t_{1/2}$ ranged from 15.9 to 20.9 hours, supportive of once daily dosing.

Table 6. GS-US-141-1219: BIC Plasma PK Parameters Following Multiple-Dose Administration of BIC (5 to 100 mg) in HIV-infected Subjects

BIC PK Parameter[a]	Mean (% CV)[b]			
	5 mg (n = 4)	25 mg (n = 4)	50 mg (n = 4)	100 mg (n = 4)
AUC_{tau} (ng*h/mL)	9983.0 (26.7)	48,950.3 (40.0)	87,538.4 (32.7)	178,901.7 (17.8)
C_{tau} (ng/mL)	225.3 (37.5)	1052.3 (54.1)	2053.0 (47.6)	4520.0 (21.9)
C_{max} (ng/mL)	741.5 (18.2)	3475.0 (20.5)	6080.0 (21.8)	12,235.0 (24.9)
T_{max} (h)	1.50 (0.75, 3.00)	1.25 (1.00, 1.50)	1.75 (1.25, 2.50)	2.74 (1.25, 3.99)
$t_{1/2}$ (h)	20.79 (17.15, 23.80)	15.86 (14.07, 19.37)	17.84 (15.50, 20.51)	20.88 (17.91, 24.47)

a Administered under fasting conditions.
b Data are presented as mean (%CV), except for T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3).
Source: GS-US-141-1219, Section 2.3.1.1

3.2.1.1.3. Comparison of BIC Pharmacokinetics between Healthy Subjects and HIV-Infected Subjects Following Administration of B/F/TAF

The influence of HIV infection status (ie, healthy vs HIV-infected subjects) as a covariate on BIC PK was evaluated in population PK modeling (BIC Population PK Report). These results are further discussed in Section 3.2.2.

3.2.1.2. Pharmacokinetics of TAF

TAF is approved for use in combination with other ARV agents for the treatment of HIV-1 infection in adults and pediatric subjects {DESCOVY® 2017, GENVOYA® 2017, Gilead Sciences International Ltd 2016, Odefsey 2017, ODEFSEY® 2017}. The PK of TAF has been extensively characterized during the clinical development of multiple products, including clinical evaluation with BIC and FTC (Study GS-US-141-1233, Section 2.2.1.1). Similar TAF exposures are observed with B/F/TAF FDC and BIC 75 mg + F/TAF.

3.2.1.2.1. Pharmacokinetics of TAF After Single- and Multiple-Dose Administration in Heathy and HIV-Infected Subjects

TAF exposures (AUC and C_{max}) are approximately dose proportional from 8 to 125 mg. The PK of TAF after single and multiple oral doses of TAF 8, 25, or 40 mg monotherapy (Day 1 and Day 10) was evaluated in HIV-infected subjects (Study GS-US-120-0104). The PK profile was characterized by rapid absorption and rapid elimination with a median plasma $t_{1/2}$ of approximately 0.5 hours. Due to the short $t_{1/2}$, TAF does not accumulate in plasma and TAF concentrations are typically below the limit of quantitation (BLQ) by approximately 8 hours postdose.

The PK of TAF 25 mg, the single-agent dose providing target therapeutic exposures, was evaluated after the administration of single (Day 1) and multiple (Day 12) oral doses of FTC+TAF in healthy subjects (Study GS-US-292-0103). Table 7 presents the single- and

multiple-dose PK of TAF and its major metabolite, TFV, following administration of FTC+TAF in healthy subjects. The mean TAF exposure following the administration of single and multiple doses was comparable (Day 1 vs 12), and the mean TFV exposure following single dosing (AUC_{inf}) was predictive of TFV multiple-dose exposure (AUC_{tau}). The PK profile of TFV (a major TAF metabolite) is characterized by rapid emergence in plasma following TAF dosing and slow elimination, with a median plasma $t_{1/2}$ of 41 hours.

Importantly, and as discussed in Section 3.1.3.2, due to the plasma stability of TAF, the overall systemic exposures of TFV is markedly lower than that observed historically following TDF (Study GS-US-120-0104, {Lee 2005, Ruane 2012}**)**.

Table 7. GS-US-292-0103: Single- and Multiple-Dose PK of TAF and TFV Following Administration of FTC+TAF in Healthy Subjects

TAF PK Parameter	FTC+TAF 25 mg[a]	
	Day 1 (Single Dose) (N = 9)	**Day 12 (Multiple Dose) (N = 19)**
TAF Parameters		
AUC_{last} (ng*h/mL)[a]	235.7 (29.2)	278.2 (28.8)
C_{max} (ng/mL)	158.8 (28.2)	179.5 (33.9)
TFV Parameters		
AUC (ng*h/mL)[b]	233.5 (19.7)	265.9 (22.2)
C_{max} (ng/mL)	8.6 (20.4)	19.2 (76.0)
C_{tau} (ng/mL) [c]	3.0 (16.6)	9.2 (23.5)

a Administered under fed conditions.
b AUC represents AUC_{inf} on Day 1 and AUC_{tau} on Day 12.
c C_{tau} represents the concentration at the end of the dosing interval for Days 1 and 12.
Data are presented as mean (%CV).
Source: GS-US-292-0103

3.2.1.2.2. Comparison of TAF Pharmacokinetics between Healthy Subjects and HIV-Infected Subjects Following Administration of B/F/TAF

The influence of HIV infection status (ie, healthy vs HIV-infected subjects) as a covariate on TAF PK was evaluated in population PK modeling (TAF Population PK Report). These results are further discussed in Section 3.2.2.

3.2.1.3. Pharmacokinetics of FTC

FTC is approved for use in combination with other ARV agents for the treatment of HIV-1 infection in adults and pediatric subjects {DESCOVY® 2017, Emtriva 2016, EMTRIVA® 2017, GENVOYA® 2017, ODEFSEY® 2017}. The PK of FTC has been extensively characterized during the clinical development of multiple products, including clinical evaluation with BIC and TAF (Study GS-US-141-1233, Section 2.2.1.1). Similar FTC exposures are observed with B/F/TAF FDC and BIC 75 mg + F/TAF).

3.2.1.3.1. Pharmacokinetics of FTC After Single- and Multiple-Dose Administration in Healthy and HIV-Infected Subjects

The PK profile of FTC has been characterized extensively in Phase 1 through 3 clinical studies following single and multiple doses in healthy subjects and HIV-infected subjects across multiple programs. Overall, FTC is rapidly and extensively absorbed after oral administration (Study FTC-101). Plasma FTC concentrations reached a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1200 mg). FTC exposures 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 8 and Table 9 present the FTC PK parameter estimates of FTC 200 mg once daily after administration of a single dose and at steady-state, respectively (Studies 143-001; FTC-101; FTC-106; FTC-107; FTC-108; FTC-110; FTC-303). The exposures of FTC were similar between healthy subjects and HIV-infected subjects.

At the therapeutic dose (200 mg once daily), the steady-state plasma FTC AUC and C_{max} averaged approximately 10 µg*h/mL and 2 µg/mL, respectively, regardless of HIV infection status. Single-dose and steady-state plasma FTC concentration-time profiles are similar.

Table 8. Summary of PK Parameter Estimates for FTC Following a Single Dose of FTC 200 mg in Healthy and HIV-Infected Subjects

Study Number	Subjects	AUC_{inf} (µg*h/mL)	C_{max} (µg/mL)	T_{max} (h)	$t_{1/2}$ (h)
143-001 (N = 12)	HIV infected	9.16 (15)	2.12 (30)	1.27 (42)	2.84 (21)
FTC-101 (N = 16)	HIV infected	6.72 (18)	1.59 (30)	1.70 (56)	2.90 (12)
FTC-106 (N = 6)	Heathy	10.42 (6)	2.14 (15)	1.17 (22)	11.97 (23)
FTC-107 (N = 6)	Heathy	11.78 (25)	2.20 (29)	1.84 (51)	14.19 (24)
FTC-108 (N = 12)	Heathy	11.30 (10)	2.35 (20)	1.17 (21)	11.00 (9)
FTC-110 (N = 12)	Heathy	10.37 (17)	2.24 (19)	1.21 (32)	8.89 (12)

Data are presented as mean (%CV).
Source: 143-001; FTC-101; FTC-106; FTC-107; FTC-108; FTC-110

Table 9. Summary of Steady-State PK Parameter Estimates for FTC Following Once-Daily Dosing of FTC 200 mg in Healthy and HIV-Infected Subjects

Study Number	Subjects	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)	HIV infected	8.00 (15)	1.72 (53)	0.05 (24)	2.00 (48)	8.24 (31)
FTC-106 (N = 5)	Heathy	10.04 (18)	1.72 (16)	0.07 (28)	1.00 (0)	10.2 (19)
FTC-303 (N = 12)	HIV infected	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

3.2.1.3.2. Comparison of FTC Pharmacokinetics between Healthy Subjects and HIV-Infected Subjects Following Administration of B/F/TAF

Table 10 presents a comparison of steady-state FTC PK (estimated by intensive PK sampling) following administration of B/F/TAF in healthy and HIV-infected subjects. Overall, the FTC exposures in healthy subjects were in the range of those observed in HIV-infected subjects. Additionally, FTC exposures following B/F/TAF are consistent with historical data of FTC as an single agent {Emtriva 2016, EMTRIVA® 2017} and as the E/C/F/TAF and F/TAF FDCs {DESCOVY® 2017, Gilead Sciences International Ltd 2016}.

Table 10. GS-US-380-1999, GS-US-380-1489, and GS-US-380-1490: Steady-State FTC Plasma PK Parameters Following Administration of B/F/TAF in Healthy Subjects or HIV-Infected Subjects

	Mean (%CV)	
	GS-US-380-1999	GS-US-380-1489 and GS-US-380-1490
	Intensive PK Healthy Subjects	Intensive PK HIV-Infected Subjects
FTC PK Parameters	B/F/TAF (N = 30)	B/F/TAF (N = 34)
AUC_{tau} (h*ng/mL)	9919.9 (12.1)	11067.2 (28.7)
C_{max} (ng/mL)	1829.7 (21.6)	1894.0 (27.9)
C_{tau} (ng/mL)	63.9 (20.5)	88.7 (38.6)[a]

All subjects received B/F/TAF 50/200/25 mg once daily.
a N = 32
Source: GS-US-380-1999, Section 2.5.1.2; Table Req8913.4

3.2.2. Population Pharmacokinetics

Population PK modeling was conducted using NONMEM and models were established to describe the plasma PK for BIC and TAF in HIV-infected subjects receiving BIC, including identification of covariates influencing PK.

3.2.2.1. BIC

For population PK analysis of BIC, plasma concentration data from 4 Phase 1 studies in healthy subjects and 4 Phase 3 studies in HIV-infected subjects following administration of B/F/TAF were evaluated for BIC population PK model development (Section 1.2.5).

Table 11 presents the number of observations and subjects included in the BIC PopPK Model Development and Demographic PK Analysis dataset.

Table 11. Number of Observations and Subjects in the Population PK Model Development and Evaluation Datasets for BIC

	Number of Measurable PK Observations	Number of Subjects
PopPK Model Development Dataset[a]	8752	1318
Demographic PK Analysis Dataset[b]	6190	1193

a PopPK Model Development Dataset included healthy and HIV-infected subjects who received B/F/TAF and had evaluable PK parameters in Study GS-US-141-1233, GS-US-380-1991, GS-US-380-1999, GS-US-380-3909, GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, or GS-US-380-1878.
b Demographic Population PK Analysis Dataset included HIV-infected subjects who received B/F/TAF and had evaluable PK parameters in Study GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, or GS-US-380-1878.
Source: BIC Population PK Report

The final population PK model that best described BIC plasma concentration data was a 1-compartment PK model with first-order absorption (k_a), an absorption lag time (T_{lag}), and first-order elimination from the central compartment, with interindividual variability terms on k_a, CL/F, and V_c/F.

Covariate analysis indicated small but statistically significant effects of weight on CL/F, weight and HIV infection status on V_c/F, and PPI usage on k_a. No other covariates tested (age, sex, race, CL_{cr}, BMI, prior HIV treatment experience, HBV or HCV coinfection status, fasting vs fed administration status, and H2RA usage) were identified as significant for the population PK of BIC. Details on the BIC population PK model and the effect of these collective covariates are described in the BIC Population PK Report (BIC Population PK Report) and in Sections 3.2.3 and 3.2.4.

Values of BIC CL/F, V_c/F, k_a, and T_{lag} for the 'typical' 80-kg HIV-infected subject (median body weight in Demographic PK Analysis Dataset) not receiving a PPI were estimated to be 0.504 L/h, 12.5 L, 2.60 h^{-1}, and 0.235 hours, respectively.

3.2.2.2. TAF

For population PK analysis of TAF, plasma concentration data from 6 Phase 1 studies in healthy subjects, 1 Phase 1 study in HIV-infected subjects, and 5 Phase 3 studies in HIV-infected subjects following administration of TAF were evaluated (Section 1.2.5).

Table 12 presents the number of observations and subjects included in the TAF PopPK Model Development and Demographic PK Analysis Datasets.

Table 12. Number of Observations and Subjects in the Population PK Model Development and Evaluation Datasets for TAF

	Number of Measurable PK Observations	Number of Subjects
PopPK Model Development Dataset[a]	4201	1409
Demographic PK Analysis Dataset[b]	991	486

a PopPK Model Development Dataset included healthy and HIV-infected subjects who received TAF as a single agent, FTC/TAF, R/F/TAF, or B/F/TAF and had evaluable PK parameters in Study GS-US-120-0104, GS-US-120-0107, GS-US-120-0108, GS-US-120-0117, GS-US-120-0118, GS-US-292-0101, GS-US-311-1089, GS-US-320-1228, GS-US-366-1160, GS-US-366-1216, GS-US-380-1489, or GS-US-380-1490.
b Demographic Population PK Analysis Dataset included HIV-infected subjects who received B/F/TAF FDC and had evaluable PK parameters in Study GS-US-380-1489 or GS-US-380-1490.
Source: TAF Population PK Report

The final population PK model that best described TAF plasma concentration data was a 2-compartment PK model with sequential zero-order (D_1) then first-order absorption (k_a), an absorption lag time, and first-order elimination from the central compartment, with interindividual variability terms on CL/F, V_c/F, and D_1.

Covariate analysis indicated small but statistically significant effects of sex and HIV infection status on CL/F and HIV infection status on D_1. No other covariates tested (age, race, body weight, BMI, baseline creatinine clearance, prior HIV treatment experience, baseline HBV coinfection, baseline HCV coinfection, fasting vs fed administration status, formulation, and concomitant medications [eg, PPI, H2RA]) were considered relevant covariates for the population PK of TAF. Details on the TAF population PK model and the effect of these collective covariates are described in the TAF Population PK Report (TAF Population PK Report) and Sections 3.2.3 and 3.2.4.

Values of TAF CL/F, V_c/F, V_p/F, Q/F, k_a, and D_1 for the 'typical' male HIV-infected subject administered B/F/TAF under fasting conditions were estimated to be 186 L/h, 42.4 L, 17.9 L, 4.07 L/h 1.68 h^{-1}, and 0.393 hours, respectively.

3.2.2.3. FTC

As expected from the renal elimination pathway of FTC and based on simple linear regression analysis and analysis of variance (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 3.2.3.3.3. Additional covariates involved in the calculation of $eGFR_{CG}$ values, 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 Population PK Report [13542v1]).

3.2.3. Effect of Intrinsic Factors

Results of dedicated Phase 1 studies in healthy subjects which specifically evaluated intrinsic factors are included in the following sections, if available. Population PK analyses of BIC and TAF evaluated the broader potential impact of demographic, organ impairment, treatment, and disease-related factors on PK as covariates in healthy and HIV-infected subjects (Section 3.2.2). Sensitivity analysis and statistical comparisons were used to further assess the magnitude of difference in exposure between healthy and HIV-infected subjects as well as the impact of model-identified statistically significant covariates on exposure within HIV-infected subjects receiving B/F/TAF.

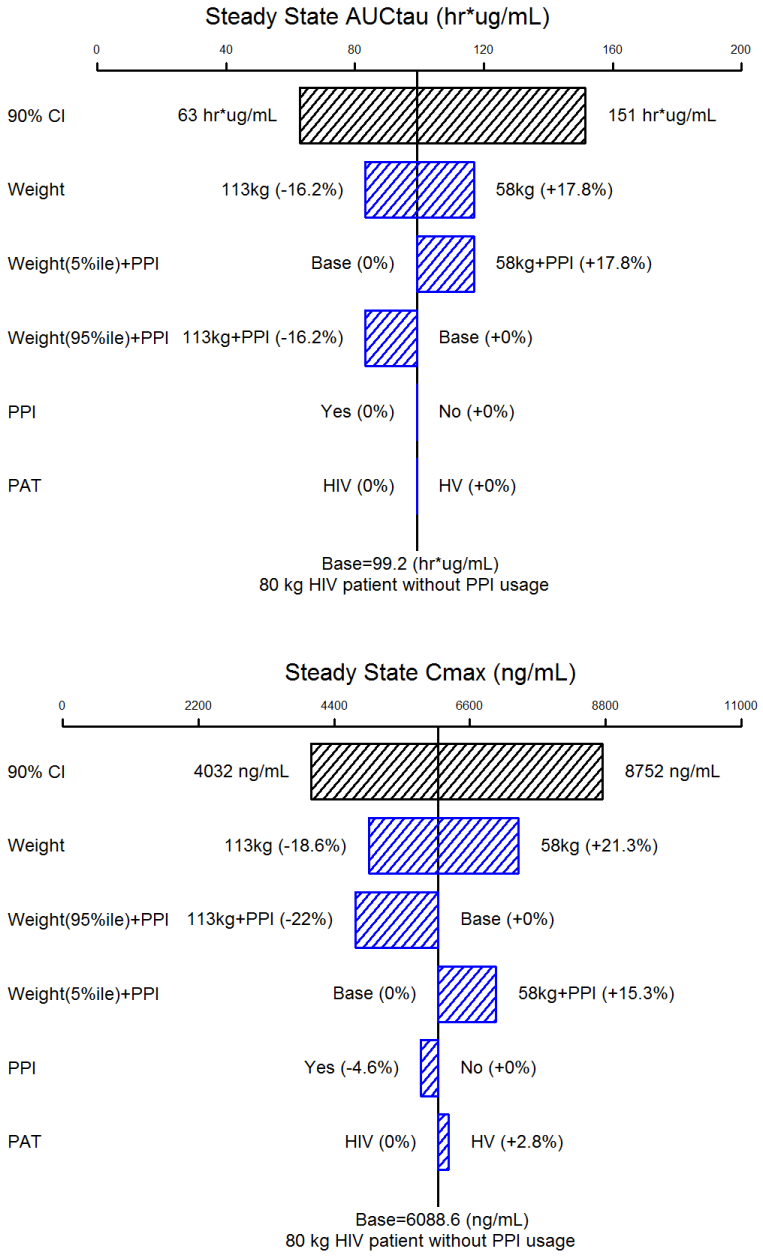
3.2.3.1. Pharmacokinetic Sensitivity Analyses of Subject Covariates

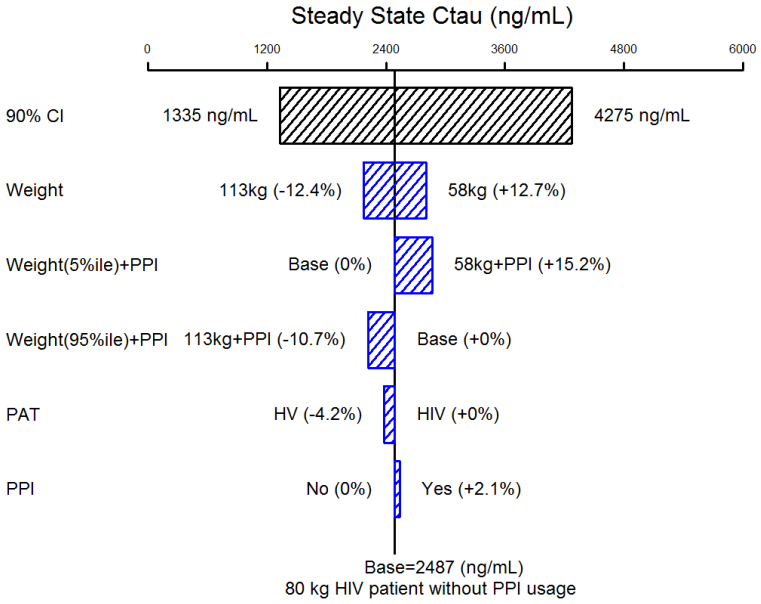
3.2.3.1.1. BIC

Population PK analysis identified HIV infection status, weight, and PPI usage as statistically significant covariates on BIC exposure (Section 3.2.2.1).

Figure 6 presents the sensitivity analysis of statistically significant covariates on BIC exposures. This analysis demonstrates that the effect of weight, HIV infection status, and PPI usage (individually or combined) on steady-state exposures is minimal (< 22% on AUC_{tau}, C_{max}, and C_{tau}). Differences in BIC exposure between healthy and HIV-infected subjects are further assessed in Section 3.2.1.1.3. BIC exposures in the Phase 3 population by weight quartiles and PPI usage status are presented in Sections 3.2.3.5.2.1 and 3.2.4.2.2.1 as part of demographic or extrinsic factors, as applicable.

Figure 6. **Impact of Statistically Significant Covariates on BIC AUC_{tau}, C_{max}, and C_{tau} (BIC Population PK Analysis)**



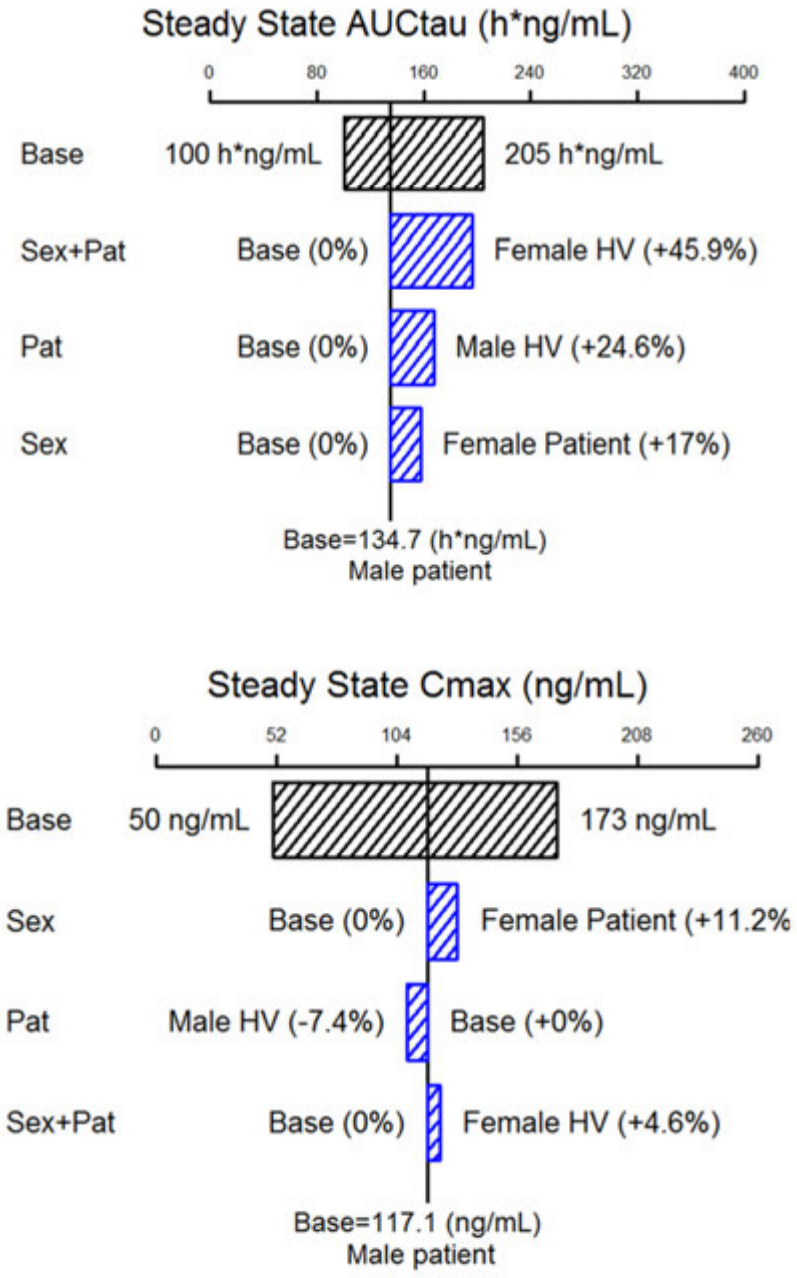


PAT= patient; HV = healthy subjects (healthy volunteers)
Base, as represented by the black vertical line and values, refers to the predicted steady-state exposure (AUC_{tau}, C_{max}, or C_{tau}) of BIC in a typical HIV-infected subject with body weight of 80 kg and no PPI usage. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the entire population. Each blue shaded bar represents the influence of a single covariate on the steady-state exposure. The label at left end of the bar represents the covariate being evaluated. The upper and lower values for each covariate capture 90% of the plausible range in the population. The length of each bar describes the potential impact of that covariate on BIC exposure at steady-state, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The most influential covariate is at the top of the plot for each exposure parameter.
Source: BIC Population PK Report

3.2.3.1.2. TAF

Population PK analysis identified HIV infection status and sex as statistically significant covariates on TAF exposure (Section 3.2.2.2). Figure 7 presents the results from the sensitivity analysis of statistically significant covariates on TAF exposure. This analysis demonstrated that the effect of sex (17% and 11.2% higher AUC_{tau} and C_{max}, respectively, in female subjects than male subjects) and HIV infection status on steady-state exposures was minimal. Differences in TAF exposure between healthy and HIV-infected subjects are further assessed in Section 3.2.1.2.2. TAF exposures in the Phase 3 population by sex are presented in Section 3.2.3.5.4.2, as part of demographic factors.

Figure 7. Impact of Statistically Significant Covariates on TAF AUC_{tau} and C_{max} (TAF Population PK Analysis)



PAT= patient; HV = healthy subjects (healthy volunteers)
Base, as represented by the black vertical line and values, refers to the predicted steady-state exposure (AUC_{tau} or C_{max}) of TAF in a typical male HIV-infected subject. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the entire population. Each blue shaded bar represents the influence of a single covariate on the steady-state exposure. The label at left end of the bar represents the covariate being evaluated. The upper and lower values for each covariate capture 90% of the plausible range in the population. The length of each bar describes the potential impact of that covariate on TAF exposure at steady state, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The most influential covariate is at the top of the plot for each exposure parameter.
Source: TAF Population PK Report

3.2.3.1.3. FTC

Statistical analysis identified baseline $eGFR_{CG}$ as a significant covariate on FTC exposure (Section 3.2.2.3). No sensitivity analyses were performed for FTC, but the effect of baseline $eGFR_{CG}$ on FTC exposure is further discussed in Section 3.2.3.3.3.

3.2.3.2. Pharmacokinetics of HIV-Infected Subjects Relative to Healthy Subjects

3.2.3.2.1. BIC

Population PK and sensitivity analyses demonstrated that HIV infection status had little impact on BIC PK exposure (Section 3.2.2.1). Nonetheless, the population PK estimated AUC_{tau}, C_{max}, and C_{tau} for BIC were evaluated following once-daily dosing to HIV-infected and healthy subjects.

Table 13 presents population PK parameters for BIC following once-daily dosing in HIV-infected and healthy subjects. The BIC exposures were comparable (%GLSM ratios of HIV infected vs healthy subjects 86.6%−87.1%), regardless of HIV infection status. Importantly, the mean (%CV) C_{tau} of BIC following administration of B/F/TAF to HIV-infected subjects (N = 1193) in the Phase 3 studies was 2610 (35.2) ng/mL, resulting in an inhibitory quotient (IQ) of 16.1-fold above the protein-adjusted 95% effective concentration ($paEC_{95}$) (162 ng/mL) against wild-type HIV-1 virus (m2.6.2, Section 1.1).

Table 13. Mean (%CV) of Population PK Parameter Estimates of BIC Following Once Daily Dosing in HIV-Infected and Healthy Subjects (Demographics PK Analysis Set)

BIC PK Parameter	HIV-Infected Subjects (Test) (N = 1193)[a]	Healthy Subjects (Reference) (N = 125)[b]	%GLSM Ratio (90% CI)
AUC_{tau} (ng*h/mL)	102001.0 (26.9)	117003.2 (23.8)	86.6 (83.3, 89.9)
C_{max} (ng/mL)	6145.8 (22.9)	7003.0 (19.6)	87.1 (84.5, 89.8)
C_{tau} (ng/mL)	2609.9 (35.2)	2978.8 (31.6)	86.7 (82.4, 91.2)

a HIV-infected subjects who received B/F/TAF and had evaluable PK parameters Study GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, or GS-US-380-1878.
b Healthy subjects who received B/F/TAF and had evaluable PK parameters in Study GS-US-141-1233, GS-US-380-1991, GS-US-380-1999, or GS-US-380-3909.
Source: BIC Population PK Report and B/F/TAF Integrated Population PK, Table Req8846.2

3.2.3.2.2. TAF

Population PK and sensitivity analyses demonstrated that HIV infection status had little impact on TAF PK exposure (Section 3.2.2.2). Nonetheless, the impact of this covariate on TAF PK exposure was further assessed by grouping subjects based on covariate category.

Table 14 presents the population PK parameter estimates for TAF following once-daily dosing in HIV-infected and healthy subjects. TAF exposures were comparable (%GLSM ratios of HIV infected vs healthy subjects 79.2%−116.1%), regardless of HIV infection status.

Table 14. Mean (%CV) of Population PK Parameter Estimates of TAF Following Once Daily Dosing in HIV-Infected and Healthy Subjects (Demographics PK Analysis Set)

TAF PK Parameter	HIV-Infected Subjects (Test) (N = 486)[a]	Healthy Subjects (Reference) (N = 202)[b]	GLSM Ratio (%) (90% CI)
AUC_{tau} (ng*h/mL)	142.0 (17.3)	186.0 (32.5)	79.2 (76.1, 82.4)
C_{max} (ng/mL)	121.3 (15.4)	116.2 (49.3)	116.1 (109.4, 123.3)

a HIV-infected subjects who received TAF as part of B/F/TAF and had evaluable PK parameters in Study GS-US-380-1489 or GS-US-380-1490.
b Healthy subjects who received TAF as TAF single agent and had evaluable PK parameters in Study GS-US-120-0107, GS-US-120-0108, GS-US-120-0117, GS-US-120-0118, GS-US-292-0101, or GS-US-320-1228.
Source: TAF Population PK Report and B/F/TAF Integrated Population PK, Table Req8846.4

3.2.3.2.3. FTC

In general, FTC PK parameter estimates following oral administration are characterized by relatively low inter-subject variability and consistent PK data have been observed between healthy and HIV-infected subjects (FTC Population PK Report [13542v1]). These characteristics are likely a result of the high oral bioavailability and that FTC is primarily excreted unchanged in the urine (approximately 65%−70% of an oral dose) rather than metabolized (< 13% of an oral dose) (FTC-106).

3.2.3.3. Renal Impairment

3.2.3.3.1. Effect of Renal Impairment on BIC

Table 15 presents BIC plasma PK parameters in subjects with severe renal impairment ($eGFR_{CG}$, 15−29 mL/min) and subjects with normal renal function ($eGFR_{CG}$, ≥ 90 mL/min) in a Phase 1 renal impairment study (Study GS-US-141-1479, Section 2.4.2.2). Consistent with the known ADME profile of BIC, severe renal impairment did not result in clinically relevant changes in BIC exposure. AUC_{inf} and C_{max} of total plasma BIC concentrations were approximately 27% and 20% lower, respectively, in subjects with severe renal impairment compared with subjects with normal renal function. The BIC fraction unbound was higher in subjects with severe renal impairment relative to normal-matched control subjects, resulting in comparable BIC free AUC_{inf} and C_{max} between the 2 groups. Based on these results, Phase 1 studies of BIC PK in subjects with mild or moderate renal impairment were not conducted.

The Phase 3 studies with B/F/TAF included HIV-infected subjects with mild or moderate renal impairment (N = 237). In agreement with the dedicated renal impairment study findings, population PK modeling did not identify $eGFR_{CG}$ as a statistically significant covariate of BIC exposure (BIC Population PK Report).

Table 15. GS-US-141-1479: Effect of Severe Renal Impairment on the PK of BIC (PK Analysis Set)

BIC PK Parameter	Mean (%CV)		GLSM Ratio (%) (90% CI)
	Severe Renal Impairment (Test) (N = 10)	Normal Renal Function (Reference) (N = 8)	
Total AUC_{inf} (h*ng/mL)	138,169.7 (44.4)	170,105.6 (24.8)	72.63 (48.80, 108.10)
Total C_{max} (ng/mL)	5977.0 (34.8)	7227.5 (29.5)	80.32 (59.56, 108.30)
F_u (%)	0.75% (72.03%)	0.49% (9.32%)	—
Free AUC_{inf} (h*ng/mL)[a]	830.6 (32.1)	824.5 (24.7)	99.29 (79.49, 124.04)
Free C_{max} (ng/mL)[a]	37.7 (21.6)	35.0 (28.4)	109.80 (87.46, 137.85)

a Free PK parameter was calculated as Mean unbound fraction (%) * PK Parameter / 100 per subject
The prespecified criterion of no clinically significant change due to renal impairment in PK parameters was that the upper bound of 90% CI for %GLSM ratios (90% CI) < 200%.
Source: GS-US-141-1479, Section 2.4.2.2

3.2.3.3.2. Effect of Renal Impairment on TAF

TAF-containing products are indicated for use once daily in renally impaired, HIV-infected subjects with $eGFR_{CG} \geq 30$ mL/min {DESCOVY® 2017, GENVOYA® 2017, ODEFSEY® 2017}.

3.2.3.3.2.1. TAF

Table 16 presents TAF plasma PK parameters in subjects with severe renal impairment ($eGFR_{CG}$, 15−29 mL/min) and subjects with normal renal function ($eGFR_{CG}$, ≥ 90 mL/min) in a Phase 1 renal impairment study (Study GS-US-120-0108). The increase in TAF exposures was < 2-fold in subjects with severe impairment compared with subjects with normal renal function and not considered clinically meaningful based on the lack of exposure-safety relationship for TAF following administration of B/F/TAF (Section 3.3).

Table 16. GS-US-120-0108: Statistical Comparisons of TAF PK Parameter Estimates in Subjects with Severe Renal Impairment and Subjects with Normal Renal Function

TAF PK Parameter	Mean (%CV)		GLSM Ratio (%) (90% CI)
	Severe Renal Impairment (Test) (N = 14)	Normal Renal Function (Reference) (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)
F_u (1 h)	20.0 (22.5)	20.1 (24.7)[a]	—
F_u (4 h)	14.2 (29.6)	13.6 (51.4)[a]	—

a N =12
Source: GS-US-120-0108

In agreement with the dedicated Phase 1 renal impairment study findings, population PK modeling did not identify $eGFR_{CG}$ as a statistically significant covariate of TAF (E/C/F/TAF Population PK Report). The model included results from a Phase 3 clinical study of E/C/F/TAF in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$, 30–69 mL/min; Study GS-US-292-0112).

Table 17 present the population PK-derived parameter estimates for TAF following administration of E/C/F/TAF once daily in HIV-infected subjects by baseline renal function. These results confirmed no clinically relevant effect of renal impairment on TAF PK.

Table 17. Summary of Population PK-Derived PK Parameter Estimates for TAF Following Administration of E/C/F/TAF Once Daily in HIV-Infected Subjects by Baseline Renal Function

	E/C/F/TAF		
TAF PK Parameter	**30 ≤ $eGFR_{CG}$ < 60 mL/min (N = 133)**	**60 ≤ $eGFR_{CG}$ < 90 mL/min (N = 204)**	**$eGFR_{CG}$ ≥ 90 mL/min (N = 769)**
AUC_{tau} (ng*h/mL)	305.0 (112.5)	223.9 (86.8)	210.4 (94.1)
C_{max} (ng/mL)	208.6 (53.0)	166.2 (43.7)	158.9 (57.1)

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: Ad hoc 6919 Table 1.1

3.2.3.3.2.2. TFV (TAF Metabolite)

Table 18 presents the statistical comparisons of TFV PK parameter estimates for subjects with severe renal impairment and subjects with normal renal function (Study GS-US-120-0108). Consistent with its renal route of elimination, AUC_{inf} and C_{max} of the TAF metabolite TFV were higher following a single dose of TAF (473.8% and 179.3%, respectively) in subjects with severe renal impairment compared with subjects with normal renal function. Importantly, the plasma TFV exposure observed in subjects with severe renal impairment in this study was below the exposure observed in historical studies after administration of TDF 300 mg in subjects with normal renal function (3300 ng*h/mL) {Gilead Sciences Inc. 2015, Gilead Sciences International Limited 2014}.

Table 18. GS-US-120-0108: Statistical Comparisons of TFV PK Parameter Estimates between Subjects with Severe Renal Impairment and Subjects with Normal Renal Function

	Mean (%CV)		
TFV PK Parameter	**Severe Renal Impairment (Test) (N = 14)**	**Normal Renal Function (Reference) (N = 13)**	**GLSM Ratio (%) (90% CI)**
AUC_{inf} (ng*h/mL)	2073.8 (47.1)	342.6 (27.2)	573.76 (457.21, 720.01)
AUC_{last} (ng*h/mL)	1694.9 (43.1)	298.0 (26.1)	545.91 (442.82, 672.99)
C_{max} (ng/mL)	26.4 (32.4)	9.5 (36.5)	279.31 (231.48, 337.02)
F_u (2 h)	99.0 (3.3)	97.4 (5.2)	—
F_u (24 h)	99.2 (3.0)	98.9 (1.6)	—

Source: GS-US-120-0108

In the population PK analysis of TFV following administration of E/C/F/TAF, which included HIV-infected subjects with mild or moderate renal impairment in Study GS-US-292-0112, a statistically significant effect of baseline $eGFR_{CG}$ on TFV exposure was observed based on covariate analyses, as expected (E/C/F/TAF TAF Population PK Report).

Table 19 presents the population PK-derived parameter estimates for TAF following administration of E/C/F/TAF once daily in HIV-infected subjects by baseline renal function. Although TFV exposure was higher in HIV-infected subjects with lower baseline $eGFR_{CG}$ relative to those with normal renal function, the TFV exposures observed in subjects with mild or moderate renal impairment were markedly lower than the exposures observed in historical studies after administration of TDF 300 mg in the setting of normal renal function (3300 ng*h/mL) {Gilead Sciences Inc. 2015, Gilead Sciences International Limited 2014}. Accordingly, the modestly higher TFV exposure in the context of TAF administration in renally impaired, HIV-infected subjects with $eGFR_{CG} \geq 30$ mL/min is not clinically meaningful and no dose adjustments are warranted for E/C/F/TAF and other TAF-containing products.

Table 19. Summary of Population PK-Derived PK Parameter Estimates for TFV Following Once-Daily Dosing of E/C/F/TAF in HIV-Infected Subjects by Baseline Renal Function

	E/C/F/TAF		
TFV PK Parameter	**$30 \leq eGFR_{CG} < 60$ mL/min (N = 155)**	**$60 \leq eGFR_{CG} < 90$ mL/min (N = 264)**	**$eGFR_{CG} \geq 90$ mL/min (N = 1053)**
AUC_{tau} (ng*h/mL)	669.7 (29.2)	421.4 (30.2)	285.5 (27.1)
C_{max} (ng/mL)	33.2 (28.7)	21.6 (33.4)	14.9 (25.4)
C_{tau} (ng/mL)	24.2 (29.4)	15.3 (30.6)	10.4 (28.6)

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: Ad hoc 6919 Table 1.2

3.2.3.3.3. Effect of Renal Impairment on FTC

As renal excretion of unchanged drug is the principal route of elimination for FTC, subjects with reduced renal function are expected to have higher exposure than subjects with normal renal function. Importantly, F/TAF-containing products are indicated for use once daily in renally impaired, HIV-infected subjects with $eGFR_{CG} \geq 30$ mL/min {DESCOVY® 2017, GENVOYA® 2017, ODEFSEY® 2017}.

Adult subjects with varying degrees of renal impairment, as determined by estimated $eGFR_{CG}$ values, were evaluated in a Phase 1 renal impairment study (Study FTC-107). Table 20 presents FTC plasma PK parameters in subjects with severe renal impairment ($eGFR_{CG}$ <30 mL/min) and subjects with normal renal function. The AUC_{inf} and C_{max} of FTC were approximately 195% and 32% higher in subjects with severe impairment compared with subjects with normal renal function, respectively.

Table 20. FTC-107: Statistical Comparisons of FTC PK Parameter Estimates in Subjects with Varying Renal Function

FTC PK Parameter	Mean (%CV)		GLSM Ratio (%) (90% CI)
	$eGFR_{CG}$ < 30 mL/min (Test) (N = 5)	$eGFR_{CG}$ ≥ 80 mL/min (Reference) (N = 6)	
AUC_{inf} (ng*h/mL)	33730 (6)	11780 (25)	295 (243, 358)
C_{max} (ng/mL)	2840 (24)	2200 (29)	132 (101, 173)

Source: FTC-107

As previously discussed, a Phase 3 clinical study evaluated the safety, efficacy, and PK of E/C/F/TAF in HIV-infected subjects with mild to moderate renal impairment ($eGFR_{CG}$, 30−69 mL/min; Study GS-US-292-0112).

Table 21 presents the FTC exposures in subjects in the PK substudy (n = 30) of Study GS-US-292-0112 compared with historical data of FTC in subjects with impaired and normal renal function {EMTRIVA® 2017}. The mean FTC exposures observed in subjects with $eGFR_{CG}$ of ≥ 30 to < 70 mL/min in Study GS-US-292-0112 is comparable with the FTC exposures in subjects with $eGFR_{CG}$ of ≥ 50 to < 80 mL/min who do not require dose adjustment {Emtriva 2016, EMTRIVA® 2017}. Accordingly, the modestly higher FTC exposure in renally impaired, HIV-infected subjects with $eGFR_{CG}$ ≥ 30 mL/min is not clinically meaningful and no dose adjustments are warranted for E/C/F/TAF and other F/TAF-containing products.

Table 21. Summary of PK Parameter Estimates for FTC Following E/C/F/TAF or FTC in Subjects with Varying Renal Function

FTC PK Parameter	E/C/F/TAF[a] 30 ≤ $eGFR_{CG}$ < 70 mL/min	FTC 50 ≤ $eGFR_{CG}$ < 80 mL/min	FTC $eGFR_{CG}$ ≥ 80 mL/min
AUC (ng*h/mL)	20,968.6 (25.5)	19,900 (6.0)	11,800 (24)
C_{max} (ng/mL)	2645.3 (24.7)	3800 (23)	2200 (27)

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: GS-US-292-0112; {EMTRIVA® 2017}

3.2.3.3.4. B/F/TAF

The recommendation for use of B/F/TAF in subjects with renal impairment is guided by the most conservative dosing recommendation for affected component in the setting of renal impairment (ie, FTC). B/F/TAF may be administered without dose adjustment in subjects with $eGFR_{CG}$ ≥ 30 mL/min. There are insufficient data available regarding the use of the B/F/TAF in subjects with renal impairment < $eGFR_{CG}$ 30 mL/min.

3.2.3.4. Hepatic Impairment

3.2.3.4.1. Effect of Hepatic Impairment on BIC

The effect of hepatic impairment on the PK of BIC has been examined in a Phase 1 hepatic impairment study (Study GS-US-141-1478, Section 2.4.2.1).

Table 22 presents the PK parameters of BIC in subjects with moderate hepatic impairment (CPT B) and subjects with normal hepatic function. The AUC_{inf} and C_{max} of BIC were 41.3% and 36.5% lower, respectively, in subjects with moderate hepatic impairment compared with subjects with normal hepatic function. BIC fraction unbound was higher in subjects with moderate hepatic impairment relative to healthy-matched control subjects, resulting in comparable BIC free AUC_{inf} and C_{max} between the 2 groups (%GLSM ratios, 77%–83%). Based on the lack of an exposure-efficacy relationship for BIC following administration of B/F/TAF (Section 3.3.2), the small decrease in exposure due to moderate hepatic impairment is not considered clinically meaningful.

Table 22. GS-US-141-1478: Effect of Moderate Hepatic Impairment on the PK of BIC

	Mean (%CV)		
	Test	Reference	
BIC PK Parameter	**Moderate Hepatic Impairment (N = 10)**	**Healthy Control (N = 10)**	**GLSM Ratio (%) (90% CI)**
AUC_{inf} (h*ng/mL)	113,086.2 (50.7)	172,883.6 (23.4)	58.71 (41.28,83.50)
C_{max} (ng/mL)	5013.0 (29.1)	7849.0 (27.8)	63.50 (49.80,80.96)
F_u (%)	0.809% (21.4)	0.610 % (6.2)	
Free AUC_{inf} (h*ng/mL)	880.9 (55.7)	1054.2 (22.7)	76.54 (56.48,103.71)
Free C_{max} (ng/mL)	39.6 (27.7)	48.1 (28.2)	82.78 (64.98,105.45)

Free PK parameter is calculated as Mean unbound fraction (%) * PK Parameter / 100 per subject.
The prespecified criterion of no clinically significant change due to renal impairment in PK parameters was that the upper bound of 90% CI for %GLSM ratios (90% CI) < 200%.
Source: GS-US-141-1478, Section 2.4.2.1

3.2.3.4.2. Effect of Hepatic Impairment on TAF

The effect of hepatic impairment on the PK of TAF has been examined. The plasma PK exposure parameters of TAF and TFV in subjects with mild or moderate hepatic impairment were comparable with those in subjects with normal hepatic function in a Phase 1 hepatic impairment study (Study GS-US-120-0114).

An additional Phase 1 study evaluated the PK of TAF and TFV following administration of TAF 25 mg as a single agent in subjects with severe hepatic impairment and subjects with normal hepatic function (Study GS-US-320-1615). Table 23 presents the TAF and TFV PK parameters following administration of TAF 25 mg in subjects with severe hepatic impairment and subjects

with normal hepatic function. In subjects with severe hepatic impairment, the plasma exposure parameters of TAF (AUC_{last} and C_{max}) were lower (48.80% and 54.90%, respectively) compared with subjects with normal hepatic function. When free fraction was taken into consideration, the free TAF exposures were comparable between both groups. Therefore, severe hepatic impairment is not considered to have a clinically significant effect on the PK of TAF or its metabolite TFV.

Table 23. GS-US-320-1615: Effect of Severe Hepatic Impairment on the PK of TAF and TFV Following Administration of TAF 25 mg

PK Parameter	Severe Hepatic Impairment Group (Test) (N = 10)	Normal Matched Control Group (Reference) (N = 10)	GLSM Ratio (%) (90% CI)
TAF 25 mg: Mean (%CV) (TAF PK Analysis Set)			
TAF PK Parameter			
AUC_{last} (ng*h/mL)	113.1 (27.3)	225.7 (37.7)	51.20 (40.11, 65.36)
C_{max} (ng/mL)	79.6 (49.4)	176.0 (45.3)	45.10 (31.66, 64.25)
F_u (%)[a]	37.76 (22.09)	20.38 (10.56)	–
Free AUC_{last} (ng*h/mL)	41.7 (26.8)	46.0 (38.6)	93.28 (72.62, 119.80)
Free C_{max} (ng/mL)	29.9 (58.0)	36.2 (50.8)	82.16 (56.58, 119.31)
TAF 25 mg: Mean (%CV) (TFV PK Analysis Set)			
TFV PK Parameter			
AUC_{inf} (ng*h/mL)	219.9 (54.0)	304.0 (23.8)	63.06 (42.90, 92.70)
C_{max} (ng/mL)	7.5 (52.4)	7.6 (24.0)	89.88 (64.77, 124.72)
F_u%[b]	99.87-104.24	97.61-99.86	–

a Mean percent unbound TAF at 0.5, 1, 2, and 3 hours postdose
b The range of mean percent unbound TFV at 0.5, 1, 2, and 3 hours postdose
Source: GS-US-320-1615

3.2.3.4.3. Effect of Hepatic Impairment on 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) in a Phase 1 human ADME study (Study FTC-106).

Table 24 summarizes the steady-state PK parameter estimates for FTC following administration of FTC 200 mg once daily. Based on the steady-state PK data in HBV-infected subjects (Study FTCB-101) and HIV-infected subjects (Study FTC-303), FTC exposures are generally similar to those in healthy subjects. Therefore, in subjects with various degrees of hepatic dysfunction, minimal change in FTC clearance is expected.

Table 24. Summary of Steady-State PK Parameter Estimates for FTC Following Once-Daily Dosing of FTC 200 mg in Various Populations

Study No.	Number of Subjects (Male/Female) 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 (5 Male/0 Female) 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 (1 Male/11 Female) 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 (6 Male/3 Female) HBV-infected 30 (29–45) years	3.00 (26%)	1.50 (69%)	0.071 (31%)	12.80 (27%)	6.96 (21%)	277 (25%)

Data are presented as mean (%CV)
Source: FTC-106; FTC-303; FTCB-101

3.2.3.4.4. B/F/TAF

PK data support the recommendation that B/F/TAF may be administered in subjects with mild to moderate hepatic impairment. There are insufficient data available regarding the use of the B/F/TAF FDC in subjects with severe hepatic impairment.

3.2.3.5. Demographic Factors

Demographic factors are discussed in the following sections. Only demographic factors identified by population PK modeling as statistically significant covariates influencing the PK of any analyte within the B/F/TAF FDC are discussed in detail, including statistical comparisons to illustrate the magnitude of any difference in the PK parameters. Additionally, a recommendation is provided for use of B/F/TAF in each demographic category.

3.2.3.5.1. Age

3.2.3.5.1.1. B/F/TAF

No impact of age was identified on the PK of BIC, TAF, or FTC (BIC Population PK Report, TAF Population PK Report, and FTC Population PK Report [13542v1]). Thus, no dose adjustment of B/F/TAF is warranted based on age.

There are insufficient data available at this time regarding the use of the B/F/TAF in pediatric subjects.

3.2.3.5.2. Weight

3.2.3.5.2.1. BIC

Body weight was identified as a statistically significant covariate for BIC PK based on population PK analyses (BIC Population PK Report).

Table 25 presents BIC PK parameters across quartiles of weight following administration of B/F/TAF once daily in HIV-infected subjects. The median of AUC_{tau}, C_{max}, and C_{tau} of BIC in Q1 of weight was 23.4%, 31.0%, and 15.3% higher, respectively, compared with those in Q4 of weight. These differences were small compared with a > 30 kg difference in median weight of Q1 versus Q4 and not considered clinically significant due to the lack of exposure-efficacy/safety relationship for BIC following administration of B/F/TAF (Section 3.3).

Table 25. Population PK Analysis: Summary of PK Parameter Estimates for BIC Following Once-Daily Dosing of B/F/TAF in HIV-Infected Subjects by Weight Range

BIC PK Parameter	Mean (CV%)				
	Q1 [43.0, 64.0, 69.8][a] (N = 300)	Q2 [69.9, 74.3, 78.9] (N = 300)	Q3 [79.0, 84.0, 90.2] (N = 296)	Q4 [90.3, 100.2, 208.7] (N = 297)	Median Q1-Q4 % difference
AUC_{tau} (ng*h/mL)	115630.6(24.9)	104048.2 (25.3)	98158.2 (25.4)	89995.9 (25.5)	23.4
C_{max} (ng /mL)	7073.5 (20.3)	6343.0 (19.3)	5902.9 (19.7)	5251.6 (21.3)	31.0
C_{tau} (ng /mL)	2886.1 (34.1)	2625.8 (35.4)	2522.4 (34.8)	2402.1 (33.4)	15.3

a Weight (kg) presented as [min, median, max]
Source: B/F/TAF Integrated PK/PD, Table Req8808.2

3.2.3.5.2.2. TAF

Weight was not identified as a statistically significant covariate for TAF PK based on population PK analyses (TAF Population PK Report).

3.2.3.5.2.3. FTC

The totality of FTC exposure data distinguishing body weight groups showed that there were no major differences in the overall range and distribution of AUC and C_{max} (FTC Population PK Report [13542v1]). Subjects with a body weight ≤ 75 kg had an approximately10% to 15% higher mean/median AUC and C_{max} values than subjects with a body weight > 75 kg.

3.2.3.5.2.4. B/F/TAF

While body weight was identified as a statistically significant covariate for BIC PK, the impact was considered not clinically meaningful. There was no impact of weight identified on TAF and FTC PK. Thus, no dose adjustment of B/F/TAF is warranted based on weight.

3.2.3.5.3. Race

3.2.3.5.3.1. B/F/TAF

No impact of race was identified on the PK of BIC, TAF, or FTC (BIC Population PK Report, TAF Population PK Report, and FTC Population PK Report [13542v1]). The PK of BIC, FTC, TAF and its metabolite TFV were also similar between Japanese and Caucasian subjects in a Phase 1 Japanese bridging PK study (Study GS-US-380-1991, Section 2.4.1.1). Based on the totality of data, no dose adjustment of B/F/TAF is warranted based on race.

3.2.3.5.4. Sex

3.2.3.5.4.1. BIC

Sex was not identified as a statistically significant covariate for BIC PK based on population PK analyses (BIC Population PK Report).

3.2.3.5.4.2. TAF

Table 26 summarizes population PK-derived parameter estimates for TAF following once daily dosing of B/F/TAF in HIV-infected subjects by sex. Sex was identified as a statistically significant covariate for TAF PK based on population PK analyses (TAF Population PK Report). AUC_{tau} and C_{max} of TAF in female HIV-infected subjects were 14.0% and 11.2% higher, respectively, than those in male HIV subjects. These differences were not considered clinically meaningful based on the lack of exposure-efficacy/safety relationship for TAF following administration of B/F/TAF (Section 3.3).

Table 26. Population PK Analysis: Summary of PK Parameter Estimates for TAF Following Once-Daily Dosing of B/F/TAF in HIV-Infected Subjects by Sex

TAF PK Parameter	Female (Test) (N = 47)	Male (Reference) (N = 439)	GLSM Ratio (%) (90% CI)
AUC_{tau} (ng*h/mL)	160.3 (18.5)	140.0 (16.6)	114.0 (108.6, 119.8)
C_{max} (ng/mL)	134.3 (16.7)	119.9 (14.7)	111.2 (105.0, 117.7)

Data are presented as mean (%CV).
Source: Source: B/F/TAF Integrated Population PK, Table Req8808.8

3.2.3.5.4.3. FTC

There were no major differences with respect to range and distribution of AUC values between males and females. Female subjects showed a 16% higher mean AUC and 20% higher C_{max}, compared with males (FTC Population PK Report [13542v1]), which is not considered clinically relevant based on the safety range of FTC {DESCOVY® 2017, EMTRIVA® 2017}.

3.2.3.5.5. B/F/TAF

Sex was identified as a statistically significant covariate influencing the PK of TAF, however, the impact is not clinically meaningful based on the lack of exposure-efficacy/safety relationships. In addition, sex has no impact on BIC and FTC PK. Thus, no dose adjustment of B/F/TAF is warranted based on sex.

3.2.4. Effect of Extrinsic Factors

An integrated summary of the results of dedicated Phase 1 studies and modeling and simulation, analyses including population PK analyses, is presented in the following sections to convey the clinical relevance, or lack thereof, regarding specific extrinsic factors and to provide dosing recommendations for use of B/F/TAF.

3.2.4.1. Effect of Food

Table 27 presents the effect of food on the PK of BIC, TAF, and FTC following administration of B/F/TAF. Administration of B/F/TAF with or without food does not result in clinically meaningful changes in the PK of its components based on the lack of exposure-safety relationship for BIC and TAF following administration of B/F/TAF (m2.7.1, Section 3.2; Section 3.3; Study GS-US-141-1233, Section 2.2.1.1).

BIC+F/TAF and B/F/TAF were administered without regard to food in Phase 2 and 3 studies, respectively. The cumulative safety, efficacy, PK, and PK/PD data support administration of B/F/TAF without regard to food.

Table 27. GS-US-141-1233: Effect of Food on the PK of BIC, TAF, and FTC Following Administration of B/F/TAF

Change in PK Parameter	Phase 1 Food Effect Study High-Fat Meal vs Fasted		
	BIC	**TAF**	**FTC**
AUC_{inf} (h*ng/mL)	↑24%	↑67%	↔
AUC_{last} (h*ng/mL)	↑24%	↑63%	↔
C_{max} (ng/mL)	↔	↔	↓14%
	Phase 1 Food Effect Study Moderate-Fat Meal vs Fasted		
	BIC	**TAF**	**FTC**
AUC_{inf} (h*ng/mL)	↑24%	↑48%	↔
AUC_{last} (h*ng/mL)	↑24%	↑48%	↔
C_{max} (ng/mL)	↑20%	↔	↔

Ninety percent CIs of the GLSM ratio were within (↔) or extended below (↓) the predetermined lack of PK alteration boundaries of 80% to 125% for all PK parameters except TAF C_{max} which was 70% to 143%.
Source: GS-US-141-1233, Section 2.2.1.1

3.2.4.2. Drug-Drug Interaction Potential

As described in Sections 3.1.3.4 and 3.1.3.5, the DDI potential between BIC, TAF, and/or FTC with drugs that may be concomitantly used by HIV-infected subjects was evaluated in vitro and in clinical studies to assess any influence of overlapping human drug metabolizing enzyme and transporter pathways affecting B/F/TAF and/or concomitant medications. These studies included, but were not limited to, representative enzyme and/or transporter inhibitors and inducers; OCs; and anti-HCV direct-acting drugs.

3.2.4.2.1. Potential for B/F/TAF to Affect Other Drugs

As described in Sections 3.1.3.4 and 3.1.3.5, there is low potential for B/F/TAF to be a perpetrator of DDIs through human drug metabolizing enzymes or drug transporters.

Coadministration of NGM/EE, a representative OC, with BIC or F/TAF demonstrated no effect on the PK of NGMN, NG, and EE, confirming that B/F/TAF may be coadministered with OCs (Study GS-US-311-1790 [Cohort 2], Section 2.5.2.2 and Study GS-US-311-1790 [Cohort 1]).

The plasma exposure (AUC_{inf}, AUC_{last}, and C_{max}) of MDZ (a probe substrate for CYP3A), was unaffected following administration with B/F/TAF, confirming that it is not a CYP3A inducer or inhibitor in vivo (Study GS-US-380-4270, Section 2.5.1.5).

The effect of B/F/TAF on metformin PK and PD was evaluated clinically due to the inhibitory potential of BIC against OCT2/MATE1 in vitro. Metformin plasma exposure (AUC_{tau}) was increased by 39% with B/F/TAF relative to placebo. The exploratory PD endpoints of metformin, such as glucose reduction and active GLP-1 and lactate increases after oral glucose tolerance test, were unaffected. Based on these findings, the change in metformin exposure is not considered clinically significant and, as such, metformin may be coadministered with B/F/TAF without restriction. B/F/TAF may also be coadministered with other OCT2/MATE1 substrates except dofetilide, which is contraindicated due to the complexity in management of dofetilide's narrow therapeutic index and the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events.

Coadministration of B/F/TAF did not impact the PK of the anti-HCV drugs SOF/VEL/VOX (Study GS-US-380-1999, Section 2.5.1.2) or LDV/SOF (Study GS-US-380-1761, Section 2.5.1.1), confirming that B/F/TAF may be coadministered with SOF/VEL/VOX and LDV/SOF as well as SOF and sofosbuvir/velpatasvir (SOF/VEL).

Table 28 summarizes the effect of B/F/TAF on the PK of coadministered drugs in healthy subjects in Phase 1 studies.

Table 28. GS-US-311-1790, GS-US-380-4270, GS-US-380-1999, GS-US-380-1761, and GS-US-380-3908: Effect of BIC, TAF, F/TAF, and B/F/TAF on the PK of Coadministered Drugs in Healthy Subjects

	GS-US-311-1790 (BIC or F/TAF)		
	NGM/EE		
Change in PK Parameter	**EE**	**NG**	**NGNM**
AUC_{tau} (h*ng/mL)	↔	↔	↔
C_{max} (ng/mL)	↔	↔	↔
C_{tau} (ng/mL)	↔	↔	↔

	GS-US-380-4270 (B/F/TAF)
Change in PK Parameter	**MDZ**
AUC_{inf} (h*ng/mL)	↔
AUC_{last} (h*ng/mL)	↔
C_{max} (ng/mL)	↔

	GS-US-380-3908 (B/F/TAF)
Change in PK Parameter	**Metformin**
AUC_{tau} (h*ng/mL)	↑39%
C_{max} (ng/mL)	↔
C_{tau} (ng/mL)	↑36%

	GS-US-380-1999 (B/F/TAF)			
Change in PK Parameter	**SOF**	**VEL**	**VOX**	**GS-331007 GS-566500**
AUC_{tau} (h*ng/mL)	↔	↔	↔	↔
C_{max} (ng/mL)	↔	↔	↔	↔
C_{tau} (ng/mL)	NA	↔	↔	NA

	GS-US-380-1761 (B/F/TAF)			
Change in PK Parameter	**SOF**	**LDV**	**GS-331007**	**GS-566500**
AUC_{tau} (h*ng/mL)	↔	↔	↔	↔
C_{max} (ng/mL)	↔	↔	↔	↔
C_{tau} (ng/mL)	NA	↔	NA	NA

Ninety percent CIs of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined lack of PK alteration boundaries of 70% to 143%.
Source: GS-US-311-1790 [Cohort 1]; GS-US-311-1790 [Cohort 2], Section 2.5.2.2; GS-US-380-1761, Section 2.5.1.1; GS-US-380-1999, Section 2.5.1.2; and GS-US-380-3908, Section 2.5.1.3; GS-US-380-4270, Section 2.5.1.5

3.2.4.2.2. Potential for Other Drugs to Affect B/F/TAF

3.2.4.2.2.1. BIC

As described in Sections 3.1.1.1, 3.1.3.4.1, and 3.1.3.5.1, BIC has the potential to interact with high dose polyvalent cation containing antacids/supplements and drugs that affect UGT1A1 and CYP3A. As such, clinical DDI studies were conducted to provide guidance upon coadministration with such agents.

Table 29 summarizes the effect of coadministered drugs on the PK of BIC.

Following simultaneous administration of B/F/TAF with 20 mL of maximum-strength antacid (ie, maximum chelation interaction scenario including aluminum hydroxide 1600 mg and magnesium hydroxide 1600 mg), calcium carbonate (1200 mg), or ferrous fumarate (324 mg) under fasted conditions, BIC exposure (AUC_{inf}) was reduced by approximately 79%, 33%, and 63%, respectively, compared with administration of B/F/TAF alone (Study GS-US-380-3909, Section 2.5.1.4). This effect was substantially reduced by staggering administration by 2 hours or by simultaneous administration with food. B/F/TAF administration under fasted conditions 2 hours before antacid completely mitigated the chelation effect on BIC exposure. B/F/TAF administration under fasted conditions 2 hours after antacid reduced BIC AUC_{inf} by approximately 52%. Simultaneous administration of B/F/TAF with antacid with a moderate-fat meal resulted in BIC AUC_{inf} reduced by 47%. In addition, simultaneous administration of B/F/TAF with calcium carbonate or ferrous fumarate with a moderate-fat meal had no effect on BIC AUC_{inf} compared with B/F/TAF alone under fasted conditions. BIC has been shown to be effective over a wide range of exposures following administration of B/F/TAF, with a high IQ (mean IQ of 16.1-fold in Phase 3 studies [N = 1193]; Table 13) and without evidence for loss of efficacy at the lowest exposures observed (Section 3.3.2 and Study GS-US-141-1219, Section 2.3.1.1). These data indicate that despite situations where approximately 50% lower trough concentrations may occur, therapeutic trough concentrations will be maintained in all subjects at values above the $paEC_{95}$. Therefore, when B/F/TAF is used with polyvalent cation containing antacids/supplements, administration should be staggered by 2 hours or should be simultaneously administered with food.

CYP3A and UGT1A1 play an approximately equal role in the clearance of BIC. Consistent with first principles associated with multiple routes of metabolism and supported by the Quantitative Pharmacology Static Modeling Study (QP-2015-1001), a weak DDI is expected for BIC in the presence of strong inhibition of CYP3A only. This weak interaction was demonstrated with coadministration of BIC and the strong CYP3A inhibitors, VORI or DRV/co; BIC AUC increased by 61% and 74%, respectively, after coadministration with these agents compared with administration of B/F/TAF alone (Study GS-US-141-1485, Section 2.5.2.1). Similarly, only a weak DDI is expected for BIC in the presence of strong inhibition of UGT1A1 only. Conversely, strong inhibition of both CYP3A and UGT1A1 may lead to a strong DDI (maximum predicted increase of 455% after complete chemical ablation of both CYP3A and UGT1A1) (QP-2015-1001). This strong interaction was demonstrated after coadministration of BIC with ATV or ATV+COBI, strong inhibitors of both CYP3A and UGT1A1; BIC AUC_{inf} of 315% and 306%, respectively after coadministration with these agents compared with administration of B/F/TAF alone.

In agreement with the identified clearance pathways of BIC, coadministration of BIC with the potent pregnane X receptor (PXR) agonist, RIF, resulted in a 75% decrease in BIC AUC. In contrast, BIC AUC was reduced by to a lesser extent (38%) upon coadministration with RBT. Based on the lack of an exposure-efficacy relationship for BIC following administration of B/F/TAF in the Phase 3 population, the small decrease in BIC exposure after coadministration with RBT is not considered clinically relevant (Section 3.3.2).

Coadministration of B/F/TAF with the anti-HCV drugs SOF/VEL/VOX (Study GS-US-380-1999, Section 2.5.1.2) or LDV/SOF (Study GS-US-380-1761, Section 2.5.1.1) did not result in clinically relevant changes in the PK of BIC, confirming that B/F/TAF may be coadministered with SOF/VEL/VOX and LDV/SOF as well as SOF and SOF/VEL.

In BIC population PK analyses, concomitant use of commonly administered medications including, but not limited to, pH modifying agents (ie, H2RAs and PPIs) was evaluated as a potential covariate influencing BIC PK due to their frequent use in HIV-infected subjects. The concomitant use of H2RAs was not identified as significant covariate for BIC PK, confirming that B/F/TAF may be coadministered with H2RAs; but concomitant use of PPIs was a significant covariate, affecting the rate, but not extent, of BIC absorption (BIC Population PK Report). Table 30 presents the PK parameter estimates for BIC following once-daily dosing of B/F/TAF in HIV-infected subjects by usage of PPIs. Usage of PPIs is deemed not clinically meaningful, supported by the similar BIC exposures observed in subjects with PPI usage compared with subjects without PPI usage, confirming that B/F/TAF may be coadministered with PPIs.

Table 29. GS-US-380-3909, GS-US-141-1485, GS-US-380-1999, GS-US-380-1761: Effect of Coadministered Drugs on the PK of BIC Following Administration of BIC Individual Agent or B/F/TAF in Healthy Subjects

Change in PK Parameters	GS-US-380-3909 (B/F/TAF)			
	Calcium carbonate, fasted (Single Dose)	Calcium carbonate, fed (Single Dose)	Ferrous Fumarate, fasted (Single Dose)	Ferrous Fumarate, fed (Single Dose)
AUC_{inf} (h*ng/mL)	↓33%	↔	↓63%	↔
C_{max} (ng/mL)	↓42%	↔	↓71%	↓25%
	Antacid with B/F/TAF, fasted (Single Dose)	Antacid given 2h before B/F/TAF, fasted (Single Dose)	Antacid given 2h after B/F/TAF, fasted (Single Dose)	Antacid with B/F/TAF, fed (Single Dose)
AUC_{inf} (h*ng/mL)	↓79%	↓52%	↔	↓47%
C_{max} (ng/mL)	↓80%	↓58%	↔	↓49%

Change in PK Parameters	GS-US-141-1485 (BIC individual agent)					
	VORI (Single Dose)	DRV/COBI (Multiple Dose)	ATV (Single Dose)	ATV + COBI (Single Dose)	RBT (Multiple Dose)	RIF (Single Dose)
AUC_{inf} for SD, AUC_{tau} for MD (h*ng/mL)	↑61%	↑74%	↑315%	↑306%	↓38%	↓75%
C_{max} (ng/mL)	↔	↑52%	↔	↔	↓20%	↓28%
C_{tau} (ng/mL)	NA	↑111%	NA	NA	↓56%	NA

	GS-US-380-1999 (B/F/TAF)	GS-US-380-1761 (B/F/TAF)
	SOF/VEL/VOX+VOX (Multiple Dose)	LDV/SOF (Multiple Dose)
AUC_{inf} (h*ng/mL)	↔	↔
C_{max} (ng/mL)	↔	↔
C_{tau} (ng/mL)	↔	↔

Ninety percent CIs of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined lack of PK alteration boundaries of 70% to 143%.
Source: GS-US-141-1485, Section 2.5.2.1; GS-US-380-1761, Section 2.5.1.1; GS-US-380-1999, Section 2.5.1.2; GS-US-380-3909, Section 2.5.1.4

Table 30. Population PK Analysis: Summary of PK Parameter Estimates for BIC Following Once-Daily Dosing of B/F/TAF in HIV-Infected Subjects by Usage of Proton Pump Inhibitors

BIC PK Parameter	B/F/TAF		GLSM Ratio (%) (90% CI)
	With PPI Usage (Test) (N = 109)	Without PPI Usage (Reference) (N = 1084)	
AUC_{tau} (ng*h/mL)	97971.9 (29.3)	102406.2 (26.7)	95.2 (90.8, 99.8)
C_{max} (ng/mL)	5643.8 (25.4)	6196.3 (22.5)	90.6 (87.0, 94.4)
C_{tau} (ng/mL)	2581.0 (38.0)	2612.8 (34.9)	98.0 (92.0, 104.4)

Source: B/F/TAF Integrated Population PK, Table Req8808.5

3.2.4.2.2.2. TAF

As described in Sections 3.1.1.2, 3.1.3.4.2, and 3.1.3.5.2, TAF is a substrate of efflux transporters P-gp and BCRP {Williams 1985}. Additionally, TAF is metabolized by esterases; however, esterase-mediated DDIs are unlikely and/or not reported. Drugs that affect P-gp and/or BCRP may lead to changes in plasma concentrations of TAF and its major metabolite TFV.

Table 31 summarizes the effect of coadministered drugs on the PK of TAF and TFV including representative enzyme/transporter inhibitors COBI, ATV+COBI, EFV, and CBZ.

Collectively, the range of TAF and TFV exposure resulting from the decrease or increase in plasma concentrations due to P-gp inducers or P-gp/BCRP inhibitors evaluated are encompassed by the wide range of safe and efficacious exposures of TAF established in Phase 3 studies based on population PK/PD analyses (Section 3.3; Studies GS-US-120-1554; GS-US-292-1316; GS-US-311-0101; and GS-US-311-1387). Importantly, the exposures of the TAF major metabolite TFV in the presence of P-gp and or BCRP inhibitors are markedly lower than that observed with TDF-containing regimens and lower than the exposures observed following TAF in the setting of moderate renal impairment (Table 16, Section 3.2.3.3.2) for which E/C/F/TAF is indicated ({GENVOYA® 2017}; Study GS-US-292-0112, m2.7.4, Section 5.1.6.4).

Although in vitro data indicated that OATP1B1 and OATP1B3 contributes minimally to TAF disposition (m2.6.4, Section 7.3), a clinical study was conducted to evaluate TAF PK following coadministration of F/TAF with ATV+COBI (potent inhibition of OAT1B1/1B3) compared with administration of F/TAF alone. Study findings demonstrated that potent inhibition of OATP1B1/1B3 did not result in further increases in exposure by ATV in addition to the already increased TAF availability resulting from the administration of COBI (weak inhibition of OAT1B1/1B3) (Study GS-US-311-1388).

Coadministration of B/F/TAF with the anti-HCV drugs SOF/VEL/VOX (Study GS-US-380-1999, Section 2.5.1.2) or LDV/SOF (Study GS-US-380-1761, Section 2.5.1.1) did not result in clinically relevant changes in the PK of TAF, confirming that B/F/TAF may be coadministered with SOF/VEL/VOX and LDV/SOF as well as SOF and SOF/VEL.

Table 31. GS-US-120-1554, GS-US-292-1316, GS-US-311-0101, GS-US-311-1387, GS-US-311-1388, GS-US-380-1761, and GS-US-380-1999: Changes in TAF and TFV PK with Coadministered Drugs

TAF PK				
	GS-US-311-0101		GS-US-311-1387	GS-US-311-1388
Change in PK Parameters	TAF 8 mg (Multiple Dose)	F/TAF 200/40 mg (Multiple Dose)	F/TAF 200/25 mg (Single Dose)	F/TAF 200/10 mg (Multiple Dose)
	COBI	EFV	CBZ	ATV+COBI
AUC_{last} (h*ng/mL)	↑165%	↔	↓55%	↑75%
C_{max} (ng/mL)	↑183%	↓22%	↓57%	↑80%
	GS-US-120-1554	GS-US-380-1999	GS-US-380-1761	GS-US-292-1316
Change in PK Parameters	F/TAF (Multiple Dose)	B/F/TAF (Multiple Dose)	B/F/TAF (Multiple Dose)	E/C/F/TAF (Multiple Dose)
	RPV	SOF/VEL/VOX+VOX	LDV/SOF	Setraline
AUC_{last} (h*ng/mL)	↔	↑57%[a]	↔ [a]	↔
C_{max} (ng/mL)	↔	↑28%	↔	↔
TFV PK				
	GS-US-311-0101		GS-US-311-1387	GS-US-311-1388
Change in PK Parameters	TAF 8 mg (Multiple Dose)	F/TAF 200/40 mg (Multiple Dose)	F/TAF 200/25 mg (Single Dose)	F/TAF 200/10 mg (Multiple Dose)
	COBI	EFV	CBZ	ATV+COBI
AUC_{inf} (single dose) AUC_{tau} (multiple dose) (h*ng/mL)	↑231%	↔	↔	↑247%
C_{max} (ng/mL)	↑234%	↓25%	↓30%	↑216%
C_{tau} (ng/mL)	↑235%	↔	NA	↑273%
	GS-US-120-1554	GS-US-380-1999	GS-US-380-1761	GS-US-292-1316
Change in PK Parameters	F/TAF (Multiple Dose)	B/F/TAF (Multiple Dose)	B/F/TAF (Multiple Dose)	E/C/F/TAF (Multiple Dose)
	RPV	SOF/VEL/VOX+VOX	LDV/SOF	Sertraline
AUC_{tau} (h*ng/mL)	↔	↑67%	↑67%	↔
C_{max} (ng/mL)	↔	↑51%	↑43%	↔
C_{tau} (ng/mL)	↔	↑74%	↑81%	↔

a AUC_{tau} represented where available.
COBI is a representative inhibitor of P-gp; EFV is a representative moderate inducer of P-gp; CBZ is a representative strong inducer of P-gp; ATV+COBI is a representative inhibitor of OATP1B1/OATP1B3; RPV is a representative weak inducer of P-gp; SOF/VEL/VOX+VOX and LDV/SOF are representative anti-HCV drugs; and sertraline is a representative antidepressant. Ninety percent CIs of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined lack of PK alteration boundaries of 70% to 143%.
Source: GS-US-120-1554; GS-US-292-1316; GS-US-311-0101; GS-US-311-1387; GS-US-311-1388; GS-US-380-1761, Section 2.5.1.1; GS-US-380-1999, Section 2.5.1.2

3.2.4.2.2.3. FTC

Based on the results of in vitro experiments, in vivo assessments, and the known elimination pathways of FTC, the potential for clinically relevant DDI involving FTC with other medicinal products is low due to nonoverlapping metabolic and/or transporter mediated pathways (m2.6.4). This result was confirmed in clinical studies.

Table 32 summarizes the effect of coadministered drugs on the PK of FTC. FTC exposure was not affected following coadministration with EFV, a moderate CYP3A inducer, or tacrolimus, a moderate CYP3A inhibitor (Studies GS-US-174-0105 and GS-US-311-0101). Additionally, coadministration of B/F/TAF with the anti-HCV drugs SOF/VEL/VOX (Study GS-US-380-1999, Section 2.5.1.2) or LDV/SOF with B/F/TAF (Study GS-US-380-1761, Section 2.5.1.1) did not result in clinically relevant changes in the PK of FTC, confirming that B/F/TAF may be coadministered with SOF/VEL/VOX and LDV/SOF as well as SOF and SOF/VEL.

Table 32. GS-US-174-0105, GS-US-311-0101, GS-US-380-1761, and GS-US-380-1999: Changes in FTC PK with Coadministered Drugs

Change in PK Parameters	GS-US-311-0101	GS-US-174-0105	GS-US-380-1999	GS-US-380-1761
	F/TAF 200/40 mg (Multiple Dose)	FTC/TDF (Multiple Dose)	B/F/TAF (Multiple Dose)	B/F/TAF (Multiple Dose)
	EFV	Tacrolimus	SOF/VEL/VOX+VOX	LDV/SOF
AUC_{tau} (h*ng/mL)	↔	↔	↔	↔
C_{max} (ng/mL)	↔	↔	↔	↔

Ninety percent CIs of the GLSM ratio were within (↔) the predetermined lack of PK alteration boundaries of 70% to 143% for Studies GS-US-311-0101, GS-US-380-1999, and GS-US-380-1761 and 80% to 125% for Study GS-US-174-0105.
Source: GS-US-174-0105; GS-US-311-0101; GS-US-380-1761, Section 2.5.1.1; GS-US-380-1999, Section 2.5.1.2

3.2.4.2.3. Summary of Potential Drug-Drug Interaction Following Administration of B/F/TAF

There is low potential for B/F/TAF to be a perpetrator of DDIs through human drug metabolizing enzymes or drug transporters, including interactions with the OCT2/MATE1substrate metformin.

While coadministration of B/F/TAF with potent inhibitors of P-gp and/or BCRP will result in increases in the plasma concentrations of TAF, these are not relevant changes in exposures based on supporting safety data for TAF following administration of B/F/TAF.

A weak DDI (≤ 2-fold) is expected for BIC in the presence of potent inhibition of either CYP3A or UGT1A1, which is not a relevant change in BIC exposure based on supporting safety data for BIC following administration of B/F/TAF. As such, dose adjustment of B/F/TAF is not necessary when B/F/TAF is used with strong inhibitors of either CYP3A or UGT1A1 or in HIV-infected patients with decreased UGT1A1 activity (eg, UGT1A1*28 genotype).

Based on the totality of data on B/F/TAF, or its components, from nonclinical and clinical studies informing on enzyme- and/or transporter-mediated DDIs, no clinically significant DDIs are observed or expected with amlodipine, atorvastatin, buprenorphine, drospirenone, EE, famotidine, fluticasone, itraconazole, ketoconazole, LDV/SOF, metformin, methadone, MDZ, naloxone, NGM, norbuprenorphine, omeprazole, sertraline, SOF, SOF/VEL, or SOF/VEL/VOX.

3.2.4.2.4. Management of Potentially Significant Drug-Drug Interactions

Coadministration of B/F/TAF with dofetilide, a substrate of OCT2/MATE1, is contraindicated because dofetilide is a narrow therapeutic index drug associated with serious and/or life-threatening events and there are no data available regarding the use of B/F/TAF with dofetilide.

Drugs that are potent inducers of CYP3A, UGT1A1 and/or P-gp may result in lower plasma exposures of BIC and/or TAF and may lead to reduced therapeutic effect of B/F/TAF, and coadministration is not recommended.

Potent inhibition of both CYP3A and UGT1A1 results in a substantial increase in BIC exposure. As such, coadministration of BIC with potent dual inhibitors of CYP3A and UGT1A1 is not recommended. Potent inhibitors of both CYP3A and UGT1A1 are not common.

Coadministration of B/F/TAF with medications or oral supplements containing polyvalent cations (eg, magnesium, aluminum, calcium, and iron) under fasted conditions will result in a decrease of BIC exposure due to chelation of BIC with these cations. Administration of medications (eg, antacid) or oral supplements containing polyvalent cations should be separated from B/F/TAF (fasted administration) by at least 2 hours. Alternatively, these medications or oral supplements can be taken simultaneously with B/F/TAF together with food.

Table 33 summarizes information for potentially significant DDIs with B/F/TAF and includes dosing recommendations. This summary includes predicted drug interactions that have not been studied in humans. As B/F/TAF is a complete regimen for the treatment of HIV infection, other ARVs are not included in the table below or proposed in product labeling except ATV, which is included as illustrative of the impact of potent inhibition of both CYP3A and UGT1A1.

Table 33. Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect[a]	Clinical Comment
Antiarrhymic: dofetilide	Effect on dofetilide concentrations unknown	Data are not available on the potential interaction of dofetilide with B/F/TAF. Due to the potential for serious and/or life-threatening events with increased dofetilide plasma concentrations, coadministration of B/F/TAF is contraindicated.
Anticonvulsants: carbamazepine[b] oxcarbazepine phenobarbital phenytoin	↓ BIC ↓ TAF	Oxcarbazepine, phenobarbital, or phenytoin, may decrease BIC and TAF plasma concentrations. Alternative anticonvulsants should be considered.
Antimycobacterials: rifabutin[b] rifampin[b] rifapentine	↓ BIC ↓ TAF	Coadministration of rifampin has been shown to decrease BIC plasma concentration substantially; rifabutin has been shown to decrease BIC exposure modestly. Rifampin or rifabutin may decrease TAF concentration. Coadministration with rifampin is contraindicated. Coadministration with rifabutin or rifapentine is not recommended.
HIV-1 Antiviral Agent: atazanavir[b]	↑ BIC	Coadministration of B/F/TAF is not recommended.
Hepatitis C Virus Antiviral Agents: boceprevir telaprevir	Effect on boceprevir, telaprevir, or TAF unknown	Coadministration with boceprevir or telaprevir has the potential to adversely affect the intracellular activation and clinical antiviral efficacy of TAF based on *in vitro* data. Coadministration of B/F/TAF and boceprevir or telaprevir is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ BIC ↓ TAF	Coadministration of B/F/TAF is not recommended.
Medications or oral supplements containing polyvalent cations (eg, Mg, Al, Ca, Fe): Calcium or iron supplements[b] Cation-containing antacids or laxatives[b] Sucralfate Buffered medications	↓ BIC	Administer B/F/TAF 2 hours before or 2 hours after taking medications or oral supplements containing polyvalent cations. Alternatively, B/F/TAF and medications or oral supplements containing polyvalent cations can be taken together with food.

Exposure refers to AUC.
a ↑ = Increase, ↓ = Decrease
b Indicates that a 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. Rationale for Dose Selection in HIV-Infected Subjects

All data for the B/F/TAF FDC in the Phase 3 clinical studies in HIV-infected subjects were generated with the intended commercial formulation of the B/F/TAF 50/200/25 mg FDC.

3.3.1.1. BIC Dose Selection

The 50-mg dose of BIC was selected for the B/F/TAF FDC based on the totality of data from the BIC first-in-human single- and multiple-ascending dose, BIC+F/TAF drug interaction study (Study GS-US-141-1218, Section 2.2.2.1), the dose-ranging proof-of-concept study (Study GS-US-141-1219, Section 2.3.1.1), the Phase 2 safety and efficacy study (Study GS-US-141-1475, m2.7.3, Section 2.1.3; single-agent BIC 75 mg coadministered with F/TAF [200/25 mg]), and a relative bioavailability study (Study GS-US-141-1233, Section 2.2.1.1), which evaluated 2 FDC tablet formulations (a 50-mg BIC B/F/TAF [50/200/25 mg] FDC and a 75-mg BIC B/F/TAF [75/200/25 mg] FDC) compared with BIC 75 mg + F/TAF (200/25 mg).

In Study GS-US-141-1218, single-ascending doses (5, 25, 50, 100, 300, or 600 mg) and multiple-ascending doses (5, 25, 50, 100, or 300 mg once daily for 7 days) of single-agent BIC were well tolerated in healthy subjects, and a lack of DDI was confirmed between BIC and F/TAF. In the proof-of-concept Study GS-US-141-1219, once-daily doses of single-agent BIC (5, 25, 50, or 100 mg) administered for 10 days were also well tolerated and led to dose-dependent decreases in HIV-1 viral load (mean [SD] $DAVG_{11}$ values ranged from −0.92 [0.104] to −1.61 [0.256] log_{10} copies/mL HIV-1 RNA across the 4 doses).

The BIC 75-mg dose was selected as a single-agent for Phase 2 development based on its predicted $paIQ_{95}$ value. Considering the C_{tau} values achieved in Study GS-US-141-1219 and an in vitro $paEC_{95}$ of 162 ng/mL for wild-type HIV-1 (PC-141-2032), $paIQ_{95}$ [median (range)] of 4.9 (4.4 to 11.7), 13.4 (5.3 to 18.6), and 25.9 (23.0 to 36.9) were estimated for BIC 25-, 50-, and 100-mg doses, respectively. Based on the linear PK of BIC in this dose range and predicted PK/PD response curve, single-agent BIC 75 mg was predicted to provide near-maximal virologic response with a $paIQ_{95}$ value of approximately 20.

An FDC formulation containing BIC 75 mg, FTC 200 mg, and TAF 25 mg was developed and the relative bioavailability of this FDC (under fasted conditions) was compared with BIC 75 mg single agent + F/TAF (200/25 mg) in Study GS-US-141-1233. BIC AUC_{inf} and C_{max} for single-dose administration of the B/F/TAF (75/200/25 mg) FDC were approximately 27% and 31% higher, respectively, relative to BIC 75 mg single agent + F/TAF (200/25 mg). Therefore, a second FDC formulation was developed that contained BIC 50 mg, FTC 200 mg, and TAF 25 mg. Upon single-dose administration of the B/F/TAF (50/200/25 mg) FDC or BIC 75 mg + F/TAF (200/25 mg) under fasted conditions, the 90% CIs of the GLSM ratios for BIC primary PK parameters were within the protocol-defined 70% to 143% boundary of equivalence. Based on these data, the B/F/TAF 50/200/25 mg FDC was chosen for further evaluation in Phase 3 clinical studies.

3.3.1.2. TAF Dose Selection

TAF, at a dose of 25 mg is approved for the treatment of HIV infection in adults and adolescents as a component of the F/TAF (Descovy), indicated for use in combination with other ARV agents, and as a component of the complete regimen, R/F/TAF (Odefsey®). In the Phase 3 B/F/TAF studies, a coformulated FDC of BIC 50 mg, FTC 200 mg, and TAF 25 mg resulted in TAF exposures consistent with the range of safe and efficacious exposures observed historically TAF-containing products/regimens. Additionally, the 25-mg dose of TAF is also approved, as a single agent, for the treatment of chronic HBV infection.

3.3.1.3. FTC Dose Selection

The 200-mg dose of FTC is approved for the treatment of HIV-1 infection in adults and adolescents. FTC is also a component of the F/TAF (Descovy), indicated for use in combination with other ARV agents, and of the complete regimens, E/C/F/TAF (Genvoya) and R/F/TAF (Odefsey). In the Phase 3 B/F/TAF studies, a coformulated FDC of BIC 50 mg, FTC 200 mg, and TAF 25 mg resulted in FTC exposures consistent with the range of safe and efficacious exposures observed historically with FTC-containing products/regimens.

3.3.2. Pharmacokinetic-Pharmacodynamic Relationships for the Treatment of HIV-1 Infection

Exposure-efficacy relationships for B/F/TAF were evaluated in ART-naive HIV-infected subjects who received B/F/TAF in Phase 3 studies (Studies GS-US-380-1489 and GS-US-380-1490) using BIC or TAF exposure estimates derived from population PK modeling (BIC Population PK Report, TAF Population PK Report, and Section 3.2.2). For PK/PD analyses, the primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. Further details are described in m2.7.3, Section 3.2. Subjects with no virologic data at Week 48 were excluded from the analysis.

Table 34 presents the number of HIV-infected subjects with evaluable BIC and TAF population PK parameters (AUC_{tau}, C_{max}, and C_{tau} [BIC only]) and virologic data at Week 48 (Snapshot Algorithm previously described) included in the exposure-response analyses.

Table 34. Number of Subjects in the Population PK Dataset with Evaluable Population PK Exposure Parameters Used for Exposure-Response Analyses (BIC and TAF PK/PD Analysis Sets)

Analysis Set	Analyte	HIV-Infected Subjects With Evaluable Exposure Estimates (N)	
		All Subjects (Safety)	Subjects With Virological Data at Week 48 (Efficacy)
Safety/Efficacy PK/PD[a]	BIC	624	584
	TAF	486	461

a BIC and TAF PK/PD Analysis Sets included all subjects who were randomized, had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing PK parameter estimated from the population PK analysis (Safety) and virologic outcome data at Week 48 (Efficacy).
Source: B/F/TAF Integrated PK/PD, Tables 4.1.1 and 4.1.2

The efficacy profile of B/F/TAF is summarized in the Summary of Clinical Efficacy (m2.7.3).

3.3.2.1. BIC

The efficacy of BIC, administered as B/F/TAF, in the treatment of HIV infection was evaluated by determining the proportion of subjects who achieved the primary efficacy endpoint as a function of Phase 3 population quartiles of BIC exposure (AUC_{tau}, C_{max}, and C_{tau}). Table 35 presents the proportion of population quartiles of BIC exposures in HIV-infected subjects. Virologic response rates were high across all exposure ranges for BIC. Taking into account the $paEC_{95}$ for wild type HIV-1 virus (162 ng/mL) (Section 3.2.3.2.1), the lowest exposure quartile for BIC trough concentrations (C_{tau} range: 757.4−1975.5 ng/mL, which corresponds to an IQ range of 4.7 to 12.2, showed similar virologic response rates as the highest exposure quartile for BIC trough concentrations (C_{tau} range: 3121.0−6498.5 ng /mL, which corresponds to an IQ range of 19.3 to 40.1). As such, no exposure-response relationship is observed following administration of B/F/TAF.

Table 35. GS-US-380-1489 and GS-US-380-1490: Percentage of Subjects with HIV-1 RNA < 50 copies/mL (Snapshot Algorithm) by Population Quartiles of BIC Exposures in ART-Naive HIV-Infected Subjects (BIC PK/PD Analysis Set, Excluding Subjects with No Virologic Data in Week 48 Window)

	B/F/TAF (N = 584)
BIC AUC_{tau} Quartile Subgroups	
BIC AUC_{tau} in Quartile 1 [147, 47879.0, 72615.3, 84804.7]	146/147 (99.3%)
BIC AUC_{tau} in Quartile 2 [146, 84863.7, 92675.0, 100644.1]	144/146 (98.6%)
BIC AUC_{tau} in Quartile 3 [142, 100725.2, 108637.8, 119277.7]	139/142 (97.9%)
BIC AUC_{tau} in Quartile 4 [149, 119511.4, 132611.9, 213739.2]	146/149 (98.0%)
BIC C_{max} Quartile Subgroups	
BIC C_{max} in Quartile 1 [149, 2866.1, 4700.1, 5329.7]	149/149 (100.0%)
BIC C_{max} in Quartile 2 [143, 5333.2, 5739.0, 6136.4]	140/143 (97.9%)
BIC C_{max} in Quartile 3 [141, 6140.5, 6567.0, 7076.8]	138/141 (97.9%)
BIC C_{max} in Quartile 4 [151, 7086.6, 7779.3, 11427.4]	148/151 (98.0%)
BIC C_{tau} Quartile Subgroups	
BIC C_{tau} in Quartile 1 [149, 757.4, 1664.5, 1975.5]	148/149 (99.3%)
BIC C_{tau} in Quartile 2 [141, 1975.7, 2257.2, 2539.8]	138/141 (97.9%)
BIC C_{tau} in Quartile 3 [145, 2540.2, 2774.7, 3118.9]	143/145 (98.6%)
BIC C_{tau} in Quartile 4 [149, 3121.0, 3641.5, 6498.5]	146/149 (98.0%)

Quartiles were determined for all subjects, so imbalances may be present when excluding subjects with no virologic data in the Week 48 window.
The BIC PK/PD Analysis Set includes all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing BIC PK parameter (AUC_{tau}, C_{max}, or C_{tau}) estimated from the population PK analysis.
Numbers presented in the square bracket were the sample size, minimum, median, and maximum for subjects included in that subgroup, excluding subjects with no virologic data.
Source: B/F/TAF Integrated PK/PD, Table 2.1

3.3.2.2. TAF

The efficacy of TAF, administered as B/F/TAF, in the treatment of HIV-infection was evaluated by determining the proportion of subjects who achieved the primary efficacy endpoint as a function of Phase 3 population quartiles of TAF exposure (AUC_{tau} and C_{max}). Table 36 presents the proportion by population quartiles of TAF exposures in HIV-infected subjects. Virologic response rates were high across all exposure ranges for TAF.

Table 36. GS-US-380-1489 and GS-US-380-1490: Percentage of Subjects with HIV-1 RNA < 50 copies/mL (Snapshot Algorithm) by Population Quartiles of TAF Exposures in ART-Naive HIV-Infected Subjects (TAF PK/PD Analysis Set, Excluding Subjects with No Virologic Data in Week 48 Window)

	B/F/TAF (N = 461)
TAF AUC_{tau} Quartile Subgroups	
TAF AUC_{tau} in Quartile 1 [114, 73.7, 115.5, 123.4]	111/114 (97.4%)
TAF AUC_{tau} in Quartile 2 [116, 123.4, 132.6, 139.8]	113/116 (97.4%)
TAF AUC_{tau} in Quartile 3 [116, 140.0, 148.8, 157.1]	115/116 (99.1%)
TAF AUC_{tau} in Quartile 4 [115, 158.2, 171.1, 222.0]	114/115 (99.1%)
TAF C_{max} Quartile Subgroups	
TAF C_{max} in Quartile 1 [113, 36.4, 108.7, 113.7]	112/113 (99.1%)
TAF C_{max} in Quartile 2 [117, 113.7, 116.4, 119.0]	112/117 (95.7%)
TAF C_{max} in Quartile 3 [115, 119.1, 123.7, 129.2]	114/115 (99.1%)
TAF C_{max} in Quartile 4 [116, 129.3, 140.0, 183.7]	115/116 (99.1%)

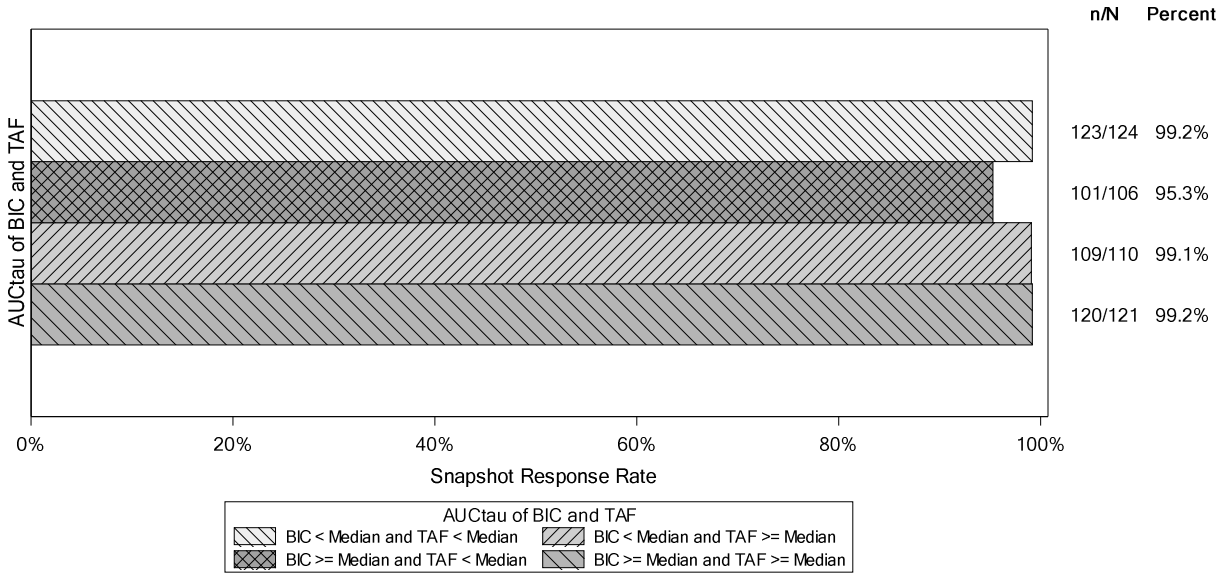
Quartiles were determined for all subjects, so imbalances may be present when excluding subjects with no virologic data in the Week 48 window.
The TAF PK/PD Analysis Set includes all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing TAF PK parameter (AUC_{tau} or C_{max}) estimated from the population PK analysis.
Numbers presented in the square bracket were the sample size, minimum, median, and maximum for subjects included in that subgroup, excluding subjects with no virologic data.
Source: B/F/TAF Integrated PK/PD, Table 2.2

3.3.2.3. BIC and TAF

The efficacy of BIC and TAF, administered as B/F/TAF, in the treatment of HIV-infection was further evaluated by determining the proportion of HIV-infected subjects who achieved the primary efficacy endpoint (Snapshot Algorithm) as a function of Phase 3 population medians of BIC and TAF exposure (AUC_{tau}).

Figure 8 presents the proportion of HIV-infected subjects who achieved HIV-1 RNA < 50 copies/mL, stratified by population medians (above/below median) of BIC and TAF AUC_{tau}. Virologic response rates were high across all BIC and TAF AUC_{tau} strata combinations. Similarly high efficacy was observed across all BIC and TAF C_{max} strata combinations (B/F/TAF Integrated PK/PD, Figure 1.3.2).

Figure 8. **GS-US-380-1489 and GS-US-380-1490: Percentage of Subjects with HIV-1 RNA < 50 copies/mL (Snapshot Algorithm) by Population Medians of BIC and TAF AUC_{tau} in ART-Naive HIV-Infected Subjects (BIC and TAF PK/PD Analysis Sets, Excluding Subjects with No Virologic Data in Week 48 Window)**



The BIC PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing BIC PK parameter (AUC_{tau}, C_{max}, or C_{tau}) estimated from the population PK analysis.
The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing TAF PK parameter (AUC_{tau} or C_{max}) estimated from the population PK analysis.
Source: B/F/TAF Integrated PK/PD, Figure 1.3.1

3.3.2.4. FTC

3.3.2.4.1. 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 study 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 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.

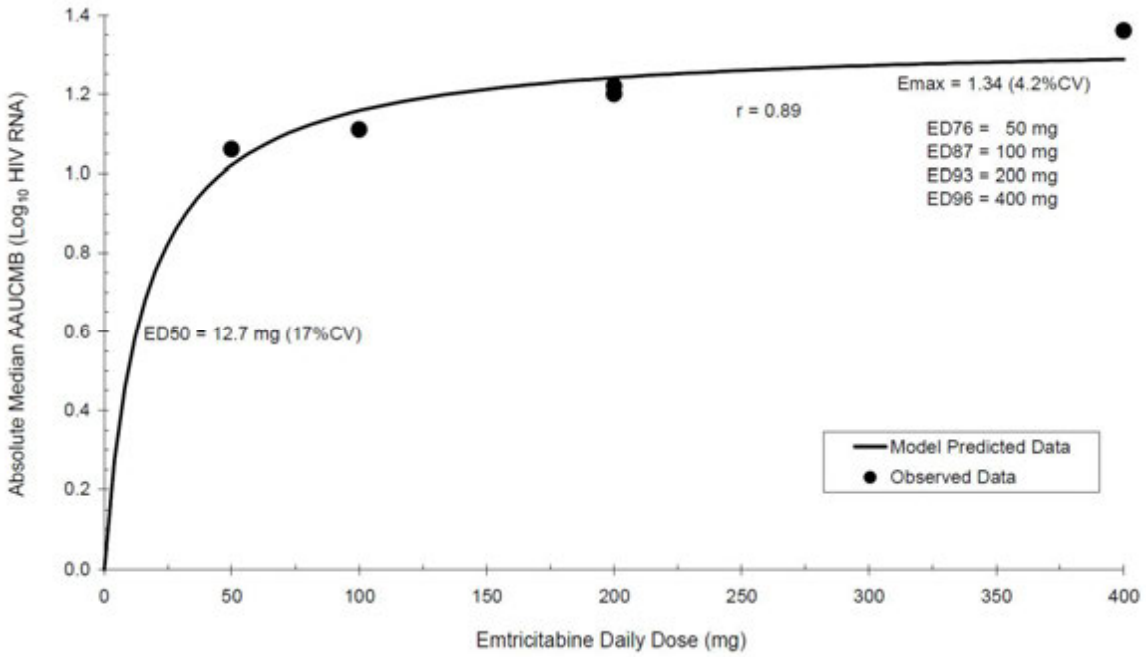
Study FTC-102 was an open-label, randomized, parallel-group study evaluating 3 once-daily dosage regimens of FTC (25, 100, and 200 mg once daily) and the 3TC 150-mg twice-daily regimen during 10 days of monotherapy. A total of 81 subjects, naive to 3TC and ABC, were randomized to 1 of the 4 treatment 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, Effect = (E_{max} × Dose)/(dose that produced a therapeutic response in 50% of subjects [ED_{50}] + Dose). The pharmacological dose-response curve (Figure 9) 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 9. FTC Study FTC-101: Dose-Response Relationship of Anti-HIV Activity of FTC: Plots of Log_{10} HIV-1 RNA AAUCMB Versus FTC Daily Dose



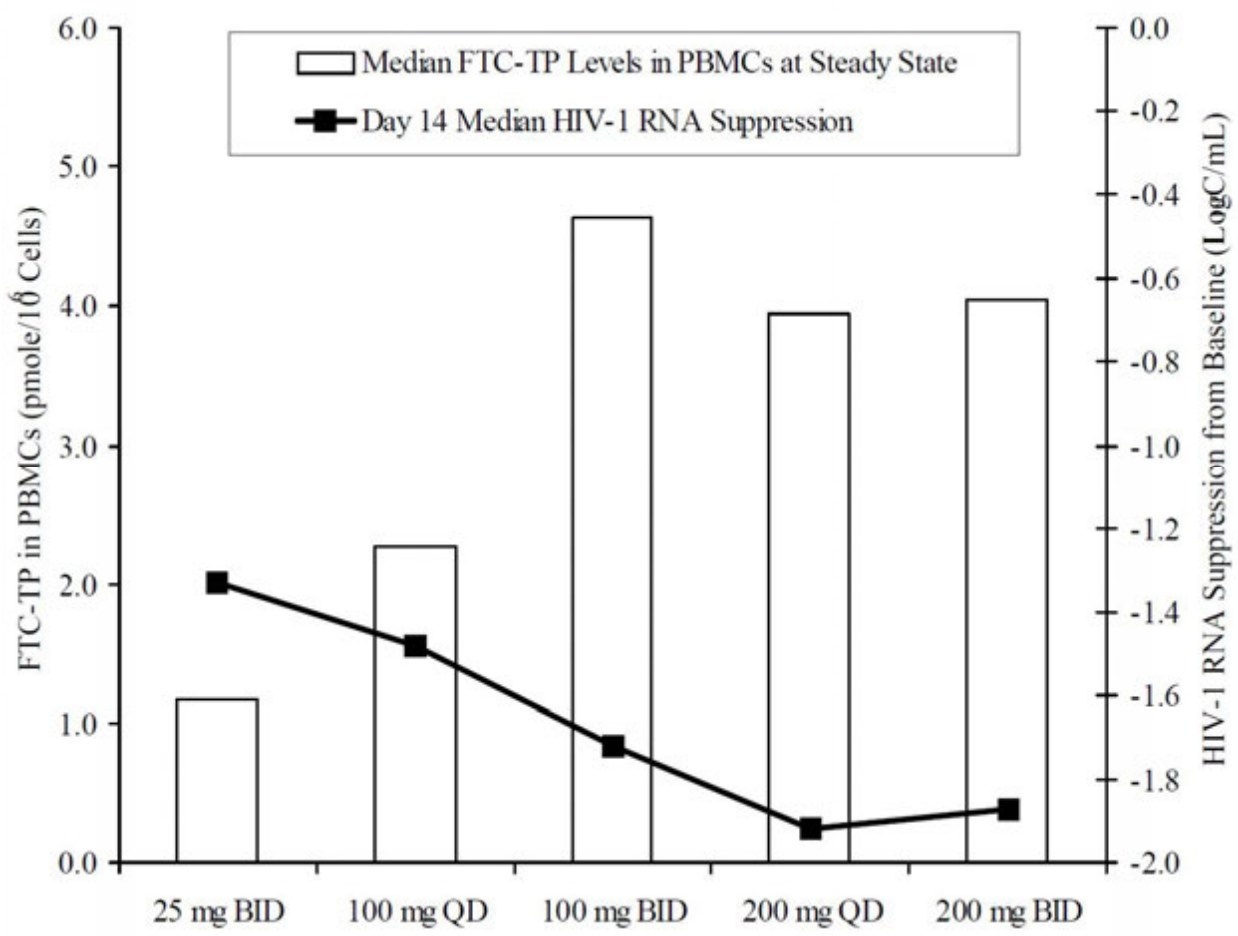
Source: {Rousseau 2001}

3.3.2.4.2. 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 10). 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 10. FTC Study FTC-101: Correlation of Antiviral Activity of FTC and FTC-Triphosphate Levels in PBMCs



Source: FTC-101, Appendix 16, PK Analysis Report, Figure 12

3.3.3. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

The PK/PD relationship between plasma concentration and the change in QTcF over a range of doses tested (BIC: 75 and 300 mg; TAF: 25 and 125 mg) were examined. In addition, exposure-safety relationships (BIC and TAF PK/PD Analysis Sets) for B/F/TAF were evaluated in ART-naive HIV-infected subjects in Phase 3 studies (Studies GS-US-380-1489 and GS-US-380-1490) who received B/F/TAF using BIC or TAF exposure estimates (AUC_{tau} and C_{max}) derived from population PK modeling (BIC Population PK Report, TAF Population PK Report, and Section 3.2.2).

The safety parameters evaluated were incidence of the 5 most common AEs observed in subjects receiving B/F/TAF in pooled Phase 3 studies; these AEs (incidences) were diarrhea (12.1%), headache (12.0%), nausea (9.0%), nasopharyngitis (7.1%), and fatigue (6.0%) (B/F/TAF Week 48 Integrated Summary of Safety [ISS], Table 7.2). No other AEs with a > 10% incidence occurred.

The number of HIV-infected subjects included in this safety exposure-response analyses are presented in Table 34 (Section 3.3.2).

The safety profile of B/F/TAF is summarized in the Summary of Clinical Safety (m2.7.4).

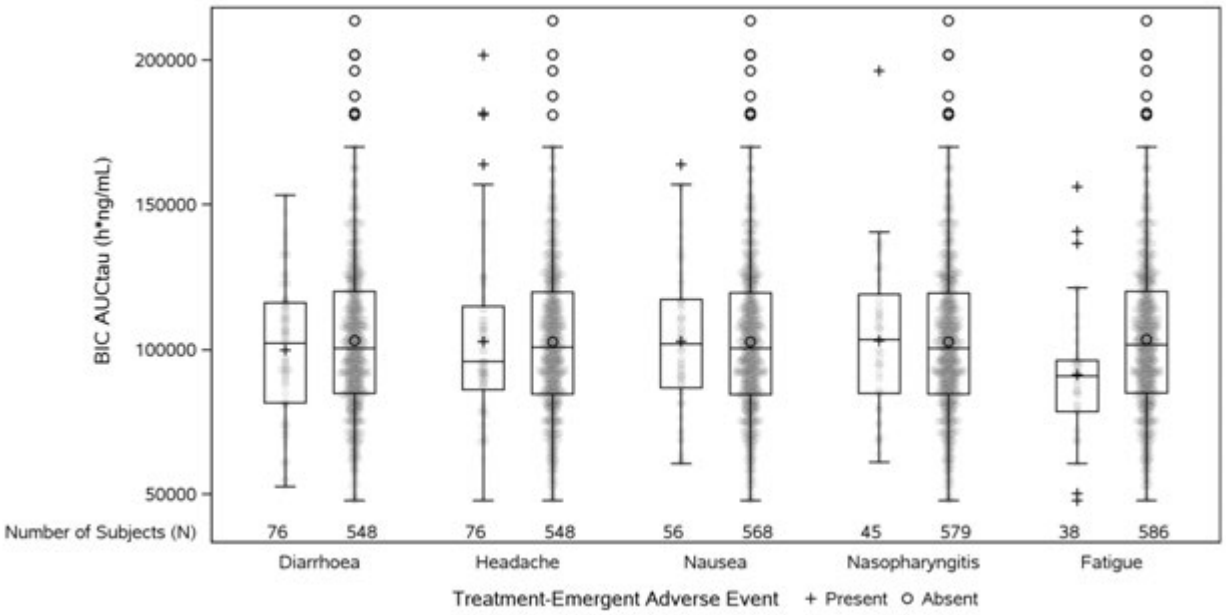
3.3.3.1. BIC

BIC did not affect the QTc interval (primary PD endpoint of QTcF), consistent with the International Council for Harmonisation (ICH) E14 definition of a negative "thorough QT/QTc study," following administration of a single therapeutic or supratherapeutic dose of BIC 75 or 300 mg, respectively (Study GS-US-141-1480, Section 2.2.2.2). Single dose BIC (75 or 300 mg) was generally well tolerated in healthy subjects. No clinically significant ECG abnormalities or changes in vital signs were observed. BIC plasma exposures at the supratherapeutic dose were approximately 5.7-fold higher for AUC and 4.0-fold higher for C_{max} compared with those observed in HIV-infected subjects receiving B/F/TAF in Phase 3 studies (Table 13 and Study GS-US-141-1480, Section 2.2.2.2).

The PK/PD relationships between BIC exposure parameters and AEs were evaluated.

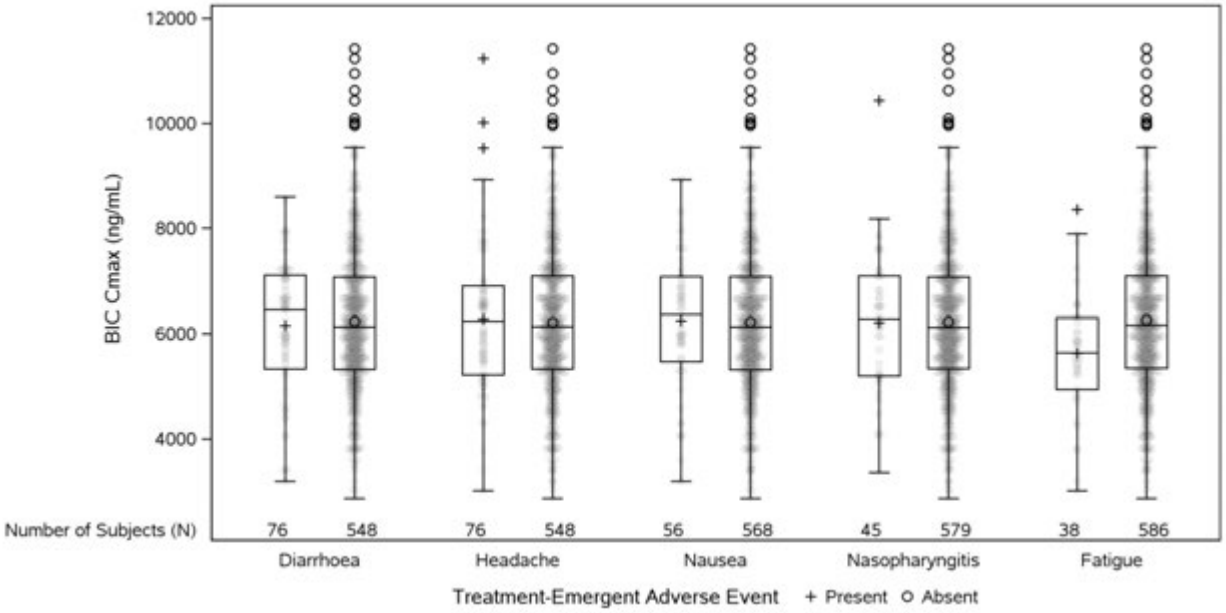
Figure 11 and Figure 12 present box plots of BIC AUC_{tau} and C_{max}, respectively, by presence or absence of common AEs in subjects receiving B/F/TAF. BIC exposures (AUC_{tau} and C_{max}) were similar regardless of the presence or absence of the evaluated adverse effect, indicating a lack of association between BIC exposure and common AEs of diarrhea, headache, nausea, nasopharyngitis, and fatigue (B/F/TAF Integrated PK/PD, Table 6.1).

Figure 11. Box Plots of BIC AUCtau by Presence or Absence of Selected Adverse Events in B/F/TAF Phase 3 Studies (BIC PK/PD Analysis Set)



The BIC PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing BIC PK parameter (AUC_{tau}) estimated from the population PK analysis.
Adverse events were coded using MedDRA 19.1.
Box plots denote median and IQR (Q3-Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
The top 5 AE categories with the highest incidence rates were included.
Grey symbols in the background represent the actual data.
Source: B/F/TAF Integrated PK/PD, Figure 3.1.1

Figure 12. Box Plots of BIC C_{max} by Presence or Absence of Selected Adverse Events in B/F/TAF Phase 3 Studies (BIC PK/PD Analysis Set)



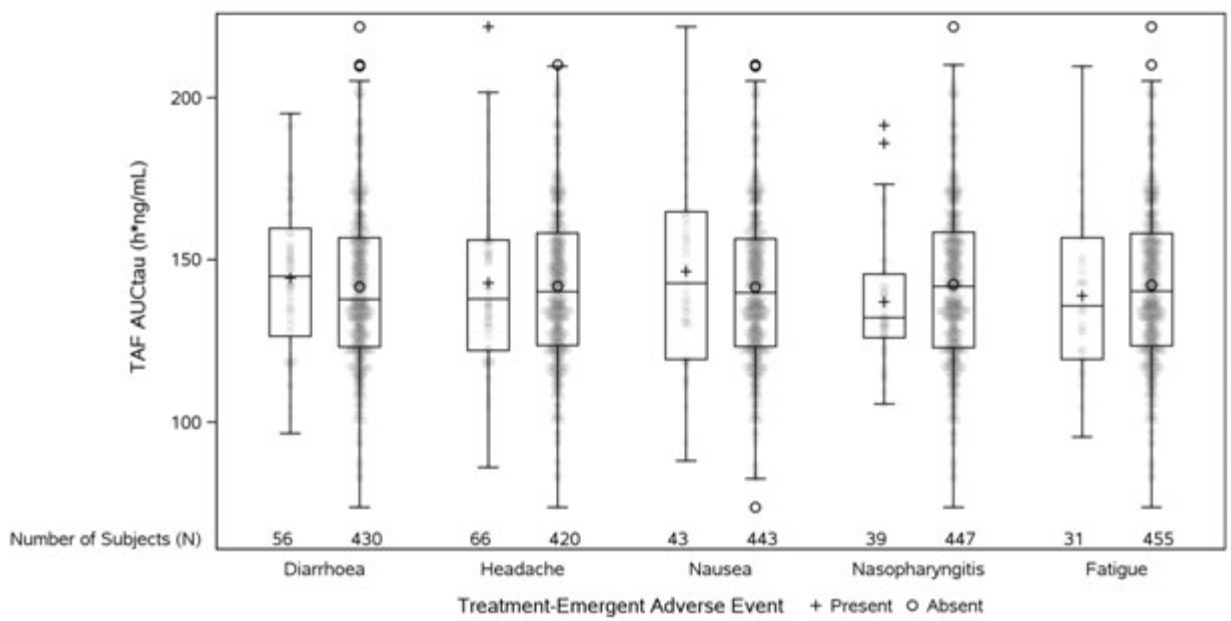
The BIC PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing BIC PK parameter (C_{max}) estimated from the population PK analysis.
Adverse events were coded using MedDRA 19.1.
Box plots denote median and IQR (Q3-Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
The top 5 AE categories with the highest incidence rates were included.
Grey symbols in the background represent the actual data.
Source: B/F/TAF Integrated PK/PD, Figure 3.1.2

3.3.3.2. TAF

TAF did not affect the QTc interval (primary PD endpoint of QTcF), consistent with the ICH E14 definition of a negative "thorough QT/QTc study," following administration of a single therapeutic or supratherapeutic dose of TAF 25 or 125 mg, respectively, administered with food (Study GS-US-120-0107). Single dose TAF (25 or 125 mg) was generally well tolerated in these healthy subjects. Most AEs were considered mild and unrelated to study drug. No clinically significant ECG abnormalities or changes in vital signs were observed. TAF plasma exposures at the supratherapeutic dose were approximately 8.2-fold higher for AUC and 6.7-fold higher for C_{max} compared with those observed in HIV-infected subjects receiving B/F/TAF in Phase 3 studies (Table 14 and Study GS-US-120-0107).

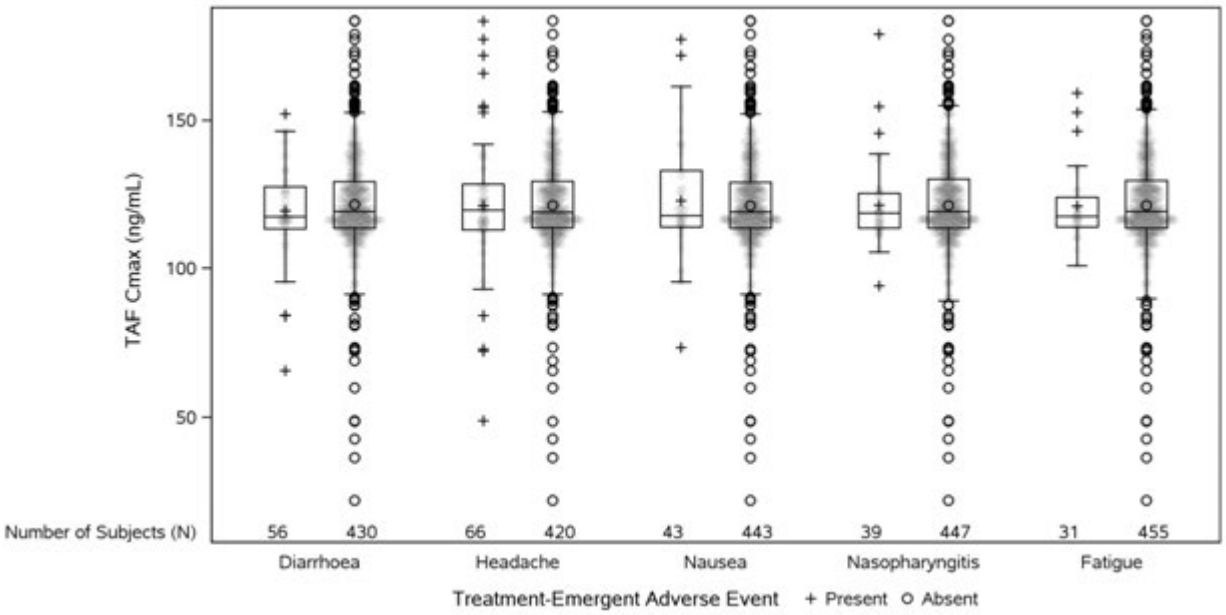
The PK/PD relationships between TAF exposure parameters and AEs were evaluated. Figure 13 and Figure 14 present box plots of TAF AUC_{tau} and C_{max}, respectively, by presence or absence of common AEs in subjects receiving B/F/TAF. TAF exposures (AUC_{tau} and C_{max}) were similar regardless of the presence or absence of the evaluated AE, indicating a lack of association between TAF exposure and common AEs of diarrhea, headache, nausea, nasopharyngitis, and fatigue (B/F/TAF Integrated PK/PD, Table 6.2).

Figure 13. **Box Plots of TAF AUC_{tau} by Presence or Absence of Common Adverse Events in B/F/TAF Phase 3 Studies (TAF PK/PD Analysis Set)**



The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing TAF PK parameter (AUC_{tau}) estimated from the population PK analysis.
Adverse events were coded using MedDRA 19.1.
Box plots denote median and IQR (Q3-Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
The top 5 AE categories with the highest incidence rates were included.
Grey symbols in the background represent the actual data.
Source: B/F/TAF Integrated PK/PD, Figure 3.2.1

Figure 14. Box Plots of TAF C_{max} by Presence or Absence of Common Adverse Events in B/F/TAF Phase 3 Studies (TAF PK/PD Analysis Set)

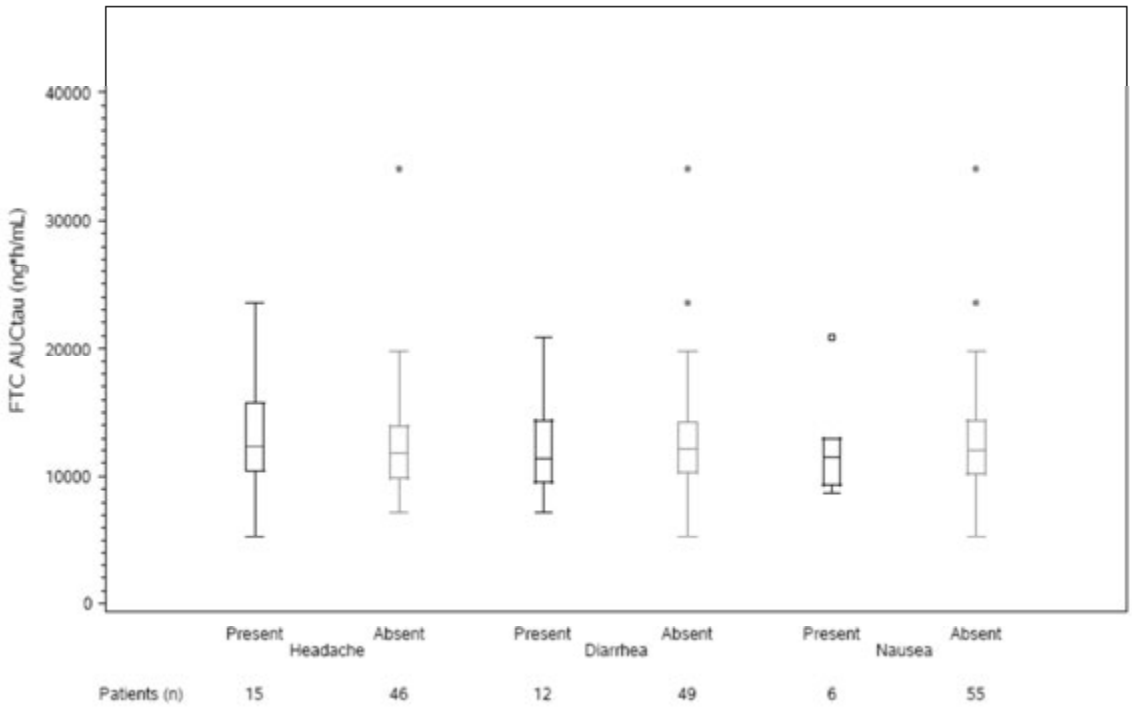


The TAF PK/PD Analysis Set included all subjects who were randomized and had at least 1 dose of B/F/TAF in Studies GS-US-380-1489 or GS-US-380-1490 and who had at least 1 nonmissing TAF PK parameter (C_{max}) estimated from the population PK analysis.
Adverse events were coded using MedDRA 19.1.
Box plots denote median and IQR (Q3-Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
The top 5 AE categories with the highest incidence rates were included.
Grey symbols in the background represent the actual data.
Source: B/F/TAF Integrated PK/PD, Figure 3.2.2

3.3.3.3. FTC

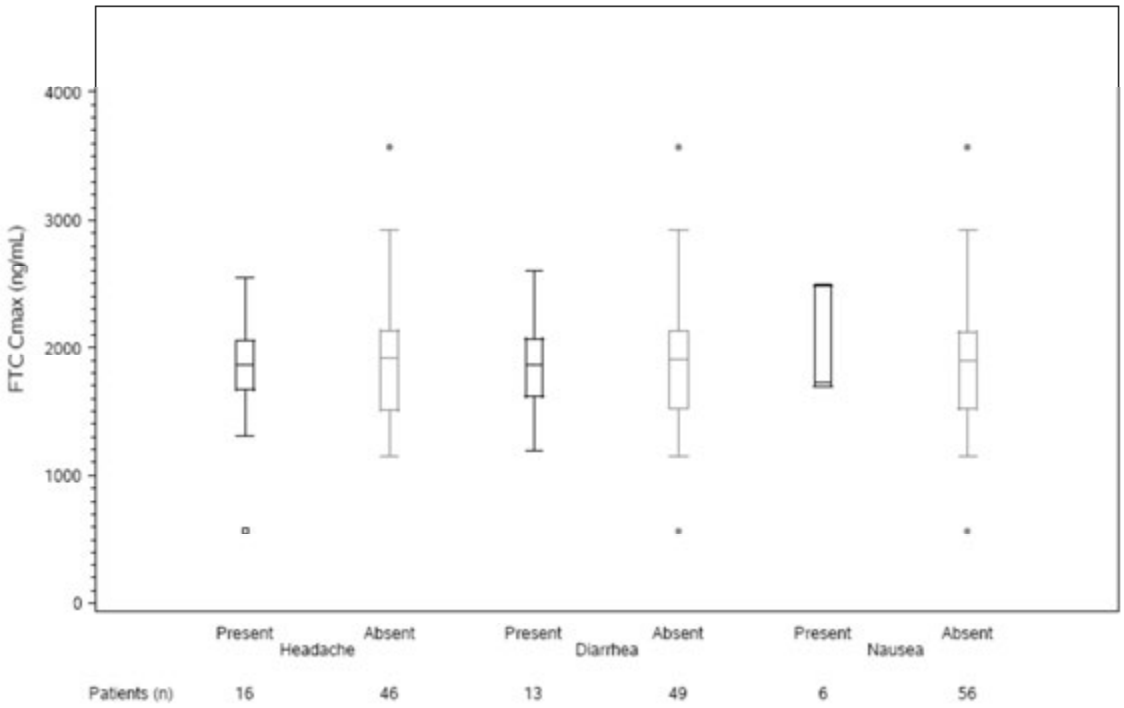
PK/PD analyses of the FTC exposure-safety relationship were performed in ART-naive HIV-infected subjects in Stribild® (STB; elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [E/C/F/TDF]) Phase 2/3 studies using FTC exposures derived from intensive PK substudies versus safety parameters that included commonly observed AEs, namely headache, nausea, or diarrhea. The relationships between FTC exposure and incidence of AEs (present/absent) are shown in Figure 15 for AUC_{tau} and in Figure 16 for C_{max}. FTC exposures were comparable regardless of the incidence of headache, nausea, or diarrhea, and no exposure-AE trends were observed.

Figure 15. Box Plot of FTC AUC_{tau} (ng*h/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set)



Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Source: STB PK/PD, Figure 4.1

Figure 16. Box Plot of FTC C_{max} (ng/mL) Versus Incidence of Selected Adverse Events (FTC PK/PD Analysis Set)

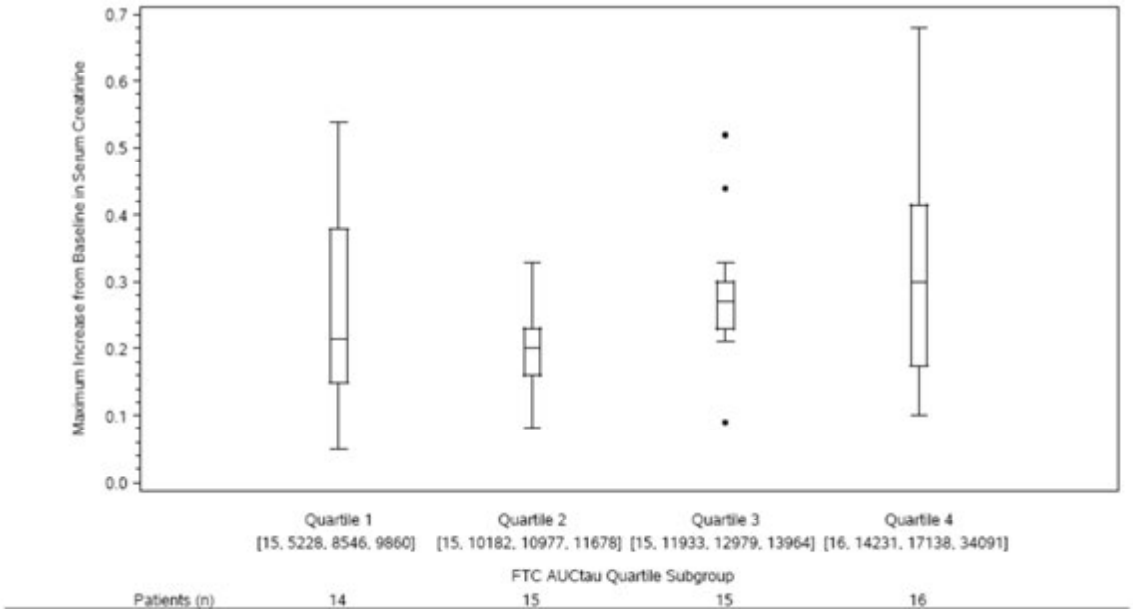


Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Source: STB PK/PD, Figure 4.2

The relationship between FTC exposure quartiles and changes in renal laboratory parameters was also evaluated; exposure versus serum creatinine change is shown in Figure 17. 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.

Figure 17. Box Plot of Maximum Increase from Baseline in Serum Creatinine (mg/dL) by FTC AUC_{tau} (ng•h/mL) Quartile Subgroup (FTC PK/PD Analysis Set)



Box plots denote median and IQR, whiskers denote maximum and minimum values within 1.5 × IQR, and circles denote outliers > 1.5 × IQR.
Subject 2003-6267 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

3.4. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Conclusions

A comprehensive clinical pharmacology program was conducted using BIC, TAF, and FTC as individual agents or as part of an FDC in Phase 1, 2, or 3 studies to support the use of B/F/TAF for the treatment of HIV infection. Phase 1 clinical studies evaluated single- and multiple-dose escalations, PK in healthy and HIV-infected subjects, ADME, the potential for B/F/TAF to affect other drugs, and the potential of food, other drugs, organ impairment, or other demographic factors to affect B/F/TAF. The steady-state PK of B/F/TAF was also evaluated in HIV-infected subjects in Phase 3 clinical studies. Population PK analyses evaluated intrinsic and extrinsic factors affecting the PK of BIC and TAF in HIV-infected subjects, and potential relationships were evaluated between BIC and TAF exposure and efficacy and safety outcomes. The PK and PK/PD conclusions based on these data are summarized in the following sections.

3.4.1. Absorption

The PK properties of BIC, TAF, and FTC have been evaluated in HIV-infected and healthy subjects. Following oral administration of the B/F/TAF with or without food, BIC, TAF, and FTC were absorbed quickly with median peak plasma concentrations (T_{max}) observed from 2.0 to 4.0 hours, 0.5 to 2.0 hours, and 1.5 to 2.0 hours postdose, respectively. There are no clinically relevant differences in BIC, TAF, and FTC exposures (AUC_{tau}, C_{max}, and/or C_{tau}) between HIV-infected and healthy subjects. BIC exposure is dose-proportional over the dose range of 25 to 100 mg; TAF exposure is dose-proportional over the dose range of 8 to 125 mg; and FTC exposure is dose-proportional over the dose range of 25 to 200 mg.

3.4.2. Distribution

BIC is > 99% bound to human plasma proteins. Following a single oral dose of [^{14}C]BIC in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.50 and 0.55 through 120 hours postdose. The ex vivo plasma protein binding of TAF was approximately 80% in healthy subjects. Following a single oral dose of [^{14}C]TAF in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity was 0.6 at 0.25 hours and 2.4 at 216 hours postdose. The protein binding of FTC was < 5% in human plasma. Following a single oral dose of [^{14}C]FTC in healthy subjects, the blood to plasma ratio of [^{14}C]- radioactivity was approximately 1.0.

3.4.3. Metabolism

BIC is primarily metabolized by CYP3A and UGT1A1 with each enzyme playing an approximately equal role in the clearance of BIC. Following a single oral dose of [^{14}C]BIC, the majority (67.9%) of radioactivity in plasma was parent drug. Hydroxy-BIC-sulfate (20.1%) and BIC-glucuronide (8.6%) were the major metabolites identified in human plasma. Unchanged drug accounted for 31% to 34% of the radioactive dose in the feces that likely represents a combination of both unabsorbed drug and deconjugated BIC glucuronide. Desfluoro-hydroxy-BIC-cysteine-conjugate (10%−13% of dose) and other minor oxidative metabolites were identified in feces. Radioactivity in urine consisted primarily of BIC-glucuronide(s) (21% of dose) and other minor oxidative metabolites and their conjugates.

TAF is rapidly metabolized to TFV primarily via hydrolysis by CES1 while CatA is the major enzyme hydrolyzing TAF to TFV in PBMCs. TFV is then further phosphorylated to the active metabolite, TFV-DP by cellular nucleotide kinases. [^{14}C]-radioactivity showed TAF as the most abundant species in the initial few hours and uric acid in the later period. The predominant species detected in feces and urine was TFV with other minor metabolites also present including xanthine, hypoxanthine, and adenine (< 2% of the dose).

FTC is not subject to significant hepatic metabolism and is eliminated primarily as unchanged drug by renal excretion. FTC is effectively metabolized intracellularly in PBMCs to form its active metabolite, FTC-TP. Following a single oral dose of [^{14}C]FTC to healthy subjects, FTC was the predominant species present in plasma. Sulfoxide metabolite(s) and direct glucuronide were primarily recovered in low levels in urine (12.9% of dose).

3.4.4. Elimination

Following a single oral dose of [^{14}C]BIC, mean total recovery of radioactivity was 95.3%, consisting of approximately 35.0% and 60.3% recovered in urine and feces, respectively. The median plasma BIC $t_{1/2}$ was approximately 17.26 hours. Radioactivity in feces consisted primarily of unchanged BIC (31%−34% of dose) and other oxidative metabolites and their conjugates. Unchanged BIC likely represents a combination of both unabsorbed drug and deconjugated BIC glucuronide. Radioactivity in urine consisted primarily of BIC-glucuronide(s) (21% of dose) and other minor oxidative metabolites and their conjugates. Renal clearance of the unchanged BIC was minimal (1.3% of dose). The nonclinical and human ADME data indicate that metabolism is the primary clearance pathway for BIC.

Following a single oral dose of [^{14}C]TAF, approximately 84.4% of radioactive dose was recovered, with 47.2% of the dose from feces and 36.2% of the dose from urine. TAF was rapidly metabolized to TFV, with a median TAF plasma $t_{1/2}$ of 0.51 hours and the median TFV T_{max} of 3.25 hours and plasma $t_{1/2}$ of 32.37 hours. The predominant species detected in feces and urine was TFV with other minor metabolites including xanthine, hypoxanthine, and adenine (< 2% of the dose). Renal excretion of TAF as unchanged parent was minimal (1.4% of dose). The nonclinical and human ADME data indicate that TAF is primarily cleared through metabolism via the purine catabolic pathway following conversion to TFV.

Following a single oral dose of [^{14}C]FTC, 99.6% of the total radioactive dose was recovered, with 85.8% of the dose from urine and 13.7% of the dose from feces. The plasma FTC $t_{1/2}$ was approximately 10.2 hours. Approximately 65.4% of dose excreted in urine as parent, indicating FTC is eliminated primarily as unchanged drug by renal excretion.

3.4.5. Effect of Intrinsic Factors

The impact of intrinsic factors on the PK of BIC, TAF, and FTC was evaluated in Phase 1 studies in non-HIV-infected subjects and as covariates in population PK analyses which included HIV-infected subjects who received B/F/TAF, TAF, or FTC. Intrinsic factors evaluated include HIV infection status, renal and hepatic impairment, and demographic factors. No clinically relevant PK differences due to HIV infection status and demographic factors, such as age, weight, sex, and race, were identified for BIC, TAF, and FTC.

Clinically significant exposure changes of the TAF metabolite, TFV, and FTC were not observed in HIV-infected subjects with mild or moderate renal impairment relative to the subjects with normal renal function in Phase 3 clinical studies. Therefore, F/TAF- containing products are indicated for use in renally impaired, HIV-infected subjects with $eGFR_{CG} \geq 30$ mL/min. Consistent with the known ADME profile of BIC, severe renal impairment did not result in clinically relevant changes in BIC exposure. The recommendation for use of B/F/TAF in subjects with renal impairment is guided by the most conservative dosing recommendation for affected components in the setting of renal impairment (ie, FTC). B/F/TAF may be administered without dose adjustment in subjects with $eGFR_{CG} \geq 30$ mL/min. There are insufficient data available regarding the use of the B/F/TAF in subjects with $eGFR_{CG} < 30$ mL/min.

The PK of TAF was evaluated in non-HIV-infected subjects with mild, moderate, and severe hepatic impairment. Hepatic impairment did not result in clinically relevant changes in TAF exposure. Minimal change in FTC exposure is expected in subjects with hepatic impairment due to its renal clearance pathway. Therefore, F/TAF-containing products can be used in HIV-infected subjects with mild and moderate hepatic impairment without dose adjustment. The PK of BIC was studied in non-HIV-infected subjects with moderate hepatic impairment. Moderate hepatic impairment did not result in clinically relevant changes in BIC exposure. Therefore, B/F/TAF may be administered without dose adjustment in subjects with mild to moderate hepatic impairment. There are insufficient data available regarding the use of the B/F/TAF FDC in subjects with severe hepatic impairment.

3.4.6. Effect of Extrinsic Factors

The impact of extrinsic factors on the PK of BIC, TAF, and FTC was evaluated in Phase 1 food effect and DDI studies as well as modeling and simulation analyses. Administration of B/F/TAF with or without food does not result in clinically meaningful changes in the PK of its components; therefore, BIC+F/TAF and B/F/TAF were administered without regard to food in Phase 2 and 3 clinical studies. The cumulative safety, efficacy, PK, and PK/PD data support administration of B/F/TAF without regard to food.

BIC is the substrate of UGT1A1 and CYP3A. Potent inhibition of both CYP3A and UGT1A1 results in a substantial increase in BIC exposure, and coadministration of BIC with potent dual inhibitors of CYP3A and UGT1A1 is not recommended. TAF is a substrate of P-gp and BCRP, and although coadministration of B/F/TAF with potent inhibitors of P-gp and/or BCRP will result in increases in the plasma concentrations of TAF, these increases are not clinically relevant changes in exposures based on supporting safety data for TAF following administration of B/F/TAF. Drugs that are potent inducers of CYP3A, UGT1A1, and/or P-gp may result in lower plasma exposures of BIC and TAF and lead to reduced therapeutic effect of B/F/TAF; coadministration with potent inducers is not recommended.

Coadministration of B/F/TAF with medications or oral supplements containing polyvalent cations (eg, magnesium, aluminum, calcium, and iron) under fasted conditions will result in a decrease of BIC exposure due to chelation of BIC with these cations. Administration of medications (eg, antacid) or oral supplements containing polyvalent cations should be separated from the fasted administration of B/F/TAF by at least 2 hours. Alternatively, these medications or oral supplements can be taken simultaneously with B/F/TAF together with food.

BIC, TAF, and FTC are not clinically relevant inhibitors or inducers of major human drug metabolizing enzymes and transporters. As such, there is low potential for B/F/TAF to be perpetrators of DDIs through human drug metabolizing enzymes or drug transporters, including with the OCT2/MATE1 substrate metformin.

3.4.7. Clinical Pharmacokinetics/Pharmacodynamics

A 50-mg dose of BIC was selected based on the totality of PK, safety, and efficacy data from Phase 1 and 2 studies in conjunction with the knowledge that trough concentration maintained above $paEC_{95}$ is desired for INSTIs. BIC 50 mg, coformulated as B/F/TAF 50/200/25 mg FDC, provided near maximal virologic response and an IQ of 16.1-fold above the $paEC_{95}$ against wild-type HIV-1 virus. The 25-mg dose of TAF and the 200-mg dose of FTC are approved for the treatment of HIV-1 infection in combination with other ARV agents and as a component of the complete regimen, R/F/TAF. TAF and FTC demonstrated a lack of DDIs with BIC and were coformulated as B/F/TAF 50/200/25 mg FDC for Phase 3 studies.

In the Phase 3 studies, exposure-efficacy relationships at BIC and TAF exposures (AUC_{tau} and C_{max}) above or below population median, as well as across quartiles for individual agents versus the primary efficacy endpoint (HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA defined snapshot algorithm), were examined. All analyses consistently revealed high virologic response rates across all groups (including subjects with the lowest quartile exposure to BIC and TAF) with no trends in exposure-response relationships. Importantly, for BIC, in particular, all subjects had trough concentrations (C_{tau}) above the $paEC_{95}$ with no loss of efficacy at lower IQ. Exposure of once-daily FTC 200 mg has consistently demonstrated efficacy in clinical studies and is a standard of care in HIV treatment.

Relationships between BIC and TAF exposure parameters and safety parameters from Phase 3 studies were evaluated. BIC and TAF exposures (AUC_{tau} and C_{max}) were similar regardless of the presence or absence of the most common AEs, indicating a lack of association between BIC or TAF and findings of diarrhea, headache, nausea, nasopharyngitis, and fatigue in the Phase 3 studies. Exposure of once daily FTC 200 mg has consistently demonstrated safety in clinical studies and is a standard of care in HIV treatment.

4. VIROLOGY SUMMARY

Nonclinical and clinical virology studies are discussed in the following sections.

4.1. Nonclinical Virology

The INSTI BIC and the N[t]RTIs FTC and TAF are potent and selective inhibitors of HIV-1 and HIV-2. FTC and TAF are also potent and selective inhibitors of HBV. All 3 drugs show potent ARV activity against diverse subtypes of HIV-1 in vitro. FTC and TAF are phosphorylated intracellularly through nonoverlapping pathways, and in combination show no antagonism for the formation of their active metabolites. Bictegravir does not require metabolic modification for activity. Two- and 3-drug combinations of BIC, FTC, and TAF consistently show synergistic anti-HIV-1 activity in vitro and no evidence of antagonism or toxicity.

The resistance profiles for the individual agents of BIC, FTC, and TAF have been well characterized. There is no cross-resistance between the nucleoside reverse transcriptase inhibitor (NRTI) and INSTI classes.

Both FTC and TAF have shown a low potential for mitochondrial toxicity in long-term toxicity studies and there was no evidence of toxicity to mitochondria in vitro and in vivo. Active metabolites of FTC and TAF have a high selectivity for HIV reverse transcriptase (RT) and are very weak inhibitors of mammalian DNA polymerases α, β, δ, and ε and mitochondrial DNA (mtDNA) polymerase γ. However, as mitochondrial toxicity has not been associated with INSTIs as a class, and as BIC is not anticipated to significantly increase the exposure of FTC or TFV, the potential for exacerbating mitochondrial toxicity is low.

Bictegravir, FTC, and TAF have no pharmacologically significant off-target binding affinity to the receptors tested. Bictegravir, FTC, and TAF have low in vitro cytotoxicity in a variety of human cell types.

Overall, the PD and pharmacological assessment of BIC, FTC, and TAF supports the effective and safe use of these 3 agents together in combination therapy for HIV-1 infection.

A summary of nonclinical virology is provided in the following sections, and a full description of nonclinical virology is provided in m2.6.2. A tabular listing of nonclinical virology studies is provided in Appendix 6.3.

4.1.1. Primary Pharmacodynamics

4.1.1.1. BIC

Bictegravir is a novel strand transfer inhibitor of HIV-1 integrase (IN) with high potency and selectivity in antiviral assays and does not require metabolic modification to exert ARV activity (PC-141-2032, PC-141-2034, and PC-141-2036). Using lymphoblastoid T-cell lines and primary human T-lymphocytes in HIV-1 antiviral assays, the estimated concentration of drug for half-maximal effective concentration (EC_{50}) of BIC ranged from 1.5 to 2.4 nM and the

selectivity indices ranged from 1500 to 8800 (PC-141-2032 and PC-141-2034). When tested in primary human PBMCs against clinical isolates of all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G, BIC displayed similar antiviral activity across all clinical isolates with mean and median EC_{50} values of 0.60 and 0.55 nM, respectively, based on a range of EC_{50} values between < 0.05 and 1.71 nM (PC-141-2035 and PC-141-2057). HIV-2 was similarly susceptible to BIC with an EC_{50} value of 1.1 nM (PC-141-2035). BIC is a specific inhibitor of HIV with no measurable antiviral activity against non-HIV viruses, including HBV, HCV, influenzas A and B, human rhinovirus, and respiratory syncytial virus (RSV) (PC-141-2043).

BIC maintains potent antiviral activity against HIV-1 variants resistant to currently approved ARVs from the NRTI, NNRTI, and PI classes (PC-141-2039). BIC displays a resistance profile similar to that of DTG and markedly improved compared with that of raltegravir (RAL) and elvitegravir (EVG). BIC retains full susceptibility against clonal isolates from virologic failures treated with E/C/F/TDF (PC-141-2040 and PC-141-2050). BIC has an improved resistance profile compared to EVG, RAL, and DTG in patient isolates, particularly for isolates with high-level INSTI resistance containing combinations of mutations such as E92Q + N155H or G140C/S + Q148R/H/K ± additional INSTI mutations, and may have unmet clinical utility in these patients (PC-141-2051). BIC has a longer dissociation half-life from HIV-1 integrase-DNA complexes compared with DTG, RAL, and EVG (PC-141-2058).

HIV-1 isolates with reduced susceptibility to BIC have been selected in cell culture (PC-141-2041, PC-141-2052, and PC-141-2056). These selections showed that BIC displayed a comparable barrier to resistance emergence as DTG, and a higher barrier than EVG. BIC selected the M50I + R163K combination and S153F with a transient T66I substitution in HIV-1 integrase. The R263K single mutant and M50I + R263K double mutant viruses had low-level reduced susceptibility to BIC, but the single M50I mutant was fully sensitive to BIC. The M50I + R263K selected variants exhibited low-level cross-resistance to RAL and DTG and intermediate cross-resistance to EVG but remained susceptible to other classes of ARVs. The effect of the T66I and S153F/Y single mutants and the T66I + S153F double mutant in IN on BIC susceptibility was minimal.

Similar to a number of other ARV agents, the in vitro activity of BIC was reduced in the presence of human serum due to significant protein binding. BIC exhibited approximately 70-fold increase in the EC_{50} value in the presence of 100% serum relative to its activity in cell culture medium. The 95% effective concentration (EC_{95}) calculated from the high density antiviral dose response was used in conjunction with the human serum shift determined by equilibrium dialysis to calculate the $PAEC_{95}$ of 361 nM (PC-141-2033).

4.1.1.2. FTC

FTC, an NRTI, is a synthetic analogue of the naturally occurring pyrimidine nucleoside, 2′-deoxycytidine. Intracellularly, FTC is converted through 3 phosphorylation reactions to its active tri-phosphorylated anabolite FTC-TP {Furman 1992, Paff 1994}. FTC-TP inhibits the activity of viral polymerases, including HIV-1 RT by direct binding competition with the natural deoxyribonucleotide substrate (deoxycytidine triphosphate) and by being incorporated into

nascent viral DNA, which results in chain termination {Wilson 1993}. FTC has activity that is specific to HIV (HIV-1 and HIV-2) and HBV. The EC_{50} of FTC against laboratory adapted strains of HIV-1 ranged from 0.001 to 0.62 μM depending on cell type and virus strain used in the assay {Jeong 1993, Painter 1995, Schinazi 1992}. With clinical isolates of HIV-1, EC_{50} values ranged from 0.002 to 0.028 μM {Schinazi 1992}. FTC-TP is a weak inhibitor of mammalian DNA polymerases α, β, and ε and mtDNA polymerase γ {Painter 1995}. There was no evidence of toxicity to mitochondria in vitro and in vivo.

The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-chemokine (C-C motif) receptor 5 (CCR5) cell line, and PBMCs. The EC_{50} values for FTC were in the range of 0.001 to 0.62 μM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.007 to 0.140 μM) and showed activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 μM).

HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 RT.

4.1.1.3. TAF

TAF is a phosphonamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). Cells are permeable to TAF, and due to increased plasma stability and intracellular activation through hydrolysis by CatA, TAF is more efficient than TDF in loading TFV into PBMCs, including T cells and macrophages {Birkus 2008, Birkus 2007}. Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV-DP {Robbins 1998}. TFV-DP inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination {Cherrington 1995b, Yokota 1994}. Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and HBV {Delaney 2006, Kalayjian 2003, Lee 2005}. In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells (PC-164-2001). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mtDNA polymerase γ {Cherrington 1994, Kramata 1998}, and there is no evidence of mitochondrial toxicity in vitro based on several assays including mtDNA analyses {Birkus 2002, Stray 2017}.

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4-T lymphocytes. The EC_{50} values for TAF were in the range of 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM) (PC-120-2004). The antiviral activity of two TAF metabolites, M18 (GS-645552) and M28 (GS-652829), were evaluated in two T-lymphoblastoid cell lines (MT-2 and MT-4) following 5 days of compound exposure (PC-120-2021). GS-645552 is also a drug product degradant. Both metabolites/degradants showed weak inhibition of HIV-1 replication with 1723 to 2630-fold lower inhibitory potency relative to TAF (EC_{50} values of 7.41 to 21.04 μM) for metabolite M28 and 121 to 130-fold lower inhibitor potency relative to TAF (EC_{50} values of 0.56 to 0.97 μM) for metabolite M18.

HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed {Margot 2006b}. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to ABC, FTC, TFV, and 3TC {Kagan 2007, Margot 2006b} (PC-120-2011). In vitro drug resistance selection studies with TAF have shown no development of high-level resistance after extended time in culture.

TFV has activity that is specific to HBV in addition to HIV-1 and HIV-2. The antiviral activity of TAF against a panel of HBV clinical isolates representing genotypes A-H was assessed in HepG2 cells. The EC_{50} values for TAF ranged from 34.7 to 134.4 nM, with an overall mean EC_{50} of 86.6 nM (PC-320-2003) {Liu 2017}. The concentration that resulted in 50% cytotoxicity (CC_{50}) in HepG2 cells was > 44,400 nM (PC-320-2003 and PC-120-2007). The combination of TFV and FTC was studied for cytotoxicity in MT-2 cells. No cytotoxicity was observed at the highest concentrations tested, up to 50 μM TFV and 5 μM FTC (PC-164-2002). Cytotoxicity studies were also conducted on the combination of TFV and FTC in HepG2 cells and no cytotoxicity was observed (TX-104-2001).

The antiviral activity of TAF was evaluated against a panel of HBV isolates containing nucleos(t)ide RT inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to LAM remained susceptible to TAF (< 2-fold change in EC_{50}) (PC-320-2007) {Liu 2017}. HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir (ETV) remained susceptible to TAF. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to TAF; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to TAF (3.7-fold change in EC_{50}). The clinical relevance of these substitutions is not known.

4.1.1.4. B/F/TAF

Bictegravir, FTC, and TAF are potent and selective inhibitors of HIV-1. All 3 drugs show potent antiretroviral activity against diverse subtypes of HIV-1 in vitro. FTC and TFV are phosphorylated intracellularly through nonoverlapping pathways, and in combination show no antagonism for the formation of their active metabolites (PC-164-2001). BIC does not require metabolic modification for activity. The anti-HIV-1 activity of 3-drug combination of BIC, FTC, and TAF were found to be highly synergistic with no evidence of antagonism in vitro, supporting the use of these agents in combination in HIV-1 infected patients (PC-141-2038). In addition, in vitro combination studies have shown that in 2-drug combination studies BIC, FTC, and TFV have additive to synergistic anti-HIV-1 activity with other approved NRTIs, NNRTIs, and PIs {Hill 1997, Miller 1999, Rimsky 2001} (PC-141-2038). The resistance profiles of the individual agents BIC, TFV, and FTC are distinct and non-overlapping (PC-141-2039).

4.1.2. Secondary Pharmacodynamics

4.1.2.1. Cytotoxicity

For BIC, the CC_{50} in primary CD4+ T-lymphocytes, MT-4, MT-2, resting and activated PBMCs, and monocyte-derived macrophages cells ranged from of 3700 to 29800 nM (PC-141-2032 and PC-141-2034).

The cytotoxicity of FTC has been evaluated extensively in vitro. In all the cell lines examined, cell growth was not affected at concentrations of FTC ≥ 100 µM {Furman 1992, Schinazi 1994, Van Draanen 1994}.

Both TAF and its metabolites M18 and M28 had no cytotoxicity up to the highest tested concentration (57 µM) (PC-120-2021).

4.1.2.2. Off-Target Activity

BIC had no pharmacologically significant binding affinity to a diverse panel of 68 protein targets, including neuroreceptors, ion channels, and nuclear receptors (PC-141-2029). Inhibition of transporters, including OCT2 and MATE1 are discussed in m2.6.4, Section 7.1.

FTC had no pharmacologically significant binding affinity to 19 different receptors (TPZZ/93/0002), showed little or no direct effect on various isolated muscle preparations (cholinergic, adrenergic, histaminergic, and serotonergic), and had no major inhibitory effects on the contractile responses to acetylcholine, norepinephrine, serotonin, isoproterenol, arachidonic acid, histamine, bradykinin, and angiotensin II (TPZZ/92/0055).

TFV showed no significant inhibition of, or increased binding to a series of 111 protein targets (neuroreceptors, ion channels, transporters, and nuclear receptors) (V2000020).

4.1.3. Pharmacodynamic Drug Interactions

The anti-HIV-1 activity of 2- and 3-drug combinations of BIC, FTC, and TAF were found to be additive to highly synergistic with no evidence of antagonism in multiple in vitro assay systems, supporting the use of these agents in combination in HIV-infected patients (PC-380-2001).

In vitro 2-drug combination studies have shown that BIC has additive to synergistic anti-HIV-1 activity with other approved NRTIs, NNRTIs, and PIs, including synergistic activity with TAF, FTC, and DRV. No antagonistic antiviral interaction was found between BIC and the tested clinically relevant classes of ARVs (PC-141-2038).

In 2-drug combination studies of FTC with NRTIs, NNRTIs, PIs, and INSTIs, additive to synergistic effects were observed. No antagonism was observed for these combinations {Hill 1997, Rimsky 2001}.

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations (PC-104-2005, PC-104-2006, PC-264-2001, and PC-120-2002).

In cell culture combination antiviral activity studies of TFV with the HBV NRTIs FTC, ETV, LAM, and telbivudine, no antagonistic activity was observed (PC-120-2001 and PC-120-2032). The anti-HCV PIs telaprevir and boceprevir were identified as the only potent inhibitors of CatA-mediated hydrolysis of TAF in a biochemical assay. The tested HIV PIs, host serine PIs, and the majority of other HCV PIs exhibit minimal potential to interfere with the intracellular activation of TAF (PC-120-2001). These data support the co-administration of the tested therapeutic PIs, with the exception of telaprevir and boceprevir, in combination with TAF, without negatively affecting its clinical pharmacology and intracellular conversion to TFV.

4.2. Clinical Virology

4.2.1. HIV

Analyses were performed for HIV-infected subjects with clinical virology data from 4 B/F/TAF Phase 3 studies (GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878). An integrated virology analysis was performed for HIV-infected subjects with clinical virology data from Studies GS-US-380-1489 and GS-US-380-1490. A summary of the main findings from these analyses are provided in Sections 4.2.1.1 and 4.2.1.2, respectively.

An analysis was performed for HIV-infected subjects with clinical virology data from the BIC Phase 2 Study GS-US-141-1475, and a summary of the main findings from this analysis is provided in the m2.7.3, Section 2.1.3.

For the purposes of screening and fulfillment of the study entry criteria, HIV-1 genotypic data confirming sensitivity to the NRTI study drugs were obtained at screening for all studies of treatment-naive subjects (Studies GS-US-380-1489 and GS-US-380-1490) using the GenoSure® MG assay for protease (PR) and RT or using historical genotypic data, if available, for subjects with suppressed HIV-1 (Studies GS-US-380-1844 and GS-US-380-1878). The GenoSure MG assay covered the entire PR gene (amino acids 1-99) and a portion of RT (amino acids 1-400). The genotype produced by the GenoSure assays encompassed all clinically-relevant PI, NRTI, and NNRTI resistance mutations. Historical genotypes consisted of reports generated by commercial or local assays and are reported in virology listings.

A retrospective analysis of the IN gene was conducted on Day 1/baseline samples from all randomized and treated subjects from studies of treatment-naive subjects (Studies GS-US-380-1489 and GS-US-380-1490) using the deep Type HIV assay (Seq-IT). INSTI-R resistance-associated mutations (RAMs) are reported using a 15% cutoff. These data were not collected prior to drug treatment and were not used as study entry criteria.

Table 37 summarizes all of the previously identified drug resistance mutations by ARV drug class.

Table 37. Resistance Substitutions by Antiretroviral Class for the B/F/TAF Program

Resistance Associated Mutations[a]	
Mutation Groups	**Codon Mutations**
Primary Integrase Strand Transfer Inhibitor (INSTI) Resistance (-R) substitutions	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R substitutions	M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A
Primary Nucleoside and Nucleotide Reverse Transcriptase Inhibitor (N(t)RTI)-R substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
Thymidine Analogue Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F, K219Q/N/E/R
Tenofovir (TFV) resistance associated substitutions	K65R/E/N, K70E
Emtricitabine (FTC) and lamivudine (3TC) resistance associated substitutions	M184V/I
Abacavir (ABC) resistance associated substitutions	K65R/E/N, K70E, L74V, Y115F, M184V/I
Secondary NRTI-R substitutions	E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, T215A/C/D/E/G/H/I/L/N/S/V[b]
Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-R substitutions	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106I, V179D/F/T
Primary Protease Inhibitor (PI)-R substitutions	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
ATV or DRV resistance associated substitutions	I47V, I50L/V, I54M/L, L76V, I84V, N88S

a Adapted from the current IAS-USA list with some modifications {Wensing 2017}.
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.

The Resistance Analysis Population (RAP) includes all subjects with virologic failure and HIV-1 RNA ≥ 200 copies/mL. Virologic failure was defined as virologic rebound or having HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation, or key study endpoints, as follows:

- Virologic rebound
  - — At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; OR
  - — At any visit, a > 1 $\log_{10}$ increase in HIV-1 RNA from the nadir which is subsequently confirmed at the following scheduled or unscheduled visit
- HIV-1 RNA ≥ 50 copies/mL at Study Drug Discontinuation or Week 48
  - — HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation, last visit (lost to follow-up), or last Week 48 result (does not require confirmation of virologic failure)

Following the unconfirmed virologic rebound, subjects were asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA ≥ 50 copies/mL) for confirmation of virologic rebound. The confirmation viral load must have been collected at a different visit than the original rebound. If the HIV-1 RNA rebound had HIV-1 RNA of ≥ 50 copies/mL and < 200 copies/mL, another aliquot of plasma from that visit may have had the HIV-1 RNA test repeated. The results of the second test were considered the final result for that study visit. If the repeat test showed HIV-1 RNA < 50 copies/mL then the patient was not required to return for a retest visit. If the HIV-1 RNA was ≥ 50 copies/mL then the patient was asked to return as described above.

Resistance analyses consisted of genotypic and phenotypic analyses of the HIV-1 RT, PR, and IN genes. Subjects who had virologic failure and met the following additional criteria were included in the RAP. If virologic rebound was confirmed at the scheduled or unscheduled visit and the HIV-1 RNA was ≥ 200 copies/mL, the plasma sample from the confirmation visit was the primary sample used for HIV-1 genotypic and phenotypic testing. Subjects with virologic failure at study drug discontinuation or last visit (at or after Week 8), or last Week 48 result were included in the RAP if the HIV-1 RNA was ≥ 200 copies/mL. Subjects with documented non-adherence within 72 hours of the visit may not have been tested for resistance. After a subject's first post-Day 1 resistance test, additional testing was conducted on a case-by-case basis. If a subject with detectable viremia at study endpoints remained on study medication and later suppressed HIV-1 RNA to < 50 copies/mL, this subject may still have resistance data available which will be tabulated. However, these subjects were excluded from the final RAP unless they had primary resistance mutations to study drugs. Any subject may have been discontinued from the study at the Investigator's discretion or per local treatment guidelines.

A summary of the results from these analyses are provided in Section 4.2.1.1 and 4.2.1.2.

A full description of the resistance analysis methodologies is provided in the virology analysis plan (PC-141-2053, Amendment 1). Full details of the RAP, Final RAP, and the clinical virology resistance analyses from the B/F/TAF Phase 3 studies and the integrated analysis can be found in the virology study reports (PC-380-2003 [Studies GS-US-380-1489 and GS-US-380-1490], PC-380-2004 [Study GS-US-380-1844], and PC-380-2005 [Study GS-US-380-1878]). A summary of the main findings is described in Sections 4.2.1.1 and 4.2.1.2.

4.2.1.1. Virology Resistance Analyses at Baseline and in the Resistance Analysis Population from Phase 3 Studies

4.2.1.1.1. GS-US-380-1489

4.2.1.1.1.1. Study Design, Baseline Characteristics, and Viral Response

Study GS-US-380-1489 is an ongoing Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF versus ABC/DTG/3TC in HIV-1 infected, antiretroviral treatment-naive adults.

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

- **Treatment Group 1:** FDC of B/F/TAF (50/200/25 mg) + placebo-to-match FDC of ABC/DTG/3TC administered orally, once daily, without regard to food (n = 314)

- **Treatment Group 2:** FDC of ABC/DTG/3TC (600/50/300 mg) + placebo-to-match FDC of B/F/TAF administered orally, once daily, without regard to food (n = 315)

Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL) at screening, CD4+ cell count (< 50 cells/µL, 50-199 cells/µL, or ≥ 200 cells/µL) at screening, and region (US vs ex-US) at randomization.

Results from the Week 48 efficacy analysis using the FDA-defined snapshot algorithm demonstrated high and comparable rates of virologic success (HIV-1 RNA < 50 copies/mL) for HIV-1 infected adults treated with B/F/TAF (92.4%) or ABC/DTG/3TC (93.0%).

4.2.1.1.1.2. 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 629 subjects in the FAS from Study GS-US-380-1489 (Table 38). Consistent with enrollment criteria, all subjects demonstrated full sensitivity to FTC and TAF based on the proprietary algorithm from [redacted] (GS-US-380-1489, Virology Listing 2). Additional baseline genotypic data was obtained for those subjects who qualified for inclusion in the RAP and those data are also included in the summary of pretreatment mutations.

No IN genotyping was conducted at screening in the study, but baseline IN genotypic data was obtained retrospectively for 628 of 629 subjects. The IN genotyping assay failed at baseline for 1 subject who had low viral load.

Pretreatment primary INSTI resistance mutations were infrequent and were present in 1.1% of subjects (7 subjects) and consisted of T97A in 6 subjects and Q148H in 1 subject.

Pretreatment primary NRTI-associated resistance mutations were observed in 1.7% of subjects (11 subjects) and consisted of Y115F (n = 1) or thymidine analog-associated mutations (TAMs) (M41L [n = 4], D67N [n = 2], K70R [n = 1], or K219Q/R [n = 3]).

Pretreatment primary NNRTI-associated resistance mutations were observed in 13.8% of subjects (87 subjects) with the most frequent substitutions consisting of K103N/S (n = 50), E138A/G/K/Q (n = 23), or Y181C (n = 5).

Pretreatment primary PI-associated resistance mutations were observed in 3.7% of subjects (23 subjects) with the most frequent substitutions consisting of M46I/L (n = 7), Q58E (n = 8), or L90M (n = 5).

Overall, the prevalence of baseline RAMs was similar between treatment groups (Table 38).

Table 38. GS-US-380-1489: Summary of IN, RT, and PR Mutations Detected Pretreatment

Mutation Class[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 314)	ABC/DTG/3TC (N = 315)	All (N = 629)
Primary INSTI-R[b]	3 (1.0)	4 (1.3)	7 (1.1)
Average Number of Primary INSTI-R Mutations	1.0	1.0	1.0
T97A	2 (0.6)	4 (1.3)	6 (1.0)
Q148H	1 (0.3)	0	1 (0.2)
Secondary INSTI-R[b]	149 (47.5)	152 (48.4)	301 (47.9)
Average Number of Secondary INSTI-R Mutations	1.1	1.2	1.2
M50I	44 (14.0)	47 (15.0)	91 (14.5)
H51Y	0	1 (0.3)	1 (0.2)
L68V	0	2 (0.6)	2 (0.3)
V72T	2 (0.6)	1 (0.3)	3 (0.5)
L74M	1 (0.3)	5 (1.6)	6 (1.0)
Q95K	1 (0.3)	0	1 (0.2)
S119P/R/T	96 (30.6)	103 (32.8)	199 (31.7)
A128T	1 (0.3)	0	1 (0.2)
E138A/K	0	2 (0.6)	2 (0.3)
G140S	1 (0.3)	0	1 (0.2)
Q146R	1 (0.3)	0	1 (0.2)
S153A	2 (0.6)	1 (0.3)	3 (0.5)
E157K/Q	16 (5.1)	12 (3.8)	28 (4.5)
G163K/R	2 (0.6)	5 (1.6)	7 (1.1)
Primary NRTI-R	6 (1.9)	5 (1.6)	11 (1.7)
Average Number of Primary NRTI-R Mutations	1.0	1.0	1.0
Any TAM	6 (1.9)	4 (1.3)	10 (1.6)
M41L	2 (0.6)	2 (0.6)	4 (0.6)
K65R/E/N	0	0	0
D67N	1 (0.3)	1 (0.3)	2 (0.3)
K70R	1 (0.3)	0	1 (0.2)
Y115F	0	1 (0.3)	1 (0.2)
K219Q/R	2 (0.6)	1 (0.3)	3 (0.5)

Mutation Class[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 314)	ABC/DTG/3TC (N = 315)	All (N = 629)
Primary NNRTI-R	36 (11.5)	51 (16.2)	87 (13.8)
Average Number of Primary NNRTI-R Mutations	1.2	1.1	1.1
L100I	2 (0.6)	0	2 (0.3)
K101E	1 (0.3)	2 (0.6)	3 (0.5)
K103N/S	23 (7.3)	27 (8.6)	50 (7.9)
V106A	0	1 (0.3)	1 (0.2)
V108I	0	3 (1.0)	3 (0.5)
E138A/G/K/Q	7 (2.2)	16 (5.1)	23 (3.7)
Y181C	3 (1.0)	2 (0.6)	5 (0.8)
Y188L	1 (0.3)	2 (0.6)	3 (0.5)
G190A/S	3 (1.0)	1 (0.3)	4 (0.6)
H221Y	1 (0.3)	1 (0.3)	2 (0.3)
P225H	1 (0.3)	1 (0.3)	2 (0.3)
Primary PI-R	12 (3.8)	11 (3.5)	23 (3.7)
Average Number of Primary PI-R Mutations	1.3	1.0	1.1
D30N	1 (0.3)	1 (0.3)	2 (0.3)
V32I	1 (0.3)	0	1 (0.2)
M46I/L	4 (1.3)	3 (1.0)	7 (1.1)
I50L	1 (0.3)	0	1 (0.2)
Q58E	3 (1.0)	5 (1.6)	8 (1.3)
V82A	2 (0.6)	0	2 (0.3)
L90M	3 (1.0)	2 (0.6)	5 (0.8)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; TAM = thymidine analogue mutation

a Drug resistance mutations are defined in PC-380-2003, Table 2

b Denominator for the IN gene analyses are 314 B/F/TAF; 314 ABC/DTG/3TC; 628 All.

Source: GS-US-380-1489, Virology Listing 1 and Virology Listing 2

The HIV-1 subtype was determined for each subject using the screening RT/PR genotype. The prevalence of different subtypes was comparable between treatment groups, with subtype B predominant in both groups (90.1% overall, 567 of 629 subjects) (Table 39).

Table 39. GS-US-380-1489: Summary of HIV-1 Subtypes

HIV-1 Subtype	Number of Subjects, n (%)		
	B/F/TAF (N = 314)	ABC/DTG/3TC (N = 315)	All (N = 629)
Subtype B	281 (89.5)	286 (90.8)	567 (90.1)
Non-B Subtype	33 (10.5)	29 (9.2)	62 (9.9)
Subtype A	0	1 (0.3)	1 (0.2)
Subtype A1	7 (2.2)	8 (2.5)	15 (2.4)
Subtype AE	3 (1.0)	1 (0.3)	4 (0.6)
Subtype AG	5 (1.6)	4 (1.3)	9 (1.4)
Subtype BC	1 (0.3)	1 (0.3)	2 (0.3)
Subtype BF	2 (0.6)	2 (0.6)	4 (0.6)
Subtype C	4 (1.3)	1 (0.3)	5 (0.8)
Subtype D	0	1 (0.3)	1 (0.2)
Subtype F1	1 (0.3)	4 (1.3)	5 (0.8)
Subtype F2	0	1 (0.3)	1 (0.2)
Subtype G	1 (0.3)	0	1 (0.2)
Complex Subtype	9 (2.9)	5 (1.6)	14 (2.2)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide;
Source: GS-US-380-1489, Virology Listing 2

4.2.1.1.1.3. Impact of Pretreatment Mutations and Subtype on Treatment Outcomes

The impact of pretreatment RAMs as well as subtype on treatment outcomes was assessed for all subjects in the FAS. For the subtype analysis, subtype B versus non-B subtype was evaluated. For the baseline RAM analysis, the presence or absence of primary INSTI-R, T97A, Q148H, secondary INSTI-R, primary NRTI-R, TAMs, K103N/S, primary NNRTI-R, and primary PI-R were evaluated.

No impact of pretreatment RAM or subtype was observed on reaching HIV-1 RNA < 50 copies/mL at Week 48 or virologic failure (HIV-1 RNA ≥ 50 copies/mL) for both treatment groups ($p > 0.05$ for all comparisons) (Table 40). Notably, the 1 subject in the B/F/TAF group with Q148H + G140S in IN at baseline achieved HIV-1 RNA < 50 copies/mL at Week 4 and maintained HIV-1 RNA < 50 copies/mL through Week 48.

Table 40. Study GS-US-380-1489: FDA Snapshot Outcome of Subjects at Week 48 by Baseline Virologic Category

	Number of Subjects n (%)					
	B/F/TAF (N = 314)			ABC/DTG/3TC (N = 315)		
Category	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data
All Subjects	290/314 (92.4)	3/314 (1.0)	21/314 (6.7)	293/315 (93.0)	8/315 (2.5)	14/315 (4.4)
HIV-1 Subtype B	262/281 (93.2)	2/281 (0.7)	17/281 (6.0)	266/286 (93.0)	8/286 (2.8)	12/286 (4.2)
HIV-1 Subtype Non-B	28/33 (84.8)	1/33 (3.0)	4/33 (12.1)	27/29 (93.1)	0/29 (0)	2/29 (6.9)
P-Value	0.15	0.28	0.26	1.0	1.0	0.38
Primary INSTI-R	3/3 (100.0)	0/3 (0.0)	0/3 (0.0)	3/4 (75.0)	0/4 (0.0)	1/4 (25.0)
No Primary INSTI-R	287/311 (92.3)	3/311 (1.0)	21/311 (6.8)	289/310 (93.2)	8/310 (2.6)	13/310 (4.2)
P-Value	1.0	1.0	1.0	0.25	1.0	0.17
T97A in IN	2/2 (100.0)	0/2 (0.0)	0/2 (0.0)	3/4 (75.0)	0/4 (0.0)	1/4 (25.0)
No T97A in IN	288/312 (92.3)	3/312 (1.0)	21/312 (6.7)	289/310 (93.2)	8/310 (2.6)	13/310 (4.2)
P-Value	1.0	1.0	1.0	0.25	1.0	0.17
Q148H in IN	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	0	0	0
No Q148H in IN	289/313 (92.3)	3/313 (1.0)	21/313 (6.7)	292/314 (93.0)	8/314 (2.5)	14/314 (4.5)
P-Value	1.0	1.0	1.0	NA	NA	NA
Secondary INSTI-R	138/149 (92.6)	0/149 (0.0)	11/149 (7.4)	140/152 (92.1)	5/152 (3.3)	7/152 (4.6)
No Secondary INSTI-R	152/165 (92.1)	3/165 (1.8)	10/165 (6.1)	152/162 (93.8)	3/162 (1.9)	7/162 (4.3)
P-Value	1.0	0.25	0.66	0.66	0.49	1.0
Primary NRTI-R	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	5/5 (100.0)	0/5 (0.0)	0/5 (0.0)
No Primary NRTI-R	284/308 (92.2)	3/308 (1.0)	21/308 (6.8)	288/310 (92.9)	8/310 (2.6)	14/310 (4.5)
P-Value	1.0	1.0	1.0	1.0	1.0	1.0
TAMs in RT	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	4/4 (100.0)	0/4 (0.0)	0/4 (0.0)
No TAMs in RT	284/308 (92.2)	3/308 (1.0)	21/308 (6.8)	289/311 (92.9)	8/311 (2.6)	14/311 (4.5)
P-Value	1.0	1.0	1.0	1.0	1.0	1.0
Primary NNRTI-R	34/36 (94.4)	0/36 (0.0)	2/36 (5.6)	48/51 (94.1)	0/51 (0.0)	3/51 (5.9)
No Primary NNRTI-R	256/278 (92.1)	3/278 (1.1)	19/278 (6.8)	245/264 (92.8)	8/264 (3.0)	11/264 (4.2)
P-Value	1.0	1.0	1.0	1.0	0.36	0.48
K103N/S in RT	23/23 (100.0)	0/23 (0.0)	0/23 (0.0)	25/27 (92.6)	0/27 (0.0)	2/27 (7.4)
No K103N/S in RT	267/291 (91.8)	3/291 (1.0)	21/291 (7.2)	268/288 (93.1)	8/288 (2.8)	12/288 (4.2)
P-Value	0.24	1.0	0.38	1.0	1.0	0.34
Primary PI-R	11/12 (91.7)	0/12 (0.0)	1/12 (8.3)	10/11 (90.9)	0/11 (0.0)	1/11 (9.1)
No Primary PI-R	279/302 (92.4)	3/302 (1.0)	20/302 (6.6)	283/304 (93.1)	8/304 (2.6)	13/304 (4.3)
P-Value	1.0	1.0	0.57	0.56	1.0	0.4

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; IN = integrase; INSTI = integrase strand transfer inhibitor; NA = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistance; RT = reverse transcriptase
P-value determined using Fisher's exact test.
Source: GS-US-380-1489, Virology Listing 1 and Virology Listing 2

4.2.1.1.1.4. Virology Analyses in Subjects Experiencing Virologic Failure through Week 48

Of the 629 randomized and treated subjects in Study GS-US-380-1489, 5 (0.8%) met the virologic failure (VF) and RAP inclusion criteria through Week 48. Reasons for inclusion in the RAP were confirmed VF (4 subjects) or > 200 copies at the last measurement in the Week 48 window (1 subject). All subjects in the RAP had adherence < 95% or had unreturned pill bottles.

The RAP comprised 1 subject (0.3%, 1 of 314) in the B/F/TAF group and 4 subjects (1.3%, 4 of 315) in the ABC/DTG/3TC group (Figure 18, Table 41). The final RAP (which did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs) comprised 1 subject (0.3%, 1 of 314) in the B/F/TAF group and 2 subjects (0.6%, 2 of 315) in the ABC/DTG/3TC group.

One subject in the B/F/TAF group was included in the RAP and was evaluated for the development of resistance through Week 48. Postbaseline genotypic and phenotypic data were available for PR/RT and IN from this subject. No resistance mutations emerged for the subject and no phenotypic resistance was detected to the components of B/F/TAF (Table 42).

Four subjects in the ABC/DTG/3TC group were included in the RAP and were evaluated for the development of resistance through Week 48. Postbaseline genotypic and phenotypic data were available for PR/RT for 3 subjects and IN for 2 subjects. None of the subjects with data in the ABC/DTG/3TC RAP had resistance mutations emerge (Table 42). There was also no phenotypic resistance detected to the components of ABC/DTG/3TC.

Table 41. GS-US-380-1489: Summary of HIV-1 Genotypic Resistance through Week 48

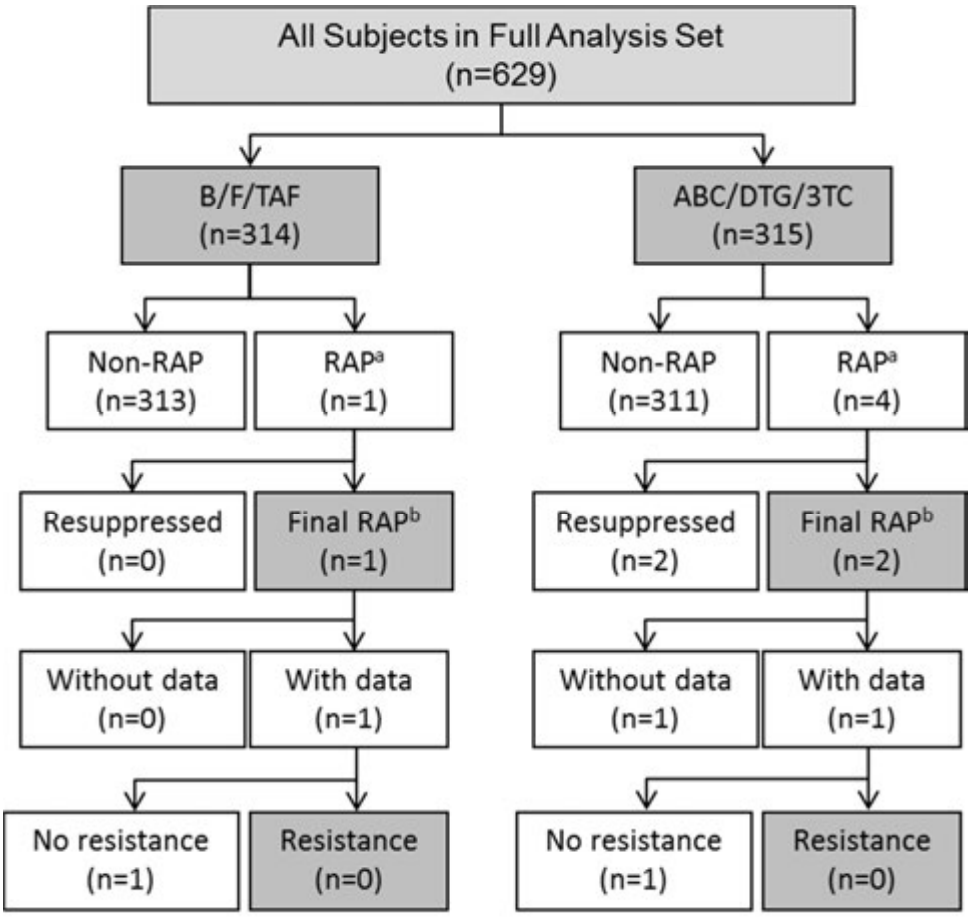
Resistance Category[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 314)	ABC/DTG/3TC (N = 315)	P-Value[b]
RAP (% of FAS)	1 (0.3)	4 (1.3)	0.37
Subjects with Data (Any Gene)	1 (100)	3 (75)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	0 (0.0)	2 (50)	
Final RAP[c] (% of FAS)	1 (0.3)	2 (0.6)	1.00
Subjects with Data (Any Gene)	1 (100)	1 (50)	
Developed Resistance Mutations to Study Drugs (% of FAS)	0 (0.0)	0 (0.0)	na
Developed Resistance Mutations to Study Drugs (% of Final RAP)	0 (0.0)	0 (0.0)	na
Developed Any INSTI-R	0	0	
Developed Primary NRTI-R	0	0	
Developed Primary NNRTI-R	0	0	
Developed Primary PI-R	0	0	

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; FAS = full analysis set; INSTI = integrase strand transfer inhibitor; INSTI = integrase strand transfer inhibitor; na = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; RAP = resistance analysis population

a Drug resistance mutations are defined in PC-380-2003, Table 2.
b P-value determined using Fisher's exact test.
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

Source: GS-US-380-1489, Virology Listing 3 and Virology Listing 4

Figure 18. GS-US-380-1489: RAP and Genotypic Disposition through Week 48



ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; RAP = resistance analysis population

a RAP criteria are summarized in PC-380-2003, Section 2.2.

b The final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

Source: GS-US-380-1489, Virology Listing 3 and Virology Listing 4

Table 42. GS-US-380-1489: Details of Subjects in the Week 48 RAP

Final RAP	Subject ID	Treatment Group	Time Point	HIV-1 RNA[a] (copies/mL)	CD4 (cells/µL)	Sub-type	Resistance-associated Mutations[b]		Drug Susceptibility (Fold Change from WT)[c]					
							IN	RT	BIC	DTG	ABC	3TC	FTC	TFV[c]
Yes	00729-1609[d]	B/F/TAF	BL	6,370	502	B	none	none	0.80	0.95	0.80	1.23	0.97	0.68
			W36	2,120	452	B	none	none	0.68	0.98	0.79	1.21	1.17	0.68
			W48	4,450	387	B	none	none	0.87	0.97	0.84	1.29	1.21	0.77
No	02825-1085[d]	ABC/DTG/3TC	BL	38,100	717	B	S119T	none	0.77	0.91	0.66	0.96	0.79	0.78
			W24	30,000	519	B	S119T	none	0.68	0.69	0.63	0.84	0.93	0.79
			W48	23,300	564	B	S119T	none	0.61	0.88	0.69	0.88	0.85	0.86
Yes	01598-1106[d]	ABC/DTG/3TC	BL	55,600	307	B	S119P	none	0.59	0.51	0.95	1.41	1.26	1.00
			W24	80,100	361	B	S119P	none	0.46	0.49	1.06	1.66	1.57	1.05
Yes	11572-1263[d]	ABC/DTG/3TC	BL	15,700	712	B	M50I	none	0.61	0.76	af	af	af	af
			W48	3,000	604	B	af	af	af	af	af	af	af	af
No	02838-1390[d]	ABC/DTG/3TC	BL	75,000	387	B	none	none	0.78	0.81	0.89	0.79	0.83	0.81
			W36	204	404[e]	B	af	none	af	af	0.85	0.91	0.82	0.70

3TC = lamivudine; ABC = abacavir; ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; af = assay failure; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BL = baseline/Day 1; DTG = dolutegravir; FTC = emtricitabine; IN = integrase; nd = no data available; RAP = resistance analysis population; RT = reverse transcriptase; TFV = tenofovir; W = week;

a Baseline viral load is the Day 1 BL visit.

b Baseline sequences are the composite of screening and baseline data. Primary resistance-associated mutations are shown in bold text and secondary resistance-associated mutations are shown in plain text. Complete genotypic and phenotypic results are presented in GS-US-380-1489, Virology Listing 3 and Virology Listing 4.

c Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical or biological cutoffs were as follows: BIC = 2.5, DTG = 4.0, ABC = 4.5, 3TC = 3.5, FTC = 3.5, TFV = 1.4. The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF.

d Adherence was < 95% or had unreturned pill bottles.

e CD4 cell count was not assessed at study visit. CD4 cell count from prior visit in the same analysis window is reported.

Source: GS-US-380-1489, Virology Listing 3 and Virology Listing 4

4.2.1.1.1.5. Resistance Conclusions

The prevalence of baseline RAMs and HIV-1 subtypes were comparable across the B/F/TAF and ABC/DTG/3TC treatment groups. Baseline RAMs and HIV-1 subtype had no impact on treatment outcomes.

Of the 629 treated subjects from both treatment groups, the RAP was comprised of 5 subjects who experienced virologic failure during the first 48 weeks of the study: 1 of 314 subjects from the B/F/TAF group (0.3%) and 4 of 315 subjects from the ABC/DTG/3TC group (1.3%).

The final RAP included 3 subjects: 1 subject from the B/F/TAF group and 2 subjects from the ABC/DTG/3TC group. Two subjects from the ABC/DTG/3TC group resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs and were not included in the final RAP.

No subject in either group developed treatment emergent resistance to study drugs.

4.2.1.1.2. GS-US-380-1490

4.2.1.1.2.1. Study Design, Baseline Characteristics, and Viral Response

Study GS-US-380-1490 is an ongoing phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF versus DTG + F/TAF in HIV-1 infected, antiretroviral treatment-naive adults.

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

- **Treatment Group 1:** FDC of B/F/TAF (50/200/25 mg) + placebo-to-match DTG + F/TAF administered orally, once daily, without regard to food (n = 320)
- **Treatment Group 2:** DTG (50 mg) + F/TAF (200/25 mg) + placebo-to-match FDC of B/F/TAF administered orally, once daily, without regard to food (n = 325)

Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL) at screening, CD4+ cell count (< 50 cells/µL, 50-199 cells/µL, or ≥ 200 cells/µL) at screening, and region (US vs ex-US) at randomization.

Results from the Week 48 efficacy analysis using the FDA-defined snapshot algorithm demonstrated high and comparable rates of virologic success (HIV-1 RNA < 50 copies/mL) for HIV-1 infected adults treated with B/F/TAF (89.4%) or DTG + F/TAF (92.9%).

4.2.1.1.2.2. 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 645 subjects in the FAS from Study GS-US-380-1490 (Table 43). Consistent with enrollment criteria, all subjects demonstrated full sensitivity to FTC and TAF based on the proprietary algorithm from

[redacted] (GS-US-380-1490, Virology Listing 2). Additional baseline genotypic data was obtained for those subjects who qualified for inclusion in the RAP and those data are also included in the summary of pretreatment mutations.

No IN genotyping was conducted at screening in the study, but baseline IN genotypic data was obtained retrospectively for 639 of 645 subjects. The baseline IN genotyping 6 subjects was missing or failed primarily due to low viral loads.

Pretreatment primary INSTI resistance mutations were present in 1.4% of subjects and consisted of T97A in 9 subjects.

Pretreatment primary NRTI-associated resistance mutations were observed in 2.3% of subjects (15 subjects) and consisted of TAMs (M41L [n = 3], D67N [n = 2], K70R [n = 2], L210W [n = 1], or K219Q/E/N [n = 9]), and L74V in 1 subject.

Pretreatment primary NNRTI-associated resistance mutations were observed in 12.6% of subjects (81 subjects) with the most frequent substitutions consisting of K103N/S (n = 39) or E138A/G/K (n = 30).

Pretreatment primary PI-associated resistance mutations were observed in 2.2% of subjects (14 subjects) with the most frequent substitutions consisting of M46I/L (n = 7), Q58E (n = 3), or L90M (n = 4).

Overall, the prevalence of baseline RAMs was similar between treatment groups (Table 43).

Table 43. GS-US-380-1490: Summary of IN, RT, and PR Mutations Detected Pretreatment

Mutation Class[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 320)	DTG + F/TAF (N = 325)	All (N = 645)
Primary INSTI-R	3 (0.9)	6 (1.9)	9 (1.4)
Average Number of Primary INSTI-R Mutations	1.0	1.0	1.0
T97A	3 (0.9)	6 (1.9)	9 (1.4)
Secondary INSTI-R	176 (55.5)	158 (49.1)	334 (52.3)
Average Number of Secondary INSTI-R Mutations	1.2	1.2	1.2
M50I	80 (25.2)	60 (18.6)	140 (21.9)
H51Y	0	1 (0.3)	1 (0.2)
L68I/V	4 (1.3)	2 (0.6)	6 (0.9)
V72T	1 (0.3)	3 (0.9)	4 (0.6)
L74M	0	2 (0.6)	2 (0.3)
S119P/R/T	101 (31.9)	99 (30.7)	200 (31.3)
A128T	2 (0.6)	0	2 (0.3)
E138K	1 (0.3)	2 (0.6)	3 (0.5)
S153A	1 (0.3)	2 (0.6)	3 (0.5)
E157K/Q	19 (6.0)	12 (3.7)	31 (4.9)
G163K/R	4 (1.3)	6 (1.9)	10 (1.6)

Mutation Class[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 320)	DTG + F/TAF (N = 325)	All (N = 645)
Primary NRTI-R	10 (3.1)	5 (1.5)	15 (2.3)
Average Number of Primary NRTI-R Mutations	1.3	1.0	1.2
Any TAM	10 (3.1)	5 (1.5)	15 (2.3)
M41L	2 (0.6)	1 (0.3)	3 (0.5)
K65R/E/N	0	0	0
D67N	2 (0.6)	0	2 (0.3)
K70R	1 (0.3)	1 (0.3)	2 (0.3)
L74V	1 (0.3)	0	1 (0.2)
L210W	0	1 (0.3)	1 (0.2)
K219E/N/Q	7 (2.2)	2 (0.6)	9 (1.4)
Primary NNRTI-R	40 (12.5)	41 (12.6)	81 (12.6)
Average Number of Primary NNRTI-R Mutations	1.1	1.1	1.1
L100I	1 (0.3)	0	1 (0.2)
K101E/P	4 (1.3)	0	4 (0.6)
K103N/S	18 (5.6)	21 (6.5)	39 (6.0)
V106A	0	2 (0.6)	2 (0.3)
V108I	0	2 (0.6)	2 (0.3)
E138A/G/K	17 (5.3)	13 (4.0)	30 (4.7)
V179L	0	1 (0.3)	1 (0.2)
Y181C	0	1 (0.3)	1 (0.2)
Y188L	0	1 (0.3)	1 (0.2)
G190A/Q	2 (0.6)	3 (0.9)	5 (0.8)
P225H	2 (0.6)	1 (0.3)	3 (0.5)
M230I	1 (0.3)	0	1 (0.2)
Primary PI-R	4 (1.3)	10 (3.1)	14 (2.2)
Average Number of Primary PI-R Mutations	1.0	1.5	1.4
D30N	1 (0.3)	0	1 (0.2)
V32I	0	1 (0.3)	1 (0.2)
M46I/L	2 (0.6)	5 (1.5)	7 (1.1)
Q58E	0	3 (0.9)	3 (0.5)
L76V	0	1 (0.3)	1 (0.2)
V82L	1 (0.3)	0	1 (0.2)
I84V	0	1 (0.3)	1 (0.2)
L90M	0	4 (1.2)	4 (0.6)

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; TAM = thymidine analogue mutation

a Drug resistance mutations are defined in PC-380-2003, Table 2.

b Denominator for the IN gene analyses are 317 B/F/TAF; 322 DTG + F/TAF; 639 All.

Source: GS-US-380-1490, Virology Listing 1 and Virology Listing 2

The HIV-1 subtype was determined for each subject using the screening RT/PR genotype. The prevalence of different subtypes was comparable between treatment groups, with subtype B predominant in both groups (88.5% overall, 571 of 645 subjects) (Table 44).

Table 44. GS-US-380-1490: Summary of HIV-1 Subtypes

HIV-1 Subtype	Number of Subjects, n (%)		
	B/F/TAF (N = 320)	DTG + F/TAF (N = 325)	All (N = 645)
Subtype B	282 (88.1)	289 (88.9)	571 (88.5)
Non-B Subtype	38 (11.9)	36 (11.1)	74 (11.5)
Subtype A	0	1 (0.3)	1 (0.2)
Subtype A1	3 (0.9)	5 (1.5)	8 (1.2)
Subtype AE	4 (1.3)	6 (1.8)	10 (1.6)
Subtype AG	9 (2.8)	3 (0.9)	12 (1.9)
Subtype BF	2 (0.6)	3 (0.9)	5 (0.8)
Subtype C	4 (1.3)	7 (2.2)	11 (1.7)
Subtype D	1 (0.3)	2 (0.6)	3 (0.5)
Subtype F	0	1 (0.3)	1 (0.2)
Subtype F1	4 (1.3)	2 (0.6)	6 (0.9)
Subtype F2	1 (0.3)	0	1 (0.2)
Subtype G	0	1 (0.3)	1 (0.2)
Subtype H	1 (0.3)	0	1 (0.2)
Complex Subtype	9 (2.8)	5 (1.5)	14 (2.2)

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide
Source: GS-US-380-1490, Virology Listing 2

4.2.1.1.2.3. Impact of Pretreatment Mutations and Subtype on Treatment Outcomes

The impact of pretreatment RAMs as well as subtype on treatment outcomes was assessed for all subjects in the FAS. For the subtype analysis, subtype B versus non-B subtype was evaluated. For the baseline RAM analysis, the presence or absence of primary INSTI-R, T97A, secondary INSTI-R, primary NRTI-R, TAMs, K103N/S, primary NNRTI-R, and primary PI-R were evaluated.

No impact of pretreatment RAM or subtype was observed on reaching HIV-1 RNA < 50 copies/mL at Week 48 or virologic failure (HIV-1 RNA ≥ 50 copies/mL) for both treatment groups. For nearly all comparisons, there was no statistical difference found between baseline virologic categories and treatment outcome ($p > 0.05$) (Table 45). In the B/F/TAF group, the proportion of patients with no data at Week 48 was statistically higher in those with pretreatment NNRTI-R; however, this is not considered clinically relevant.

Table 45. Study GS-US-380-1490: FDA Snapshot Outcome of Subjects at Week 48 by Baseline Virologic Category

	Number of Subjects n (%)					
	B/F/TAF (N = 320)			DTG + F/TAF (N = 325)		
Category	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data
All Subjects	286/320 (89.4)	14/320 (4.4)	20/320 (6.2)	302/325 (92.9)	4/325 (1.2)	19/325 (5.8)
HIV-1 Subtype B	251/282 (89.0)	14/282 (5.0)	17/282 (6.0)	269/289 (93.1)	3/289 (1.0)	17/289 (5.9)
HIV-1 Subtype Non-B	35/38 (92.1)	0/38 (0)	3/38 (7.9)	33/36 (91.7)	1/36 (2.8)	2/36 (5.6)
P-Value	0.78	0.39	0.72	0.73	0.38	1.0
Primary INSTI-R	3/3 (100.0)	0/3 (0.0)	0/3 (0.0)	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)
No Primary INSTI-R	282/314 (89.8)	14/314 (4.5)	18/314 (5.7)	294/316 (93.0)	3/316 (0.9)	19/316 (6.0)
P-Value	1.0	1.0	1.0	1.0	1.0	1.0
T97A in IN	3/3 (100.0)	0/3 (0.0)	0/3 (0.0)	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)
No T97A in IN	282/314 (89.8)	14/314 (4.5)	18/314 (5.7)	294/316 (93.0)	3/316 (0.9)	19/316 (6.0)
P-Value	1.0	1.0	1.0	1.0	1.0	1.0
Secondary INSTI-R	160/176 (90.9)	7/176 (4.0)	9/176 (5.1)	149/158 (94.3)	1/158 (0.6)	8/158 (5.1)
No Secondary INSTI-R	125/141 (88.7)	7/141 (5.0)	9/141 (6.4)	151/164 (92.1)	2/164 (1.2)	11/164 (6.7)
P-Value	0.58	0.79	0.63	0.51	1.0	0.64
Primary NRTI-R	8/10 (80.0)	0/10 (0.0)	2/10 (20.0)	4/5 (80.0)	0/5 (0.0)	1/5 (20.0)
No Primary NRTI-R	278/310 (89.7)	14/310 (4.5)	18/310 (5.8)	298/320 (93.1)	4/320 (1.2)	18/320 (5.6)
P-Value	0.29	1.0	0.12	0.31	1.0	0.26
TAMs in RT	8/10 (80.0)	0/10 (0.0)	2/10 (20.0)	4/5 (80.0)	0/5 (0.0)	1/5 (20.0)
No TAMs in RT	278/310 (89.7)	14/310 (4.5)	18/310 (5.8)	298/320 (93.1)	4/320 (1.2)	18/320 (5.6)
P-Value	0.29	1.0	0.12	0.31	1.0	0.26
Primary NNRTI-R	34/40 (85.0)	0/40 (0.0)	6/40 (15.0)	38/41 (92.7)	1/41 (2.4)	2/41 (4.9)
No Primary NNRTI-R	252/280 (90.0)	14/280 (5.0)	14/280 (5.0)	264/284 (93.0)	3/284 (1.1)	17/284 (6.0)
P-Value	0.41	0.23	0.03	1.0	0.42	1.0
K103N/S in RT	15/18 (83.3)	0/18 (0.0)	3/18 (16.7)	20/21 (95.2)	0/21 (0.0)	1/21 (4.8)
No K103N/S in RT	271/302 (89.7)	14/302 (4.6)	17/302 (5.6)	282/304 (92.8)	4/304 (1.3)	18/304 (5.9)
P-Value	0.42	1.0	0.09	1.0	1.0	1.0
Primary PI-R	4/4 (100.0)	0/4 (0.0)	0/4 (0.0)	10/10 (100.0)	0/10 (0.0)	0/10 (0.0)
No Primary PI-R	282/316 (89.2)	14/316 (4.4)	20/316 (6.3)	292/315 (92.7)	4/315 (1.3)	19/315 (6.0)
P-Value	1.0	1.0	1.0	1.0	1.0	1.0

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide;
IN = integrase; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor;
NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistance;
RT = reverse transcriptase; TAMs = thymidine analog mutations
P-value determined using Fisher's exact test.
Source: GS-US-380-1490, Virology Listing 1 and Virology Listing 2

4.2.1.1.2.4. Virology Analyses in Subjects Experiencing Virologic Failure Through Week 48

Of the 645 randomized and treated subjects in Study GS-US-380-1490, 12 (1.9%) met the VF and RAP inclusion criteria through Week 48. Reasons for inclusion in the RAP were confirmed VF (4 subjects), > 200 copies/mL at last visit at or after Week 8 (early study discontinuation or lost to follow-up) (7 subjects), or > 200 copies at the last measurement in the Week 48 window (1 subject) (GS-US-380-1490, Virology Listing 4).

The RAP was comprised of 7 subjects (2.2%, 7 of 320) in the B/F/TAF group and 5 subjects (1.5%, 5 of 325) in the DTG + F/TAF group (Figure 19, Table 46). The final RAP (which did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs) was comprised of 7 subjects (2.2%, 7 of 320) in the B/F/TAF group and 3 subjects (0.9%, 3 of 325) in the DTG + F/TAF group.

Seven subjects in the B/F/TAF group were included in the RAP and were evaluated for the development of resistance through Week 48. None of these subjects in the B/F/TAF group subsequently achieved HIV-1 RNA resuppression to < 50 copies/mL; however, none had follow-up HIV-1 RNA data available. Postbaseline genotypic and phenotypic data were available for PR/RT and IN from all 7 subjects. None of the 7 subjects in the B/F/TAF RAP had resistance mutations emerge (Table 46). Other substitutions that emerged in IN and/or RT were at polymorphic sites and none of these changes were associated with a phenotypic change to BIC, FTC, or TFV (Table 46).

Table 46. GS-US-380-1490: Summary of HIV-1 Genotypic Resistance through Week 48

Resistance Category[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 320)	DTG + F/TAF (N = 325)	P-Value[b]
RAP (% of FAS)	7 (2.2)	5 (1.5)	0.57
Subjects with Data (Any Gene)	7 (100)	5 (100)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	0	2 (40.0)	
Final RAP[c] (% of FAS)	7 (2.2)	3 (0.9)	0.22
Subjects with Data (Any Gene)	7 (100)	3 (100)	
Developed Resistance Mutations to Study Drugs (% of FAS)	0 (0.0)	0 (0.0)	na
Developed Resistance Mutations to Study Drugs (% of Final RAP)	0 (0.0)	0 (0.0)	na
Developed Any INSTI-R	0	0	
Developed Primary NRTI-R	0	0	
Developed Primary NNRTI-R	0	0	
Developed Primary PI-R	0	0	

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; FAS = full analysis set; F/TAF = emtricitabine/tenofovir alafenamide; INSTI = integrase strand transfer inhibitor; na = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; RAP = resistance analysis population

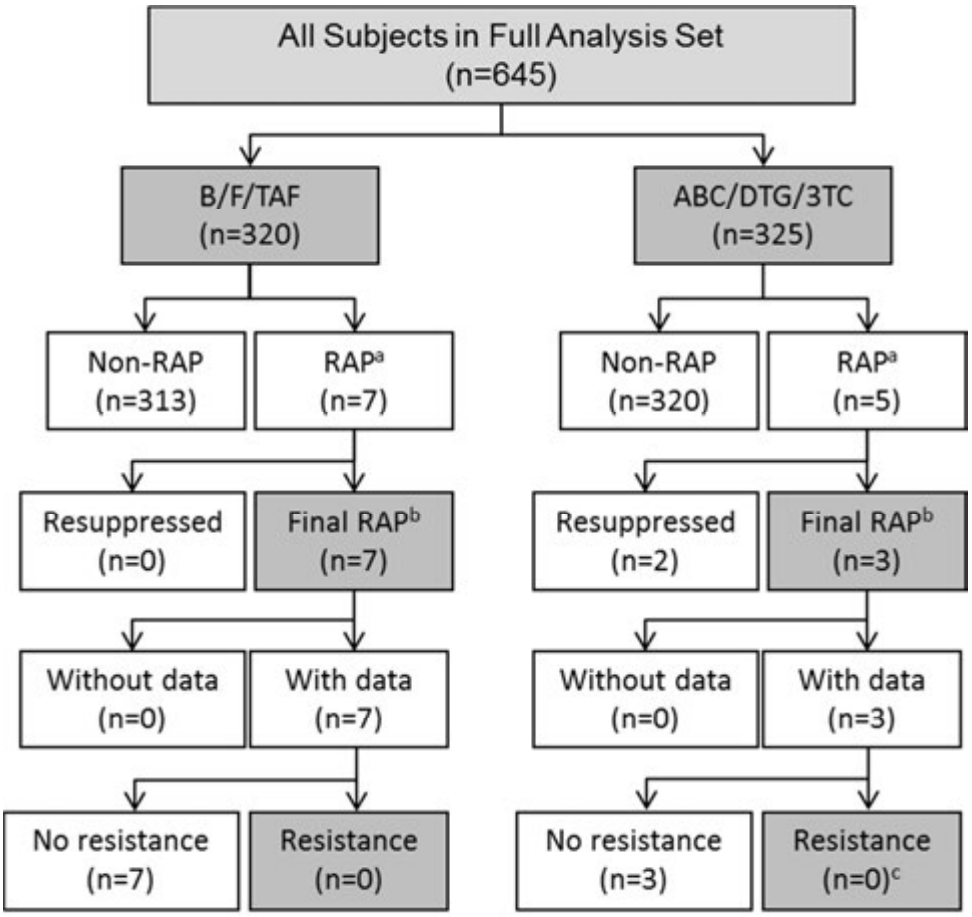
a Drug resistance mutations are defined in PC-380-2003, Table 2.

b P-value determined using Fisher's exact test.

c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

Source: GS-US-380-1490, Virology Listing 3 and Virology Listing 4

Figure 19. GS-US-380-1490: RAP and Genotypic Disposition through Week 48



B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide; RAP = resistance analysis population

a RAP criteria are summarized in PC-380-2003, Section 2.2.

b The final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

c One subject in the DTG + F/TAF group had K103K/N at baseline and Week 48.

Source: GS-US-380-1490, Virology Listing 3 and Virology Listing 4

Table 47. GS-US-380-1490: Details of Subjects in the Week 48 RAP

Final RAP	Subject ID	Treatment Group	Time Point	HIV-1 RNA (copies/mL)[a]	CD4 (cells/µL)	Sub-type	Resistance-associated Mutations[b]		Drug Susceptibility (Fold Change from WT)[c]					
							IN	RT	BIC	DTG	ABC	3TC	FTC	TFV[c]
Yes	00031-2093[d]	B/F/TAF	BL	97,200	2	B	none	none	0.96	1.16	0.85	1.24	1.09	0.76
			W8	19,000	11	B	none	none	0.87	0.85	0.57	0.97	0.94	0.60
Yes	01543-2111[d]	B/F/TAF	BL	184,000	430	B	S119P	V179V/D	af	af	1.06	1.13	0.94	1.04
			W36	8,630	462	B	S119P	none	0.59	0.84	1.04	1.16	0.99	1.17
Yes	01624-2140[d]	B/F/TAF	BL	2,770	948	B	none	none	0.93	0.99	1.03	1.06	0.85	1.01
			W24	4,440	801	B	none	none	0.92	0.90	1.01	0.96	0.85	1.06
Yes	11678-2182	B/F/TAF	BL	3,830,000	31	B	none	none	0.79	0.91	0.82	0.94	0.95	1.04
			W24	967	217	B	none	none	0.98	0.84	0.99	1.35	1.00	1.25
			W48	688	195	B	none	none	0.81	0.88	0.86	1.00	0.91	1.03
Yes	02511-2326	B/F/TAF	BL	25,200	943	B	V72T/I[e] S119P	none	nd	nd	af	af	af	af
			W48	22,200	954	B	V72T/I S119P	none	0.84	0.95	1.25	1.53	1.26	1.19
Yes	02035-2333	B/F/TAF	BL	16,800	900	B	S119P E157E/K	none	0.95	1.00	1.00	1.02	1.02	0.77
			W24	23,400	742	B	S119P	none	0.90	1.10	1.07	1.06	1.01	0.88
Yes	01624-2534[d]	B/F/TAF	BL	3,560,000	289	B	S119P	none	0.91	0.98	0.97	1.26	0.97	0.79
			W8	317,000	533	B	S119P	none	0.79	0.88	0.91	0.95	1.07	0.82
Yes	02106-2037	DTG + F/TAF	BL	42,300	358	B	none	none	1.04	0.98	0.85	1.02	0.98	0.76
			W8	22,800	278	B	af	none	af	af	0.87	0.96	0.87	0.81
Yes	00031-2272[d]	DTG + F/TAF	BL	23,800	8	B	M50M/I	**K103K/N**	af	af	1.00	1.40	1.55	0.87
			W48	221	228	B	af	**K103K/N**	af	af	af	af	af	af
No	00310-2435[d]	DTG + F/TAF	BL	25,000	315	B	M50I E157E/K	T69D	0.82	0.73	0.95	1.58	1.31	0.89
			W24	362	390[f]	B	M50I	T69A/D	0.96	0.91	0.94	1.21	1.24	0.93

Final RAP	Subject ID	Treatment Group	Time Point	HIV-1 RNA (copies/mL)[a]	CD4 (cells/µL)	Sub-type	Resistance-associated Mutations[b]		Drug Susceptibility (Fold Change from WT)[c]					
							IN	RT	BIC	DTG	ABC	3TC	FTC	TFV[c]
Yes	01942-2507[d]	DTG + F/TAF	BL	56,400	385	B	none	none	0.76	1.00	0.74	0.74	0.83	0.91
			W12	5,480	279	B	none	none	0.84	0.93	0.90	0.93	0.89	0.99
			W36	12,000	339	B	none	none	0.82	0.98	0.68	0.83	0.89	0.86
No	00310-2556[d]	DTG + F/TAF	BL	42,700	442	B	none	none	0.72	0.88	0.83	1.15	0.99	0.93
			W36	1,140	779	B	none	none	0.66	1.06	0.87	0.98	1.12	0.91

3TC = lamivudine; ABC = abacavir; af = assay failure; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BL = baseline/Day 1; DTG = dolutegravir; FTC = emtricitabine; F/TAF = emtricitabine/tenofovir alafenamide; IN = integrase; nd = no data available; RT = reverse transcriptase; TFV = tenofovir; W = week

a Baseline viral load is the Day 1 BL visit.

b Baseline sequences are the composite of screening and baseline data. Primary resistance-associated mutations are shown in bold text and secondary resistance-associated mutations are shown in plain text. Complete genotypic and phenotypic results are presented in GS-US-380-1490, Virology Listing 3 and Virology Listing 4

c Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical or biological cutoffs were as follows: BIC = 2.5, DTG = 4.0, ABC = 4.5, 3TC = 3.5, FTC = 3.5, TFV = 1.4. The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF.

d Adherence was < 95% or there were unreturned pill bottles.

e Patient 02511-2326 had V72T present at 2.83% by deep sequencing at Day 1.

f CD4 cell count was not assessed at study visit. CD4 cell count from prior visit in the same analysis window is reported.

Source: GS-US-380-1490, Virology Listing 3 and Virology Listing 4

4.2.1.1.2.5. Resistance Conclusions

The prevalence of baseline RAMs and HIV-1 subtypes were comparable across the B/F/TAF and DTG + F/TAF treatment groups. Baseline RAMs and HIV-1 subtype had no impact on treatment outcomes.

Of the 645 treated subjects from both treatment groups, the RAP was comprised of 12 subjects who experienced virologic failure during the first 48 weeks of the study: 7 of 320 subjects from the B/F/TAF group (2.2%) and 5 of 325 subjects from the DTG + F/TAF group (1.5%).

The final RAP included 10 subjects: 7 subjects from the B/F/TAF group and 3 subjects from the DTG + F/TAF group. Two subjects from the DTG + F/TAF group resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs and were not included in the final RAP.

No subject in either group developed treatment emergent resistance to study drugs.

4.2.1.1.3. GS-US-380-1844

4.2.1.1.3.1. Study Design, Baseline Characteristics, and Viral Response

Study GS-US-380-1844 is an ongoing phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy and safety of switching from a regimen containing DTG and ABC/3TC to an FDC of B/F/TAF versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects.

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

- **Treatment Group 1:** Switch to FDC of B/F/TAF (50/200/25 mg) + placebo to match ABC/DTG/3TC administered orally, once daily, without regard to food (n = 282)

- **Treatment Group 2:** FDC of ABC/DTG/3TC (600/50/300mg) + placebo to match FDC of B/F/TAF administered orally, once daily, without regard to food (n = 281)

Results from the Week 48 efficacy analysis using the FDA-defined snapshot algorithm demonstrated low and comparable rates of virologic failure (HIV-1 RNA ≥ 50 copies/mL) for HIV-1 infected adults treated with B/F/TAF (1.1%, 3 of 282 subjects) versus ABC/DTG/3TC (0.4%, 1 of 281 subjects). The proportion of subjects with virologic success (HIV-1 RNA < 50 copies/mL) at Week 48 was also similar between the 2 treatment groups: 93.6% for the B/F/TAF group (264 of 282 subjects) versus 95.0% for the ABC/DTG/3TC group (267 of 281 subjects).

4.2.1.1.3.2. Pretreatment Virology Data

HIV-1 historical genotypes with PR and RT data were available for 277 of 563 (49.2%) subjects in the FAS in Study GS-US-380-1844. Historical IN genotypic data were also available for 30 of these subjects (5.3% of 563 subjects in the FAS). Additional baseline genotypic data for PR, RT, and IN were obtained for 4 subjects using the GenoSure Archive® assay and those data were combined with available historical genotypic data and included in the summary of pretreatment mutations. Altogether, pretreatment IN genotypic data were obtained for 33 of 563 (5.9%) subjects and pretreatment PR/RT genotypic data were obtained for 278 of 563 (49.4%) subjects (Table 48).

Pretreatment primary INSTI resistance mutations were present in 6.1% of subjects (2 of 33) with pretreatment IN genotypic data, and consisted of T97A in 1 subject and T66I in 1 subject, both in the ABC/DTG/3TC group.

Pretreatment primary NRTI-associated resistance mutations were observed in 2.2% of subjects (6 of 278) with pretreatment RT genotypic data and consisted of M41L in 3 subjects, K219Q/R in 3 subjects, and L210W in 1 subject.

Pretreatment primary NNRTI-associated resistance mutations were observed in 9.4% of subjects (26 of 278) with data and consisted of K103N/S in 15 subjects, E138A/K/Q in 7 subjects, H221Y in 3 subjects, K101E/P, V108I, and Y181C each in 2 subjects, and M230I in 1 subject.

Pretreatment primary PI-associated resistance mutations were observed in 4.0% of subjects (11 of 278) with pretreatment PR genotypic data and consisted of M46I/L in 6 subjects, L90M in 4 subjects, and Q58E, V82L, and I84V each in 1 subject.

Overall, the prevalence of baseline RAMs was similar between treatment groups (Table 48).

Table 48. GS-US-380-1844: Summary of IN, RT, and PR Mutations Detected Pretreatment

Mutation Class[a]	Number of Subjects with Pretreatment Data, n (%)		
	B/F/TAF (N = 140)	ABC/DTG/3TC (N = 138)	All (N = 278)
Subjects with IN data	20 (14.3)	13 (9.4)	33 (11.9)
Primary INSTI-R	0	2 (15.4)	2 (6.1)
Average Number of Primary INSTI-R Mutations	0	1.0	1.0
T66I	0	1 (7.7)	1 (3.0)
T97A	0	1 (7.7)	1 (3.0)
Secondary INSTI-R	13 (65.0)	5 (38.5)	18 (54.5)
Average Number of Secondary INSTI-R Mutations	1.3	1.6	1.4
M50I	6 (30.0)	3 (23.1)	9 (27.3)
L68V	1 (5.0)	0	1 (3.0)
L74M	2 (10.0)	0	2 (6.1)
S119P/R/T	7 (35.0)	3 (23.1)	10 (30.3)
E157Q	0	2 (15.4)	2 (6.1)
G163R	1 (5.0)	0	1 (3.0)
Subjects with PR/RT data	140 (100)	138 (100)	278 (100)
Primary NRTI-R	2 (1.4)	4 (2.9)	6 (2.2)
Average Number of Primary NRTI-R Mutations	1.0	1.3	1.2
K65E/N/R	0	0	0
Any TAM	2 (1.4)	4 (2.9)	6 (2.2)
M41L	1 (0.7)	2 (1.4)	3 (1.1)
L210W	0	1 (0.7)	1 (0.4)
K219Q/R	1 (0.7)	2 (1.4)	3 (1.1)
Primary NNRTI-R	13 (9.3)	13 (9.4)	26 (9.4)
Average Number of Primary NNRTI-R Mutations	1.2	1.2	1.2
K101E/P	2 (1.4)	0	2 (0.7)
K103N/S	10 (7.1)	5 (3.6)	15 (5.4)
V108I	0	2 (1.4)	2 (0.7)
E138A/K/Q	2 (1.4)	5 (3.6)	7 (2.5)
Y181C	2 (1.4)	0	2 (0.7)
H221Y	0	3 (2.2)	3 (1.1)
M230I/L	0	1 (0.7)	1 (0.4)
Primary PI-R	6 (4.3)	5 (3.6)	11 (4.0)
Average Number of Primary PI-R Mutations	1.2	1.2	1.2
M46I/L	3 (2.1)	3 (2.2)	6 (2.2)
Q58E	0	1 (0.7)	1 (0.4)
V82/L	1 (0.7)	0	1 (0.4)
I84V	1 (0.7)	0	1 (0.4)
L90M	2 (1.4)	2 (1.4)	4 (1.4)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; IN = integrase; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistance; RT = reverse transcriptase; TAM = thymidine analogue mutation

a Drug resistance mutations are defined in PC-380-2004, Table 2.

Source: GS-US-380-1844, Virology Listing 1 and Virology Listing 2

The HIV-1 subtype was determined for 216 of 278 (77.7%) subjects with pretreatment genotypic data. The prevalence of different subtypes was comparable between treatment groups, with subtype B predominant in both groups (72.3% overall, 201 of 278 subjects) (Table 49).

Table 49. GS-US-380-1844: Summary of HIV-1 Subtypes

HIV-1 Subtype	Number of Subjects with Pretreatment Data, n (%)		
	B/F/TAF (N = 140)	ABC/DTG/3TC (N = 138)	All (N = 278)
Subtype Unknown	28 (20.0)	34 (24.6)	62 (22.3)
Subtype Known	112 (80.0)	104 (75.4)	216 (77.7)
Subtype B	103 (73.6)	98 (71.0)	201 (72.3)
Non-B Subtype	9 (6.4)	6 (4.3)	15 (5.4)
Subtype A1	1 (0.7)	0	1 (0.4)
Subtype AE	2 (1.4)	3 (2.2)	5 (1.8)
Subtype AG	1 (0.7)	0	1 (0.4)
Subtype B/G	1 (0.7)	0	1 (0.4)
Subtype C	0	1 (0.7)	1 (0.4)
Subtype F	1 (0.7)	0	1 (0.4)
Complex Subtype	3 (2.1)	2 (1.4)	5 (1.8)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide
Source: GS-US-380-1844, Virology Listing 2

4.2.1.1.3.3. Impact of Pretreatment Mutations and Subtype on Treatment Outcomes

The impact of pretreatment RAMs as well as subtype on treatment outcomes was assessed for all subjects in the FAS. For the subtype analysis, subtype B versus non-B subtype was evaluated. Although the number of subjects with pretreatment RAMs was small, the presence or absence of primary INSTI-R, T97A and T66I in IN, secondary INSTI-R, primary NRTI-R, TAMs, K103N/S in RT, primary NNRTI-R, and primary PI-R were evaluated.

No impact of pretreatment RAMs was observed on the occurrence of virologic failure (HIV-1 RNA ≥ 50 copies/mL) or the maintenance of virologic suppression (HIV-1 RNA < 50 copies/mL) through Week 48 for both treatment groups. For nearly all comparisons, there was no statistical difference found between baseline virologic categories and treatment outcome (Table 50). In the B/F/TAF group, although the proportion with virologic suppression to < 50 copies/mL at Week 48 in the non-subtype B subjects (6 of 9 subjects, 66.7%) was numerically lower than the proportion of subtype B subjects with virologic suppression at Week 48 (94 of 103 subjects, 91.3%; p = 0.06), this difference was not statistically significant mainly due to the low number of subjects with non-B subtypes in the B/F/TAF group (9 subjects) and the lack of virologic data at Week 48 in non-B subtype subjects (3 subjects). The proportion of subjects missing Week 48 window data was statistically different between groups, but this outcome is not considered clinically relevant. No subject with non-B subtypes had HIV-1 RNA ≥ 50 copies/mL in the Week 48 window. There was no statistically significant correlation between the presence of RAMs at baseline and the proportion of subjects treated with either B/F/TAF or ABC/DTG/3TC who had HIV-1 RNA < 50 copies/mL or ≥ 50 copies/mL at Week 48.

Table 50. Study GS-US-380-1844: FDA Snapshot Outcome of Subjects at Week 48 by Baseline Virologic Category

	Number of Subjects with Pretreatment Data n (%)					
	B/F/TAF (N = 140)			ABC/DTG/3TC (N = 138)		
Category	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data
All Subjects	127/140 (90.7)	3/140 (2.1)	10/140 (7.1)	134/138 (97.1)	0/138 (0)	4/138 (2.9)
HIV-1 Subtype B	94/103 (91.3)	3/103 (2.9)	6/103 (5.8)	95/98 (96.9)	0/98 (0)	3/98 (3.1)
HIV-1 Subtype Non-B	6/9 (66.7)	0/9 (0)	3/9 (33.3)	5/6 (83.3)	0/6 (0)	1/6 (16.7)
P-Value	0.06	1.0	0.02	0.21	na	0.21
Primary INSTI-R	0	0	0	1/2 (50.0)	0/2 (0.0)	1/2 (50.0)
No Primary INSTI-R	16/20 (80.0)	3/20 (15.0)	1/20 (5.0)	11/11 (100.0)	0/11 (0.0)	0/11 (0.0)
P-Value	na	na	na	0.15	na	0.15
T66I in IN	0	0	0	0/1 (0.0)	0/1 (0.0)	1/1 (100.0)
No T66I in IN	16/20 (80.0)	3/20 (15.0)	1/20 (5.0)	12/12 (100.0)	0/12 (0.0)	0/12 (0.0)
P-Value	na	na	na	0.077	na	0.077
T97A in IN	0	0	0	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)
No T97A in IN	16/20 (80.0)	3/20 (15.0)	1/20 (5.0)	11/12 (91.7)	0/12 (0.0)	1/12 (8.3)
P-Value	na	na	na	1.0	na	1.0
Secondary INSTI-R	9/13 (69.2)	3/13 (23.1)	1/13 (7.7)	5/5 (100.0)	0/5 (0.0)	0/5 (0.0)
No Secondary INSTI-R	7/7 (100.0)	0/7 (0.0)	0/7 (0.0)	7/8 (87.5)	0/8 (0.0)	1/8 (12.5)
P-Value	0.25	0.52	1.0	1.0	na	1.0
Primary NRTI-R	2/2 (100.0)	0/2 (0.0)	0/2 (0.0)	4/4 (100.0)	0/4 (0.0)	0/4 (0.0)
No Primary NRTI-R	125/138 (90.6)	3/138 (2.2)	10/138 (7.2)	130/134 (97.0)	0/134 (0.0)	4/134 (3.0)
P-Value	1.0	1.0	1.0	1.0	na	1.0
TAMs in RT	2/2 (100.0)	0/2 (0.0)	0/2 (0.0)	4/4 (100.0)	0/4 (0.0)	0/4 (0.0)
No TAMs in RT	125/138 (90.6)	3/138 (2.2)	10/138 (7.2)	130/134 (97.0)	0/134 (0.0)	4/134 (3.0)
P-Value	1.0	1.0	1.0	1.0	na	1.0
Primary NNRTI-R	12/13 (92.3)	0/13 (0.0)	1/13 (7.7)	13/13 (100.0)	0/13 (0.0)	0/13 (0.0)
No Primary NNRTI-R	115/127 (90.6)	3/127 (2.4)	9/127 (7.1)	121/125 (96.8)	0/125 (0.0)	4/125 (3.2)
P-Value	1.0	1.0	1.0	1.0	na	1
K103N/S in RT	9/10 (90.0)	0/10 (0.0)	1/10 (10.0)	5/5 (100.0)	0/5 (0.0)	0/5 (0.0)
No K103N/S in RT	118/130 (90.8)	3/130 (2.3)	9/130 (6.9)	129/133 (97.0)	0/133 (0.0)	4/133 (3.0)
P-Value	1.0	1.0	0.54	1.0	na	1.0
Primary PI-R	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	5/5 (100.0)	0/5 (0.0)	0/5 (0.0)
No Primary PI-R	121/134 (90.3)	3/134 (2.2)	10/134 (7.5)	129/133 (97.0)	0/133 (0.0)	4/133 (3.0)
P-Value	1.0	1.0	1.0	1.0	na	1.0

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; IN = integrase; INSTI = integrase strand transfer inhibitor; na = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistance; RT = reverse transcriptase
P values were determined by Fisher's exact test.
Source: GS-US-380-1844, Virology Listing 1 and Virology Listing 2

4.2.1.1.3.4. Virology Analyses in Subjects Experiencing Virologic Failure Through Week 48

Of the 563 subjects in the FAS in Study GS-US-380-1844, 5 (0.9%) met the VF and RAP inclusion criteria through Week 48 (Table 51). Reasons for inclusion in the RAP were confirmed VF (2 subjects) or HIV-1 RNA > 200 copies/mL at last visit (study discontinuation or lost to follow-up) (3 subjects). Postbaseline genotypic data for at least one HIV-1 gene were obtained for 3 of 5 (60%) subjects in the RAP. Assay failures were attributed to low viral loads (HIV-1 RNA < 1000 copies/mL).

The RAP was comprised of 3 subjects (1.1%, 3 of 282) in the B/F/TAF group and 2 subjects (0.7%, 2 of 281) in the ABC/DTG/3TC group (Figure 20). The final RAP (which did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs) was comprised of 2 subjects (0.7%, 2 of 282) in the B/F/TAF group and 1 subject (0.4%, 1 of 281) in the ABC/DTG/3TC group.

Three subjects in the B/F/TAF group were included in the RAP and evaluated for the development of resistance through Week 48. Postbaseline genotypic and phenotypic data are available for PR/RT from 1 subject and for IN from 0 subjects. No resistance mutations emerged for the 1 subject with data (Table 52). This subject subsequently achieved HIV-1 RNA resuppression to < 50 copies/mL with further B/F/TAF treatment and was not included in the final RAP.

Two subjects in the ABC/DTG/3TC group were included in the RAP and evaluated for the development of resistance through Week 48. Postbaseline genotypic and phenotypic data are available for PR/RT and IN from both subjects. Neither subject had resistance mutations emerge (Table 52). One of these 2 subjects resuppressed HIV-1 RNA to < 50 copies/mL and was not included in the final RAP.

Table 51. GS-US-380-1844: Summary of HIV-1 Genotypic Resistance through Week 48

Resistance Category[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)	P-Value[b]
RAP (% of FAS)	3 (1.1)	2 (0.7)	1.0
Subjects with Data (Any Gene)	1 (33.3)	2 (100.0)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	1 (33.3)	1 (50.0)	
Final RAP[c] (% of FAS)	2 (0.7)	1 (0.4)	1.0
Subjects with Data (Any Gene)	0 (0.0)	1 (100.0)	
Developed Resistance Mutations to Study Drugs (% of FAS)	0 (0.0)	0 (0.0)	na
Developed Resistance Mutations to Study Drugs (% of Final RAP)	0 (0.0)	0 (0.0)	na
Developed Any INSTI-R	0	0	
Developed Primary NRTI-R	0	0	
Developed Primary NNRTI-R	0	0	
Developed Primary PI-R	0	0	

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; INSTI = integrase strand transfer inhibitor; FAS = full analysis set; na = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; RAP = resistance analysis population

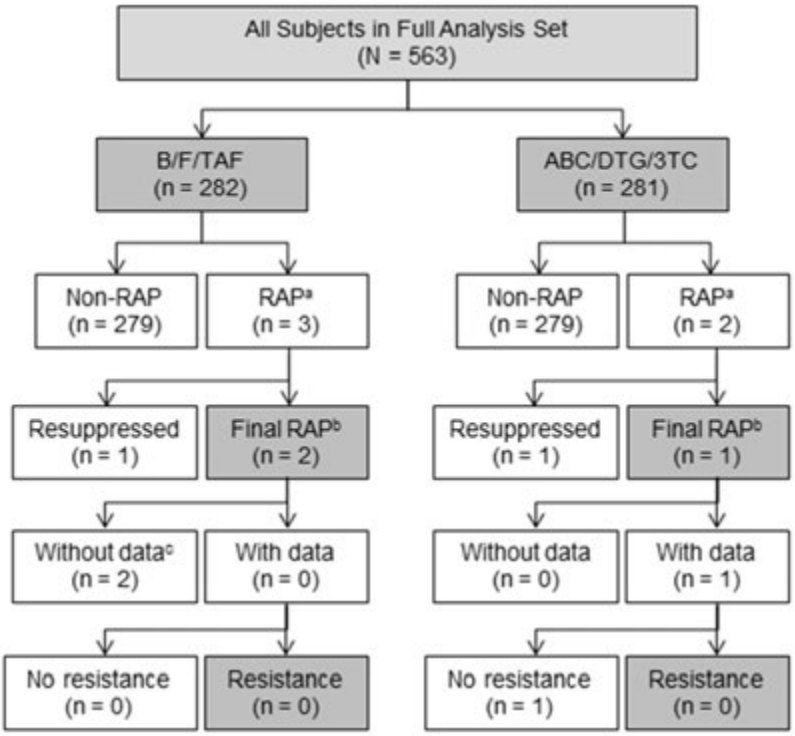
a Drug resistance mutations are defined in PC-380-2004, Table 2.

b P values were determined by Fisher's exact test.

c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

Source: GS-US-380-1844, Virology Listing 3 and Virology Listing 4

Figure 20. GS-US-380-1844: RAP and Genotype Disposition through Week 48



ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide;
RAP = resistance analysis population
a RAP criteria are summarized in PC-380-2004, Section 2.2.
b The final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.
c Subjects without data due to assay failure.
Source: GS-US-380-1844, Virology Listings 3 and Virology Listing 4

Table 52. GS-US-380-1844: Details of Subjects in the Week 48 RAP

Final RAP	Subject ID	Treatment Group	Time Point	HIV-1 RNA (copies/mL)[a]	CD4 (cells/µL)[a]	Subtype	Resistance-associated Mutations[b]		Drug Susceptibility (Fold Change from WT)[c]					
							IN	RT	BIC	DTG	ABC	3TC	FTC	TFV[c]
Yes	03946-3305	B/F/TAF	BL	19	660	B	S119T	none	na	na	na	na	na	na
			W24	499	715	af	nd[d]	af	nd[d]	nd[d]	af	af	af	af
No	01808-3475[e]	B/F/TAF	BL	159	285	B	none	V106V/I	na	na	na	na	na	na
			W4	206	242[f]	B	af	V106I	af	af	0.75	1.09	0.98	0.75
			W8	117	318	B	af	V106I	af	af	0.94	1.22	0.96	0.84
Yes	00364-3561[e]	B/F/TAF	BL	19	876	B	M50I	none	na	na	na	na	na	na
			W12	928	1008	af	af	af	af	af	af	af	af	af
No	02728-3121[e]	ABC/DTG/3TC	BL	19	698	B	M50I S119R E157Q	none	na	na	na	na	na	na
			W12	1,200	516[f]	B	M50I S119R E157Q	none	0.54	0.64	0.68	0.84	0.96	0.62
Yes	02191-3182	ABC/DTG/3TC	BL	19	366	nd[d]	nd[d]	nd[d]	na	na	na	na	na	na
			W8	12,600	275	B	none	none	0.80	0.97	0.88	1.09	1.09	0.81

3TC = lamivudine; ABC = abacavir; ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; af = assay failure; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BL = baseline/Day 1; DTG = dolutegravir; FTC = emtricitabine; IN = integrase; na = not applicable; nd = not determined; RAP = resistance analysis population; −R = resistance; RT = reverse transcriptase; TFV = tenofovir

a Baseline viral load and CD4 cell count are from the Day 1 BL visit. Undetectable HIV-1 RNA or values < 20 copies/mL were imputed as 19.

b Baseline sequences are the composite of historical genotypic and baseline data. Drug resistance mutations are defined in PC-380-2004, Table 2. Primary resistance mutations, if present, are shown in bold text and secondary resistance mutations are shown in plain text. Complete genotypic and phenotypic results are presented in GS-US-380-1844, Virology Listing 3 and Virology Listing 4

c Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug, if present. The clinical or biological cutoffs were as follows: BIC = 2.5, DTG = 4.0, ABC = 4.5, 3TC = 3.5, FTC = 3.5, TFV = 1.4. The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF.

d Inadequate sample volume for testing.

e Adherence was <95% or pill bottles were not returned.

f CD4 cell count was not assessed at study visit. CD4 cell count from prior visit in the same analysis window is reported.

Source: GS-US-380-1844, Virology Listing 3 and Virology Listing 4

4.2.1.1.3.5. Resistance Conclusions

For Study GS-US-380-1844, the prevalence of baseline RAMs and HIV-1 subtypes was comparable across the B/F/TAF and ABC/DTG/3TC treatment groups. The presence of RAMs at baseline and HIV-1 subtype had no impact on treatment outcomes.

The RAP was comprised of 5 subjects who experienced virologic failure during the first 48 weeks of the study. Three subjects were from the B/F/TAF group (1.1%, 3 of 282 subjects) and 2 subjects were from the ABC/DTG/3TC group (0.7%, 2 of 281 subjects).

Two of the 5 subjects who met VF and RAP criteria maintained study drugs and subsequently had resuppression of HIV-1 RNA to < 50 copies/mL: 1 subject was from the B/F/TAF group and 1 subject was from the ABC/DTG/3TC group. These 2 subjects were not included in the final RAP.

The final RAP included 3 subjects: 2 subjects were from the B/F/TAF group and 1 subject was from the ABC/DTG/3TC group. No subject in either group developed treatment emergent drug resistance in RT or IN.

4.2.1.1.4. GS-US-380-1878

4.2.1.1.4.1. Study Design, Baseline Characteristics, and Viral Response

Study GS-US-380-1878 is an ongoing Phase 3, randomized, open-label, multicenter, active-controlled study to evaluate the efficacy and safety of switching to an FDC of B/F/TAF versus remaining on current antiretroviral regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC in HIV-1 infected subjects who are virologically suppressed. Subjects were randomized in a 1:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1:** Switch to FDC of B/F/TAF (50/200/25 mg) administered orally, once daily without regard to food (n = 290)

- **Treatment Group 2:** Stay on baseline regimen (SBR) consisting of ritonavir (RTV) or cobicistat boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally, once daily with food (n = 287)

Results from the Week 48 efficacy analysis using the FDA-defined snapshot algorithm demonstrated low and comparable rates of virologic failure (HIV-1 RNA ≥ 50 copies/mL) for HIV-1 infected adults in the B/F/TAF group (1.7%, 5 of 290 subjects) versus the SBR group (1.7%, 5 of 287 subjects). The proportion of subjects with virologic success (HIV-1 RNA < 50 copies/mL) at Week 48 was also similar between the two treatment groups: 92.1% for the B/F/TAF group (267 of 290 subjects) versus 88.9% for the SBR group (255 of 287 subjects).

4.2.1.1.4.2. Pretreatment Virology Data

Pretreatment HIV-1 genotypic data consisted of any available historical genotypes and provial DNA genotyping of Day 1 viral isolates from subjects included in the RAP. Altogether, pretreatment IN genotypic data were obtained for 21 of 577 (3.6%) subjects in the FAS in Study GS-US-380-1878 and pretreatment PR/RT genotypic data were obtained for 266 of 577 (46.1%) subjects (Table 53). HIV-1 historical genotypes with PR and RT data were available for 264 of 577 (45.8%) subjects. Historical IN genotypic data were also available for 16 of these subjects (2.8% of 577 subjects in the FAS). Additional baseline genotypic data for PR, RT, and IN were obtained for 7 subjects using the GenoSure Archive® assay and those data were combined with available historical genotypic data and included in the summary of pretreatment mutations.

Pretreatment primary INSTI resistance mutations were present in 4.8% of subjects (1 of 21) with pretreatment IN genotypic data, and consisted of T97A in 1 subject in the B/F/TAF group.

Pretreatment primary NRTI-associated resistance mutations were observed in 6.8% of subjects (18 of 266) with pretreatment RT genotypic data and consisted of one or more TAMs in 16 subjects, T215F/Y in 4 subjects, M184I/V in 3 subjects, and K65R, L74V, and Y115F each in 1 subject. One of the 3 subjects with M184V/I was identified retrospectively at baseline in the B/F/TAF group, and the other 2 subjects were in the SBR group. The subject with K65R was in the SBR group.

Pretreatment primary NNRTI-associated resistance mutations were observed in 20.7% of subjects (55 of 266) with data and consisted of K103N/S in 33 subjects, E138A/K in 10 subjects, Y181C/I in 7 subjects, G190A in 5 subjects, H221Y and V108I each in 3 subjects, K101E in 2 subjects, and V179L, Y188L, P225H, and M230I each in 1 subject.

Pretreatment primary PI-associated resistance mutations were observed in 4.1% of subjects (11 of 266) with pretreatment PR genotypic data and consisted of M46I/L, V82A/L, and L90M each in 3 subjects and D30N and Q58E each in 1 subject.

Overall, the prevalence of baseline RAMs was similar between treatment groups (Table 53).

Table 53. GS-US-380-1878: Summary of IN, RT, and PR Mutations Detected Pretreatment

Mutation Class[a]	Number of Subjects with Pretreatment Data, n (%)		
	B/F/TAF (N = 141)	SBR (N = 125)	All (N = 266)
Subjects with IN data	7 (5.0)	14 (11.2)	21 (7.9)
Primary INSTI-R	1 (14.3)	0	1 (4.8)
Average Number of Primary INSTI-R Mutations	1.0	0	1.0
T97A	1 (14.3)	0	1 (4.8)
Secondary INSTI-R	3 (42.9)	6 (42.9)	9 (42.9)
Average Number of Secondary INSTI-R Mutations	1.3	1.2	1.2
M50I	1 (14.3)	2 (14.3)	3 (14.3)
L68V	1 (14.3)	0	1 (4.8)
S119P/R/T	2 (28.6)	4 (28.6)	6 (28.6)
G163K	0	1 (7.1)	1 (4.8)
Subjects with PR-RT data	141 (100)	125 (100)	266 (100)
Primary NRTI-R	8 (5.7)	10 (8.0)	18 (6.8)
Average Number of Primary NRTI-R Mutations	1.5	2.8	2.2
K65R	0	1 (0.8)	1 (0.4)
L74V	0	1 (0.8)	1 (0.4)
Y115F	0	1 (0.8)	1 (0.4)
M184I/V	1 (0.7)	2 (1.6)	3 (1.1)
Any TAM	8 (5.7)	8 (6.4)	16 (6.0)
M41L	3 (2.1)	2 (1.6)	5 (1.9)
D67N	3 (2.1)	6 (4.8)	9 (3.4)
K70R	2 (1.4)	5 (4.0)	7 (2.6)
T215F/Y	0	4 (3.2)	4 (1.5)
K219N/Q	3 (2.1)	6 (4.8)	9 (3.4)
Primary NNRTI-R	29 (20.6)	26 (20.8)	55 (20.7)
Average Number of Primary NNRTI-R Mutations	1.1	1.3	1.2
K101E	1 (0.7)	1 (0.8)	2 (0.8)
K103N/S	19 (13.5)	14 (11.2)	33 (12.4)
V108I	1 (0.7)	2 (1.6)	3 (1.1)
E138A/K	7 (5.0)	3 (2.4)	10 (3.8)
V179L	0	1 (0.8)	1 (0.4)
Y181C/I	2 (1.4)	5 (4.0)	7 (2.6)
Y188L	1 (0.7)	0	1 (0.4)
G190A	1 (0.7)	4 (3.2)	5 (1.9)
H221Y	0	3 (2.4)	3 (1.1)
P225H	1 (0.7)	0	1 (0.4)
M230I	0	1 (0.8)	1 (0.4)

Mutation Class[a]	Number of Subjects with Pretreatment Data, n (%)		
	B/F/TAF (N = 141)	SBR (N = 125)	All (N = 266)
Primary PI-R	6 (4.3)	5 (4.0)	11 (4.1)
Average Number of Primary PI-R Mutations	1.0	1.0	1.0
D30N	0	1 (0.8)	1 (0.4)
M46I/L	1 (0.7)	2 (1.6)	3 (1.1)
Q58E	1 (0.7)	0	1 (0.4)
V82A/L	2 (1.4)	1 (0.8)	3 (1.1)
L90M	2 (1.4)	1 (0.8)	3 (1.1)

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; IN = integrase; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistance; RT = reverse transcriptase; SBR = stay on baseline regimen; TAM = thymidine analogue mutation
a Drug resistance mutations are defined in PC-380-2005, Table 2.
Source: GS-US-380-1878, Virology Listing 1 and Virology Listing 2

The HIV-1 subtype was determined for 209 of 266 (78.6%) subjects with pretreatment genotypic data. The prevalence of different subtypes was comparable between treatment groups, with subtype B predominant in both groups (67.7% overall, 180 of 266 subjects) (Table 54).

Table 54. GS-US-380-1878: Summary of HIV-1 Subtypes

HIV-1 Subtype	Number of Subjects with Pretreatment Data, n (%)		
	B/F/TAF (N = 141)	SBR (N = 125)	All (N = 266)
Subtype Unknown	26 (18.4)	31 (24.8)	57 (21.4)
Subtype Known	115 (81.6)	94 (75.2)	209 (78.6)
Subtype B	101 (71.6)	79 (63.2)	180 (67.7)
Non-B Subtype	14 (9.9)	15 (12.0)	29 (10.9)
Subtype A	1 (0.7)	0	1 (0.4)
Subtype A1	1 (0.7)	0	1 (0.4)
Subtype AB	1 (0.7)	0	1 (0.4)
Subtype AE	1 (0.7)	0	1 (0.4)
Subtype AG	2 (1.4)	5 (4.0)	7 (2.6)
Subtype C	4 (2.8)	6 (4.8)	10 (3.8)
Subtype D	1 (0.7)	0	1 (0.4)
Subtype H	0	1 (0.8)	1 (0.4)
Complex Subtype	3 (2.1)	3 (2.4)	6 (2.3)

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; SBR = stay on baseline regimen
Source: GS-US-380-1878, Virology Listing 2

4.2.1.1.4.3. Impact of Pretreatment Mutations and Subtype on Treatment Outcomes

The impact of pretreatment RAMs as well as subtype on treatment outcomes was assessed for all subjects in the FAS. For the subtype analysis, subtype B versus non-B subtype was evaluated. Although the number of subjects with pretreatment RAMs was small, the presence or absence of primary INSTI-R, T97A in IN, secondary INSTI-R, primary NRTI-R, TAMs, K103N/S in RT, primary NNRTI-R, and primary PI-R were evaluated.

No impact of pretreatment RAMs was observed on the occurrence of virologic failure (HIV-1 RNA ≥ 50 copies/mL) or the maintenance of virologic suppression (HIV-1 RNA < 50 copies/mL) through Week 48 for both treatment groups. For nearly all comparisons, there was no statistical difference found between baseline virologic categories and treatment outcome (Table 55). In the B/F/TAF group, although the proportion of subjects with virologic suppression to < 50 copies/mL at Week 48 with non-B subtype HIV-1 (11 of 14 subjects, 78.6%) was statistically lower than the proportion of subjects with subtype B HIV-1 with virologic suppression at Week 48 (97 of 101 subjects, 96.0%; p = 0.04), this difference was mainly due to the low number of subjects with non-B subtypes in the B/F/TAF group (14 subjects) and the lack of virologic data at Week 48 in non-B subtype subjects (2 subjects), and is not considered clinically relevant. There was no statistically significant correlation between the presence of RAMs at baseline and the proportion of subjects in either B/F/TAF or SBR treatment groups who achieved HIV-1 RNA < 50 copies/mL or ≥ 50 copies/mL at Week 48.

The subject in the B/F/TAF group with T97A in IN at baseline maintained HIV-1 RNA < 50 copies/mL at Week 48. The subject in the B/F/TAF group with the preexisting M184V substitution in RT discontinued the study at Week 12 with HIV-1 RNA ≥ 50 copies/mL (due to poor adherence) and is described further in the next section.

Table 55. GS-US-380-1878: FDA Snapshot Outcome of Subjects at Week 48 by Baseline Virologic Category

	Number of Subjects with Pretreatment Data n (%)					
	B/F/TAF (N = 141)			SBR (N = 125)		
Category	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data
All Subjects	133/141 (94.3)	3/141 (2.1)	5/141 (3.5)	108/125 (86.4)	4/125 (3.2)	13/125 (10.4)
HIV-1 Subtype B	97/101 (96.0)	2/101 (2.0)	2/101 (2.0)	68/79 (86.1)	4/79 (5.1)	7/79 (8.9)
HIV-1 Subtype Non-B	11/14 (78.6)	1/14 (7.1)	2/14 (14.3)	12/15 (80.0)	0/15 (0)	3/15 (20.0)
P-Value	0.04	0.32	0.07	0.69	1.0	0.20
Primary INSTI-R	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	0	0	0
No Primary INSTI-R	4/6 (66.7)	1/6 (16.7)	1/6 (16.7)	9/14 (64.3)	3/14 (21.4)	2/14 (14.3)
P-Value	1.0	1.0	1.0	na	na	na
T97A in IN	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	0	0	0
No T97A in IN	4/6 (66.7)	1/6 (16.7)	1/6 (16.7)	9/14 (64.3)	3/14 (21.4)	2/14 (14.3)
P-Value	1.0	1.0	1.0	na	na	na
Secondary INSTI-R	3/3 (100.0)	0/3 (0.0)	0/3 (0.0)	4/6 (66.7)	1/6 (16.7)	1/6 (16.7)
No Secondary INSTI-R	2/4 (50.0)	1/4 (25.0)	1/4 (25.0)	5/8 (62.5)	2/8 (25.0)	1/8 (12.5)
P-Value	0.43	1.0	1.0	1.0	1.0	1.0
Primary NRTI-R	7/8 (87.5)	1/8 (12.5)	0/8 (0.0)	8/10 (80.0)	1/10 (10.0)	1/10 (10.0)
No Primary NRTI-R	126/133 (94.7)	2/133 (1.5)	5/133 (3.8)	100/115 (87.0)	3/115 (2.6)	12/115 (10.4)
P-Value	0.38	0.16	1.0	0.63	0.29	1.0
TAMs in RT	7/8 (87.5)	1/8 (12.5)	0/8 (0.0)	7/8 (87.5)	0/8 (0.0)	1/8 (12.5)
No TAMs in RT	126/133 (94.7)	2/133 (1.5)	5/133 (3.8)	101/117 (86.3)	4/117 (3.4)	12/117 (10.3)
P-Value	0.38	0.16	1.0	1.0	1.0	0.60
Primary NNRTI-R	29/29 (100.0)	0/29 (0.0)	0/29 (0.0)	20/26 (76.9)	2/26 (7.7)	4/26 (15.4)
No Primary NNRTI-R	104/112 (92.9)	3/112 (2.7)	5/112 (4.5)	88/99 (88.9)	2/99 (2.0)	9/99 (9.1)
P-Value	0.21	1.0	0.58	0.12	0.19	0.47
K103N/S in RT	19/19 (100.0)	0/19 (0.0)	0/19 (0.0)	11/14 (78.6)	1/14 (7.1)	2/14 (14.3)
No K103N/S in RT	114/122 (93.4)	3/122 (2.5)	5/122 (4.1)	97/111 (87.4)	3/111 (2.7)	11/111 (9.9)
P-Value	0.60	1.0	1.0	0.41	0.38	0.64
Primary PI-R	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	5/5 (100.0)	0/5 (0.0)	0/5 (0.0)
No Primary PI-R	127/135 (94.1)	3/135 (2.2)	5/135 (3.7)	103/120 (85.8)	4/120 (3.3)	13/120 (10.8)
P-Value	1.0	1.0	1.0	1.0	1.0	1.0

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; IN = integrase; INSTI = integrase strand transfer inhibitor; na = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistance; RT = reverse transcriptase; SBR = stay on baseline regimen
P values were determined by Fisher's exact test.
Source: GS-US-380-1878, Virology Listing 1 and Virology Listing 2

4.2.1.1.4.4. Resistance Analyses in Subjects Experiencing Virologic Failure Through Week 48

Of the 577 subjects in the FAS in Study GS-US-380-1878, 7 (1.2%) met the VF and RAP inclusion criteria through Week 48 (Table 56). Reasons for inclusion in the RAP were confirmed VF (5 subjects) or HIV-1 RNA > 200 copies/mL at last visit (study discontinuation or lost to follow-up) (2 subjects). Postbaseline genotypic data for at least one HIV-1 gene were obtained for 6 of 7 (85.7%) subjects in the RAP.

The RAP was comprised of 2 subjects (0.7%, 2 of 290) in the B/F/TAF group and 5 subjects (1.7%, 5 of 287) in the SBR group (Figure 21, Table 57). The final RAP (which did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs and without resistance development) was comprised of 1 subject (0.3%, 1 of 290) in the B/F/TAF group and 3 subjects (1.0%, 3 of 287) in the SBR group.

The B/F/TAF subject in the final RAP had a history of poor adherence to B/F/TAF treatment by pill count assessment (76.2%) and consequently had virologic rebound at Week 12 (Study GS-US-380-1878, Listing 16.2.5.3). Furthermore, the plasma concentration of BIC at Week 12 for this subject was below the limit of quantification, which is not consistent with once daily dosing of B/F/TAF (Study GS-US-380-1878, Listing 16.2.5.5). HIV-1 isolates from this subject from both the pre-dose Day 1 and Week 12 visits contained the preexisting M184V mutation in RT but no treatment emergent resistance. The extensive ARV medication history of this subject, including NRTI-only regimens for the first 5 years of treatment, is also consistent with the development of the M184V mutation prior to study entry (Study GS-US-380-1878 Listing 16.2.4.6). In 19[redacted], the subject was treated with zidovudine (ZDV) monotherapy, and didanosine was added to ZDV in 19[redacted]. The subject discontinued ZDV and didanosine and switched to 3TC and stavudine in 19[redacted], and then switched again to nevirapine and nelfinavir in 19[redacted]. The subject discontinued this regimen in 20[redacted] and received no ARV treatment for 9 years. In 20[redacted], the subject initiated a new regimen consisting of fosamprenavir and FTC/TDF. In 20[redacted], the subject switched to a regimen of RTV-boosted DRV plus FTC/TDF until starting study drug on [redacted] 20[redacted]. Following virologic rebound at Week 12 of the study, the subject switched to a regimen of RPV and COBI-boosted DRV and achieved HIV-1 RNA < 50 copies/mL at Week 36. There was no treatment emergent resistance in this subject in the B/F/TAF group.

Of the 3 SBR subjects in the final RAP, 1 subject had elevated HIV-1 RNA levels at Day 1 (≥ 200 copies/mL) and continued to have elevated HIV-1 RNA through Week 8. HIV-1 isolates from both the Day 1 and Week 8 visits contained the preexisting M184I mutation in RT but no treatment emergent resistance (PK and adherence data were not available). The second SBR subject in the final RAP, whose regimen consisted of RTV-boosted DRV and ABC/3TC, had elevated HIV-1 RNA levels at Day 1 (≥ 200 copies/mL) and discontinued the study at Week 4 with HIV-1 RNA ≥ 200 copies/mL. The HIV-1 isolate from the Week 4 visit contained the ABC resistance mutation L74V in RT as a mixture with wild-type. The viral isolate from Day 1 did not contain this mutation, indicating L74V was treatment emergent (historical genotype was not available for this subject). The third SBR subject in the final RAP had confirmed VF at Weeks 36 and 48 with development of the primary NNRTI-R mutation E138K in RT as a mixture with wild-type; however, this subject was not treated with an NNRTI and viral isolates from these time points were phenotypically sensitive to all components of their regimen. Therefore, this subject was not considered to have treatment emergent resistance to study drugs.

Table 56. GS-US-380-1878: Summary of HIV-1 Genotypic Resistance through Week 48

Resistance Category[a]	Number of Subjects, n (%)		
	B/F/TAF (N = 290)	SBR (N = 287)	P-Value[b]
RAP (% of FAS)	2 (0.7)	5 (1.7)	0.28
Subjects with Data (Any Gene)	1 (50)	5 (100)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	1 (50)	2 (40)	
Final RAP[c] (% of FAS)	1 (0.3)	3 (1.0)	0.37
Subjects with Data (Any Gene)	1 (100)	3 (100)	
Developed Resistance Mutations to Study Drugs (% of FAS)	0	1 (0.3)[d]	0.50
Developed Resistance Mutations to Study Drugs (% of Final RAP)	0	1 (33.3)[d]	1.0
Developed Any INSTI-R	0	0	
Developed Primary NRTI-R[e]	0	1 (0.3)	
K65E/N/R	0	0	
M184V/I	0[f]	0[f]	
L74V	0	1	
Developed Primary NNRTI-R[e]	0	1 (0.3)	
E138K	0	1	
Developed Primary PI-R	0	0	

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; FAS = full analysis set; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; RAP = resistance analysis population; SBR = stay on baseline regimen

a Drug resistance mutations are defined in PC-380-2005, Table 2.

b P values were determined by Fisher's exact test.

c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

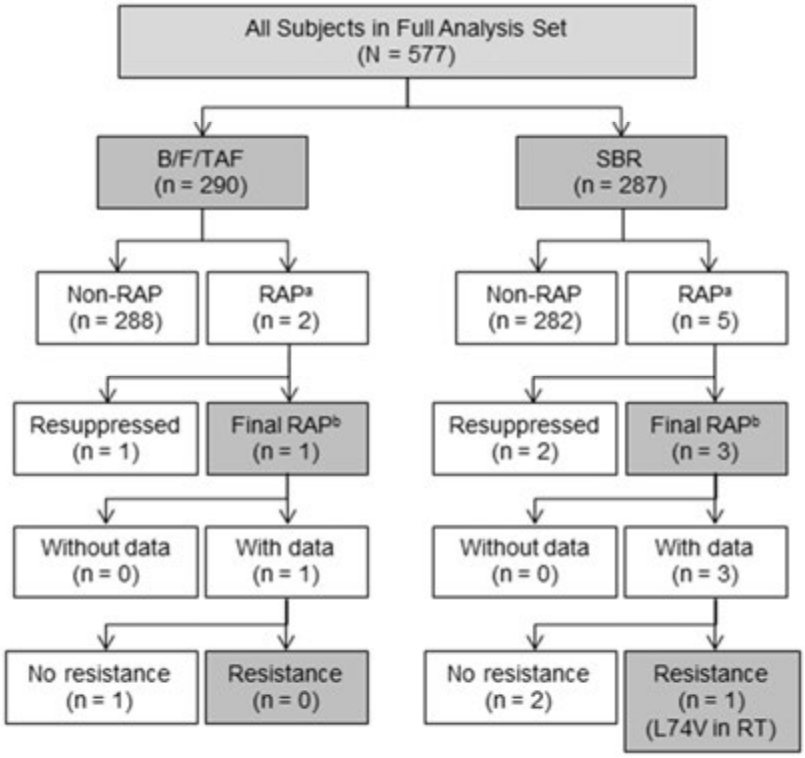
d One subject who developed E138K in RT, which was not associated with resistance to any components of their regimen, was not counted as having developed resistance mutations to study drugs.

e Percentage based on FAS population denominator.

f One subject in each group had virologic rebound associated with poor adherence to study drugs with their preexisting HIV-1 strain that contained M184V/I.

Source: GS-US-380-1878, Virology Listing 3 and Virology Listing 4

Figure 21. GS-US-380-1878: RAP and Genotype Disposition through Week 48



B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; RAP = resistance analysis population; RT = reverse transcriptase; SBR = stay on baseline regimen

a RAP criteria are summarized in PC-380-2005, Section 2.2.

b The final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

Source: GS-US-380-1878, Virology Listings 3 and Virology Listing 4

Table 57. GS-US-380-1878: Details of Subjects in the Week 48 RAP

Final RAP	Subject ID	Treatment Group	Time Point	HIV-1 RNA (copies/mL)[a]	CD4 (cells/µL)	Subtype	Resistance-associated Mutations[b]		Drug Susceptibility (Fold Change from WT)[c]						
							IN	RT	BIC	DRV	ATV	ABC	3TC	FTC	TFV[c]
Yes	06748-4201[d]	B/F/TAF	BL	28	432	B	none	**K70K/R**, **M184M/V**	na	na	na	na	na	na	na
			W12	2,860	560	B	none	**M184V**	0.78	0.79	1.01	3.51	>141	>95	0.54
No	05126-4279	B/F/TAF	BL	19	805	B	S119P	**K103N**	na	na	na	na	na	na	na
			W36	1,500	804[e]	B	af	af	af	af	af	af	af	af	af
No	00433-4598	SBR (DRV/COBI + FTC/TDF)	BL	19	308	B	none	V106V/I	na	na	na	na	na	na	na
			W8	384	307[e]	B	af	none	af	0.49	0.97	0.79	1.14	1.03	0.86
No	02825-4606	SBR (DRV/COBI + FTC/TDF)	BL	19	425	B	M50M/I	none	na	na	na	na	na	na	na
			W12	357	250[e]	B	af	none	af	0.56	0.72	1.00	1.30	1.26	0.82
Yes	00608-4660	SBR (ATV + RTV + FTC/TDF)	BL	19	431	B	S119S/A/G/T	**K103N**	na	na	na	na	na	na	na
			W36	1,580	385[e]	B	none	**K103N E138E/K**	0.84	0.33	0.51	1.01	1.05	1.23	0.85
			W48	982	858	B	nd	**K103N E138E/K**	nd	0.41	0.54	0.81	1.06	0.98	0.85
Yes	01236-4680	SBR (DRV/COBI + FTC/TDF)	BL	99,900	424	B	none	V90I **M184I**	0.89	0.47	0.64	2.17	>141	>95	0.50
			W8	1060	328[e]	B	none	V90I **M184I**	0.84	0.43	0.69	2.31	>127	>94	0.50
Yes	00554-4695	SBR (DRV + RTV + ABC/3TC)	BL	6,980	606	B	none	**M230M/I** V118I	af	0.64	0.97	0.94	1.02	1.09	0.92
			W4	874	421	B	af	**L74L/V**, V118I	af	0.80	0.86	1.22	1.17	1.35	0.85

3TC = lamivudine; ABC = abacavir; ABC/3TC = abacavir/lamivudine; AF = assay failure; ATV = atazanavir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BL = baseline/Day 1; COBI = cobicistat; DRV = darunavir; FTC = emtricitabine; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; IN = integrase; na = not applicable; nd = not determined; -R = resistance; RT = reverse transcriptase; RAP = resistance analysis population; RTV = ritonavir; SBR = stay on baseline regimen; TFV = tenofovir

a Baseline viral load is Day 1 BL visit. Undetectable HIV-1 RNA or values < 20 copies/mL were imputed as 19.

b Baseline sequences are the composite of screening and baseline data. Drug resistance mutations are defined in PC-380-2005, Table 2. Primary resistance mutations are shown in bold text and secondary resistance mutations are shown in plain text. Complete genotypic and phenotypic results are presented in GS-US-380-1878 Virology Listing 3 and Virology Listing 4.

c Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical or biological cutoffs were as follows: BIC = 2.5, DRV = 10, ATV = 5.2, ABC = 4.5, 3TC = 3.5, FTC = 3.5, TFV = 1.4. The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF.

d Adherence was < 95%

e CD4 cell count was not assessed at study visit. CD4 cell count from prior or following visit in the same analysis window is reported.

Source: GS-US-380-1878, Virology Listing 3 and Virology Listing 4

4.2.1.1.4.5. Resistance Conclusions

For Study GS-US-380-1878, the prevalence of baseline RAMs and HIV-1 subtypes was comparable across the B/F/TAF and SBR treatment groups. The presence of RAMs at baseline and HIV-1 subtype had no impact on treatment outcomes.

The RAP was comprised of 7 subjects who experienced virologic failure during the first 48 weeks of the study. Two subjects were from the B/F/TAF group (0.7%, 2 of 290 subjects) and 5 subjects were from the SBR group (1.7%, 5 of 287 subjects).

Three of the 7 subjects who met virologic failure criteria remained on study drugs and subsequently had HIV-1 RNA < 50 copies/mL: 1 subject was from the B/F/TAF group and 2 subjects were from the SBR group. These 3 subjects were not included in the final RAP.

The final RAP included 4 subjects; 1 subject was from the B/F/TAF group and 3 subjects were from the SBR group. No subject in the B/F/TAF group developed treatment emergent drug resistance in RT or IN. One subject in the SBR group developed a treatment emergent ABC resistance mutation in RT, L74V as a mixture with wild-type, at Week 4.

4.2.1.2. Integrated Virology Analyses at Baseline and in Subjects Experiencing Virologic Failure

Integrated virology analyses were performed for the Phase 3 Studies GS-US-380-1489 and GS-US-380-1490. The resistance analyses from the 2 separate Phase 3 studies are based on at least 48 weeks of treatment in the majority of subjects.

Resistance analyses were performed on plasma samples for all subjects who were included in the RAP. All of the integrated analyses were performed using initial RAP. None of the subjects in the B/F/TAF groups with data had emergence of drug resistance mutations to study drugs.

4.2.1.2.1. Study Design, Baseline Characteristics, and Viral Response for Studies GS-US-380-1489 and GS-US-380-1490

Study GS-US-380-1489 is an ongoing phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF versus ABC/DTG/3TC in HIV-1 infected, antiretroviral treatment-naive adults.

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

- **Treatment Group 1:** FDC of B/F/TAF (50/200/25 mg) + placebo-to-match FDC of ABC/DTG/3TC administered orally, once daily, without regard to food (n = 314)

- **Treatment Group 2**: FDC of ABC/DTG/3TC (600/50/300 mg) + placebo-to-match FDC of B/F/TAF administered orally, once daily, without regard to food (n = 315)

Study GS-US-380-1490 is an ongoing phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF versus DTG + F/TAF in HIV-1 infected, antiretroviral treatment-naive adults.

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

- **Treatment Group 1:** FDC of B/F/TAF (50/200/25 mg) + placebo-to-match DTG + F/TAF administered orally, once daily, without regard to food (n = 320)
- **Treatment Group 2:** DTG (50 mg) + F/TAF (200/25 mg) + placebo-to-match FDC of B/F/TAF administered orally, once daily, without regard to food (n = 325)

Randomization in both studies was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL) at screening, CD4+ cell count (< 50 cells/µL, 50-199 cells/µL, or ≥ 200 cells/µL) at screening, and region (US vs ex-US) at randomization.

Results from the Integrated Week 48 efficacy analysis using the Food and Drug Administration (FDA)-defined snapshot algorithm demonstrated high and comparable rates of virologic success (HIV-1 RNA < 50 copies/mL) for HIV-1 infected adults treated with B/F/TAF (90.9%), ABC/DTG/3TC (93.0%), and DTG + F/TAF (92.9%).

4.2.1.2.2. Baseline Virology Data for Studies GS-US-380-1489 and GS-US-380-1490

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 1274 subjects in the FAS from Studies GS-US-380-1489 and GS-US-380-1490 (Table 58). Consistent with enrollment criteria, all subjects demonstrated full sensitivity to FTC and TAF based on the proprietary algorithm from [redacted] (Integrated Virology Listing 2). Additional baseline genotypic data was obtained for those subjects who qualified for inclusion in the RAP and those data are also included in the summary of pretreatment mutations.

No IN genotyping was conducted at screening in the study, but baseline IN genotypic data was obtained retrospectively for 1267 of 1274 subjects. The baseline IN genotyping for 7 subjects was missing or failed primarily due to low viral load.

Pretreatment primary INSTI resistance mutations were infrequent and were present in 1.3% (16 of 1267) of subjects with IN data and consisted of T97A in 15 subjects and Q148H in 1 subject.

Pretreatment primary NRTI-associated resistance mutations were observed in 2.0% (26 of 1274) of subjects and consisted of M41L (n = 7), D67N (n = 4), K70R (n = 3), L74V (n = 1), Y115F (n = 1), L210W (n = 1), and K219E/N/Q/R (n = 12).

Pretreatment primary NNRTI-associated resistance mutations were observed in 13.2% (168 of 1274) of subjects with the most frequent substitutions consisting of K103N/S (n = 89) or E138A/G/K/Q (n = 53).

Pretreatment primary PI-associated resistance mutations were observed in 2.9% (37 of 1274) of subjects with the most frequent substitutions consisting of M46I/L (n = 14), Q58E (n = 11), or L90M (n = 9).

Overall, the prevalence of baseline RAMs was similar across all 3 treatment groups (Table 58).

Table 58. Integrated Analysis: IN, RT, and PR Mutations Detected Pretreatment for Studies GS-US-380-1489 and GS-US-380-1490

Mutation Class[a]	Number of Subjects, n (%)			
	B/F/TAF 380-1489,1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	All (N = 1274)
Primary INSTI-R	6 (1.0)	4 (1.3)	6 (1.9)	16 (1.3)
Average Number of Primary INSTI-R Mutations	1.0	1.0	1.0	1.0
T97A	5 (0.8)	4 (1.3)	6 (1.9)	15 (1.2)
Q148H	1 (0.2)	0	0	1 (0.1)
Secondary INSTI-R	325 (51.5)	152 (48.4)	158 (49.1)	635 (50.1)
Average Number of Secondary INSTI-R Mutations	1.2	1.2	1.2	1.2
M50I	124 (19.7)	47 (15.0)	60 (18.6)	231 (18.2)
H51Y	0	1 (0.3)	1 (0.3)	2 (0.2)
L68I/V	4 (0.6)	2 (0.6)	2 (0.6)	8 (0.6)
V72T	3 (0.5)[c]	1 (0.3)	3 (0.9)	7 (0.6)[c]
L74M	1 (0.2)	5 (1.6)	2 (0.6)	8 (0.6)
Q95K	1 (0.2)	0	0	1 (0.1)
S119P/R/T	197 (31.2)	103 (32.8)	99 (30.7)	399 (31.5)
A128T	3 (0.5)	0	0	3 (0.2)
E138A/K	1 (0.2)	2 (0.6)	2 (0.6)	5 (0.4)
G140S	1 (0.2)	0	0	1 (0.1)
Q146R	1 (0.2)	0	0	1 (0.1)
S153A	3 (0.5)	1 (0.3)	2 (0.6)	6 (0.5)
E157K/Q	35 (5.5)	12 (3.8)	12 (3.7)	59 (4.7)
G163K/R	6 (1.0)	5 (1.6)	6 (1.9)	17 (1.3)
Primary NRTI-R	16 (2.5)	5 (1.6)	5 (1.5)	26 (2.0)
Average Number of Primary NRTI-R Mutations	1.2	1.0	1.0	1.1
Any TAM	16 (2.5)	4 (1.3)	5 (1.5)	25 (2.0)
M41L	4 (0.6)	2 (0.6)	1 (0.3)	7 (0.5)
K65R/E/N	0	0	0	0
D67N	3 (0.5)	1 (0.3)	0	4 (0.3)
K70R	2 (0.3)	0	1 (0.3)	3 (0.2)
L74V	1 (0.2)	0	0	1 (0.1)
Y115F	0	1 (0.3)	0	1 (0.1)
L210W	0	0	1 (0.3)	1 (0.1)
K219E/N/Q/R	9 (1.4)	1 (0.3)	2 (0.6)	12 (0.9)

Mutation Class[a]	Number of Subjects, n (%)			
	B/F/TAF 380-1489,1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	All (N = 1274)
Primary NNRTI-R	76 (12.0)	51 (16.2)	41 (12.6)	168 (13.2)
Average Number of Primary NNRTI-R Mutations	1.1	1.1	1.1	1.1
L100I	3 (0.5)	0	0	3 (0.2)
K101E/P	5 (0.8)	2 (0.6)	0	7 (0.5)
K103N/S	41 (6.5)	27 (8.6)	21 (6.5)	89 (7.0)
V106A	0	1 (0.3)	2 (0.6)	3 (0.2)
V108I	0	3 (1.0)	2 (0.6)	5 (0.4)
E138A/G/K/Q	24 (3.8)	16 (5.1)	13 (4.0)	53 (4.2)
V179L	0	0	1 (0.3)	1 (0.1)
Y181C	3 (0.5)	2 (0.6)	1 (0.3)	6 (0.5)
Y188L	1 (0.2)	2 (0.6)	1 (0.3)	4 (0.3)
G190A/Q/S	5 (0.8)	1 (0.3)	3 (0.9)	9 (0.7)
H221Y	1 (0.2)	1 (0.3)	0	2 (0.2)
P225H	3 (0.5)	1 (0.3)	1 (0.3)	5 (0.4)
M230I	1 (0.2)	0	0	1 (0.1)
Primary PI-R	16 (2.5)	11 (3.5)	10 (3.1)	37 (2.9)
Average Number of Primary PI-R Mutations	1.2	1.0	1.5	1.2
D30N	2 (0.3)	1 (0.3)	0	3 (0.2)
V32I	1 (0.2)	0	1 (0.3)	2 (0.2)
M46I/L	6 (0.9)	3 (1.0)	5 (1.5)	14 (1.1)
I50L	1 (0.2)	0	0	1 (0.1)
Q58E	3 (0.5)	5 (1.6)	3 (0.9)	11 (0.9)
L76V	0	0	1 (0.3)	1 (0.1)
V82A/L	3 (0.5)	0	0	3 (0.2)
I84V	0	0	1 (0.3)	1 (0.1)
L90M	3 (0.5)	2 (0.6)	4 (1.2)	9 (0.7)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide;
DTG = dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide; INSTI = integrase strand transfer inhibitor;
NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor;
PI = protease inhibitor; -R = resistance; TAM = thymidine analogue mutation
a Drug resistance mutations are defined in PC-380-2003, Table 2.
b Denominator for the IN gene analyses are 631 B/F/TAF; 314 ABC/DTG/3TC; 322 for DTG + F/TAF; 1267 All.
c One patient had V72T at Day 1 at 2.83% and was included in this analysis.
Source: Integrated Virology Listing 1 and Integrated Virology Listing 2

The HIV-1 subtype was determined for each subject using the screening RT/PR genotype. The prevalence of different subtypes was comparable across all three treatment groups, with subtype B predominant in both groups (89.3% overall, 1138 of 1274 subjects) (Table 59).

Table 59. Integrated Analysis: HIV-1 Subtypes for Studies GS-US-380-1489 and GS-US-380-1490

HIV-1 Subtype	Number of Subjects, n (%)			
	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	All (N = 1274)
Subtype B	563 (88.8)	286 (90.8)	289 (88.9)	1138 (89.3)
Non-B Subtype	71 (11.2)	29 (9.2)	36 (11.1)	136 (10.7)
Subtype A	0	1 (0.3)	1 (0.3)	2 (0.2)
Subtype A1	10 (1.6)	8 (2.5)	5 (1.5)	23 (1.8)
Subtype AE	7 (1.1)	1 (0.3)	6 (1.8)	14 (1.1)
Subtype AG	14 (2.2)	4 (1.3)	3 (0.9)	21 (1.6)
Subtype BC	1 (0.2)	1 (0.3)	0	2 (0.2)
Subtype BF	4 (0.6)	2 (0.6)	3 (0.9)	9 (0.7)
Subtype C	8 (1.3)	1 (0.3)	7 (2.2)	16 (1.3)
Subtype D	1 (0.2)	1 (0.3)	2 (0.6)	4 (0.3)
Subtype F	0	0	1 (0.3)	1 (0.1)
Subtype F1	5 (0.8)	4 (1.3)	2 (0.6)	11 (0.9)
Subtype F2	1 (0.2)	1 (0.3)	0	2 (0.2)
Subtype G	1 (0.2)	0	1 (0.3)	2 (0.2)
Subtype H	1 (0.2)	0	0	1 (0.1)
Complex Subtype	18 (2.8)	5 (1.6)	5 (1.5)	28 (2.2)

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide
Source: Integrated Virology Listing 2

4.2.1.2.3. Impact of Pretreatment Mutations and Subtype on Treatment Outcomes for Studies GS-US-380-1489 and GS-US-380-1490

The impact of pretreatment RAMs as well as subtype on treatment outcomes was assessed for all subjects in the FAS. For the subtype analysis, subtype B versus non-B subtype was evaluated. For the baseline RAM analysis, the presence or absence of primary INSTI-R, T97A, Q148H, secondary INSTI-R, primary NRTI-R, TAMs, K103N/S, primary NNRTI-R, and primary PI-R were evaluated.

No impact of pretreatment RAMs or subtype reaching HIV-1 RNA < 50 copies/mL at Week 48 or virologic failure (HIV-1 RNA ≥ 50 copies/mL) for all treatment groups ($p > 0.05$ for all comparisons) (Table 60).

In the B/F/TAF group, all 5 subjects with T97A and the one subject with Q148H + G140S in IN at baseline achieved HIV-1 RNA < 50 copies/mL at Week 4 and maintained HIV-1 RNA < 50 copies/mL through Week 48.

Table 60. Integrated Analysis: FDA Snapshot Outcome of Subjects at Week 48 by Baseline Virologic Category for Studies GS-US-380-1489 and GS-US-380-1490

	Number of Subjects n (%)								
	B/F/TAF 380-1489, 1490 (N = 634)			ABC/DTG/3TC 380-1489 (N = 315)			DTG + F/TAF 380-1490 (N = 325)		
Category[a]	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data
All Subjects	576/634 (90.9)	17/634 (2.7)	41/634 (6.5)	293/315 (93.0)	8/315 (2.5)	14/315 (4.4)	302/325 (92.9)	4/325 (1.2)	19/325 (5.8)
HIV-1 Subtype B	513/563 (91.1)	16/563 (2.8)	34/563 (6.0)	266/286 (93.0)	8/286 (2.8)	12/286 (4.2)	269/289 (93.1)	3/289 (1.0)	17/289 (5.9)
HIV-1 Subtype Non-B	63/71 (88.7)	1/71 (1.4)	7/71 (9.9)	27/29 (93.1)	0/29 (0)	2/29 (6.9)	33/36 (91.7)	1/36 (2.8)	2/36 (5.6)
P-Value	0.51	0.71	0.2	1.0	1.0	0.38	0.73	0.38	1.0
Primary INSTI-R	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	3/4 (75.0)	0/4 (0.0)	1/4 (25.0)	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)
No Primary INSTI-R	569/625 (91.0)	17/625 (2.7)	39/625 (6.2)	289/310 (93.2)	8/310 (2.6)	13/310 (4.2)	294/316 (93.0)	3/316 (0.9)	19/316 (6.0)
P-Value	1.0	1.0	1.0	0.25	1.0	0.17	1.0	1.0	1.0
T97A in IN	5/5 (100.0)	0/5 (0.0)	0/5 (0.0)	3/4 (75.0)	0/4 (0.0)	1/4 (25.0)	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)
No T97A in IN	570/626 (91.1)	17/626 (2.7)	39/626 (6.2)	289/310 (93.2)	8/310 (2.6)	13/310 (4.2)	294/316 (93.0)	3/316 (0.9)	19/316 (6.0)
P-Value	1.0	1.0	1.0	0.25	1.0	0.17	1.0	1.0	1.0
Q148H in IN	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	0	0	0	0	0	0
No Q148H in IN	574/630 (91.1)	17/630 (2.7)	39/630 (6.2)	292/314 (93.0)	8/314 (2.5)	14/314 (4.5)	300/322 (93.2)	3/322 (0.9)	19/322 (5.9)
P-Value	1.0	1.0	1.0	NA	NA	NA	NA	NA	NA
Secondary INSTI-R	298/325 (91.7)	7/325 (2.2)	20/325 (6.2)	140/152 (92.1)	5/152 (3.3)	7/152 (4.6)	149/158 (94.3)	1/158 (0.6)	8/158 (5.1)
No Secondary INSTI-R	277/306 (90.5)	10/306 (3.3)	19/306 (6.2)	152/162 (93.8)	3/162 (1.9)	7/162 (4.3)	151/164 (92.1)	2/164 (1.2)	11/164 (6.7)
P-Value	0.67	0.46	1.0	0.66	0.49	1.0	0.51	1.0	0.64

	Number of Subjects n (%)								
	B/F/TAF 380-1489, 1490 (N = 634)			ABC/DTG/3TC 380-1489 (N = 315)			DTG + F/TAF 380-1490 (N = 325)		
Category[a]	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data	HIV-1 RNA < 50 copies/mL	HIV-1 RNA ≥ 50 copies/mL	No data
Primary NRTI-R	14/16 (87.5)	0/16 (0.0)	2/16 (12.5)	5/5 (100.0)	0/5 (0.0)	0/5 (0.0)	4/5 (80.0)	0/5 (0.0)	1/5 (20.0)
No Primary NRTI-R	562/618 (90.9)	17/618 (2.8)	39/618 (6.3)	288/310 (92.9)	8/310 (2.6)	14/310 (4.5)	298/320 (93.1)	4/320 (1.2)	18/320 (5.6)
P-Value	0.65	1.0	0.28	1.0	1.0	1.0	0.31	1.0	0.26
TAMs in RT	14/16 (87.5)	0/16 (0.0)	2/16 (12.5)	4/4 (100.0)	0/4 (0.0)	0/4 (0.0)	4/5 (80.0)	0/5 (0.0)	1/5 (20.0)
No TAMs in RT	562/618 (90.9)	17/618 (2.8)	39/618 (6.3)	289/311 (92.9)	8/311 (2.6)	14/311 (4.5)	298/320 (93.1)	4/320 (1.2)	18/320 (5.6)
P-Value	0.65	1.0	0.28	1.0	1.0	1.0	0.31	1.0	0.26
Primary NNRTI-R	68/76 (89.5)	0/76 (0.0)	8/76 (10.5)	48/51 (94.1)	0/51 (0.0)	3/51 (5.9)	38/41 (92.7)	1/41 (2.4)	2/41 (4.9)
No Primary NNRTI-R	508/558 (91.0)	17/558 (3.0)	33/558 (5.9)	245/264 (92.8)	8/264 (3.0)	11/264 (4.2)	264/284 (93.0)	3/284 (1.1)	17/284 (6.0)
P-Value	0.67	0.25	0.13	1.0	0.36	0.48	1.0	0.42	1.0
K103N/S in RT	38/41 (92.7)	0/41 (0.0)	3/41 (7.3)	25/27 (92.6)	0/27 (0.0)	2/27 (7.4)	20/21 (95.2)	0/21 (0.0)	1/21 (4.8)
No K103N/S in RT	538/593 (90.7)	17/593 (2.9)	38/593 (6.4)	268/288 (93.1)	8/288 (2.8)	12/288 (4.2)	282/304 (92.8)	4/304 (1.3)	18/304 (5.9)
P-Value	1.0	0.618	0.742	1.0	1.0	0.341	1.0	1.0	1.0
Primary PI-R	15/16 (93.8)	0/16 (0.0)	1/16 (6.2)	10/11 (90.9)	0/11 (0.0)	1/11 (9.1)	10/10 (100.0)	0/10 (0.0)	0/10 (0.0)
No Primary PI-R	561/618 (90.8)	17/618 (2.8)	40/618 (6.5)	283/304 (93.1)	8/304 (2.6)	13/304 (4.3)	292/315 (92.7)	4/315 (1.3)	19/315 (6.0)
P-Value	1.0	1.0	1.0	0.56	1.0	0.4	1.0	1.0	1.0

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide; IN = integrase; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistance; RT = reverse transcriptase

a Drug resistance mutations are defined in PC-380-2003, Table 2.

P-value was determined using Fisher's exact test.

Source: Integrated Virology Listing 1 and Integrated Virology Listing 2

4.2.1.2.4. Resistance Analysis in Subjects Experiencing Virologic Failure Through Week 48 for Studies GS-US-380-1489 and GS-US-380-1490

Of the 1274 FAS subjects in Studies GS-US-380-1489 and GS-US-380-1490, 17 (1.3%) met the VF and RAP inclusion criteria through Week 48. Reasons for inclusion in the RAP were confirmed VF (7 subjects), > 200 copies/mL at last visit at or after Week 8 (early study discontinuation or lost to follow-up) (8 subjects), or > 200 copies at the last measurement in the Week 48 window (2 subjects) (Integrated Virology Listing 4).

The RAP was comprised of 8 subjects (1.3%, 8 of 634) in the B/F/TAF group, 4 subjects (1.3%, 4 of 315) in the ABC/DTG/3TC group, and 5 subjects (1.5%, 5 of 325) in the DTG + F/TAF group (Figure 22, Table 61). The final RAP (which did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs) was comprised of 8 subjects (1.3%, 8 of 634) in the B/F/TAF group, 2 subjects (0.6%, 2 of 315) in the ABC/DTG/3TC group, and 3 subjects (0.9%, 3 of 325) in the DTG + F/TAF group.

Eight subjects in the B/F/TAF group were included in the RAP and were evaluated for the development of resistance through Week 48. None of these subjects achieved HIV-1 RNA resuppression to < 50 copies/mL, however, none had follow-up HIV-1 RNA data available. Postbaseline genotypic and phenotypic data were available for PR/RT and IN from all 8 subjects. None of the 8 subjects in the B/F/TAF group RAP had resistance mutations emerge (Table 61 and Table 62). Other substitutions in IN and/or RT that developed were at polymorphic sites; none of these changes were associated with a phenotypic change to BIC, FTC, or TFV (Table 62).

Table 61. Integrated Summary: HIV-1 Genotypic Resistance through Week 48 for Studies GS-US-380-1489 and GS-US-380-1490

	Number of Subjects, n (%)			
Resistance Category[a]	**B/F/TAF 380-1489, 1490 (N = 634)**	**ABC/DTG/3TC 380-1489 (N = 315)**	**DTG + F/TAF 380-1490 (N = 325)**	**P-Value[b]**
RAP (% of FAS)	8 (1.3)	4 (1.3)	5 (1.5)	1.00; 0.77
Subjects with Data (Any Gene)	8 (100)	3 (75)	5 (100)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	0	2 (50)	2 (40)	
Final RAP[c] (% of FAS)	8 (1.3)	2 (0.6)	3 (0.9)	0.51; 0.76
Subjects with Data (Any Gene)	8 (100)	1 (50)	3 (100)	
Developed Resistance Mutations to Study Drugs (% of FAS)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Developed Resistance Mutations to Study Drugs (% of Final RAP)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Developed Any INSTI-R	0	0	0	
Developed Primary NRTI-R	0	0	0	
Developed Primary NNRTI-R	0	0	0	
Developed Primary PI-R	0	0	0	

3TC = lamivudine; ABC = abacavir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; FAS = full analysis set; INSTI = integrase strand transfer inhibitor; INSTI = integrase strand transfer inhibitor; NA = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance

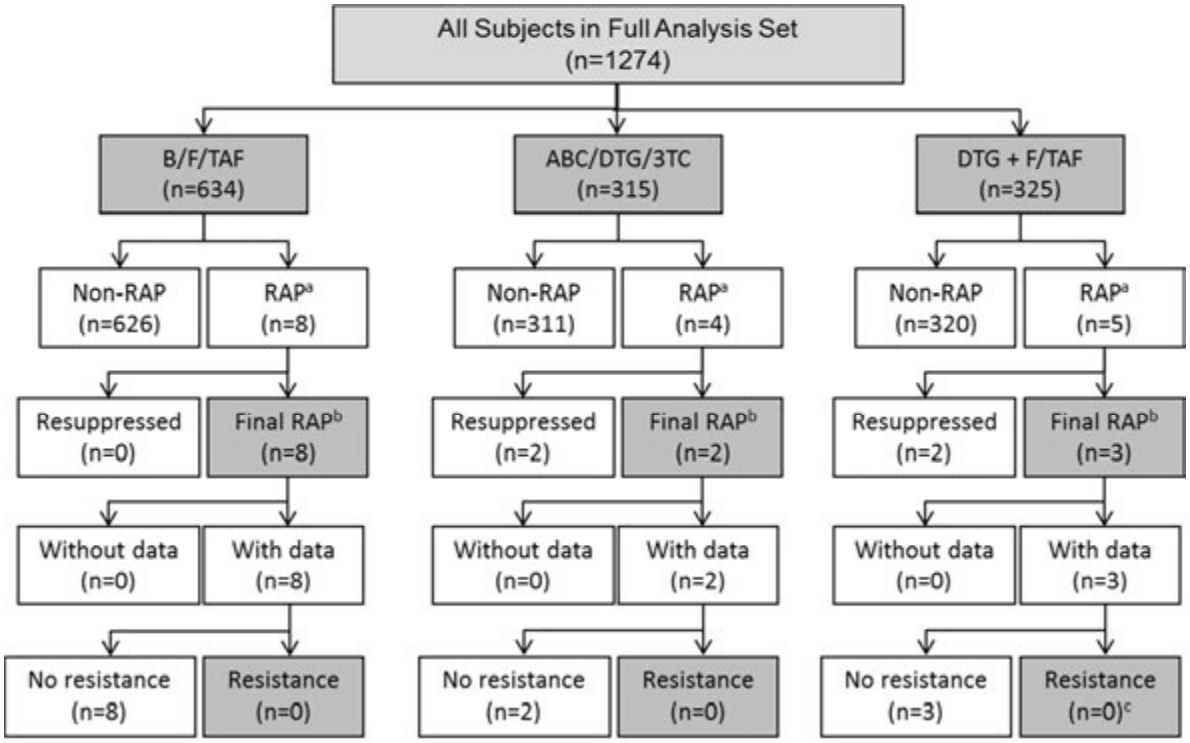
a Drug resistance mutations are defined in PC-380-2003, Table 2.

b P-value determined using Fisher's exact test; (B/F/TAF vs ABC/DTG/3TC; B/F/TAF vs DTG + F/TAF)

c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

Source: Integrated Virology Listing 3 and Integrated Virology Listing 4

Figure 22. Integrated Analysis: RAP and Genotypic Disposition through Week 48 for Studies GS-US-380-1489 and GS-US-380-1490



3TC = lamivudine; ABC = abacavir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DTG = dolutegravir; F/TAF = emtricitabine/tenofovir alafenamide; RAP = resistance analysis population

a RAP criteria are summarized in PC-380-2003, Section 2.2.

b The final RAP did not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

c One subject in the DTG + F/TAF group had K103K/N at baseline and Week 48.

Source: Integrated Virology Listing 3 and Integrated Virology Listing 4

Table 62. Integrated Analysis: Details of Subjects in the Week 48 RAP for Studies GS-US-380-1489 and GS-US-380-1490

Final RAP	Subject ID	Treatment Group	Time Point	HIV-1 RNA (copies/mL)[a]	CD4 (cells/µL)	Subtype	Resistance-associated Mutations[b]		Drug Susceptibility (Fold Change from WT)[c]					
							IN	RT	BIC	DTG	ABC	3TC	FTC	TFV[c]
Yes	00729-1609[d]	B/F/TAF	BL	6,370	502	B	none	none	0.80	0.95	0.80	1.23	0.97	0.68
			W36	2,120	452	B	none	none	0.68	0.98	0.79	1.21	1.17	0.68
			W48	4,450	387	B	none	none	0.87	0.97	0.84	1.29	1.21	0.77
Yes	00031-2093[d]	B/F/TAF	BL	97,200	2	B	none	none	0.96	1.16	0.85	1.24	1.09	0.76
			W8	19,000	11	B	none	none	0.87	0.85	0.57	0.97	0.94	0.60
Yes	01543-2111[d]	B/F/TAF	BL	184,000	430	B	S119P	V179V/D	af	af	1.06	1.13	0.94	1.04
			W36	8,630	462	B	S119P	none	0.59	0.84	1.04	1.16	0.99	1.17
Yes	01624-2140[d]	B/F/TAF	BL	2,770	948	B	none	none	0.93	0.99	1.03	1.06	0.85	1.01
			W24	4,440	801	B	none	none	0.92	0.90	1.01	0.96	0.85	1.06
Yes	11678-2182	B/F/TAF	BL	3,830,000	31	B	none	none	0.79	0.91	0.82	0.94	0.95	1.04
			W24	967	217	B	none	none	0.97	0.84	0.99	1.35	1.00	1.25
			W48	688	195	B	none	none	0.81	0.88	0.86	1.00	0.91	1.03
Yes	02511-2326	B/F/TAF	BL	25,200	943	B	V72T/I[e] S119P	none	nd	nd	af	af	af	af
			W48	22,200	954	B	V72T/I S119P	none	0.84	0.95	1.25	1.53	1.26	1.19
Yes	02035-2333	B/F/TAF	BL	16,800	900	B	S119P E157E/K	none	0.95	1.00	1.00	1.02	1.02	0.77
			W24	23,400	742	B	S119P	none	0.90	1.10	1.07	1.06	1.01	0.88
Yes	01624-2534[d]	B/F/TAF	BL	3,560,000	289	B	S119P	none	0.91	0.98	0.97	1.26	0.97	0.79
			W8	317,000	533	B	S119P	none	0.79	0.88	0.91	0.95	1.07	0.82
No	02825-1085[d]	ABC/DTG/3TC	BL	38,100	717	B	S119T	none	0.77	0.91	0.66	0.96	0.79	0.78
			W24	30,000	519	B	S119T	none	0.68	0.69	0.63	0.84	0.93	0.79
			W48	23,300	564	B	S119T	none	0.61	0.88	0.69	0.88	0.85	0.86
Yes	01598-1106[d]	ABC/DTG/3TC	BL	55,600	307	B	S119P	none	0.59	0.51	0.95	1.41	1.26	1.00
			W24	80,100	361	B	S119P	none	0.46	0.49	1.06	1.66	1.57	1.05

Final RAP	Subject ID	Treatment Group	Time Point	HIV-1 RNA (copies/mL)[a]	CD4 (cells/µL)	Subtype	Resistance-associated Mutations[b]		Drug Susceptibility (Fold Change from WT)[c]					
							IN	RT	BIC	DTG	ABC	3TC	FTC	TFV[c]
Yes	11572-1263[d]	ABC/DTG/3TC	BL	15,700	712	B	M50I	none	0.61	0.76	af	af	af	af
			W48	3,000	604	B	af	af	af	af	af	af	af	af
No	02838-1390[d]	ABC/DTG/3TC	BL	75,000	387	B	none	none	0.78	0.81	0.89	0.79	0.83	0.81
			W36	204	404[f]	B	af	none	af	af	0.85	0.91	0.82	0.70
Yes	02106-2037	DTG+F/TAF	BL	42,300	358	B	none	none	1.04	0.98	0.85	1.02	0.98	0.76
			W8	22,800	278	B	af	none	af	af	0.87	0.96	0.87	0.81
Yes	00031-2272[d]	DTG+F/TAF	BL	23,800	8	B	M50M/I	**K103K/N**	af	af	1.00	1.40	1.55	0.87
			W48	221	228	B	af	**K103K/N**	af	af	af	af	af	af
No	00310-2435[d]	DTG+F/TAF	BL	25,000	315	B	M50I E157E/K	T69D	0.82	0.73	0.95	1.58	1.31	0.89
			W24	362	390[f]	B	M50I	T69A/D	0.96	0.91	0.94	1.21	1.24	0.93
Yes	01942-2507[d]	DTG+F/TAF	BL	56,400	385	B	none	none	0.76	1.00	0.74	0.74	0.83	0.91
			W12	5,480	279[f]	B	none	none	0.84	0.93	0.90	0.93	0.89	0.99
			W36	12,000	339	B	none	none	0.82	0.98	0.68	0.83	0.89	0.86
No	00310-2556[d]	DTG+F/TAF	BL	42,700	442	B	none	none	0.72	0.88	0.83	1.15	0.99	0.93
			W36	1,140	779	B	none	none	0.66	1.06	0.87	0.98	1.12	0.91

3TC = lamivudine; ABC = abacavir; ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; af = assay failure; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BL = baseline/Day 1; DTG = dolutegravir; FTC = emtricitabine; IN = integrase; nd = no data available; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistance; RT = reverse transcriptase; TFV = tenofovir; W = week

a Baseline viral load is the Day 1 BL visit.

b Drug resistance mutations are defined in PC-380-20013, Table 2. Baseline sequences are the composite of screening and baseline data. Primary resistance-associated mutations are shown in bold text and secondary resistance-associated mutations are shown in plain text. Complete genotypic and phenotypic results are presented in Integrated Virology Listing 3 and Integrated Virology Listing 4.

c Phenotypic fold change compared with wild-type control. Shaded cells represent a fold-change value ≥ the clinical cutoff for each drug. The clinical or biological cutoffs were as follows: BIC = 2.5, DTG = 4.0, ABC = 4.5, 3TC = 3.5, FTC = 3.5, TFV = 1.4. The Monogram Biosciences PhenoSense GT Assay was performed with TFV, the parent compound of TAF.

d Adherence was < 95% and/or there were unreturned pill bottles.

e Patient 02511-2326 had V72T present at 2.83% by deep sequencing at Day 1.

f CD4 cell count was not assessed at study visit. CD4 cell count from prior visit in the same analysis window is reported.

Source: Integrated Virology Listing 3 and Integrated Virology Listing 4

4.2.1.2.5. Integrated Resistance Conclusions of Studies GS-US-380-1489 and GS-US-380-1490

The prevalence of baseline RAMs and HIV-1 subtypes were comparable across the B/F/TAF, ABC/DTG/3TC, and DTG + F/TAF treatment groups. Baseline RAMs and HIV-1 subtype had no impact on treatment outcomes for all treatment groups.

Of the 1274 treated subjects from all arms across the 2 studies, 17 subjects experienced virologic failure during the first 48 weeks and comprised the resistance analysis population (RAP): 8 of 634 subjects from the combined B/F/TAF groups (1.3%), 4 of 315 subjects from the ABC/DTG/3TC group (1.3%), and 5 of 325 subjects from the DTG + F/TAF group (1.5%).

The final RAP included 13 subjects: 8 subjects (1.3%; 8 of 634) from the combined B/F/TAF groups, 2 subjects (0.6%; 2 of 315) from the ABC/DTG/3TC group, and 3 subjects (0.9%; 3 of 325) from the DTG + F/TAF group. Two subjects from the ABC/DTG/3TC group and 2 subjects from the DTG + F/TAF group resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs and were not included in the final RAP.

No subject in any group developed treatment emergent resistance to study drugs.

4.2.2. HIV/HBV

4.2.2.1. Virology Analysis in Subjects with HIV/HBV Coinfection in Study GS-US-292-1249

Study GS-US-292-1249 was a Phase 3b open-label, single-arm, dual-cohort, multicenter study of the safety, efficacy, and tolerability of E/C/F/TAF in HIV/HBV coinfected adult subjects (m2.7.4, Section 5.1.8.1.2). Data from HIV-suppressed subjects in Cohort 2 are summarized in this section and data from HIV/HBV-coinfected subjects in Cohort 1 are presented in the virology study report (PC-120-2024).

4.2.2.1.1. Baseline Virology Data

HBV baseline virology analyses were conducted on 7 (9.7%) HBV viremic subjects (HBV DNA ≥ 69 IU/mL) out of the 72 subjects included in the Full Analysis Set (FAS). Subjects were assessed for pre-existing resistance mutations using the INNO-LiPA Multi-DR v2/3 hybridization assay. Of the 7 viremic subjects that qualified for testing, 2 were classified as wild-type. Four subjects had primary lamivudine resistance (LAM-R) mutations detected. Four of the five subjects with LAM-R were in Cohort 2 (HIV-suppressed), which included treatment-experienced subjects. The remaining subject had an rtL180L/M substitution, which by itself does not confer resistance to any known HBV treatment.

4.2.2.1.2. Virology Analyses

Of the 72 HIV-suppressed subjects (Cohort 2) in Study GS-US-292-1249, 2 subjects met the virologic failure criteria through Week 48 and were not included in the HIV RAP (HIV-1 RNA < 400 copies/mL).

Of the 72 HIV-suppressed subjects in Study GS-US-292-1249, 67 of 72 subjects (93.1%) achieved HBV DNA < 69 IU/mL at Week 48. Three HIV-suppressed subjects discontinued the study prior to Week 24 with HBV DNA < 69 IU/mL. One HIV-suppressed subject had missing data at Week 48, but was below 29 IU/mL the visit before and after Week 48 and 1 HIV-suppressed subject (1.4%) had HBV DNA ≥ 69 IU/mL at Week 48 without virologic breakthrough (Table 63).

Table 63. GS-US-292-1249: Subject Disposition at Week 48 (Cohort 2)

Category n (%)	HIV-1 Suppressed (n = 72)
Discontinued Prior to Week 24 with HBV DNA < 69 IU/mL	3
HBV DNA < 69 IU/mL at Week 48	67
HBV DNA < 29 IU/mL	66
HBV DNA < 69 IU/mL but > 29 IU/mL	1
HBV DNA Missing at Random with HBV DNA < 69 copies/mL at the Flanking Visits	1
Sequence Analysis of pol/RT Conducted at Week 48	1
HBV DNA ≥ 69 IU/mL at Week 48 Without Virologic Breakthrough[a]	1
Experienced Virologic Breakthrough at Week 48	0
Discontinued at/after Week 24 with HBV DNA > 69 IU/mL	0

a Includes subjects who were persistently viremic through Week 48 and subjects with a virologic blip at Week 48
Source: GS-US-292-1249 Interim Week 48 CSR, Appendix 16.2, Listing 4.2.1

One HIV-suppressed subject qualified for HBV polymerase/reverse transcriptase (pol/RT) sequencing and results showed the subject had a reversion of a LAM compensatory mutation towards wild-type (rtL173V/L).

4.2.2.1.3. Resistance Conclusions

For Study GS-US-292-1249 through 48 weeks of treatment, no HBV-suppressed subjects were included in the HIV RAP in Cohort 2. One HIV-suppressed subject qualified for HBV sequence analysis, but no mutations associated with resistance to TAF were observed.

No subject had both persistent HIV and HBV observed through 48 weeks of E/C/F/TAF treatment.

4.2.3. HBV

4.2.3.1. Integrated Virology Analysis in Subjects with CHB in Studies GS-US-320-0108 and GS-US-320-0110

Integrated virology analyses were performed for the 2 Phase 3 Studies GS-US-320-0108 and GS-US-320-0110. A summary of the integrated analysis are described in the following sections. Full details of the clinical virology resistance analyses from the 2 TAF Phase 3 studies in subjects with chronic hepatitis B (CHB) as well as the integrated analysis are provided in the virology study report (PC-320-2009 and PC-320-2009 Amendment 2). A full description of the resistance analysis methodologies for TAF in CHB is provided in the virology analysis plan (PC-320-2002).

4.2.3.1.1. Study Design

Studies GS-US-320-0108 and GS-US-320-0110 are ongoing Phase 3, randomized, double-blind, noninferiority studies to evaluate the safety and efficacy of TAF 25 mg compared with TDF 300 mg in HBeAg-negative and HBeAg-positive subjects with CHB, respectively (m2.7.3, Section 3.3.3.3).

4.2.3.1.2. Baseline Virology Analyses

All subjects in the FAS for Studies GS-US-320-0108 (N = 425) and GS-US-320-0110 (N = 873) were assessed for the presence of preexisting resistance mutations in pol/RT at baseline using the HBV INNO-LiPA Multi-DR v2/v3 hybridization assay. In total, 1298 subjects were evaluated (866 in the TAF group, 432 in the TDF group) and results were successfully obtained for all subjects (Table 64). Overall, 89.2% of subjects (1158 of 1298) were classified as wild-type, with a higher percentage of oral antiviral (OAV)-naive subjects (92.4%) being classified as wild-type compared to OAV-experienced subjects (78.4%). The remaining 10.8% of subjects (140 of 1298) were found to harbor mutations in pol/RT, with the percentage of subjects with mutations higher for OAV-experienced subjects (21.6%) than for OAV-naive subjects (7.6%). The distribution of subjects with wild-type and mutant pol/RT was similar between treatment groups (TAF: 89.5% wild-type, 10.5% mutant; TDF: 88.7% wild-type, 11.3% mutant). Primary resistance mutations were observed in 5.4% of subjects overall (70 of 1298), with a higher percentage observed in OAV-experienced subjects (17.2%) compared to OAV-naive subjects (1.9%). LAM-R mutations were predominant, observed in 2.5% of subjects (32 of 1298). Overall, 5.4% of subjects (70 of 1298) harbored other mutations, with similar percentages observed between OAV-naive (5.7%) and OAV-experienced (4.4%) subjects. The distribution of primary resistance mutations and other mutations was similar between treatment groups (TAF: 4.7% primary resistance mutations, 5.8% other mutations; TDF: 6.7% primary resistance mutations, 4.6% other mutations).

Table 64. TAF Integrated Analysis: Summary of pol/RT Resistance Mutations Detected at Baseline

	TAF			TDF			All		
Resistance Category, n (%)	**OAV Naive (N = 669)**	**OAV Exp (N = 197)**	**All (N = 866)**	**OAV Naive (N = 333)**	**OAV Exp (N = 99)**	**All (N = 432)**	**OAV Naive (N = 1002)**	**OAV Exp (N = 296)**	**All (N = 1298)**
Wild type	616 (92.1)	159 (80.7)	775 (89.5)	310 (93.1)	73 (73.7)	383 (88.7)	926 (92.4)	232 (78.4)	1158 (89.2)
Mutant	53 (7.9)	38 (19.3)	91 (10.5)	23 (6.9)	26 (26.3)	49 (11.3)	76 (7.6)	64 (21.6)	140 (10.8)
Primary Mutation(s)[a]	11 (1.6)	30 (15.2)	41 (4.7)	8 (2.4)	21 (21.2)	29 (6.7)	19 (1.9)	51 (17.2)	70 (5.4)
LAM-R Mutation(s)	3 (0.4)	20 (10.2)	23 (2.7)	3 (0.9)	6 (6.1)	9 (2.1)	6 (0.6)	26 (8.8)	32 (2.5)
ADV-R Mutation(s)	8 (1.2)	2 (1.0)	10 (1.2)	4 (1.2)	5 (5.1)	9 (2.1)	12 (1.2)	7 (2.4)	19 (1.5)
ETV-R Mutation(s)	0	5 (2.5)	5 (0.6)	0	8 (8.1)	8 (1.9)	0	13 (4.4)	13 (1.0)
LAM-R+ADV-R Mutation(s)	0	3 (1.5)	3 (0.3)	1 (0.3)	2 (2.0)	3 (0.7)	1 (0.1)	5 (1.7)	6 (0.5)
Other Mutations[a]	42 (6.3)	8 (4.1)	50 (5.8)	15 (4.5)	5 (5.1)	20 (4.6)	57 (5.7)	13 (4.4)	70 (5.4)

ADV = adefovir dipivoxil; ETV = entecavir; Exp = experienced; LAM = lamivudine; OAV = oral antiviral; -R = resistant; TAF= tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

a Primary resistance mutations included rtM204V/I/S (LAM resistance); rtA181T/V, rtN236T (ADV resistance); and rtM204V/I ± rtT184X[e]± rtS202X ± rtM250X (ETV resistance). Other mutations included rtL80V/I, rtV173L, rtL180M, rtT184X, rtA194T, rtS202X, rtM250X, and unknown variants. X = any amino acid

Source: PC-320-2009, Section 5.2, Table 14

The HBV genotype was determined for 1296 of 1298 subjects at baseline. The genotype distribution was comparable between treatment groups, with genotype C predominant in both groups (47.5% overall, 617 of 1298 subjects) (Table 65).

Table 65. TAF Integrated Analysis: Summary of HBV Genotypes

HBV Genotype	Number of Subjects, n (%)		
	TAF (N = 866)	TDF (N = 432)	All (N = 1298)
A	54 (6.2)	31 (7.2)	85 (6.5)
B	160 (18.5)	88 (20.4)	248 (19.1)
C	418 (48.3)	199 (46.1)	617 (47.5)
D	224 (25.9)	105 (24.3)	329 (25.3)
E	7 (0.8)	3 (0.7)	10 (0.8)
F	3 (0.3)	2 (0.5)	5 (0.4)
H	0	2 (0.5)	2 (0.2)
Unknown	0	2 (0.5)	2 (0.2)

TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
Source: PC-320-2009, Section 5.2, Table 15

4.2.3.1.3. Week 48 Virology Analyses

Sequence analysis of the pol/RT region was attempted for any subject in Studies GS-US-320-0108 and GS-US-320-0110 who experienced virologic breakthrough at Week 48, as well as for any subject who discontinued the study at or after Week 24 with HBV DNA ≥ 69 IU/mL. Of the 1298 subjects in the FAS in Studies GS-US-320-0108 and GS-US-320-0110, the majority (1026 of 1298 subjects, 79%) achieved HBV DNA < 69 IU/mL, with a similar distribution between treatment groups (Table 66). One hundred ninety-one subjects (14.7%) remained viremic at Week 48 in the absence of virologic breakthrough. Overall, 38 subjects (2.9%) met the criteria for sequence analysis, with 29 subjects (2.2%) experiencing virologic breakthrough at Week 48 and 9 subjects (0.7%) discontinuing at or after Week 24 with HBV DNA ≥ 69 IU/mL.

Table 66. TAF Integrated Analysis: Subject Disposition at Week 48

Category, n (%)	TAF (N = 866)	TDF (N = 432)	All (N = 1298)
Discontinued Prior to Week 24	15 (1.7)	12 (2.8)	27 (2.1)
Discontinued at/after Week 24 with HBV DNA < 69 IU/mL	12 (1.4)	1 (0.2)	13 (1.0)
Missing Week 48 visit	2 (0.2)	1 (0.2)	3 (0.2)
HBV DNA < 69 IU/mL at Week 48	680 (78.5)	346 (80.1)	1026 (79.0)
HBV DNA < 29 IU/mL	639 (73.8)	325 (75.2)	964 (74.3)
HBV DNA < 69 IU/mL but ≥ 29 IU/mL	41 (4.7)	21 (4.9)	62 (4.8)
HBV DNA ≥ 69 IU/mL at Week 48 Without Virologic Breakthrough	133 (15.4)	58 (13.4)	191 (14.7)
Persistently viremic at Week 48	118 (13.6)	53 (12.3)	171 (13.2)
Virologic blip at Week 48[a]	15 (1.7)	5 (1.2)	20 (1.5)
Sequence Analysis of pol/RT Conducted at Week 48	24 (2.8)	14 (3.2)	38 (2.9)
Experienced Virologic Breakthrough at Week 48	16 (1.8)	13 (3.0)	29 (2.2)
Discontinued at/after Week 24 with HBV DNA ≥ 69 IU/mL	8 (0.9)	1 (0.2)	9 (0.7)

TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
a Includes subjects who did not reach their Week 56 visit (TAF: Subjects 6330-5137, 6963-5215, 8599-5171, 8599-5375, 9695-5332; TDF: Subject 2757-5265)
Source: PC-320-2009, Section 5.3, Table 19

4.2.3.1.3.1. Week 48 Virology Analyses: TAF

Twenty-four of 866 (2.8%) subjects in the TAF group qualified for sequence analysis, with 16 subjects experiencing virologic breakthrough at Week 48 and 8 subjects discontinuing at or after Week 24 with HBV DNA ≥ 69 IU/mL. Among the 24 subjects in the TAF treatment group who qualified for sequence analysis, 15 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, and 5 had polymorphic site substitutions (Table 67).

Table 67. TAF Integrated Analyses: Sequence Analysis Results for Subjects in the TAF Group Who Qualified for Testing Through Week 48

Subject	Baseline HBV DNA[a]	HBV DNA at Qualifying Timepoint[a]	Changes in HBV pol/RT at Qualifying Timepoint
1659-4788	8.03	4.00 (Week 48)	No change from baseline
4296-4510	7.86	2.05 (Week 48)	No change from baseline
5606-5140	8.40	5.04 (Week 48)	No change from baseline
5613-1163	7.53	2.15 (Week 48)	No change from baseline
5617-4966	8.55	3.07 (follow-up Week 4)	No change from baseline
5691-4944	8.67	5.99 (Week 48)	No change from baseline
6336-5050	4.63	4.11 (follow-up Week 4)	No change from baseline
6958-5201	8.69	5.22 (Week 48)	No change from baseline
6958-1318	7.81	3.19 (Week 48)	No change from baseline
6965-5170	7.22	2.36 (Week 36)	No change from baseline
7515-5071	8.52	5.10 (Week 28)	No change from baseline
8006-5282	9.09	3.16 (Week 48)	No change from baseline
8312-4689	6.79	6.97 (follow-up Week 4)	No change from baseline
8600-4558	8.58	2.42 (Week 48)	No change from baseline
9695-5283	8.80	5.70 (Week 24)	No change from baseline
4074-4571	4.28	3.43 (Week 48)	Unable to sequence
4164-5252	8.72	1.94 (Week 48)	Unable to sequence
5691-4594	8.27	2.23 (follow-up Week 4)	Unable to sequence
8569-5132	8.41	1.96 (Week 48)	Unable to sequence
2826-4527	8.24	2.31 (Week 36)	rtD134E, rtM309K
4296-5147	4.62	4.68 (Week 48)	rtS256S/C
8017-4565	8.21	2.61 (Week 48)	rtI80L/I, rtI91I/L, rtI204M/I, rtE271A/E
8758-5188	4.74	1.96 (Week 48)	rtR153Q
9035-5187	4.94	2.21 (Week 48)	rtS13N/S, rtS117S/P, rtL267Q/L, rtL269I/L

pol/RT = polymerase/ reverse transcriptase
a HBV DNA expressed as $\log_{10}$ IU/mL
Source: PC-320-2009, Section 5.3.1, Table 20

4.2.3.1.3.2. Week 48 Virology Analyses: TDF

Fourteen of 432 (3.2%) subjects in the TDF group qualified for sequence analysis, with 13 subjects experiencing virologic breakthrough at Week 48 and 1 subject discontinuing at or after Week 24 with HBV DNA ≥ 69 IU/mL. Among the 14 subjects in the TDF treatment group who qualified for sequence analysis, 6 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, 2 had polymorphic site substitutions, and 2 had conserved site substitutions (Table 68).

Table 68. TAF Integrated Analyses: Sequence Analysis Results for Subjects in the TDF Group Who Qualified for Testing Through Week 48

Subject	Baseline HBV DNA[a]	HBV DNA at Qualifying Timepoint[a]	Changes in HBV pol/RT at Qualifying Timepoint[b]
0481-4873	8.84	1.97 (Week 48)	No change from baseline
1659-4721	8.98	7.91 (Week 48)	No change from baseline
3912-5084	8.48	2.33 (Week 48)	No change from baseline
8599-4712	9.56	7.94 (Week 48)	No change from baseline
8599-4790	9.48	5.90 (Week 48)	No change from baseline
8599-5374	5.34	2.66 (Week 48)	No change from baseline
4164-4604	7.72	2.58 (Week 48)	Unable to sequence
6338-4707	6.54	2.15 (Week 48)	Unable to sequence
6963-1339	5.58	2.20 (follow-up Week 4)	Unable to sequence
8519-1176	6.07	2.33 (Week 48)	Unable to sequence
1507-4546	8.07	3.00 (Week 48)	rtD134D/E, rtV214V/A, rtA317A/S
9035-4845	6.62	4.38 (Week 48)	rtR110R/G, rtL269I/L
5620-5225	7.68	2.29 (Week 48)	rtQ67Q/H[b], rtN118N/T, rtN123N/D, rtM207V/M
8569-5131	5.87	1.96 (Week 48)	rtQ288Q/stop[b]

pol/RT = polymerase/ reverse transcriptase
a HBV DNA expressed as $\log_{10}$ IU/mL
b Conserved site substitutions
Source: PC-320-2009, Section 5.3.2, Table 21

4.2.3.1.4. Impact of HBV Genotype and Baseline Resistance Mutations on Treatment Outcomes

Table 69 presents the proportion of subjects achieving HBV DNA < 29 IU/mL at Week 48 based on the viral genotype (A-D) at baseline. No significant differences were observed in the proportion of subjects with HBV DNA < 29 IU/mL in the TAF group compared with the TDF group at Week 48 by HBV genotype (PC-320-2009). The proportion of subjects achieving HBV DNA < 29 IU/mL at Week 48 was significantly lower for genotype D as compared with genotypes A, B, and C in the TAF group and genotypes B and C in the TDF group ($p < 0.05$).

Table 69. TAF Integrated Analysis: Proportion of Subjects with HBV DNA < 29 IU/mL at Week 48 by Baseline HBV Genotype

	TAF		TDF		
Genotype[a]	Mean Baseline HBV DNA ($\log_{10}$ IU/mL ± SD)	Number of Subjects with HBV DNA < 29 IU/mL, n (%)[b,c]	Mean Baseline HBV DNA ($\log_{10}$ IU/mL ± SD)	Number of Subjects with HBV DNA < 29 IU/mL, n (%)[b,c]	p-value[c]
A	7.15 ± 1.54	45/54 (83.3)	7.52 ± 1.55	23/31 (74.2)	0.3998
B	7.08 ± 1.52	118/160 (73.8)	6.68 ± 1.66	70/88 (79.5)	0.3541
C	6.85 ± 1.54	328/418 (78.5)	7.03 ± 1.47	156/199 (78.4)	1.0
D	7.12 ± 1.74	140/224 (62.5)	7.16 ± 1.80	69/105 (65.7)	0.6239

a Only the predominant viral genotypes are presented due to small numbers of genotypes E, F, G, and H.
b Number of subjects as a proportion of total subjects in that category
c Comparison of treatment outcome between treatment groups performed using Fisher's Exact Test in a pair-wise fashion
Source: PC-320-2009, Section 5.2.1, Table 16

The impact of baseline resistance mutations as determined by INNO-LiPA on the proportion of subjects achieving HBV DNA < 29 IU/mL at Week 48 was assessed for all subjects. For this analysis, subjects were classified as being wild type, harboring primary resistance mutations, or harboring other mutations. For each resistance category, no significant differences were observed in the proportion of subjects with HBV DNA < 29 IU/mL in the TAF group as compared with the TDF group at Week 48 (wild type p = 0. 0.83; primary resistance p = 0.23; other p = 1.0) (PC-320-2009).

For both the TAF and TDF treatment groups, the proportion of subjects with primary resistance mutations achieving HBV DNA < 29 IU/mL was lower compared with wild type subjects and subjects with other mutations. An additional analysis was conducted to determine if baseline resistance mutations impacted the proportion of subjects who experienced virologic breakthrough (2 consecutive visits with HBV DNA ≥ 69 IU/mL after having been < 69 IU/mL or 1.0 $\log_{10}$ or greater increase in HBV DNA from nadir) through Week 48. As shown on Table 70, similar proportions of subjects experienced virologic breakthrough between resistance categories (TAF: 1.9% wild type, 2.4% primary resistance mutations, 0 other mutations; TDF: 2.9% wild type, 3.4% primary resistance mutations, 5.0% other mutations). These data suggest that the lower rate of HBV DNA suppression (< 29 IU/mL) at Week 48 in subjects with baseline primary resistance mutations was not associated with increased rates of virologic breakthrough.

Table 70. Percentage of Subjects Qualifying for Resistance Testing at Week 48 by Baseline Resistance Mutation

Resistance Category[a]	TAF Virologic Breakthrough, n (%)[b]	TDF Virologic Breakthrough, n (%)[b]
Wild type	15/775 (1.9)	11/383 (2.9)
Primary Resistance Mutation(s)[a]	1/41 (2.4)	1/29 (3.4)
Other Mutations[a]	0/50	1/20 (5.0)

a Primary resistance mutations and other mutations are defined in PC-320-2009, Section 2.4.2, Table 2
b Number of subjects as a proportion of total subjects in that category
Source: PC-320-2009, Section 5.2.2, Table 18

4.2.3.1.5. Week 48 Phenotypic Analysis

Phenotypic evaluations were performed on all subjects who experienced virologic breakthrough while maintaining study drug as well as for subjects with emergent-conserved site substitutions. Further details are provided in the virology analysis plan (PC-320-2002). Full details of the phenotypic analyses are provided the integrated virology study report, Amendment 2 (PC-320-2009 Amendment 2).

Overall, 5 subjects from the TAF group qualified for phenotypic analysis. Phenotypic analysis of 1 additional subject from the TAF group was completed prior to PK analysis of plasma TFV levels. Table 71 summarizes the results from the phenotypic analysis of 6 subjects in the TAF group evaluating sensitivity to TAF. All postbaseline virus pools tested remained sensitive to TAF.

Table 71. Phenotypic Evaluation of Qualified Subjects in the TAF Group

Study	Isolate	Visit	Baseline and Changes from Baseline in HBV pol/RT[a]	EC_{50} (nM)	Fold Change[b]
				TAF	
GS-US-320-0108	5613-1163	Baseline	NA	31.90	NA
GS-US-320-0108		Week 48	No change from baseline	40.55	1.26
GS-US-320-0108	6958-1318	Baseline	NA	33.79	NA
GS-US-320-0108		Week 48	No change from baseline	48.10	1.42
GS-US-320-0110	1659-4788	Baseline	NA	15.35	NA
GS-US-320-0110		Week 48	No change from baseline	21.80	1.41
GS-US-320-0110	4296-4510	Baseline	NA	31.35	NA
GS-US-320-0110		Week 48	No change from baseline	42.40	1.43
GS-US-320-0110	9035-5187	Baseline	NA	28.80	NA
GS-US-320-0110		Week 48	rtS13N/S, rtS117S/P, rtL267Q/L, rtL269I/L	23.05	0.74
GS-US-320-0110	9695-5283	Baseline	NA	44.25	NA
GS-US-320-0110		Week 24	No change from baseline	34.00	0.69
Controls					
NA	pHY92	NA	NA	33.50	NA
NA	ADV-R	NA	rtA181V+rtN236T	155.25	5.41[c]

NA = not applicable
a Amino acid substitution changes from baseline detected by population sequencing, conserved site changes are noted in **bold**
b Defined as the EC_{50} fold change from reference of the last on treatment sample/ EC_{50} fold change from reference of the baseline sample. A value < 2-fold is within assay variability
c Fold change from reference (pHY92)
Source: PC-320-2009 Amendment 2, Table 2

Overall, 4 subjects from the TDF group qualified for phenotypic analysis. Table 72 summaries the results from phenotypic analysis of the 4 subjects in the TDF group evaluating sensitivity to TFV. All post-baseline virus pools evaluated exhibited susceptibility to TFV.

Table 72. Phenotypic Evaluation of Qualified Subjects in the TDF Group

Study	Isolate	Visit	Baseline and Changes from Baseline in HBV pol/RT[a]	EC_{50} (µM)	Fold Change[b]
				Tenofovir	
GS-US-320-0110	0481-4873	Baseline	NA	4.08	NA
GS-US-320-0110		Week 48	No change from baseline	3.05	0.75
GS-US-320-0110	3912-5084	Baseline	NA	3.72	NA
GS-US-320-0110		Week 48	No change from baseline	3.79	0.96
GS-US-320-0110	5620-5225	Baseline	NA	3.88	NA
GS-US-320-0110		Week 48	**rtQ67Q/H**, rtN118N/T, rtN123N/D, rtM207V/M	4.06	1.03
GS-US-320-0110		Week 48 SDM	**rtQ67H**	3.94	1.01
GS-US-320-0110	8569-5131	Baseline	NA	4.34	NA
GS-US-320-0110		Week 48	**rtQ288Q/stop**	2.95	0.66
GS-US-320-0110		Week 48 SDM	**rtQ288stop**	AF[c]	NA
Controls					
NA	pHY92	NA	NA	3.20	NA
NA	ADV-R	NA	rtA181V+rtN236T	9.66	3.19[d]

AF = assay failure, NA = not applicable; SDM = site directed mutant
a Amino acid substitution changes from baseline detected by population sequencing, conserved site changes are noted in bold
b Defined as the EC_{50} fold change from reference of the last on treatment sample/ EC_{50} fold change from reference of the baseline sample. A value < 2-fold is within assay variability
c Unable to replicate in cell culture
d Fold change from reference (pHY92)
Source: PC-320-2009 Amendment 2, Table 3

4.2.3.1.6. Integrated Virology Analysis Conclusions

A total of 1298 subjects with CHB were enrolled in Studies GS-US-320-0108 and GS-US-320-0110 and treated with either TAF (N = 866) or TDF (N = 432).

Across the 2 randomized and controlled studies comparing TAF with TDF, the distribution of baseline pol/RT mutations and HBV genotype was comparable across the TAF and TDF treatment groups.

After up to 48 weeks of treatment, the number of subjects qualifying for sequence analysis was low: 24 subjects in the TAF group (2.8%) and 14 subjects in the TDF group (3.2%). Many of the HBV DNA profiles for subjects with virologic breakthrough are similar to virologic breakthrough profiles for subjects with transient non-adherence to study medication. Among the 24 subjects in the TAF treatment group who qualified for sequence analysis, 15 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, and 5 had polymorphic site substitutions. Among the 14 subjects in the TDF treatment group who qualified for sequence analysis, 6 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, 2 had polymorphic site substitutions, and 2 had conserved site

substitutions. No conserved site substitutions were observed in the TAF group and no polymorphic site substitutions were observed in more than one subject in the TAF group or the TDF group. Of the 38 total subjects that qualified for population sequencing analysis through Week 48, 6 subjects from the TAF group and 4 subjects from the TDF group were evaluated by phenotypic analysis. Overall, no HBV pol/RT amino acid substitutions associated with resistance to TFV were detected by genotypic or phenotypic analyses through 48 weeks of the study in either treatment group.

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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

Appendix Table 1. BIC and B/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
Healthy Subject PK and Initial Tolerability	GS-US-141-1218	Evaluate the PK, safety, and tolerability of single- and multiple-ascending doses of BIC in healthy subjects Evaluate the effect of food on the PK of BIC Evaluate the effect of F/TAF on the PK of BIC Evaluate the effect of BIC on the PK of FTC and TAF and its major metabolite TFV	Phase 1, double blind, randomized, placebo-controlled, first-in-human, single- and multiple-ascending dose study	Part A SAD: • BIC 5 mg, BIC 25 mg, BIC 50 mg, BIC 100 mg, BIC 300 mg, or BIC 600 mg or placebo-to-match PO (1 day, fasted) Part B MAD: • BIC 5 mg, BIC 25 mg, BIC 50 mg, BIC 100 mg, BIC 300 mg ,or placebo-to-match QD PO (14 days, fasted) Part C Food Effect: • BIC 100 mg, single dose PO, Day 1 fasted and Day 9 fed (high-fat meal) Part D BIC+F/TAF (DDI): Subjects randomized to 1 of 2 treatment sequences and received the following: • F/TAF (200/25 mg) QD PO (7 days, fed) • F/TAF (200/25 mg) + BIC 100 mg QD PO (7 days, fed) • BIC 100 mg QD PO (7 days, fed)	Part A: 1 day Part B: 14 days Part C: 2 days Part D: 21 days	Enrolled: 130 Completed: 128	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-141-1219	To evaluate the short-term antiviral potency of BIC at multiple oral doses ranging from 5 mg to 100 mg compared to placebo-to-match BIC each administered once daily as monotherapy for 10 days, with respect to the time-weighted average change from baseline to study Day 11 in plasma HIV-1 RNA (log_{10} copies/mL) in ARV treatment-naive adult subjects and subjects who were ART-experienced but INSTI naive.	Phase 1b, double-blind, adaptive, sequential cohort, placebo-controlled study	Part 1: Cohort 1: • BIC 25 mg or placebo-to-match BIC 25 mg QD PO for 10 days Cohort 2: • BIC 100 mg or placebo-to-match BIC 100 mg QD PO for 10 days Part 2: Cohort 3: • BIC 5 mg or placebo-to-match BIC 5 mg QD PO for 10 days Cohort 4: • BIC 50 mg or placebo-to-match BIC 50 mg QD PO for 10 days	BIC 5, 25, 50, & 100 mg, & placebo-to-match were administered for 10 days each. The total study duration was 17 days for both Parts 1 and 2.	Randomized: 23 Completed: 20	HIV-infected adults	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	GS-US-141-1233	Evaluate the relative BA of 2 FDC tablets containing BIC 75 mg or 50 mg, FTC 200 mg and TAF 25 mg, compared with BIC 75 mg plus F/TAF (200/25 mg) under fasted conditions Assess the effect of food on the PK of BIC, FTC, and TAF when administered as the B/F/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets	Phase 1, open-label, two-cohort, multiple-period, fixed-sequence, single-center crossover study	3-period sequence; subjects received single doses of the following treatments: Cohort 1: • F/TAF (200/25 mg) + BIC 75 mg administered simultaneously, PO, fasted (A) • B/F/TAF (75/200/25 mg) administered PO, fasted (B) • B/F/TAF (75/200/25 mg) administered PO, fed, high fat meal (C) Cohort 2: • F/TAF (200/25 mg) + BIC 75 mg administered simultaneously, PO, fasted (A) • B/F/TAF (50/200/25 mg) administered PO, fasted (D) • B/F/TAF (50/200/25 mg) administered PO, fed, high-fat meal (E) • B/F/TAF (50/200/25 mg) administered PO, fed, moderate-fat meal (F)	Cohort 1: 28 days (3 single doses on Days 1, 9, & 17) Cohort 2: 36 days (4 single doses on Days 1, 9, 17, & 25)	Enrolled: 56 Completed: 55	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-141-1478	Evaluate the PK profile of a single oral dose of BIC; in subjects with impaired hepatic function relative to matched, healthy controls with normal hepatic function	Phase 1, open-label, parallel group, adaptive, single-dose study	BIC 75 mg PO (fed)	Single dose	Enrolled: 20 Completed: 20	Adult subjects with moderate hepatic impairment (CPT Class B) and healthy matched control subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-141-1479	Evaluate the PK profile of oral BIC in subjects with impaired renal function relative to matched, healthy controls with normal renal function	Phase 1, open-label, parallel-group, adaptive single-dose study	BIC 75 mg PO (fed)	Single dose	Enrolled: 19 Completed: 18	Cohort 1: Adult subjects with severe renal impairment ($eGFR_{CG}$ 15 to 29 mL/min) and matched control subjects with normal renal function	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-141-1480	Evaluate the effects of BIC (at therapeutic and supratherapeutic doses) on time-matched, baseline-adjusted, placebo-corrected QT interval corrected for heart rate (QTc) using the Fridericia formula (ΔΔQTcF)	Phase 1, partially-blinded, randomized, placebo and positive-controlled, 4-period, single-dose crossover study	Subjects were randomized to 1 of 2 Williams squares and then to 1 of 4 treatment sequences per Williams square, and received single doses of the following 4 treatments in the assigned sequence given orally under fed conditions: Therapeutic exposure: • BIC 75 mg plus 3 × placebo-to-match BIC) (A) Supratherapeutic exposure): • BIC 300 mg (4 × BIC 75 mg tablets) (B) Placebo control: • 4 × placebo-to-match BIC (C) Positive control: • moxifloxacin 1 × 400 mg (D)	22 days (4 single-dose treatment days separated by 7 days of washout between doses)	Randomized: 48 Completed: 48	Healthy adult subjects	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-141-1481	Determine the mass balance of BIC following administration of a single, oral dose of radiolabeled carbon-14 ([^{14}C])BIC	Phase 1, open-label, single center, mass-balance study	• BIC 100 mg (99 mg nonradiolabeled BIC plus approximately 100 µCi [1 mg] radiolabeled [^{14}C]BIC) administered orally as an approximately 40-mL ethanolic solution	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
Extrinsic Factor PK	GS-US-141-1485	Evaluate the effect of mixed UGT1A1/CYP3A4/ P-gp inhibition on the PK of BIC Evaluate the effect of CYP3A4/P-gp/ UGT1A1 induction on the PK of BIC	Phase 1, open-label, multiple-dose, multiple-cohort, adaptive design study	Eligible subjects were initially assigned to 1 of 2 cohorts and received study treatments in parallel as shown below: Cohort 1: • UGT1A1/CYP3A4/ P-gp Inhibitor: ATV 300 mg + COBI 150 mg Cohort 2: • CYP3A4/P-gp/ UGT1A1 Inducer: RIF 600 mg Cohorts 3 and 4 were adaptive and were initiated in parallel: Cohort 3: • UGT1A1/CYP3A4 Inhibitor: ATV 400 mg Cohort 4: • CYP3A4 Inhibitor: VORI 300 mg Two additional adaptive cohorts (Cohorts 5 and 6) were initiated in parallel following review of PK data from Cohorts 3 and 4: Cohort 5: • CYP3A4/P-gp Inducer: RBT 300 mg Cohort 6: • CYP3A4 Inhibitor: DRV/co 800/150 mg	Cohorts 1, 3, and 4: 9 days (with a 3-day washout between the first and second doses of study treatment) Cohort 2: 15 days (with a 3-day washout between the first and second doses of study treatment) Cohorts 5 and 6: 20 days	Enrolled: 90 Completed: 85	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-141-1487	Assess renal function before, during, and after administration of BIC versus placebo via determination of aGFR as assessed by iohexol clearance	Phase 1, randomized, blinded, placebo-controlled, 2-group, multiple-dose, parallel-design study	Subjects were randomized to receive 1 of the following 2 treatments (A or B), with iohexol administered to all subjects as described: • BIC 75 mg QD PO for 14 days, fed (A) • Placebo-to-match BIC administered QD PO for 14 days, fed (B) • Iohexol on Days −1, 7, 14, and 21	31 days; study drug dosing: 14 days	Randomized: 40 Completed: 40	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-311-1790 (Cohort 2)	Evaluate the effect of F/TAF FDC tablet or GS-9883 on the PK of a representative hormonal contraceptive medication, norgestimate/ ethinyl estradiol. Evaluate the safety and tolerability of F/TAF FDC or GS-9883 when given with a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol.	Phase 1, randomized, open-label, single-center, fixed sequence, multiple-dose, multiple cohort study	**Part A:** Lead-in period (Lead-in Days 1–28) with norgestimate/ethinyl estradiol QD **Part B:** **Cycle 1:** norgestimate/ ethinyl estradiol QD for Study Days 1–28 **Cycle 2:** Subjects were randomized to 1 of 2 cohorts and received the following treatments: **Cohort 1:** norgestimate/ ethinyl estradiol QD for Study Days 29–56 plus F/TAF 200/25 mg on Study Days 29–42 **Cohort 2:** norgestimate/ ethinyl estradiol QD for Study Days 29–56 plus GS-9883 75 mg on Study Days 29–42 All treatments were administered QD in the morning with food.	84 days	Randomized: 32 Treated: 32 Completed Study Treatment: Cohort 1: 13 Cohort 2: 15	Healthy adult female 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-380-1761	Evaluate the steady-state PK of BIC, FTC, and TAF upon administration of B/F/TAF FDC with LDV/SOF FDC Evaluate the steady-state PK of SOF, its metabolites GS-566500 and GS-331007, and LDV upon administration of LDV/SOF FDC with B/F/TAF FDC	Phase 1, fixed-sequence, open-label, single-center, multiple-dose, 3-period study	Subjects received the following 3 treatments under fed conditions: • LDV/SOF (90/400 mg) QD PO (10 days) • BIC/F/TAF (75/200/25 mg) QD PO (10 days) • LDV/SOF (90/400 mg)QD PO plus BIC/F/TAF (75/200/25 mg) QD PO (10 days)	30 days; each treatment administered for 10 days	Enrolled: 30 Completed: 30	Healthy adult subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-380-1991	Investigate the single dose PK of BIC, FTC, F, TAF, and TFV when administered as B/F/TAF FDC in healthy Japanese and Caucasian subjects	Phase 1, open-label, single dose study	• B/F/TAF (50/200/25 mg) PO, fasted	Single dose (1 day)	Enrolled: 50 (25 subjects per ethnic group) Completed: 50	Healthy Japanese and Caucasian adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-380-1999	Evaluate the steady-state PK of BIC, FTC, TAF, and TFV upon administration of B/F/TAF FDC with SOF/VEL/VOX Evaluate the steady-state PK of SOF, its metabolites (GS-566500 and GS-331007), VEL and VOX upon administration of B/F/TAF FDC with SOF/VEL/VOX	Phase 1, randomized, open-label, multiple-dose, single-center, 3-period, study	Subjects were randomized into 1 of 6 treatment sequences to receive the following 3 treatments under fed conditions: • B/F/TAF (50/200/25 mg) QD PO (10 days) • B/F/TAF (50/200/25 mg) plus SOF/VEL/VOX (400/100/100 mg) + VOX (100 mg) QD PO (10 days) • SOF/VEL/VOX (400/100/100 mg) + VOX (100 mg) QD PO (10 days)	30 days; each treatment administered for 10 days	Randomized: 30 Completed 30	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-380-3908	Evaluate the effect of BIC; on the PK and PD of metformin following the steady-state coadministration of B/F/TAF FDC with metformin in healthy subjects	Phase 1, blinded, placebo-controlled, multiple-dose, single-center, 2-period, crossover study	Subjects were randomized to 1 of 2 treatment sequences and received the following treatments: Treatment A: • Placebo to match B/F/TAF QD PO, Days 1-9 or 13–21 (fasted) • Metformin 850 mg QD PO on Day 5 or 17 at 12-hours postdose of placebo-to-match B/F/TAF • Metformin 500 mg BID PO on Days 6–8 or 18–20 • Metformin 500 mg coadministered QD PO on Day 9 or 21 with placebo-to-match B/F/TAF in the morning Treatment B: • B/F/TAF (50/200/25 mg) QD PO on Days 1–9 or 13–21(fasted) • Metformin 850 mg QD PO on Day 5 or 17 at 12-hours postdose of B/F/TAF • Metformin 500 mg BID PO on Days 6–8 or 18–20: • Metformin 500 mg coadministered QD PO on Day 9 or 21 with B/F/TAF in the morning	18 days	Randomized: 32 Completed : 30	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-380-3909	Evaluate the effect of simultaneous administration of antacid, calcium, or iron supplements with B/F/TAF FDC compared to administration of B/F/TAF FDC alone under fasted and fed conditions on BIC PK Evaluate the effect of staggered administration of B/F/TAF FDC and antacid compared to administration of B/F/TAF FDC alone on BIC PK	Phase 1, open-label, single-center, single-dose, fixed-sequence, multiple-cohort, multiple-period, adaptive study	Subjects were enrolled, assigned to 1 of 3 cohorts, and received single PO doses of the following: Cohort 1 Simultaneous Administration (Fasted): • B/F/TAF (50/200/25 mg) • B/F/TAF (50/200/25 mg) with 20 mL maximum-strength antacid oral suspension • B/F/TAF (50/200/25 mg) with calcium carbonate (2 × 600 mg tablets) • B/F/TAF (50/200/25 mg) with ferrous fumarate (1 × 324 mg tablet) Cohort 2: Staggered Administration (Fasted): • B/F/TAF (50/200/25 mg) • B/F/TAF (50/200/25 mg), 2 hours before 20 mL maximum-strength antacid oral suspension • B/F/TAF (50/200/25 mg), 2 hours after 20 mL maximum-strength antacid oral suspension	Cohorts 1 and 3: 4 days Cohort 2: 3 days	Enrolled: 42 Completed : 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
				Cohort 3: Simultaneous Administration: • B/F/TAF (50/200/25 mg), fasted • B/F/TAF (50/200/25 mg) with a 20 mL maximum-strength antacid oral suspension, fed • B/F/TAF (50/200/25 mg) with calcium carbonate (2 × 600 mg tablets), fed • B/F/TAF (50/200/25 mg) with a ferrous fumarate (1 × 324 mg tablet), fed				

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-380-4270	To evaluate the effect of BIC when administered as the B/F/TAF FDC on the PK of the CYP3A probe, MDZ	Phase 1, open-label, fixed-sequence, single- and multiple-dose study	Subjects were enrolled to receive the following three treatments: • single dose MDZ 2 mg oral syrup, fed (A) • B/F/TAF 50/200/25 mg QD PO for 9 days, fed (B) • single dose MDZ 2 mg oral syrup, fed administered 5 hours after single dose B/F/TAF 50/200/25 mg PO, fed (C)	23 days; study drug dosing: 11 days	Enrolled: 14 Completed: 14	Healthy adult subjects	Study completed; Final CSR

3TC = lamivudine; ABC = abacavir; aGFR = actual glomerular filtration rate; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BA = bioavailability; BE = bioequivalence; BIC = bictegravir (GS-9883); BID = twice daily; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated); ^{14}C = radiolabeled carbon 14; CBZ = carbamazepine; COBI = cobicistat (Tybost®); CHB = chronic hepatitis B; ®); CPT = Child-Pugh-Turcotte; CSR = clinical study report; CYP = cytochrome P450 enzyme; DDI = drug-drug interaction; DVR = darunavir; DTG = dolutegravir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated); $eGFR_{CG}$ = estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; EVG = elvitegravir (Vitekta®); FCV = famiciclovir; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); FTC = emtricitabine (Emtriva®); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); GEN = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated, Genvoya® (previously referred to as E/C/F/TAF); HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; INSTI = integrase strand-transfer inhibitor; IV = intravenous; LDV = ledipasvir; LDV/SOF = ledipasvir/sofosbuvir (coformulated; Harvoni®); LPV = lopinavir; LPV/r = lopinavir boosted with ritonavir; MAD = multiple ascending dose; MDZ = midazolam; NGM/EE = norgestimate/EE = ethinyl estradiol; OL = open label; PBMC = peripheral blood mononuclear cells NNRTI = nonnucleoside reverse transcriptase inhibitor; P-gp = P-glycoprotein; PI = protease inhibitor; PK = pharmacokinetic(s); PO = orally; QD = once daily; QT = electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur; QTc = QT interval corrected for heart rate; QTcF = QT interval corrected for heart rate using the Fridericia formula; RNA = ribonucleic acid; RPV = rilpivirine; RTV = ritonavir; SAD = single ascending dose; SER = sertraline; SOF = sofosbuvir; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir (coformulated); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate (Viread®); TFV = tenofovir; UGT1A1 = uridine diphosphate glucuronosyltransferase 1A1; VEL = velpatasvir (GS-5816); VORI = voriconazole; VOX = voxilaprevir (GS-9857); ZDV = zidovudine

6.2. Pharmacokinetic/Pharmacodynamic and Ad Hoc Analyses

Outputs presenting data from prespecified B/F/TAF PK/PD analyses are included in this submission. Additional outputs with numbering beginning with "Table Req" or "Ad hoc" present data from analyses that were not prespecified in a Statistical Analysis Plan.

6.3. Tabular Summary of Nonclinical Studies

6.3.1. BIC Tabular Summary of Nonclinical Virology Studies

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
BIC Primary Pharmacodynamics					
Antiviral Activity and Selectivity of GS-9883 in T-Cell Lines	No	Human Lymphoblastoid T-cell lines MT-2 and MT-4, HIV-1 IIIb virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2032
Effect of Human Serum and Serum Components on the Antiviral Activity of GS-9883	No	Human Lymphoblastoid T-cell line MT-2, HIV-1 IIIb virus, recombinant HIV-1 virus LAI-RLuc containing Renilla luciferase reporter gene	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2033
Antiviral Activity and Cytotoxicity of GS-9883 in Primary $CD4^+$ T Lymphocytes and Monocyte-Derived Macrophages	No	Human CD4+ T-lymphocytes, human monocyte derived macrophages, human PBMCs, HIV-1 BaL virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2034
Antiviral Activity of GS-9883 against HIV Clinical Isolates	No	Human PBMCs, HIV of various subtypes and HIV-2	In Vitro	[redacted], USA.	PC-141-2035
Antiviral Activity of BIC against HIV-1 O and N	No	Human PBMCs, HIV-1 O and N	In Vitro	[redacted], USA.	PC-141-2057
Inhibition of HIV-1 Integrase Strand Transfer and 3'Processing Activities by GS-9883	No	Purified recombinant HIV-1 integrase expressed and isolated from E. coli, synthetic oligonucleotide strand transfer and 3'processing substrates	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2036
Association and Dissociation of BIC with HIV-1 IN/DNA Complexes	No	Scintillation proximity assay	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2058
Activity of GS-9883 against Drug-Resistant HIV-1 Mutant Variants	No	Human lymphoblastoid T-cell line MT-2, HIV-1 IIIb virus, HIV-1 HXB2 virus and HXB2 virus variants containing various site-directed mutations associated with NRTI, NNRTI and PI resistance	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2039

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Activity of GS-9883 Against INSTI-resistant Mutants of HIV-1	No	Human lymphoblastoid T-cell line MT-2, HIV-1 HXB2 virus and HXB2 virus variants containing various site-directed mutations associated with INSTI resistance	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2040
Antiviral Activity of GS-9883 against HIV-1 Clinical Isolate Clones with Integrase Strand Transfer Inhibitor Mutations	No	Human embryonic kidney 293 cells, HIV-1 NL4-3 and patient-derived resistance test vectors	In Vitro	[redacted], USA	PC-141-2050
Antiviral Activity of GS-9883 against HIV-1 Isolates with Integrase Strand Transfer Inhibitor Mutations	No	Human embryonic kidney 293 cells, HIV-1 NL4-3 and patient-derived resistance test vectors	In Vitro	[redacted], USA	PC-141-2051
Viral Resistance Selection Studies with BIC	No	Human lymphoblastoid T-cell line MT-2, HIV-1 IIIb virus, inhibitor-selected HIV-1 IIIb variants	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2041
Viral Resistance Selection Studies with BIC	No	Human lymphoblastoid T-cell line MT-2, HIV-1 IIIb virus, inhibitor-selected HIV-1 IIIb variants	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2052
Viral Resistance Selection Studies with BIC	No	Human lymphoblastoid T-cell line MT-2, HIV-1 strain xxLAI, inhibitor-selected HIV-1 xxLAI varaints	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2056

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
BIC Secondary Pharmacodynamics					
Antiviral Activity of GS-9883 against Non-HIV Viruses	No	Chronically HBV infected AD38 cells, Huh 7-Lunet derived stable HCV replicon cell lines containing either HCV1b replicon or HCV2a replicon, H1-HeLa cells infected with human rhinoviruses (HRV1A, HRV14, HRV16), normal human bronchial/ tracheal epithelial cells (NHBE) infected with Influenza A virus (A/Port Chalmers/1/73) or Influenza B virus (B/LEE/40), Hep-2 Cells infected with RSV	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2043
Molecular Target Screen of GS-9883	No	Human, rabbit, rat, hamster, and mouse receptors	In vitro	[redacted], Taiwan, R.O.C.	PC-141-2029 ([redacted] AB19482)
BIC Pharmacodynamic Drug Interactions					
In vitro Antiviral Activity of GS-9883 in Combination with Other Anti-retroviral Agents	No	Human lymphoblastoid T-cell line MT-2, HIV-1 IIIb virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-141-2038
Three-Drug Combination Study of the Antiviral Activity of BIC, FTC and TAF	No	Human lymphoblastoid T-cell line MT-2, HIV-1 IIIb virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-380-2001

a An entry of "Yes" indicates that the study includes a Good Laboratory Practice (GLP) compliance statement.

6.3.2. FTC Tabular Summary of Nonclinical Virology Studies

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study No and Reference
FTC Primary Pharmacodynamics					
Inhibition of HIV-1 reverse transcriptase	No	Endogenous RT assay Chain-termination substrate assays Purified HIV-1 reverse transcriptase enzyme assay	In vitro	[redacted]	Antimicrob Agents Chemother 1993;37:1270–2 {Wilson 1993}
Antiviral activity vs HIV-1 and HIV-2	No	Human PBMCs and various T cell lines	In vitro	[redacted], Georgia	Antimicrob Agents Chemother 1992;36:2423–31 {Schinazi 1992}
FTC Secondary Pharmacodynamics					
Antiviral activity vs human hepatitis B virus (HBV), Cytotoxicity	No	Human hepatoma cell line HepG2.2.15	In vitro	[redacted], USA	Antimicrob Agents Chemother 1994;38:2172–2174 {Schinazi 1994}
Antiviral activity vs human HBV, Cytotoxicity	No	Human hepatoma cell line HepG2.2.15	In vitro	[redacted] USA	Antimicrob Agents Chemother 1992;36:2686–2692 {Furman 1992}
In Vitro Receptor Binding Potencies of FTC	No	In vitro binding assay	In vitro	[redacted] USA	TPZZ/93/0002
In Vitro Autonomic Pharmacology Cholinergic (Muscarinic) Activity Alpha-adrenoceptor Activity Beta-adrenoceptor Activity Serotonin Receptor Activity	No	Guinea pig ileum Rabbit aortic strips Guinea pig trachea and atria Rat fundus strips	In vitro	[redacted] USA	TPZZ/92/0055
Cytotoxicity Assay	No	MT-4, CEM, IM9, Molt-4, and HepG2.2.15 cells	In vitro	[redacted] USA	Antimicrob Agents Chemother. 1994; 38:868-871 {Van Draanen 1994}

a An entry of "Yes" indicates that the study includes a Good Laboratory Practice (GLP) compliance statement.

6.3.3. TAF Tabular Summary of Nonclinical Virology Studies

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
TAF Primary Pharmacodynamics					
Drug Combination Studies with TAF	No	MT-2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2002
Profiling of TAF Antiviral Activity Against HIV-1 and HIV-2 Clinical Isolates in Primary Cells	No	Primary Cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2004
Cytotoxicity Assay with TAF	No	MT-2, MT-4, and HepG2 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2007
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
Antiviral Activity and Cytotoxicity of TAF Metabolites	No	MT-2 and MT-4 cells	In Vitro	Gilead Sciences Foster City, CA USA	PC-120-2021
Mechanism of action (activation of tenofovir via phosphorylation)	No	Human T lymphoid cells (CEMss, CEMss^{r-1})	In vitro	[redacted], USA	Antimicrob Agents Chemother 1995 Oct;39(10):2304–8 {Kalayjian 2003}
Antiviral activity of PMPA vs prodrugs of PMPA against wild-type HIV_{IIIB} and evaluation of cytotoxicity	No	Human resting/activated PBMCs and T lymphocyte (MT-2) cells	In vitro	[redacted], USA	Antimicrob Agents Chemother 1998 Mar;42(3):612–7 {Robbins 1998}
Molecular basis of antagonism between K70E and K65R tenofovir-associated mutations in HIV-1 reverse transcriptase	No	In vitro	In vitro	[redacted], USA; USA; [redacted], USA; and [redacted], USA	Antivir Res 2007;75:210–218 {Kagan 2007}
Antiviral activity and replication capability vs HIV-1 expressing the 3TC-associated M184V mutation	No	MT-2 cells and PBMCs	In vitro	Gilead Sciences, Inc., USA	J Infect Dis 1999 Jan; 179(1):92–100 {Miller 1999}

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Phosphorylation of tenofovir and FTC	No	CEM CRFF cells	In vitro	Gilead Sciences, Inc., USA	PC-164-2001
Selective Intracellular Activation of a Novel Prodrug of the Human Immunodeficiency Virus Reverse Transcriptase Inhibitor Tenofovir Leads to Preferential Distribution and Accumulation in Lymphatic Tissue	No	Dog	Oral	Gilead Sciences Foster City, CA, USA	Antimicrob Agents Chemother 2005;49(5):1898-1906 {Lee 2005}
Tenofovir Alafenamide Demonstrates Broad Cross-Genotype Activity Against Wild-type HBV Clinical Isolates In Vitro	No	HepG2 cells	In vitro	Gilead Sciences Foster City, CA, USA	PC-320-2003
Antiviral Activity of TAF Against Drug-Resistant HBV Isolates	No	HepG2 cells	In vitro	Gilead Sciences Foster City, CA, USA	PC-320-2007
Effect of TAF on CatA-mediated Activation and Antiretroviral Activity	No	Purified CatA and primary CD4+ T lymphocytes	In vitro	Gilead Sciences, Inc., Foster City, CA USA	PC-120-2001
Intracellular Metabolism and In Vitro Activity of Tenofovir Against Hepatitis B Virus	No	HBV reverse transcriptase	In vitro	Gilead Sciences Foster City, CA, USA	Antimicrob Agents Chemother 2006;50(7):2471-2477 {Delaney 2006}
Antiviral activity vs human HBV	No	Human hepatoblastoma cell line (HB611)	In vitro	[redacted], Japan	Antiviral Chemistry and Chemother 1994;5(2):57–63. {Yokota 1994}
Inhibitory Effects of Tenofovir & TDF on Human HIV_{IIIB} RT and Human DNA Polymerases	No	HIV_{IIIB} RT, human DNA polymerase (α, β, γ)	In vitro	Gilead Sciences Foster City, CA, USA	Antiviral Chemistry and Chemotherapy 1995;6(4):217–221 {Cherrington 1995a}

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
TAF Secondary Pharmacodynamics					
Binding Screen to Neuroreceptors, Ion Channels, Transporters, Nuclear Receptors	No	Protein targets	In vitro	[redacted], Taiwan	V2000020
Mitochondrial Toxicity with TFV	No	HepG2, SKMC, RPTECs	In vitro	Gilead Sciences, Inc., Foster City, CA USA	P1278-00042 Antimicrob Agents Chemother 2002; 45: 716-723 {Birkus 2002}
Effect of TAF on Mitochondrial DNA	No	HepG2 cells	In vitro	Gilead Sciences, Inc., Foster City, CA USA	PC-120-2006 {Stray 2017}
Mitochondrial Toxicity of Necleos(t)ide RT Inhibitors	No	HepG2 cells	In vitro	[redacted], Germany	TX-104-2001
Resistance Development Over 144 Weeks in Treatment-Naive Patients Receiving Tenofovir Disoproxil Fumarate or Stavudine with Lamivudine and Efavirenz in Study 903	No	In vitro	In vitro	Gilead Sciences Foster City, CA, USA	HIV Med 2006;7(7):442-450 {Margot 2006a}
TAF Pharmacodynamic Drug Interactions					
Antiviral activity in combination with other antiretroviral drugs	No	MT-2 cells	In vitro	Gilead Sciences, Inc., USA	PC-104-2005
Antiviral activity in combination with other antiretroviral drugs	No	MT-2 cells	In vitro	Gilead Sciences, Inc., USA	PC-104-2006
Antiviral activity in combination with other antiretroviral drugs	No	MT-2 cells	In vitro	Gilead Sciences, Inc., USA	PC-164-2002
Antiviral HIV-1 dual drug combination study of FTC, RPV, and TFV	No	MT-2 cells	In Vitro	Gilead Sciences, Inc., USA	PC-264-2001
Effect of Sofosbuvir on the HIV-1 Antiviral Activity of TAF	No	MT-2 cells	In vitro	Gilead Sciences Foster City, CA, USA	PC-120-2032

a An entry of "Yes" indicates that the study includes a Good Laboratory Practice (GLP) compliance statement.