SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.2—SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

LEGACY APPENDICES

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.2—SUMMARY OF CLINICAL PHARMACOLOGY STUDIES 1

TABLE OF CONTENTS 2

1. APPENDIX 3

1.1. Narratives for Previously Submitted Studies with TAF 3
1.1.1. Studies in Healthy Subjects 3
1.1.2. Studies in HIV-or HBV-Infected Subjects 7
1.1.3. Intrinsic Factor Studies 13
1.1.4. Extrinsic Factor Studies 20
1.2. Narratives for Previously Submitted Studies with F/TAF 29
1.2.1. Studies in Healthy Subjects 29
1.2.2. Extrinsic Factor Studies 31
1.3. Narratives for Previously Submitted Studies with E/C/F/TAF 41
1.3.1. Studies in Healthy Subjects 41
1.3.2. Extrinsic Factor Studies 44
1.4. Narratives for Previously Submitted Studies with FTC or FTC/TDF 45
1.4.1. Studies in Healthy Subjects 45
1.4.2. Studies in HIV-Infected Subjects 49
1.4.3. Intrinsic Factor Studies 57
1.4.4. Extrinsic Factor Studies 59
1.5. References 63
1.6. Tabular Summary of Legacy Clinical Pharmacology Studies 64

1. APPENDIX

Summaries of studies conducted with TAF, F/TAF (Descovy®), E/C/F/TAF (Genvoya®), and FTC or FTC/TDF (Truvada®) which provide supportive information for the B/F/TAF Summary of Clinical Pharmacology are provided by study type in Sections 1.1 to 1.4, respectively. The narrative for Study GS-US-292-0112 is provided in m2.7.4. Data from these studies have been previously reviewed by regulatory authorities in the context of a marketing application in at least 1 region. Further details on all of these studies are provided in the CSRs located in module 5.

1.1. Narratives for Previously Submitted Studies with TAF

1.1.1. Studies in Healthy Subjects

1.1.1.1. GS-US-120-0107

Location:	GS-US-120-0107
Title:	Study GS-US-120-0107: A Phase 1, Partially Blinded, Randomized, Placebo and Positive Controlled Study to Evaluate the Effect of GS-7340 on the QT/QTc Interval in Healthy Subjects
Primary Objective(s):	To evaluate the effects of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on time-matched, baseline-adjusted, placebo-corrected QTcF (corrected QT calculated using the Fridericia formula)
Study Design and Subject Population:	This Phase 1, partially-blinded, randomized, placebo- and positive-controlled, 4-period, single-dose, crossover study evaluated the effect of TAF on time-matched, baseline-adjusted, and placebo-corrected QTcF, QTcB (QT corrected for heart rate using the Bazett formula), QTcN (QT corrected for heart rate using the population correction formula), and QTcI (QT interval corrected using the individual correction formula), and explored the effect of TAF on electrocardiogram (ECG) parameters in healthy subjects. The following treatments were administered during the study: • **Treatment A (therapeutic exposure):** TAF 25 mg (1 × 25-mg TAF tablet + 4 × TAF placebo-to-match) • **Treatment B (supratherapeutic exposure):** TAF 125 mg (5 × 25-mg TAF tablets) • **Treatment C (placebo control):** 5 × TAF placebo-to-match • **Treatment D (positive control):** 1 × moxifloxacin 400 mg Placebo and TAF study drugs in Treatments A, B, and C were administered double blind. Moxifloxacin given in Treatment D was administered open label. Subjects completed 4 dosing periods; each period consisted of 1 day of dosing with 1 of 4 study drug treatments. Eligible subjects were healthy males and nonpregnant, nonlactating females with normal 12-lead ECGs. A total of 59 subjects were randomized into the study, and 58 subjects completed the study. One subject was discontinued during the first treatment period and was replaced. Ten subjects were replaced due to damaged ECG flash cards in the third period. These 11 subjects were included in the Safety Analysis Set but were excluded from PK, PD, and PK/PD Analysis Sets due to incomplete ECG data (the primary endpoint).

Summary of Results and Conclusions:

Pharmacokinetic Results:

Pharmacokinetic parameters for TAF and TFV following single oral doses of TAF 25 or 125 mg were approximately proportional to dose, as presented in the table below.

Statistical Analysis of Dose Proportionality

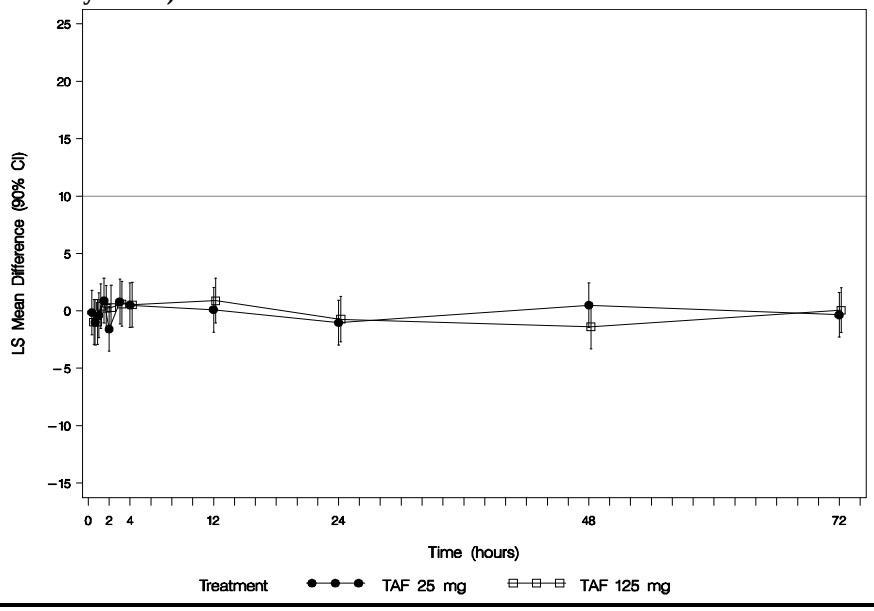
	Mean (%CV)		
	TAF 125 mg (Test) (N = 48)	**TAF 25 mg (Reference) (N = 48)**	**GLSM Ratio (90% CI), %**
TAF PK Parameter			
AUC_{last} (ng•h/mL)	1214.3 (33.2)	225.9 (44.0)	551.85 (525.61, 579.40)
AUC_{inf} (ng•h/mL)	1228.0 (32.6)[a]	228.2 (43.4)	542.04 (517.16, 568.13)
C_{max} (ng/mL)	859.0 (35.1)	174.3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

Pharmacodynamic Results:

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

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

Noninferiority Evaluation for Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF (PD Analysis Set)



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

Categorical Analysis of QTc (msec) by Treatment (PD Analysis Set)

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

QTcI = QT interval corrected for heart rate using the individual correction formula; QTcN = QT interval corrected for heart rate using the population-specific correction formula

Pharmacokinetic/Pharmacodynamic Results:

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

Safety Results:

Three subjects had adverse events (AEs) that could be associated with cardiac disease: palpitations associated with no ECG changes in 1 subject during the TAF 25-mg treatment, dizziness (concurrent with nausea and headache) associated with ST segment depression on ECG in 1 subject during the TAF 125 mg treatment, and presyncope (described as a mild vasovagal reaction) with no associated clinically significant ECG changes in 1 subject during the moxifloxacin treatment.

Conclusions:

- Exposures of TAF and TFV were approximately proportional to dose.
- The expected increase in QTc upon administration of 400-mg moxifloxacin demonstrated assay sensitivity. TAF, administered at doses of 25 and 125 mg, did not lead to changes in the QTc interval in healthy adults. Thus, this study is a negative thorough QT study as defined by International Conference on Harmonisation (ICH) guidance.
- There was no pharmacologically meaningful association between time-matched, baseline-adjusted, placebo-corrected QTcF and TAF or TFV plasma concentrations.
- Single doses of TAF administered at therapeutic (25 mg) and supratherapeutic (125 mg) doses were generally well tolerated in these healthy subjects. No deaths, serious adverse events (SAEs), Grade 3 or 4 AEs, or AEs leading to discontinuation of study drug were reported during the TAF or placebo treatment periods.

1.1.1.2. GS-US-120-0109

Location:	GS-US-120-0109
Title:	Study GS-US-120-0109: A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism and Excretion of GS-7340
Primary Objective(s):	To determine the mass balance of TAF following administration of a single, oral dose of radiolabeled carbon 14 ([^{14}C])TAF
Study Design and Subject Population:	This was an open-label, Phase 1, mass balance study to evaluate the PK, metabolism, and excretion of TAF following administration of a single, oral dose of radiolabeled [^{14}C]TAF in healthy subjects. A total of 8 subjects were enrolled, completed study drug administration, and included in the Safety and PK Analysis Sets. Six subjects completed the study, and 2 subjects withdrew consent.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The results of this mass balance study confirmed that TAF was extensively metabolized in urine and feces. The total mean ± SD recovery of [^{14}C]-radioactivity in feces plus urine was 84.4% ± 2.45% (N = 7), with the percentage of radioactive dose recovered from feces at 47.2% ± 4.62% (N = 7) and the percentage of radioactive dose recovered from urine at 36.2% ± 5.62% (N = 8). The predominant species detected in feces and urine was TFV, accounting for 99% of the radioactivity recovered in feces, and 86% of the radioactivity recovered in urine. All other metabolites detected in the feces and urine were in trace amounts, with no values exceeding 2% of the administered radioactive dose. Only 1.41% ± 0.561% of the total radioactive dose was identified in urine as TAF, suggesting very low renal TAF clearance. No radioactive TAF was detected in feces. There were 2 concentration peaks present in the plasma [^{14}C]-radioactivity time profile. At the first maximal plasma radioactivity concentration around 2 hours postdose, the predominant species was TAF, accounting for 72.6% of the total [^{14}C]-radioactivity quantified. At the second maximal plasma radioactivity concentration around 24 to 48 hours postdose, the predominant species was uric acid, accounting for 97.6% of the total [^{14}C]-radioactivity quantified. Over the 96-hour period following TAF administration, the predominant species circulating in plasma was uric acid, which accounted for 73.9% of the total [^{14}C]-radioactivity AUC over the 96-hour period; TAF and TFV AUC represented 1.8% and 1.5% of the total [^{14}C]-radioactivity AUC, respectively. In addition to TFV and uric acid, additional low quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine. They are identical to the endogenous products of purine metabolism and should not cause any safety risk. **Conclusions:** • TAF was extensively metabolized and eliminated in urine and feces. The mean ± SD cumulative urinary and fecal recovery of [^{14}C]-radioactivity was 84.4% ± 2.45% (N = 7), with the percentage of radioactive dose recovered from feces at 47.2% ± 4.62% (N = 7) and the percentage of radioactive dose recovered from urine at 36.2% ± 5.62% (N = 8). The predominant species detected in feces and urine was TFV. Renal excretion of TAF as parent drug was a very minor pathway for elimination. • The predominant species circulating in plasma was uric acid, which accounted for 73.9% of the total [^{14}C]-radioactivity AUC over the 96-hour period. At the first maximal plasma radioactivity concentration around 2 hours postdose, the predominant species was TAF. At the second maximal plasma radioactivity concentration around 24 to 48 hours postdose, the predominant species was uric acid. Additional low quantities of metabolites were formed, including xanthine, hypoxanthine, and adenine, which were identical to the endogenous products of purine metabolism. • TAF 25-mg capsules, administered together with a tracer dose of [^{14}C]-radiolabeled TAF as a single oral capsule, were well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to discontinuation of study drug were reported during this study.

1.1.2. Studies in HIV-or HBV-Infected Subjects

1.1.2.1. GS-US-120-0104

Location:	GS-US-120-0104
Title:	Study GS-US-120-0104: A Phase 1, Randomized, Partially Blinded, Active and Placebo Controlled Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-7340 Monotherapy in Subjects with HIV-1
Primary Objective(s):	To evaluate the short-term antiviral potency of TAF 8 mg, 25 mg, and 40 mg as compared with placebo-to-match TAF or TDF 300 mg, each administered once daily as monotherapy for 10 days, with respect to the time-weighted average change from baseline at Day 11 ($DAVG_{11}$) in plasma HIV-1 RNA (log_{10} copies/mL)
Study Design and Subject Population:	This Phase 1, randomized, partially-blinded, active- and placebo-controlled study evaluated the safety, PK, and antiviral activity of TAF monotherapy in HIV-infected subjects. Subjects were randomized in a 2:2:2:1:2 ratio to one of the following 5 treatment groups: • **Treatment Group 1:** TAF 8 mg • **Treatment Group 2:** TAF 25 mg • **Treatment Group 3:** TAF 40 mg • **Treatment Group 4:** TDF 300 mg • **Treatment Group 5:** Placebo-to-match TAF tablet Treatments 1, 2, 3 and 5 (TAF and matched placebo) were blinded, while Treatment 4 (TDF) was open label. A total of 38 eligible subjects were randomized into the study and received treatment. Nine subjects received TAF 8 mg, 8 subjects received TAF 25 mg, 8 subjects received TAF 40 mg, 6 subjects received open-label TDF 300 mg, and 7 subjects received placebo-to-match TAF. All 38 subjects completed the study drug. A total of 37 subjects completed the study; 1 subject was lost to follow-up. At baseline, the median estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) was 113.8 mL/min (range: 64.2 to 173.9 mL/min). At baseline, no subjects showed resistance to NRTIs or protease inhibitors (PIs); 2 subjects showed resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs).
Summary of Results and Conclusions:	**Efficacy Results:** Median $DAVG_{11}$ for plasma HIV-1 RNA (log_{10} copies/mL) levels showed significantly greater decreases in the TAF treatment groups and TDF 300-mg treatment group compared with the placebo-to-match TAF treatment group (TAF 8 mg [−0.76 versus −0.01], 25 mg [−0.94 versus −0.01], and 40 mg [−1.08 versus −0.01], p = 0.001 each TAF treatment group and TDF 300 mg [−0.48 versus −0.01], p = 0.038). The median $DAVG_{11}$ (log_{10} copies/mL) in the TAF 25-mg and 40-mg treatment groups showed significantly greater decreases compared with the TDF 300-mg treatment group (−0.94 and −1.08 versus −0.48, p = 0.017 and p = 0.006, respectively) with a statistically significant difference also observed between the TAF 8-mg and 40-mg treatment groups (−0.76 versus −1.08, p = 0.003). The decrease in plasma HIV-1 RNA levels from baseline to Day 11 was significantly greater for groups that received TAF 25 mg (p = 0.024) and TAF 40 mg (p = 0.003) compared with the group that received TDF 300 mg. The first phase decay slopes for plasma HIV-1 RNA for the TAF-25 mg and TAF-40 mg treatment groups were significantly steeper than for the TDF 300-mg treatment group (p = 0.012 and p = 0.006, respectively). There was no statistically significant difference in changes from baseline in cluster determinant (CD) 4 cell count when comparing treatment groups at any visit during the study.

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

Pharmacokinetic/Pharmacodynamic Results:

Pharmacokinetic parameters of plasma TAF, plasma TFV, and intracellular TFV-DP (previously referred to as PMPApp) are presented in the following 3 tables, respectively.

Summary of Steady-State PK Parameter Estimates for TAF Following Once-Daily Dosing of TAF (TAF PK Analysis Set)

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

a n = 8.

AUC_{last} is presented for multiple-dose PK because TAF concentrations are BLQ by approximately 5 hours postdose and utilizing AUC_{last} instead of AUC_{inf} or AUC_{tau}, respectively, provides a more appropriate measure of exposure assessment. To account for the variability in the data, the mean and median AUC_{last} and C_{max} are presented.

Summary of Single-Dose and Steady-State PK Parameter Estimates for TFV Following Once-Daily Dosing of TAF (TFV PK Analysis Set)

	TFV Single-Dose PK[a] Day 1				TFV Multiple-Dose PK Day 10			
TFV PK Parameter	**TAF 8 mg (n = 9)**	**TAF 25 mg (n = 8)**	**TAF 40 mg (n = 8)**	**TDF 300 mg (n = 6)**	**TAF 8 mg (n = 9)**	**TAF 25 mg (n = 8)**	**TAF 40 mg (n = 8)**	**TDF 300 mg (n = 6)**
AUC^{b}, Mean (%CV)	49.4 (30.3)	195.9 (27.2)	287.3 (33.7)	1719.2 (57.9)	65.5 (23.5)	267.7 (26.7)	405.8 (12.7)	1918.0 (39.4)
C_{max} (ng/mL), Mean (%CV)	2.0 (31.1)	6.5 (40.1)	14.0 (20.3)	181.2 (50.5)	4.2 (24.7)	15.7 (22.1)	28.3 (8.7)	252.1 (36.6)
C_{tau} (ng/mL), Mean (%CV)	0.7 (19.8)	2.4 (23.5)	4.0 (27.2)	23.9 (57.5)	2.1 (33.8)	9.2 (26.1)	13.3 (16.0)c	38.7 (44.7)
T_{max} (h), Median (Q1, Q3)	1.00 (1.00, 2.00)	1.50 (1.03, 1.75)	1.00 (0.75, 1.00)	1.25 (0.53, 1.50)	1.50 (1.00, 1.98)	1.50 (1.25, 1.75)	1.29 (1.04, 1.50)	1.25 (0.58, 2.00)
$t_{1/2}$ (h), Median (Q1, Q3)	23.85 (18.32, 37.17)[c]	29.83 (26.87, 44.00)[c]	24.55 (20.33, 28.25)	15.56 (14.17, 17.07)	30.77 (26.90, 55.61)[d]	40.19 (28.98, 44.84)	35.95 (26.38, 42.90)c	14.86 (12.18, 16.81)

a AUC_{inf} and C_{24h} are presented for single-dose PK.
b AUC_{inf} is presented for single-dose PK and AUC_{tau} is presented for multiple-dose PK.
c n = 7.
d n = 8.

Summary of Steady-State PK Parameter Estimates for Intracellular TFV-DP Following Once-Daily Dosing of TAF (TFV-DP PK Analysis Set)

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

To account for the variability in the data, the mean and median AUC_{tau} are presented.

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

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

Conclusions:

- The antiviral effect of TAF 8 mg was similar to TDF 300 mg, and increased with higher doses of TAF. As measured by change from baseline in HIV-1 RNA and $DAVG_{11}$, statistically greater decreases were observed between the 25-mg ($p = 0.017$) and 40-mg ($p = 0.006$) doses of TAF compared with the TDF 300-mg treatment group. The decrease in plasma HIV-1 RNA levels from baseline to Day 11 was significantly greater for groups that received TAF 25 mg ($p = 0.024$) and TAF 40 mg ($p = 0.003$) compared with the group that received TDF 300 mg. Analysis of early decline in plasma HIV-1 RNA indicates that the 25-mg and 40-mg doses of TAF may be more potent than TDF 300 mg. There was no statistically significant difference in changes from baseline in CD4 cell count when comparing treatment groups at any visit during the study. Viral resistance to TAF or TDF did not develop in this study. Postbaseline virology data were available for 37 of the 38 subjects (97.4%); none of whom developed NRTI-R, NNRTI-R, or PI-R mutations by standard genotypic analyses.
- In comparison to TDF, which is undetectable in plasma, plasma PK of TAF in this study lends support to existing evidence that TAF is more stable in plasma. TAF was rapidly absorbed with detectable levels by 0.25 hours postdose, with a $t_{1/2}$ of approximately 0.40 hours. TFV plasma concentrations were substantially higher when given as TDF. At steady state, following multiple dose administration of TAF 8 mg, 25 mg, and 40 mg, the mean TFV AUC_{tau} values were 97%, 86%, and 79% lower, respectively, as compared with the mean TFV AUC_{tau} observed when dosed as TDF 300 mg. Intracellular PBMC TFV-DP AUC_{tau} was similar when given as TAF 8 mg or TDF 300 mg, whereas for TAF 25 mg and 40 mg, the mean intracellular TFV-DP AUC_{tau} values were approximately 7-fold and approximately 25-fold higher, relative to TDF 300 mg.
- The 8-mg, 25-mg, and 40-mg doses of TAF were well tolerated during this clinical study of HIV-infected subjects and showed safety profiles similar to that of the TDF 300-mg treatment group. One subject receiving TAF 25 mg experienced a treatment-emergent SAE (chest pain), considered unrelated to study drug. No Grade 3 or 4 AEs occurred in subjects who received TAF. No deaths or AEs leading to study drug discontinuation occurred during this study.

1.1.2.2. GS-US-320-0101

Location:	GS-US-320-0101
Title:	Study GS-US-320-0101: A Phase 1b Randomized, Open Label, Active Controlled Study to Assess the Safety, Viral Kinetics, and Anti-HBV Activity of GS-7340 in Treatment Naive Adults with Chronic Hepatitis B (CHB) Infection
Primary Objective(s):	To evaluate the differences in short-term antiviral activity between doses of TAF (8, 25, 40, and 120 mg) with respect to the time weighted average change from baseline through Week 4 ($DAVG_4$) in serum HBV DNA (log_{10} IU/mL)
Study Design and Subject Population:	This Phase 1b, randomized, open-label, active-controlled study assessed the safety, viral kinetics, and anti-HBV activity of TAF in adult subjects with CHB over 28 days of therapy. In addition, PK of TFV and TAF following administration of TAF and the PK of TFV following administration of TDF were investigated. Subjects were randomized 1:1:1:1:1 to receive treatment with TAF at 8, 25, 40, or 120 mg or TDF 300 mg orally once daily. Eligible subjects were males or nonpregnant, nonlactating females with documented CHB infection at least 6 months in duration, treatment naive, 18 to 65 years old, with an estimated creatinine clearance (CL_{cr}) ≥ 70 mL/min (using the Cockcroft-Gault method), and noncirrhotic based on recent biopsy or noninvasive assessment. A total of 51 subjects were randomized into the study. Ten subjects received TAF 8 mg, 10 subjects received TAF 25 mg, 11 subjects received TAF 40 mg, 10 subjects received TAF 120 mg, and 10 subjects received TDF 300 mg. A total of 50 subjects completed the study, 1 subject completed study drug treatment and was subsequently lost to follow-up. Of the 51 randomized subjects, 27 (52.9%) and 24 (47.1%) were hepatitis B e antigen (HBeAg)-negative and HBeAg-positive, respectively. The most common HBV genotype at enrollment was genotype C (16/51; 31.4%), with similar proportions within groups of other genotypes: A (7/51; 13.7%), B (10/51; 19.6%), D (9/51; 17.6%), and E (9/51; 17.6%).
Summary of Results and Conclusions:	**Efficacy Results:** Similar declines in HBV DNA levels were observed across TAF groups as well as in the TDF group over 28 days of treatment (51 subjects completing 28 days of treatment). Given this, the inferential comparison between TAF treatment groups to select the optimal dose and noninferiority assessment between the TAF optimal dose and TDF based on $DAVG_4$, which were planned in the study protocol, were not done for the final analysis. Only summary statistics were provided for the primary and secondary efficacy endpoints. The median $DAVG_4$ for serum HBV DNA after 28 days of treatment were −2.18, −2.05, −1.69, −2.15, and −2.31 log_{10} IU/mL in TAF 8, 25, 40, 120 mg and TDF 300 mg, respectively. Median $DAVG_1$, $DAVG_2$, and $DAVG_3$ were comparable across all TAF treatment groups, except TAF 40 mg, and were comparable with the TDF group. As early as Week 2, smaller DAVG values were seen in the TAF 40-mg group, which was reflective of the lower baseline HBV DNA values seen in this treatment group as some subjects had reached the lower limit of assay detection (29 IU/mL) prior to Week 2. All treatment groups demonstrated similar viral suppression over the treatment duration of 28 days (4 weeks), with no perceivable differences in the potency of TAF across the dose range of 8 to 120 mg. Viral suppression with TAF 8, 25, 40, and 120 mg was comparable with that seen with TDF 300 mg over 4 weeks. Consistently smaller declines in HBV DNA, and slightly lower median change from baseline in HBV DNA at Day 29 were observed in the TAF 40-mg group, which is likely due to lower baseline HBV DNA values in comparison to the other groups. In the TAF 40-mg group, the first quartile (Q1) at baseline (3.42 log_{10} IU/mL) was the smallest among all groups indicating more subjects with lower baseline values were randomized into this group. Consistent with this finding, in the TAF 40-mg group, 8 of 11 subjects (72.7%) were HBeAg-negative and mean changes in HBV DNA were similar for this group compared with the other TAF groups and TDF. Median first phase decay slopes were −0.101, −0.090, −0.071, −0.097, and −0.087 log_{10} IU/mL for the TAF 8-, 25-, 40-, 120-mg, and TDF 300-mg treatment groups, respectively. No inferential comparisons were made between the TAF and TDF treatment groups.

Over 28 days of treatment, alanine aminotransferase (ALT) levels changed minimally across treatment groups. Consistent slight declines in median ALT levels were observed in the TAF 8- and 25-mg groups, whereas consistent slight increases or no change in ALT levels were observed in the TAF 40-and 120-mg groups. At Day 29, median change from baseline in ALT was greatest for the TAF 25-mg group (−9.0 U/L) followed by the TAF 8-mg group (−2.5 U/L). The TDF group showed fluctuations in median change from baseline in ALT over the treatment period with a median change of 0 U/L at Day 29. During the 4-week follow-up period, persistent slight declines in ALT were seen in the TAF 8- and 25-mg groups, while ALT levels remained relatively stable in the other two groups (40- and 120-mg). At the end of the study (follow-up Week 8), the median change from baseline in ALT level in the TDF 300-mg group (−4.0 U/L) was comparable with the TAF 8- and 25-mg groups (−7.5 U/L and −5.5 U/L, respectively).

No discernible changes from baseline in quantitative HBsAg levels after 28 days of treatment were observed. The median changes from baseline at Day 29 were the following: 0.00 $\log_{10}$ IU/mL for TAF 8 and 25 mg, −0.02 $\log_{10}$ IU/mL for TAF 40 and 120 mg, and 0.04 $\log_{10}$ IU/mL for TDF 300 mg.

Although allowed by protocol, the majority of subjects did not receive oral anti-HBV therapy during the follow-up period of the study. Overall, 10 of 10 subjects (100%) in the TAF 8-mg group, 9 of 10 (90%) subjects in the 25-mg group, 10 of 11 subjects (91%) in the TAF 40-mg group, 8 of 10 subjects (80%) in the TAF 120-mg group, and all 10 subjects (100%) in the TDF 300-mg group elected not to receive OAV therapy. Four subjects elected to receive antiviral therapy (ETV) during the follow-up phase of the study. The median HBV DNA levels at Day 29 for subjects who did not receive oral anti-HBV therapy were 3.98, 3.45, 2.12, 1.69, and 1.74 $\log_{10}$ IU/mL in the TAF 8-, 25-, 40-, 120- mg and TDF 300-mg groups, respectively. By the end of the study, follow-up Week 8, median HBV DNA levels had returned toward baseline levels. The median changes from Day 29 at follow-up Week 8 for subjects who did not have oral anti-HBV therapy during the follow-up period in the TAF 8-, 25-, and 120-mg groups (2.25, 2.24, and 2.17 $\log_{10}$ IU/mL, respectively) were comparable with the median change in subjects from the TDF 300-mg group (2.21 $\log_{10}$ IU/mL). The TAF 120-mg group showed a lag in the smallest increase in HBV DNA levels from Day 29 until follow-up Week 6; however, from follow-up Week 6 to follow-up Week 8, the levels in this group increased to values comparable with the other groups, including the TDF group.

Pharmacokinetic Results:

At the dose of TAF 25 mg, mean TFV exposure (AUC_{inf}) was reduced by 92% in comparison with TDF 300 mg. The TAF dose of 25 mg was selected as it is consistent with exposures seen in the HIV program (Studies GS-US-120-0104 and GS-US-120-1101) and offers the greatest opportunity to demonstrate noninferior efficacy to TDF 300 mg in Phase 3 studies. Furthermore, the incremental reduction in TFV exposure with TAF 8 mg compared with TAF 25 mg was only 5% and was not expected to offer an important safety advantage over TAF 25 mg.

Conclusions:

- TAF was safe and well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to discontinuation of study drug were reported during this study. The safety profile for TAF did not differ among dose groups and was similar to that of TDF. Furthermore, at Day 29, declines in CL_{cr} with TAF 25 mg were found to be smaller than those seen with TDF 300 mg.
- At the TAF doses studied, no differences were observed in HBV DNA declines among the TAF groups and in comparison with the TDF 300-mg group at Day 29.
- TAF exposures were dose proportional and linear on Day 1 over the dose range of 8 to 120 mg.
- At lower TAF doses (8 mg and 25 mg), substantial reductions in TFV exposures (≥ 92%) relative to TFV exposures with TDF 300 mg were observed. The reduced TFV exposure seen with TAF 25 mg in CHB subjects is comparable with the reduction seen in HIV infected subjects treated with TAF 25 mg as a standalone product. Furthermore, the reduction in TFV exposure with TAF 25 mg in CHB subjects is therapeutically consistent with that seen with TAF 10 mg when included in the E/C/F/TAF FDC (due to an inhibitory drug interaction between TAF and COBI included in the FDC).
- These data support the selection of TAF 25 mg for future pivotal studies in subjects with CHB.

1.1.3. Intrinsic Factor Studies

1.1.3.1. GS-US-120-0108

Location:	GS-US-120-0108
Title:	Study GS-US-120-0108: A Phase 1, Open Label, Parallel Design Study to Evaluate the Pharmacokinetics of GS-7340 in Subjects with Severe Renal Impairment
Primary Objective(s):	To evaluate the PK of TAF and its metabolite TFV following administration of TAF in subjects with severe renal impairment and matched healthy subjects (control group)
Study Design and Subject Population:	This was a Phase 1 open-label, parallel-design, single-dose, PK study of TAF in subjects with severe renal impairment (defined as having an $eGFR_{CG}$ of $15 \leq eGFR_{CG} \leq 29$ mL/min at screening [severe renal impairment group]) and matched healthy subjects with normal renal function (control group). Each subject received a single dose of TAF 25 mg (1 × 25-mg tablet) administered orally on Day 1. A total of 14 subjects with severe renal impairment ($eGFR_{CG}$ 15-29 mL/min) and 13 matched control subjects with normal renal function ($eGFR_{CG} \geq 90$ mL/min) were enrolled and received a single oral dose of TAF 25 mg. Median $eGFR_{CG}$ at predose was 25.5 mL/min (range: 13.1 to 32.6 mL/min) in the severe renal impairment group and was 94.2 mL/min (range: 84.3 to 140.2 mL/min) in the normal renal function group. All 27 subjects completed the study and were included in the PK and Safety Analysis Sets.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure as assessed by AUC_{inf} relative to subjects with normal renal function, as presented in the table below. This difference was not considered clinically relevant as it was less than a 2-fold difference. Subjects with severe renal impairment had a 6.05-fold mean increase in systemic TFV exposure as assessed by AUC_{inf} relative to subjects with normal renal function, as presented in the table below. The TFV exposure encountered in subjects with severe renal impairment in this study after a single dose of TAF 25 mg was within or below the range of TFV plasma exposures measured in other studies after administration of TDF 300 mg in subjects and patients with normal renal function. TAF plasma protein binding measured at 1 and 4 hours was similar between subjects with severe renal impairment and subjects with normal renal function (mean percentage unbound was approximately 20% at 1 hour and approximately 14% at 4 hours in both groups). TFV plasma protein binding measured at 2 and 24 hours was also similar between subjects with severe renal impairment and subjects with normal renal function (mean percentage unbound ranged from 97% to 99% at both time points in both groups).

Summary of PK Parameter Estimates for TAF and TFV Following a Single Dose of TAF 25 mg in Subjects with Severe Renal Impairment or Normal Renal Function

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

Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Subjects With Severe Renal Impairment and Subjects With Normal Renal Function

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

Conclusions:

- Plasma TAF exposure in subjects with severe renal impairment was less than 2-fold higher than TAF exposure in matched controls with normal renal function. Plasma TFV exposure in subjects with severe renal impairment, while higher, was within or below the range of TFV exposures achieved as part of a TDF-containing regimen in historical subjects with normal renal function. There were no differences in the protein binding of TAF and TFV between subjects with severe renal impairment and subjects with normal renal function.
- Single doses of TAF 25 mg were well tolerated in subjects with severe renal impairment and in subjects with normal renal function in this study. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to study drug discontinuation occurred during this study.
- Given the extensive safety data available for TDF and the observation that TFV exposure in subjects with severe renal impairment in this study was within or below the range of those from TDF in subjects with normal renal function, TAF dose or schedule modification may not be required and warrants further study.

1.1.3.2. GS-US-120-0114

Location:	GS-US-120-0114
Title:	Study GS-US-120-0114: A Phase 1, Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of Tenofovir Alafenamide in Subjects with Normal and Impaired Hepatic Function
Primary Objective(s):	To evaluate the PK of TAF in subjects with normal and impaired hepatic function
Study Design and Subject Population:	This was a Phase 1, 2-cohort, open-label, multicenter, single-dose, parallel-group study of the safety, tolerability, and PK of TAF in subjects with normal and impaired hepatic function. Subjects were enrolled in 1 of the following 2 cohorts, each containing a group of subjects with impaired hepatic function and a group of normal, matched controls: **Cohort 1:** • **Group 1:** Subjects with mild hepatic impairment (Child-Pugh-Turcotte [CPT] Class A score of 5 to 6) (n = 10) • **Group 2:** Subjects with normal hepatic function (n = 10) **Cohort 2:** • **Group 1:** Subjects with moderate hepatic impairment (CPT Class B score of 7 to 9) (n = 10) • **Group 2:** Subjects with normal hepatic function (n = 10) All subjects received a single, oral dose of TAF 25 mg on Day 1. A total of 40 subjects (10 subjects each in the mild or moderate hepatic impairment group and 20 subjects in the normal hepatic function group, each matched to a mildly or moderately impaired subject, respectively) were enrolled in and completed the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The means (%CV) and geometric least-squares mean (GLSM) ratios (%; 90% CI) of TAF and TFV plasma exposure parameters following a single dose of TAF to subjects with mild or moderate hepatic impairment and to normal matched control subjects are shown in the tables below . **Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Subjects With Mild Hepatic Impairment and Subjects With Normal Hepatic Function**

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

GLSMs were obtained using a mixed-effects model.

Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function

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

GLSMs were obtained using a mixed-effects model.

TAF Exposure

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

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

TFV Exposure

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

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

Protein Binding

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

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

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

Conclusions:

- No clinically relevant changes in TAF or TFV PK were observed in subjects with mild or moderate hepatic impairment compared with the normal matched control subjects following administration of a single dose of TAF. There were no clinically relevant differences in protein binding of TAF and TFV between hepatically impaired subjects and their matched controls. No clinically relevant correlation between TAF or TFV exposure parameters (AUC_{inf}, AUC_{last}, and C_{max}) and CPT score or its individual laboratory components were observed. Accordingly, the results from this study indicate that no dose adjustment of TAF is necessary in subjects with mild or moderate hepatic impairment.
- Single doses of TAF 25 mg were generally well tolerated in subjects with mild or moderate hepatic impairment and in subjects with normal hepatic function. No Grade 3 or 4 AEs, deaths, SAEs, or AEs leading to permanent discontinuation of study drug were reported during this study.

1.1.3.3. GS-US-320-1615

Location:	GS-US-320-1615
Title:	Study GS-US-320-1615: A Phase 1, Open-Label, Parallel-Group, Single Dose Study to Evaluate the Pharmacokinetics of Tenofovir Alafenamide (TAF) in Subjects with Normal Hepatic Function and Subjects with Severe Hepatic Impairment
Primary Objective(s):	To evaluate the single-dose PK of TAF and its metabolite TFV in subjects with normal hepatic function and subjects with severe hepatic impairment
Study Design and Subject Population:	This Phase 1, open-label, multicenter, single-dose, parallel-group study evaluated the safety, tolerability, and PK of TAF in subjects with normal hepatic function or severe hepatic impairment (CPT C: score 10-15). Each subject in the healthy control group (hereafter referred to as the normal matched control group) was matched with a subject in the severe hepatic impairment group by age, sex, and BMI. All subjects received a single oral dose of TAF 25 mg on Day 1. In addition to PK sampling, additional aliquots for determination of percent protein binding in plasma were collected. Protein binding of TAF was determined at 37°C by the ultrafiltration method using Centrifree® ultrafiltration devices. Protein binding of TFV in human plasma samples was determined at 37°C by an equilibrium dialysis method using the single-use plate rapid equilibrium dialysis (RED) device. A total of 20 subjects were enrolled in the study with 10 subjects in each of the treatment groups (ie, severe hepatic impairment and normal matched control). All 20 subjects received study drug and completed the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The plasma exposure parameters of TAF (AUC_{inf}, AUC_{last}, and C_{max}) were lower in subjects with severe hepatic impairment compared with normal matched control subjects, with GLSM ratios (%) of 54.04%, 51.20%, and 45.10%, respectively. Similar to TAF, lower plasma exposures of TFV were observed in the severe hepatic impairment group compared with the normal matched control group. The GLSM ratios (%) of TFV were 63.06% (AUC_{inf}), 62.04% (AUC_{last}), and 89.88% (C_{max}).

PK Parameter	Severe Hepatic Impairment Group (N = 10)	Normal Matched Control Group (N = 10)	GLSM Ratio (%) (90% CI)
TAF 25 mg: Mean (%CV) (TAF PK Analysis Set)			
AUC_{inf} (ng•h/mL)	120.6 (28.2)	228.2 (37.4)	54.04 (41.98, 69.56)
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)
TAF 25 mg: Mean (%CV) (TFV PK Analysis Set)			
AUC_{inf} (ng•h/mL)	219.9 (54.0)	304.0 (23.8)	63.06 (42.90, 92.70)
AUC_{last} (ng•h/mL)	184.2 (54.2)	256.7 (23.3)	62.04 (41.92, 91.82)
C_{max} (ng/mL)	7.5 (52.4)	7.6 (24.0)	89.88 (64.77, 124.72)

	The lower mean total TAF exposures observed were accompanied by an increase of free fraction (as percent unbound TAF) in subjects with severe hepatic impairment (37.8%) compared with normal matched control subjects (20.4%). When the free fraction was considered, the free TAF exposures were comparable between the 2 study groups (AUC_{last} of 41.7 ng•h/mL and AUC_{inf} of 42.8 ng•h/mL in the severe hepatic impairment group versus AUC_{last} of 46.0 ng•h/mL and AUC_{inf} of 46.5 ng•h/mL in the normal matched control group). The percent unbound TFV was high in all subjects (> 95%) regardless of hepatic status. The GLSM ratios (%) of free TAF were 94.42% (free AUC_{inf}), 93.28% (free AUC_{last}), and 82.16% (free C_{max}). Exploratory analyses indicated no clinically relevant correlations between TAF or TFV exposures (total concentrations) versus baseline CPT score. When TAF exposures (total concentrations) in all subjects were plotted against the individual laboratory components (ie, albumin, total bilirubin, and prothrombin time or international normalized ratio [INR]), correlations were consistent with the lower PK exposures of TAF and the characteristics of the severe hepatic impairment group. In severe hepatic impairment subjects, lower albumin values, higher total bilirubin, prolonged prothrombin time, and higher INR were correlated with lower TAF exposures. Similar but less prominent trends were observed with TFV. When the free fraction of TAF was considered, no significant correlation was observed between the free TAF exposures and the individual laboratory components of the CPT score. **Conclusions:** • Total (bound and unbound) TAF exposure (AUC_{last}) was 49% lower in subjects with severe hepatic impairment relative to normal matched control subjects; however, due to an increase of free fraction (ie, as percent unbound TAF) in subjects with severe hepatic impairment, the free TAF exposure was comparable between the 2 study groups. Accordingly, as the free TAF moiety is associated with therapeutic effect, no change in TAF efficacy is expected in patients with severe hepatic impairment. • Dose adjustment of TAF is not necessary for patients with severe hepatic impairment • A single dose of TAF 25 mg was safe and well tolerated by subjects with severe hepatic impairment and normal matched control subjects. No deaths, Grade 4 AEs, or AEs leading to study drug discontinuation occurred during this study. One subject in the severe hepatic impairment group had an SAE of Grade 3 hepatic failure (unrelated to study drug) during the posttreatment follow-up phase of the study.

1.1.4. Extrinsic Factor Studies

1.1.4.1. GS-US-120-0117

Location:	GS-US-120-0117
Title:	Study GS-US-120-0117: A Phase 1 Single-Dose Study Evaluating the Pharmacokinetic Drug Interaction Potential between Rilpivirine and Tenofovir Alafenamide
Primary Objective(s):	To evaluate the PK of RPV and TAF following single-dose administration of RPV and TAF alone and in combination in healthy subjects
Study Design and Subject Population:	This was a Phase 1, open-label, single-center, single-dose, crossover study in healthy adult subjects. Subjects were enrolled in 1 of the following 2 cohorts to receive 2 treatments in a randomized sequence with a 10-day washout period between treatments: **Cohort 1:** • **Treatment A:** TAF 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal • **Treatment B:** TAF 25 mg + RPV 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal **Cohort 2:** • **Treatment B:** TAF 25 mg + RPV 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal • **Treatment C:** RPV 25 mg administered in the morning within 5 minutes of completion of a standard moderate-fat meal All 36 randomized subjects completed the study (18 subjects in Cohort 1 and 18 subjects in Cohort 2). All subjects were included in the Safety Analysis Set and all PK Analysis Sets.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** There was no clinically meaningful drug interaction between TAF and RPV as the 90% CIs of the GMRs were all contained in the predefined no-drug interaction boundary of 70% to 143% in exposure or C_{max} of TAF, TFV, or RPV when TAF is coadministered with RPV versus when TAF or RPV was administered alone. **Statistical Comparisons of TAF, TFV, and RPV PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)**

	Mean (%CV) by Treatment			
TAF PK Parameter	**TAF+RPV Cohort 1 (N = 18)**	**TAF+RPV Cohort 2 (N = 18)**	**TAF Cohort 1 (N = 18)**	**GLSM Ratio (90% CI), %**
AUC_{inf} (ng•h/mL)	262.4 (54.6)	247.8 (27.3)	263.4 (42.7)	95.91 (83.65, 109.97)
AUC_{last} (ng•h/mL)	260.1 (55.3)	245.2 (27.2)	261.4 (43.1)	95.55 (82.89, 110.13)
C_{max} (ng/mL)	231.8 (91.9)	200.9 (45.6)	201.4 (54.3)	101.19 (82.76, 123.71)
	Mean (%CV) by Treatment			
TFV PK Parameter	**TAF+RPV Cohort 1 (N = 18)**	**TAF+RPV Cohort 2 (N = 18)**	**TAF Cohort 1 (N = 18)**	**GLSM Ratio (90% CI), %**
AUC_{inf} (ng•h/mL)	279.5 (27.1)	268.9 (22.1)	257.3 (27.9)	108.75 (102.43, 115.46)
AUC_{last} (ng•h/mL)	238.4 (26.1)	237.1 (21.9)	222.4 (25.8)	106.99 (101.69, 112.58)
C_{max} (ng/mL)	8.7 (33.8)	8.1 (27.1)	7.2 (25.3)	118.10 (107.33, 129.96)

RPV PK Parameter	Mean (%CV) by Treatment			GLSM Ratio (90% CI), %
	TAF+RPV Cohort 1 (N = 18)	TAF+RPV Cohort 2 (N = 18)	RPV Cohort 2 (N = 18)	
AUC_{inf} (ng•h/mL)	3201.7 (45.2)	3677.9 (40.0)	3949.8 (30.2)	89.18 (76.15,104.44)
AUC_{last} (ng•h/mL)	2425.2 (41.0)	2662.3 (32.9)	2767.3 (26.2)	93.46 (80.70,108.23)
C_{max} (ng/mL)	89.3 (36.5)	104.3 (40.2)	105.9 (30.1)	94.50 (79.74,112.00)

Conclusions:

- Rilpivirine and TAF coadministration does not result in clinically relevant changes in RPV, TAF, or TFV exposure and no dose adjustments are necessary.
- Single doses of TAF 25 mg, TAF 25 mg + RPV, and RPV were generally well tolerated in these healthy subjects. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to discontinuation of study drug were reported.

1.1.4.2. GS-US-120-0118

Location:	GS-US-120-0118
Title:	Study GS-US-120-0118: A Pharmacokinetic Study Evaluating the Drug Interaction Potential of Tenofovir Alafenamide with a Boosted Protease Inhibitor or Unboosted Integrase Inhibitor in Healthy Subjects
Primary Objective(s):	• To evaluate the effect of common boosted PIs ATV+ritonavir (RTV); darunavir (DRV)+RTV; RTV-boosted lopinavir (LPV/r), or the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) on the PK of TAF • To evaluate the PK of ATV, DRV, LPV, and DTG alone and in combination with FTC and TAF
Study Design and Subject Population:	This was a Phase 1, open-label study of the PK drug interaction potential of TAF with the RTV-boosted PIs ATV+RTV, DRV+RTV, and LPV/r, or the INSTI DTG, in healthy adult subjects. Subjects received a single dose of TAF 10 mg + FTC 200 mg, followed by 13 days of daily dosing of ATV+RTV, DRV+RTV, LPV/r, or DTG, followed by an additional single dose of TAF 10 mg + FTC 200 mg administered in the presence of steady-state RTV-boosted PI or unboosted DTG. Subjects were enrolled in 1 of 4 treatment cohorts. The following study treatments were administered: • **Treatment A = Treatment F:** FTC 200 mg + TAF 10 mg once, administered in the morning with food • **Treatment B:** ATV 300 mg + RTV 100 mg once daily, administered in morning with food • **Treatment C:** DRV 800 mg + RTV 100 mg once daily, administered in morning with food • **Treatment D:** 4 × LPV/r 200/50 mg once daily, administered in morning with food • **Treatment E:** DTG 50 mg once daily, administered in the morning with food

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

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

Summary of Results and Conclusions:

Pharmacokinetic Results:

Coadministration of ATV+RTV or LPV/r with FTC+TAF increased TAF exposures approximately 91% and 47%, respectively, versus FTC+TAF alone, as shown in the table below. Following dosing with DRV+RTV or DTG, the TAF exposure was unchanged.

Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

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

Coadministration of ATV+RTV, DRV+RTV, or LPV/r with FTC+TAF increased TFV exposures approximately 162%, 105%, and 316%, respectively, versus FTC+TAF alone, as presented in the table below. Following dosing with DTG, TFV exposures were unchanged.

Statistical Comparisons of TFV PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

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

Coadministration of TAF 10 mg + FTC 200 mg had no effect on the PK of RTV-boosted PIs or DTG, as presented in the table below.

Statistical Comparisons of ATV, DRV, LPV, and DTG PK Parameter Estimates Between Test and Reference Treatments (PK Analysis Sets)

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

Conclusions:

- Coadministration of FTC+TAF with DTG does not result in clinically relevant changes in TAF or TFV exposure. Coadministration of FTC+TAF with ATV+RTV or LPV/r resulted in increased TAF and TFV exposures. Coadministration of FTC+TAF with DRV+RTV does not result in clinically relevant changes in TAF but resulted in increased TFV exposures.
- Coadministration of FTC+TAF with ATV+RTV, DRV+RTV, LPV/r, and DTG was generally well tolerated in these healthy subjects. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to discontinuation of study drug were reported.

1.1.4.3. GS-US-120-1538

Location: GS-US-120-1538

Title: Study GS-US-120-1538: A Fixed-Sequence, Open-Label, Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Midazolam (Oral and Intravenous) in Healthy Volunteers

Primary Objective(s): To evaluate the effect of TAF on the PK of oral midazolam (MDZ_{oral}) and intravenous (IV) midazolam (MDZ_{IV})

Study Design and Subject Population: This Phase 1, open-label, fixed-sequence, multiple-dose, single-center study evaluated PK and potential drug interactions between TAF and MDZ (oral and IV) in healthy subjects. All study drugs were administered in the morning under fed conditions in a fixed-sequence as follows:

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

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

A total of 18 subjects were enrolled in the study, all of whom completed study treatment in the protocol-specified sequence, and all completed the study.

Summary of Results and Conclusions:

Pharmacokinetic Results:

Following administration of TAF+MDZ_{oral} compared with MDZ alone, the 90% CIs of the AUC_{last}, AUC_{inf}, and C_{max} GLSMs for MDZ and a MDZ metabolite (1′-OH MDZ; 1′-hydroxymidazolam) were within the lack-of-interaction bounds (70% to 143%), as shown in the first table below. Following administration of TAF+MDZ_{IV} compared with MDZ_{IV} alone, the 90% CIs of the AUC_{last}, AUC_{inf}, and C_{max} GLSMs for MDZ and 1′-OH MDZ were also within the lack-of-interaction bounds, as shown in the second table below. These data suggest that multiple-dose TAF does not affect presystemic or systemic cytochrome P450 enzyme (CYP) 3A activity.

Statistical Comparisons of MDZ_{oral} and 1′-OH MDZ_{oral} PK Parameter Estimates Between Study Treatments (MDZ_{oral} PK Analysis Set)

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

Statistical Comparisons of MDZ_{IV} and 1′-OH MDZ_{IV} PK Parameter Estimates Between Study Treatments (MDZ_{IV} PK Analysis Set)

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

Conclusions:

- Following coadministration of MDZ (oral or IV) and TAF relative to MDZ alone, no clinically relevant differences in MDZ exposures were observed, indicating that multiple dose TAF does not inhibit or induce CYP3A in vivo, either presystemically or systemically.
- TAF administered alone or with MDZ (IV or oral) was well tolerated with few AEs and clinical laboratory abnormalities and no Grade 3 or 4 AEs, SAEs, deaths, or discontinuations due to AEs.

1.1.4.4. GS-US-120-1554

Location:	GS-US-120-1554
Title:	Study GS-US-120-1554: A Fixed-Sequence, Randomized, Open-Label, 2-Cohort, 2-Period, Multiple-Dose Study Evaluating the Pharmacokinetics and Drug Interaction Potential between Tenofovir Alafenamide and Rilpivirine in Healthy Subjects
Primary Objective(s):	• To evaluate the effect of TAF on the PK of RPV • To evaluate the effect of RPV on the PK of TAF
Study Design and Subject Population:	This was a Phase 1, open-label, fixed-sequence, randomized, 2-cohort, 2-period, multiple-dose, single-center study to evaluate the PK and drug interaction potential between TAF and RPV in healthy adult subjects. Subjects were randomized (1:1) to 1 of 2 treatment cohorts. The following study treatments were administered: • **Treatment A:** TAF 25 mg, administered orally once daily in the morning, under fed conditions • **Treatment B:** RPV 25 mg, administered orally once daily in the morning, under fed conditions • **Treatment C:** TAF 25 mg + RPV 25 mg, administered orally once daily in the morning, under fed conditions

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

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

Summary of Results and Conclusions:

Pharmacokinetic Results:

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

Statistical Comparisons of TAF, TFV, and RPV PK Parameter Estimates Between Study Treatments (PK Analysis Sets)

	Mean (%CV) by Treatment		
	TAF+RPV (Test) (N = 32)	TAF (Reference) (N = 17)	GLSM Ratio (90% CI), %
TAF PK Parameter			
AUC_{tau} (ng•h/mL)	335.6 (29.9)	307.6 (18.4)	101.43 (93.93, 109.52)
AUC_{last} (ng•h/mL)	334.1 (30.0)	306.3 (18.4)	101.31 (93.77, 109.46)
C_{max} (ng/mL)	242.8 (38.2)	238.2 (25.5)	101.26 (84.23, 121.73)
TFV PK Parameter			
AUC_{tau} (ng•h/mL)	267.6 (16.9)	237.9 (14.0)	110.66 (107.32, 114.11)
C_{max} (ng/mL)	16.5 (35.9)	14.4 (12.9)	112.27 (102.19, 123.33)
C_{tau} (ng/mL)	9.4 (17.4)	7.9 (16.9)	117.72 (112.85, 122.80)

RPV PK Parameter	Mean (%CV) by Treatment		GLSM Ratio (90% CI), %
	TAF+RPV (Test) (N = 32)	RPV (Reference) (N = 16)	
AUC_{tau} (ng•h/mL)	3052.2 (31.6)	3264.7 (34.3)	101.27 (96.42, 106.36)
C_{max} (ng/mL)	202.6 (31.0)	227.3 (35.3)	92.91 (87.44, 98.72)
C_{tau} (ng/mL)	123.4 (37.7)	122.2 (40.1)	112.77 (103.58, 122.77)

Conclusions:

- Following multiple-dose administration of TAF 25 mg and RPV 25 mg, there were no clinically relevant changes in TAF, TFV, or RPV exposure; no dose adjustment of either agent is necessary when TAF and RPV are administered together. TAF and RPV can be chronically administered together.
- Study drugs were generally well tolerated in this study. There were no new or unexpected safety findings in this short-term, multiple-dose study in healthy subjects. No AEs leading to premature study drug discontinuation were reported for subjects following administration of TAF or TAF+RPV. No deaths, SAEs, or Grade 3 or 4 AEs were reported.

1.2. Narratives for Previously Submitted Studies with F/TAF

1.2.1. Studies in Healthy Subjects

1.2.1.1. GS-US-311-1473

Location:	GS-US-311-1473
Title:	A Phase 1, Randomized, Open-Label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine/Tenofovir Alafenamide (200/25 mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets
Primary Objective:	To evaluate the bioequivalence of FTC and TAF administered as F/TAF (200/25 mg) FDC or as E/C/F/TAF (150/150/200/10 mg) FDC tablets
Study Design and Subject Population:	This Phase 1, randomized, open-label, single-dose, 2-way crossover study evaluated the bioequivalence of TAF and FTC administered as F/TAF (200/25 mg) or as E/C/F/TAF (150/150/200/10 mg) in healthy volunteers. Following screening and Day –1 procedures, eligible subjects were randomized to 1 of 2 treatment sequences (ie, AB or BA) and received a single dose of 1 of the following treatments on Days 1 and 7: • Treatment A: Single dose of F/TAF (200/25 mg) FDC tablet administered orally under fed conditions • Treatment B: Single dose of E/C/F/TAF (150/150/200/10 mg) FDC tablet administered orally under fed conditions Subjects were admitted to the study clinic on Day –1 and remained confined to the clinic until Day 13. Subjects received follow-up phone calls on Day 21 ± 2 days. Enrolled subjects were 18 to 45 year-old healthy males or nonpregnant, nonlactating females. A total of 116 subjects were enrolled into the study.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Statistical comparisons of plasma TAF and FTC pharmacokinetic (PK) parameters AUC_{last}, AUC_{inf}, and C_{max} (F/TAF [200/25 mg] vs E/C/F/TAF [150/150/200/10 mg]) were evaluated and are presented below.

TAF PK Parameter	Test n	Test Mean (%CV)	Reference n	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32	96.48, 104.31
AUC_{inf} (h•ng/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54	94.61, 102.62
C_{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63	95.46, 112.49

FTC PK Parameter	Test n	Test Mean (%CV)	Reference n	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h•ng/mL)	116	9423.9 (19.3)	116	10475.3 (19.7)	90.01	88.88, 91.16
AUC_{inf} (h•ng/mL)	116	9654.6 (19.3)	116	10706.6 (19.6)	90.20	89.06, 91.35
C_{max} (ng/mL)	116	1577.4 (26.8)	116	1601.7 (19.6)	97.26	94.57, 100.03

GLSM = geometric least-squares mean

	The GLSM ratios and corresponding 90% CIs of AUC_{last}, AUC_{inf}, and C_{max} for TAF and FTC were contained within the 80% to 125% boundary criteria specified for bioequivalence. The median T_{max} for TAF was the same (1.50 hours), while the median T_{max} for FTC was 2.00 hours following administration of F/TAF (200/25 mg) compared with 3.00 hours following administration of E/C/F/TAF. **Conclusions:** • The FTC and TAF components of F/TAF FDC (200/25 mg) were bioequivalent to E/C/F/TAF FDC (150/150/200/10 mg). • F/TAF FDC (200 mg/25 mg) and E/C/F/TAF (150/150/200/10 mg) FDC tablets were generally safe and well tolerated in healthy volunteers.

1.2.2. Extrinsic Factor Studies

1.2.2.1. GS-US-311-0101

Location:	GS-US-311-0101
Title:	Study GS-US-311-0101: A Phase 1 Study Evaluating the Drug Interaction Potential Between Once-Daily FTC/GS-7340 Fixed Dose Combination and Efavirenz or Cobicistat-Boosted Darunavir
Primary Objective(s):	• To evaluate the PK of TAF, TFV, and FTC, following once-daily coadministration of F/TAF (200/40 mg) + efavirenz (EFV) relative to administration of F/TAF alone (Cohort 1) • To evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF (200/25 mg) + DRV+COBI relative to administration of F/TAF alone and DRV+COBI alone (Cohorts 2 and 3) • To evaluate the PK of TAF, TFV, and COBI following once-daily coadministration of TAF 8 mg and COBI relative to administration of TAF 8 mg alone (Cohort 4)
Study Design and Subject Population:	This was a Phase 1, open-label, crossover, nonrandomized, multicohort, single-center, multiple-dose study designed to evaluate the drug interaction potential between once-daily F/TAF and EFV or DRV+COBI, and between TAF as a single agent and COBI in healthy subjects. Eligible subjects were assigned to a cohort (1, 2, 3, or 4) and administered the following study treatments once daily in the morning:

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

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

Summary of Results and Conclusions:

Pharmacokinetic Results:

Pharmacokinetic results for the primary exposure parameters of TAF, TFV, COBI, FTC, and DRV following administration of the test and reference treatments are summarized in the following 5 tables, respectively, by cohort.

Statistical Comparisons of TAF PK Parameter Estimates Between Test and Reference Treatments (TAF PK Analysis Set)

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

Statistical Comparisons of TFV PK Parameter Estimates Between Test and Reference Treatments (TFV PK Analysis Set)

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

Statistical Comparisons of COBI PK Parameter Estimates Between Test and Reference Treatments (COBI PK Analysis Set)

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

Statistical Comparisons of FTC PK Parameter Estimates Between Test and Reference Treatments (FTC PK Analysis Set)

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

Statistical Comparisons of DRV PK Parameter Estimates Between Test and Reference Treatments (DRV PK Analysis Set)

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

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

	Following administration of F/TAF 200/25 mg + DRV+COBI in Cohort 2, the GLSM ratio and 90% CIs for TAF and FTC were within the lack of interaction boundary, relative to F/TAF dosed alone. However, the GLSM ratios for TFV AUC_{tau} and C_{max} were 323.88% and 316.03%, respectively, consistent with the higher TFV exposure observed in Cohort 4 of this study (TAF 8 mg + COBI versus TAF 8 mg alone) and with E/C/F/TAF versus TAF 25 mg single agent in Study GS-US-292-0101). The increase in TFV exposure, without a change in TAF exposure, upon multiple-dose coadministration with DRV+COBI is indicative of a mixed inhibitory/inductive effect on P-glycoprotein (P-gp) influencing TAF absorption. An increase in TAF exposure (AUC_{last} and C_{max}) following a single dose of F/TAF+DRV+COBI, as compared with a single dose of F/TAF alone, suggested the presence of an inhibitory drug interaction resulting in increased availability of TAF following a single dose that is abated following multiple dosing. The comparable exposure of TAF following multiple-dose coadministration with DRV+COBI versus TAF alone may be due to an inductive effect of DRV on P-gp. Following administration of F/TAF 200/25 mg + DRV+COBI in Cohort 3, the GLSM ratio and 90% CIs for DRV and COBI were within the lack of interaction boundary, relative to DRV+COBI dosed alone. The stricter 80% to 125% boundary criterion for bioequivalence was also met for DRV and COBI, with the exception of COBI C_{tau} (125.06%), which was slightly above the upper limit. TAF and TFV exposures were comparable with those observed when dosed as DRV+COBI + F/TAF 200/25 mg in Cohort 2. COBI and FTC exposures were consistent with historical data from previous studies. Following coadministration of TAF 8 mg + COBI in Cohort 4, the GLSM ratio and 90% CIs for TAF and TFV were above the lack of interaction boundary, relative to TAF dosed alone. The GLSM ratios of TAF AUC_{last} and C_{max} (265.06% and 283.31%, respectively) and TFV AUC_{tau} and C_{max} (330.88% and 334.09%, respectively) were consistent with the higher TAF and TFV exposures observed with E/C/F/TAF versus TAF single agent in Study GS-US-292-0101, indicating the presence of a COBI-mediated interaction, likely due to inhibition of P-gp-mediated intestinal secretion of TAF. COBI exposure was in the range of those observed previously (Studies GS-US-216-0112 and GS-US-216-0124). **Conclusions:** • Administration of F/TAF+EFV resulted in no clinically relevant changes in FTC, TFV, or TAF exposure, as compared with F/TAF dosed alone. Based on these data, it is concluded that no dose adjustments are needed when EFV is coadministered with F/TAF or TAF single agent. • Administration of F/TAF+DRV+COBI resulted in comparable exposures of TAF and FTC, but substantially higher TFV exposure, relative to F/TAF dosed alone. • Administration of F/TAF+DRV+COBI resulted in comparable exposures of DRV and COBI, relative to DRV+COBI dosed alone. • Administration of TAF+COBI resulted in substantially higher TAF and TFV exposures relative to TAF dosed alone, with COBI exposure in the range of historical data. • Multiple doses of F/TAF, administered alone or coadministered with EFV or DRV+COBI, were well tolerated in this study. Two subjects experienced AEs leading to study drug discontinuation: a study drug-related Grade 2 AE of anxiety after the first dose of F/TAF 200/40 mg + EFV, and a Grade 2 AE of joint abscess with F/TAF 200/25 mg, considered unrelated to study drug. Additionally, multiple doses of TAF 8 mg administered alone or coadministered with COBI were well tolerated. No deaths, SAEs, or Grade 3 or 4 AEs were reported during the study.

1.2.2.2. GS-US-311-1387

Location: GS-US-311-1387

Title: Study GS-US-311-1387: A Phase 1, Open-Label, Adaptive, Two-Part, Three Period, Fixed Sequence Study to Evaluate the Effect of Carbamazepine on the PK of TAF and GS-9883 in Healthy Adult Subjects

Primary Objective(s): Part A: To evaluate the effect of steady state carbamazepine (CBZ) on the PK of TAF when administered as F/TAF FDC

Study Design and Subject Population: This is a Phase 1, open-label, adaptive, 2-part, 3-period, fixed-sequence, single-center study in healthy subjects. In Part A, subjects were administered a single dose of F/TAF FDC alone and with CBZ at steady-state. Part B has not yet been conducted and is dependent on the review of PK data from Part A; if Part B is conducted, subjects will be administered a single dose of GS-9883/F/TAF FDC alone and with CBZ at steady-state.
Study drugs were administered in Part A as described in the table below.

Period 1		Period 2			Period 3	
Day 1	**Days 2–5**	**Days 6–8**	**Days 9–11**	**Days 12–25**	**Day 26**	**Days 27–32**
F/TAF FDC 200/25 mg	–	CBZ 100 mg BID	CBZ 200 mg BID	CBZ 300 mg BID	CBZ 300 mg BID + F/TAF FDC 200/25 mg	–

A total of 26 subjects were enrolled. Of these, 4 subjects (15.4%) discontinued study drug (and the study) during CBZ 300 mg BID dosing in Period 2, all due to AEs. The remaining 22 subjects (84.6%) completed study drug dosing and the study.

Summary of Results and Conclusions:

Pharmacokinetic Results:
Mean (%CV) TAF AUC_{last} was 223.4 (41.7) h*ng/mL and 110.4 (61.2) h*ng/mL following the administration of F/TAF FDC alone and with steady-state CBZ, respectively; mean (%CV) TAF C_{max} was 219.6 (37.3) ng/mL and 99.4 (47.8) ng/mL, respectively. Mean (%CV) TFV AUC_{inf} was 245.1 (15.8) h*ng/mL and 186.3 (15.5) h*ng/mL following the administration of F/TAF FDC alone and with steady-state CBZ, respectively; mean (%CV) TFV C_{max} was 7.3 (19.4) ng/mL and 5.0 (18.9) ng/mL, respectively.
The statistical comparisons of TAF and TFV plasma PK parameters, following the administration of a single dose of F/TAF FDC alone and with CBZ at steady-state, are presented in the table below.

	GLSM		
TAF PK Parameter	**CBZ 300 mg BID+ F/TAF FDC 200/25 mg (Test) (N = 22)**	**F/TAF FDC 200/25 mg (Reference) (N = 26)**	**GLSM Ratio (%) (90% CI) Test/Reference**
AUC_{last} (h*ng/mL)	92.08	204.61	45.00 (39.66, 51.06)
AUC_{inf} (h*ng/mL)	103.81[a]	224.68[b]	46.21 (39.68, 53.81)
C_{max} (ng/mL)	87.80	204.59	42.92 (35.87, 51.35)
TFV PK Parameter	**CBZ 300 mg BID+ F/TAF FDC 200/25 mg (Test) (N = 22)**	**F/TAF FDC 200/25 mg (Reference) (N = 26)**	**GLSM Ratio (%) (90% CI) Test/Reference**
AUC_{last} (h*ng/mL)	157.05	208.91[c]	75.18 (71.39, 79.17)
AUC_{inf} (h*ng/mL)	185.06[d]	239.47[b]	77.28 (73.51, 81.24)
C_{max} (ng/mL)	4.96	7.13[c]	69.61 (65.18, 74.34)

a n = 13
b n = 23
c n = 24
d n = 21

	Conclusions: • TAF exposure (AUC_{last}) decreased by approximately 55% when the F/TAF FDC tablet (200/25 mg) was coadministered with CBZ at steady-state compared with the F/TAF FDC tablet administered alone. • TFV exposure (AUC_{inf}) decreased by approximately 23% when the F/TAF FDC tablet (200/25 mg) was coadministered with CBZ at steady-state compared with the F/TAF FDC tablet administered alone. • TAF exposure when coadministered with CBZ under fed conditions (mean AUC_{last} of ~110 ng*h/mL) was in the range of exposures associated with potent antiviral activity for HIV-1 and HBV. • A single dose of the F/TAF FDC tablet (200/25 mg) was generally well tolerated when administered alone, and there was no relevant difference in tolerability when the F/TAF FDC tablet was coadministered with CBZ at steady-state. No deaths were reported. Three subjects experienced Grade 3 or 4 AEs: Grade 4 thrombocytopenia (also an SAE) following CBZ which led to discontinuation of the study drugs; Grade 3 myositis following CBZ which led to discontinuation of the study drugs; and Grade 3 angioedema and Grade 4 Stevens-Johnson syndrome (also an SAE), both following CBZ+F/TAF. Four subjects experienced AEs leading to study drug discontinuation, all following CBZ (thrombocytopenia and headache; hyponatremia; rash maculo-papular; and myositis). All AEs that led to study drug discontinuation and SAEs are associated with CBZ.

1.2.2.3. GS-US-311-1388

Location:	GS-US-311-1388
Title:	Study GS-US-311-1388: A Fixed-Sequence, Open-Label, 3-Period Cross-Over Pharmacokinetic Study Evaluating the Drug Interaction Potential between Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet and Atazanavir Boosted by Cobicistat in Healthy Subjects
Primary Objective(s):	• To evaluate the effect of ATV+COBI on the PK of TAF and its major metabolite TFV • To evaluate the effect of ATV+COBI on the PK of FTC • To evaluate the effect of TAF on the PK of ATV and COBI
Study Design and Subject Population:	This was a Phase 1, open-label, fixed-sequence, single-center, 3-period, cross-over study evaluating the drug interaction potential between F/TAF and ATV+COBI in healthy subjects. The following study treatments were administered orally under fed conditions following an overnight fast. • **Treatment A (Days 1-7):** F/TAF (200/10 mg), administered once daily in the morning with food • **Treatment B (Days 8-14):** ATV 300 mg + COBI 150 mg + F/TAF (200/10 mg), administered once daily in the morning with food • **Treatment C (Days 15-21):** ATV 300 mg + COBI 150 mg, administered once daily in the morning with food A total of 20 subjects were screened, enrolled in the study, and received at least 1 dose of study drug. Of these, 20 subjects (100.0%) were included in the PK Analysis Set for each of TAF, TFV, FTC, ATV, and COBI. All 20 subjects (100.0%) completed study drug, 19 subjects (95.0%) completed the study, and 1 subject (5.0%) was lost to follow-up.
Summary of Results and Conclusions:	**Pharmacokinetic Results:** Comparisons of the primary PK parameters for TAF, TFV, and FTC following the administration F/TAF alone or ATV+COBI in combination with F/TAF, and the results of the statistical analysis are summarized in the table below.

PK Parameter	GLSMs by Treatment: Test: ATV+COBI+F/TAF (N = 20)	GLSMs by Treatment: Reference: F/TAF (N = 20)	%GLSM Ratio (90% CI)
TAF			
AUC_{last} (h•ng/mL)	182.21	104.08	175.06 (154.81, 197.96)
C_{max} (ng/mL)	133.52	74.28	179.76 (148.45, 217.67)
TFV			
AUC_{tau} (h•ng/mL)	340.26	97.92[a]	347.49 (329.34, 366.65)
C_{tau} (ng/mL)	12.37	3.31	373.16 (353.91, 393.45)
C_{max} (ng/mL)	18.43	5.83	315.98 (299.75, 333.10)
FTC			
AUC_{last} (h•ng/mL)	11,576.49	10,023.15	115.50 (110.68, 120.53)
C_{tau} (ng/mL)	90.87	66.52	136.62 (131.55, 141.89)
C_{max} (ng/mL)	1844.78	1696.16	108.76 (100.15, 118.11)

GLSM = geometric least-squares mean
a n = 19

Compared to administration of F/TAF alone, F/TAF+ATV+COBI led to increases in TAF exposure (AUC_{last}) of 75% and TAF C_{max} of 80%. Compared to the administration of F/TAF alone, coadministration of F/TAF with ATV+COBI led to increases in TFV exposure (AUC_{tau}) of 248%, and TFV C_{tau} of 273%. These differences were expected and consistent with the effect of a P-gp inhibitor on TAF exposure and, as a result, its metabolite TFV. Coadministration of ATV+COBI with F/TAF did not notably affect the PK of FTC.

Comparisons of the primary PK parameters for ATV and COBI following the administration ATV+COBI alone or ATV+COBI in combination with F/TAF, and the results of the statistical analysis are summarized in the table below.

PK Parameter	GLSMs by Treatment		%GLSM Ratio (90% CI)
	Test: ATV+COBI+F/TAF (N = 20)	Reference: ATV+COBI (N = 20)	
ATV			
AUC_{tau} (h•ng/mL)	77,270.03	72,906.44	105.99 (100.91, 111.31)
C_{tau} (ng/mL)	2006.71	1701.77	117.92 (106.43, 130.65)
C_{max} (ng/mL)	6344.22	6456.65	98.26 (94.27, 102.41)
COBI			
AUC_{tau} (h•ng/mL)	13,881.31	13,272.25	104.59 (100.25, 109.12)
C_{tau} (ng/mL)	88.81	65.83	134.91 (120.73, 150.75)
C_{max} (ng/mL)	1516.32	1575.56	96.24 (92.47, 100.16)

Coadministration of ATV+COBI with F/TAF did not notably affect the PK of ATV or COBI.

Conclusions:

- Coadministration of F/TAF and ATV+COBI did not notably affect the PK of FTC, ATV, or COBI.
- Coadministration of F/TAF and ATV+COBI led to an increase in TAF and TFV exposures, as expected and consistent with the effect of a P-gp inhibitor on TAF exposures and, subsequently, its metabolite TFV.
- F/TAF and ATV+COBI were generally well tolerated when administered alone or in combination. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to discontinuation of study drug were reported during this study

1.2.2.4. GS-US-311-1790 (Cohort 1)

Location: GS-US-311-1790

Title: Study GS-US-311-1790: 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(s): To determine the effect of FTC and TAF administered as the F/TAF 200/25 mg FDC tablet or GS-9883 75 mg on the PK of a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol (Ortho Tri-Cyclen Lo)

Study Design and Subject Population: This was a Phase 1, randomized, open-label, single center, fixed-sequence, multiple-dose, multiple-cohort study to determine the effect of FTC and TAF, administered as F/TAF FDC tablet, or GS-9883 on the PK of a representative hormonal contraceptive medication (Ortho Tri-Cyclen Lo; OC). Following screening and Study Day Lead-in (L)−1 procedures, eligible subjects were randomized to 1 of 2 cohorts. Since Cohort 2 of the study evaluated the drug-drug interaction potential between GS-9883 and OC, the data from this cohort are not detailed in this tabular summary but are available in the full CSR. Subjects enrolled in Cohort 1 received the treatments in the table below starting on Study Day L1. The Lead-in period (Part A) was used to synchronize dosing schedules.

	Part A	**Part B**		
	Lead-in	**Cycle 1**	**Cycle 2**	
Study Day	**L1-L28**	**1-28**	**29-42**	**43-56**
Cycle Day	**1-28**	**1-28**	**1-14**	**15-28**
OC[a]	X	X	X	X
F/TAF 200/25 mg[a]			X	

a Administered once daily in the morning with food

A total of 16 female subjects were enrolled in Cohort 1 and received at least 1 dose of study drug. In Cohort 1, 13 subjects completed the study and 3 subjects discontinued study drug and the study early: 1 subject was not treated in Part B due to violation of the protocol; 1 subject withdrew consent, and 1 subject was lost to follow up.

Summary of Results and Conclusions:

Pharmacokinetics and Pharmacodynamics Results:

Systemic exposures of norelgestromin (major metabolite of norgestimate), norgestrel (minor metabolite of norgestimate), and ethinyl estradiol when OC was coadministered with F/TAF were similar to those achieved when OC was administered alone. The GLSM ratios and the associated 90% CIs of all primary PK parameters of norelgestromin, norgestrel, and ethinyl estradiol were within the prespecified no-effect bounds of 70% to 143%. The PK of OC was not altered by F/TAF.

TAF, TFV, and FTC exposures (given with food) were consistent with historical data.

Luteinizing hormone, FSH, and progesterone median concentrations were generally comparable across all treatment cycles.

Luteinizing hormone median values were lower than those expected for the ovulatory phase (range: 8.7 to 76.3 mIU/mL); FSH median values were within (range: 3.1 to 17.7 mIU/mL) or lower than the reference range for the ovulatory phase. 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 oral contraceptive cycle were substantially lower in all treatment cycles than those expected for the luteal phase (range: 3.0 to 31.4 ng/mL).

	Conclusions: • No loss of contraceptive efficacy is expected with coadministration of OC with F/TAF: — Similar plasma exposures of norelgestromin, norgestimate, and ethinyl estradiol were achieved when OC was coadministered with F/TAF — FSH, LH and progesterone were generally comparable across all treatment cycles • When F/TAF was coadministered with OC, PK exposures of FTC, TAF, and TFV were consistent with historical data. • Taking OC as an oral contraceptive concurrent with F/TAF treatment is safe and well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to study drug discontinuation were reported.

1.3. Narratives for Previously Submitted Studies with E/C/F/TAF

1.3.1. Studies in Healthy Subjects

1.3.1.1. GS-US-292-0103

Location:	GS-US-292-0103
Title:	A Phase 1, Multiple Dose Study Evaluating the Relative Bioavailability of Elvitegravir/Cobicistat/Emtricitabine/ GS-7340 STR Relative to the Administration of Individual Components Cobicistat-Boosted Elvitegravir, Emtricitabine, and GS-7340
Primary Objective(s):	To evaluate the pharmacokinetic (PK) and relative bioavailability of elvitegravir (EVG), cobicistat (COBI), FTC, TAF, and TFV administered as E/C/F/TAF FDC relative to the administration of the individual components: EVG, COBI, FTC, and TAF
Study Design and Subject Population:	This was a single-center, randomized, open-label, multiple-dose, multiple-cohort, 2-period, crossover study in healthy adult subjects. Study treatments were as follows: **Cohort 1:** • **Treatment A:** E/C/F/TAF 150/150/200/10-mg FDC tablet • **Treatment B:** EVG 150 mg + COBI 150 mg **Cohort 2:** • **Treatment A:** E/C/F/TAF 150/150/200/10-mg FDC tablet • **Treatment C:** FTC 200 mg + TAF 25 mg Each treatment was administered orally once daily, in the morning, with food, for 12 days. Within each cohort, subjects were randomized in a 1:1 ratio to receive treatments in 1 of 2 sequences, as follows:

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

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

Summary of Results and Conclusions:

Pharmacokinetic Results:

Primary PK exposure parameters of TAF, TFV, EVG, COBI, and FTC following administration of E/C/F/TAF 150/150/200/10 mg, EVG+COBI, and EVG+TAF 25 mg, and statistical comparisons of each between treatments, are presented in the table below.

TAF PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (%) (90% CI)**
Cohort 2 E/C/F/TAF 150/150/200/10 mg (Test) vs FTC+TAF 25 mg (Reference) (N = 19)			
AUC_{last} (ng•h/mL)	250.2 (24.7)	278.2 (28.8)	91.42 (84.12, 99.35)
C_{max} (ng/mL)	176.9 (35.1)	179.5 (33.9)	98.68 (84.57, 115.13)

TFV PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (%) (90% CI)**
Cohort 2 E/C/F/TAF 150/150/200/10 mg (Test) vs FTC+TAF 25 mg (Reference) (N = 19)			
AUC_{tau} (ng•h/mL)	324.2 (15.4)	265.9 (22.2)	123.63 (116.97, 130.67)
C_{max} (ng/mL)	19.6 (13.9)	19.2 (76.0)	114.16 (97.52, 133.64)
C_{tau} (ng/mL)	11.4 (17.8)	9.2 (23.5)	125.37 (117.72, 133.51)

EVG PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (%) (90% CI)**
Cohort 1 E/C/F/TAF 150/150/200/10 mg (Test) vs EVG+COBI (Reference) (N = 14)			
AUC_{tau} (ng•h/mL)	22067.1 (26.3)	23099.2 (22.7)	94.87 (91.51, 98.36)
C_{max} (ng/mL)	1943.5 (23.9)	2161.0 (27.0)	90.32 (85.07, 95.89)
C_{tau} (ng/mL)	422.2 (54.4)	418.6 (42.2)	97.83 (88.39, 108.27)

COBI PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (%) (90% CI)**
Cohort 1 E/C/F/TAF 150/150/200/10 mg (Test) vs EVG+COBI (Reference) (N = 14)			
AUC_{tau}(ng•h/mL)	11209.8 (27.4)	10931.2 (25.5)	102.00 (98.10, 106.06)
C_{max} (ng/mL)	1560.7 (26.1)	1489.4 (23.2)	104.07 (99.41, 108.94)
C_{tau} (ng/mL)	34.6 (85.5)	26.7 (62.1)	116.43 (102.05, 132.83)

FTC PK Parameter	**Test Mean (%CV)**	**Reference Mean (%CV)**	**GLSM Ratio (%) (90% CI)**
Cohort 2 E/C/F/TAF 150/150/200/10 mg (Test) vs FTC+TAF 25 mg (Reference) (N = 19)			
AUC_{tau}(ng•h/mL)	12352.6 (13.5)	10520.9 (13.8)	117.57 (113.72, 121.55)
C_{max} (ng/mL)	1947.0 (21.2)	1788.8 (19.2)	108.99 (102.81, 115.55)
C_{tau} (ng/mL)	107.4 (25.8)	87.5 (20.6)	121.26 (114.66, 128.24)

	In the present study, TAF and resultant TFV exposures following administration of the reduced dose TAF 10 mg as a constituent of the E/C/F/TAF FDC were comparable to those observed following administration of the TAF 25 mg dose (coadministered with FTC), confirming the 2- to 3-fold change in exposures observed previously when TAF was dosed with COBI or as a constituent of the E/C/F/TAF FDC relative to its administration as a single agent (Studies GS-US-311-0101 and GS-US-292-0101). This increased exposure is likely due to inhibition by COBI of P-glycoprotein-mediated intestinal secretion of TAF (Studies GS-US-311-0101 and GS-US-292-0101). Specifically, following the administration of E/C/F/TAF 150/150/200/10 mg (test treatment), the 90% CIs of the geometric least-squares mean (GLSM) ratios for TAF and TFV exposures relative to FTC+TAF 25 mg (reference treatment) were contained within the protocol-defined 70% to 143% lack-of-effect boundary. Mean (%CV) TFV exposure parameters (AUC and C_{max}) following multiple doses of E/C/F/TAF 150/150/200/10 mg and FTC+TAF 25 mg were > 90% lower than observed following administration of the STB FDC (mean [%CV] AUC_{tau} and C_{max} for TFV were 4066.2 [24.1] ng•h/mL and 485.6 [31.1] ng/mL, respectively; Study GS-US-236-0110). Following the administration of E/C/F/TAF 150/150/200/10 mg, the GLSM ratios and 90% CIs for EVG, COBI, and FTC were all contained within the protocol-defined 70% to 143% lack-of-effect boundary relative to EVG+COBI or FTC+TAF 25 mg, indicating no clinically relevant differences. The stricter 80% to 125% boundary was also met for the relevant EVG, COBI, and FTC exposure parameters, consistent with previous findings from Study GS-US-292-0101. Overall, the data support the selection of a 10-mg dose of TAF for clinical development of the E/C/F/TAF FDC. **Conclusions:** • While mean TFV exposures (AUC_{tau} and C_{max}) following E/C/F/TAF 10 mg or FTC+TAF 25 mg were markedly lower than historical TFV exposures following administration of STB FDC, administration of E/C/F/TAF 150/150/200/10 mg resulted in comparable TAF and TFV exposures relative to FTC+TAF 25 mg. • Administration of E/C/F/TAF 150/150/200/10 mg provided EVG, COBI, and FTC exposures comparable with those observed following administration of EVG + COBI and EVG+TAF 25 mg, and to those observed historically following administration of the STB FDC. • E/C/F/TAF 150/150/200/10 mg was generally safe and well tolerated by healthy subjects. No deaths, serious adverse events, Grade 3 or 4 adverse events, or adverse events leading to discontinuation of study drug were reported during this study.

1.3.2. Extrinsic Factor Studies

1.3.2.1. GS-US-292-1316

Location:	GS-US-292-1316
Title:	Study GS-US-292-1316: A Phase 1, Open-Label, Fixed Sequence Study Evaluating the Pharmacokinetics and Drug Interaction Potential Between Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen and Sertraline in Healthy Subjects
Primary Objective(s):	To evaluate the PK of EVG, TAF, and sertraline following the coadministration of E/C/F/TAF and sertraline relative to the administration of E/C/F/TAF or sertraline alone
Study Design and Subject Population:	This was a Phase 1, open-label, 3-period, fixed-sequence, single-center study to evaluate the PK and drug interaction potential between E/C/F/TAF and sertraline in healthy adult subjects. The following study treatments were administered: • **Treatment A:** sertraline 50 mg, single dose, administered orally in the morning with food • **Treatment B:** E/C/F/TAF (150/150/200/10 mg), single dose, administered orally in the morning with food for 12 days • **Treatment C:** sertraline 50 mg, single dose + E/C/F/TAF (150/150/200/10 mg), single dose, administered orally in the morning with food Twenty subjects were enrolled and received a single dose of sertraline (Treatment A) and ≥ 1 dose of E/C/F/TAF (Treatment B). Nineteen of the 20 subjects received E/C/F/TAF+ sertraline (Treatment C). One subject withdrew consent prior to study completion (Day 3).
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The mean and %CV of the primary PK parameters for TAF, TFV, EVG, COBI, FTC, and sertraline following the administration E/C/F/TAF and sertraline alone or in combination, and the results of the statistical analysis, are summarized in the table below.

Statistical Comparisons of TAF, TFV, EVG, COBI, FTC, and Sertraline PK Parameter Estimates Between Test and Reference Treatments (All PK Analysis Set)

	Mean (%CV) by Treatment		
	E/C/F/TAF+Sertraline (Test) (N = 19)	**E/C/F/TAF (Reference) (N = 19)**	**GLSM Ratio (90% CI), %**
TAF PK Parameter			
AUC_{last} (ng•h/mL)	254.3 (35.7)	269.7 (38.5)	95.63 (89.18, 102.54)
C_{max} (ng/mL)	287.9 (52.2)	303.9 (61.4)	100.16 (86.45, 116.05)
TFV PK Parameter			
AUC_{tau} (ng•h/mL)	316.8 (19.9)	311.3 (20.5)	101.80 (99.95, 103.68)
C_{max} (ng/mL)	22.4 (38.6)	19.8 (25.0)	109.94 (100.27, 120.53)
C_{tau} (ng/mL)	10.8 (24.1)	10.7 (25.2)	101.01 (98.91, 103.15)
EVG PK Parameter			
AUC_{tau} (ng•h/mL)	20,600.2 (19.3)	22,077.5 (20.2)	93.54 (89.46, 97.81)
C_{max} (ng/mL)	1812.1 (17.3)	2112.6 (27.3)	87.50 (82.25, 93.09)
C_{tau} (ng/mL)	346.2 (32.3)	349.1 (37.2)	99.21 (93.45, 105.34)
COBI PK Parameter			
AUC_{tau} (ng•h/mL)	11,862.1 (28.5)	11,873.4 (28.7)	99.92 (97.00, 102.92)
C_{max} (ng/mL)	1905.8 (20.0)	1804.2 (19.9)	105.67 (101.28, 110.24)
C_{tau} (ng/mL)	26.9 (117.8)	27.8 (97.1)	86.81 (79.41, 94.90)
FTC PK Parameter			
AUC_{tau} (ng•h/mL)	9186.4 (15.9)	10,935.7 (18.8)	84.35 (81.11, 87.73)
C_{max} (ng/mL)	1922.6 (26.6)	2126.8 (24.8)	89.61 (82.03, 97.90)
C_{tau} (ng/mL)	73.8 (42.3)	77.9 (39.6)	94.15 (89.93, 98.56)
Sertraline PK Parameter			
AUC_{last} (ng•h/mL)	258.3 (25.1)	256.5 (33.6)	109.17 (90.03, 132.37)
AUC_{inf} (ng•h/mL)	379.7 (29.8)	440.3 (38.7)	93.31 (77.04, 113.00)
C_{max} (ng/mL)	19.4 (25.4)	18.6 (32.5)	113.68 (93.67, 137.98)

	Following the coadministration of E/C/F/TAF and sertraline, no clinically relevant alterations in the PK of TAF, TFV, EVG, COBI, FTC, or sertraline were observed relative to the administration of E/C/F/TAF or sertraline alone. The 90% CIs for the relevant PK parameters of TAF, TFV, EVG, COBI, FTC, and sertraline were within the protocol-specified lack of PK alteration boundary of 70% to 143%, indicating a lack of CYP-mediated drug interaction upon coadministration of E/C/F/TAF and sertraline. Overall, the exposures of all analytes following E/C/F/TAF and/or sertraline were consistent with historical data. Based on these study results, no dose adjustment is needed when coadministering E/C/F/TAF and sertraline. **Conclusions:** • Coadministration of E/C/F/TAF with sertraline had no effect on the PK of TAF, TFV, EVG, COBI, FTC, or sertraline. • Coadministration of sertraline with E/C/F/TAF had no effect on the PK of TAF, TFV, EVG, COBI, or FTC. • Coadministration of E/C/F/TAF with sertraline was generally well tolerated in these healthy subjects. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to study drug discontinuation were reported. • Since no clinically relevant drug interactions were observed upon coadministration of E/C/F/TAF and sertraline, no dose adjustments are needed when coadministering E/C/F/TAF and sertraline. This recommendation can be extrapolated to F/TAF based on the nonclinical profile of TAF.

1.4. Narratives for Previously Submitted Studies with FTC or FTC/TDF

1.4.1. Studies in Healthy Subjects

1.4.1.1. FTC-106

Title

An Evaluation of the ADME of [^{14}C]FTC in Healthy Male Volunteers

Objectives

The primary objectives of Study FTC-106 were to determine the mass balance of orally administered FTC by measuring ^{14}C-labeled materials in urine and fecal samples; to estimate the extent of oral absorption of FTC; to evaluate the extent of FTC distribution in semen; to determine the metabolic profile of FTC in man by analyzing the urinary and fecal excretion profiles of FTC and its metabolites following an orally administered dose of [^{14}C]FTC given under steady-state condition. A secondary objective was to explore the PK of FTC-TP in PBMCs after a single oral dose of [^{14}C]FTC administered at steady state.

Study Design and Methodology

This was an open-label study to evaluate the ADME of [^{14}C]FTC following administration of a single oral dose of [^{14}C]FTC under steady-state conditions in 6 healthy male volunteers. On Day 1, after the first 200-mg dose of FTC in capsules under fasting conditions, serial blood (plasma) and cumulative urine samples were collected up to 48 hours postdose for PK

evaluation. From Days 3 to 10, subjects took 200 mg of FTC in capsules once daily (8 consecutive days) to reach a steady-state condition. On Day 11, subjects received a single oral dose of [^{14}C]FTC (250 μCi in an oral solution formulation containing 200 mg of unlabeled FTC) under fasting conditions and then began an extended sample collection period, wherein serial samples of blood/plasma and blood/PBMCs and cumulative urine and stools were collected up to 168 hours postdose. In addition, a single semen sample was collected on Day 11 at approximately the anticipated peak time (approximately 1.5 hours postdose).

FTC concentrations in plasma and urine following dosing on Day 1 (0 to 48 hours postdose) and on Day 11 (0 to 120 hours postdose for plasma and 0 to 168 hours postdose for urine) and in semen on Day 11 (at approximately 1.5 to 3.5 hours postdose) were determined by a validated LC/MS/MS method. Total ^{14}C-radioactivity concentrations following dosing on Day 11 in blood and plasma (0 to 120 hours), in urine and feces (0 to 168 hours), and in semen were determined by liquid scintillation counting. Metabolic profiling of urine, plasma, and fecal samples collected on Day 11 were analyzed by HPLC radiochemical analysis coupled with LC/MS/MS for metabolite identification. The FTC-TP concentrations in PBMCs on Day 11 (0 to 120 hours postdose) were determined by LC/MS/MS.

Further details on the design and results of this study are available in the CSR (FTC-106).

Number of Subjects (Planned and Analyzed)

The study design allowed 6 subjects to be recruited and required at least 4 of the subjects to complete the study and be fully evaluable. Six subjects were enrolled, and 5 subjects completed the study. Pharmacokinetic analyses included all subjects who had evaluable PK data (6 subjects for the Day 1 evaluations and 5 subjects for the Day 11 evaluations). Data from all 6 subjects were included in the safety analyses.

Safety Results

Two subjects reported a total of 3 AEs (Grade 1 headache, pharyngitis, and facial acne). There were no deaths or other SAEs reported, and there were no subject discontinuations due to AEs. There were no clinically significant changes in clinical laboratory test results, vital signs measurements, or physical examination findings. Individual changes in clinical laboratory test results tended to be consistent with pretreatment levels, and/or they were just outside of the laboratory normal ranges. There were no trends in clinical laboratory test results that were clearly related to the administration of FTC.

Results and Conclusions

FTC was rapidly and extensively absorbed following oral administration. Plasma FTC was measurable within 15 minutes of dosing and reached a peak level of approximately 2 μg/mL at 1 to 1.5 hours postdose. At least 86% of an oral dose of FTC was absorbed.

FTC disposition followed linear, first-order kinetics, with steady-state plasma profiles that were predictable based on single-dose data. The steady-state condition was achieved following 4 consecutive daily doses. The AUC_{tau} over a steady-state dosing interval averaged 10 μg•h/mL following 200-mg once-daily dosing regimen.

Unchanged FTC was the predominant and nearly the only quantifiable compound in plasma following oral administration of FTC. Systemic FTC was rapidly eliminated from the body, with a complete recovery of a single [^{14}C]FTC dose in urine (approximately 86%) and feces (approximately 14%) within 7 days following dosing. Renal excretion (glomerular filtration along with tubular section) was the primary elimination route of FTC in plasma. Approximately 65% to 70% of an oral FTC dose was recovered in urine as unchanged parent drug. The clinically relevant plasma $t_{1/2}$ of FTC was 10 hours, on average.

Metabolism was a minor elimination pathway for FTC, as only 13% of the dose was recovered in urine as 3 putative metabolites. The biotransformation of FTC included oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). No other metabolites were identifiable.

FTC did not have a high affinity for red blood cells, as the mean plasma-to-blood concentration ratio was about 1.0. FTC had good semen penetration, with a mean semen-to-plasma concentration ratio of approximately 4.0.

The relatively long plasma $t_{1/2}$ (approximately 10 hours) and high plasma FTC concentrations and, additionally, the long intracellular (PBMC) $t_{1/2}$ of the active moiety FTC-TP (approximately 39 hours), support FTC as a once-daily ARV agent.

1.4.1.2. FTC-110

Title

A Study to Evaluate the Relative and Absolute Bioavailability of Emtricitabine in Healthy Volunteers

Objectives

The objectives of this study were as follows:

- To determine the relative bioavailability of FTC administered as the 200-mg capsule formulation in comparison to an oral solution formulation containing 10 mg/mL of FTC
- To determine the absolute bioavailability of FTC, when administered as the 200-mg capsule formulation or the oral solution, compared with an intravenous dose of FTC

Study Design

This was an open-label, randomized, 3-way crossover study. Subjects each received 3 single 200-mg FTC treatments as follows:

- Treatment A: one 200-mg FTC oral capsule
- Treatment B: 20 mL of the 10-mg/mL FTC oral solution
- Treatment C: 20 mL of a 10-mg/mL FTC intravenous solution (administered intravenously by continuous slow infusion over a period of 1 hour)

There was a ≥ 1-week washout between successive doses and all 3 treatments were administered under fasting conditions. Serial blood (plasma) and cumulative urine samples were collected for 48 hours after each dose for determination of plasma and urine concentrations of FTC.

Further details on the design and results of this study are available in the CSR (FTC-110).

Study Population

12 healthy volunteers, 7 males and 5 females, aged 21 to 44 years (mean: 32 years)

Pharmacokinetic Results

Geometric mean ratios between the various formulations were as follows:

- For the 200-mg capsule in relation to the intravenous solution, the ratio (A/C) for C_{max} was 56% (90% CI: 52%-61%) and that for $AUC_{0-\infty}$ was 93% (90% CI: 87%-99%).

- For the oral solution in relation to the intravenous solution, the ratio (B/C) for C_{max} was 37% (90% CI: 34%-40%) and that for $AUC_{0-\infty}$ was 75% (90% CI: 70%-80%).

- For the 200-mg capsule in relation to the oral solution, the ratio (A/B) for C_{max} was 153% (90% CI: 142%-166%) and that for $AUC_{0-\infty}$ was 124% (90% CI: 117%-133%).

Safety Results

Single 200-mg doses of FTC, administered as the oral capsule and solution formulations intended for commercialization or administered intravenously by continuous slow infusion over a period of 1 hour, were well tolerated, based on reported AEs, physical examination findings, including vital signs measurements and clinical laboratory test results. A total of 45 AEs were reported by 9 of the 12 subjects (75%). There were no SAEs reported. All of the AEs were Grade 1 (39 of 45) or Grade 2 (6 of 45) in severity, and all events resolved without requiring treatment.

Conclusions

- Based on the $AUC_{0-\infty}$ estimate, the absolute bioavailability of the 200-mg FTC capsule formulation is 93%. Based on the $AUC_{0-\infty}$ estimate, the absolute bioavailability of 20 mL of the 10-mg/mL FTC oral solution formulation is 75%.

- The relative bioavailability of the capsule formulation compared with oral solution was 124%. The finding of a lower bioavailability of the solution compared with the capsule was unexpected and difficult to explain. Nevertheless, the magnitude (approximately 24%) of the difference between the 2 oral formulations is considered unlikely to be of any clinical importance.

1.4.2. Studies in HIV-Infected Subjects

1.4.2.1. 143-001

Title

A Phase 1, Randomized, Single-Dose, Placebo-Controlled Trial to Evaluate the Safety and Pharmacokinetics of 524W91 (Emtricitabine) (Burroughs Wellcome Co. study)

Objectives

The objectives of the study were to determine the safety and PK of single, escalating oral doses of FTC administered to HIV-infected subjects. In addition, the effect of food on the oral bioavailability of FTC was assessed.

Study Design and Methodology

This was single-blind, placebo-controlled, dose-escalation study conducted at 2 sites. Subjects were randomized (2:1) to receive FTC or placebo. Subjects randomized to FTC received single, escalating doses of 100, 200, 400, 800, and 1200 mg orally under fasting conditions, with a ≥ 1-week washout interval between doses. The 400-mg dose was also administered with a standard high-fat meal in a randomized, crossover fashion. Serial blood (plasma) and cumulative urine samples were collected up to 24 hours after each dose for determination of plasma and urine concentrations of FTC by validated HPLC with ultraviolet detection (HPLC-UV) methods. Plasma concentration-time data were analyzed using noncompartmental methods. Safety was assessed based on reported AEs; physical examination findings, including vital sign measurements; and clinical laboratory test results.

Further details on the design and results of this study are available in the CSR (143-001).

Number of Subjects (Planned and Analyzed)

Planned: 18 subjects (12 FTC, 6 placebo)
Analyzed: 18 subjects (12 FTC, 6 placebo)

Safety Results

Eleven of the 12 subjects (92%) who received FTC and 5 of the 6 subjects (83%) who received placebo experienced ≥ 1 AE during the study. No SAEs were reported during or after the study. One subject discontinued prematurely after the 800-mg dose of FTC due to a Grade 1 rash. No clinically significant changes from baseline were observed in any hematological, serum chemistry, or urinalysis parameters.

Results and Conclusions

Single oral doses of FTC up to 1200 mg were well tolerated by HIV-infected subjects.

FTC was rapidly and well absorbed following oral administration. Administration of FTC with a high-fat meal decreased the rate of absorption, but did not affect the extent of absorption.

The disposition of FTC followed linear kinetics in the dose range of 100 to 1200 mg and intra- and intersubject variability in PK parameters was low.

Systemic exposure to FTC at concentrations far exceeding its in vitro IC_{50} can be achieved following administration of a 100-mg dose.

1.4.2.2. FTC-101

Title

A Dose-Escalation Study to Investigate the Safety, Tolerance, Pharmacokinetics, and Antiviral Activity of Multiple Repeat Doses of FTC in Subjects Who are Infected with HIV-1

Objectives

The objectives of Study FTC-101 were to evaluate the safety, tolerance, and antiviral activity of repeat doses of FTC and to characterize the PK of FTC in plasma and FTC 5'-triphosphate (FTC-TP) in target cells following single- and multiple-dose administration to HIV infected, treatment-naive subjects. The ultimate goal of this study was to select a dosage regimen for FTC for subsequent therapeutic trials.

Study Design and Methodology

This was an open-label, dose-escalation study to evaluate the safety, tolerance, PK, and anti-HIV activity of 5 dosage regimens (25 mg twice daily, 100 mg twice daily, 200 mg twice daily, 100 mg once daily, and 200 mg once daily) of FTC for 14 days in 5 groups of HIV infected subjects who were naive to lamivudine and ABC and had screening plasma HIV-1 RNA ≥ 5000 c/mL and CD4 cell count ≥ 200/mm^3. Serial blood (plasma) samples were collected for 12 hours after the first dose on Day 1 and after the morning dose on Day 10 (at steady state) for PK evaluation. Cumulative urine for PK evaluation was collected over the same interval on Day 10. Plasma and urine concentrations of FTC were analyzed using validated LC/MS/MS and HPLC with mass-selective detection (single-ion monitoring) methods, respectively. Peripheral blood mononuclear cells were obtained on Days 1 and 12 for determination of FTC-TP concentrations using a validated HPLC with ultraviolet detection (HPLC/UV) method. Plasma HIV-1 RNA measurements were obtained at baseline and at frequent intervals over the 14 days of treatment by quantitative polymerase chain reaction (PCR, Roche Amplicor® HIV-1 Monitor™ Test).

Further details on the design and results of this study are available in the CSR (FTC-101).

Number of Subjects (Planned and Analyzed)

Planned: 40 subjects (5 cohorts, each with 8 subjects)
Analyzed: 41 subjects

Safety Results

FTC was well tolerated by the study population, with no study drug-related AEs requiring discontinuation of study medication. Abnormalities in clinical laboratory values were generally Grade 1 and not clinically significant, with the exception of increased CPK in 2 subjects and increased amylase in 1 subject. The increased amylase was considered by the investigator to be possibly related to FTC. One subject had an SAE during the study, self-hospitalization for drug dependency, which was unrelated to study drug. This subject was discontinued from study medication. Dose-limiting toxicity was not evident in this study. Most treatment-emergent AEs were Grade 1 or 2 in intensity. Adverse events considered Grade 3 in intensity were asthenia and headache, each in 1 subject in the 25-mg twice-daily cohort (n = 9); depression and increased CPK (1 subject each) in the 100-mg once-daily cohort; depression and drug-dependency (1 subject) and 1 subject with increased amylase > 5 times the upper limit of normal in the 100-mg twice-daily cohort (n = 8); and dyspepsia in 1 subject in the 200-mg once-daily cohort (n = 8). No Grade 3 AE was observed or reported in the 200-mg twice-daily cohort (n = 8).

Results and Conclusions

FTC was well tolerated by the study population, with no study drug-related AE requiring discontinuation of study medication.

FTC was rapidly and extensively absorbed following oral administration, with peak plasma FTC concentrations generally occurring between 1 to 2 hours postdose. At least 60% to 70% of an oral dose of FTC was absorbed and subsequently recovered in urine as unchanged drug.

Plasma FTC was primarily eliminated as unchanged FTC in urine, with an elimination $t_{1/2}$ of 8 to 9 hours from plasma with a 24-hour sampling time interval.

Plasma concentrations of FTC (C_{max}, AUC, and C_{min}) increased in a dose-proportional manner following both single- and multiple-dose administration.

Following once daily dosing regimens, plasma trough FTC concentrations at 24 hours postdose were still about 2- to 4-fold higher than the in vitro IC_{90} value for inhibition of HIV-1 replication.

The mean CL/F value of FTC was relatively constant across the dose range studied and ranged from 400 to 500 mL/min. Mean renal clearance of FTC ranged from 250 to 330 mL/min, which was 2- to 3-fold higher than the estimated CL_{cr}.

FTC demonstrated linear kinetics over the dose range studied, and steady-state concentrations were predictable based on single-dose data.

Concentrations of intracellular (PBMC) FTC-TP, the active moiety, increased in a dose-related fashion reaching a plateau level of approximately4 pmol/10^6 cells following doses of 200 mg/day. The $t_{1/2}$ of FTC-TP was estimated to be longer than 20 hours, which supports a once-daily regimen.

FTC exhibited substantial antiviral activity in a dose-dependent manner. At a daily dose of 200 mg or more, plasma HIV-1 RNA viral load suppression ranged from 1.7 to 1.9 $\log_{10}$ following 14 days of dosing.

Both the viral load suppression and intracellular FTC-TP levels increased with FTC dose, but reached a plateau at daily doses > 200 mg. The anti-HIV activity at a dose of 200 mg per day would have already achieved close to 95% of the maximal activity with little additional (approximately 3%) activity observed at double the dose (400 mg/day).

In this study, plasma and intracellular PK, as well as the plasma HIV-1 RNA suppression data, support a once-daily dose of 200 mg FTC for therapeutic studies.

1.4.2.3. FTC-102

Title

A Randomized, Comparative Trial of FTC Administered Once Daily versus 3TC Administered Twice Daily to HIV-1 Infected Patients in a 10-Day Dosing Regimen

Objectives

Study FTC-102 was a Phase 1, open-label, randomized, comparative trial designed to evaluate the safety, tolerability, and antiviral activity of multiple doses of FTC following 3 different once-daily dosage regimens in comparison to 3TC 150 mg twice daily in HIV-1 infected ART-naive subjects. The primary objective of the study was to evaluate the antiviral activity of FTC 200 mg once daily versus 3TC 150 mg twice daily. Secondary objectives were the following: to evaluate the antiviral activities of 25 mg and 100 mg FTC once daily versus 3TC 150 mg twice daily; to compare FTC 200 mg once daily versus FTC 100 mg once daily; and to determine the safety profile of the 3 FTC doses.

Study Design and Methodology

This was a randomized, open-label, comparative study of 3 doses of FTC (25 mg once daily, 100 mg once daily, and 200 mg once daily) versus 3TC (150 mg twice daily) administered for 10 days. Throughout the 10-day dosing period, blood (plasma) samples were drawn frequently for measurement of plasma HIV-1 RNA levels by quantitative PCR (Roche Amplicor® HIV-1 Monitor™ Test). Blood (plasma) samples were drawn immediately prior to dosing in the morning of Days 5 and 10 for measurement of FTC plasma trough levels using a validated LC/MS/MS method. Safety was assessed based on reported AEs and clinical laboratory test results.

Further details on the design and results of this study are available in the CSR (FTC-102).

Number of Subjects (Planned and Analyzed)

Planned: 80 subjects (4 cohorts, each with 20 subjects)
Analyzed: 81 subjects

Safety Results

FTC was well tolerated in all 3 dosing regimens. The most commonly reported AEs were headache, infection, and nausea. The incidences were similar to those reported for the 3TC treatment group. The majority of AEs were Grade 1 to 2 in severity. Abnormalities in clinical laboratory values were generally Grade 1 to 2 and did not require dosing modification. Overall, the short-term tolerability and safety profile of FTC was comparable to that of 3TC.

Results and Conclusions

FTC was well tolerated, with no evidence of dose-limiting toxicity or safety concern at the dosages studied. At all dose levels, the AE profile was unremarkable and similar to that of 3TC.

A dose-response relationship for FTC was observed when viral suppression was expressed as time-averaged area under the curve minus baseline. The activity of the 200-mg once-daily dose of FTC was superior to the 100- and 25-mg once-daily doses. The activities of the 100- and 25-mg once-daily doses of FTC were not significantly different.

The measurements in this study of FTC trough plasma concentrations support once-daily administration. At the 100- and 200-mg once-daily doses, mean trough concentrations of 0.04 and 0.06 μg/mL, respectively, were ≥ 3-fold higher than the mean IC_{90} in vitro necessary to inhibit HIV replication.

Overall, the results of safety, antiviral activity, and PK analyses performed in this study extended and confirmed the results obtained in Study FTC-101 and supported the selection of 200-mg once-daily FTC as the dose for subsequent Phase 2 and 3 clinical trials.

1.4.2.4. FTC-303

Title

A Randomized, Open-Label Equivalence Study of FTC Versus Lamivudine in Patients on a Stable Triple Antiretroviral Therapy Regimen Containing Lamivudine, Stavudine or Zidovudine, and a Protease Inhibitor or a Non-Nucleoside Reserve Transcriptase Inhibitor

Objective

The primary objective of this study was to establish the equivalence of antiviral activity between FTC and lamivudine by comparing the proportion of randomized subjects at 48 weeks whose plasma HIV-1 RNA level remained ≤ 400 c/mL.

Study Design/Subject Population

Study FTC-303 was a Phase 3, 48-week, open-label, randomized, parallel group, multicenter study to evaluate the equivalence in terms of safety and efficacy, of FTC to lamivudine in HIV-1 infected subjects. Subjects who met the entry criteria were randomized in a 2:1 (FTC: lamivudine) ratio. Subjects randomized to FTC were switched from lamivudine to FTC PO while continuing on their current background therapy. Subjects randomized to lamivudine continued on their current lamivudine-containing therapy.

Of 459 subjects randomized, 440 received ≥ 1 dose of study medication; these 440 subjects comprised the ITT population.

Further details on the design and results of this study are available in the FTC-303 Final CSR.

Efficacy Results

Using a noncompleter equals failure analysis, the proportion of subjects with HIV-1 RNA ≤ 400 c/mL through 48 weeks of therapy was 73% in the FTC arm and 82% in the lamivudine arm. The stratum-adjusted difference between treatment groups (FTC minus lamivudine) was −5.8 % yielding a stratum adjusted 95% CI of −13.5 % to 1.8%. The lower limit of the CI was within the protocol's pre-defined criteria (−15%) to conclude the noninferiority of FTC to lamivudine. Similarly, using a noncompleter equals failure analysis, the proportion of subjects with HIV-1 RNA ≤ 50 c/mL through 48 weeks of therapy was 68% in the FTC arm and 75% in the lamivudine arm (stratum adjusted treatment difference of −4.7%, 95% CI of −13.0% to 3.5%). For each of these response endpoints, the difference was largely attributed to attrition from the study and not loss of virologic activity.

The mean increase from baseline in CD4 cells was 29 cells/mm^3 in the FTC group and 61 cells/mm^3 in the lamivudine group, (stratum-adjusted 95% CI of −66 to 6 cells/mm^3) with a corresponding mean increase in percent CD4 from baseline of 2.5% and 1.7%, respectively, (stratum-adjusted 95% CI of 0.0% to 1.6%).

In addition to the aforementioned endpoints, no remarkable differences between treatment groups were observed for a number of other secondary efficacy endpoints including the proportion of subjects that were considered efficacy failures.

Pharmacokinetic Results

The PK substudy in Study FTC-303 evaluated the steady-state plasma profiles and PK of FTC in HIV infected subjects receiving once daily dosing of 200 mg FTC in combination with other antiretrovirals including NRTIs, NNRTIs, and HIV PIs. Emtricitabine demonstrated desirable PK characteristics, ie, rapid oral absorption producing high plasma concentrations over a prolonged period. The mean trough (lowest) plasma concentration measured at steady state in each subject was 8-fold than the average in vitro IC_{90} of HIV suppression. This high plasma exposure to FTC, along with the relatively long plasma half-life (approximately 8 hours), supports the once daily dosing regimen. In addition, the relatively small intersubject variabilities in FTC PK would provide consistent plasma exposure to FTC over a broad subject population.

Safety Results

There were no significant differences between the FTC and lamivudine treatment groups with respect to the overall incidence of AEs or the incidence of SAEs.

The majority of AEs were mild to moderate in severity. In the case of specific AEs, the incidence of most AEs was comparable between treatment groups with the exception of infection, headache, rhinitis, flu syndrome, and lymphadenopathy which had a higher incidence in the FTC treatment group.

There was a statistically significant difference between the treatment arms in terms of subjects who discontinued the study due to an AE. Thirteen FTC-treated subjects discontinued the study due to an AE compared to 1 subject in the lamivudine treatment group who died during the study. Notably, all subjects discontinuing FTC due to AEs had plasma HIV-1 RNA levels < 50 c/mL at the time of discontinuation. Of the 13 FTC-treated subjects who withdrew due to an AE, 10 did so for AEs that were mild or moderate in severity. In the study overall, 3% of subjects discontinued due to an AE.

When considering more objective measures of safety, specifically laboratory abnormalities, no remarkable differences in the incidence of Grade 3 or 4 events between the 2 treatment groups were observed.

Conclusions

- When subjects who were on a stable lamivudine-based regimen were randomized to switch to once daily FTC in combination with their same background medications or to stay on their original regimen, there was no significant difference in virologic activity, immunologic response, or safety between the FTC and lamivudine treatment groups.

1.4.2.5. FTCB-101

Title

A Dose-Escalation Cohort Study to Investigate the Safety, Tolerance, Pharmacokinetics and Antiviral Activity of Single and Multiple Repeat Doses of FTC in Patients who are Infected with HBV

Objectives

The primary objective of this study was to evaluate the safety, tolerance, and PK of multiple repeat doses of FTC at different dosage levels. The secondary objective was to evaluate the preliminary antiviral activity of FTC and to correlate this activity with PK parameters.

Study Design and Methodology

This study was a multicenter evaluation of the safety and efficacy of FTC therapy administered to HBV-infected subjects daily. Subjects received treatment for 8 weeks, with evaluations at Days 1 (prior to commencement of study medication), 7, 14, 28, 42, and 56. Clinical, immunologic, serologic, and viral load evaluations were completed during scheduled clinic

visits. Once the cohort was full, another cohort of 8 subjects was enrolled to receive FTC at the next highest dose. Two additional cohorts (FTC doses 50 and 300 mg) were deemed necessary after preliminary results were assessed. All subjects were evaluated 24 and 48 hours posttreatment for HBV DNA. They then had a complete follow-up examination 4 weeks after completing the 8-week therapy. Every cohort of 8 subjects received an initial oral dose of FTC in the fasted state. Serial PK sampling was performed over the next 24 hours (prior to dosing on Day 2). Study medication was given every 24 hours. Blood samples for PK monitoring were collected regularly during the 8-week period for determination of plasma concentrations of FTC for all subjects.

Further details on the design and results of this study are available in the CSR (FTCB-101).

Number of Subjects (Planned and Analyzed)

Planned: 40 subjects (5 cohorts of 8 subjects each)
Analyzed: 49 subjects

Safety Results

Thirty-eight of the 49 subjects (78%) in this study reported ≥ 1 AE. There were no SAEs or deaths in this study. One subject discontined study medication due to possible study drug-related AEs (Grade 1 vertigo and Grade 3 headache). Treatment-emergent AEs were Grades 1 to 2, with the exception of 1 subject with a Grade 3 headache, and another with Grade 3 urticaria that were possibly related to the study drug. The subject with the headache was discontinued from the study medication. The urticaria resolved while the subject continued to receive the study medication. Abnormalities in clinical laboratory values were generally Grade 1 and not clinically significant, with the exceptions of increased creatine phosphokinase in 1 subject and increased serum amylase in another. The creatine phosphokinase increase was transient and resolved by the next follow-up visit. The elevation in serum amylase occurred at the midpoint of the 8-week treatment period and remained elevated during the posttreatment follow-up period, ie, after withdrawal of study drug. Dose-limiting toxicity was not evident in this study.

Results and Conclusions

There was no dose-limiting toxicity at the dosages studied, nor any dose-response relationship to any of the safety evaluations. FTC was well tolerated with no SAEs reported.

FTC exhibited substantial anti-HBV activity at all doses, confirming in vitro and experimental activity {Painter 1995, Schinazi 1992}.

A dose response, primarily driven by a lesser antiviral effect at 25 mg, was observed.

At a daily dose of ≥ 50 mg, $\log_{10}$ HBV DNA viral load suppression ranged from 2.6 to 3.4. It was not possible to identify the optimal dose from the Study FTCB-101 results with absolute certainty. However, based on the dose-response analysis using maximum (pharmacodynamics) effect (E_{max}) modeling, the anti-HBV activity of FTC at a dose of 200 mg/day would have already achieved close to 95% of the maximal antiviral activity with little additional (approximately 2%) activity observed as dose was increased to 300 mg/day.

In HBV-infected subjects, FTC was rapidly and well absorbed following oral administration over a wide dose range (25 to 300 mg); the peak plasma FTC concentrations generally occurred within 1.5 hours postdose.

Plasma concentrations of FTC (C_{max} and AUCs) increased in a dose-proportional manner following both single-dose and multiple-dose administration over the 25 to 300 mg (once daily) dose range in HBV-infected subjects. The mean CL/F value of FTC was relatively constant over the wide dose range and averaged approximately 300 mL/min. Plasma FTC was eliminated with an average $t_{1/2}$ of approximately 8.5 hours across dose levels.

FTC demonstrated linear pharmacokinetics over the 25 to 300 mg dose range studied and steady-state concentrations were predictable based on single-dose data in HBV-infected subjects.

In general, PK parameter estimates of FTC in HBV-infected subjects are similar to those determined previously in healthy subjects and HIV-infected subjects.

1.4.3. Intrinsic Factor Studies

1.4.3.1. FTC-107

Title

An Evaluation of the Pharmacokinetics of Emtricitabine in Volunteers with Varying Degrees of Renal Impairment

Objectives

The primary objective of Study FTC-107 was to assess the effects of renal impairment on the PK of FTC following a single oral dose in subjects with varying degrees of renal insufficiency in comparison to subjects with normal renal function. A secondary objective was to determine the effects of hemodialysis on the removal of FTC in subjects with end-stage renal disease (ESRD).

Study Design and Methodology

This open-label, parallel group study planned to enroll male or female subjects with varying degrees of renal function, as determined by estimated CL_{cr} (Cockcroft-Gault method), into each of the following 5 groups (6 subjects per group):

Group	Description	Estimated CL_{cr} (mL/min)
I	Normal renal function	> 80
II	Mild renal impairment	50–80
III	Moderate renal impairment	30–49
IV	Severe renal impairment (not requiring dialysis)	< 30
V	ESRD (requiring dialysis)	Functional anephric

Creatinine clearance was subsequently confirmed by a 24-hour urine collection for all subjects in Groups I to IV prior to dosing. Subjects in Groups I to IV each received a single 200-mg oral dose of FTC, with serial blood (plasma) samples and cumulative urine collected for 48 hours (Groups I and II) or 72 hours (Groups III and IV) postdose. Group V subjects received a first 200-mg FTC dose shortly after completing their normal 3-hour hemodialysis, with serial blood (plasma) samples collected for 72 hours postdose. After a minimum 1-week washout, Group V subjects received a second 200-mg dose at approximately 1.5 hours prior to the start of their normal 3-hour hemodialysis, with blood (plasma) samples and all dialysate collected until the end of dialysis (ie, approximately 4.5 hours postdose). Plasma, urine, and dialysate samples were assayed for FTC concentrations using a validated LC/MS/MS method.

Pharmacokinetic analysis was performed using noncompartmental methods, and statistical analysis was performed by ANOVA followed by 2 one-sided t-tests. The A_e and the CL_r of FTC were calculated. For Group V subjects, FTC concentrations in dialysate were measured and the amount of FTC recovered in dialysate and clearance via hemodialysis were calculated. Linear regression analysis was performed to characterize the relationship between FTC clearance values (CL/F, CL_r) and CL_{cr}.

Safety was assessed based on reported AEs, physical examination findings, which included vital signs measurements, and clinical laboratory test results.

Further details on the design and results of this study are available in the CSR (FTC-107).

Number of Subjects (Planned and Analyzed)

At least 30 subjects were planned for enrollment into this study (at least 6 subjects each in Groups I through V). A total of 44 subjects were screened for participation in this study, and 29 were enrolled, including 6 subjects each in Groups I, II, III, and V; and 5 subjects in Group IV. All 29 enrolled subjects completed the study. All subjects took ≥ 1 dose of study medication and were included in the safety and PK analyses.

Safety Results

No deaths or other SAEs were reported during this study, and no subject discontinued the study due to an AE. The overall incidence of AEs was low, and there was no apparent relationship between the incidence of AEs and the degree of renal impairment. Fourteen treatment-emergent AEs were reported by 8 of the 29 subjects (28%). All of the AEs were reported during Dose Period 1. The majority of the AEs (9 of 14 events) were Grade 1 in severity; whereas 4 of 13 events were Grade 2 in severity. One Group I subject experienced a Grade 3 laboratory abnormality (hyperkalemia) that was reported as an AE.

Serum chemistry values changed little from Day 0 of Dose Period 1 (prior to dosing) to Days 3 and 4 after dosing in Groups I through IV. For Group V, values for laboratory parameters associated with renal impairment (ie, serum creatinine and blood urea nitrogen) increased substantially from Day 0 to Day 4 in all 6 subjects during Dose Period 1, as expected for these subjects because hemodialysis was performed 3 days earlier. During Dose Period 2, increases in the number of abnormalities were observed after dosing for blood urea nitrogen (less than the

lower limit of normal) and uric acid (less than the lower limit of normal) for subjects in Group V, consistent with the subjects having just undergone hemodialysis. Hematology values changed little from Day 0 of Dose Period 1 (prior to dosing) to Days 3 and 4 after dosing in Groups I through IV. In Group V, hematocrit and hemoglobin values at Day 4 decreased compared with predose values in all 6 subjects. However, in all cases, the decreases were small and clinically insignificant and were primarily due to blood loss from PK sampling. No such trends were noted during Dose Period 2. Several urinalysis abnormalities were observed and were attributed to underlying disease (chronic renal failure, diabetes mellitus, or hypertension); these abnormalities were present at screening or Day 0 of Dose Period 1 and did not worsen after dosing with FTC. No clinically significant changes were observed in vital sign measurements or physical examination findings across measurement time points in any study group.

Pharmacokinetic Results and Conclusions

Single doses of 200 mg FTC were well tolerated by volunteers with varying degrees of renal insufficiency.

Urinary excretion is the primary route of FTC elimination, with approximately 70% of an oral dose recovered in urine as unchanged drug in subjects with normal renal function or mild renal impairment.

The PK of FTC was significantly affected by renal impairment. There was a graded increase in AUC values (by approximately 2- to 4.5-fold) and corresponding graded decrease in CL/F values as the degree of renal impairment increased. In addition, C_{max} value increased by 1.3- to 1.8-fold in subjects with mild to severe renal impairment.

There was a statistically significant linear relationship between the CL/F of FTC and estimated CL_{cr}. Thus, individual CL/F values of FTC can be estimated based on CL_{cr} values.

1.4.4. Extrinsic Factor Studies

1.4.4.1. FTC-108

Title

An Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics of FTC and Famciclovir Administered Alone or in Combination in Healthy Volunteers

Objectives

The primary objectives of Study FTC-108 were to determine the effects of the penciclovir prodrug, famciclovir, on the PK of FTC and to determine the effects of FTC on the PK of penciclovir. Both FTC and penciclovir (the active moiety of famciclovir) are primarily eliminated as unchanged drug by urinary excretion.

Study Design and Methodology

This was an open-label, single-dose, randomized, 3-way crossover study in 12 healthy male and female subjects. Each subject received the following 3 treatments: two 100-mg FTC capsules (Treatment A), one 500-mg famciclovir tablet (Treatment B), and two 100-mg FTC capsules plus one 500-mg famciclovir tablet (Treatment C). All treatments were administered in a randomized, crossover fashion under fasting conditions, and there was a ≥ 1-week washout interval between treatments. Serial blood (plasma) and cumulative urine samples were collected for 48 hours after each dose for determination of plasma and urine concentrations of FTC and penciclovir using validated LC/MS/MS methods. Pharmacokinetic analysis was performed using noncompartmental methods, and statistical analysis was performed using ANOVA on the log-transformed PK parameters, with the exception of T_{max} (untransformed). The two 1-sided t-tests procedure was used to construct 90% CIs for the GLSM parameter ratios of combination (test) versus single drug administration (reference). A conclusion of no significant difference between the test and reference treatments was made if the 90% CI of the test/reference ratios for AUC_{inf} and C_{max} were each within the range of 70% to 143%, representing a maximum of 30% difference between treatments. Urinary data were analyzed to calculate the amount of FTC or penciclovir and the percentage of dose excreted in urine as FTC or penciclovir for each treatment.

Safety was assessed based on reported AEs, physical examination findings, including vital sign measurements, and clinical laboratory test results.

Further details on the design and results of this study are available in the CSR (FTC-108).

Number of Subjects (Planned and Analyzed)

Twelve subjects (9 males and 3 females) were enrolled in the study; all subjects completed the 3 dose periods and all study procedures, and all were included in the PK, statistical, and safety analyses.

Safety Results

Twenty-six treatment-emergent AEs were reported by 8 of the 12 subjects (67%) between the administration of the first study treatment and 10 days after administration of the third (latest) study treatment. Adverse events reported by > 1 subject included headache (5 subjects; 42%), rhinitis (3 subjects; 25%), pharyngitis (2 subjects; 17%), and asthenia (2 subjects; 17%). All of the reported AEs were Grade 1or 2 in severity; there were no Grade 3 or 4 events reported during this period. There were no deaths or other SAEs reported, and there were no subject discontinuations due to AEs. There were no clinically significant changes or apparent trends in physical examination findings or vital sign and body weight measurements.

Pharmacokinetic Results and Conclusions

There were no deaths or other SAEs reported, and no subject was prematurely discontinued due to an AE. Single doses of FTC (200 mg) and famciclovir (500 mg), administered either alone or in combination, were generally well tolerated. Headache and rhinitis were the most common

AEs; these events were observed following each of the 3 treatments. There were no clinically significant changes or apparent trends in physical examination findings or vital sign and body weight measurements. There were no apparent trends in clinical laboratory test results that were clearly drug related.

A single dose of famciclovir, coadministered with FTC, had no clinically significant effect on the single-dose PK of FTC.

A single dose of FTC, coadministered with famciclovir, had no clinically significant effect on the single-dose PK of penciclovir, the active moiety of famciclovir.

1.4.4.2. GS-US-174-0105

Title

An Open-label, Randomized, Three-way Crossover Study to Evaluate the Potential for and Extent of Pharmacokinetic Interactions Between the Combination of Emtricitabine and Tenofovir Disoproxil Fumarate and Tacrolimus When Administered Alone and Together in Healthy Volunteers

Objectives

The primary objective of this study was as follows:

- To evaluate the effect of coadministration of tacrolimus on the steady-state PK of FTC and TFV (administered as the combination of FTC and TDF) and vice versa in healthy volunteers.

The secondary objective of this study was as follows:

- To evaluate the safety/tolerability of tacrolimus and the combination of FTC and TDF when coadministered for up to 7 days in healthy volunteers.

Study Design

This was a Phase 1, open-label, randomized, 3-way crossover, drug-drug interaction study of tacrolimus, administered as Prograf® capsules, and the combination of FTC and TDF, administered as FDC tablets. Eligible subjects were randomized to receive each of the following 3 open-label treatments, with a minimum 2-week washout interval between successive treatments:

- Treatment 1: FTC/TDF (200/300 mg) administered once daily for 7 days
- Treatment 2: tacrolimus (0.1 mg/kg/day) administered as 2 equal doses for 7 days
- Treatment 3: FTC/TDF (200/300 mg) administered once daily and tacrolimus (0.1 mg/kg/day) administered as 2 equal doses for 7 days

The order in which each subjects received the 3 treatments was determined by a randomization.

Further details on the design and results of this study are available in the CSR (GS-US-174-0105).

Study Population

A total of 31 subjects were enrolled and received at least 1 dose of study drug. Ten subjects did not complete the study: 1 did not meet eligibility criteria, 1 was noncompliant, and 8 withdrew consent.

In the Safety Analysis Set, most subjects were male (87%), with 68% white subjects, 16% black subjects, 3% Asian subjects, and 13% subjects of other ethnicity. At baseline, the median age was 22.3 years (range: 18.1 to 45.1 years), median weight was 71.2 kg, median height was 174.0 cm, median elbow width was 6.8 cm, and median estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) was 110.2 mL/min.

Pharmacokinetic Results

The PK of tacrolimus was not altered when coadministered with FTC/TDF. With the exception of C_{max} for TFV, all primary FTC and TFV PK parameters (C_{max}, C_{tau}, and AUC_{tau}) were bioequivalent when administered alone or in combination with tacrolimus. The 90% CI upper-bound of the geometric least-squares mean ratio for TFV C_{max} was just outside the predefined limit of 125%. However, the geometric mean C_{max} for TFV was increased by only 13% in the presence of tacrolimus and, therefore, is unlikely to be of any clinical significance.

Safety Results

Treatment-emergent AEs were reported in 22 of 31 subjects (71%) overall, 10 of 25 subjects (40%) after administration of FTC/TDF, 9 of 26 subjects (35%) after administration of tacrolimus, and 13 of 27 subjects (48%) after administration of FTC/TDF + tacrolimus. Most treatment-emergent AEs were Grade 1 in severity, and most resolved without therapy. No SAEs, deaths, or pregnancies occurred during this study. No subject discontinued because of an AE. No clinical laboratory abnormality was reported as an AE.

Conclusions

- No clinically important drug-drug interactions between FTC/TDF and tacrolimus were observed.

- Oral administration of 200 mg of FTC and 300 mg of TDF as an FDC tablet once daily alone or coadministered with 0.1 mg/kg/day of tacrolimus for up to 7 days was generally well tolerated in study subjects. Most AEs were mild, and most resolved without therapy.

- The PK and safety results from this drug-drug interaction study indicate that TDF at a dose of 300 mg and FTC at a dose of 200 mg, either separately or in combination, can be coadministered with tacrolimus without dose adjustment.

1.5. References

Painter G, St. Clair MH, Chingm S, Noblin J, Wang L, Furman PA. 524W91. Anti-HIV, Anti-Hepatitis B Virus. Drugs of the Future 1995;20 (8):761-5.

Schinazi RF, Boudinot FD, Ibrahim SS, Manning C, McClure HM, Liotta DC. Pharmacokinetics and metabolism of racemic 2',3'-dideoxy-5-fluoro-3'-thiacytidine in rhesus monkeys. Antimicrob Agents Chemother 1992;36 (11):2432-8.

1.6. Tabular Summary of Legacy Clinical Pharmacology Studies

Appendix Table 1. 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
Patient PD and PK/PD	GS-US-120-0104	Evaluate the short-term antiviral potency of TAF 8 mg, 25 mg, and 40 mg compared to placebo-to-match TAF or TDF 300 mg	Phase 1, randomized, partially-blinded, active- and placebo-controlled study	• TAF 8 mg QD PO (A) • TAF 25 mg QD PO (B) • TAF 40 mg QD PO (C) • TDF 300 mg QD PO (D) • Placebo-to-match TAF QD PO (E)	10 days	Randomized: 40 Completed: 37 Safety Analysis Set: A: 9 B: 8 C: 8 D: 6 E: 7	HIV-infected adult subjects, who had not received ART within 90 days of screening	Study completed; Final CSR
Healthy Subjects PD and PK/PD	GS-US-120-0107	Evaluate the effects of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, randomized, partially-blinded, placebo- and positive-controlled, 4-period, single-dose crossover study	Subjects were randomized to 1 of 8 treatment sequences and received the following treatments: • TAF 25 mg + 4 × placebo-to-match TAF QD PO (A) • TAF 125 mg (5 × 25 mg) QD PO (B) • Placebo-to-match TAF (C) • Moxifloxacin 400 mg PO, administered open-label (D)	37 days (4 single-dose treatment days separated by 11 days of washout between doses)	Randomized: 59 Completed: 58 Safety Analysis Set: A: 58 B: 58 C: 59 D: 58	Healthy adult subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0108	Evaluate the PK of TAF and its metabolite TFV following administration of TAF in subjects with and without severe renal impairment	Phase 1, open-label, parallel-design, single-dose, PK study	• TAF 25 mg PO	Single dose	Enrolled: 27 Completed: 27 Safety Analysis Set: Subjects with severe renal impairment: 14 Age and sex matched controls: 13	Adult subjects with severe renal impairment ($eGFR_{CG}$ of 15 to ≤ 29 mL/min) or healthy matched control subjects ($eGFR_{CG}$ of ≥ 90 mL/min)	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Tolerability	GS-US-120-0109	Determine the mass balance of TAF following administration of a single, oral dose of radiolabeled [^{14}C]TAF	Phase 1, open-label, mass-balance study	• TAF 25 mg (mixture of unlabeled TAF and [^{14}C]TAF) PO	Single dose	Enrolled: 8 Completed: 8 Safety Analysis Set: 8	Healthy adult male subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0114	Evaluate the PK of TAF in subjects with normal and impaired hepatic function	Phase 1, open-label, 2-cohort, parallel-group, single-dose, multicenter study	• TAF 25 mg PO	Single dose	Enrolled: 40 Completed: 40 Safety Analysis Set: Cohort 1: Subjects with mild hepatic impairment: 10 Matched controls: 10 Cohort 2: Subjects with moderate hepatic impairment: 10 Matched controls: 10	Cohort 1: Adult subjects with mild hepatic impairment (CPT Class A) and healthy matched control subjects Cohort 2: Adult subjects with moderate hepatic impairment (CPT Class B) and healthy matched control subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-120-0117	Evaluate the PK of RPV and TAF following single-dose administration of RPV and TAF alone and in combination in healthy subjects	Phase 1, open-label, single-center, single-dose, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments: Cohort 1: • TAF 25 mg QD PO (A) • TAF 25 mg + RPV 25 mg QD PO (B) Cohort 2: • TAF 25 mg + RPV 25 mg QD PO (B) • RPV 25 mg QD PO (C)	2 days (Days 1 and 12)	Randomized: 36 Completed: 36 Safety Analysis Set: Cohort 1: 18 Cohort 2: 18	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-0118	Evaluate the effect of common boosted PIs ATV+RTV; DRV+RTV; LPV/r, or the INSTI DTG on the PK of TAF, and evaluate the PK of ATV, DRV, LPV, and DTG alone and in combination with FTC and TAF	Phase 1, open-label, DDI study	Cohort 1: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • ATV 300 mg + RTV 100 mg QD PO (Days 2-14) (B) • A + B (Day 15) Cohort 2: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • DRV 800 mg + RTV 100 mg QD PO (Days 2-14) (C) • A + C (Day 15) Cohort 3: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • LPV/r (4 × 200/50 mg) QD PO (Days 2-14) (D) • A + D (Day 15) Cohort 4: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (F) • DTG 50 mg QD PO (Days 2-14) (E) • F + E (Day 15)	15 days	Enrolled: 40 Completed: 39 Safety Analysis Set: Cohort 1: 10 Cohort 2: 10 Cohort 3: 10 Cohort 4: 10 (1 subject excluded from the FTC+TAF+ DTG safety analysis)	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-1538	Evaluate the PK and drug interaction potential between TAF and MDZ (Oral and IV)	Phase 1, open-label, multiple-dose, single-center study	Subjects received the following treatments in a fixed sequence under fed conditions in the morning: • Day 1: MDZ_{oral} 2.5 mg syrup (A) • Day 3: MDZ_{IV} 1 mg solution (B) • Days 4-15 and 17: TAF 25 mg PO (C) • Day 16: TAF 25 mg PO + MDZ_{oral} 2.5 mg syrup coadministered (D) • Day 18: TAF 25 mg PO + MDZ_{IV} 1 mg solution administered within 5 min of each other (E)	18 days (Day 1, washout on Day 2, and doses on Days 3-18)	Enrolled: 18 Completed: 18 Safety Analysis Set: A: 18 B: 18 C: 18 D: 18 E: 18	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-120-1554	Evaluate the PK and drug interaction potential between TAF and RPV	Phase 1, open-label, randomized, fixed-sequence, 2-cohort, 2-period, multiple-dose study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments under fed conditions: Cohort 1: • TAF 25 mg QD PO (Days 1-14) (A) • TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C) Cohort 2: • RPV 25 mg QD PO (Days 1-14) (B) • TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C)	28 days	Randomized: 34 Completed: 32 Safety Analysis Set: Cohort 1: 17 Cohort 2: 17	Healthy adult subjects	Study completed; 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-320-0101	Evaluate the short-term antiviral activity of TAF and compare with TDF. Characterize the viral dynamics of HBV DNA associated with the use of TAF. Investigate the PK of TFV and TAF.	Phase 1b, randomized, open-label, active-controlled study	Subjects were randomized to receive the following treatments. • TAF 8 mg QD PO • TAF 25 mg QD PO • TAF 40 mg QD PO • TAF 120 mg QD PO • TDF 300 mg QD PO	28 days	Randomized: 51 Treated: 51 Completed Study Treatment: 51 10 subjects per group (11 subjects TAF 40 mg group)	Treatment-naive adults with CHB infection	Study completed; Final CSR
Intrinsic Factor PK	GS-US-320-1615	Evaluate the PK of TAF and its metabolite TFV in subjects with normal hepatic function and subjects with severe hepatic impairment.	Phase 1, open-label, parallel-group, single-dose, multicenter study	Subjects were enrolled in 1 of 2 groups (normal hepatic function or severe hepatic impairment) and received the following treatment. • TAF 25 mg tablet PO	Single dose	Randomized: 20 Treated: 20 Completed Study Treatment: 20 10 subjects per group	Adult subjects with severe hepatic impairment (CPT C) and healthy matched control subjects	Study completed; Final CSR

Appendix Table 2. F/TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-311-0101	Cohort 1: Evaluate the PK of TAF, TFV, and FTC following once-daily coadministration of F/TAF FDC and EFV relative to the administration of F/TAF FDC alone Cohorts 2 and 3: Evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF FDC and DRV+COBI relative to the administration of these agents alone Cohort 4: Evaluate the PK of TAF, TFV, and COBI following once-daily coadministration of TAF+COBI relative to the administration of TAF alone	Phase 1, nonrandomized, open-label, crossover, multicohort, multiple-dose study	Cohort 1: • F/TAF (200/40 mg) QD PO (Days 1-12, fasted) (A) • F/TAF (200/40 mg) + EFV 600 mg QD PO (Days 13-26, fasted) (B) Cohort 2: • F/TAF (200/25 mg) QD PO (Days 1-12, fed) (C) • F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 13-22, fed) (D) Cohort 3: • DRV 2 × 400 mg + COBI 150 mg QD PO (Days 1-10, fed) (E) • F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 11-22, fed) (F) Cohort 4: • TAF 8 mg QD PO (Days 1-12, fed) (G) • TAF 8 mg + COBI 150 mg QD PO (Days 13-22, fed) (H)	Cohort 1: 26 days Cohorts 2-4: 22 days	Enrolled:50 Completed: 48 Safety Analysis Set: A: 12 B: 12 C: 12 D: 25[a] E: 14 F: n/a G: 12 H: 12	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-311-1387	Part A: To evaluate the effect of steady-state CBZ on the PK of TAF when administered as F/TAF FDC Examine the safety and tolerability of F/TAF FDC when administered alone or with CBZ	Phase 1, open-label, adaptive, 2-part, 3-period, fixed-sequence, single-center study	Eligible subjects were administered the following treatments in Part A: Period 1: • F/TAF (200/25 mg) (Day 1) Period 2: • CBZ 100 mg BID (Days 6-8) • CBZ 200 mg BID (Days 9-11) • CBZ 300 mg BID (Days 12-25) Period 3: • CBZ 300 mg BID + F/TAF (200/25 mg) (Day 26)	26 days	Enrolled: 26 Completed: 22	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-311-1388	Evaluate the effect of ATV+COBI on the PK of TAF and its major metabolite TFV Evaluate the effect of ATV+COBI on the PK of FTC Evaluate the effect of TAF on the PK of ATV and COBI	Phase 1, open-label, fixed-sequence, single-center, 3-period, cross-over study	Subjects were administered the following treatments QD in the morning with food starting on Day 1: • F/TAF (200/10 mg) (Days 1-7) (A) • ATV 300 mg + COBI 150 mg + F/TAF (200/10 mg) (Days 8-14) (B) • ATV 300 mg + COBI 150 mg (Days 15-21) (C)	28 days	Enrolled:20 Completed: 19	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-311-1473	Evaluate the bioequivalence of FTC and TAF administered as F/TAF FDC, or as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences and received the following treatments: • F/TAF 200/25 mg FDC PO (A) • E/C/F/TAF (150/150/200/10 mg) FDC PO (B)	7 days; study drug dosing: 2 days	Enrolled: 116 Completed: 116	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-311-1790 (Cohort 1)	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

Appendix Table 3. E/C/F/TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-292-0103	Evaluate the PK and relative bioavailability of EVG, COBI, FTC, TAF, and TFV administered as E/C/F/TAF FDC relative to the administration of the individual components	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort, 2-period, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatment: Cohort 1: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • EVG 150 mg + COBI 150 mg QD PO (B) Cohort 2: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • FTC 200 mg + TAF 25 mg QD PO (C)	24 days (12 days for each treatment period within a sequence)	Randomized: 34 Completed: 33 Safety Analysis Set: Cohort 1: 14 Cohort 2: 20	Healthy adult subjects	Study completed; Final CSR
Uncontrolled Clinical Studies	GS-US-292-0112	Evaluate the effect of the GEN on renal parameters at Week 24 Evaluate the safety and tolerability of GEN through 144 weeks of treatment	Phase 3, open-label, multicenter, multi-cohort study	• E/C/F/TAF (150/150/200/10 mg) QD PO	144 weeks Extension Phase: Subjects have option to continue study drug for another 48 weeks until GEN is commercially available, becomes available through an access program, or development is terminated	Enrolled: 252 Safety Analysis Set: Cohort 1: 242 Cohort 2: 6	HIV infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min Cohort 1: ART-experienced Cohort 2: ART-naive	Study ongoing; Interim Week 24 CSR Interim Week 144 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-292-1316	Evaluate the PK of EVG, TAF, and SER following the coadministration of E/C/F/TAF FDC and SER relative to the administration of E/C/F/TAF or SER alone	Phase 1, open-label, 3-period, fixed-sequence, single-center study	• SER 50 mg QD PO (Day 1) (A) • E/C/F/TAF (150/150/200/10 mg) QD PO (Days 2-13) (B) • SER 50 mg + E/C/F/TAF (150/150/200/10 mg) QD PO (Day 14) (C)	14 days	Enrolled: 20 Completed: 19 Safety Analysis Set: 20	Healthy adult subjects	Study completed; Final CSR

Appendix Table 4. FTC and FTC/TDF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Patient PK and Initial Tolerability	FTC-101	Evaluate the safety, tolerance, PK, and antiviral activity of repeat doses of FTC	Phase 1, open-label, dose-ranging study with 14 days of repeated doses of monotherapy	Multiple escalating oral doses of FTC administered as capsules for: 25 mg BID (N = 9) 100 mg BID (N = 8) 200 mg BID (N = 8) 100 mg QD (N = 8) 200 mg QD (N = 8)	14 days	Enrolled: 41 Completed: 41	HIV-infected, therapy-naive adult subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	FTC-102	Safety, antiviral activity, dose-defining, comparison with 3TC	Phase 1/2, randomized, open-label, 3TC-controlled, 3 doses of FTC, 10-day repeated doses of monotherapy in adult HIV infected, ART-naive patients	• FTC 25 mg QD PO (N = 20) (A) • FTC 100 mg QD PO (N = 21) (B) • FTC 200 mg QD PO (N = 19) (C) • 3TC 150 mg BID PO (N = 21) (D)	10 days	As treated: 81 Completed: 81 Safety Analysis Set: 81	HIV-infected adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	FTC-106	Evaluate ADME of [^{14}C]FTC, mass balance by urinary and fecal recovery, plasma and PBMCs (FTC-triphosphate)	Phase 1, open-label, single-dose and 8-day repeated doses of FTC (with a single [^{14}C]FTC dose) in healthy adult volunteers	• Day 1: 200 mg single dose PO (N = 6) • Days 3−11: 200 mg QD PO for 8 days, single 250 µCi [^{14}C]FTC dose PO on the last day (N = 5)	11 days	Enrolled: 6 Completed: 5 Safety Analysis Set: 6	Healthy male subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Intrinsic Factor PK	FTC-107	Assess the PK profiles in subjects with various degrees of renal insufficiency (for potential dosage adjustment) and effect of hemodialysis	Phase 1, open-label, single-dose study of FTC in adult volunteers with varying degrees of renal insufficiency without and with hemodialysis	One single dose of FTC 200 mg administered PO in capsule formulation to: • Group 1 (normal renal function, CL_{cr} > 80 mL/min, N=6) • Group 2 (mild renal impairment, CL_{cr} = 50−80 mL/min, N=6) • Group 3 (moderate renal impairment, CL_{cr} = 30−49 mL/min, N=6) • Group 4 (severe renal impairment, CL_{cr} < 30 mL/min, N=5) • Group 5 (end-stage renal disease, requiring hemodialysis, N=6) For Group 5 subjects, a second FTC 200 mg dose PO was administered ~1.5 hour before the start of a 3-hour hemodialysis	1−2 single doses	Enrolled: 29 Completed: 29	Adult subjects with varying degrees of renal insufficiency with and without hemodialysis	Study completed; Final CSR
Extrinsic Factor PK	FTC-108	Assess potential PK interactions with concomitant antiviral drug (ie, famciclovir) with extensive renal excretion	Phase 1, randomized, open-label, single-dose, 3-way crossover study	3 single crossover doses (all PO) of: • FTC 200 mg alone • FCV 500 mg alone • FTC 200 mg + FCV 500 mg 1-week washout interval between doses	Single dose	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
BA	FTC-110	Evaluate relative and absolute BA of FTC	Phase 1, open-label, randomized, 3-way crossover, single 200-mg doses administered as IV solution, oral solution, or oral capsule	• FTC 1 × 200-mg capsule, PO, fasted (A) • 20 mL of FTC 10 mg/mL solution, PO, fasted (B) • 20 mL of FTC 10 mg/mL solution, IV infused over 1 hour, fasted (C)	3 single doses	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-303	Compare FTC to 3TC in HIV-infected subjects with copies/mL (HIV-1 RNA ≤400) on a stable (≥12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI	Phase 3, randomized (2:1) open-label, multi-center equivalence study	• Subjects switch from 3TC to FTC PO while continuing on current background therapy (A) • Subjects continue on current 3TC-containing regimen (B)	48 weeks	Randomized: 459 ITT: 440 A: 294 B: 146	HIV-infected, 3TC-experienced, adult subjects with stable HIV-1 RNA	Study completed; Final CSR and Addendum
Intrinsic Factor PK	FTCB-101	Assess the safety, tolerance, antiviral activity, and PK of FTC	Phase 1, open-label, dose-escalation, multiple repeat doses, 8 week study	• FTC 25 mg QD PO • FTC 50 mg QD PO • FTC 100 mg QD PO • FTC 200 mg QD PO • FTC 300 mg QD PO	56 days with 28 day follow up	Enrolled: 49 Completed: 45 Safety Analysis Set: 49	HBV-infected adult subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	Burroughs Wellcome 143-001	Assess the safety, PK, and effect of food on the BA of FTC	Phase 1, randomized, single-blind, single-dose, placebo-controlled, escalating doses (100 to 1200 mg)	• Single escalating oral doses of FTC administered as capsules: 100, 200, 400 (± food), 800, and 1200 mg, PO • Placebo, PO	6 total doses, each given 1 week apart	Enrolled: 18 Active: 12 Placebo: 6 Completed: 17	HIV-infected adult subjects	Study completed; Final CSR

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-174-0105	Evaluate the PK interactions between FTC/TDF FDC and TCL when administered alone and together	Single-center, open-label, randomized, 3-way crossover study	Subjects received each of the following treatments: • FTC/TDF • (200/300 mg) QD PO • TCL 0.1 mg/kg/day in 2 divided doses BID PO	21 days (7 days FTC/TDF FDC, 7 days TCL, 7 days FTC/TDF FDC + TCL)	Enrolled: 31 Completed: 21 Safety Analysis Set: 31	Healthy adult subjects	Study completed; Final CSR

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

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY 1
TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 3
LIST OF IN-TEXT FIGURES 4
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 5
1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY 7
1.1. Background 7
1.2. Overview of Clinical Efficacy 7
1.2.1. Primary Studies Supporting Efficacy of B/F/TAF 7
1.2.2. Other Studies Supporting Efficacy of B/F/TAF 12
2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES 14
2.1. HIV-Infected, ART-Naive Adult Subjects: Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475 14
2.1.1. Study GS-US-380-1489 14
2.1.2. Study GS-US-380-1490 16
2.1.3. Study GS-US-141-1475 18
2.2. HIV-Infected, Virologically Suppressed Adult Subjects: Studies GS-US-380-1844 and GS-US-380-1878 20
2.2.1. Study GS-US-380-1844 20
2.2.2. Study GS-US-380-1878 22
3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES 24
3.1. Study Populations 24
3.1.1. Subject Disposition 24
3.1.2. Demographic and Other Baseline Characteristics 32
3.1.3. Analysis Populations 47
3.2. Comparison of Efficacy Results of All Studies 51
3.2.1. ART-Naive Adult Subjects: Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475 51
3.2.2. Virologically Suppressed Adult Subjects: Studies GS-US-380-1844 and GS-US-380-1878 61
3.3. Comparison of Results in Subpopulations 66
3.3.1. ART-Naive Subjects: Studies GS-US-380-1489 and GS-US-380-1490 66
3.3.2. Virologically Suppressed Subjects: Studies GS-US-380-1844 and GS-US-380-1878 70
3.3.3. Subjects Coinfected with HIV and HBV 72
4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS 80
5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS 82
6. REFERENCES 83
7. APPENDIX 85
7.1. Tabular Summary of Studies Relevant for Efficacy 86
7.2. Additional Efficacy Analysis 89

LIST OF IN-TEXT TABLES

Table 1. Primary Studies Supporting Efficacy of B/F/TAF 8
Table 2. Number of HIV-Infected Subjects Who Received B/F/TAF in Phase 2 and Phase 3 Studies Included in the Submission by Region 10
Table 3. Other Studies Supporting Efficacy of B/F/TAF 13
Table 4. GS-US-380-1489 and GS-US-380-1490: Subject Disposition – Week 48 Pooled Data (All Randomized Subjects) 25
Table 5. GS-US-141-1475: Disposition of Subjects (All Screened Subjects) 27
Table 6. GS-US-380-1844: Disposition of Subjects (All Screened Subjects) 29
Table 7. GS-US-380-1878: Disposition of Subjects (All Screened Subjects) 31
Table 8. GS-US-380-1489 and GS-US-380-1490: Demographics and Baseline Characteristics (Safety Analysis Set) 33
Table 9. GS-US-141-1475: Demographic and Baseline Characteristics (Safety Analysis Set) 34
Table 10. GS-US-380-1844: Demographics and Baseline Characteristics (Safety Analysis Set) 35
Table 11. GS-US-380-1878: Demographic and Baseline Characteristics (Safety Analysis Set) 36
Table 12. GS-US-380-1489 and GS-US-380-1490: Baseline Disease Characteristics (Safety Analysis Set) 38
Table 13. GS-US-141-1475: Baseline Disease Characteristics (Safety Analysis Set) 40
Table 14. GS-US-380-1844: Baseline Disease Characteristics (Safety Analysis Set) 42
Table 15. GS-US-380-1878: Baseline Disease Characteristics (Safety Analysis Set) 45
Table 16. GS-US-380-1489: Analysis Sets at Week 48 (All Randomized Analysis Set) 47
Table 17. GS-US-380-1490: Analysis Sets at Week 48 (All Randomized Analysis Set) 48
Table 18. GS-US-141-1475: Analysis Sets at Week 48 (All Randomized Analysis Set) 49
Table 19. GS-US-380-1844: Analysis Sets at Week 48 (All Randomized Analysis Set) 50
Table 20. GS-US-380-1878: Analysis Sets at Week 48 (All Randomized Analysis Set) 51
Table 21. GS-US-380-1489 and GS-US-380-1490: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Individual Studies (Full Analysis Set) 53
Table 22. GS-US-380-1489 and GS-US-380-1490: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL – Pooled Data (Full Analysis Set) 55
Table 23. GS-US-141-1475: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) 56
Table 24. GS-US-380-1844: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (FAS) 62
Table 25. GS-US-380-1878: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (FAS) 63
Table 26. GS-US-380-1489 and GS-US-380-1490: Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm – Individual Studies and Pooled Data 67
Table 27. GS-US-380-1490: Proportion of Subjects with HBV DNA < 29 IU/mL at Baseline and On-treatment HBV DNA < 29 IU/mL at Week 48: Missing = Excluded, Subjects with HIV/HBV Coinfection at Baseline (Full Analysis Set) 74
Table 28. GS-US-380-1878: Proportion of Subjects with HBV DNA < 29 IU/mL at Baseline and On-treatment HBV DNA < 29 IU/mL at Week 48: Missing = Excluded, Subjects with HIV/HBV Coinfection at Baseline (Full Analysis Set) 76

LIST OF IN-TEXT FIGURES

Figure 1. GS US-380-1489 and GS US-380-1490: Mean and 95% CIs of Change from Baseline in CD4 Cell Count (cells/µL) by Visit (FAS) 60
Figure 2. GS-US-141-1475: Mean and 95% CI of Change from Baseline in CD4 Cell Count (cells/µL) by Visit (FAS) 61
Figure 3. GS-US-380-1489 and GS-US-380-1490: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm – Pooled Data 69
Figure 4. GS-US-380-1844: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS) 71
Figure 5. GS-US-380-1878: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS) 72

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
anti-HBe	antibody against hepatitis B e antigen
anti-HBs	antibody against hepatitis B surface antigen
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated)
BIC	bictegravir (GS-9883)
BMD	bone mineral density
BMI	body mass index
CHB	chronic hepatitis B
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COBI	cobicistat (Tybost®)
CRF	case report form
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval
DNA	deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine (Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
GEN	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

HIV-1	human immunodeficiency virus type 1
INSTI	integrase strand-transfer inhibitor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	intravenous
LOCF	last observation carried forward
LSM	least-squares mean
M = E	missing = excluded
M = F	missing = failure
MH	Mantel-Haenszel
NRTI	nucleoside reverse transcriptase inhibitor
OL	open label
$paEC_{95}$	protein-adjusted 95% effective concentration
$paIQ_{95}$	protein-adjusted inhibitory quotient of 95%
PK	pharmacokinetic(s)
PP	per protocol
Q1	first quartile
Q3	third quartile
QD	once daily
RNA	ribonucleic acid
ROW	rest of world
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
ULN	upper limit of normal
US	United States
vs	versus

1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

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, rilpivirine, 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}. Virologically suppressed HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}.

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 an 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.

1.2. Overview of Clinical Efficacy

An overview of the primary studies supporting efficacy of B/F/TAF is presented in Section 1.2.1. An overview of other studies supporting efficacy of B/F/TAF is presented in Section 1.2.2.

1.2.1. Primary Studies Supporting Efficacy of B/F/TAF

Primary studies that support efficacy of the B/F/TAF (50/200/25 mg) FDC are 2 Phase 3 studies in HIV-infected, ART-naive adult subjects (Studies GS-US-380-1489 and GS-US-380-1490) and 2 Phase 3 studies in HIV-infected, virologically suppressed adult subjects (Studies GS-US-380-1844 and GS-US-380-1878). These are supported by a Phase 2 study in HIV-infected, ART-naive adult subjects (Study GS-US-141-1475). Information on study design and populations for these studies is presented in Table 1.

Table 1. Primary Studies Supporting Efficacy of B/F/TAF

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	Narrative Location
HIV-Infected, ART-Naive Adult Subjects				
GS-US-380-1489	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs ABC/DTG/3TC	B/F/TAF (N = 314) ABC/DTG/3TC (N = 315)	Week 48 efficacy, PK, and safety	Section 2.1.1
GS-US-380-1490	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	B/F/TAF (N = 320) DTG+F/TAF (N = 325)	Week 48 efficacy, PK, and safety	Section 2.1.2
GS-US-141-1475	Phase 2, randomized, double-blind study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF Open-label extension phase allowed crossover from DTG+F/TAF to B/F/TAF or continuation of BIC+F/TAF as the B/F/TAF FDC	Double-blind phase: BIC 75 mg + F/TAF (N = 65) DTG+F/TAF (N = 33) Open-label extension phase: Continue BIC and F/TAF as the B/F/TAF FDC (N = 62) Switch to the B/F/TAF FDC from DTG+F/TAF (N = 30)	Double-blind phase: Week 48 efficacy, PK, and safety Open-label extension phase: Week 72 efficacy and safety	Section 2.1.3
HIV-Infected, Virologically Suppressed Adult Subjects				
GS-US-380-1844	Phase 3, randomized, double-blind 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 ABC/DTG/3TC FDC	Switch to B/F/TAF (N = 282) Stay on DTG and ABC/3TC as the ABC/DTG/3TC FDC (N = 281)	Week 48 efficacy, PK, and safety	Section 2.2.1
GS-US-380-1878	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	Randomized phase: Switch to B/F/TAF (N = 290) Stay on baseline regimen (N = 287) Open-label extension phase: Continue B/F/TAF (N = 241) Switch to B/F/TAF from SBR (N = 213)	Randomized phase: Week 48 efficacy, PK, and safety Open-label extension phase: deaths, SAEs, and discontinuations due to AEs	Section 2.2.2

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

The proposed indication for B/F/TAF is the treatment of HIV-1 infection in adults without any known mutations associated with resistance to the individual components of B/F/TAF.

The efficacy of B/F/TAF for the treatment of HIV-1 infection in ART-naive adult patients is supported by data from 2 Phase 3, randomized, double-blind, active-controlled studies, GS-US-380-1489 and GS-US-380-1490. Study GS-US-380-1489 uses ABC/DTG/3TC as the comparator, allowing for comparison of B/F/TAF with a guideline-recommended, INSTI-based, once-daily FDC {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Eligible subjects were ART-naive, HLA-B*5701-negative, HIV-infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL; a screening genotype showing sensitivity to FTC, tenofovir (TFV), lamivudine (3TC), and abacavir (ABC); an estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 50 mL/min (in accordance with the ABC/DTG/3TC product label {TRIUMEQ 2017a, Triumeq 2017b}); and the absence of chronic hepatitis B (CHB) infection. 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 to 199 cells/µL, or ≥ 200 cells/µL) at screening, and region (US vs ex-US) at randomization.

Study GS-US-380-1490 uses DTG administered with the F/TAF (200/25 mg) FDC (DTG+F/TAF) as the comparator, allowing for direct and exclusive comparison between the INSTIs BIC and DTG, as both were administered with the guideline-recommended NRTI FDC of FTC and TAF {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Eligible subjects were ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL; a screening genotype showing sensitivity to FTC and TFV; and an $eGFR_{CG}$ ≥ 30 mL/min (in accordance with the Descovy® and DTG product labels {Descovy 2017, DESCOVY® 2017, Tivicay 2017, TIVICAY® 2017}). Subjects with CHB coinfection were permitted to enter the study, based on the demonstrated efficacy and safety of TAF for the treatment of hepatitis B virus (HBV) infection {VEMLIDY® 2017} and guideline recommendations for the use of TFV-based regimens for use in coinfected subjects.

Data from Studies GS-US-380-1489 and GS-US-380-1490 are supported by data from the Phase 2 study GS-US-141-1475, in which single-agent BIC (75 mg) and DTG (50 mg), each administered with the F/TAF (200/25 mg) FDC, were compared. Subjects eligible for Study GS-US-141-1475 were ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL and CD4 cell count ≥ 200 cells/µL at screening; a screening genotype showing sensitivity to TFV and FTC; and an $eGFR_{CG}$ ≥ 70 mL/min. Subjects who participated in the open-label extension phase of Study GS-US-141-1475 received the B/F/TAF (50/200/25 mg) FDC.

The efficacy of B/F/TAF for the treatment of HIV-1 infection in virologically suppressed adult patients is supported by data from 2 Phase 3 studies, GS-US-380-1844 and GS-US-380-1878. The double-blind study GS-US-380-1844 compares continuing ABC/DTG/3TC FDC with switching to B/F/TAF in subjects who were virologically suppressed on ABC/DTG/3TC or a regimen consisting of those components {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}.

Eligible subjects were HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG administered with the ABC/3TC FDC or the ABC/DTG/3TC FDC for ≥ 3 consecutive months prior to screening; no documented resistance to FTC, TFV, DTG, ABC, or 3TC; an $eGFR_{CG}$ ≥ 50 mL/min; and the absence of CHB infection.

The open-label study GS-US-380-1878 uses ART regimens consisting of boosted ATV or DRV plus either the FTC/TDF FDC or the ABC/3TC FDC as comparator. Boosted PIs are recognized for having high barriers to viral resistance {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. The use of boosted DRV or ATV with 2 NRTIs allows comparison of B/F/TAF with non-INSTI-containing regimens. Eligible subjects were HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of once-daily ritonavir (RTV)- or cobicistat (COBI)-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening; no previous use of any approved or experimental INSTI; no documented or suspected resistance to FTC, TFV, ABC, or 3TC; and an $eGFR_{CG}$ ≥ 50 mL/min. Subjects with CHB coinfection were permitted to enter the study, providing they were on a TDF-containing regimen at screening. Randomization was stratified by the prior treatment regimen group (ie, TDF-containing regimens [RTV- or COBI-boosted ATV or DRV plus FTC/TDF] and non-TDF-containing regimens [RTV- or COBI-boosted ATV or DRV plus ABC/3TC]) at screening.

A total of 1511 subjects have received at least 1 dose of B/F/TAF in the Phase 2 and 3 studies. This includes 1206 subjects in the randomized phases of the Phase 3 studies. In addition, 92 subjects received B/F/TAF in the extension phase of Study GS-US-141-1475, and 213 subjects switched from the comparator regimens to receive B/F/TAF in the extension phase of Study GS-US-380-1878.

In the Phase 3 studies, subjects who received B/F/TAF were from sites in the US, Europe, and Rest of World (Table 2).

Table 2. Number of HIV-Infected Subjects Who Received B/F/TAF in Phase 2 and Phase 3 Studies Included in the Submission by Region

	US	Europe	Rest of World (ROW)	Total Enrolled
Phase 3 Studies[a]	928	341	150	1419
Phase 2 Studies[b]	92	0	0	92
TOTAL	**1020**	**341**	**150**	**1511**

a Phase 3 studies: GS-US-380-1489 (US: 228; Europe: 66; ROW: 20), GS-US-380-1490 (US:193; Europe: 84; ROW: 43); GS-US-380-1844 (US: 203; Europe: 57; ROW: 22); GS-US-380-1878 (randomized phase—US: 166; Europe: 87; ROW: 37) (extension phase—US: 138; Europe: 47; ROW: 28)
b Phase 2 study: GS-US-141-1475 (only includes subjects who received open-label B/F/TAF)
Source: GS-US-380-1489 Interim Week 48, Table 15.8.1.1; GS-US-380-1490 Interim Week 48, Table 15.8.1.1; GS-US-380-1844 Interim Week 48, Table 15.8.1.1; GS-US-380-1878 Interim Week 48, Table 15.8.1.1

The primary efficacy endpoint for the Phase 3 studies in ART-naive adult subjects (Studies GS-US-380-1489 and GS-US-380-1490) was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the United States (US) Food and Drug

Administration (FDA)-defined snapshot algorithm {Smith 2011, U. S. Department of Health and Human Services 2015}; this was a secondary efficacy endpoint for the Phase 2 study in ART-naive adult subjects (Study GS-US-141-1475; primary endpoint at Week 24) and the Phase 3 studies in virologically suppressed adult subjects (Studies GS-US-380-1844 and GS-US-380-1878). The primary efficacy endpoint for the Phase 3 studies in virologically suppressed adult subjects (Studies GS-US-380-1844 and GS-US-380-1878) was the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 (US FDA-defined snapshot algorithm).

Other efficacy endpoints presented for ART-naive and virologically suppressed adult subjects in this summary are the proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 48 (US FDA-defined snapshot algorithm), the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by missing data imputation methods (Missing = Excluded [M = E] and Missing = Failure [M = F]), and change from baseline in CD4 cell count at Week 48. Additionally, change from baseline in HIV-1 RNA at Week 48 is presented for Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475 in ART-naive subjects.

Data from the B/F/TAF treatment groups in Studies GS-US-380-1489 and GS-US-380-1490 were pooled and compared with each of the comparator treatment groups (ie, pooled B/F/TAF vs ABC/DTG/3TC and pooled B/F/TAF vs DTG+F/TAF) for analysis of the primary and selected secondary efficacy endpoints (ie, HIV-1 RNA < 50 copies/mL and HIV-1 RNA < 20 copies/mL [US FDA-defined snapshot algorithm] at Week 48, and change from baseline in CD4 cell count at Week 48). For subgroup analyses of the primary endpoint in Studies GS-US-380-1489 and GS-US-380-1490, pooled B/F/TAF treatment group data were compared with data from the pooled comparator treatment groups (ie, ABC/DTG/3TC and DTG+F/TAF). Pooled analyses are labeled as such in this summary document, with data from individual studies presented in side-by-side comparisons or stand-alone tables, as applicable. Data from the other B/F/TAF studies were not pooled due to differences in study design (open label vs double blind), prior treatment regimen and duration of prior treatment, and subject populations evaluated. Subgroup analysis in the switch studies GS-US-380-1844 and GS-US-380-1878 was conducted for the proportion of subjects with HIV-1 RNA < 50 copies/mL [US FDA-defined snapshot algorithm] at Week 48, a secondary efficacy endpoint, rather than the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL, the primary efficacy endpoint, because the percentage of subjects in the latter was expected to be very low (around 2%).

HIV resistance analyses for all B/F/TAF studies are presented in m2.7.2, Section 4.2.1.

Statistical methods are presented in the statistical analysis plans (SAPs) for the individual studies (GS-US-380-1489 Interim Week 48, Appendix 16.1.9, SAP; GS-US-380-1490 Interim Week 48, Appendix 16.1.9, SAP; GS-US-141-1475 Interim Week 72, Appendix 16.1.9, SAP; GS-US-380-1844 Interim Week 48, Appendix 16.1.9, SAP; GS-US-380-1878 Interim Week 48, Appendix 16.1.9, SAP) and the B/F/TAF Week 48 Integrated Summary of Efficacy (ISE) SAP for the pooled studies (GS-US-380-1489 and GS-US-380-1490).

A tabular summary of study designs for the primary studies of B/F/TAF is provided in Appendix 7.1.

1.2.2. Other Studies Supporting Efficacy of B/F/TAF

Phase 3 studies that provide support for the efficacy of B/F/TAF in HIV/HBV-coinfected adult subjects are also included in this submission. These studies include results for the anti-HIV and anti-HBV efficacy of elvitegravir/COBI/F/TAF (Genvoya; GEN) in HIV/HBV-coinfected subjects in Study GS-US-292-1249, and the anti-HBV efficacy of TAF (Vemlidy) in HBV-monoinfected subjects in Studies GS-US-320-0108 and GS-US-320-0110. Information on study design and populations for these studies is presented in Table 3.

Table 3. Other Studies Supporting Efficacy of B/F/TAF

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented
HIV/HBV-Coinfected Adult Subjects			
GS-US-292-1249	Phase 3b, open-label, single-arm, multicenter, dual-cohort study to assess the safety, efficacy, and tolerability of GEN	GEN HIV Suppressed (N = 74) HIV/HBV ART Naive (N = 3)[b]	Weeks 24 and 48 efficacy and safety
CHB-Infected Adult Subjects without HIV Infection			
GS-US-320-0108	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-negative subjects with CHB	TAF 25 mg once daily (N = 285) TDF 300 mg once daily (N = 140)	Week 48 efficacy, PK, and safety
GS-US-320-0110	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-positive subjects with CHB	TAF 25 mg once daily (N = 581) TDF 300 mg once daily (N = 292)	Week 48 efficacy, PK, and safety

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).
b Because only 3 HIV/HBV-coinfected, treatment-naive subjects were treated in Study GS-US-292-1249, data for these subjects are not summarized; however, these data are presented in the CSR.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Complete study descriptions and results for Studies GS-US-380-1489, GS-US-380-1490, GS-US-141-1475, GS-US-380-1844, and GS-US-380-1878 are available in the clinical study reports (CSRs). Brief narratives of these studies are presented in the following sections.

2.1. HIV-Infected, ART-Naive Adult Subjects: Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475

2.1.1. Study GS-US-380-1489

Location:	GS-US-380-1489 Interim Week 48
Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naive Adults
Primary and Key Secondary Objectives:	The primary objective of this study is as follows: • To evaluate the efficacy of B/F/TAF versus ABC/DTG/3TC in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48 The secondary objectives of this study are as follows: • To evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Weeks 48, 96, and 144 • To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Weeks 48, 96, and 144 (results are presented through 48 weeks of treatment)
Study Design and Subject Population:	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of B/F/TAF versus ABC/DTG/3TC in HIV-infected, ART-naive adult subjects. Subjects who provided written consent and met all eligibility criteria were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: • **Treatment Group 1:** B/F/TAF (50/200/25 mg) FDC tablet + placebo-to-match ABC/DTG/3TC FDC administered orally, once daily, without regard to food (planned n = 300) • **Treatment Group 2:** ABC/DTG/3TC (600/50/300 mg) FDC tablet + placebo-to-match B/F/TAF FDC administered orally, once daily, without regard to food (planned n = 300) 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. Subjects will be treated for at least 144 weeks during the blinded treatment phase, with an option to receive B/F/TAF in an open-label extension phase for up to 48 weeks if safety and efficacy of B/F/TAF are demonstrated following review of unblinded Week 144 data. Eligible subjects were ART-naive, HLA-B*5701-negative, HIV-infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL; a screening genotype showing sensitivity to FTC, TFV, 3TC, and ABC; $eGFR_{CG}$ ≥ 50 mL/min; and the absence of chronic hepatitis B (CHB) infection. Of the 739 subjects screened, 631 were randomized to study drug (B/F/TAF 316 subjects; ABC/DTG/3TC 315 subjects). Two subjects randomized to B/F/TAF did not receive study drug due to withdrawn consent.

	Of the 629 subjects randomized and treated, 94.4% of subjects (594 subjects; B/F/TAF 93.9%, 295 subjects; ABC/DTG/3TC 94.9%, 299 subjects) were continuing study drug, and 5.6% (35 subjects) prematurely discontinued study drug (B/F/TAF 6.1%, 19 subjects; ABC/DTG/3TC 5.1%, 16 subjects) as of the Week 48 data cut date. Reasons for premature discontinuation of study drug were generally comparable between study groups. The most common reasons for discontinuation of study drug were lost to follow up (15 subjects; B/F/TAF 9 subjects, ABC/DTG/3TC 6 subjects), subject decision (9 subjects; B/F/TAF 4 subjects, ABC/DTG/3TC 5 subjects), and AE (4 subjects; B/F/TAF 0 subjects, ABC/DTG/3TC 4 subjects).
Summary of Results and Conclusions:	• B/F/TAF has potent antiviral efficacy that is comparable to ABC/DTG/3TC. B/F/TAF was determined to be noninferior to ABC/DTG/3TC. The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were similar for both treatment groups (B/F/TAF 92.4%; ABC/DTG/3TC 93.0%; difference in percentages: −0.6%, 95.002% CI: −4.8% to 3.6%). Because the lower bound of the 95.002% CI of the difference between treatment groups (B/F/TAF – ABC/DTG/3TC) was greater than the prespecified −12% margin, B/F/TAF was determined to be noninferior to ABC/DTG/3TC. • No subject developed treatment-emergent resistance to any study drug. • Immunologic benefits were demonstrated by improvements in CD4 cell counts and CD4 percentages. Mean (SD) changes from baseline in CD4 cell counts at Week 48 for the FAS were as follows: B/F/TAF 233 (185.2) cells/μL; ABC/DTG/3TC 229 (188.8) cells/μL; difference in LSM: 4 cells/μL, 95% CI: −27 to 34 cells/μL. The mean (SD) changes from baseline in CD4% at Week 48 were as follows: B/F/TAF 9.0% (5.55%); ABC/DTG/3TC 8.6% (5.69%); difference in LSM: 0.4%, 95% CI: −0.5% to 1.3%. • BIC trough concentrations (C_{tau}) were higher than the protein-adjusted 95% effective concentration ($paEC_{95}$) against wild type HIV-1 virus; FTC and TAF exposures were consistent with historical data from approved FTC/TAF containing products. The mean (%CV) C_{tau} of BIC following administration of B/F/TAF was 2311.7 (40.7) ng/mL, compared with 162 ng/mL against wild type HIV-1 virus. • B/F/TAF was safe and well tolerated. Common AEs were generally consistent with those expected in the subject population and the known safety profiles of FTC- and TAF-containing regimens or ABC/DTG/3TC. • No subject met Hy's Law criteria. In the B/F/TAF group, no subject had a hepatic SAE or discontinued study drug due to hepatic AEs. No clinically relevant changes from baseline in liver-related laboratory parameters were seen in the B/F/TAF group. • B/F/TAF demonstrated bone and renal safety profiles comparable with ABC/DTG/3TC. — No clinically relevant changes from baseline in BMD at the hip or spine were seen for either treatment group. — Subjects who received B/F/TAF had comparable increase in serum creatinine and decrease in eGFR compared to those who received ABC/DTG/3TC. The renal safety profile was generally comparable between treatment groups.

2.1.2. Study GS-US-380-1490

Location:	GS-US-380-1490 Interim Week 48
Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults
Primary and Key Secondary Objectives:	The primary objective of this study is as follows: • To evaluate the efficacy of B/F/TAF versus DTG+F/TAF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48 The secondary objective of this study is as follows: • To evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Weeks 48, 96, and 144 (results are presented through 48 weeks of treatment)
Study Design and Subject Population:	Randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of B/F/TAF versus DTG + F/TAF in HIV-infected, ART-naive adult subjects. Subjects who provided written consent and met all eligibility criteria were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: • **Treatment Group 1:** B/F/TAF (50/200/25 mg) FDC + placebo-to-match DTG (50 mg) and placebo-to-match F/TAF (200/25 mg) FDC administered orally, once daily, without regard to food (planned n = 300) • **Treatment Group 2:** DTG (50 mg) + F/TAF (200/25 mg) FDC+ placebo-to-match B/F/TAF FDC administered orally, once daily, without regard to food (planned n = 300) 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. Subjects will be treated for at least 144 weeks during the blinded treatment phase, with an option to receive B/F/TAF in an open-label extension phase for up to 48 weeks if safety and efficacy of B/F/TAF are demonstrated following review of unblinded Week 144 data. Eligible subjects were ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL and a screening genotype showing sensitivity to FTC and TFV, and $eGFR_{CG}$ ≥ 30 mL/min (≥ 50 mL/sec). Subjects with CHB coinfection were permitted to enter the study. Of the 742 subjects screened, 657 were randomized to study drugs (B/F/TAF 327 subjects; DTG+F/TAF 330 subjects). Seven subjects randomized to B/F/TAF and 5 subjects randomized to DTG+F/TAF did not receive study drugs (4 due to withdrawn consent, 3 due to investigator's discretion, 3 due to lost to follow-up, and 2 due to protocol violation). Of the 645 subjects randomized and treated, 92.6% of subjects (597 subjects; B/F/TAF 91.3%, 292 subjects; DTG+F/TAF 93.8%, 305 subjects) were continuing study drugs, and 7.4% (48 subjects) prematurely discontinued study drugs (B/F/TAF 8.8%, 28 subjects; DTG+F/TAF 6.2%, 20 subjects), as of the Week 48 data cut date. Reasons for premature discontinuation of study drugs were generally comparable between study groups. The most common reasons for discontinuation of study drugs were subject decision (14 subjects; 7 per treatment group), lost to follow-up (13 subjects; B/F/TAF 8 subjects; DTG+F/TAF 5 subjects), and AE (6 subjects; B/F/TAF 5 subjects; DTG+F/TAF 1 subject).

Summary of Results and Conclusions:	• B/F/TAF has potent antiviral efficacy that is comparable to DTG+F/TAF. B/F/TAF was determined to be noninferior to DTG+F/TAF. The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were similar for both treatment groups (B/F/TAF 89.4%; DTG+F/TAF 92.9%; difference in percentages: −3.5%, 95.002% CI: −7.9% to 1.0%). Because the lower bound of the 95.002% CI of the difference between treatment groups (B/F/TAF – DTG+F/TAF) was greater than the prespecified −12% margin, B/F/TAF was determined to be noninferior to DTG+F/TAF. • No subject developed treatment emergent resistance to any study drug. • Antiviral HIV response was also as robust in HIV/HBV coinfected subjects as it was in HIV monoinfection. At Week 48, 11 of 13 HIV/HBV baseline-coinfected subjects with baseline HBV DNA ≥ 29 IU/mL and postbaseline HBV DNA assessments had HBV DNA < 29 IU/mL (M = E). Two subjects who were HBeAg positive at baseline and had HBV DNA > 170,000,000 IU/mL had HBV DNA ≥ 29 IU/mL at Week 48. One subject in the DTG+F/TAF group maintained HBV DNA < 29 IU/mL from baseline through Week 48. The subject also experienced HBsAg loss and seroconversion at Week 24. All 13 HIV/HBV baseline-coinfected subjects who were continuing treatment at Week 48 had HIV-1 RNA < 50 copies/mL at Week 48. • Immunologic benefits were demonstrated by improvements in CD4 cell counts and CD4 percentages. The mean (SD) changes from baseline to Week 48 in CD4 cell counts for the FAS were as follows: B/F/TAF 180 (166.6) cells/µL; DTG+F/TAF 201 (166.4) cells/µL; difference in LSM: −22 cells/µL, 95% CI: −49 to 5 cells/µL. The mean (SD) changes from baseline in CD4% at Week 48 were as follows: B/F/TAF 8.7% (5.20%); DTG+F/TAF 8.9% (4.94%); difference in LSM: −0.2%, 95% CI: −1.0% to 0.6%. • BIC trough concentrations (C_{tau}) were higher than the $paEC_{95}$ against wild type HIV-1 virus; FTC and TAF exposures were consistent with historical data from approved FTC and TAF-containing products/regimens. The mean (%CV) C_{tau} of BIC following administration of B/F/TAF was 2576.0 (52.0) ng/mL, compared with a $paEC_{95}$ of 162 ng/mL against wild type HIV-1 virus. • B/F/TAF was safe and well tolerated. Common AEs were generally consistent with those expected in the subject population and the known safety profiles of FTC- and TAF containing regimens and DTG. • No subject met Hy's Law criteria and no subjects had hepatic SAEs or discontinued study drugs due to hepatic AEs. No clinically relevant changes from baseline in liver-related laboratory parameters were seen for either treatment group. • B/F/TAF demonstrated renal safety comparable to DTG+F/TAF. • B/F/TAF was safe and well tolerated in subjects with HIV/HBV and HIV/HCV coinfection at baseline. Antiviral HIV response was also as robust in HIV/HBV coinfected subjects as it was in HIV monoinfection.

2.1.3. Study GS-US-141-1475

Location:	GS-US-141-1475 Interim Week 72
Title:	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9883 + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults
Primary and Key Secondary Objectives:	The primary objective of this study was as follows: • To evaluate the efficacy of a regimen containing BIC+F/TAF versus DTG+F/TAF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 24. The secondary objectives of this study were to evaluate the following: • The efficacy of a regimen containing BIC+F/TAF versus DTG+F/TAF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 12 and Week 48. • The change from baseline in $\log_{10}$ HIV-1 RNA and CD4 cell count at Weeks 12, 24, and 48. • The safety and tolerability of the 2 treatment regimens through 48 weeks of treatment. • The pharmacokinetics (PK) of BIC, FTC, and TAF in HIV-1 infected ART-naive adult subjects receiving BIC+F/TAF. (results are presented through 72 weeks of treatment)
Study Design and Subject Population:	Phase 2, randomized, double-blind, active-controlled study to assess the safety and efficacy of BIC+F/TAF versus DTG+F/TAF in HIV-infected, ART-naive adult subjects. Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups: • **Treatment Group 1:** BIC (75 mg) + F/TAF (200/25 mg) FDC + placebo-to-match DTG (50 mg) once daily without regard to food (planned n = 50) • **Treatment Group 2:** DTG (50 mg) + F/TAF (200/25 mg) FDC + placebo-to-match BIC (75 mg) once daily without regard to food (planned n = 25) Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL or > 400,000 copies/mL) at screening. Subjects received randomized treatment for 48 weeks. After Week 48, subjects continued to take their randomized study drug and attended visits every 12 weeks until treatment assignments were unblinded, at which point all subjects returned for an Unblinding Visit and were given the option to participate in an open-label rollover extension to receive the B/F/TAF FDC. Eligible subjects were ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL and CD4 cell count ≥ 200 cells/μL at screening; a screening genotype showing sensitivity to TFV and FTC; $eGFR_{CG}$ ≥ 70 mL/min; and the absence of CHB and hepatitis C infection. Of the 125 subjects screened, 98 were randomized to study drug (BIC+F/TAF 65 subjects; DTG+F/TAF 33 subjects). All 98 randomized subjects received at least 1 dose of randomized study drug and were included in the Safety Analysis Set and Full Analysis Set (FAS). In the double-blind phase, 6.1% (6 subjects) prematurely discontinued study drug and the study (BIC+F/TAF 4.6%, 3 subjects; DTG+F/TAF 9.1%, 3 subjects). Reasons for premature discontinuation of study drug were as follows: lost to follow-up (2 subjects; 1 per treatment group), noncompliance with study drug (DTG+F/TAF, 2 subjects), AE (BIC+F/TAF 1 subject), and withdrawal of consent (BIC+F/TAF 1 subject). Overall, 93.9% (92 subjects; BIC+F/TAF 95.4%, 62 subjects; DTG+F/TAF 90.9%, 30 subjects) completed the double-blind phase of the study. All 92 subjects who completed the double-blind phase of the study entered the open-label extension phase and received an FDC of B/F/TAF. At the data cut date, 98.9% (91 subjects) were still continuing treatment (BIC+F/TAF to B/F/TAF 98.4%, 61 subjects; DTG+F/TAF to B/F/TAF 100%, 30 subjects). One subject in the BIC+F/TAF to B/F/TAF group withdrew consent and discontinued study drug and the study during the open-label extension.

Summary of Results and Conclusions:	• HIV-infected, ART-naive subjects receiving BIC+F/TAF or DTG+F/TAF achieved and maintained high rates of virologic suppression through 24 and 48 weeks of treatment as assessed using the FDA-defined snapshot algorithm with HIV-1 RNA < 50 copies/mL (for the FAS, Week 24: BIC+F/TAF 96.9%; DTG+F/TAF 93.9%; difference in percentages 2.9%, 95% CI –8.5% to 14.2%. Week 48: BIC+F/TAF 96.9%; DTG+F/TAF 90.9%; difference in percentages 6.4%, 95% CI –6.0% to 18.8%). Because the lower bound of the 95% CI for the difference in response rate at Week 24 was greater than the prespecified –12% margin, BIC+F/TAF was determined to be noninferior to DTG+F/TAF. • Both groups showed increases from baseline in CD4 cell count. Mean (SD) increases from baseline to Week 48 (FAS) were: BIC+F/TAF 258 (221.7) cells/µL; DTG+F/TAF 188 (238.7) cells/µL; difference in LSM 76 cells/µL, 95% CI –25 to 176 cells/µL. • Virologic suppression was achieved and maintained, and improvements in CD4 cell count were observed through 72 weeks of treatment with BIC+F/TAF followed by open-label B/F/TAF. At Week 72, 100.0% of subjects had HIV-1 RNA < 50 copies/mL, and the mean (SD) increase from baseline in CD4 cell count (M = E) was 276 (225.1) cells/µL. • Among subjects who switched to open-label B/F/TAF from DTG+F/TAF, the percentage of subjects with HIV-1 RNA < 50 copies/mL at open-label Week 12 was 100.0% and the mean change from preswitch in CD4 cell count was -17 cells/µL. • No subject developed resistance to study drugs or had integrase (IN) mutations in the BIC+F/TAF group. One subject in the DTG+F/TAF group had a T97A substitution in IN. • The steady state exposures of BIC, FTC, and TAF were consistent with historical data associated with efficacy and safety; steady state TFV exposures were markedly lower than those observed following TDF-containing regimens. • Both BIC+F/TAF and DTG+F/TAF were well tolerated through 60 weeks of treatment. Common AEs were consistent with those observed for FTC- and TAF-containing regimens, and common concurrent conditions. • In the open-label extension phase, B/F/TAF was well-tolerated with a safety profile similar to that observed through the double-blinded phase.

2.2. HIV-Infected, Virologically Suppressed Adult Subjects: Studies GS-US-380-1844 and GS-US-380-1878

2.2.1. Study GS-US-380-1844

Location:	GS-US-380-1844 Interim Week 48
Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed
Primary and Key Secondary Objectives:	The primary objective of this study is as follows: • To evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or an FDC of ABC/DTG/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 as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 The secondary objectives of this study are as follows: • To evaluate the safety and tolerability of the 2 treatment groups through Week 48 • To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine BMD through Week 48 (results presented through 48 weeks of treatment)
Study Design and Subject Population:	Randomized, double-blind, multicenter, active-controlled study to evaluate the efficacy, safety, and tolerability of switching to B/F/TAF versus continuing DTG and ABC/3TC as the ABC/DTG/3TC FDC in HIV-infected subjects who were virologically suppressed on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 months prior to screening. Subjects who provided written consent and met all eligibility criteria were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: • **Treatment Group 1:** B/F/TAF (50/200/25 mg) FDC + placebo-to-match ABC/DTG/3TC FDC administered orally, once daily, without regard to food (planned n = 260) • **Treatment Group 2:** ABC/DTG/3TC (600/50/300 mg) FDC + placebo-to-match B/F/TAF FDC administered orally, once daily, without regard to food (planned n = 260) Subjects were treated for at least 48 weeks during the blinded treatment phase, with an option to receive B/F/TAF in an open-label extension phase for up to 96 weeks. Eligible subjects were HIV-infected adults who were virologically suppressed on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 consecutive months prior to screening, with no documented resistance to any of the study agents; $eGFR_{CG}$ ≥ 50 mL/min; and the absence of CHB infection. Of the 646 subjects screened, 567 were randomized to study drugs (B/F/TAF 284 subjects; ABC/DTG/3TC 283 subjects). Four subjects randomized to study drug (B/F/TAF 2 subjects; ABC/DTG/3TC 2 subjects) did not receive study drugs due to withdrawn consent or protocol violation. Of the 563 subjects randomized and treated, 95.0% of subjects (535 subjects; B/F/TAF 94.7%, 267 subjects; ABC/DTG/3TC 95.4%, 268 subjects) were continuing study drugs, and 5.0% (28 subjects) prematurely discontinued study drugs (B/F/TAF 5.3%, 15 subjects; ABC/DTG/3TC 4.6%, 13 subjects) as of the Week 48 data cut date. Reasons for premature discontinuation of study drugs were generally comparable between treatment groups.

Summary of Results and Conclusions:	• Switching to B/F/TAF resulted in low rates of virologic failure and high rates of maintained virologic suppression. The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were as follows: B/F/TAF 1.1%; ABC/DTG/3TC 0.4%; difference in percentages: 0.7%, 95.002% CI: −1.0% to 2.8%. Because the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF – ABC/DTG/3TC) was less than the prespecified 4% margin, switching to B/F/TAF was determined to be noninferior to maintaining ABC/DTG/3TC. The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were as follows: B/F/TAF 93.6%; ABC/DTG/3TC 95.0%; difference in percentages: −1.4%, 95.002% CI: −5.5% to 2.6%. Because the lower bound of the 2-sided 95.002% CI for the difference between treatment groups (B/F/TAF – ABC/DTG/3TC) was greater than the prespecified −10% margin, switching to B/F/TAF was determined to be noninferior to maintaining ABC/DTG/3TC.No subject developed treatment-emergent resistance to any study drug. • CD4 cell counts and CD4 percentage were maintained in each group. The mean (SD) changes from baseline to Week 48 in CD4 cell counts for the FAS were as follows: B/F/TAF −31 (181.3) cells/µL; ABC/DTG/3TC 4 (191.0) cells/µL; difference in LSM (after adjusting for baseline CD4 cell count level): −21 cells/µL, 95% CI: −51 to 9 cells/µL. The mean (SD) changes from baseline in CD4% at Week 48 were as follows: B/F/TAF 1.0% (3.77%); ABC/DTG/3TC 0.5% (3.84%); difference in LSM: 0.5%, 95% CI: −0.1% to 1.2%. • Bictegravir trough concentrations (C_{tau}) were higher than the $paEC_{95}$ against wild-type HIV-1 virus; FTC and TAF exposures were consistent with historical data from approved FTC- and TAF-containing products/regimens. • B/F/TAF was safe and well tolerated. Common AEs were generally consistent with those expected in the subject population and the known safety profiles of study drugs. • No subject met Hy's Law criteria. In the B/F/TAF group, no subject had a hepatic SAE or discontinued study drugs due to hepatic AEs. No clinically relevant changes from baseline in liver-related laboratory parameters were seen in the B/F/TAF group. • B/F/TAF demonstrated bone and renal safety profiles comparable with ABC/DTG/3TC. — No clinically relevant changes from baseline in BMD at the hip or spine were seen for either treatment group. — No subject in the B/F/TAF group had proximal tubulopathy (including Fanconi syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE.

2.2.2. Study GS-US-380-1878

Location:	GS-US-380-1878 Interim Week 48
Title:	A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults
Primary and Key Secondary Objectives:	The primary objective of this study is as follows: • To evaluate the efficacy of switching to an FDC of B/F/TAF versus continuing on a regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC in HIV-1 infected adult subjects who are virologically suppressed as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 The secondary objective of this study is as follows: • To evaluate the safety and tolerability of the 2 treatment groups through Week 48
Study Design and Subject Population:	Randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to B/F/TAF in HIV-infected subjects who are virologically suppressed on a regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening. Subjects who provided written consent and met all eligibility criteria were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: • **Treatment Group 1:** Switch to B/F/TAF (50/200/25 mg) FDC administered orally, once daily without regard to food (n = 260) • **Treatment Group 2:** Remain on current ARV regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally, once daily with food (n = 260) Randomization was stratified by the prior treatment regimen group (ie, TDF-containing regimens [RTV- or COBI-boosted ATV or DRV plus FTC/TDF] and non-TDF-containing regimens [RTV- or COBI-boosted ATV or DRV plus ABC/3TC]) at screening. Subjects were treated for at least 48 weeks, with an option to receive B/F/TAF for an additional 96 weeks. Eligible subjects were HIV-infected adults who were virologically suppressed on a stable regimen of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening; $eGRF_{CG}$ ≥ 50 mL/min; no previous use of any approved or experimental INSTI; and no documented or suspected resistance to FTC, TFV, ABC, or 3TC. Of the 707 subjects screened, 578 were randomized to study drugs (B/F/TAF 290 subjects; stay-on-baseline regimen [SBR] 288 subjects). One subject randomized to the SBR group was never dosed with study drug. As of the Week 48 data cut date, 82.7% of randomized and treated subjects (477 subjects; B/F/TAF 83.8%, 243 subjects; SBR 81.5%, 234 subjects) had completed study drug in the randomized phase, and 10.1% of subjects (58 subjects; B/F/TAF 10.7%, 31 subjects; SBR 9.4%, 27 subjects) were continuing study drug in the randomized phase. Overall, 7.3% of subjects (42 subjects; B/F/TAF 5.5%, 16 subjects; SBR 9.1%, 26 subjects) prematurely discontinued study drug in the randomized phase prior to the Week 48 data cut date. Reasons for premature discontinuation of study drug were generally comparable between treatment groups. The most common reasons for discontinuation of study drugs were subject decision (B/F/TAF 9 subjects; SBR 14 subjects), protocol violation (B/F/TAF 1 subject; SBR 5 subjects), AE (B/F/TAF 2 subjects; SBR 1 subject) and lost to follow-up (B/F/TAF 0 subject; SBR 3 subjects). As of the Week 48 data cut date, 454 subjects had entered and were treated with B/F/TAF in the extension phase (241 subjects initially randomized to B/F/TAF; 213 subjects initially randomized to SBR).

Summary of Results and Conclusions:	• Switching to B/F/TAF resulted in low rates of virologic failure and high rates of maintained virologic suppression. The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were as follows: B/F/TAF 1.7%; SBR 1.7%; difference in percentages: −0.0%, 95.002% CI: −2.5% to 2.5%.). Because the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF – SBR) was less than the prespecified 4% margin, switching to B/F/TAF was determined to be noninferior to maintaining a boosted protease inhibitor (PI)-based regimen. The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were as follows: B/F/TAF 92.1%; SBR 88.9%; difference in percentages: 3.2%, 95.002% CI: −1.6% to 8.2%. Because the lower bound of the 2-sided 95.002% CI for the difference between treatment groups (B/F/TAF – SBR) was greater than the prespecified −10% margin, switching to B/F/TAF was determined to be noninferior to maintaining a boosted PI-based regimen. No subject developed treatment-emergent resistance to B/F/TAF. • CD4 cell counts and CD4 percentages were maintained in each group. The mean (SD) changes from baseline to Week 48 in CD4 cell counts for the FAS were as follows: B/F/TAF 25 (151.2) cells/μL; SBR 0 (159.4) cells/μL; difference in least-squares mean (LSM): 25 cells/μL, 95% CI: −2 to 52 cells/μL. The mean (SD) changes from baseline in CD4% at Week 48 were as follows: B/F/TAF 0.5% (3.56%); SBR 0.5% (3.53%); difference in LSM: −0.1%, 95% CI: −0.7% to 0.6%. • Bictegravir trough concentrations (C_{tau}) were higher than the $paEC_{95}$ against wild-type HIV-1 virus; FTC and TAF exposures were consistent with historical data from approved FTC- and TAF-containing products/regimens. • B/F/TAF was safe and well tolerated. Common AEs were generally consistent with those expected in the subject population and the known safety profiles of the study drugs. • No subject met Hy's Law criteria. No subject discontinued study drugs due to hepatic AEs. No clinically relevant changes from baseline in liver-related laboratory parameters were seen in the B/F/TAF group. • The renal safety profile was generally comparable between treatment groups. No subject in the B/F/TAF group had proximal tubulopathy (including Fanconi syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE. • B/F/TAF was also safe and efficacious in subjects with HIV/HBV and HIV/HCV coinfection at baseline.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Study Populations

Subject disposition, demographic and general baseline characteristics, baseline disease characteristics, and analysis populations are presented for the pooled B/F/TAF group from Studies GS-US-380-1489 and GS-US-380-1490 and by study for Studies GS-US-141-1475, GS-US-380-1844, and GS-US-380-1878.

Detailed results are presented in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 8; GS-US-380-1490 Interim Week 48, Section 8; GS-US-141-1475 Interim Week 72, Section 8; GS-US-380-1844 Interim Week 48, Section 8; and GS-US-380-1878 Interim Week 48, Section 8).

3.1.1. Subject Disposition

3.1.1.1. ART-Naive Adult Subjects: Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475

Pooled Studies GS-US-380-1489 and GS-US-380-1490

Subject disposition for the pooled B/F/TAF group from Studies GS-US-380-1489 and GS-US-380-1490 is summarized in Table 4.

Of the 1274 subjects randomized and treated, 93.5% of subjects (1191 subjects; B/F/TAF 92.6%, 587 subjects; ABC/DTG/3TC 94.9%, 299 subjects; DTG/F/TAF 93.8%, 305 subjects) were continuing study drug, and 6.5% (83 subjects) prematurely discontinued study drug (B/F/TAF 7.4%, 47 subjects; ABC/DTG/3TC 5.1%, 16 subjects; DTG+F/TAF 6.2%, 20 subjects), as of the Week 48 data cut date. Reasons for premature discontinuation of study drug were generally comparable between treatment groups. The most common reasons for discontinuation of study drug were lost-to-follow-up (2.2%, 28 subjects; B/F/TAF 2.7%, ABC/DTG/3TC 1.9%, DTG+F/TAF 1.5%), subject decision (1.8%, 23 subjects; B/F/TAF 1.7%, ABC/DTG/3TC 1.6%, DTG+F/TAF 2.2%, and AE (0.8%, 10 subjects; B/F/TAF 0.8%, ABC/DTG/3TC 1.3%, DTG+F/TAF 0.3%).

Table 4. GS-US-380-1489 and GS-US-380-1490: Subject Disposition – Week 48 Pooled Data (All Randomized Subjects)

	B/F/TAF 380-1489, 1490	ABC/DTG/3TC 380-1489	DTG + F/TAF 380-1490	Total
Subjects Randomized	643	315	330	1288
Subjects Randomized and Never Treated	9	0	5	14
Subjects in Safety Analysis Set	634	315	325	1274
Subjects in Full Analysis Set (FAS)	634	315	325	1274
Subjects Still on Study Drug up to the Data Cut Date	587 (92.6%)	299 (94.9%)	305 (93.8%)	1191 (93.5%)
Subjects Prematurely Discontinuing Study Drug Prior to the Data Cut Date	47 (7.4%)	16 (5.1%)	20 (6.2%)	83 (6.5%)
Reasons for Prematurely Discontinuing Study Drug				
Adverse Event	5 (0.8%)	4 (1.3%)	1 (0.3%)	10 (0.8%)
Death	0	0	2 (0.6%)	2 (0.2%)
Pregnancy	3 (0.5%)	0	2 (0.6%)	5 (0.4%)
Lack of Efficacy	0	0	0	0
Investigator's Discretion	7 (1.1%)	0	0	7 (0.5%)
Non-Compliance with Study Drug	1 (0.2%)	1 (0.3%)	2 (0.6%)	4 (0.3%)
Protocol Violation	3 (0.5%)	0	1 (0.3%)	4 (0.3%)
Subject Decision	11 (1.7%)	5 (1.6%)	7 (2.2%)	23 (1.8%)
Lost to Follow-Up	17 (2.7%)	6 (1.9%)	5 (1.5%)	28 (2.2%)
Study Terminated by Sponsor	0	0	0	0
Subjects Still on Study up to the Data Cut Date	592 (93.4%)	301 (95.6%)	307 (94.5%)	1200 (94.2%)
Subjects Prematurely Discontinuing from Study Prior to the Data Cut Date	42 (6.6%)	14 (4.4%)	18 (5.5%)	74 (5.8%)
Reasons for Prematurely Discontinuing from Study				
Adverse Event	3 (0.5%)	3 (1.0%)	1 (0.3%)	7 (0.5%)
Death	1 (0.2%)	0	2 (0.6%)	3 (0.2%)
Pregnancy	0	0	0	0
Lack of Efficacy	0	0	0	0
Investigator's Discretion	6 (0.9%)	0	0	6 (0.5%)
Non-Compliance with Study Drug	2 (0.3%)	0	1 (0.3%)	3 (0.2%)
Protocol Violation	3 (0.5%)	0	1 (0.3%)	4 (0.3%)
Withdrew Consent	10 (1.6%)	5 (1.6%)	8 (2.5%)	23 (1.8%)
Lost to Follow-Up	17 (2.7%)	6 (1.9%)	5 (1.5%)	28 (2.2%)
Study Terminated by Sponsor	0	0	0	0

The denominator for percentage is the number of subjects in the Safety Analysis Set.
Source: B/F/TAF Week 48 Integrated Summary of Safety (ISS), Table 1

Study GS-US-141-1475

Subjects in Study GS-US-141-1475 were enrolled at a total of 22 study sites in the US. Of the 125 subjects screened, 98 were randomized to study drug (BIC+F/TAF 65 subjects; DTG+F/TAF 33 subjects; Table 5). All 98 randomized subjects received at least 1 dose of randomized study drug. In the double-blind phase, 6.1% (6 subjects) prematurely discontinued study drug and the study (BIC+F/TAF 4.6%, 3 subjects; DTG+F/TAF 9.1%, 3 subjects). Reasons for premature discontinuation of study drug were as follows: lost to follow-up (2 subjects; 1 per treatment group), noncompliance with study drug (DTG+F/TAF 2 subjects), AE (BIC+F/TAF 1 subject, and withdrawal of consent (BIC+F/TAF 1 subject). Overall, 93.9% (92 subjects; BIC+F/TAF 95.4%, 62 subjects; DTG+F/TAF 90.9%, 30 subjects) completed the double-blind phase of the study.

All 92 subjects who completed the double-blind phase of the study entered the open-label extension phase and received an FDC of B/F/TAF. At the data cut date, 98.9% (91 subjects) were still continuing treatment (BIC+F/TAF to B/F/TAF 98.4%, 61 subjects; DTG+F/TAF to B/F/TAF 100%, 30 subjects). One subject in the BIC+F/TAF to B/F/TAF group withdrew consent and discontinued study drug and discontinued the study during the open-label extension.

Table 5. GS-US-141-1475: Disposition of Subjects (All Screened Subjects)

Subject Disposition	BIC+F/TAF n (%)	DTG+F/TAF n (%)	Total n (%)
Subjects Screened			125
Screen Failure Subjects who were not Randomized			25
Subject met all Eligibility Criteria and not Randomized[a]			2
Subjects Randomized	65	33	98
Subjects in Safety Analysis Set	65	33	98
Subjects in Full Analysis Set (FAS)	65	33	98
Subjects Completing Study Drug in the Double-Blind Phase	62 (95.4%)	30 (90.9%)	92 (93.9%)
Subjects Prematurely Discontinuing Study Drug and Study in the Double-Blind Phase	3 (4.6%)	3 (9.1%)	6 (6.1%)
Reasons for Prematurely Discontinuing Study Drug and Study in the Double-Blind Phase			
Adverse Event	1 (1.5%)	0	1 (1.0%)
Noncompliance with Study Drug	0	2 (6.1%)	2 (2.0%)
Withdrew Consent	1 (1.5%)	0	1 (1.0%)
Lost to Follow-up	1 (1.5%)	1 (3.0%)	2 (2.0%)
Lack of Efficacy	0	0	0
Subjects Entering the Open-Label Extension Phase	62 (95.4%)	30 (90.9%)	92 (93.9%)
Subjects Still on Study Drug in the Open-Label Extension Phase at the Week 72 Analysis	61 (98.4%)	30 (100.0%)	91 (98.9%)
Subjects Prematurely Discontinuing Study Drug and Study in the Open-Label Extension Phase	1 (1.6%)	0	1 (1.1%)
Reasons for Prematurely Discontinuing Study Drug and Study in the Open-Label Extension Phase			
Withdrew Consent	1 (1.6%)	0	1 (1.1%)

a For subjects who met all eligibility criteria and were not randomized, both withdrew consent.
The denominator for percentages for each category in the Double-Blind Phase is the number of subjects in the Safety Analysis Set.
The denominator for percentages in each category in the Open-Label (OL) Extension Phase is the number of subjects treated in the Open-Label Extension Phase.
The number of screen failures is counted by unique subject based on date of birth, race, ethnicity, sex, country, and initials.
CRF data collected up to [redacted] 20[redacted] and laboratory data up to [redacted] 20[redacted] were included in the Week 72 interim analysis, including data collected after the OL Week 12 visit.
Source: GS-US-141-1475 Interim Week 72, Table 15.8.1.3

3.1.1.2. Virologically Suppressed Adult Subjects: Studies GS-US-380-1844 and GS-US-380-1878

Study GS-US-380-1844

Subjects in Study GS-US-380-1844 were enrolled and treated at a total of 96 study centers in 9 countries. Of the 646 subjects screened, 567 were randomized to study drug (B/F/TAF 284 subjects; ABC/DTG/3TC 283 subjects) (Table 6). Four subjects randomized to study drug (B/F/TAF 2 subjects; ABC/DTG/3TC 2 subjects) did not receive study drug due to withdrawn consent or protocol violation.

Of the 563 subjects randomized and treated, 95.0% of subjects (535 subjects; B/F/TAF 94.7%, 267 subjects; ABC/DTG/3TC 95.4%, 268 subjects) were continuing study drug, and 5.0% (28 subjects) prematurely discontinued study drug (B/F/TAF 5.3%, 15 subjects; ABC/DTG/3TC 4.6%, 13 subjects) as of the Week 48 data cut date. Reasons for premature discontinuation of study drug were generally comparable between treatment groups. The most common reasons for discontinuation of study drug were subject decision (12 subjects; B/F/TAF 4 subjects; ABC/DTG/3TC 8 subjects), AE (8 subjects; B/F/TAF 6 subjects; ABC/DTG/3TC 2 subjects), and lost to follow-up (4 subjects; B/F/TAF 2 subject; ABC/DTG/3TC 2 subjects). Two subjects in the B/F/TAF group discontinued from the study due to death. Two subjects in the B/F/TAF group were unblinded during the course of the study. Subject 04140-3252 was unblinded due to an SAE (cerebrovascular accident). Subject 00754-3067 was unblinded after withdrawing consent.

Table 6. GS-US-380-1844: Disposition of Subjects (All Screened Subjects)

	B/F/TAF	ABC/DTG/3TC	Total
Subjects Screened			646
Screen Failure Subjects Who Were Not Randomized			67
Subjects Met All Eligibility Criteria and Not Randomized*			12
Subjects Randomized	284	283	567
Subjects Randomized and Never Treated	2	2	4
Subjects in Safety Analysis Set	282	281	563
Subjects in Full Analysis Set (FAS)	282	281	563
Subjects Still on Study Drug up to the Data Cut Date	267 (94.7%)	268 (95.4%)	535 (95.0%)
Subjects Prematurely Discontinuing Study Drug Prior to the Data Cut Date	15 (5.3%)	13 (4.6%)	28 (5.0%)
Reasons for Prematurely Discontinuing Study Drug			
Adverse Event	6 (2.1%)	2 (0.7%)	8 (1.4%)
Death	2 (0.7%)	0	2 (0.4%)
Pregnancy	1 (0.4%)	1 (0.4%)	2 (0.4%)
Lack of Efficacy	0	0	0
Investigator's Discretion	0	0	0
Non-Compliance with Study Drug	0	0	0
Protocol Violation	0	0	0
Subject Decision	4 (1.4%)	8 (2.8%)	12 (2.1%)
Lost to Follow-Up	2 (0.7%)	2 (0.7%)	4 (0.7%)
Study Terminated by Sponsor	0	0	0
Subjects Still on Study up to the Data Cut Date	272 (96.5%)	269 (95.7%)	541 (96.1%)
Subjects Prematurely Discontinuing from Study Prior to the Data Cut Date	10 (3.5%)	12 (4.3%)	22 (3.9%)
Reasons for Prematurely Discontinuing from Study			
Adverse Event	3 (1.1%)	2 (0.7%)	5 (0.9%)
Death	2 (0.7%)	0	2 (0.4%)
Pregnancy	0	1 (0.4%)	1 (0.2%)
Lack of Efficacy	0	0	0
Investigator's Discretion	0	0	0
Non-Compliance with Study Drug	0	0	0
Protocol Violation	0	0	0
Withdrew Consent	3 (1.1%)	7 (2.5%)	10 (1.8%)
Lost to Follow-Up	2 (0.7%)	2 (0.7%)	4 (0.7%)
Study Terminated by Sponsor	0	0	0

The denominator for percentage is the number of subjects in the Safety Analysis Set.
The number of screen failures is counted by unique subject based on the date of birth, race, ethnicity, sex, country, and initials.
CRF data collected up to [redacted] 20[redacted] (except for 6 subjects, [redacted] 20[redacted]) and lab data up to [redacted] 20[redacted] are included in the Week 48 analysis, including data collected after the Week 48 visit.

* Among 12 subjects who met all eligibility criteria and were not randomized, 7 were due to withdrawal of consent, 4 due to lost to follow-up, and 1 was due to outside of visit window. Screen failure subjects are the subjects who didn't meet all eligibility criteria.

Source: GS-US-380-1844 Interim Week 48, Table 15.8.1.2

Study GS-US-380-1878

Subjects in Study GS-US-380-1878 were enrolled and treated at a total of 121 study centers in 10 countries. Of the 707 subjects screened, 578 were randomized to study drugs (B/F/TAF 290 subjects; SBR 288 subjects) (Table 7). One subject randomized to the SBR group was never dosed with study drug due to a protocol violation.

As of the Week 48 data cut date, 82.7% of randomized and treated subjects (477 subjects; B/F/TAF 83.8%, 243 subjects; SBR 81.5%, 234 subjects) had completed study drug in the randomized phase, and 10.1% of subjects (58 subjects; B/F/TAF 10.7%, 31 subjects; SBR 9.4%, 27 subjects) were continuing study drug in the randomized phase.

Overall, 7.3% of subjects (42 subjects; B/F/TAF 5.5%, 16 subjects; SBR 9.1%, 26 subjects) prematurely discontinued study drug in the randomized phase prior to the Week 48 data cut date. Reasons for premature discontinuation of study drug were generally comparable between treatment groups. The most common reasons for discontinuation of study drugs were subject decision (B/F/TAF 9 subjects; SBR 14 subjects), protocol violation (B/F/TAF 1 subject; SBR 5 subjects), AE (B/F/TAF 2 subjects; SBR 1 subject), and lost to follow-up (B/F/TAF 0 subject; SBR 3 subjects). One subject in each treatment group discontinued from the study due to death.

As of the Week 48 data cut date, 454 subjects had entered and were treated with B/F/TAF in the extension phase (241 subjects initially randomized to B/F/TAF; 213 subjects initially randomized to SBR). One subject initially randomized to SBR had prematurely discontinued B/F/TAF in the extension phase due to AEs.

Table 7. GS-US-380-1878: Disposition of Subjects (All Screened Subjects)

	B/F/TAF	SBR	Total
Subjects Screened			707
Screen Failure Subjects Who Were Not Randomized			112
Subjects Met All Eligibility Criteria and Not Randomized*			17
Subjects Randomized	290	288	578
Subjects Randomized and Never Treated	0	1	1
Subjects in Safety Analysis Set	290	287	577
Subjects in Full Analysis Set (FAS)	290	287	577
Subjects Still on Study Drug in the Randomized Phase	31 (10.7%)	27 (9.4%)	58 (10.1%)
Subjects Completed Study Drug in the Randomized Phase	243 (83.8%)	234 (81.5%)	477 (82.7%)
Subjects Prematurely Discontinuing Study Drug in the Randomized Phase	16 (5.5%)	26 (9.1%)	42 (7.3%)
Reasons for Prematurely Discontinuing Study Drug in the Randomized Phase			
Adverse Event	2 (0.7%)	1 (0.3%)	3 (0.5%)
Death	1 (0.3%)	1 (0.3%)	2 (0.3%)
Pregnancy	0	0	0
Lack of Efficacy	1 (0.3%)	0	1 (0.2%)
Investigator's Discretion	1 (0.3%)	1 (0.3%)	2 (0.3%)
Non-Compliance with Study Drug	1 (0.3%)	1 (0.3%)	2 (0.3%)
Protocol Violation	1 (0.3%)	5 (1.7%)	6 (1.0%)
Subject Decision	9 (3.1%)	14 (4.9%)	23 (4.0%)
Lost to Follow-Up	0	3 (1.0%)	3 (0.5%)
Study Terminated by Sponsor	0	0	0
Subjects Still on Study in the Randomized Phase	32 (11.0%)	27 (9.4%)	59 (10.2%)
Subjects Completed Study in the Randomized Phase	245 (84.5%)	240 (83.6%)	485 (84.1%)
Subjects Prematurely Discontinuing from Study in the Randomized Phase	13 (4.5%)	20 (7.0%)	33 (5.7%)
Reasons for Prematurely Discontinuing from Study in the Randomized Phase			
Adverse Event	2 (0.7%)	0	2 (0.3%)
Death	1 (0.3%)	1 (0.3%)	2 (0.3%)
Pregnancy	0	0	0
Lack of Efficacy	0	0	0
Investigator's Discretion	0	1 (0.3%)	1 (0.2%)
Non-Compliance with Study Drug	1 (0.3%)	1 (0.3%)	2 (0.3%)
Protocol Violation	1 (0.3%)	0	1 (0.2%)
Withdrew Consent	8 (2.8%)	14 (4.9%)	22 (3.8%)
Lost to Follow-Up	0	3 (1.0%)	3 (0.5%)
Study Terminated by Sponsor	0	0	0
Subjects Entering and Treated in the Extension Phase	241	213	454
Subjects Still on Study Drug in the Extension Phase	241 (100.0%)	212 (99.5%)	453 (99.8%)
Subjects Prematurely Discontinuing Study Drug in the Extension Phase	0	1 (0.5%)	1 (0.2%)

CRF data collected up to [redacted] 20[redacted] (except for 10 subjects, [redacted] 20[redacted]) and lab data collected up to [redacted] 20[redacted] are included in the Week 48 analysis, including data collected after the Week 48 visit.
The denominator for percentages of subjects is the number of subjects in the Safety Analysis Set except for the last 2 categories based on subjects entering and treated in the extension phase.
The number of screen failures (defined as subjects not meeting all eligibility criteria) is counted by unique subject based on the date of birth, race, ethnicity, sex, country, and initials. * Among 17 subjects who met all eligibility criteria but were not randomized, the reasons (N) were: investigator's discretion (3); lost to follow-up (5); outside of visit window (1); withdrew consent (6); and Other (2).
Source: GS-US-380-1878 Interim Week 48, Table 15.8.1.3

3.1.2. Demographic and Other Baseline Characteristics

3.1.2.1. Demographic and General Baseline Characteristics

3.1.2.1.1. ART-Naive Adult Subjects: Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475

Pooled Studies GS-US-380-1489 and GS-US-380-1490

Demographic and baseline characteristics were similar between the 3 treatment groups in the pooled dataset from Studies GS-US-380-1489 and GS-US-380-1490 (Table 8). Most subjects were male (89.1%) and not Hispanic/Latino (76.3%). Most subjects were either white (57.9%) or black (33.3%); 2.6% were Asian. Median (mean) age was 33 (35) years (range: 18 to 77 years). Median (Q1, Q3) BMI was 24.9 (22.3, 28.5) kg/m^2.

Table 8. GS-US-380-1489 and GS-US-380-1490: Demographics and Baseline Characteristics (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	Total (N = 1274)
Age (Years)				
N	634	315	325	1274
Mean (SD)	35 (11.7)	34 (10.8)	37 (11.6)	35 (11.5)
Median	32	32	34	33
Q1, Q3	26, 44	26, 40	27, 46	26, 43
Min, Max	18, 71	18, 68	18, 77	18, 77
Sex at Birth				
Male	565 (89.1%)	282 (89.5%)	288 (88.6%)	1135 (89.1%)
Female	69 (10.9%)	33 (10.5%)	37 (11.4%)	139 (10.9%)
Race				
American Indian or Alaska Native	3 (0.5%)	4 (1.3%)	1 (0.3%)	8 (0.6%)
Asian	13 (2.1%)	10 (3.2%)	10 (3.1%)	33 (2.6%)
Black	211 (33.4%)	112 (35.6%)	100 (30.8%)	423 (33.3%)
Native Hawaiian or Pacific Islander	2 (0.3%)	2 (0.6%)	0	4 (0.3%)
White	363 (57.4%)	179 (56.8%)	195 (60.0%)	737 (57.9%)
Other	40 (6.3%)	8 (2.5%)	19 (5.8%)	67 (5.3%)
Not Permitted	2	0	0	2
Ethnicity				
Hispanic or Latino	155 (24.5%)	65 (20.7%)	81 (24.9%)	301 (23.7%)
Not Hispanic or Latino	477 (75.5%)	249 (79.3%)	244 (75.1%)	970 (76.3%)
Not Permitted	2	1	0	3
Baseline Weight (kg)				
N	634	315	325	1274
Mean (SD)	79.6 (17.59)	80.3 (18.41)	80.3 (20.68)	79.9 (18.61)
Median	76.7	78.0	76.2	76.6
Q1, Q3	68.0, 88.0	68.2, 89.8	67.1, 89.3	67.8, 88.6
Min, Max	43.0, 146.5	43.6, 194.7	46.2, 206.3	43.0, 206.3
Baseline Height (cm)				
N	634	315	325	1274
Mean (SD)	175.3 (8.53)	175.2 (8.77)	175.0 (8.01)	175.2 (8.45)
Median	175.3	175.3	175.3	175.3
Q1, Q3	170.2, 181.0	169.8, 182.0	170.2, 180.3	170.2, 180.3
Min, Max	147.3, 203.2	149.9, 196.0	152.4, 198.1	147.3, 203.2
Baseline Body Mass Index (kg/m^2)				
N	634	315	325	1274
Mean (SD)	25.9 (5.18)	26.1 (5.73)	26.2 (6.25)	26.0 (5.60)
Median	25.1	24.9	24.6	24.9
Q1, Q3	22.3, 28.6	22.5, 29.1	22.2, 28.0	22.3, 28.5
Min, Max	15.8, 46.5	15.5, 64.3	15.7, 61.7	15.5, 64.3

Not Permitted = Local regulators did not allow collection of race or ethnicity information.
For race and ethnicity, subjects who reported "Not Permitted" were excluded from the percentage calculation.
Source: B/F/TAF Week 48 ISS, Table 2

Study GS-US-141-1475

Demographic and baseline characteristics were similar between the 2 treatment groups in Study GS-US-141-1475 (Table 9). Most subjects were male (95.9%) and not Hispanic/Latino (84.7%). Most subjects were either white (57.1%) or black (36.7%). Median age was 31 years (range: 19 to 68). Median (Q1, Q3) BMI was 25.3 (22.7, 27.8) kg/m^2.

Table 9. GS-US-141-1475: Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic	BIC+F/TAF (N = 65)	DTG+F/TAF (N = 33)	Total (N = 98)	BIC+F/TAF vs DTG+F/TAF p-value[a]
Age (year)				
Mean (SD)	34 (11.4)	38 (12.9)	35 (12.1)	0.10
Median	30	36	31	
Q1, Q3	25, 41	26, 51	25, 45	
Min, Max	19, 68	21, 61	19, 68	
Sex (n, %)				
Male	64 (98.5%)	30 (90.9%)	94 (95.9%)	0.076
Female	1 (1.5%)	3 (9.1%)	4 (4.1%)	
Race (n, %)				
American Indian or Alaska Native	1 (1.5%)	0	1 (1.0%)	0.49
Asian	1 (1.5%)	2 (6.1%)	3 (3.1%)	
Black	24 (36.9%)	12 (36.4%)	36 (36.7%)	
Native Hawaiian or Pacific Islander	1 (1.5%)	0	1 (1.0%)	
White	38 (58.5%)	18 (54.5%)	56 (57.1%)	
Other	0	1 (3.0%)	1 (1.0%)	
Ethnicity (n, %)				
Hispanic or Latino	11 (16.9%)	4 (12.1%)	15 (15.3%)	0.53
Not Hispanic or Latino	54 (83.1%)	29 (87.9%)	83 (84.7%)	
Body Mass Index (kg/m^2)				
Mean (SD)	26.2 (5.64)	26.4 (4.81)	26.2 (5.35)	0.58
Median	25.1	25.8	25.3	
Q1, Q3	22.5, 27.8	23.5, 27.4	22.7, 27.8	
Min, Max	16.4, 45.0	17.1, 37.1	16.4, 45.0	

The denominator for the percentages is the number of subjects in the Safety Analysis Set.
a For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
Source: GS-US-141-1475 Interim Week 72, Table 15.8.3.1

3.1.2.1.2. Virologically Suppressed Adult Subjects: Studies GS-US-380-1844 and GS-US-380-1878

Study GS-US-380-1844

Demographic and baseline characteristics were similar between the 2 treatment groups in Study GS-US-380-1844 (Table 10). Most subjects were male (88.6%) and not Hispanic/Latino (82.5%). Most subjects were either white (72.9%) or black (21.6%). Median (mean) age was 46 (45) years (range: 20 to 71 years). Median (Q1, Q3) BMI was 26.1 (23.7, 29.3) kg/m^2.

Table 10. GS-US-380-1844: Demographics and Baseline Characteristics (Safety Analysis Set)

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)	Total (N = 563)	B/F/TAF vs. ABC/DTG/3TC p-value
Age (Years)				
N	282	281	563	0.32
Mean (SD)	46 (11.1)	45 (11.5)	45 (11.3)	
Median	47	45	46	
Q1, Q3	36, 54	37, 53	37, 54	
Min, Max	21, 71	20, 70	20, 71	
Sex at Birth				
Male	247 (87.6%)	252 (89.7%)	499 (88.6%)	0.43
Female	35 (12.4%)	29 (10.3%)	64 (11.4%)	
Race				
American Indian or Alaska Native	2 (0.7%)	2 (0.7%)	4 (0.7%)	0.69
Asian	9 (3.2%)	9 (3.2%)	18 (3.2%)	
Black	59 (20.9%)	62 (22.3%)	121 (21.6%)	
Native Hawaiian or Pacific Islander	3 (1.1%)	0	3 (0.5%)	
White	206 (73.0%)	202 (72.7%)	408 (72.9%)	
Other	3 (1.1%)	3 (1.1%)	6 (1.1%)	
Not Permitted	0	3	3	
Ethnicity				
Hispanic or Latino	46 (16.3%)	52 (18.6%)	98 (17.5%)	0.47
Not Hispanic or Latino	236 (83.7%)	227 (81.4%)	463 (82.5%)	
Not Permitted	0	2	2	
Baseline Weight (kg)				
N	282	281	563	0.85
Mean (SD)	83.7 (18.52)	83.8 (18.29)	83.7 (18.39)	
Median	80.4	80.1	80.2	
Q1, Q3	71.9, 92.5	72.1, 90.7	71.9, 91.6	
Min, Max	44.9, 208.7	48.5, 160.2	44.9, 208.7	
Baseline Height (cm)				
N	282	281	563	0.49
Mean (SD)	175.0 (7.78)	175.6 (8.70)	175.3 (8.25)	
Median	175.3	176.0	175.3	
Q1, Q3	170.2, 180.3	170.2, 180.5	170.2, 180.3	
Min, Max	149.9, 195.6	147.3, 197.4	147.3, 197.4	
Baseline Body Mass Index (kg/m^2)				
N	282	281	563	0.77
Mean (SD)	27.3 (5.87)	27.1 (5.25)	27.2 (5.57)	
Median	26.3	25.9	26.1	
Q1, Q3	23.7, 29.3	23.9, 29.1	23.7, 29.3	
Min, Max	16.5, 69.6	16.9, 48.7	16.5, 69.6	

For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
Not Permitted = local regulators did not allow collection of race or ethnicity information.
For race and ethnicity, subjects who reported "Not Permitted" were excluded from the percentage and p-value calculation.
Source: GS-US-380-1844 Interim Week 48, Table 15.8.3.1

Study GS-US-380-1878

Demographic and baseline characteristics were similar between the 2 treatment groups in Study GS-US-380-1878 (Table 11). Most subjects were male (82.7%) and not Hispanic/Latino (81.5%). Most subjects were white (65.5%) or black (26.2%). Median (mean) age was 48 (46) years (range: 20 to 79 years). Median (Q1, Q3) BMI was 26.1 (23.5, 29.2) kg/m^2.

Table 11. GS-US-380-1878: Demographic and Baseline Characteristics (Safety Analysis Set)

	B/F/TAF (N = 290)	SBR (N = 287)	Total (N = 577)	B/F/TAF vs. SBR p-value
Age (Years)				
N	290	287	577	0.19
Mean (SD)	47 (10.5)	46 (10.5)	46 (10.5)	
Median	48	47	48	
Q1, Q3	39, 53	38, 52	39, 53	
Min, Max	20, 74	21, 79	20, 79	
Sex at Birth				
Male	243 (83.8%)	234 (81.5%)	477 (82.7%)	0.47
Female	47 (16.2%)	53 (18.5%)	100 (17.3%)	
Race				
American Indian or Alaska Native	3 (1.0%)	3 (1.0%)	6 (1.0%)	0.83
Asian	6 (2.1%)	10 (3.5%)	16 (2.8%)	
Black	79 (27.2%)	72 (25.1%)	151 (26.2%)	
Native Hawaiian or Pacific Islander	0	0	0	
White	188 (64.8%)	190 (66.2%)	378 (65.5%)	
Other	14 (4.8%)	12 (4.2%)	26 (4.5%)	
Ethnicity				
Hispanic or Latino	60 (20.7%)	47 (16.4%)	107 (18.5%)	0.18
Not Hispanic or Latino	230 (79.3%)	240 (83.6%)	470 (81.5%)	
Baseline Weight (kg)				
N	290	287	577	0.23
Mean (SD)	82.2 (14.89)	81.4 (18.59)	81.8 (16.82)	
Median	80.0	78.5	79.5	
Q1, Q3	71.8, 90.4	69.0, 90.7	70.4, 90.5	
Min, Max	54.9, 142.4	42.8, 192.6	42.8, 192.6	

	B/F/TAF (N = 290)	SBR (N = 287)	Total (N = 577)	B/F/TAF vs. SBR p-value
Baseline Height (cm)				
N	290	287	577	0.27
Mean (SD)	174.7 (9.11)	173.8 (9.74)	174.2 (9.43)	
Median	175.3	174.0	175.0	
Q1, Q3	169.0, 180.3	168.0, 181.0	168.5, 180.3	
Min, Max	147.3, 198.1	137.2, 195.6	137.2, 198.1	
Baseline Body Mass Index (kg/m^2)				
N	290	287	577	0.44
Mean (SD)	27.0 (4.97)	27.0 (6.13)	27.0 (5.57)	
Median	26.1	25.9	26.1	
Q1, Q3	23.6, 29.2	23.3, 29.5	23.5, 29.2	
Min, Max	18.1, 53.2	17.3, 72.9	17.3, 72.9	

For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
Source: GS-US-380-1878 Interim Week 48, Table 15.8.3.1

3.1.2.2. Baseline Disease Characteristics

3.1.2.2.1. ART-Naive Adult Subjects: Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475

Pooled Studies GS-US-380-1489 and GS-US-380-1490

Baseline disease characteristics were similar between he 3 treatment groups in the pooled dataset from Studies GS-US-380-1489 and GS-US-380-1490 (Table 12). The median (Q1, Q3) baseline HIV-1 RNA value was 4.46 (4.02, 4.87) $\log_{10}$ copies/mL. At baseline 82.5% (1051 subjects) had HIV-1 RNA ≤ 100,000 copies/mL, 14.0% (178 subjects) had HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL, and 3.5% (45 subjects) had HIV-1 RNA > 400,000 copies/mL. The median (Q1, Q3) baseline CD4 cell count was 443 (300, 597) cells/µL. At baseline, 3.5% (45 subjects) had CD4 cell counts < 50 cells/µL, 7.9% (101 subjects) had CD4 cell counts ≥ 50 to < 200 cells/µL, 21.3% (271 subjects) had CD4 cell counts ≥ 200 to < 350 cells/µL, 28.5% (363 subjects) had CD4 cell counts ≥ 350 to < 500 cells/µL, and 38.8% (494 subjects) had CD4 cell counts ≥ 500 cells/µL.

The most common HIV risk factors were homosexual sex (77.6% of subjects), and heterosexual sex (22.1% of subjects). The majority of subjects (90.0%) had asymptomatic HIV-1 infection, 4.0% had symptomatic HIV-1 infection, and 6.0% were diagnosed with AIDS. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 122.4 (104.3, 144.1) mL/min.

At baseline, 1.1% of subjects overall had HIV/HBV coinfection (GS-US-380-1490 2.2%) and 1.1% of subjects overall had HIV/HCV coinfection (GS-US-380-1489 0.6%; GS-US-380-1490 1.6%).

Table 12. GS-US-380-1489 and GS-US-380-1490: Baseline Disease Characteristics (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	Total (N = 1274)
HIV-1 RNA (log_{10} copies/mL)				
N	634	315	325	1274
Mean (SD)	4.40 (0.690)	4.42 (0.685)	4.42 (0.669)	4.41 (0.683)
Median	4.42	4.51	4.45	4.46
Q1, Q3	4.00, 4.88	4.04, 4.87	4.03, 4.84	4.02, 4.87
Min, Max	2.23, 6.58	1.28, 6.19	2.76, 6.15	1.28, 6.58
HIV-1 RNA Categories (copies/mL)				
<= 100,000	515 (81.2%)	265 (84.1%)	271 (83.4%)	1051 (82.5%)
> 100,000 to <= 400,000	99 (15.6%)	38 (12.1%)	41 (12.6%)	178 (14.0%)
> 400,000	20 (3.2%)	12 (3.8%)	13 (4.0%)	45 (3.5%)
CD4 Cell Count (/uL)				
N	634	315	325	1274
Mean (SD)	455 (238.6)	476 (231.4)	454 (231.5)	460 (235.0)
Median	442	450	441	443
Q1, Q3	293, 590	324, 608	297, 597	300, 597
Min, Max	0, 1636	2, 1332	3, 1458	0, 1636
CD4 Cell Count Categories (/uL)				
< 50	22 (3.5%)	10 (3.2%)	13 (4.0%)	45 (3.5%)
>= 50 to < 200	58 (9.1%)	22 (7.0%)	21 (6.5%)	101 (7.9%)
>= 200 to < 350	136 (21.5%)	58 (18.4%)	77 (23.7%)	271 (21.3%)
>= 350 to < 500	178 (28.1%)	91 (28.9%)	94 (28.9%)	363 (28.5%)
>= 500	240 (37.9%)	134 (42.5%)	120 (36.9%)	494 (38.8%)
CD4%				
N	634	315	325	1274
Mean (SD)	24.4 (9.70)	25.7 (9.56)	23.9 (9.40)	24.6 (9.60)
Median	24.0	25.7	23.7	24.3
Q1, Q3	18.0, 30.6	19.3, 32.0	17.6, 30.1	18.4, 30.8
Min, Max	0.2, 51.2	0.4, 51.3	0.6, 48.2	0.2, 51.3
Mode of Infection (HIV Risk Factors)				
Heterosexual Sex	142 (22.4%)	62 (19.7%)	77 (23.7%)	281 (22.1%)
Homosexual Sex	488 (77.0%)	250 (79.4%)	250 (76.9%)	988 (77.6%)
IV Drug Use	8 (1.3%)	4 (1.3%)	6 (1.8%)	18 (1.4%)
Transfusion	3 (0.5%)	1 (0.3%)	1 (0.3%)	5 (0.4%)
Vertical Transmission	0	0	0	0
Other	12 (1.9%)	7 (2.2%)	4 (1.2%)	23 (1.8%)
Unknown	16 (2.5%)	14 (4.4%)	7 (2.2%)	37 (2.9%)
HIV Disease Status				
Asymptomatic	572 (90.2%)	286 (90.8%)	288 (88.6%)	1146 (90.0%)
Symptomatic HIV Infection	26 (4.1%)	14 (4.4%)	11 (3.4%)	51 (4.0%)
AIDS	36 (5.7%)	15 (4.8%)	26 (8.0%)	77 (6.0%)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	Total (N = 1274)
$eGFR_{CG}$				
N	634	315	325	1274
Mean (SD)	126.9 (35.90)	128.8 (33.32)	129.2 (40.57)	127.9 (36.53)
Median	122.4	123.0	120.6	122.4
Q1, Q3	104.1, 143.4	107.0, 144.3	102.8, 145.1	104.3, 144.1
Min, Max	25.0, 376.4	52.4, 296.2	51.0, 370.7	25.0, 376.4
Medical History of Diabetes Mellitus				
Yes	41 (6.5%)	9 (2.9%)	22 (6.8%)	72 (5.7%)
No	593 (93.5%)	306 (97.1%)	303 (93.2%)	1202 (94.3%)
Medical History of Hypertension				
Yes	94 (14.8%)	41 (13.0%)	62 (19.1%)	197 (15.5%)
No	540 (85.2%)	274 (87.0%)	263 (80.9%)	1077 (84.5%)
Medical History of Cardiovascular Disease				
Yes	16 (2.5%)	9 (2.9%)	6 (1.8%)	31 (2.4%)
No	618 (97.5%)	306 (97.1%)	319 (98.2%)	1243 (97.6%)
Medical History of Hyperlipidemia				
Yes	89 (14.0%)	34 (10.8%)	44 (13.5%)	167 (13.1%)
No	545 (86.0%)	281 (89.2%)	281 (86.5%)	1107 (86.9%)
HIV/HBV Coinfection Status				
Yes	8 (1.3%)	0	6 (1.9%)	14 (1.1%)
No	623 (98.7%)	312 (100.0%)	318 (98.1%)	1253 (98.9%)
Missing	3	3	1	7
HIV/HCV Coinfection Status				
Yes	5 (0.8%)	4 (1.3%)	5 (1.5%)	14 (1.1%)
No	628 (99.2%)	311 (98.7%)	320 (98.5%)	1259 (98.9%)
Missing	1	0	0	1

Missing categories were excluded from the percentage calculation.
A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100%.
Diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia were determined by past medical history, adverse events, and medications.
HIV/HBV and/or HIV/HCV coinfection status were considered missing when test was not done at screening.
One subject in 380-1489 had screening eGFR at 114.3 mL/min, 25.0 mL/min at Day 1, and back to 96.3, 96.4, and 94.5 mL/min at following visits.
Source: B/F/TAF Week 48 ISS, Table 3

Study GS-US-141-1475

Baseline disease characteristics were similar between the 2 treatment groups in Study GS-US-141-1475 (Table 13). Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.45 (3.96, 4.79) $\log_{10}$ copies/mL. At baseline, 82.7% of subjects (81 subjects) had HIV-1 RNA ≤ 100,000 copies/mL, 12.2% (12 subjects) had > 100,000 to ≤ 400,000 copies/mL, and 5.1% (5 subjects) had > 400,000 copies/mL. Overall, the median (Q1, Q3) baseline CD4 cell count was 444 (316, 595) cells/µL. At baseline, 93.9% of subjects had a CD4 cell count ≥ 200 cells/µL. The majority of subjects (93.9%) had asymptomatic HIV-1 infection; 6.1% had symptomatic HIV-1 infection, and none were diagnosed with AIDS. At baseline, the median (Q1, Q3) $eGFR_{CG}$ was 125.3 (105.7, 147.0) mL/min.

Table 13. GS-US-141-1475: Baseline Disease Characteristics (Safety Analysis Set)

Disease Characteristic[a]	BIC+F/TAF (N = 65)	DTG+F/TAF (N = 33)	Total (N = 98)	BIC+F/TAF vs DTG+F/TAF p-value[a]
HIV-1 RNA (log_{10} copies/mL)				
Mean (SD)	4.39 (0.764)	4.38 (0.866)	4.39 (0.795)	0.81
Median	4.41	4.48	4.45	
Q1, Q3	4.01, 4.78	3.94, 4.82	3.96, 4.79	
Min, Max	1.94, 6.67	1.74, 6.51	1.74, 6.67	
HIV-1 RNA category (copies/mL)				
≤ 100,000	55 (84.6%)	26 (78.8%)	81 (82.7%)	0.81
> 100,000 to ≤ 400,000	6 (9.2%)	6 (18.2%)	12 (12.2%)	
> 400,000	4 (6.2%)	1 (3.0%)	5 (5.1%)	
CD4 Cell Count (/µL)				
Mean (SD)	471 (190.9)	507 (271.0)	483 (220.3)	0.78
Median	441	455	444	
Q1, Q3	316, 574	273, 677	316, 595	
Min, Max	174, 934	117, 1201	117, 1201	
CD4 Cell Count Category (/µL)				
< 200	3 (4.6%)	3 (9.1%)	6 (6.1%)	0.88
≥ 200 to < 350	17 (26.2%)	8 (24.2%)	25 (25.5%)	
≥ 350 to < 500	20 (30.8%)	6 (18.2%)	26 (26.5%)	
≥ 500	25 (38.5%)	16 (48.5%)	41 (41.8%)	
CD4 Percentage (%)				
Mean (SD)	24.5 (7.24)	24.6 (9.08)	24.5 (7.86)	0.90
Median	23.9	24.9	24.1	
Q1, Q3	20.3, 28.7	17.8, 30.5	19.6, 29.1	
Min, Max	10.9, 45.1	4.4, 44.9	4.4, 45.1	
Mode of Infection (HIV Risk Factors)[b]				
Heterosexual Sex	8 (12.3%)	8 (24.2%)	16 (16.3%)	
Homosexual Sex	56 (86.2%)	25 (75.8%)	81 (82.7%)	
IV Drug Use	1 (1.5%)	1 (3.0%)	2 (2.0%)	
Unknown	2 (3.1%)	0	2 (2.0%)	
HIV disease status				
Asymptomatic	61 (93.8%)	31 (93.9%)	92 (93.9%)	0.99
Symptomatic HIV infection	4 (6.2%)	2 (6.1%)	6 (6.1%)	
AIDS	0	0	0	
$eGFR_{CG}$ (mL/min)				
Mean (SD)	134.3 (36.70)	121.6 (31.32)	130.0 (35.33)	0.13
Median	130.1	122.2	125.3	
Q1, Q3	111.4, 148.2	97.0, 144.6	105.7, 147.0	
Min, Max	79.0, 273.1	70.4, 198.0	70.4, 273.1	

The denominator for the percentage is the number of subjects in the Safety Analysis Set.

a For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.

b A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100%.

Source: GS-US-141-1475 Interim Week 72, Table 15.8.3.2

3.1.2.2.2. Virologically Suppressed Adult Subjects: Studies GS-US-380-1844 and GS-US-380-1878

Study GS-US-380-1844

Baseline disease characteristics were similar between the 2 treatment groups in Study GS-US-380-1844, except baseline CD4 cell count (Table 14). The study enrolled a virologically suppressed, HIV-infected population; therefore, 97.7% of subjects in the Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL, and 93.1% had baseline HIV-1 RNA < 20 copies/mL. Overall, the median (Q1, Q3) baseline CD4 cell count was 695 (510, 910) cells/µL (B/F/TAF 732 cells/µL; ABC/DTG/3TC 661 cells/µL, p = 0.011), with approximately three-quarters (76.7%) of subjects having a baseline CD4 count ≥ 500 cells/µL. The median (Q1, Q3) baseline CD4% was 35.7% (28.0%, 41.4%).The most common HIV risk factor was homosexual sex (74.8% of subjects); 21.8% of subjects reported heterosexual sex as an HIV risk factor. The majority of subjects (86.7%) had asymptomatic HIV-1 infection; 3.2% had symptomatic HIV-1 infection, and 10.1% were diagnosed with AIDS. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 100.7 (84.6, 120.1) mL/min.

Overall, 7.6% of subjects had a medical history of diabetes, 27.2% had a medical history of hypertension, 2.7% had a medical history of cardiovascular disease, and 34.8% had a medical history of hyperlipidemia. In addition, 26.3% of subjects were current smokers, 20.4% were former smokers, and 53.3% had never smoked. At baseline, 1 subject in the ABC/DTG/3TC group had HIV/HCV coinfection.

Table 14. GS-US-380-1844: Baseline Disease Characteristics (Safety Analysis Set)

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)	Total (N = 563)	B/F/TAF vs. ABC/DTG/3TC p-value
HIV-1 RNA Categories (copies/mL)				
< 50	278 (98.6%)	272 (96.8%)	550 (97.7%)	0.16
>= 50	4 (1.4%)	9 (3.2%)	13 (2.3%)	
CD4 Cell Count (/uL)				
N	282	281	563	0.011
Mean (SD)	752 (302.2)	694 (291.6)	723 (298.1)	
Median	732	661	695	
Q1, Q3	554, 936	478, 874	510, 910	
Min, Max	124, 2444	125, 1570	124, 2444	
CD4 Cell Count Categories (/uL)				
< 50	0	0	0	0.061
>= 50 to < 200	6 (2.1%)	4 (1.4%)	10 (1.8%)	
>= 200 to < 350	16 (5.7%)	30 (10.7%)	46 (8.2%)	
>= 350 to < 500	33 (11.7%)	42 (14.9%)	75 (13.3%)	
>= 500	227 (80.5%)	205 (73.0%)	432 (76.7%)	
CD4 Percentage (%)				
N	282	281	563	0.18
Mean (SD)	35.4 (9.64)	34.1 (10.28)	34.8 (9.98)	
Median	35.9	35.5	35.7	
Q1, Q3	29.1, 41.8	26.7, 41.3	28.0, 41.4	
Min, Max	9.4, 63.5	7.1, 60.2	7.1, 63.5	
Mode of Infection (HIV Risk Factors)				
Heterosexual Sex	64 (22.7%)	59 (21.0%)	123 (21.8%)	
Homosexual Sex	207 (73.4%)	214 (76.2%)	421 (74.8%)	
IV Drug Use	6 (2.1%)	8 (2.8%)	14 (2.5%)	
Transfusion	1 (0.4%)	0	1 (0.2%)	
Vertical Transmission	0	0	0	
Other	3 (1.1%)	3 (1.1%)	6 (1.1%)	
Unknown	8 (2.8%)	9 (3.2%)	17 (3.0%)	
HIV Disease Status				
Asymptomatic	243 (86.2%)	245 (87.2%)	488 (86.7%)	0.69
Symptomatic HIV Infection	9 (3.2%)	9 (3.2%)	18 (3.2%)	
AIDS	30 (10.6%)	27 (9.6%)	57 (10.1%)	

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)	Total (N = 563)	B/F/TAF vs. ABC/DTG/3TC p-value
Estimated Glomerular Filtration Rate by Cockcroft-Gault (mL/min)				
N	282	281	563	0.73
Mean (SD)	104.3 (32.16)	104.9 (30.78)	104.6 (31.45)	
Median	100.5	100.7	100.7	
Q1, Q3	84.5, 119.0	84.9, 122.4	84.6, 120.1	
Min, Max	49.9, 319.0	52.5, 283.1	49.9, 319.0	
Medical History of Diabetes Mellitus				
Yes	22 (7.8%)	21 (7.5%)	43 (7.6%)	0.88
No	260 (92.2%)	260 (92.5%)	520 (92.4%)	
Medical History of Hypertension				
Yes	82 (29.1%)	71 (25.3%)	153 (27.2%)	0.31
No	200 (70.9%)	210 (74.7%)	410 (72.8%)	
Medical History of Cardiovascular Disease				
Yes	10 (3.5%)	5 (1.8%)	15 (2.7%)	0.19
No	272 (96.5%)	276 (98.2%)	548 (97.3%)	
Medical History of Hyperlipidemia				
Yes	106 (37.6%)	90 (32.0%)	196 (34.8%)	0.17
No	176 (62.4%)	191 (68.0%)	367 (65.2%)	
HIV/HBV Coinfection Status				
Yes	0	0	0	N/A
No	282 (100.0%)	281 (100.0%)	563 (100.0%)	
HIV/HCV Coinfection Status				
Yes	0	1 (0.4%)	1 (0.2%)	0.32
No	282 (100.0%)	280 (99.6%)	562 (99.8%)	
Smoking Status				
Never Smoker	142 (50.4%)	158 (56.2%)	300 (53.3%)	0.11
Former Smoker	58 (20.6%)	57 (20.3%)	115 (20.4%)	
Current Smoker	82 (29.1%)	66 (23.5%)	148 (26.3%)	

Missing categories were excluded from the percentage calculation.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistic was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100%.
Medical history of diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia were determined by medical history, adverse events, and concomitant medications started on or prior to the first dose date.
Source: GS-US-380-1844 Interim Week 48, Table 15.8.3.2

Study GS-US-380-1878

Baseline disease characteristics were generally similar between the 2 treatment groups in Study GS-US-380-1878 (Table 15). The study enrolled a virologically suppressed, HIV-infected population; therefore, 97.4% of subjects in the Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL, and 91.0% had baseline HIV-1 RNA < 20 copies/mL. Overall, the median (Q1, Q3) baseline CD4 cell count was 624 (456, 818) cells/μL, with 67.1% of subjects having a baseline CD4 count ≥ 500 cells/μL. The median (Q1, Q3) baseline CD4% was 32.7% (26.7%, 40.1%). The majority of subjects (84.6%, 488 subjects) were receiving TDF-containing ARV regimens at baseline.

The most common HIV risk factor was homosexual sex (67.4% of subjects); 30.2% of subjects reported heterosexual sex as an HIV risk factor. The majority of subjects (82.1%) had asymptomatic HIV-1 infection; 6.2% had symptomatic HIV-1 infection, and 11.6% were diagnosed with AIDS. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 105.6 (87.1, 124.8) mL/min.

At baseline, 2.4% and 1.7% of subjects were coinfected with HBV and HCV.

Overall, 26.3% of subjects had a medical history of hypertension and 5.7% of subjects had a medical history of cardiovascular disease. The percentages of subjects with the following medical histories were higher in the B/F/TAF group than in the SBR group: diabetes (10.7% and 5.9%, respectively); and hyperlipidemia (36.2% and 27.5%, respectively). Overall, 30.8% of subjects were current smokers, 19.9% were former smokers, and 49.2% had never smoked.

Table 15. GS-US-380-1878: Baseline Disease Characteristics (Safety Analysis Set)

	B/F/TAF (N = 290)	SBR (N = 287)	Total (N = 577)	B/F/TAF vs. SBR p-value
HIV-1 RNA Categories (copies/mL)				
< 50	285 (98.3%)	277 (96.5%)	562 (97.4%)	0.18
>= 50	5 (1.7%)	10 (3.5%)	15 (2.6%)	
CD4 Cell Count (/uL)				
N	290	287	577	0.86
Mean (SD)	669 (303.4)	657 (285.0)	663 (294.2)	
Median	617	626	624	
Q1, Q3	469, 809	437, 821	456, 818	
Min, Max	147, 2582	62, 1684	62, 2582	
CD4 Cell Count Categories (/uL)				
< 50	0	0	0	0.28
>= 50 to < 200	4 (1.4%)	8 (2.8%)	12 (2.1%)	
>= 200 to < 350	26 (9.0%)	30 (10.5%)	56 (9.7%)	
>= 350 to < 500	62 (21.4%)	60 (20.9%)	122 (21.1%)	
>= 500	198 (68.3%)	189 (65.9%)	387 (67.1%)	
CD4 Percentage (%)				
N	290	287	577	0.19
Mean (SD)	33.9 (9.68)	32.7 (10.35)	33.3 (10.03)	
Median	34.3	32.1	32.7	
Q1, Q3	27.5, 40.1	26.4, 40.0	26.7, 40.1	
Min, Max	11.0, 64.1	9.0, 62.2	9.0, 64.1	
Mode of Infection (HIV Risk Factors)				
Heterosexual Sex	87 (30.0%)	87 (30.3%)	174 (30.2%)	
Homosexual Sex	195 (67.2%)	194 (67.6%)	389 (67.4%)	
IV Drug Use	12 (4.1%)	10 (3.5%)	22 (3.8%)	
Transfusion	1 (0.3%)	2 (0.7%)	3 (0.5%)	
Vertical Transmission	0	0	0	
Unknown	7 (2.4%)	9 (3.1%)	16 (2.8%)	
Other	6 (2.1%)	3 (1.0%)	9 (1.6%)	
HIV Disease Status				
Asymptomatic	240 (82.8%)	234 (81.5%)	474 (82.1%)	0.86
Symptomatic HIV Infection	16 (5.5%)	20 (7.0%)	36 (6.2%)	
AIDS	34 (11.7%)	33 (11.5%)	67 (11.6%)	
Estimated Glomerular Filtration Rate by Cockcroft-Gault (mL/min)				
N	290	287	577	0.51
Mean (SD)	109.9 (30.97)	108.4 (31.75)	109.2 (31.34)	
Median	106.7	104.9	105.6	
Q1, Q3	87.0, 124.2	87.1, 125.3	87.1, 124.8	
Min, Max	42.4, 259.2	44.1, 260.1	42.4, 260.1	

	B/F/TAF (N = 290)	SBR (N = 287)	Total (N = 577)	B/F/TAF vs. SBR p-value
Medical History of Diabetes Mellitus				
Yes	31 (10.7%)	17 (5.9%)	48 (8.3%)	0.038
No	259 (89.3%)	270 (94.1%)	529 (91.7%)	
Medical History of Hypertension				
Yes	77 (26.6%)	75 (26.1%)	152 (26.3%)	0.91
No	213 (73.4%)	212 (73.9%)	425 (73.7%)	
Medical History of Cardiovascular Disease				
Yes	21 (7.2%)	12 (4.2%)	33 (5.7%)	0.11
No	269 (92.8%)	275 (95.8%)	544 (94.3%)	
Medical History of Hyperlipidemia				
Yes	105 (36.2%)	79 (27.5%)	184 (31.9%)	0.025
No	185 (63.8%)	208 (72.5%)	393 (68.1%)	
HIV/HBV Coinfection Status				
Yes	8 (2.8%)	6 (2.1%)	14 (2.4%)	0.59
No	278 (97.2%)	280 (97.9%)	558 (97.6%)	
- Missing -	4	1	5	
HIV/HCV Coinfection Status				
Yes	5 (1.7%)	5 (1.7%)	10 (1.7%)	1.00
No	283 (98.3%)	282 (98.3%)	565 (98.3%)	
- Missing -	2	0	2	
Smoking Status				
Never Smoker	148 (51.0%)	136 (47.4%)	284 (49.2%)	0.52
Former Smoker	54 (18.6%)	61 (21.3%)	115 (19.9%)	
Current Smoker	88 (30.3%)	90 (31.4%)	178 (30.8%)	
Prior ARV Regimen				
Boosted ATV + ABC/3TC	21 (7.2%)	23 (8.0%)	44 (7.6%)	0.90
Boosted DRV + ABC/3TC	24 (8.3%)	21 (7.3%)	45 (7.8%)	
Boosted ATV + FTC/TDF	105 (36.2%)	110 (38.3%)	215 (37.3%)	
Boosted DRV + FTC/TDF	140 (48.3%)	133 (46.3%)	273 (47.3%)	

Missing categories were excluded from percentage calculation. HIV/HBV and HIV/HCV coinfection status were missing when test was not done at screening.
For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistic was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.
A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100%.
Medical history of diabetes mellitus, hypertension, cardiovascular disease, and hyperlipidemia were determined by medical history, adverse events, and concomitant medications started on or prior to the randomized phase first dose date.
Prior antiretroviral (ARV) regimen was determined by ARV medications reported on ARV eCRF.
Source: GS-US-380-1878 Interim Week 48, Table 15.8.3.2

3.1.3. Analysis Populations

Study GS-US-380-1489

Overall, the 629 subjects (B/F/TAF 314; ABC/DTG/3TC 315) who were randomized and received at least 1 dose of the blinded study drugs in Study GS-US-380-1489 were included in both the Safety Analysis Set and FAS (Table 16). A total of 47 subjects (B/F/TAF 25; ABC/DTG/3TC 22) were excluded from the Week 48 PP Analysis Set.

The PK Analysis Set included 314 subjects overall (B/F/TAF 314; ABC/DTG/3TC 0) and the PK Substudy Analysis Set included 17 subjects overall (B/F/TAF 17; ABC/DTG/3TC 0).

The Hip DXA Analysis Set included 597 subjects (B/F/TAF 300; ABC/DTG/3TC 297), and the Spine DXA Analysis Set included 603 subjects (B/F/TAF 304; ABC/DTG/3TC 299).

Table 16. GS-US-380-1489: Analysis Sets at Week 48 (All Randomized Analysis Set)

	B/F/TAF	ABC/DTG/3TC	Total
Subjects Randomized	316	315	631
Subjects in Safety Analysis Set	314 (99.4%)	315 (100.0%)	629 (99.7%)
Subjects in Full Analysis Set (FAS)	314 (99.4%)	315 (100.0%)	629 (99.7%)
Subjects in Week 48 Per Protocol (PP) Analysis Set	289 (91.5%)	293 (93.0%)	582 (92.2%)
Reasons for Exclusion from Week 48 PP Analysis Set			
Did Not Have On-Treatment HIV-1 RNA in Week 48 Analysis Window Unless due to Discontinuation of Study Drug for Lack of Efficacy	22	16	38
Screening Genotype Did Not Show Sensitivity to FTC, TFV, ABC, and 3TC	0	0	0
Took Protocol Prohibited Medications	0	1	1
Adherence Rate for Active Study Drug up to Week 48 Visit Below the 2.5th Percentile	7	8	15
Subjects in PK Analysis Set	314 (99.4%)	0	314 (49.8%)
Subjects in PK Substudy Analysis Set	17 (5.4%)	0	17 (2.7%)
Subjects in Hip DXA Analysis Set	300 (94.9%)	297 (94.3%)	597 (94.6%)
Subjects in Spine DXA Analysis Set	304 (96.2%)	299 (94.9%)	603 (95.6%)

Exclusion criteria from the PP Analysis Set are only applicable to FAS subjects. A subject may fit more than 1 exclusion criterion from the PP set.
Source: GS-US-380-1489 Interim Week 48, Table 15.8.5

Study GS-US-380-1490

Overall, the 645 subjects (B/F/TAF 320; DTG+F/TAF 325) who were randomized and received at least 1 dose of the blinded study drugs in Study GS-US-380-1490 were included in both the Safety Analysis Set and FAS (Table 17). A total of 66 subjects (B/F/TAF 38; DTG+F/TAF 28) were excluded from the Week 48 PP Analysis Set.

For the B/F/TAF group, the PK Analysis Set included 313 subjects, and the PK Substudy Analysis Set included 17 subjects.

Table 17. GS-US-380-1490: Analysis Sets at Week 48 (All Randomized Analysis Set)

	B/F/TAF	DTG + F/TAF	Total
Subjects Randomized	327	330	657
Subjects in Safety Analysis Set	320 (97.9%)	325 (98.5%)	645 (98.2%)
Subjects in Full Analysis Set (FAS)	320 (97.9%)	325 (98.5%)	645 (98.2%)
Subjects in Week 48 Per Protocol (PP) Analysis Set	282 (86.2%)	297 (90.0%)	579 (88.1%)
Reasons for Exclusion from Week 48 PP Analysis Set			
Did Not Have On-Treatment HIV-1 RNA in Week 48 Analysis Window Unless due to Discontinuation of Study Drug for Lack of Efficacy	31	22	53
Screening Genotype Did Not Show Sensitivity to FTC and TFV	0	0	0
Took Protocol Prohibited Medications	0	0	0
Adherence Rate for Active Study Drug up to Week 48 Visit Below the 2.5th Percentile	8	7	15
Subjects in PK Analysis Set	313 (95.7%)	0	313 (47.6%)
Subjects in PK Substudy Analysis Set	17 (5.2%)	0	17 (2.6%)

Exclusion criteria from the PP Analysis Set are only applicable to FAS subjects. A subject may fit more than 1 exclusion criterion from the PP Set.
Source: GS-US-380-1490 Interim Week 48, Table 15.8.5

Pooled Studies GS-US-380-1489 and GS-US-380-1490

Pooled efficacy analyses were based on the FAS, which included all subjects who were randomized into Study GS-US-380-1489 or Study GS-US-380-1490 and received at least 1 dose of study drug. The pooled B/F/TAF FAS consisted of 634 subjects (Table 4).

Study GS-US-141-1475

Overall, the 98 subjects (BIC+F/TAF 65; DTG+F/TAF 33) who were randomized and received at least 1 dose of randomized study drug in Study GS-US-141-1475 were included in both the Safety Analysis Set and the FAS for the double-blind phase (Table 18). A total of 7 subjects (4 BIC+F/TAF; 3 DTG+F/TAF) were excluded from the Week 48 per protocol (PP) Analysis Set.

The All B/F/TAF Analysis Set included 95 subjects: the 65 randomized subjects who received at least 1 dose of BIC+F/TAF in the double-blind phase and 30 randomized subjects who received DTG+F/TAF in the double-blind phase and then switched to B/F/TAF in the open-label extension phase. This was the primary analysis set for the All B/F/TAF efficacy and safety analyses.

Table 18. GS-US-141-1475: Analysis Sets at Week 48 (All Randomized Analysis Set)

Analysis Set, n	BIC+F/TAF (N = 65)	DTG+F/TAF (N = 33)	Total (N = 98)
Subjects Randomized	65	33	98
Subjects in Safety Analysis Set	65 (100.0%)	33 (100.0%)	98 (100.0%)
Subjects in Full Analysis Set (FAS)	65 (100.0%)	33 (100.0%)	98 (100.0%)
Subjects in Week 48 Per Protocol (PP) Analysis Set	61 (93.8%)	30 (90.9%)	91 (92.9%)
Reasons for Exclusion from Week 48 PP Analysis Set[a]			
Did not have On-Treatment HIV-1 RNA in Week 48 Window Unless due to Discontinuation of Study Drug for Lack of Efficacy	2	2	4
Took Protocol-Prohibited Medication	0	2	2
Adherence Rate for Active Study Drug up to Week 48 Visit Below the 2.5th Percentile	2	0	2
Subjects in the All B/F/TAF Analysis Set	65 (100.0%)	30 (90.9%)	95 (96.9%)

The denominator for percentages is the number of subjects in the All Randomized Analysis Set.
a Exclusion criteria for the Week 48 PP Analysis Set are only applicable to FAS subjects. A subject may fit more than 1 exclusion criterion for the PP Analysis Set.
Source: GS-US-141-1475 Interim Week 72, Table 15.8.5

Study GS-US-380-1844

Overall, the 563 subjects (B/F/TAF 282; ABC/DTG/3TC 281) who were randomized and received at least 1 dose of the blinded study drugs in Study GS-US-380-1844 were included in both the Safety Analysis Set and FAS (Table 19). A total of 50 subjects (B/F/TAF 25; ABC/DTG/3TC 25) were excluded from the Week 48 PP Analysis Set.

The PK Analysis Set included 281 subjects overall (B/F/TAF 281; ABC/DTG/3TC 0) and the PK Substudy Analysis Set included 15 subjects overall (B/F/TAF 15; ABC/DTG/3TC 0).

The Hip DXA Analysis Set included 521 subjects (B/F/TAF 256; ABC/DTG/3TC 265), and the Spine DXA Analysis Set included 518 subjects (B/F/TAF 256; ABC/DTG/3TC 262).

Table 19. GS-US-380-1844: Analysis Sets at Week 48 (All Randomized Analysis Set)

	B/F/TAF	ABC/DTG/3TC	Total
Subjects Randomized	284	283	567
Subjects in Safety Analysis Set	282 (99.3%)	281 (99.3%)	563 (99.3%)
Subjects in Full Analysis Set (FAS)	282 (99.3%)	281 (99.3%)	563 (99.3%)
Subjects in Week 48 Per Protocol (PP) Analysis Set	257 (90.5%)	256 (90.5%)	513 (90.5%)
Reasons for Exclusion from Week 48 PP Analysis Set			
Did Not Have On-Treatment HIV-1 RNA in Week 48 Window Unless due to Discontinuation of Study Drug for Lack of Efficacy	17	14	31
Did Not Meet the Criterion of Taking DTG + ABC/3TC, or ABC/DTG/3TC FDC for >= 3 Months Before Screening Visit	1	0	1
Did Not Meet the Criterion of HIV-1 RNA < 50 copies/mL for >= 3 months before Screening visit	3	3	6
Adherence Rate for Active Study Drug up to Week 48 Visit Below the 2.5th	4	10	14
Subjects in PK Analysis Set	281 (98.9%)	0	281 (49.6%)
Subjects in PK Substudy Analysis Set	15 (5.3%)	0	15 (2.6%)
Subjects in Hip DXA Analysis Set	256 (90.1%)	265 (93.6%)	521 (91.9%)
Subjects in Spine DXA Analysis Set	256 (90.1%)	262 (92.6%)	518 (91.4%)

Exclusion criteria from the PP Analysis Set are only applicable to FAS subjects. A subject may fit more than 1 exclusion criterion from the PP set.
Source: GS-US-380-1844 Interim Week 48, Table 15.8.5

Study GS-US-380-1878

Overall, 577 subjects (B/F/TAF 290, SBR 287) who were randomized and received at least 1 dose of study drug in Study GS-US-380-1878 were included in both the Safety Analysis Set and FAS (Table 20). A total of 58 subjects (B/F/TAF 21; SBR 37) were excluded from the Week 48 PP Analysis Set. The most common reason for exclusion from the Week 48 PP Analysis Set was no on-treatment HIV-1 RNA in the Week 48 window unless due to discontinuation of study drugs for lack of efficacy.

The PK Analysis Set included 289 subjects and the PK Substudy Analysis Set included 28 subjects, all of whom were from the B/F/TAF group.

Table 20. GS-US-380-1878: Analysis Sets at Week 48 (All Randomized Analysis Set)

	B/F/TAF	SBR	Total
Subjects Randomized	290	288	578
Subjects in Safety Analysis Set	290 (100.0%)	287 (99.7%)	577 (99.8%)
Subjects in Full Analysis Set (FAS)	290 (100.0%)	287 (99.7%)	577 (99.8%)
Subjects in Week 48 Per Protocol (PP) Analysis Set	269 (92.8%)	250 (86.8%)	519 (89.8%)
Reasons for Exclusion from Week 48 PP Analysis Set			
Did Not Have On-Treatment HIV-1 RNA in Week 48 Analysis Window Unless due to Discontinuation of Study Drug for Lack of Efficacy	20	30	50
Previous Use of Any Approved or Experimental INSTI	1	4	5
Did Not Meet the Criterion of Having no Resistance to any Component of Study Regimen	0	2	2
Took Protocol Prohibited Medications	1	2	3
Subjects in PK Analysis Set	289 (99.7%)	0	289 (50.0%)
Subjects in PK Substudy Analysis Set	28 (9.7%)	0	28 (4.8%)

Exclusion criteria from the PP Analysis Set are only applicable to FAS subjects. A subject may fit more than 1 exclusion criterion from the PP set.
INSTI = integrase strand transfer inhibitor.
Source: GS-US-380-1878 Interim Week 48, Table 15.8.5

3.2. Comparison of Efficacy Results of All Studies

3.2.1. ART-Naive Adult Subjects: Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475

A summary supporting efficacy of B/F/TAF in HIV-infected, ART-naive adult subjects is presented below. Results are presented for the individual studies and for the pooled studies, GS-US-380-1489 and GS-US-380-1490 (ie, pooled B/F/TAF vs ABC/DTG/3TC and pooled B/F/TAF vs DTG+F/TAF), as applicable. Detailed efficacy results are presented in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 9; GS-US-380-1490 Interim Week 48, Section 9; and GS-US-141-1475 Interim Week 72, Section 9).

3.2.1.1. Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using the US FDA-Defined Snapshot Algorithm

Study GS-US-380-1489

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 in Study GS-US-380-1489 were similar for both treatment groups (B/F/TAF 92.4%; ABC/DTG/3TC 93.0%; difference in percentages: −0.6%, 95.002% CI: −4.8% to 3.6%) (Table 21). Because the lower bound of the 95.002% CI of the difference between treatment groups (B/F/TAF – ABC/DTG/3TC) was greater than the prespecified −12% margin, B/F/TAF was determined to be noninferior to ABC/DTG/3TC.

The percentages of subjects in the Week 48 PP Analysis Set with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were consistent with those for the FAS, and confirmed noninferiority of B/F/TAF to ABC/DTG/3TC (B/F/TAF 99.3%; ABC/DTG/3TC 98.6%; difference in percentages: 0.7%, 95.002% CI: −1.4% to 2.8%) (GS-US-380-1489 Interim Week 48, Table 15.9.1.2).

Study GS-US-380-1490

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 in Study GS-US-380-1490 were similar for both treatment groups (B/F/TAF 89.4%; DTG+F/TAF 92.9%; difference in percentages: −3.5%, 95.002% CI: −7.9% to 1.0%) (Table 21). Because the lower bound of the 95.002% CI of the difference between treatment groups (B/F/TAF - DTG+F/TAF) was greater than the prespecified −12% margin, B/F/TAF was determined to be noninferior to DTG+F/TAF.

The percentages of subjects in the Week 48 PP Analysis Set with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were consistent with those for the FAS, and confirmed noninferiority of B/F/TAF to DTG+F/TAF (B/F/TAF 98.9%; DTG+F/TAF 99.7%; difference in percentages: −0.7%, 95.002% CI: −2.6% to 1.2% (GS-US-380-1490 Interim Week 48, Table 15.9.1.2).

Table 21. GS-US-380-1489 and GS-US-380-1490: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Individual Studies (Full Analysis Set)

	380-1489		380-1490	
	B/F/TAF (N = 314)	ABC/DTG/3TC (N = 315)	B/F/TAF (N = 320)	DTG + F/TAF (N = 325)
HIV-1 RNA < 50 copies/mL	290 (92.4%)	293 (93.0%)	286 (89.4%)	302 (92.9%)
Difference in Percentages (95.002% CI)	-0.6% (-4.8% to 3.6%)		-3.5% (-7.9% to 1.0%)	
p-value	0.78		0.12	
HIV-1 RNA >= 50 copies/mL	3 (1.0%)	8 (2.5%)	14 (4.4%)	4 (1.2%)
HIV-1 RNA >= 50 copies/mL in Week 48 Window	2 (0.6%)	6 (1.9%)	3 (0.9%)	1 (0.3%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0	0
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA >= 50 copies/mL	1 (0.3%)	2 (0.6%)	11 (3.4%)	3 (0.9%)
No Virologic Data in Week 48 Window	21 (6.7%)	14 (4.4%)	20 (6.3%)	19 (5.8%)
Discontinued Study Drug Due to AE/Death	0	4 (1.3%)	3 (0.9%)	3 (0.9%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	16 (5.1%)	9 (2.9%)	11 (3.4%)	14 (4.3%)
Missing Data During Window but on Study Drug	5 (1.6%)	1 (0.3%)	6 (1.9%)	2 (0.6%)

Week 48 window is between Day 295 and 378 (inclusive).

* Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

P-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the CMH test stratified by baseline HIV-1 RNA stratum (<= 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95.002% CI were calculated based on the MH proportion adjusted by baseline HIV-1 RNA stratum (<= 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US).

Source: B/F/TAF Week 48 ISE, Table 1.1

Pooled Data from Studies GS-US-380-1489 and GS-US-380-1490

In comparisons of the pooled B/F/TAF group with each of the comparator groups in Studies GS-US-380-1489 and GS-US-380-1490, results for the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were consistent with those observed in the individual studies (Table 22). The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were as follows:

- Pooled B/F/TAF 90.9%; ABC/DTG/3TC 93.0%; difference in percentages: –2.1%, 95% CI –5.9% to 1.6%

- Pooled B/F/TAF 90.9%; DTG+F/TAF 92.9%; difference in percentages: –1.9%, 95% CI: –5.6% to 1.8%

Treatment with B/F/TAF was determined to be noninferior to treatment with ABC/DTG/3TC and to treatment with DTG+F/TAF because the lower bounds of the 2-sided 95% CIs of the differences between treatments (pooled B/F/TAF − ABC/DTG/3TC and pooled B/F/TAF − DTG+F/TAF) were greater than the prespecified -12% margin.

Table 22. GS-US-380-1489 and GS-US-380-1490: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL – Pooled Data (Full Analysis Set)

	B/F/TAF 380-1489,1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG+F/TAF 380-1490 (N = 325)
HIV-1 RNA < 50 copies/mL	576 (90.9%)	293 (93.0%)	302 (92.9%)
B/F/TAF vs. ABC/DTG/3TC			
Difference in Percentages (95% CI)	-2.1% (−5.9% to 1.6%)		
p-value	0.26		
B/F/TAF vs. DTG + F/TAF			
Difference in Percentages (95% CI)	-1.9% (-5.6% to 1.8%)		
p-value	0.32		
HIV-1 RNA >= 50 copies/mL	17 (2.7%)	8 (2.5%)	4 (1.2%)
HIV-1 RNA >= 50 copies/mL in Week 48 Window	5 (0.8%)	6 (1.9%)	1 (0.3%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA >= 50 copies/mL	12 (1.9%)	2 (0.6%)	3 (0.9%)
No Virologic Data in Week 48 Window	41 (6.5%)	14 (4.4%)	19 (5.8%)
Discontinued Study Drug Due to AE/Death	3 (0.5%)	4 (1.3%)	3 (0.9%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	27 (4.3%)	9 (2.9%)	14 (4.3%)
Missing Data During Window but on Study Drug	11 (1.7%)	1 (0.3%)	2 (0.6%)

Week 48 window is between Day 295 and 378 (inclusive).

* Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

P-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the CMH test stratified by baseline HIV-1 RNA stratum (<= 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI was calculated based on the MH proportion adjusted by baseline HIV-1 RNA stratum (<= 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US).

Source: B/F/TAF Week 48 ISE, Table 1.2

Study GS-US-141-1475

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 in Study GS-US-141-1475 were as follows: BIC+F/TAF 96.9%; DTG+F/TAF 90.9%; difference in percentages: 6.4%, 95% CI: −6.0% to 18.8% (Table 23).

Table 23. GS-US-141-1475: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	B/F/TAF (N = 65)	DTG+F/TAF (N = 33)	B/F/TAF vs DTG+F/TAF	
			p-value[a]	Difference in Percentages (95% CI)[b]
HIV-1 RNA < 50 copies/mL	63 (96.9%)	30 (90.9%)	0.17	6.4% (−6.0% to 18.8%)
HIV-1 RNA ≥ 50 copies/mL	1 (1.5%)	2 (6.1%)		
HIV-1 RNA ≥ 50 copies/mL in Week 48 Window	0	1 (3.0%)		
Discontinued Study Drug due to Lack of Efficacy	0	0		
Discontinued Study Drug due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[c]	1 (1.5%)	1 (3.0%)		
No Virologic Data in Week 48 Window	1 (1.5%)	1 (3.0%)		
Discontinued Study Drug due to AE/Death	1 (1.5%)	0		
Discontinued Study Drug due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	0	1 (3.0%)		
Missing Data During Window but on Study Drug	0	0		

Week 48 window was between Day 295 and 378 (inclusive).

a p-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the CMH test stratified by baseline HIV-1 RNA stratum (≤ 100,000 copies/mL vs > 100,000 copies/mL).

b Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the baseline HIV-1 RNA stratum-adjusted MH proportion.

c Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Source: GS-US-141-1475 Interim Week 72, Table 15.9.2.2.1

The percentage of subjects in the PP Analysis Set with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were consistent with those for the FAS, and were as follows: BIC+F/TAF 100.0%, 61 of 61 subjects; DTG+F/TAF 96.7%, 29 of 30 subjects; difference in percentages: 3.5%, 95% CI: −6.2% to 13.1% (GS-US-141-1475 Interim Week 72, Table 15.9.2.2.2).

3.2.1.2. Proportion of Subjects with HIV-1 RNA < 20 copies/mL at Week 48 Using the US FDA-Defined Snapshot Algorithm

Pooled Data from Studies GS-US-380-1489 and GS-US-380-1490

In comparisons of the pooled B/F/TAF group with each of the comparator groups in Studies GS-US-380-1489 and GS-US-380-1490, results for the proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were consistent with those observed in the individual studies (B/F/TAF Week 48 ISE, Table 2.1 and Table 2.2). The percentages of subjects with HIV-1 RNA < 20 copies/mL at Week 48 were similar between treatment groups (pooled B/F/TAF − ABC/DTG/3TC and pooled B/F/TAF − DTG+F/TAF), as follows:

- Pooled B/F/TAF 84.9%; ABC/DTG/3TC 87.3%; difference in percentages: –2.2%, 95% CI: –6.8% to 2.4%

- Pooled B/F/TAF 84.9%; DTG+F/TAF 87.1%; difference in percentages: –1.6%, 95% CI: –6.2% to 3.0%

Study GS-US-141-1475

The percentages of subjects in the FAS with HIV-1 RNA < 20 copies/mL at Week 48 in Study GS-US-141-1475 were as follows: BIC+F/TAF 90.8%; DTG+F/TAF 87.9%; difference in percentages: 2.8%, 95% CI: −11.9% to 17.5% (GS-US-141-1475 Interim Week 72, Table 15.9.3.2.3).

3.2.1.3. Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 48 Using Missing Data Imputation Methods (M = F and M = E)

Study GS-US-380-1489

Similar percentages of subjects had HIV-1 RNA < 50 copies/mL in the 2 treatment groups in Study GS-US-380-1489 as assessed using the M = F and M = E methods at Week 48 for the FAS, as follows:

- M = F: B/F/TAF 92.4%; ABC/DTG/3TC 93.3%; difference in percentages: −0.9%, 95% CI: −5.1% to 3.2%

- M = E: B/F/TAF 99.3%; ABC/DTG/3TC 97.7%; difference in percentages: 1.6%, 95% CI: −0.7% to 4.0%

The majority of subjects achieved viral suppression by Week 4; 77.4% and 74.9% of subjects in the B/F/TAF and ABC/DTG/3TC groups had HIV-1 RNA < 50 copies/mL (M = F), respectively, at Week 4 (GS-US-380-1489 Interim Week 48, Table 15.9.2.2). Corresponding values for M = E were 77.4% and 75.9%, respectively (GS-US-380-1489 Interim Week 48, Table 15.9.2.3).

Study GS-US-380-1490

Similar percentages of subjects had HIV-1 RNA < 50 copies/mL in the 2 treatment groups in Study GS-US-380-1490 as assessed using the M = F and M = E methods at Week 48 for the FAS, as follows:

- M = F: B/F/TAF 90.0%; DTG+F/TAF 93.5%; difference in percentages: −3.4%, 95% CI: −7.7% to 0.9%

- M = E: B/F/TAF 99.0%; DTG+F/TAF 99.3%; difference in percentages: −0.4%, 95% CI: −2.3% to 1.6%

The majority of subjects achieved viral suppression by Week 4; 73.1% and 79.4% of subjects in the B/F/TAF and DTG+F/TAF groups had HIV-1 RNA < 50 copies/mL (M = F), respectively, at Week 4 (GS-US-380-1490 Interim Week 48, Table 15.9.2.2). Corresponding values for M = E were 75.2% and 79.6%, respectively (GS-US-380-1490 Interim Week 48, Table 15.9.2.3).

Study GS-US-141-1475

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 in Study GS-US-141-1475 using the M = F and M = E methods were as follows:

- M = F: BIC+F/TAF 96.9%; DTG+F/TAF 93.9%; difference in percentages: 3.3%, 95% CI: −7.9% to 14.5% (GS-US-141-1475 Interim Week 72, Table 15.9.2.4 and Figure 15.9.2.1)

- M = E: BIC+F/TAF 100.0%; DTG+F/TAF 96.9%; difference in percentages: 3.2%, 95% CI: −5.8% to 12.3% (GS-US-141-1475 Interim Week 72, Table 15.9.2.5.1)

Virologic suppression with BIC+F/TAF or B/F/TAF (BIC+F/TAF to B/F/TAF group) was maintained through Week 72, with HIV-1 RNA < 50 copies/mL in 100.0% of subjects (61 of 61 subjects) using the M = E data imputation method (GS-US-141-1475 Interim Week 72, Table 15.9.2.5.2).

3.2.1.4. Change from Baseline in Plasma HIV-1 RNA at Week 48

Study GS-US-380-1489

In Study GS-US-380-1489, HIV-1 RNA values decreased in each treatment group, with the fastest decreases from baseline observed in the first 4 weeks following initiation of study drugs (GS-US-380-1489 Interim Week 48, Table 15.9.2.4). Mean (SD) baseline HIV-1 RNA values were as follows: B/F/TAF 4.41 (0.647) $\log_{10}$ copies/mL; ABC/DTG/3TC 4.42 (0.685) $\log_{10}$ copies/mL. The mean (SD) changes from baseline in HIV-1 RNA at Week 48 were as follows: B/F/TAF −3.11 (0.660) $\log_{10}$copies/mL; ABC/DTG/3TC −3.08 (0.719) $\log_{10}$ copies/mL; difference in least-squares mean (LSM): −0.02 $\log_{10}$ copies/mL, 95% CI: −0.11 to 0.07 $\log_{10}$ copies/mL.

Study GS-US-380-1490

In Study GS-U-380-1490, HIV-1 RNA values decreased in each treatment group, with the fastest decreases from baseline observed in the first 4 weeks following initiation of study drugs (GS-U-380-1490 Interim Week 48, Table 15.9.2.4). Mean (SD) baseline HIV-1 RNA values were as follows: B/F/TAF 4.39 (0.730) $\log_{10}$ copies/mL; DTG+F/TAF 4.42 (0.669) $\log_{10}$ copies/mL. The mean (SD) changes from baseline in HIV-1 RNA at Week 48 were as follows: B/F/TAF −3.08 (0.716) $\log_{10}$copies/mL; DTG+F/TAF −3.12 (0.671) $\log_{10}$ copies/mL; difference in least-squares mean (LSM): 0.07 $\log_{10}$ copies/mL, 95% CI: −0.01 to 0.16 $\log_{10}$ copies/mL.

Study GS-US-141-1475

In Study GS-US-141-1475, HIV-1 RNA values decreased rapidly in the first 4 weeks following initiation of study drug in both treatment groups (GS-US-141-1475 Interim Week 72, Table 15.9.2.6 and Figure 15.9.2.2). Mean (SD) baseline HIV-1 RNA values were as follows: BIC+F/TAF 4.39 (0.764) $\log_{10}$ copies/mL; DTG+F/TAF 4.38 (0.866) $\log_{10}$ copies/mL. Mean (SD) changes from baseline in HIV-1 RNA at Week 48 were as follows: BIC+F/TAF −3.09 (0.752) $\log_{10}$ copies/mL; DTG+F/TAF −3.11 (0.852) $\log_{10}$ copies/mL; difference in LSM: −0.06 $\log_{10}$ copies/mL, 95% CI: −0.32 to 0.20 $\log_{10}$ copies/mL.

3.2.1.5. Change from Baseline in CD4 at Week 48

Pooled Data from Studies GS-US-380-1489 and GS-US-380-1490

In comparisons of the pooled B/F/TAF group with each of the comparator groups in Studies GS-US-380-1489 and GS-US-380-1490, increases from baseline in CD4 cell counts at Week 48 were seen in all treatment groups (Figure 1; B/F/TAF Week 48 ISE, Table 5.1).

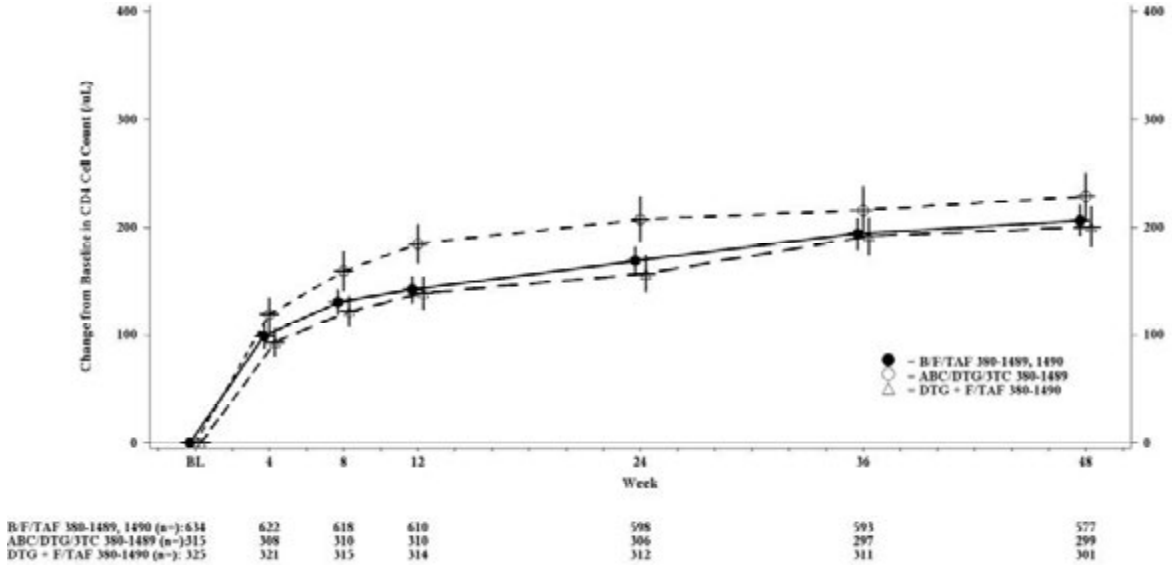
Mean (SD) baseline CD4 cell counts were as follows: pooled B/F/TAF 455 (238.6) cells/μL; ABC/DTG/3TC 476 (231.4) cells/μL; DTG+F/TAF 454 (231.5) cells/μL.

Mean (SD) changes from baseline at Week 48 were similar between treatment groups (pooled B/F/TAF − ABC/DTG/3TC and pooled B/F/TAF − DTG+F/TAF), as follows:

- Pooled B/F/TAF 207 (178.0) cells/μL; ABC/DTG/3TC 229 (188.8) cells/μL; difference in LSM: –23 cells/μL, 95% CI: –48 to 3 cells/μL.
- Pooled B/F/TAF 207 (178.0) cells/μL; DTG+F/TAF 201 (166.4) cells/μL; difference in LSM: 4 cells/μL, 95% CI: –21 to 28 cells/μL.

Using LOCF to impute missing values, the changes from baseline in CD4 cell counts in each treatment group were consistent with the observed data (B/F/TAF Week 48 ISE, Table 5.2).

Figure 1. GS US-380-1489 and GS US-380-1490: Mean and 95% CIs of Change from Baseline in CD4 Cell Count (cells/µL) by Visit (FAS)



On-treatment data include all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug.
Source: B/F/TAF Week 48 ISE, Figure 2

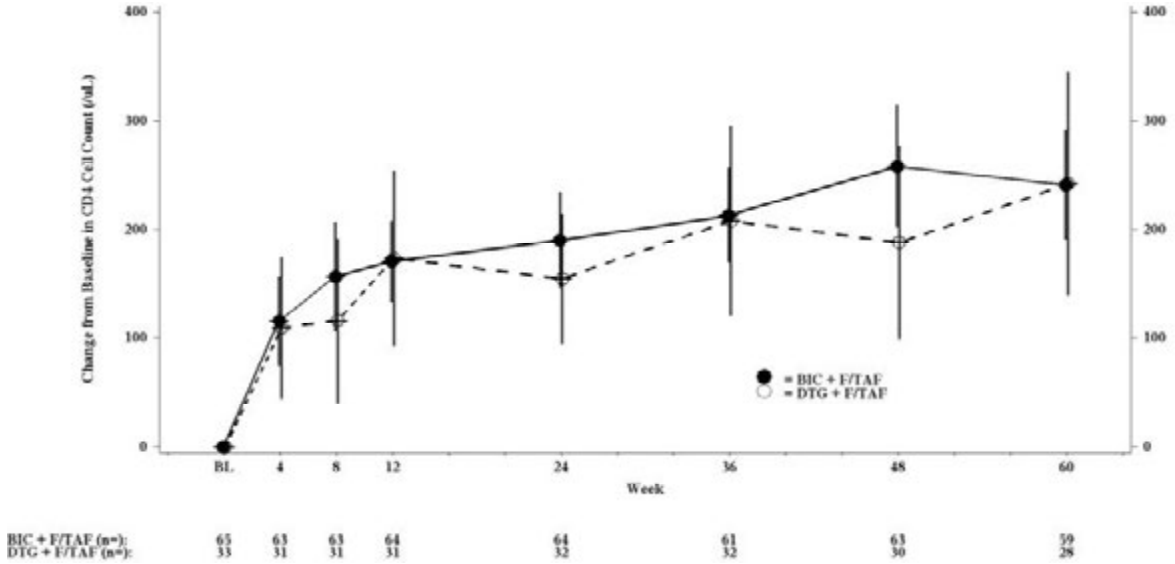
Study GS-US-141-1475

Following initiation of study drug, CD4 cell count increased in both treatment groups in Study GS-US-141-1475 (Figure 2 and GS-US-141-1475 Interim Week 72, Table 15.9.2.7.1). Mean (SD) baseline CD4 cell counts were as follows: BIC+F/TAF 471 (190.9) cells/µL; DTG+F/TAF 507 (271.0) cells/µL. Mean (SD) increases from baseline to Week 48 in CD4 cell count for the FAS were as follows: BIC+F/TAF 258 (221.7) cells/µL; DTG+F/TAF 188 (238.7) cells/µL; difference in LSM: 76 cells/µL, 95% CI: −25 to 176 cells/µL.

Results for the Week 48 PP Analysis Set were consistent with those for the FAS (GS-US-141-1475 Interim Week 72, Table 15.9.2.7.2).

At Week 72, the mean (SD) increase from baseline in CD4 cell count in the BIC+F/TAF to B/F/TAF group was 276 (225.1) cells/µL (GS-US-141-1475 Interim Week 72, Table 15.9.2.7.3).

Figure 2. GS-US-141-1475: Mean and 95% CI of Change from Baseline in CD4 Cell Count (cells/µL) by Visit (FAS)



On-treatment data included all data from Study Day 1 for subjects who were ongoing and data from Study Day 1 up to 1 day after the last dose of study drug for subjects who completed or prematurely discontinued study drug.
Source: GS-US-141-1475 Interim Week 72, Figure 15.9.2.3.1

3.2.2. Virologically Suppressed Adult Subjects: Studies GS-US-380-1844 and GS-US-380-1878

A summary supporting efficacy of B/F/TAF in virologically suppressed adult subjects is presented below. Detailed efficacy results are presented in the CSRs (GS-US-380-1844 Interim Week 48, Section 9 and GS-US-380-1878 Interim Week 48, Section 9).

3.2.2.1. Primary Endpoint: Proportion of Subjects with Plasma HIV-1 RNA ≥ 50 copies/mL at Week 48 Using the US FDA-Defined Snapshot Algorithm

Study GS-US-380-1844

The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 in Study GS-US-380-1844 were similar for each treatment group (B/F/TAF 1.1%; ABC/DTG/3TC 0.4%; difference in percentages: 0.7%, 95.002% CI: −1.0% to 2.8%) (Table 24). Because the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF − ABC/DTG/3TC) was less than the prespecified 4% margin, switching to B/F/TAF was determined to be noninferior to maintaining ABC/DTG/3TC.

The percentages of subjects in the Week 48 PP Analysis Set with HIV-1 RNA ≥ 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were consistent with those for the FAS, and confirmed noninferiority of B/F/TAF to ABC/DTG/3TC (B/F/TAF 0.4%; ABC/DTG/3TC 0.0%; difference in percentages: 0.4%, 95.002% CI: −1.1% to 2.2%).

Table 24. GS-US-380-1844: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (FAS)

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)	B/F/TAF vs ABC/DTG/3TC	
			p-value	Difference in Percentages (95.002% CI)
HIV-1 RNA < 50 copies/mL	264 (93.6%)	267 (95.0%)	0.59	-1.4% (−5.5% to 2.6%)
HIV-1 RNA ≥ 50 copies/mL	3 (1.1%)	1 (0.4%)	0.62	0.7% (−1.0% to 2.8%)
HIV-1 RNA ≥ 50 copies/mL in Week 48 Window	1 (0.4%)	0		
Discontinued study drug due to lack of efficacy	0	0		
Discontinued study drug due to AE/death and last available HIV-1 RNA ≥ 50 copies/mL	1 (0.4%)	0		
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL[a]	1 (0.4%)	1 (0.4%)		
No virologic data in Week 48 window	15 (5.3%)	13 (4.6%)		
Discontinued study drug due to AE/death and last available HIV-1 RNA < 50 copies/mL	5 (1.8%)	2 (0.7%)		
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[a]	5 (1.8%)	9 (3.2%)		
Missing data during window but on study drug	5 (1.8%)	2 (0.7%)		

The Week 48 window is between Days 295 and 378 (inclusive).
a Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
P-values for the superiority tests comparing the percentages of subjects between treatment groups were from the Fisher exact test. The differences in percentages of subjects between treatment groups and their 95.002% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.
Source: GS-US-380-1844 Interim Week 48, Table 15.9.1.1

Study GS-US-380-1878

The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 in Study GS-US-380-1878 were similar for each treatment group (B/F/TAF 1.7%; SBR 1.7%; difference in percentages: −0.0%, 95.002% CI: −2.5% to 2.5%) (Table 25). Because the upper bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF − SBR) was less than the prespecified 4% margin, switching to B/F/TAF was determined to be noninferior to maintaining baseline regimen.

The percentages of subjects in the Week 48 PP Analysis Set with HIV-1 RNA ≥ 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were consistent with those for the FAS, and confirmed noninferiority of B/F/TAF to SBR (B/F/TAF 1.1%; SBR 0.8%; difference in percentages: 0.3%, 95.002% CI: −1.9% to 2.5%).

Table 25. GS-US-380-1878: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (FAS)

	B/F/TAF (N = 290)	SBR (N = 287)	B/F/TAF vs SBR	
			p-value	Difference in Percentages (95.002% CI)
HIV-1 RNA < 50 copies/mL	267 (92.1%)	255 (88.9%)	0.20	3.2% (−1.6% to 8.2%)
HIV-1 RNA ≥ 50 copies/mL	5 (1.7%)	5 (1.7%)	1.00	-0.0% (−2.5% to 2.5%)
HIV-1 RNA ≥ 50 copies/mL in Week 48 Window	2 (0.7%)	2 (0.7%)		
Discontinued study drug due to lack of efficacy	1 (0.3%)	0		
Discontinued study drug due to AE/death and last available HIV-1 RNA ≥ 50 copies/mL	0	0		
Discontinued study drug due to other reasons* and last available HIV-1 RNA ≥ 50 copies/mL	2 (0.7%)	3 (1.0%)		
No Virologic Data in Week 48 Window	18 (6.2%)	27 (9.4%)		
Discontinued study drug due to AE/death and last available HIV-1 RNA < 50 copies/mL	3 (1.0%)	2 (0.7%)		
Discontinued study drug due to other reasons* and Last Available HIV-1 RNA < 50 copies/mL	10 (3.4%)	19 (6.6%)		
Missing data during window but on study drug	5 (1.7%)	6 (2.1%)		

Week 48 window was between Day 295 and 378 (inclusive).
* Other reasons included subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
P-value for the superiority test comparing the percentages between treatment groups were from the Fisher exact test.
The differences in percentages between treatment groups and their 95.002% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.
Source: GS-US-380-1878 Interim Week 48, Table 15.9.1.1

3.2.2.2. Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using the US FDA-Defined Snapshot Algorithm

Study GS-US-380-1844

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 in Study GS-US-380-1844 were similar for each treatment group (B/F/TAF 93.6%; ABC/DTG/3TC 95.0%; difference in percentages: −1.4%, 95.002% CI: −5.5% to 2.6%) (Table 24). Because the lower bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF − ABC/DTG/3TC) was greater than the prespecified −10% margin, switching to B/F/TAF was determined to be noninferior to maintaining ABC/DTG/3TC.

The percentages of subjects in the Week 48 PP Analysis Set with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were consistent with those for the FAS, and confirmed noninferiority of B/F/TAF to ABC/DTG/3TC (B/F/TAF 99.6%; ABC/DTG/3TC 100.0%; difference in percentages: −0.4%, 95.002% CI: −2.2% to 1.1%).

Study GS-US-380-1878

The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 in Study GS-US-380-1878 were similar for each treatment group (B/F/TAF 92.1%; SBR 88.9%; difference in percentages: 3.2%, 95.002% CI: −1.6% to 8.2%) (Table 25). Because the lower bound of the 2-sided 95.002% CI of the difference between treatment groups (B/F/TAF − SBR) was greater than the prespecified −10% margin, switching to B/F/TAF was determined to be noninferior to maintaining baseline regimen.

The percentages of subjects in the Week 48 PP Analysis Set with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were consistent with those for the FAS, and confirmed noninferiority of B/F/TAF to maintaining baseline regimen (B/F/TAF 98.9%; SBR 99.2%; difference in percentages: −0.3%, 95.002% CI: −2.5% to 1.9%).

3.2.2.3. Proportion of Subjects with Plasma HIV-1 RNA < 20 copies/mL at Week 48 Using the US FDA-Defined Snapshot Algorithm

Study GS-US-380-1844

The percentages of subjects in the FAS with HIV-1 RNA < 20 copies/mL at Week 48 in Study GS-US-380-1844 were similar in each treatment group (B/F/TAF 90.1%; ABC/DTG/3TC 91.5%; difference in percentages: −1.4%, 95% CI: −6.4% to 3.5%).

Study GS-US-380-1878

The percentages of subjects in the FAS with HIV-1 RNA < 20 copies/mL at Week 48 in Study GS-US-380-1878 were similar in each treatment group (B/F/TAF 85.9%; SBR 84.7%; difference in percentages: 1.2%, 95% CI: −4.7% to 7.1%).

3.2.2.4. Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48 Using Missing Data Imputation Methods (M = F and M = E)

Study GS-US-380-1844

Similar percentages of subjects maintained HIV-1 RNA < 50 copies/mL in the 2 treatment groups as assessed using the M = F and M = E methods at Week 48 for the FAS in Study GS-US-380-1844, as follows:

- M = F: B/F/TAF 95.0%; ABC/DTG/3TC 95.4%; difference in percentages: −0.3%, 95% CI: −4.1% to 3.4%
- M = E: B/F/TAF 99.6%; ABC/DTG/3TC 100.0%; difference in percentages: −0.4%, 95% CI: −2.1% to 1.1%

Study GS-US-380-1878

Similar percentages of subjects maintained HIV-1 RNA < 50 copies/mL in the 2 treatment groups as assessed using the M = F and M = E methods at Week 48 for the FAS in Study GS-US-380-1878, as follows:

- M = F: B/F/TAF 92.8%; SBR 90.9%; difference in percentages: 1.8%, 95% CI: −2.8% to 6.5%

- M = E: B/F/TAF 98.9%; SBR 98.9%; difference in percentages: 0.0%, 95% CI: −2.2% to 2.4%

3.2.2.5. Change from Baseline in CD4 at Week 48

Study GS-US-380-1844

Mean (SD) baseline CD4 cell counts were statistically significantly higher in the B/F/TAF group than the ABC/DTG/3TC group in Study GS-US-380-1844 (B/F/TAF 752 [302.2] cells/μL; ABC/DTG/3TC 694 [291.6] cells/μL; difference in LSM: 58 cells/uL, 95% CI: 9 to 107 cells/uL, p = 0.021). Mean (SD) changes from baseline at Week 48 for the FAS were statistically significantly different between treatment groups (B/F/TAF −31 [181.3] cells/μL; ABC/DTG/3TC 4 [191.0] cells/μL; difference in LSM: −35 cells/μL, 95% CI: −67 to −3 cells/uL, p = 0.031).

After adjusting for baseline CD4 cell count, the difference in the mean (SD) CD4 count changes from baseline at Week 48 for the FAS between treatment groups was not statistically different (difference in LSM −21 cells/μL, 95% CI: −51 to 9 cells/μL, p = 0.18). Mean (SD) CD4 cell counts at Week 48 for the FAS were similar between treatment groups (B/F/TAF 724 [281.5] cells/μL; ABC/DTG/3TC 691 [302.0] cells/μL; difference in LSM: 33 cells/uL, 95% CI: −17 to 83 cells/uL, p = 0.19).

Using LOCF to impute missing values, the change from baseline in CD4 cell counts in each treatment group was consistent with the observed data. Results for the Week 48 PP Analysis Set were consistent with those for the FAS.

Mean (SD) baseline CD4% was similar for each treatment group (B/F/TAF 35.4% [9.64%]; ABC/DTG/3TC 34.1% [10.28%]). Mean (SD) changes from baseline in CD4% at Week 48 were as follows: B/F/TAF 1.0% (3.77 %); ABC/DTG/3TC 0.5% (3.84%); difference in LSM: 0.5%, 95% CI: −0.1% to 1.2%.

Study GS-US-380-1878

Mean (SD) baseline CD4 cells counts were similar between treatment groups in Study GS-US-380-1878 (B/F/TAF 669 [303.4] cells/μL; SBR 657 [285.0] cells/μL). CD4 cell counts were maintained in both groups. Mean (SD) changes from baseline at Week 48 for the FAS were as follows: B/F/TAF 25 (151.2) cells/μL; SBR 0 (159.4) cells/μL; difference in least-squares mean (LSM): 25 cells/μL, 95% CI: −2 to 52 cells/μL.

Using LOCF to impute missing values, the change from baseline in CD4 cell counts in each treatment group was consistent with the observed data. Results for the Week 48 PP Analysis Set were consistent with those for the FAS.

Mean (SD) baseline CD4% was similar for each treatment group (B/F/TAF 33.9% [9.68%]; SBR 32.7% [10.35%]). Mean (SD) changes from baseline in CD4% at Week 48 were as follows: B/F/TAF 0.5% (3.56%); SBR 0.5% (3.53%); difference in LSM: −0.1%, 95% CI: −0.7% to 0.6%.

3.3. Comparison of Results in Subpopulations

3.3.1. ART-Naive Subjects: Studies GS-US-380-1489 and GS-US-380-1490

Subgroup analyses of the primary efficacy endpoint in Studies GS-US-380-1489 and GS-US-380-1490 were performed to compare BIC versus DTG administered in the context of a double-NRTI backbone in ART-naive subjects. Using the pooled B/F/TAF groups ("B/F/TAF") and the pooled ABC/DTG/3TC and DTG+F/TAF groups ("Control"), the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as determined by the US FDA-defined snapshot algorithm, was analyzed in the following subgroups:

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack
- Baseline HIV-1 RNA level (copies/mL): (a) ≤ 100,000 and (b) > 100,000
- Baseline CD4 cell count (/μL): (a) < 200 and (b) ≥ 200
- Region: (a) US and (b) ex-US
- Study drug adherence (%): (a) < 95 and (b) ≥ 95 (based on adherence up to Week 48 visit)

Statistical methods for subgroup analysis of pooled data from Studies GS-US-380-1489 and GS-US-380-1490 are provided in the B/F/TAF Week 48 Integrated Summary of Efficacy (ISE) SAP.

In comparisons of the B/F/TAF group with the Control group, the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm was similar between groups for each of the subgroups analyzed (age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region, and study drug adherence) (Table 26 and Figure 3). The 95% CIs for differences between groups (ie, B/F/TAF vs Control) included zero for all subgroups evaluated, suggesting no differences in treatment between B/F/TAF and the DTG-containing regimens.

Homogeneity tests performed for comparisons of the B/F/TAF group with the Control group did not show a difference in treatment effects between subgroups (B/F/TAF Week 48 ISE, Table 4).

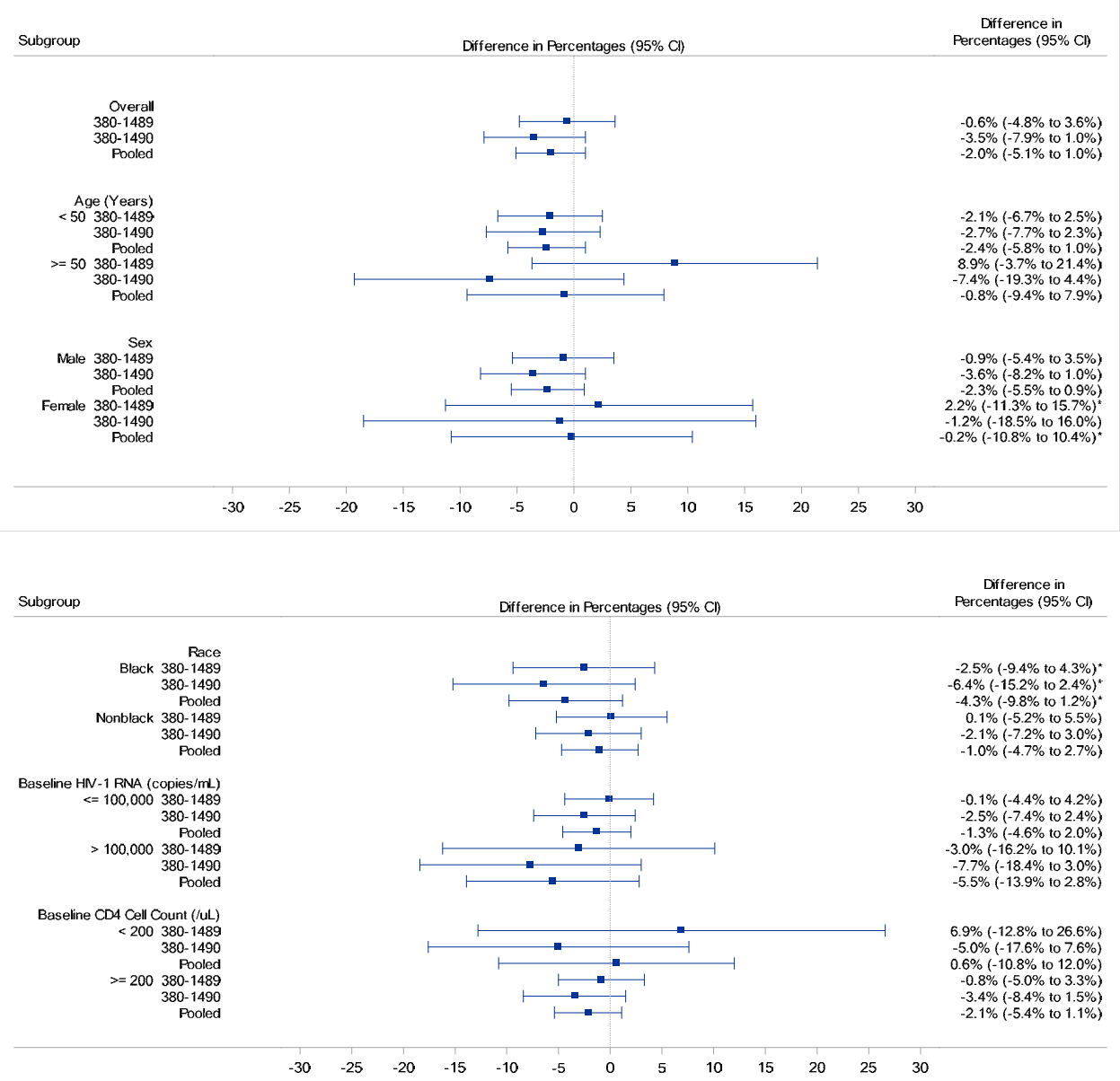
Table 26. GS-US-380-1489 and GS-US-380-1490: Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm – Individual Studies and Pooled Data

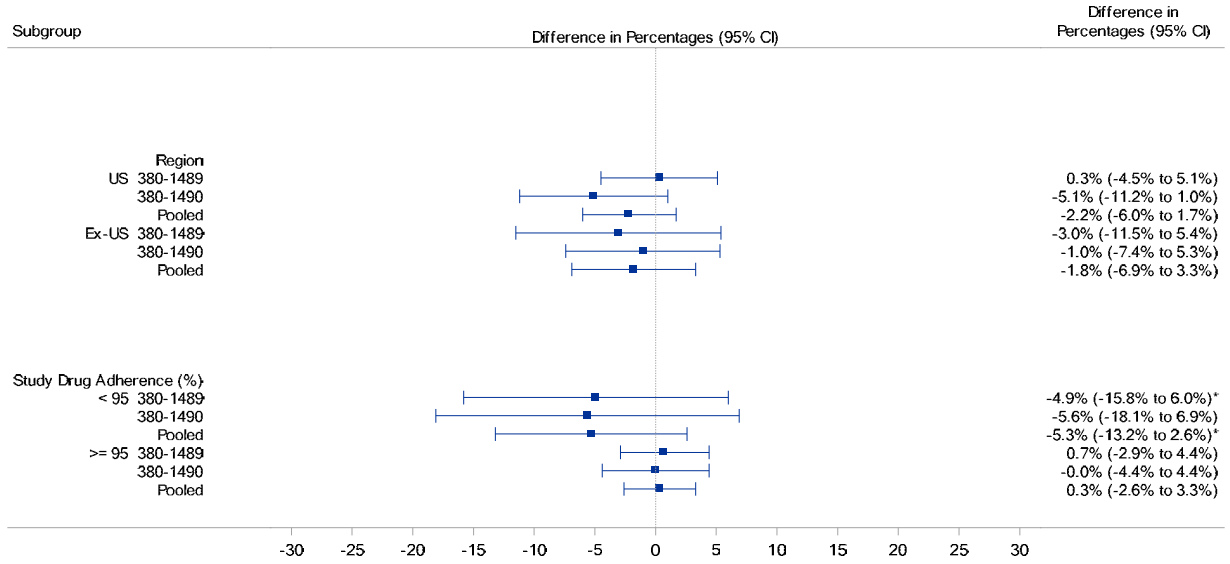
		B/F/TAF (N = 634)	Control (N = 640)	B/F/TAF vs. Control Difference in Percentages (95% CI)
Overall				
380-1489		290/314 (92.4%)	293/315 (93.0%)	-0.6% (-4.8% to 3.6%)
380-1490		286/320 (89.4%)	302/325 (92.9%)	-3.5% (-7.9% to 1.0%)
Pooled		576/634 (90.9%)	595/640 (93.0%)	-2.0% (-5.1% to 1.0%)
Age (Years)				
< 50	380-1489	250/274 (91.2%)	256/274 (93.4%)	-2.1% (-6.7% to 2.5%)
	380-1490	237/264 (89.8%)	246/266 (92.5%)	-2.7% (-7.7% to 2.3%)
	Pooled	487/538 (90.5%)	502/540 (93.0%)	-2.4% (-5.8% to 1.0%)
>= 50	380-1489	40/40 (100.0%)	37/41 (90.2%)	8.9% (-3.7% to 21.4%)
	380-1490	49/56 (87.5%)	56/59 (94.9%)	-7.4% (-19.3% to 4.4%)
	Pooled	89/96 (92.7%)	93/100 (93.0%)	-0.8% (-9.4% to 7.9%)
Sex				
Male	380-1489	263/285 (92.3%)	263/282 (93.3%)	-0.9% (-5.4% to 3.5%)
	380-1490	252/280 (90.0%)	270/288 (93.8%)	-3.6% (-8.2% to 1.0%)
	Pooled	515/565 (91.2%)	533/570 (93.5%)	-2.3% (-5.5% to 0.9%)
Female	380-1489	27/29 (93.1%)	30/33 (90.9%)	2.2% (-11.3% to 15.7%)*
	380-1490	34/40 (85.0%)	32/37 (86.5%)	-1.2% (-18.5% to 16.0%)
	Pooled	61/69 (88.4%)	62/70 (88.6%)	-0.2% (-10.8% to 10.4%)*
Race				
Black	380-1489	104/114 (91.2%)	105/112 (93.8%)	-2.5% (-9.4% to 4.3%)*
	380-1490	83/97 (85.6%)	92/100 (92.0%)	-6.4% (-15.2% to 2.4%)*
	Pooled	187/211 (88.6%)	197/212 (92.9%)	-4.3% (-9.8% to 1.2%)*
Nonblack	380-1489	184/198 (92.9%)	188/203 (92.6%)	0.1% (-5.2% to 5.5%)
	380-1490	203/223 (91.0%)	210/225 (93.3%)	-2.1% (-7.2% to 3.0%)
	Pooled	387/421 (91.9%)	398/428 (93.0%)	-1.0% (-4.7% to 2.7%)
Baseline HIV-1 RNA (copies/mL)				
<= 100,000	380-1489	244/261 (93.5%)	248/265 (93.6%)	-0.1% (-4.4% to 4.2%)
	380-1490	229/254 (90.2%)	251/271 (92.6%)	-2.5% (-7.4% to 2.4%)
	Pooled	473/515 (91.8%)	499/536 (93.1%)	-1.3% (-4.6% to 2.0%)
> 100,000	380-1489	46/53 (86.8%)	45/50 (90.0%)	-3.0% (-16.2% to 10.1%)
	380-1490	57/66 (86.4%)	51/54 (94.4%)	-7.7% (-18.4% to 3.0%)
	Pooled	103/119 (86.6%)	96/104 (92.3%)	-5.5% (-13.9% to 2.8%)

		B/F/TAF (N = 634)	Control (N = 640)	B/F/TAF vs. Control Difference in Percentages (95% CI)
Baseline CD4 Cell Count (/uL)				
< 200	380-1489	30/36 (83.3%)	26/32 (81.3%)	6.9% (-12.8% to 26.6%)
	380-1490	42/44 (95.5%)	34/34 (100.0%)	-5.0% (-17.6% to 7.6%)
	Pooled	72/80 (90.0%)	60/66 (90.9%)	0.6% (-10.8% to 12.0%)
>= 200	380-1489	260/278 (93.5%)	267/283 (94.3%)	-0.8% (-5.0% to 3.3%)
	380-1490	244/276 (88.4%)	268/291 (92.1%)	-3.4% (-8.4% to 1.5%)
	Pooled	504/554 (91.0%)	535/574 (93.2%)	-2.1% (-5.4% to 1.1%)
Region				
US	380-1489	212/228 (93.0%)	216/233 (92.7%)	0.3% (-4.5% to 5.1%)
	380-1490	168/193 (87.0%)	178/193 (92.2%)	-5.1% (-11.2% to 1.0%)
	Pooled	380/421 (90.3%)	394/426 (92.5%)	-2.2% (-6.0% to 1.7%)
Ex-US	380-1489	78/86 (90.7%)	77/82 (93.9%)	-3.0% (-11.5% to 5.4%)
	380-1490	118/127 (92.9%)	124/132 (93.9%)	-1.0% (-7.4% to 5.3%)
	Pooled	196/213 (92.0%)	201/214 (93.9%)	-1.8% (-6.9% to 3.3%)
Study Drug Adherence (%)				
< 95	380-1489	65/80 (81.3%)	87/101 (86.1%)	-4.9% (-15.8% to 6.0%)*
	380-1490	57/68 (83.8%)	56/62 (90.3%)	-5.6% (-18.1% to 6.9%)
	Pooled	122/148 (82.4%)	143/163 (87.7%)	-5.3% (-13.2% to 2.6%)*
>= 95	380-1489	225/232 (97.0%)	206/214 (96.3%)	0.7% (-2.9% to 4.4%)
	380-1490	229/244 (93.9%)	245/261 (93.9%)	-0.0% (-4.4% to 4.4%)
	Pooled	454/476 (95.4%)	451/475 (94.9%)	0.3% (-2.6% to 3.3%)

Week 48 window is between Day 295 and 378 (inclusive).
Control groups are ABC/DTG/3TC in Study GS-US-380-1489, DTG + F/TAF in Study GS-US-380-1490, ABC/DTG/3TC and DTG + F/TAF in pooled analysis.
The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the MH proportion adjusted by baseline HIV-1 RNA and region stratum (if not the subgroup factor), and study (for pooled analysis).
Study drug adherence subgroup analyses are based on the adherence up to Week 48 visit for active study drug.
* Proportion difference and 95% CI from normal approximation without stratification as they were not calculable by stratum-adjusted MH method.
Source: B/F/TAF Week 48 ISE, Table 3

Figure 3. **GS-US-380-1489 and GS-US-380-1490: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm – Pooled Data**





Week 48 window is between Day 295 and Day 378 (inclusive)
Control groups are ABC/DTG/3TC in Study GS-US-380-1489, DTG+F/TAF in Study GS-US-380-1490, ABC/DTG/3TC and DTG+F/TAF in pooled analysis.
The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the MH proportion adjusted by baseline HIV-1 RNA and region stratum (if not the subgroup factor) and study (for pooled analysis).
Study drug adherence subgroup analyses are based on the adherence up to Week 48 visit for active study drug.
* Proportion difference and 95% CI from normal approximation without stratification as they were not calculable by stratum-adjusted MH method.
Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the Control group.
Source: B/F/TAF Week 48 ISE, Figure 1

3.3.2. Virologically Suppressed Subjects: Studies GS-US-380-1844 and GS-US-380-1878

In virologically supressed subjects from Studies GS-US-380-1844 and GS-US-380-1878, the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm was analyzed by study in the following subgroups:

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack
- Region: (a) US and (b) Ex-US

The following subgroup was analyzed in Study GS-US-380-1844 only:

- Study drug adherence (%): (a) < 95 and (b) ≥ 95 (based on adherence up to Week 48 visit)

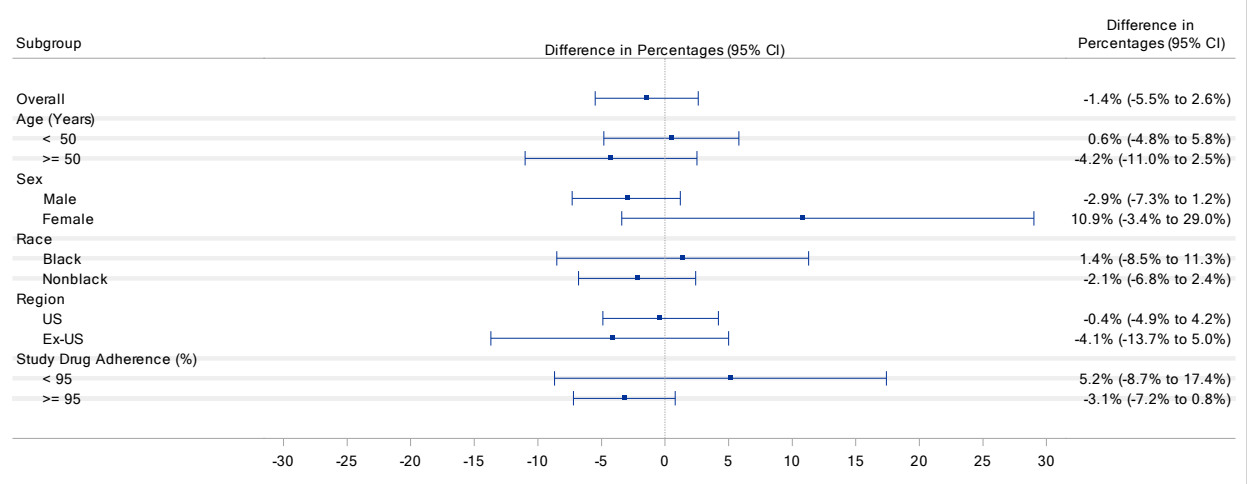
Statistical methods for subgoup analysis for Studies GS-US-380-1844 and GS-US-380-1878 are provided in the SAPs (GS-US-380-1844 Interim Week 48, Appendix 16.1.9, SAP and GS-US-380-1878 Interim Week 48, Appendix 16.1.9, SAP).

Study GS-US-380-1844

At Week 48, analysis of the percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS in Study GS-US-380-1844 was similar between the 2 treatment groups for each of the subgroups analyzed (age, sex, race, region, and study drug adherence) (Figure 4). The 95% CIs for differences between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments.

Homogeneity tests performed did not show a difference in treatment effects between subgroups.

Figure 4. GS-US-380-1844: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



The Week 48 window is between Days 295 and 378 (inclusive).
The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests.
Study drug adherence subgroup analyses are based on the adherence up to Week 48 visit for active study drug.
Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the ABC/DTG/3TC group.
Source: GS-US-380-1844 Interim Week 48, Figure 15.9.3

Analyses evaluating the interaction between regions and treatment showed no differences across 8 predefined regions in treatment effect (HIV-1 RNA< 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm) comparing switching to B/F/TAF with maintaining ABC/DTG/3TC; the 95% CIs for differences between treatment groups in each region included zero.

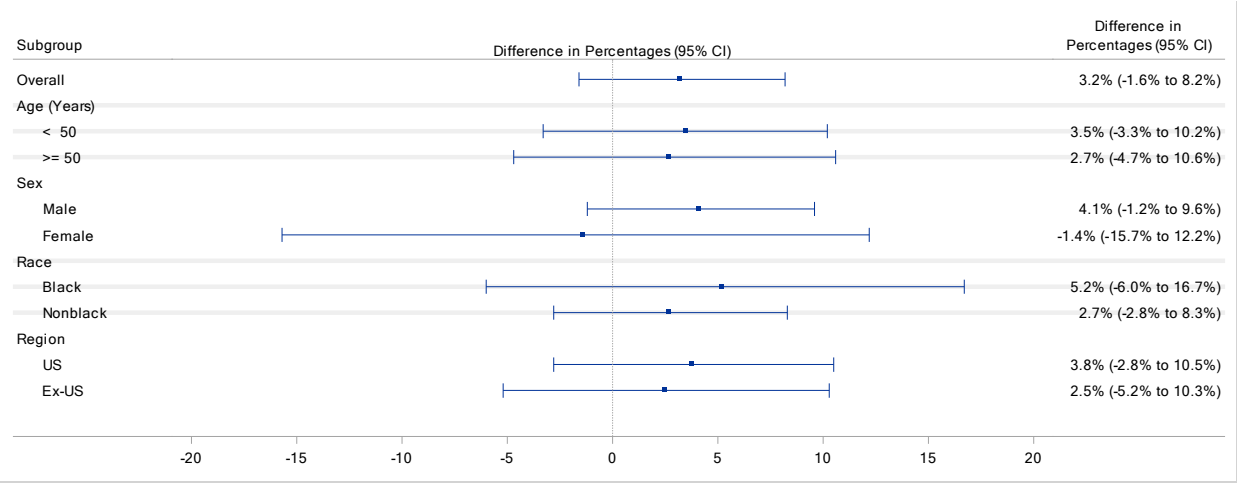
Homogeneity tests performed did not show a difference in treatment effects across regions.

Study GS-US-380-1878

At Week 48, analysis of the percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS in Study GS-US-380-1878 was similar between the 2 treatment groups for each of the subgroups analyzed (age, sex, race, and region) (Figure 5). The 95% CIs for differences between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments.

Homogeneity tests performed did not show a difference in treatment effects between subgroups.

Figure 5. GS-US-380-1878: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



Week 48 window was between Day 295 and 378 (inclusive).
The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-isded tests.
Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the SBR group.
Source: GS-US-380-1878 Interim Week 48, Figure 15.9.3

Analyses evaluating the interaction between regions and treatment showed no differences across 8 predefined regions in treatment effect (HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm) comparing switching to B/F/TAF with maintaining baseline regimen; the 95% CIs for differences between treatment groups in each region included zero.

Homogeneity tests performed did not show a difference in treatment effects across regions.

3.3.3. Subjects Coinfected with HIV and HBV

Efficacy of B/F/TAF in HIV/HBV-coinfected patients is supported by data from Studies GS-US-380-1490 and GS-US-380-1878. Both studies permitted coinfected subjects to enroll; virologically suppressed subjects in Study GS-US-380-1878 must have been on a TDF-containing regimen at screening. Detailed results for subjects with HIV/HBV coinfection in these studies are provided in the CSRs (GS-US-380-1490 Interim Week 48, Section 9.3.2 and GS-US-380-1878 Interim Week 48, Section 9.3.2).

Efficacy of B/F/TAF in HIV/HBV coinfection is also supported by data from a study of an F/TAF-containing regimen (GEN) in HIV/HBV-coinfected subjects (Study GS-US-292-1249), and from studies of TAF (Vemlidy) in HBV-monoinfected subjects (Studies GS-US-320-0108 and GS-US-320-0110).

3.3.3.1. Studies GS-US-380-1490 and GS-US-380-1878

Study GS-US-380-1490

Subjects with HIV/HBV Coinfection at Baseline

At baseline, 14 (2.2%) subjects had HIV/HBV coinfection in Study GS-US-380-1490 (B/F/TAF 8 [2.5%] subjects; DTG+F/TAF 6 [1.9%] subjects) (GS-US-380-1490 Interim Week 48, Table 15.8.3.2). Of the 14 subjects who met SAP-defined criteria for HIV/HBV coinfection at study entry, 13 subjects had HBV DNA ≥ 29 IU/mL at baseline, while 1 subject (Subject 00550-2198 in the DTG+F/TAF group) had positive HBsAg and hepatitis B core antibody (HBcAb) but HBV DNA < 29 IU/mL at baseline (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.9.3).

Proportion of Subjects with HBV DNA < 29 IU/mL at Week 48 as Defined by Missing = Excluded Data Imputation Method

One of the 14 HIV/HBV baseline-coinfected subjects discontinued the study prior to Week 48 in Study GS-US-380-1490. Subject 01950-2219 in the B/F/TAF group discontinued on Study Day 68 due to the investigator's discretion (the subject moved out of state), with no postbaseline HBV DNA assessments available (GS-US-380-1490 Interim Week 48, Listings 16.2.1.3 and 16.2.8.1.9.3).

Of the 13 HIV/HBV baseline-coinfected subjects with baseline HBV DNA ≥ 29 IU/mL and postbaseline HBV DNA assessments, 11 subjects had HBV DNA < 29 IU/mL at Week 48 (M = E) (Table 27). Two subjects had HBV DNA ≥ 29 U/mL at Week 48. Subjects 01549-2113 and 02475-2013, both in the DTG+F/TAF group, were both HBeAg positive at baseline (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.5.2), and both had baseline HBV DNA > 170,000,000 IU/mL, which steadily decreased to 303 U/mL and 80 U/mL at Week 48, respectively (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.9.3). Study drug adherence up to Week 48 was 100.0% for Subject 01549-2113 and 99.4% for Subject 02475-2013 (GS-US-380-1490 Interim Week 48, Listing 16.2.5.3).

The 1 subject with baseline HBV DNA < 29 IU/mL (Subject 00550-2198 in the DTG+F/TAF group) remained suppressed at Week 48. The subject was HBsAg positive and HBsAb negative at baseline. At Week 24, the subject was HBsAg negative and HBsAb positive, indicating HBsAg loss and seroconversion during the study (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.9.3).

All 13 HIV/HBV baseline-coinfected subjects who were continuing treatment at Week 48 had HIV-1 RNA < 50 copies/mL at Week 48 (GS-US-380-1490 Interim Week 48, Listings 16.2.6 and 16.2.8.1.9.3).

Table 27. GS-US-380-1490: Proportion of Subjects with HBV DNA < 29 IU/mL at Baseline and On-treatment HBV DNA < 29 IU/mL at Week 48: Missing = Excluded, Subjects with HIV/HBV Coinfection at Baseline (Full Analysis Set)

	B/F/TAF (N = 8)	DTG + F/TAF (N = 6)	Total (N = 14)
HBV DNA at Baseline			
< 29 IU/mL	0/8	1/6 (16.7%)	1/14 (7.1%)
>= 29 IU/mL	8/8 (100.0%)	5/6 (83.3%)	13/14 (92.9%)
HBV DNA at Week 48			
< 29 IU/mL	7/7 (100.0%)	4/6 (66.7%)	11/13 (84.6%)
>= 29 IU/mL	0/7	2/6 (33.3%)	2/13 (15.4%)
- Missing -	1	0	1

The denominator for percentage is the number of subjects in the FAS with HIV/HBV coinfection and with nonmissing HBV DNA at each visit.
Source: GS-US-380-1490 Interim Week 48, Table 15.9.4.1

Change from Baseline in Log_{10} HBV DNA

In Study GS-US-380-1490, mean (SD) baseline HBV DNA levels overall were 4.89 (2.932) log_{10} IU/mL: B/F/TAF 5.08 (3.042) log_{10} IU/mL; DTG+F/TAF 4.65 (3.044) log_{10} IU/mL. Mean (SD) overall changes from baseline to Week 48 in HBV DNA levels were -3.22 (2.701) log_{10} IU/mL: B/F/TAF -3.36 (2.992) log_{10} IU/mL; DTG+F/TAF −3.06 (2.591) log_{10} IU/mL (GS-US-380-1490 Interim Week 48, Table 15.9.4.2).

ALT Normalization

Two HIV/HBV baseline-coinfected subjects had elevated ALT (≥ Grade 1 laboratory abnormality) at the baseline visit in Study GS-US-380-1490 (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.9.3). Neither subject experienced ALT normalization. Subject 02475-2013 had ALT of 67 U/L (Grade 1) at baseline and 55 U/L (Grade 1) at Week 48. Subject 00994-2530 had ALT of 118 U/L (Grade 2) at baseline, increasing to 1477 U/L (Grade 4) at Week 12 and decreasing to 54 U/L (Grade 1) at Week 48.

Serological Analyses

Of the 14 subjects who met SAP-defined criteria for HIV/HBV coinfection at baseline in Study GS-US-380-1490, 12 subjects had positive HBsAg at the baseline visit (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.9.3). Of these 12 subjects, 2 subjects (Subjects 01021-2183 and 00550-2198) experienced HBsAg loss at Week 48. Both subjects were also positive for HBsAb (ie, seroconverted) at Week 48 and had HBV DNA < 29 IU/mL at Week 48. Subject 01021-2183 had HBV DNA 354,000 IU/mL at the Day -1 visit (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.9.3).

Overall, 1 subject experienced HBeAg loss (GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.5.2). Subject 00994-2530 in the B/F/TAF group was HBeAg positive from baseline through Week 24 and HBeAg negative at Week 48. The subject was also positive for HBeAb at Week 48.

Study GS-US-380-1878

Subjects with HIV/HBV Coinfection at Baseline

At baseline, 14 (2.4%) subjects were identified as being coinfected with HIV-1 and HBV in Study GS-US 380-1878 (B/F/TAF 8 [2.8%] subjects; SBR 6 [2.1%] subjects) (GS-US-380-1878 Interim Week 48, Table 15.8.3.2). HIV/HBV coinfection at baseline was defined as subjects with (1) positive HBsAg on or prior to the randomized phase first dose date, or (2) negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 29 IU/mL) on or prior to the randomized phase first dose date.

All HIV/HBV baseline-coinfected subjects were on a TDF-containing regimen, except for Subject 03379-4615 in the SBR group who was on a regimen consisting of RTV-boosted ATV plus ABC/3TC (GS-US-380-1878 Interim Week 48, Listings 16.2.4.6 and 16.2.8.1.9.3). This was a protocol deviation as the subject was coinfected with HBV but not on a regimen including TDF at baseline. The subject had a baseline HBV DNA of > 170,000,000 IU/mL but was otherwise healthy and permitted to enter the study; however, the subject was lost to follow up and discontinued on Study Day 1 (GS-US-380-1878 Interim Week 48, Listings 16.2.1.3 and 16.2.8.1.9.3).

Overall, 3 HIV/HBV baseline-coinfected subjects were hepatitis B e antigen (HBeAg) positive at baseline (B/F/TAF 1 subject, SBR 2 subjects) (GS-US-380-1878 Interim Week 48, Listing 16.2.8.1.5.2). Another HIV/HBV baseline-coinfected subject in the B/F/TAF group had borderline HBeAg at baseline.

Proportion of Subjects with HBV DNA < 29 IU/mL at Week 48 as Defined by Missing = Excluded Data Imputation Methods

At baseline in Study GS-US-380-1878, the percentages of HIV/HBV coinfected subjects with HBV DNA < 29 IU/mL were as follows: B/F/TAF 100.0%, 8 of 8 subjects; SBR 66.7%, 4 of 6 subjects (GS-US-380-1878 Interim Week 48, Table 15.9.4.1). Two HIV/HBV baseline-coinfected subjects in the SBR group had HBV DNA ≥ 29 IU/mL: Subject 02856-4632 was on a treatment regimen of RTV-boosted ATV+FTC/TDF and had baseline HBV DNA of 8300 IU/mL; Subject 03379-4615 was on a treatment regimen of RTV-boosted ATV plus ABC+3TC.

All 12 HIV/HBV baseline-coinfected subjects with on-treatment HBV DNA assessment at Week 48 maintained HBV DNA < 29 IU/mL (B/F/TAF 8 subjects; SBR 4 subjects) (Table 28 and GS-US-380-1878 Interim Week 48, Listing 16.2.8.1.9.3). These 12 subjects also had HIV-1 RNA < 50 copies/mL at Week 48 (GS-US-380-1878 Interim Week 48, Listing 16.2.6).

One of the 2 HIV/HBV baseline-coinfected subjects in the SBR group with baseline HBV DNA ≥ 29 IU/mL (Subject 02856-4632) had a baseline HBV DNA of 8300 IU/mL, was HBeAg positive at baseline and received RTV-boosted ATV+FTC/TDF through Day 335 (GS-US-380-1878 Interim Week 48, Listings 16.2.1.3, 16.2.8.1.5.2, and 16.2.8.1.9.3). Two days later (Day 337), when the subject was off treatment, Week 48 serology assessments showed, positive HBeAg and HBV DNA > 170,000,000 IU/mL; HIV RNA was 16,800 copies/mL (GS-US-380-1878 Interim Week 48, Listings 16.2.6, 16.2.8.1.5.2, and 16.2.8.1.9.3). The other subject in the SBR group with baseline HBV DNA ≥ 29 IU/mL (Subject 03379-4615) discontinued on Study Day 1.

Table 28. GS-US-380-1878: Proportion of Subjects with HBV DNA < 29 IU/mL at Baseline and On-treatment HBV DNA < 29 IU/mL at Week 48: Missing = Excluded, Subjects with HIV/HBV Coinfection at Baseline (Full Analysis Set)

	B/F/TAF (N = 8)	SBR (N = 6)
HBV DNA at Baseline		
< 29 IU/mL	8/8 (100.0%)	4/6 (66.7%)
≥ 29 IU/mL	0/8	2/6 (33.3%)
Missing	0	0
HBV DNA at Week 48		
< 29 IU/mL	8/8 (100.0%)	4/4 (100.0%)
≥ 29 IU/mL	0/8	0/4
Missing	0	2

The denominator for percentage is the number of subjects in the Full Analysis Set with HIV/HBV baseline coinfection and with nonmissing HBV DNA at each visit.
Source: GS-US-380-1878 Interim Week 48, Table 15.9.4.1

ALT Normalization

In Study GS-US-380-1878, ALT normalization was not assessed, as no HIV/HBV baseline-coinfected subject had elevated ALT (≥ Grade 1 laboratory abnormality) at the baseline visit (GS-US-380-1878 Interim Week 48, Listing 16.2.8.1.9.3).

Serological Analyses

In Study GS-US-380-1878, all HIV/HBV baseline-coinfected subjects were HBsAg positive at baseline. No subject experienced HBsAg loss at Week 48 (GS-US-380-1878 Interim Week 48, Listing 16.2.8.1.9.3).

As described above, three HIV/HBV baseline-coinfected subjects were HBeAg positive at baseline and another subject had a borderline baseline HBeAg result (GS-US-380-1878 Interim Week 48, Listing 16.2.8.1.5.2).

HBeAg loss was experienced by 1 of the subjects in the B/F/TAF group (Subject 03946-4105) who was HBeAg positive at baseline, with no available hepatitis B e antibody (HBeAb) assessment. The subject was HBeAg and HBeAb negative at Week 48 and had HBV DNA < 20 IU/mL (GS-US-380-1878 Interim Week 48, Listings 16.2.8.1.5.2 and 16.2.8.1.9.3). One subject in the SBR group who was HBeAg positive at baseline (Subject 02856-4632) remained HBeAg positive at Week 48 and another subject in the SBR group (Subject 03379-4615) who was HBeAg positive at baseline discontinued on Study Day 1. One subject in the B/F/TAF group (Subject 06259-4069) had borderline HBeAg at baseline, with no available HBeAb assessment. The subject was HBeAg and HBeAb negative at Week 48 and had undetectable HBV DNA.

3.3.3.2. Study GS-US-292-1249

Study GS-US-292-1249 is a Phase 3b study to assess the safety, efficacy, and tolerability of GEN in HIV/HBV-coinfected adult subjects who were either HIV/HBV treatment naive (Cohort 1) or HIV suppressed (with or without HBV suppression; Cohort 2). Subjects received GEN once daily with food for 48 weeks. GEN contains FTC and TAF, which are also components of B/F/TAF and have activity against HBV. Therefore, Study GS-US-292-1249 provides supportive data on the efficacy of FTC and TAF-containing regimens in patients coinfected with HIV and HBV.

Because only 3 HIV/HBV-coinfected ART-naive subjects (Cohort 1) were treated in Study GS-US-292-1249, data for these subjects are not summarized; however, these data are presented in the CSR.

HIV and HBV resistance analyses for Study GS-US-292-1249 are presented in m2.7.2, Section 4.2.2.

In HIV/HBV-coinfected adults who were HIV-suppressed (Cohort 2, N = 72 FAS), efficacy results were as follows:

- High virologic success (HIV-1 RNA < 50 copies/mL using the FDA-defined snapshot algorithm) was maintained at Week 48 using the FAS: 91.7%.

- There were no clinically relevant differences in virologic success at Week 48 (FDA-defined snapshot algorithm, HIV-1 RNA < 50 copies/mL) between age subgroups (< and ≥ 50 years). This was the only meaningful comparison that could be made as the majority of subjects were male, white, and had an overall drug adherence ≥ 95%.

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the M = F method was 91.7%.

- No subject developed resistance to GEN (analysis of Study GS-US-292-1249).

- CD4 cell counts remained stable during treatment with GEN; mean (SD) change from baseline in CD4 cell counts at Week 48 using the FAS (observed data) was −2 (131.2) cells/μL.

- High HBV DNA suppression (< 29 IU/mL) was achieved and maintained. The percentage of subjects with HBV DNA levels < 29 IU/mL using the M = F method was 86.1% at Week 24 and increased to 91.7% at Week 48.
- The rates of seroconversion to antibody against hepatitis B surface antigen (HBsAg) (anti-HBs) in 70 subjects HBsAg positive at baseline and to antibody against hepatitis B e-antigen (anti-HBe) in 30 subjects HBeAg positive at baseline were 2.9% (2 of 70 subjects) and 3.3% (1 of 30 subjects) at Week 48, respectively. Alanine aminotransferase (ALT) normalization at Week 48 was achieved by 40% (4/10) of subjects that had ALT levels > upper limit of normal (ULN) at baseline.

In HIV/HBV-coinfected adults who were HIV-suppressed (Study GS-US-292-1249) treatment with GEN was associated with continued HIV and HBV virologic control, as evidenced by suppression at Week 48 (HIV-1 RNA < 50 copies/mL using the FDA snapshot method, 91.7%; HBV DNA < 29 IU/mL using the M = F method, 91.7%). These results demonstrate the efficacy of GEN in HIV/HBV-coinfected adults. The rates of seroconversion to anti-HBs and anti-HBe achieved in treatment-experienced subjects who were HBV antigen positive at baseline were 2.9% and 3.3%, respectively. ALT normalization was achieved by 40% of subjects with ALT greater than ULN at baseline.

A complete study description and detailed results are provided in the CSR (GS-US-292-1249 Interim Week 48).

3.3.3.3. Studies GS-US-320-0108 and GS-US-320-0110

Studies GS-US-320-0108 and GS-US-320-0110 are randomized, double-blind, active-controlled studies of TAF (Vemlidy®, VEM) in HBeAg-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) subjects with CHB monoinfection. TAF and TFV are first-line treatment options for CHB in EASL clinical practice guidelines {European Association for the Study of the Liver (EASL) 2017}. Because TAF is a component of B/F/TAF, the efficacy of TAF 25 mg in HBV monoinfection is applicable to B/F/TAF in HIV/HBV-coinfected subjects. Eligible subjects were randomized in a 2:1 ratio to receive TAF 25 mg or TDF 300 mg once daily for 96 weeks, followed by an optional open-label extension phase during which all subjects received TAF 25 mg for 48 weeks.

HBV resistance analyses for Studies GS-US-320-0108 and GS-US-320-0110 are presented in m2.7.2, Section 4.2.3.

Results from the primary efficacy analysis demonstrated that TAF was noninferior to TDF when administered for 48 weeks to HBeAg-negative and HBeAg-positive subjects with CHB. In both studies, the lower bound of the 2-sided 95% CI of the difference (TAF – TDF) in the response rate was greater than the prespecified −10% margin; therefore, the TAF group met the primary endpoint of noninferiority to the TDF group. The percentages of subjects with HBV DNA levels < 29 IU/mL at Week 48 were as follows:

- **Study GS-US-320-0108:** TAF 94.0%, TDF 92.9%; difference in proportions (baseline stratum-adjusted): 1.8%, 95% CI: −3.6% to 7.2%
- **Study GS-US-320-0110:** TAF 63.9%, TDF 66.8%; difference in proportions (baseline stratum-adjusted): −3.6%, 95% CI: −9.8% to 2.6%

The percentage of subjects with ALT normalization (ie, ALT > ULN at baseline but within the normal range at Week 48) was higher in the TAF group than in the TDF group using both the central laboratory and AASLD criteria, and the difference was statistically significant when evaluated using the AASLD criteria.

In Study GS-US-320-0108, no subjects in either treatment group experienced HBsAg loss or seroconversion by Week 48. In Study GS-US-320-0110, no significant differences between the TAF and TDF groups were observed for subjects who experienced HBsAg or HBeAg loss or seroconversion at Week 48.

At Week 48, small decreases from baseline in FibroTest score were observed in the TAF and TDF groups, with a greater decrease in the TAF group compared with the TDF group.

For both studies, rates of virologic breakthrough through Week 48 were low and similar in the TAF and TDF groups. There was no development of resistance among subjects treated with TAF or TDF.

High rates of HBV DNA suppression were achieved in all subgroups evaluated, including those based on age, sex, race, baseline HBV DNA level, treatment status, region, study drug adherence, HBV genotype, baseline ALT, and baseline FibroTest score, with no statistically significant differences between treatment groups.

In both studies, subjects with high baseline HBV DNA levels (≥ 7 $\log_{10}$ IU/mL in Study GS-US-320-0108 and ≥ 8 $\log_{10}$ IU/mL in Study GS-US-320-0110) in the TAF group achieved HBV DNA levels < 29 IU/mL at Week 48 at numerically lower rates compared with subjects in the TDF group, though these differences were not statistically significant. Further analyses did not identify a biologic rationale for the difference between the TAF and TDF groups in viral suppression in subjects with high baseline HBV DNA.

In summary, similar rates of virologic suppression (HBV DNA < 29 IU/mL at Week 48) were observed for the TAF and TDF groups in both studies. Higher rates of ALT normalization, which were significant for the AASLD criteria, were observed for the TAF group compared with the TDF group in both studies.

Complete study descriptions and results are provided in the CSRs (GS-US-320-0108 Week 48 and GS-US-320-0110 Week 48).

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

FTC and TAF Dose Selection

The 200-mg dose of FTC and the 25-mg dose of TAF are approved doses for the treatment of HIV-1 infection in adults and adolescents. Emtricitabine and TAF are also components of the DVY FDC, indicated for use in combination with other ARV agents, and of the complete regimens, Genvoya® and 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 and TAF exposures consistent with the wide range of safe and efficacious exposures observed historically with F/TAF-containing products.

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 (GS-US-141-1218), the dose-ranging proof-of-concept study (GS-US-141-1219), the Phase 2 safety and efficacy study (GS-US-141-1475; single-agent BIC 75 mg coadministered with F/TAF [200/25 mg]), and a relative bioavailability study (GS-US-141-1233), 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 drug-drug interaction 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] time-weighted average change from baseline to study Day 11 [$DAVG_{11}$] 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 protein-adjusted 95% inhibitory quotient ($paIQ_{95}$) value. Considering the C_{tau} values achieved in Study GS-US-141-1219 and an in vitro protein-adjusted 95% effective concentration ($paEC_{95}$) of 162 ng/mL for wild-type HIV-1 (Study PC-141-2032), median (range) $paIQ_{95}$ values 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.

The BIC single-agent tablet formulation was subsequently modified to incorporate FTC and TAF fumarate. The resulting B/F/TAF 75/200/25 mg FDC tablets containing 75 mg of BIC were compared to BIC 75 mg single-agent coadministered with F/TAF 200/25 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 75/200/25 mg FDC, the dose of BIC was reduced from 75 mg to 50 mg, and a new B/F/TAF 50/200/25 mg FDC tablet was developed. When B/F/TAF tablets containing 50 mg of BIC were then administered in Study GS-US-141-1233, similar exposures of BIC, FTC, and TAF were observed as compared with subjects that received coadministered BIC 75 mg single agent and F/TAF 200/25 mg tablets. As such, the B/F/TAF 50/200/25 mg tablets were used to initiate Phase 3 studies.

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

In the Phase 3 B/F/TAF 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 using the US FDA-defined snapshot algorithm), were examined (m2.7.2, Section 3.3.2). All analyses consistently revealed high percentages of subjects with HIV-1 RNA < 50 copies/mL across all groups 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.

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

In Study GS-US-141-1475, subjects had the option to receive B/F/TAF in an open-label extension phase after unblinding at the end of the double-blind randomized phase.

Of the 98 subjects treated with BIC+F/TAF or DTG+F/TAF during the randomized phase, 92 subjects entered the extension phase and received B/F/TAF. Of these, 91 subjects are currently continuing treatment; 1 subject in the BIC+F/TAF to B/F/TAF group withdrew consent and discontinued study drug and the study during the open-label extension phase (GS-US-141-1475 Interim Week 72, Section 8.1).

Virologic suppression was achieved and maintained through Week 72 for 100.0% of subjects (61 of 61 subjects) in the BIC+F/TAF to B/F/TAF group in the extension phase using the M = E data imputation method (Section 3.2.1.3). The CD4 cell count continued to increase through the extension phase. The mean (SD) increase from double-blind baseline at Week 72 was 276 (225.1) cells/μL (Section 3.2.1.5).

All Phase 2 and Phase 3 B/F/TAF studies are ongoing, and longer-term data will be presented in future CSRs.

6. REFERENCES

Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? Curr Med Res Opin 2014;30 (1):89-97.

Descovy, Gilead Sciences Ireland UC. Descovy 200 mg/10 mg film-coated tablets. Summary of Product Characteristics (SmPC). County Cork, Ireland. Revised 31 March. 2017:

DESCOVY®, Gilead Sciences Inc. DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA. Revised April. 2017:

European AIDS Clinical Society (EACS). European AIDS Clinical Society (EACS) Guidelines Version 8.2 January, 2017.

European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. [Article In Press]. J Hepatol 2017:1-29.

Gallant J, Thompson M, DeJesus E, Voskuhl G, Wei X, Zack J, et al. Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1–Infected Patients [Poster PW-030]. ASM Microbe; 2016 16-20 June; Boston, MA.

Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2016:191-210. vol 316).

Joint United Nations Programme on HIV/AIDS (UNAIDS). Fact Sheet 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf . 2016.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC) Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated 14 July. 2016.

Sax PE, DeJesus E, Crofoot G, Ward D, Benson P, Dretler R, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. The lancet. HIV 2017.

Smith F, Hammerstrom T, Soon G, Zhou S, Chen B, Mai Y, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. Drug Information Journal 2011;45:291-300.

Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. Patient preference and adherence 2012;6:427-33.

Tivicay, GlaxoSmithKline. Tivicay 10 mg/25 mg/50 mg film-coated tablets. Summary of Product Characteristics (SmPC). Poznan, Poland. Revised 28 February. 2017:

TIVICAY®, GlaxoSmithKline. TIVICAY® (dolutegravir) tablets, for oral use. US Prescribing Information. Research Triangle Park, NC. Revised March. 2017:

TRIUMEQ, GlaxoSmithKline. TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use. US Prescribing Information. Research Triangle Park, NC. Revised March. 2017a:

Triumeq, GlaxoSmithKline Pharmaceuticals S.A. Triumeq 50 mg/600 mg/300 mg film-coated tablets. Summary of Product Characteristics (SmPC). Poznan, Poland. Revised 22 February. 2017b:

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Silver Spring, MD. November, 2015.

VEMLIDY®. VEMLIDY® (tenofovir alafenamide) 25 mg film-coated tablets. Full Annexes. Gilead Sciences International Ltd., Cambridge, UK. Date of first authorisation 09 January. 2017:

7. APPENDIX

Appendix Number	Appendix Title
7.1	Tabular Summary of Studies Relevant for Efficacy
7.2	Additional Efficacy Analysis

7.1. Tabular Summary of Studies Relevant for Efficacy

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-141-1475	Evaluate the efficacy of a regimen containing BIC + F/TAF versus DTG + F/TAF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 12, 24, and Week 48.	Phase 2, randomized, double-blind, active-controlled study	Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • BIC 75 mg + F/TAF (200/25 mg) + placebo-to-match DTG 50 mg QD without regard to food Treatment Group 2: • DTG 50 mg + F/TAF (200/25 mg) + placebo-to-match BIC 75 mg QD without regard to food	48 weeks followed by optional open-label extension in which all subjects receive B/F/TAF FDC	Randomized: 98 Completed: 92	HIV-1 infected, ART-naive adult subjects.	Study completed; Interim Week 72 CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1489	Evaluate the efficacy of B/F/TAF FDC versus ABC/DTG/3TC FDC in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48	Phase 3 randomized, double-blind, multicenter, active-controlled study	Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • B/F/TAF (50/200/25 mg) FDC + placebo-to-match ABC/DTG/3TC QD, PO, without regard to food Treatment Group 2: • ABC/DTG/3TC (600/50/300 mg) FDC + placebo-to-match B/F/TAF QD, PO, without regard to food	144 weeks of randomized, double-blind treatment, followed by an optional open-label extension in which all subjects receive B/F/TAF for up to 48 weeks.	Randomized: 631 Safety Analysis Set: 629 B/F/TAF: 314 ABC/DTG/3TC: 315	HIV-infected ART-naive adults	Study ongoing; Interim Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1490	Evaluate the efficacy of B/F/TAF FDC versus DTG) + F/TAF FDC in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48	Phase 3 randomized, double-blind, multicenter, active-controlled study	Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • B/F/TAF 50/200/25 mg FDC + placebo-to-match DTG 50 mg and placebo-to-match F/TAF (200/25 mg) FDC QD, PO, without regard to food Treatment Group 2: • DTG 50 mg + F/TAF (200/25 mg) FDC+ placebo-to-match B/F/TAF FDC QD, PO, without regard to food	144 weeks of randomized, double-blind treatment, followed by optional OL extension in which all subjects receive B/F/TAF for up to 48 weeks.	Randomized: 657 Safety Analysis Set: 645 B/F/TAF: 320 DTG + F/TAF: 325	HIV-infected ART-naive adults	Study ongoing; Interim Week 48 CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1844	Evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or ABC/DTG/3TC FDC to B/F/TAF FDC versus continuing DTG and ABC/3TC as the ABC/DTG/3TC FDC in virologically suppressed HIV-1 infected adult subjects, as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48	Phase 3, randomized, double-blind, active-control, multicenter study	Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • B/F/TAF (50/200/25 mg) FDC + placebo-to-match ABC/DTG/3TC QD, PO, without regard to food Treatment Group 2: • ABC/DTG/3TC (600/50/300 mg) FDC + placebo-to-match B/F/TAF QD, PO, without regard to food	48 weeks followed by an optional open-label extension in which all subjects will receive B/F/TAF for up to 96 weeks	Randomized: 567 Safety Analysis Set: 563 B/F/TAF: 282 ABC/DTG/3TC: 281	HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 consecutive months prior to screening	Study ongoing; Interim Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1878	Evaluate the efficacy of switching to B/F/TAF FDC versus continuing on a regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC in virologically suppressed, HIV-1-infected adult subjects, as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48	Phase 3, randomized, open-label, multicenter, active-controlled study	Treatment Group 1: • Switch to B/F/TAF (50/200/25 mg) FDC tablet QD, PO, without regard to food Treatment Group 2: Stay on Baseline Regimen (SBR) • Remain on RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC QD, PO, without regard to food	48 weeks followed by an optional open-label extension in which subjects in countries where B/F/TAF is not available will receive B/F/TAF for up to 96 weeks	Randomized: 578 Safety Analysis Set: 577 B/F/TAF: 290 SBR: 287	HIV-1 infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months preceding and at the screening visit	Study ongoing; Interim Week 48 CSR

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir (GS-9883); B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated); COBI = cobicistat (Tybost®); CSR = clinical study report; DRV = darunavir; DTG = dolutegravir; FDC = fixed-dose combination; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); FTC/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); HIV-1 = human immunodeficiency virus type 1; OL = open label; PO = orally; QD = once daily; RNA = ribonucleic acid; RTV = ritonavir; TAF = tenofovir alafenamide

7.2. Additional Efficacy Analysis

Outputs from the integrated efficacy analysis of Studies GS-US-380-1489 and GS-US-380-1490 are described in the B/F/TAF Week 48 ISE SAP and are included in this submission.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

LEGACY APPENDICES

Gilead Sciences

[redacted] **20**[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY 1

TABLE OF CONTENTS 2

1. EFFICACY OF B/F/TAF 3

1.1. Study GS-US-320-0108 3
1.2. Study GS-US-320-0110 5
1.3. Tabular Listing of Clinical TAF HBV Studies 7

1. EFFICACY OF B/F/TAF

Studies included in this submission that provide support for the efficacy of B/F/TAF in HIV/HBV-coinfected adult subjects are 2 ongoing Phase 3, randomized, double-blind studies in which oral antiviral treatment-naive and treatment-experienced adults with HBeAg-negative (Study GS-US-320-0108) or HBeAg-positive (Study GS-US-320-0110) chronic hepatitis B (CHB) received at least 1 dose of TAF 25 mg (N = 866) once daily for 96 weeks. Efficacy data were evaluated through at least Week 48 of the study in an interim analysis. A summary of methods and results is provided below.

1.1. Study GS-US-320-0108

Study GS-US-320-0108	
Location:	GS-US-320-0108 Interim Week 48
Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B
Primary Objective(s):	• To compare the efficacy of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-negative CHB at Week 48 in treatment-naive and treatment-experienced subjects. The primary efficacy parameter is the proportion of subjects with plasma HBV DNA levels below 29 IU/mL. • To compare the safety and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-negative CHB at Week 48 in treatment-naive and treatment-experienced subjects
Study Design and Subject Population:	This ongoing Phase 3, randomized, double-blind, noninferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-negative CHB infection in treatment-naive and treatment-experienced subjects. Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups: • **TAF group:** TAF 25 mg once daily and matched placebo of TDF 300 mg once daily for 96 weeks (n = 285) • **TDF group:** TDF 300 mg once daily and matched placebo of TAF 25 mg once daily for 96 weeks (n = 141) Randomization was stratified by plasma HBV DNA level (< 7 $\log_{10}$ IU/mL, ≥ 7 to < 8 $\log_{10}$ IU/mL, ≥ 8 $\log_{10}$ IU/mL), and oral antiviral treatment status (treatment naive versus treatment experienced) at screening. Subjects who complete 96 weeks of double-blind treatment will continue in an open-label extension period to receive 25 mg TAF once daily for up to an additional 48 weeks.

Study GS-US-320-0108	
Summary of Results and Conclusions:	The conclusions from this Week 48 interim analysis are as follows: • The study met its primary efficacy endpoint, demonstrating that TAF 25 mg once daily was noninferior to TDF 300 mg once daily in treatment-naive and treatment-experienced, HBeAg-negative subjects with CHB. The percentages of subjects with HBV DNA levels < 29 IU/mL at Week 48 were as follows: TAF 94.0%, TDF 92.9%; difference in proportions (stratum-adjusted): 1.8%, 95% CI: −3.6% to 7.2%. • Higher rates of ALT normalization were seen with TAF than with TDF; the differences were statistically significant when evaluated by the American Association for the Study of Liver Diseases (AASLD) criteria. • Population sequence analysis results showed no HBV polymerase /reverse transcriptase (pol/RT) amino acid substitutions associated with resistance to tenofovir through 48 weeks of the study in either treatment group. • No subject in either group experienced HBsAg loss. • Small decreases from baseline in FibroTest score were seen in both groups at Week 48, with a greater decrease in the TAF group compared with the TDF group. The clinical relevance of the change in FibroTest score at Week 48 is unclear. • In 1 subject receiving TAF 25 mg and 2 subjects receiving TDF who participated in the pharmacokinetic (PK) substudy, the steady-state plasma exposures of TAF and TFV and intracellular TFV-DP concentrations were consistent with historical data and data from concurrent studies in subjects with CHB and HIV-infected subjects. • Low and comparable rates of Grade 3 or 4 adverse events (AEs), serious adverse events (SAEs), and AEs resulting in study drug discontinuations were seen for both treatment groups. • Statistically significant differences favoring TAF over TDF were seen at Week 48 for the first and second key (alpha-controlled) safety endpoints: mean percentage changes from baseline in hip bone mineral density (BMD) ($p < 0.001$) and spine BMD ($p < 0.001$). • At Week 48, TAF was associated with an improved bone and renal safety profile compared with TDF, as evidenced by the following for subjects who received TAF: — Less percentage decline in mean hip and spine BMD, alpha-controlled endpoints — Smaller median percentage changes in bone biomarkers, including the bone formation markers procollagen type 1 N-terminal propeptide (P1NP), bone-specific alkaline phosphatase (bsAP), and osteocalcin (OC) and the bone resorption marker C-type collagen sequence (CTX) — Less reduction in median estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) — No cases of proximal renal tubulopathy (including Fanconi syndrome), renal SAEs or renal AEs resulting in discontinuation of study drugs, renal failure, or acute kidney injury. Quantitative markers of proteinuria (urine protein to creatinine ratio [UPCR] and urine albumin to creatinine ratio [UACR]) and markers of proximal tubular dysfunction (urine retinol-binding protein (RBP) to creatinine ratio and urine beta-2-microglobulin to creatinine ratio) also indicated that TAF has less of an effect compared with TDF on proximal renal tubular function. • In the TDF group, decreases in the fasting lipid parameters total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were seen at Week 48. TAF was not associated with a lipid lowering effect; however, the increases in median values of total cholesterol, LDL, and triglycerides, or decreases in HDL seen in the TAF group were not considered clinically relevant.

1.2. Study GS-US-320-0110

Study GS-US-320-0110	
Location:	GS-US-320-0110 Interim Week 48
Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg Positive, Chronic Hepatitis B
Primary Objective(s):	• To compare the efficacy of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-positive CHB at Week 48 in treatment-naive and treatment-experienced subjects. The primary efficacy parameter is the proportion of subjects with plasma HBV DNA levels below 29 IU/mL. • To compare the safety and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-positive CHB at Week 48 in treatment-naive and treatment-experienced subjects
Study Design and Subject Population:	This ongoing Phase 3, randomized, double-blind, noninferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-positive CHB infection in treatment-naive and treatment-experienced subjects. Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups: • **TAF group:** TAF 25 mg tablet once daily and matched placebo of TDF 300 mg once daily for 96 weeks (n = 582) • **TDF group:** TDF 300 mg once daily and matched placebo of TAF 25 mg once daily for 96 weeks (n = 293) Randomization was stratified by plasma HBV DNA level (< 8 $\log_{10}$ IU/mL versus ≥ 8 $\log_{10}$ IU/mL) and oral antiviral treatment status (treatment naive versus treatment experienced) at screening. Subjects who complete 96 weeks of double-blind treatment may begin an open-label extension period to receive 25 mg TAF once daily for up to an additional 48 weeks (ie, Weeks 96 through 144).
Summary of Results and Conclusions:	The conclusions from this Week 48 interim analysis are as follows: • The study met its primary efficacy endpoint, demonstrating that TAF 25 mg once daily was noninferior to TDF 300 mg once daily in treatment-naive and treatment-experienced, HBeAg-positive subjects with CHB. The percentages of subjects with HBV DNA levels < 29 IU/mL at Week 48 were as follows: TAF 63.9%, TDF 66.8%; difference in proportions (stratum-adjusted): −3.6%, 95% CI: −9.8% to 2.6%. • Higher rates of ALT normalization were seen with TAF than with TDF; the differences were statistically significant when evaluated by the AASLD criteria. • Population sequence analysis results showed no HBV pol/RT amino acid substitutions associated with resistance to tenofovir through 48 weeks of the study in either treatment group. • Few subjects in either group experienced HBsAg loss or seroconversion to anti-HBs. HBsAg seroconversion was observed only in the TAF group at Week 48. • A similar percentage of subjects in each group achieved HBeAg loss at Week 48. • Small decreases from baseline in FibroTest score were seen in both groups at Week 48, with a greater decrease in the TAF group compared with the TDF group. The clinical relevance of the change in FibroTest score at Week 48 is unclear. • The steady-state plasma exposures of TAF and TFV and intracellular TFV-DP concentrations were consistent with historical data and data from concurrent studies in subjects with CHB and HIV-infected subjects.

Study GS-US-320-0110	
	• For the subjects who received TAF 25 mg, the mean systemic TFV exposure (AUC_{tau}) was 88.56% lower than for subjects who received TDF 300 mg; markedly higher TFV-DP concentrations were also observed for subjects who received TAF 25 mg versus subjects who received TDF 300 mg. • Low and comparable rates of Grade 3 or 4 AEs, SAEs, and AEs resulting in study drug discontinuations were seen for both treatment groups. • Statistically significant differences favoring TAF over TDF were seen at Week 48 for 3 of the 4 key (alpha-controlled) safety endpoints: mean percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$) at Week 48, and mean change from baseline in serum creatinine at Week 48 ($p = 0.020$). • At Week 48, TAF was associated with an improved bone and renal safety profile compared with TDF, as evidenced by the following for subjects who received TAF: — Less percentage decline in mean hip and spine BMD — Smaller median percentage changes in bone biomarkers, including the bone formation markers P1NP and OC, the bone resorption marker CTX, as well as PTH — Less increase in serum creatinine and less reduction in eGFR in subjects — No cases of proximal renal tubulopathy (including Fanconi syndrome), renal SAEs or renal AEs resulting in discontinuation of study drugs. Quantitative markers of proteinuria (UPCR and UACR) and markers of proximal tubular dysfunction (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio) also indicated that TAF has less of an effect compared with TDF on proximal renal tubular function. • In the TDF group, decreases in the fasting lipid parameters total cholesterol, LDL, HDL, and triglycerides were seen at Week 48. Changes in median values of total cholesterol, LDL, HDL, and triglycerides seen in the TAF group were not considered clinically relevant.

1.3. Tabular Listing of Clinical TAF HBV Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-320-0108	Evaluate the safety and efficacy of TAF 25 mg QD vs TDF 300 mg QD for the treatment of HBeAg-negative CHB	Phase 3, randomized, double-blind, multicenter study	Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups. • TAF 25 mg tablet QD and matched placebo of TDF 300 mg QD (A) • TDF 300 mg QD and matched placebo of TAF 25 mg QD (B) This double-blind treatment period was followed by an open-label extension period where subjects received the following treatment. • TAF 25 mg QD	96 weeks of double-blind treatment followed by 48 weeks of open-label treatment	Randomized: 426 Treated: 425 TAF: Treated: 285 TDF: Treated: 140	Treatment-naive and treatment-experienced adult HBeAg-negative CHB subjects	Study ongoing; Interim Week 48 CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-320-0110	Evaluate the safety and efficacy of TAF 25 mg QD vs TDF 300 mg QD for the treatment of HBeAg-positive CHB	Phase 3, randomized, double-blind, multicenter study	Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups. • TAF 25 mg tablet QD and matched placebo of TDF 300 mg QD (A) • TDF 300 mg QD and matched placebo of TAF 25 mg QD (B) This double-blind treatment period was followed by an open-label extension period where subjects received the following treatment. • TAF 25 mg QD	96 weeks of double-blind treatment followed by 48 weeks of open-label treatment	Randomized: 875 Treated: 873 TAF: Treated: 581 TDF: Treated: 292	Treatment-naive and treatment-experienced adult HBeAg-positive CHB subjects	Study ongoing; Interim Week 48 CSR

CHB = chronic hepatitis B; CSR = clinical study report; HBeAg = hepatitis B e antigen; QD = once daily; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate (Viread®)

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY 1
TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 3
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 5
INTRODUCTION 8
1. EXPOSURE TO THE DRUG 9
1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies 9
1.1.1. Primary Studies Supporting Clinical Safety of B/F/TAF 9
1.1.2. Other Studies Supporting Clinical Safety of B/F/TAF 13
1.1.3. Safety Assessments 14
1.1.4. Summary of Results of Individual Studies 15
1.2. Overall Extent of Exposure 15
1.3. Demographic and Other Characteristics of Study Population 17
1.4. Analysis Sets 17
1.4.1. Safety Analysis Sets 17
1.4.2. DXA Analysis Sets 18
2. ADVERSE EVENTS 19
2.1. Analysis of Adverse Events 19
2.1.1. Common Adverse Events 24
2.1.2. Deaths 33
2.1.3. Other Serious Adverse Events 34
2.1.4. Other Significant Adverse Events 36
2.1.5. Analysis of Adverse Events by Organ System or Syndrome 38
2.2. Narratives 61
3. CLINICAL LABORATORY EVALUATIONS 62
3.1. ART-Naive Adult Subjects 62
3.1.1. Studies GS-US-380-1489 and GS-US-380-1490 62
3.1.2. Study GS-US-141-1475 67
3.2. Virologically Suppressed Adult Subjects 69
3.2.1. Study GS-US-380-1844 69
3.2.2. Study GS-US-380-1878 72
4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY 75
4.1. Vital Signs and Body Weight 75
4.2. ECG Findings 75
4.2.1. ART-Naive Adult Subjects 75
4.2.2. Virologically Suppressed Adult Subjects 76
5. SAFETY IN SPECIAL GROUPS AND SITUATIONS 77
5.1. Intrinsic Factors 77
5.1.1. Age 77
5.1.2. Sex 78
5.1.3. Race 79
5.1.4. HIV-1 RNA Stratum at Baseline 80
5.1.5. CD4 Cell Count at Baseline 80
5.1.6. Renal Impairment 80
5.1.7. Hepatic Impairment 83

5.1.8. Coinfection with HIV-1 and HBV or HCV 85
5.1.9. CHB Monoinfection 90
5.2. Extrinsic Factors 93
5.2.1. Region 93
5.3. Drug Interactions 93
5.4. Use in Pregnancy and Lactation 94
5.4.1. Phase 1 Studies with Single-agent BIC or Regimens Containing BIC and F/TAF 94
5.4.2. Phase 2 and 3 B/F/TAF Studies 94
5.4.3. F/TAF 96
5.5. Overdose 97
5.6. Drug Abuse 97
5.7. Withdrawal and Rebound 98
5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability 98
6. POSTMARKETING DATA 99
7. REFERENCES 100
8. APPENDIX 103
8.1. B/F/TAF FDC: Integrated Safety Analysis 103

LIST OF IN-TEXT TABLES

Table 1. Primary Studies Supporting Clinical Safety of B/F/TAF 10
Table 2. Phase 1 Studies Supporting Clinical Safety of B/F/TAF 13
Table 3. GEN, FTC, and TAF Studies Supporting Clinical Safety of B/F/TAF 14
Table 4. GS-US-380-1489, GS-US-380-1490, GS-US-141-1475, GS-US-380-1844, GS-US-380-1878: Duration of Exposure to Randomized Study Drug (Safety Analysis Set) 16
Table 5. GS-US-380-1489 and GS-US-380-1490: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set) 20
Table 6. GS-US-141-1475: Overall Summary of Adverse Events Occurring During the Double-Blinded Phase (Safety Analysis Set) 21
Table 7. GS-US-380-1844: Overall Summary of Adverse Events (Safety Analysis Set) 22
Table 8. GS-US-380-1878: Overall Summary of Adverse Events (Safety Analysis Set) 23
Table 9. GS-US-380-1489 and GS-US-380-1490: Adverse Events Reported for at Least 5% of Subjects in Any Treatment Group (Safety Analysis Set) 25
Table 10. GS-US-380-1489 and GS-US-380-1490: Study Drug–Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set) 26
Table 11. GS-US-141-1475: Adverse Events Reported During the Double-Blinded Phase for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set) 27
Table 12. GS-US-141-1475: Study Drug–Related Adverse Events by Preferred Term (Safety Analysis Set) 29
Table 13. GS-US-380-1844: Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set) 30
Table 14. GS-US-380-1844: Study Drug-Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set) 31
Table 15. GS-US-380-1878: Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set) 32
Table 16. GS-US-380-1878: Study Drug-Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set) 33
Table 17. Phase 1 Safety Population: Discontinuations Due to Adverse Events 37

Table 18. GS-US-380-1489 and GS-US-380-1490: Changes from Baseline in Liver-Related Laboratory Parameters at Week 48 (Safety Analysis Set) 41
Table 19. GS-US-380-1844: Changes from Baseline in Liver Related Laboratory Parameters at Week 48 (Safety Analysis Set) 45
Table 20. GS-US-380-1878: Changes from Baseline in Liver Related Laboratory Parameters at Week 48 (Safety Analysis Set) 47
Table 21. GS-US-380-1489: Renal Biomarkers to Urine Creatinine Ratios at Week 48 (Safety Analysis Set) 55
Table 22. GS-US-380-1844: Renal Biomarkers at Week 48 (Safety Analysis Set) 57
Table 23. GS-US-380-1878: Renal Biomarkers to Urine Creatinine Ratios at Week 48 (Safety Analysis Set) 58
Table 24. GS-US-380-1878: Renal Biomarkers to Urine Creatinine Ratios at Week 48 by Prior Treatment Regimen (Safety Analysis Set) 59
Table 25. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Adverse Events in the Eye Disorders System Organ Class and Potential Uveitis Adverse Events (Safety Analysis Set) 60
Table 26. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Suicide Events by Suicide/Self-Injury SMQ (Safety Analysis Set) 61
Table 27. GS-US-380-1489 and GS-US-380-1490: Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set) 63
Table 28. GS-US-380-1489, GS-US-380-1490: Changes from Baseline in Fasting Metabolic Laboratory Parameters at Week 48 (Safety Analysis Set) 66
Table 29. GS-US-141-1475: Grade 3 or 4 Laboratory Abnormalities Reported During the Double-Blinded Phase in Either Treatment Group (Safety Analysis Set) 67
Table 30. GS-US-141-1475: Changes from Baseline in Fasting Metabolic Laboratory Parameters During the Double-Blinded Phase (Safety Analysis Set) 68
Table 31. GS-US-380-1844: Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set) 70
Table 32. GS-US-380-1844: Changes from Baseline in Fasting Metabolic Laboratory Parameters at Week 48 (Safety Analysis Set) 71
Table 33. GS-US-380-1878: Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set) 73
Table 34. GS-US-380-1878: Changes from Baseline in Fasting Metabolic Laboratory Parameters at Week 48 (Safety Analysis Set) 74

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

%CV	percentage coefficient of variation
3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APR	Antiviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BA	bioavailability
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated)
BIC	bictegravir (GS-9883)
BMD	bone mineral density
CD4	cluster determinant 4
CHB	chronic hepatitis B
CI	confidence interval
C_{max}	maximum observed concentration of drug
C_{min}	minimum observed concentration of drug
CPT	Child-Pugh-Turcotte
CRF	case report form
CSR	clinical study report
DDI	drug-drug interaction
ddI	didanosine
DHHS	Department of Health and Human Services
DRV	darunavir
DTG	dolutegravir
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation

F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FDC	fixed-dose combination
FTC	emtricitabine (Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
GEN	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)
GGT	gamma-glutamyltransferase
Gilead	Gilead Sciences
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
INSTI	integrase strand-transfer inhibitor
ISS	Integrated Summary of Safety
LDL	low-density lipoprotein
MAD	multiple ascending dose
MATE1	multidrug and toxin extrusion 1
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OCT2	organic cation transporter 2
PK	pharmacokinetic(s)
PSUR	periodic safety update report
PT	preferred term
Q1	first quartile
Q3	third quartile
RBC	red blood cell
RBP	retinol binding protein
RNA	ribonucleic acid
RTV	ritonavir
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir

TQT	thorough QT
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
US	United States

INTRODUCTION

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, rilpivirine, or the boosted protease inhibitor, darunavir {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}.

Virologically suppressed HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily fixed-dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {Aldir 2014, Sterrantino 2012}.

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 an 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 document is a summary of the clinical safety data that support the proposed prescribing information for the B/F/TAF FDC tablet. This document includes new data from studies conducted with single-agent BIC or the B/F/TAF FDC that have not been previously submitted as part of a marketing application in any region. Data from studies of products containing components of B/F/TAF that have been reviewed as part of previous marketing applications are also provided, including studies conducted with Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated [E/C/F/TAF]); Descovy® (DVY; emtricitabine/tenofovir alafenamide, coformulated [F/TAF]); Emtriva® (emtricitabine; [FTC]); or Vemlidy® (VEM; tenofovir alafenamide; [TAF]).

1. EXPOSURE TO THE DRUG

1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

1.1.1. Primary Studies Supporting Clinical Safety of B/F/TAF

Primary studies that support safety of the B/F/TAF (50/200/25 mg) FDC are 2 Phase 3 studies in HIV-infected, ART-naive adult subjects (Studies GS-US-380-1489 and GS-US-380-1490) and 2 Phase 3 studies in HIV-infected, virologically suppressed adult subjects (Studies GS-US-380-1844 and GS-US-380-1878). These are supported by a Phase 2 study in HIV-infected, ART-naive adult subjects (Study GS-US-141-1475). Information on study design and populations for these studies is provided in Table 1.

Table 1. Primary Studies Supporting Clinical Safety of B/F/TAF

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented	Narrative Locations
HIV-Infected, ART-Naive Adult Subjects				
GS-US-380-1489	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs ABC/DTG/3TC	B/F/TAF (N = 314) ABC/DTG/3TC (N = 315)	Week 48 efficacy, PK, and safety	m2.7.3, Section 2.1.1
GS-US-380-1490	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	B/F/TAF (N = 320) DTG+F/TAF (N = 325)	Week 48 efficacy, PK, and safety	m2.7.3, Section 2.1.2
GS-US-141-1475	Phase 2, randomized, double-blinded study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF Open-label extension phase allowed crossover to B/F/TAF from DTG+F/TAF, or continuation of BIC and F/TAF as the B/F/TAF FDC	Double-blinded phase: BIC 75 mg + F/TAF (N = 65) DTG+F/TAF (N = 33) Open-label extension phase: Continue BIC and F/TAF as the B/F/TAF FDC (N = 62) Switch to the B/F/TAF FDC from DTG+F/TAF (N = 30)	Double-blinded phase: Week 48 efficacy, PK, and safety Open-label extension phase: Week 72 efficacy and safety	m2.7.3, Section 2.1.3
HIV-Infected, Virologically Suppressed Adult Subjects				
GS-US-380-1844	Phase 3, randomized, double-blind 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 ABC/DTG/3TC FDC	Switch to B/F/TAF (N = 282) Stay on DTG and ABC/3TC as the ABC/DTG/3TC FDC (N = 281)	Week 48 efficacy, PK, and safety	m2.7.3, Section 2.2.1
GS-US-380-1878	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 Open-label extension phase allowed crossover to B/F/TAF from SBR, or continuation of B/F/TAF	Randomized phase: Switch to B/F/TAF (N = 290) Stay on baseline regimen (N = 287) Open-label extension phase: Continue B/F/TAF (N = 241) Switch to B/F/TAF from SBR (N = 213)	Randomized phase: Week 48 efficacy, PK, and safety Open-label extension phase: Safety	m2.7.3, Section 2.2.2

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

1.1.1.1. ART-Naive Adult Subjects

Safety of B/F/TAF for the treatment of HIV-1 infection in ART-naive adult patients is supported by data from 2 Phase 3, randomized, double-blind, active-controlled studies, GS-US-380-1489 and GS-US-380-1490.

Study GS-US-380-1489 uses ABC/DTG/3TC as the comparator, allowing for comparison of B/F/TAF with a guideline-recommended, INSTI-based, once-daily FDC {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Eligible subjects were ART-naive, HLA-B*5701-negative, HIV-infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL; a screening genotype showing sensitivity to FTC, tenofovir (TFV), lamivudine (3TC), and abacavir (ABC); an estimated glomerular filtration rate (eGFR) according to the Cockcroft-Gault formula ($eGFR_{CG}$) ≥ 50 mL/min (in accordance with the ABC/DTG/3TC product label {TRIUMEQ 2017a, Triumeq 2017b}); and the absence of chronic hepatitis B (CHB) infection.

Study GS-US-380-1490 uses DTG administered with the F/TAF (200/25 mg) FDC (DTG+F/TAF) as the comparator, allowing for direct and exclusive comparison between the INSTIs BIC and DTG, as both were administered with the guideline-recommended NRTI FDC of FTC and TAF {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Eligible subjects were ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL, a screening genotype showing sensitivity to FTC and TFV, and an $eGFR_{CG}$ ≥ 30 mL/min (in accordance with the DVY and DTG product labels {Descovy 2017, DESCOVY® 2017, Tivicay 2017, TIVICAY® 2017}. Subjects with CHB coinfection were permitted to enter the study, based on the demonstrated efficacy and safety of TAF for the treatment of CHB monoinfection {Vemlidy 2017, VEMLIDY® 2017}.

Data are presented for the primary analyses in Studies GS-US-380-1489 and GS-US-380-1490, which were performed when all randomized subjects had completed the Week 48 visit or had discontinued study drugs before the Week 48 visit. All data up to the Week 48 data cut date are summarized, including any data collected after the Week 48 visit.

Data from the B/F/TAF treatment groups in Studies GS-US-380-1489 and GS-US-380-1490 were pooled and compared with each of the comparator treatment groups (ie, pooled B/F/TAF vs ABC/DTG/3TC and pooled B/F/TAF vs DTG+F/TAF) for analysis of selected safety endpoints. Pooled analyses are labeled as such in this summary document, with data from individual studies presented in side-by-side comparisons or stand-alone tables, as applicable. Data from the other primary B/F/TAF studies were not pooled due to differences in study design (open label vs double blind), prior treatment regimen and duration of prior treatment, and subject populations evaluated. Pooled safety data from the B/F/TAF treatment groups in Studies GS-US-380-1489 and GS-US-380-1490 are presented alongside individual study data for the comparator treatment groups (ABC/DTG/3TC and DTG+F/TAF, respectively).

Studies GS-US-380-1489 and GS-US-380-1490 are supported by a Phase 2, randomized, double-blinded, active-controlled study, GS-US-141-1475, which evaluated the safety and efficacy of single-agent BIC 75 mg compared with DTG 50 mg, each administered with the

F/TAF (200/25 mg) FDC in ART-naive adult subjects. Eligible subjects were ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL and CD4 cell count ≥ 200 cells/μL at screening; a screening genotype showing sensitivity to FTC and TFV; an $eGFR_{CG}$ ≥ 70 mL/min; and absence of CHB and HCV coinfection.

Data are presented for the double-blinded phase of Study GS-US-141-1475, which was approximately 60 weeks at unblinding, and for the open-label extension phase, in which all continuing subjects received treatment with the B/F/TAF FDC. Among the subjects who switched from double-blinded BIC+F/TAF to open-label B/F/TAF, nearly all received at least 72 weeks of a regimen containing BIC, FTC, and TAF.

1.1.1.2. Virologically Suppressed Adult Subjects

Safety of B/F/TAF for the treatment of HIV-1 infection in virologically suppressed adult patients is supported by data from 2 Phase 3, randomized, active-controlled studies, GS-US-380-1844 and GS-US-380-1878.

The double-blind study, GS-US-380-1844, compares continuing ABC/DTG/3TC FDC with switching to B/F/TAF in subjects who were virologically suppressed on ABC/DTG/3TC or a regimen consisting of those components {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016}. Eligible subjects were HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG administered with the ABC/3TC FDC or on the ABC/DTG/3TC FDC for ≥ 3 consecutive months prior to screening; no documented resistance to FTC, TFV, DTG, ABC, or 3TC; an $eGFR_{CG}$ ≥ 50 mL/min; and the absence of CHB coinfection. Subjects were randomized to either switch to B/F/TAF or stay on a regimen of DTG, ABC, and 3TC administered as the ABC/DTG/3TC FDC.

Data are presented for the primary analyses in Study GS-US-380-1844, which were performed when all randomized subjects had completed the Week 48 visit or had discontinued study drugs before the Week 48 visit. All data up to the Week 48 data cut date are summarized, including any data collected after the Week 48 visit.

The open-label study, GS-US-380-1878, uses ART regimens consisting of boosted ATV or DRV, plus either the FTC/TDF FDC or the ABC/3TC FDC, as comparators. Boosted protease inhibitors (PIs) are components of guideline-recommended ARV regimens {European AIDS Clinical Society (EACS) 2017, Gunthard 2016, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016} and are recognized for having high barriers to viral resistance {Lefebvre 2008, Llibre 2013}. The use of boosted DRV or ATV with 2 NRTIs allows comparison of B/F/TAF with non-INSTI-containing regimens. Eligible subjects were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of ritonavir (RTV)- or cobicistat (COBI)-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 consecutive months prior to screening; no previous use of any approved or experimental INSTI; no documented or suspected resistance to FTC, TFV, ABC, or 3TC; and an $eGFR_{CG}$ ≥ 50 mL/min. Subjects with CHB coinfection were permitted to enter the study, providing they were receiving a TDF-containing regimen at screening. Subjects were randomized to either switch to B/F/TAF or to stay on baseline regimen (SBR).

Data are presented for the primary analyses in Study GS-US-380-1878, which were performed when all randomized subjects had completed the Week 48 visit or had discontinued study drugs before the Week 48 visit. All data up to the Week 48 data cut date (end of the randomized phase) are included in the analyses. Safety data from the open-label extension phase of the study, during which subjects who completed 48 weeks of randomized treatment were given the option to receive B/F/TAF, are included in data listings and summarized in text, as applicable.

1.1.2. Other Studies Supporting Clinical Safety of B/F/TAF

Other studies that support safety of the B/F/TAF FDC are Phase 1 studies of single-agent BIC or regimens containing BIC and F/TAF (Table 2). Deaths, SAEs, and discontinuations due to AEs are summarized for these Phase 1 studies.

Table 2. Phase 1 Studies Supporting Clinical Safety of B/F/TAF

Safety Population	Studies Included in Population	No. Receiving BIC or B/F/TAF
BIC Phase 1	GS-US-141-1219 (proof of concept)	16
	GS-US-141-1218 (SAD, MAD, DDI, food effect)	108
	GS-US-141-1478 (hepatic impairment)	20
	GS-US-141-1479 (renal impairment)	18
	GS-US-141-1480 (TQT)	48
	GS-US-141-1481 (ADME)	8
	GS-US-141-1485 (DDI)	90
	GS-US-141-1487 (renal function)	20
	GS-US-311-1790 (DDI)	16
BIC and F/TAF Phase 1	GS-US-141-1233 (BA/food effect)	56
	GS-US-380-1761 (DDI)	30
	GS-US-380-1991 (race/ethnicity)	50
	GS-US-380-1999 (DDI)	30
	GS-US-380-3908 (DDI)	32
	GS-US-380-3909 (DDI)	42
	GS-US-380-4270 (DDI)	14

Additional data that support safety of the B/F/TAF FDC are provided by studies that were conducted using GEN, TAF, or FTC (Table 3). These studies provide information relevant to safety of the components of B/F/TAF in subjects with renal or hepatic impairment, subjects with HIV/HBV-coinfection, or subjects with CHB monoinfection.

Table 3. GEN, FTC, and TAF Studies Supporting Clinical Safety of B/F/TAF

Safety Population	Product–Phase	Studies Included in Population
CHB Infection (HIV-negative)	FTC–Phase 1	FTCB-101
	TAF–Phase 1	GS-US-320-0101
	TAF–Phase 3	GS-US-320-0108
	TAF–Phase 3	GS-US-320-0110
Hepatic Impairment	TAF–Phase 1	GS-US-120-0114
	TAF–Phase 1	GS-US-320-1615
HIV/HBV Coinfection	GEN–Phase 3b	GS-US-292-1249
Renal Impairment	GEN–Phase 3	GS-US-292-0112
	FTC–Phase 1	FTC-107
	TAF–Phase 1	GS-US-120-0108

1.1.3. Safety Assessments

Clinical and laboratory adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1, with system organ class, high-level group term, high-level term, preferred term (PT), and lower-level term attached to the clinical databases. All AEs presented were treatment emergent and are referred to as AEs. All AEs were assessed by the investigator or qualified designee and recorded on the AE electronic case report form (eCRF). The AE entry indicated whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug or to a study procedure, the action taken with the study drug due to the AE, and the severity of the AE. The investigator was responsible for final review and confirmation of the accuracy of events, relationship, and severity, confirmed by the signature on the eCRF.

Laboratory abnormalities were not usually recorded as AEs or SAEs; however, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that required medical or surgical intervention or led to study drug interruption or discontinuation were recorded as an AE or SAE, if applicable, at the discretion of the investigator. In addition, laboratory or other abnormal assessments (eg, electrocardiogram [ECG], X-rays, or vital signs) associated with signs and/or symptoms were recorded as an AE or SAE if the assessment met the definition. If a laboratory abnormality was part of a syndrome, the syndrome or diagnosis was recorded (eg, anemia), rather than the laboratory result (eg, decreased hemoglobin).

All AEs and laboratory abnormalities were recorded according to uniform guidelines and were graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

Further details on the statistical methods, safety data definitions, and grading scales are provided in the B/F/TAF Integrated Summary of Safety (ISS) Statistical Analysis Plan (SAP), and are described briefly in this summary, when appropriate. Further details on the statistical methods for the individual safety studies are provided in the SAP for each study (GS-US-380-1489 Interim Week 48, Appendix 16.1.9, SAP; GS-US-380-1490 Interim Week 48, Appendix 16.1.9, SAP; GS-US-141-1475 Interim Week 72, Appendix 16.1.9, SAP; GS-US-380-1844 Interim Week 48, Appendix 16.1.9, SAP; and GS-US-380-1878 Interim Week 48, Appendix 16.1.9, SAP).

1.1.4. Summary of Results of Individual Studies

Study narratives, including safety data, for individual clinical pharmacology and efficacy studies are presented in m2.7.2 and m2.7.3, respectively.

1.2. Overall Extent of Exposure

A total of 1511 subjects have received at least 1 dose of B/F/TAF in the Phase 2 and 3 studies. This includes 1206 subjects in the randomized phases of the Phase 3 studies. In addition, 92 subjects received B/F/TAF in the extension phase of Study GS-US-141-1475, and 213 subjects switched to receive B/F/TAF from the comparator regimens in the extension phase of Study GS-US-380-1878. A total of 254 subjects received at least 1 dose of a regimen containing BIC and F/TAF in Phase 1 studies.

The median (Q1, Q3) duration of exposure to B/F/TAF during randomized treatment was similar across the Phase 3 B/F/TAF studies: pooled studies GS-US-380-1489 and GS-US-380-1490 (49.2 [45.6, 56.1] weeks), Study GS-US-380-1844 (49.9 [45.1, 56.3] weeks), and Study GS-US-380-1878 (46.7 [44.0, 48.0] weeks).

The median (Q1, Q3) duration of exposure to BIC+F/TAF in ART-naive adult subjects in the double-blinded portion of the Phase 2 study GS-US-141-1475 (N = 65) was 59.9 (59.1, 60.0) weeks. Among the 65 subjects who received BIC+F/TAF in the double-blinded phase (62 of whom received B/F/TAF in the open-label extension phase), median (Q1, Q3) exposure to BIC+F/TAF followed by B/F/TAF was 75.9 (74.7, 77.1) weeks. Among the 30 subjects who switched from DTG+F/TAF to B/F/TAF in the open-label extension phase, median (Q1, Q3) exposure to B/F/TAF was 16.1 (14.9, 17.7) weeks.

The disposition for subjects in the Phase 2 and 3 B/F/TAF studies is presented in m2.7.3, Section 3.1.1.

Table 4. GS-US-380-1489, GS-US-380-1490, GS-US-141-1475, GS-US-380-1844, GS-US-380-1878: Duration of Exposure to Randomized Study Drug (Safety Analysis Set)

	ART-Naive Adult Subjects					Virologically Suppressed Adult Subjects			
	GS-US-380-1489/GS-US-380-1490			GS-US-141-1475[a]		GS-US-380-1844		GS-US-380-1878[b]	
	Pooled	380-1489	380-1490						
	B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG + F/TAF (N = 325)	BIC + F/TAF (N = 65)	DTG + F/TAF (N = 33)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Exposure Duration									
Mean (SD)	49.8 (11.97)	51.6 (10.60)	49.7 (10.88)	58.0 (8.69)	57.4 (10.43)	50.7 (10.59)	50.9 (10.20)	44.9 (7.09)	44.3 (8.92)
Median	49.2	51.3	48.6	59.9	60.0	49.9	50.3	46.7	46.7
Q1, Q3	45.6, 56.1	46.3, 57.6	45.6, 55.1	59.1, 60.0	59.7, 60.1	45.1, 56.3	45.1, 56.3	44.0, 48.0	44.0, 48.0
Min, Max	0.1, 74.3	0.6, 72.6	1.4, 74.4	0.1, 63.0	2.3, 61.1	0.1, 72.9	7.6, 72.4	1.3, 56.6	0.1, 56.7
Exposure Cutoffs									
≥ 4 Weeks (28 days)	631 (99.5%)	314 (99.7%)	324 (99.7%)	64 (98.5%)	32 (97.0%)	281 (99.6%)	281 (100.0%)	289 (99.7%)	285 (99.3%)
≥ 8 Weeks (56 days)	622 (98.1%)	312 (99.0%)	321 (98.8%)	64 (98.5%)	32 (97.0%)	279 (98.9%)	280 (99.6%)	287 (99.0%)	282 (98.3%)
≥ 12 Weeks (84 days)	615 (97.0%)	312 (99.0%)	317 (97.5%)	64 (98.5%)	32 (97.0%)	278 (98.6%)	280 (99.6%)	284 (97.9%)	277 (96.5%)
≥ 24 Weeks (168 days)	605 (95.4%)	307 (97.5%)	314 (96.6%)	63 (96.9%)	32 (97.0%)	273 (96.8%)	273 (97.2%)	281 (96.9%)	273 (95.1%)
≥ 36 Weeks (252 days)	595 (93.8%)	301 (95.6%)	310 (95.4%)	63 (96.9%)	32 (97.0%)	271 (96.1%)	269 (95.7%)	276 (95.2%)	265 (92.3%)
≥ 48 Weeks (336 days)	370 (58.4%)	204 (64.8%)	180 (55.4%)	63 (96.9%)	31 (93.9%)	169 (59.9%)	172 (61.2%)	98 (33.8%)	102 (35.5%)
≥ 60 Weeks (420 days)	102 (16.1)	63 (20.0%)	49 (15.1%)	29 (44.6%)	20 (60.6%)	46 (16.3%)	47 (16.7%)	—	—
≥ 72 Weeks (504 days)	5 (0.8%)	3 (1.0%)	3 (0.9%)	—	—	5 (1.8%)	5 (1.8%)	—	—

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of randomized study drug.
For subjects who had prematurely discontinued randomized study drug, if the last dose date of randomized study drug was completely missing or only year was known, the latest of randomized study drug start and end dates or randomized clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date.
For subjects who had not prematurely discontinued randomized study drug, the data cut date was used to impute the last dose date.
a Includes only double-blinded, randomized treatment
b Includes only randomized treatment
Source: B/F/TAF Week 48 ISS, Table 4; GS-US-141-1475 Interim Week 72 CSR, Table 15.11.1.1.1; GS-US-380-1844 Interim Week 48 CSR, Table 15.11.1.1; GS-US-380-1878 Interim Week 48 CSR, Table 15.11.1.1

1.3. Demographic and Other Characteristics of Study Population

The demographics, general baseline characteristics, and baseline disease characteristics for subjects in the Phase 2 and 3 B/F/TAF studies are described in m2.7.3, Section 3.1.2.

1.4. Analysis Sets

1.4.1. Safety Analysis Sets

ART-Naive Adult Subjects

The Safety Analysis Set in the integrated analysis of the 2 pooled Phase 3 studies GS-US-380-1489 and GS-US-380-1490 included all subjects who were randomized into either study and had received at least 1 dose of study drug. All data collected up to 30 days after permanent discontinuation of study drugs are presented in the safety summaries, unless specified otherwise. Subjects were grouped according to the treatment they actually received. The Safety Analysis Set for each individual study was defined in the same manner.

In the Phase 2 study GS-US-141-1475, the Safety Analysis Set included all subjects who were randomized and had received at least 1 dose of study drug in the double-blinded phase. All data collected up to 30 days after permanent discontinuation of randomized study drugs and prior to the first dose of open-label study drug (if applicable) are presented in the safety summaries, unless specified otherwise. Subjects were grouped according to the treatment they actually received. Where appropriate, safety data are also presented for subjects who received open-label B/F/TAF treatment in the extension phase.

The number of subjects in the Safety Analysis Set for each study and treatment group is provided for the individual Phase 2 and 3 B/F/TAF studies (Table 1) and the pooled studies GS-US-380-1489 and GS-US-380-1490 (Table 4).

Safety data for subjects in Study GS-US-141-1475 who switched from DTG+F/TAF during the double-blinded phase to open-label B/F/TAF during the extension phase (N = 30) are presented in the CSR, but not summarized herein due to the short duration of exposure to B/F/TAF (approximately 16 weeks), and the availability of a much larger safety dataset from virologically suppressed adult subjects in Studies GS-US-380-1844 and GS-US-380-1878, as described in the following section.

Virologically Suppressed Adult Subjects

The Safety Analysis Set in the individual Phase 3 studies GS-US-380-1844 and GS-US-380-1878 included all subjects who were randomized and received at least 1 dose of randomized study drug. Subjects were grouped according to the treatment they actually received. In Study GS-US-380-1844, all data collected up to 30 days after permanent discontinuation of study drugs are presented in the safety summaries, unless specified otherwise. In Study GS-US-380-1878, all randomized phase safety data collected up to 30 days from the randomized phase last dose date are presented in the safety summaries, unless specified

otherwise. Where appropriate, safety data are also presented for subjects who received open-label B/F/TAF treatment in the extension phase of Study GS-US-380-1878.

The number of subjects in the Safety Analysis Set for each study and treatment group is provided in Table 1.

1.4.2. DXA Analysis Sets

Bone mineral density (BMD), as measured by dual energy x-ray absorptiometry (DXA), was assessed in ART-naive adult subjects in Study GS-US-380-1489, and in virologically suppressed adult subjects in Study GS-US-380-1844. The Hip DXA Analysis Set and Spine DXA Analysis Set included all subjects who were randomized into the study, received at least 1 dose of study drug, and had nonmissing values for baseline hip and spine BMD, respectively. Subjects were grouped according to the treatment they actually received.

The number of subjects in the DXA analysis sets for each study and treatment group is as follows:

- Study GS-US-380-1489
  - Hip DXA Analysis Set: B/F/TAF N = 300; ABC/DTG/3TC N = 297
  - Spine DXA Analysis Set: B/F/TAF N = 304; ABC/DTG/3TC N = 299
- Study GS-US-380-1844
  - Hip DXA Analysis Set: B/F/TAF N = 256; ABC/DTG/3TC N = 265
  - Spine DXA Analysis Set: B/F/TAF N = 256; ABC/DTG/3TC N = 262

2. ADVERSE EVENTS

An overall summary of AEs in the B/F/TAF development program is provided in this section, with focus on the Phase 2 and 3 studies in HIV-infected, ART-naive or virologically suppressed adult subjects. All AEs presented in this summary were treatment emergent and are referred to as AEs throughout this document. Additionally, the relationship of AEs to study drugs was investigator assigned.

Adverse event data from the B/F/TAF treatment groups in the 2 Phase 3 studies in ART-naive adult subjects (Studies GS-US-380-1489 and GS-US-380-1490) were pooled and presented alongside AE data from the comparator group from each individual study (pooled B/F/TAF vs ABC/DTG/3TC or pooled B/F/TAF vs DTG+F/TAF), unless specified otherwise. Adverse event data from the Phase 2 study in ART-naive adult subjects (Study GS-US-141-1475) and Phase 3 studies in virologically suppressed adult subjects (Studies GS-US-380-1844 and GS-US-380-1878) are presented for the individual studies.

Treatment-emergent AEs and AEs considered related to study drugs from the supportive Phase 1 studies with single-agent BIC or regimens containing BIC and F/TAF are not described in detail in this summary, as these AEs were generally consistent with those from the Phase 2 and 3 B/F/TAF studies; deaths, SAEs, and AEs leading to discontinuation are summarized for the supportive studies, where applicable. Adverse event data from studies conducted using GEN, TAF, or FTC (Table 3) are briefly summarized in Section 5 to provide further support for the safety of the components of B/F/TAF in specific patient populations.

2.1. Analysis of Adverse Events

Summaries of AEs in the 5 primary studies that support safety of B/F/TAF are provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.2; GS-US-380-1490 Interim Week 48, Section 11.2; GS-US-141-1475 Interim Week 72, Section 11.2; GS-US-380-1844 Interim Week 48, Section 11.2; and GS-US-380-1878 Interim Week 48, Section 11.2).

ART-Naive Adult Subjects

Pooled Studies GS-US-380-1489 and GS-US-380-1490

The percentages of subjects with any AE in the pooled studies GS-US-380-1489 and GS-US-380-1490 were as follows: pooled B/F/TAF 83.4%, 529 of 634 subjects; ABC/DTG/3TC 89.8%, 283 of 315 subjects; DTG+F/TAF 83.7%, 272 of 325 subjects (Table 5).

Serious adverse events were reported for a similar percentage of subjects in each treatment group (pooled B/F/TAF 9.1%, 58 subjects; ABC/DTG/3TC 7.9%, 25 subjects; DTG+F/TAF 7.1%, 23 subjects). The percentage of SAEs considered related to study drugs was low in each treatment group (pooled B/F/TAF 0.5%, 3 subjects; ABC/DTG/3TC 0.3%, 1 subject; DTG+F/TAF 0 subjects). Treatment-emergent deaths were reported as follows: pooled B/F/TAF 1 subject; ABC/DTG/3TC 0 subjects; DTG+F/TAF 2 subjects.

The percentages of subjects who had adverse events considered related to study drugs were as follows: pooled B/F/TAF 21.9%, 139 subjects; ABC/DTG/3TC 40.3%, 127 subjects; DTG+F/TAF 25.5%, 83 subjects. A similar percentage of subjects in each treatment group had any Grade 3 or 4 AEs (pooled B/F/TAF 8.8%, 56 subjects; ABC/DTG/3TC 7.6%, 24 subjects; DTG+F/TAF 7.7%, 25 subjects). The percentage of subjects with any Grade 3 or 4 AEs considered related to study drugs was low in each treatment group (pooled B/F/TAF 0.8%, 5 subjects; ABC/DTG/3TC 1.3%, 4 subjects; DTG+F/TAF 0 subjects).

Adverse events that led to discontinuation of study drugs were reported for a low percentage of subjects in each treatment group (pooled B/F/TAF 0.8%, 5 subjects; ABC/DTG/3TC 1.3%, 4 subjects; DTG+F/TAF 0.3%, 1 subject).

Stage 3 opportunistic illnesses in HIV indicative of an AIDS-defining diagnosis were reported in 11 subjects (pooled B/F/TAF 0.9%, 6 subjects; ABC/DTG/3TC 0 subjects; DTG+F/TAF 1.5%, 5 subjects). The majority of these illnesses started within approximately 12 weeks of the start of study drug dosing. Events of mycobacterium avium complex infection (onset Day 267), meningitis cryptococcal (onset Day 13), and central nervous system lymphoma (onset Day 40), all in the B/F/TAF group, were each SAEs not considered related to study drugs.

Table 5. GS-US-380-1489 and GS-US-380-1490: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Subjects Experiencing Any Treatment-Emergent Adverse Event	529 (83.4%)	283 (89.8%)	272 (83.7%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	276 (43.5%)	142 (45.1%)	132 (40.6%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	56 (8.8%)	24 (7.6%)	25 (7.7%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	139 (21.9%)	127 (40.3%)	83 (25.5%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event	29 (4.6%)	28 (8.9%)	5 (1.5%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	5 (0.8%)	4 (1.3%)	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	58 (9.1%)	25 (7.9%)	23 (7.1%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event	3 (0.5%)	1 (0.3%)	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	5 (0.8%)	4 (1.3%)	1 (0.3%)
Subjects who had Treatment-Emergent Death	1 (0.2%)	0	2 (0.6%)

Adverse events were coded using MedDRA 19.1.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Relatedness to study drug is assessed by the investigator.
Source: B/F/TAF Week 48 ISS, Table 6

Study GS-US-141-1475

During the double-blinded phase of Study GS-US-141-1475, AEs were reported as follows: BIC+F/TAF 87.7% (57 of 65 subjects), DTG+F/TAF 72.7% (24 of 33 subjects) (Table 6).

The majority of AEs were Grade 1 or Grade 2 in severity. Grade 3 AEs were reported as follows: BIC+F/TAF 6.2% (4 subjects), DTG+F/TAF no subjects. No Grade 4 AEs, pregnancies or deaths were reported.

Serious AEs were reported as follows: BIC+F/TAF 4.6% (3 subjects), DTG+F/TAF no subjects. No SAE was considered related to study drug.

The incidence of AEs considered related to study drug was as follows: BIC+F/TAF 20.0% (13 subjects) and DTG+F/TAF 21.2% (7 subjects). Nearly all study drug-related AEs were Grade 1 in severity, with Grade 3 study drug-related AEs reported as follows: BIC+F/TAF 1.5% (1 subject), DTG+F/TAF no subjects.

One subject in the BIC+F/TAF group had an AE that led to premature discontinuation of study drug (an AE of urticaria that occurred after the Week 24 visit).

A Stage 3 opportunistic illness in HIV indicative of an AIDS-defining diagnosis was reported for 1 subject in the BIC+F/TAF group (Kaposi sarcoma).

Table 6. GS-US-141-1475: Overall Summary of Adverse Events Occurring During the Double-Blinded Phase (Safety Analysis Set)

	BIC+F/TAF (N = 65)	**DTG+F/TAF (N = 33)**
Any AE	57 (87.7%)	24 (72.7%)
Any Grade 2, 3, or 4 AE	18 (27.7%)	11 (33.3%)
Any Grade 3 or 4 AE	4 (6.2%)	0
Any study drug-related AE	13 (20.0%)	7 (21.2%)
Any Grade 2, 3, or 4 study drug-related AE	3 (4.6%)	1 (3.0%)
Any Grade 3 or 4 study drug-related AE	1 (1.5%)	0
Any SAE	3 (4.6%)	0
Any study drug-related SAE	0	0
Any AE leading to premature study drug discontinuation	1 (1.5%)	0
Death	0	0

Source: GS-US-141-1475 Interim Week 72, Table 15.11.2.1.1.1

Through 72 weeks of treatment with BIC+F/TAF or B/F/TAF, the AE profile was similar to that reported in the double-blinded phase. There were no reports during the open-label extension phase of Grade 3 or 4 AEs, SAEs, deaths, or AEs leading to study drug discontinuation.

Virologically Suppressed Adult Subjects

Study GS-US-380-1844

Similar percentages of subjects in each treatment group of Study GS-US-380-1844 had any AE (B/F/TAF 79.8%, 225 of 282 subjects; ABC/DTG/3TC 80.1%, 225 of 281 subjects) (Table 7).

Serious AEs were reported for a similar percentage of subjects in each treatment group (B/F/TAF 5.3%, 15 subjects; ABC/DTG/3TC 7.8%, 22 subjects). The incidence of SAEs considered related to study drugs was low (B/F/TAF 0.4%, 1 subject; ABC/DTG/3TC 0 subjects). Two subjects in the B/F/TAF group died. Neither death was considered related to study drugs.

Adverse events considered related to study drugs were reported as follows: B/F/TAF 8.2%, 23 subjects; ABC/DTG/3TC 15.7%, 44 subjects. A similar percentage of subjects in each treatment group had any Grade 3 or Grade 4 AEs (B/F/TAF 5.7%, 16 subjects; ABC/DTG/3TC 3.6%, 10 subjects). The percentage of subjects with any Grade 3 or 4 AE considered related to study drugs was low (B/F/TAF 0.7%, 2 subjects; ABC/DTG/3TC 0 subjects).

Adverse events that led to discontinuation of study drugs were reported as follows: B/F/TAF 2.1%, 6 subjects; ABC/DTG/3TC 0.7%, 2 subjects.

No subject had any Stage 3 HIV-related opportunistic illness reported during the study.

Table 7. GS-US-380-1844: Overall Summary of Adverse Events (Safety Analysis Set)

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)
Subjects Experiencing Any Treatment-Emergent Adverse Event	225 (79.8%)	225 (80.1%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	88 (31.2%)	84 (29.9%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	16 (5.7%)	10 (3.6%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	23 (8.2%)	44 (15.7%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event	11 (3.9%)	11 (3.9%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	2 (0.7%)	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	15 (5.3%)	22 (7.8%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event	1 (0.4%)	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	6 (2.1%)	2 (0.7%)
Subjects who had Treatment-Emergent Death	2 (0.7%)	0

Adverse events were coded using MedDRA 19.1.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Source: GS-US-380-1844 Interim Week 48, Table 15.11.2.1.1

Study GS-US-380-1878

Similar percentages of subjects in each treatment group of Study GS-US-380-1878 had any AE (B/F/TAF 80.3%, 233 of 290 subjects; SBR 78.7%, 226 of 287 subjects) (Table 8).

Serious AEs were reported for a similar percentage of subjects in each treatment group (B/F/TAF 5.9%, 17 subjects; SBR 7.0%, 20 subjects). Hepatitis A was the only SAE reported for > 1 subject in either treatment group (B/F/TAF 0.7%, 2 subjects; SBR 0 subjects). The incidence of SAEs considered related to study drugs was low (B/F/TAF 0.3%, 1 subject; SBR 0 subjects). Treatment-emergent deaths were reported for 1 subject in each treatment group; neither death was considered related to study drugs.

Adverse events considered related to study drugs were reported as follows: B/F/TAF 18.6%, 54 subjects; SBR 2.1%, 6 subjects. A similar percentage of subjects in each treatment group had any Grade 3 or Grade 4 AEs (B/F/TAF 4.5%, 13 subjects; SBR 6.3%, 18 subjects). The percentage of subjects with any Grade 3 or 4 AE considered related to study drugs was low (B/F/TAF 0.7%, 2 subjects; SBR 0 subjects).

Adverse events that led to discontinuation of study drugs were reported for a low percentage of subjects in each treatment group (B/F/TAF 0.7%, 2 subjects; SBR 0.3%, 1 subject).

No subject had any Stage 3 HIV-related opportunistic illness reported during the study.

Table 8. GS-US-380-1878: Overall Summary of Adverse Events (Safety Analysis Set)

	B/F/TAF (N = 290)	**SBR (N = 287)**
Subjects Experiencing Any Treatment-Emergent Adverse Event	233 (80.3%)	226 (78.7%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	125 (43.1%)	93 (32.4%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	13 (4.5%)	18 (6.3%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	54 (18.6%)	6 (2.1%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event	15 (5.2%)	1 (0.3%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	2 (0.7%)	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	17 (5.9%)	20 (7.0%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event	1 (0.3%)	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	2 (0.7%)	1 (0.3%)
Subjects who had Treatment-Emergent Death	1 (0.3%)	1 (0.3%)

Adverse events were coded using MedDRA 19.1.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Source: GS-US-380-1878 Interim Week 48, Table 15.11.2.1.1.1

2.1.1. Common Adverse Events

2.1.1.1. ART-Naive Adult Subjects

2.1.1.1.1. Studies GS-US-380-1489 and GS-US-380-1490

Adverse events that occurred in at least 5% of subjects in any treatment group in the pooled studies GS-US-380-1489 and GS-US-380-1490 are presented in Table 9.

The most commonly reported AEs for each treatment group were as follows:

- Pooled B/F/TAF group: diarrhea (12.1%, 77 of 634 subjects), headache (12.0%, 76 subjects), and nausea (9.0%, 57 subjects)
- ABC/DTG/3TC group: nausea (22.9%, 72 of 315 subjects), headache (13.7%, 43 subjects), and diarrhea (13.0%, 41 subjects)
- DTG+F/TAF group: headache (12.3%, 40 of 325 subjects), diarrhea (12.0%, 39 subjects), and nasopharyngitis (9.5%, 31 subjects)

The overall incidence and types of common AEs were similar between the pooled B/F/TAF group and comparator groups and were consistent with those expected in the study population, with the exception of the following:

- Nausea (pooled B/F/TAF 9.0%, 57 subjects; ABC/DTG/3TC 22.9%, 72 subjects) occurred in a lower proportion of subjects in the pooled B/F/TAF group than the ABC/DTG/3TC group ($p < 0.001$; B/F/TAF Week 48 ISS, Table req8951.5.1)
- Upper respiratory tract infection (pooled B/F/TAF 5.5%, 35 subjects; ABC/DTG/3TC 10.8%, 34 subjects) occurred in a lower proportion of subjects in the pooled B/F/TAF group than the ABC/DTG/3TC group ($p = 0.005$; B/F/TAF Week 48 ISS, Table req8951.5.1)

Table 9. GS-US-380-1489 and GS-US-380-1490: Adverse Events Reported for at Least 5% of Subjects in Any Treatment Group (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	529 (83.4%)	283 (89.8%)	272 (83.7%)
Headache	76 (12.0%)	43 (13.7%)	40 (12.3%)
Nausea	57 (9.0%)	72 (22.9%)	29 (8.9%)
Diarrhoea	77 (12.1%)	41 (13.0%)	39 (12.0%)
Nasopharyngitis	45 (7.1%)	29 (9.2%)	31 (9.5%)
Upper respiratory tract infection	35 (5.5%)	34 (10.8%)	23 (7.1%)
Fatigue	38 (6.0%)	27 (8.6%)	26 (8.0%)
Insomnia	30 (4.7%)	20 (6.3%)	14 (4.3%)
Back pain	25 (3.9%)	15 (4.8%)	20 (6.2%)
Syphilis	23 (3.6%)	25 (7.9%)	12 (3.7%)
Pyrexia	24 (3.8%)	12 (3.8%)	21 (6.5%)
Arthralgia	27 (4.3%)	19 (6.0%)	9 (2.8%)
Vomiting	26 (4.1%)	17 (5.4%)	10 (3.1%)
Lymphadenopathy	24 (3.8%)	9 (2.9%)	18 (5.5%)
Bronchitis	15 (2.4%)	16 (5.1%)	13 (4.0%)
Abdominal pain	21 (3.3%)	16 (5.1%)	6 (1.8%)

Adverse events were coded using MedDRA 19.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: B/F/TAF Week 48 ISS, Table 7.2

Adverse Events by Severity

The majority of AEs in the pooled studies GS-US-380-1489 and GS-US-380-1490 were Grade 1 or 2 in severity (B/F/TAF Week 48 ISS, Table 6).

A similar percentage of subjects in each treatment group had any Grade 3 or 4 AE, as follows: B/F/TAF 8.8%, 56 of 634 subjects; ABC/DTG/3TC: 7.6%, 24 of 315 subjects; DTG+F/TAF 7.7%, 25 of 325 subjects (B/F/TAF Week 48 ISS, Table 10.1).

No individual Grade 3 or 4 AEs were reported for ≥ 1% of subjects in any treatment group (B/F/TAF Week 48 ISS, Table 10.2).

Adverse Events by Relationship to Study Drugs

Adverse events considered related to study drugs in the pooled studies GS-US-380-1489 and GS-US-380-1490 were reported as follows: pooled B/F/TAF 21.9%, 139 subjects; ABC/DTG/3TC 40.3%, 127 subjects; DTG+F/TAF 25.5%, 83 subjects (Table 10).

The differences between groups were mainly in the incidence of study drug-related gastrointestinal disorders (pooled B/F/TAF 11.0%, 70 subjects; ABC/DTG/3TC 27.0%, 85 subjects; DTG+F/TAF 14.5%, 47 subjects), primarily nausea, as described below.

The most commonly reported AEs considered related to study drugs for each treatment group were as follows:

- Pooled B/F/TAF group: diarrhea or headache (4.6%, 29 subjects each), and nausea (4.1%, 26 subjects)
- ABC/DTG/3TC group: nausea (17.5%, 55 subjects), headache (4.8%, 15 subjects), and diarrhea (4.1%, 13 subjects)
- DTG+F/TAF group: nausea (5.2%, 17 subjects), diarrhea (3.4%, 11 subjects), and headache (3.1%, 10 subjects)

Table 10. GS-US-380-1489 and GS-US-380-1490: Study Drug–Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	139 (21.9%)	127 (40.3%)	83 (25.5%)
Nausea	26 (4.1%)	55 (17.5%)	17 (5.2%)
Headache	29 (4.6%)	15 (4.8%)	10 (3.1%)
Diarrhoea	29 (4.6%)	13 (4.1%)	11 (3.4%)
Fatigue	16 (2.5%)	10 (3.2%)	7 (2.2%)
Dizziness	13 (2.1%)	9 (2.9%)	2 (0.6%)
Insomnia	11 (1.7%)	9 (2.9%)	1 (0.3%)
Abnormal dreams	9 (1.4%)	8 (2.5%)	2 (0.6%)
Abdominal distension	7 (1.1%)	5 (1.6%)	4 (1.2%)
Flatulence	6 (0.9%)	2 (0.6%)	7 (2.2%)
Vomiting	6 (0.9%)	5 (1.6%)	2 (0.6%)
Constipation	7 (1.1%)	2 (0.6%)	3 (0.9%)
Abdominal discomfort	4 (0.6%)	4 (1.3%)	3 (0.9%)
Abdominal pain	3 (0.5%)	6 (1.9%)	2 (0.6%)
Dyspepsia	4 (0.6%)	4 (1.3%)	3 (0.9%)
Somnolence	4 (0.6%)	3 (1.0%)	2 (0.6%)
Decreased appetite	3 (0.5%)	3 (1.0%)	2 (0.6%)
Sleep disorder	3 (0.5%)	5 (1.6%)	0
Anxiety	1 (0.2%)	3 (1.0%)	1 (0.3%)

Adverse events were coded using MedDRA 19.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Relatedness to study drug is assessed by the investigator.
Source: B/F/TAF Week 48 ISS, Table 11.2

2.1.1.1.2. Study GS-US-141-1475

Adverse events that occurred in at least 5% of subjects in either treatment group during the double-blinded phase of Study GS-US-141-1475 are presented in Table 11. The most commonly reported AEs by treatment group were as follows:

- BIC+F/TAF group: diarrhea (13.8%, 9 of 65 subjects); upper respiratory tract infection (10.8%, 7 subjects), headache (9.2%, 6 subjects).
- DTG+F/TAF group: diarrhea and nausea (each 12.1%, 4 of 33 subjects).

The incidence and types of common AEs were generally similar between the 2 treatment groups.

Through 72 weeks of treatment with BIC+F/TAF or B/F/TAF, the most commonly reported AEs were similar to those observed during the double-blinded phase.

Table 11. GS-US-141-1475: Adverse Events Reported During the Double-Blinded Phase for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set)

	BIC+F/TAF (N = 65)	DTG+F/TAF (N = 33)
Any AE	57 (87.7%)	24 (72.7%)
Diarrhoea	9 (13.8%)	4 (12.1%)
Nausea	5 (7.7%)	4 (12.1%)
Upper respiratory tract infection	7 (10.8%)	1 (3.0%)
Headache	6 (9.2%)	1 (3.0%)
Arthralgia	4 (6.2%)	2 (6.1%)
Chlamydial infection	4 (6.2%)	2 (6.1%)
Fatigue	4 (6.2%)	2 (6.1%)
Furuncle	3 (4.6%)	2 (6.1%)
Urethritis	3 (4.6%)	2 (6.1%)
Back pain	4 (6.2%)	0
Exposure to communicable disease	2 (3.1%)	2 (6.1%)
Vomiting	2 (3.1%)	2 (6.1%)
Anal fissure	1 (1.5%)	2 (6.1%)
Anxiety	1 (1.5%)	2 (6.1%)
Flatulence	1 (1.5%)	2 (6.1%)
Gastroenteritis	1 (1.5%)	2 (6.1%)
Rhinitis allergic	1 (1.5%)	2 (6.1%)
Chest pain	0	2 (6.1%)
Costochondritis	0	2 (6.1%)
Haemorrhoids	0	2 (6.1%)
Pain	0	2 (6.1%)
Pruritus	0	2 (6.1%)
Viral infection	0	2 (6.1%)

Adverse events were coded using MedDRA, Version 19.1
Preferred term was presented by descending order of the total frequencies
Multiple AEs were counted only once per subject for each preferred term
Source: GS-US-141-1475 Interim Week 72, Table 15.11.2.1.3.2

Adverse Events by Severity

The majority of AEs reported in Study GS-US-141-1475 were Grade 1 or Grade 2 in severity. Grade 3 AEs were reported as follows BIC+F/TAF 6.2% (4 subjects: diabetic ketoacidosis; phosphorus metabolism disorder, psychotic disorder/suicidal ideation; urticaria; 1 subject each), DTG+F/TAF no subjects. No Grade 4 AEs were reported.

No new Grade 3 or Grade 4 events were reported in the open-label phase.

Adverse Events Considered Related to Study Drug

In the double-blinded phase of Study GS-US-141-1475, similar percentages of subjects in each group had any AE considered related to treatment (BIC+F/TAF 20%, 13 subjects; DTG+F/TAF 21.2%, 7 subjects (Table 12). The most commonly reported AEs considered related to study drug by treatment group were as follows:

- BIC+F/TAF group: diarrhea (4.6%, 3 subjects), headache, vomiting, decreased appetite, proteinuria, and somnolence (each 3.1%, 2 subjects)

- DTG+F/TAF group: diarrhea (9.1%, 3 of 33 subjects) and nausea (6.1%, 2 subjects)

Nearly all study drug-related AEs were Grade 1 in severity. The only Grade 3 study drug-related AE reported (urticaria for a BIC+F/TAF subject) was also the only AE leading to premature study drug discontinuation.

The incidence of study drug-related AEs for the BIC+F/TAF to B/F/TAF group through the open-label extension phase is summarized in the CSR.

Table 12. GS-US-141-1475: Study Drug–Related Adverse Events by Preferred Term (Safety Analysis Set)

	BIC+F/TAF (N = 65)	DTG+F/TAF (N = 33)
Any study drug-related AE	13 (20.0%)	7 (21.2%)
Diarrhoea	3 (4.6%)	3 (9.1%)
Headache	2 (3.1%)	1 (3.0%)
Nausea	1 (1.5%)	2 (6.1%)
Vomiting	2 (3.1%)	1 (3.0%)
Decreased appetite	2 (3.1%)	0
Proteinuria	2 (3.1%)	0
Somnolence	2 (3.1%)	0
Abnormal dreams	1 (1.5%)	0
Dizziness	1 (1.5%)	0
Fatigue	1 (1.5%)	0
Flatulence	0	1 (3.0%)
Gastrointestinal disorder	1 (1.5%)	0
Hunger	1 (1.5%)	0
Hyperbilirubinaemia	1 (1.5%)	0
Hyperhidrosis	0	1 (3.0%)
Nightmare	1 (1.5%)	0
Urticaria	1 (1.5%)	0

Adverse events were coded using MedDRA, Version 19.1
Preferred term was presented by descending order of the total frequencies
Multiple AEs were counted only once per subject for each preferred term
Source: GS-US-141-1475 Interim Week 72, Table 15.11.2.3.2.1

2.1.1.2. Virologically Suppressed Adult Subjects

In Study GS-US-380-1844, study treatment was double-blind; in Study GS-US-380-1878, study treatment was open-label.

2.1.1.2.1. Study GS-US-380-1844

Adverse events that occurred in at least 5% of subjects in either treatment group as of the Week 48 analysis data cut date in Study GS-US-380-1844 are presented in Table 13. The most commonly reported AEs for each treatment group were as follows:

- B/F/TAF group: upper respiratory tract infection (10.3%, 29 subjects), diarrhea (8.5%, 24 subjects), and nasopharyngitis (7.1%, 20 subjects)
- ABC/DTG/3TC group: upper respiratory tract infection (9.6%, 27 subjects), nasopharyngitis (7.8%, 22 subjects), and headache (7.5%, 21 subjects)

The incidence and types of common AEs were generally similar between the 2 treatment groups and consistent with those expected in the study population.

Table 13. GS-US-380-1844: Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set)

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	225 (79.8%)	225 (80.1%)
Upper respiratory tract infection	29 (10.3%)	27 (9.6%)
Nasopharyngitis	20 (7.1%)	22 (7.8%)
Headache	19 (6.7%)	21 (7.5%)
Diarrhoea	24 (8.5%)	14 (5.0%)
Arthralgia	19 (6.7%)	10 (3.6%)
Insomnia	8 (2.8%)	14 (5.0%)

Adverse events were coded using MedDRA 19.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-380-1844 Interim Week 48, Table 15.11.2.1.2.2

Adverse Events by Severity

The majority of the AEs reported in Study GS-US-380-1844 were Grade 1 or 2 in severity.

A similar percentage of subjects in each treatment group had any Grade 3 or 4 AEs (B/F/TAF 5.7%, 16 subjects; ABC/DTG/3TC 3.6%, 10 subjects). Suicidal ideation was the only Grade 3 or 4 AE reported for > 1 subject in either treatment group (B/F/TAF 2 subjects, ABC/DTG/3TC 1 subject). All 3 events were reported as SAEs and none were considered related to study drugs. The SAEs resolved for both subjects in the B/F/TAF group while continuing study treatment; the subject in the ABC/DTG/3TC group interrupted study drugs as a result of suicidal ideation.

Adverse Events by Relationship to Study Drugs

Adverse events considered related to study drugs in Study GS-US-380-1844 were reported as follows: B/F/TAF 8.2%, 23 subjects; ABC/DTG/3TC 15.7%, 44 subjects (Table 14). The difference between groups in related AEs was mainly in the gastrointestinal disorders and psychiatric disorders system organ classes.

The most commonly reported AEs considered related to study drugs for each treatment group were as follows:

- B/F/TAF group: headache (2.5%, 7 subjects), diarrhea (0.7%, 2 subjects)
- ABC/DTG/3TC group: headache (2.8%, 8 subjects), abnormal dreams, flatulence, and nausea (each 1.8%, 5 subjects), diarrhea (1.4%, 4 subjects)

Table 14. GS-US-380-1844: Study Drug-Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	23 (8.2%)	44 (15.7%)
Headache	7 (2.5%)	8 (2.8%)
Abnormal dreams	1 (0.4%)	5 (1.8%)
Diarrhoea	2 (0.7%)	4 (1.4%)
Flatulence	0	5 (1.8%)
Nausea	0	5 (1.8%)
Fatigue	1 (0.4%)	3 (1.1%)
Insomnia	0	3 (1.1%)

Adverse events were coded using MedDRA 19.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Relatedness to study drug is assessed by the investigator.
Source: GS-US-380-1844 Interim Week 48, Table 15.11.2.3.1.2

2.1.1.2.2. Study GS-US-380-1878

Adverse events that occurred in at least 5% of subjects in either treatment group as of the Week 48 analysis data cut date in Study GS-US-380-1878 are presented in Table 15.

The most commonly reported AEs for each treatment group were as follows:

- B/F/TAF group: headache (12.1%, 35 of 290 subjects), diarrhea (8.3%, 24 subjects), and nasopharyngitis and upper respiratory tract infection (each 7.2%, 21 subjects)
- SBR group: nasopharyngitis (11.8%, 34 of 287 subjects), upper respiratory tract infection (7.7%, 22 subjects), and diarrhea (6.3%, 18 subjects)

The overall incidence and types of common AEs were similar between the 2 treatment groups and consistent with those expected in the study population, with the exception of headache, which was more common in the B/F/TAF group than the SBR group (B/F/TAF 12.1%, 35 subjects; SBR 4.2%, 12 subjects; $p < 0.001$).

All AEs of headache were Grade 1 or 2 in severity; none were serious or resulted in discontinuation of study drugs. In the first 4 weeks of treatment, the incidence of headache was as follows: B/F/TAF 6.2%, SBR 1.4%. The incidence of headache was < 3% in each treatment group within each subsequent 4-week interval through Week 48.

Table 15. GS-US-380-1878: Adverse Events Reported for at Least 5% of Subjects in Either Treatment Group (Safety Analysis Set)

	B/F/TAF (N = 290)	SBR (N = 287)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	233 (80.3%)	226 (78.7%)
Nasopharyngitis	21 (7.2%)	34 (11.8%)
Headache	35 (12.1%)	12 (4.2%)
Upper respiratory tract infection	21 (7.2%)	22 (7.7%)
Diarrhea	24 (8.3%)	18 (6.3%)
Back pain	13 (4.5%)	17 (5.9%)
Arthralgia	12 (4.1%)	15 (5.2%)

Adverse events were coded using MedDRA 19.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-380-1878 Interim Week 48, Table 15.11.2.1.2.4

Adverse Events by Severity

The majority of the AEs reported in Study GS-US-380-1878 were Grade 1 or 2 in severity.

A similar percentage of subjects in each treatment group had any Grade 3 or 4 AEs (B/F/TAF 4.5%, 13 subjects; SBR 6.3%, 18 subjects).

No individual Grade 3 or 4 AEs were reported for > 1 subject in either treatment group.

Adverse Events by Relationship to Study Drugs

Adverse events considered related to study drugs in Study GS-US-380-1878 were reported as follows: B/F/TAF 18.6%, 54 subjects; SBR 2.1%, 6 subjects (Table 16). The difference between treatment groups in related AEs was mainly in the gastrointestinal disorders (B/F/TAF 7.2%, SBR 0%) and nervous system disorders (B/F/TAF 7.6%, SBR 0%) system organ classes and likely related to the open-label switch design of the study.

The most commonly reported AEs considered related to study drugs in each treatment group were as follows:

- B/F/TAF group: headache (4.8%, 14 of 290 subjects), and flatulence and nausea (each 2.4%, 7 subjects)
- SBR group: proteinuria was the only study drug-related AE reported for > 1 subject (0.7%, 2 of 287 subjects)

Table 16. GS-US-380-1878: Study Drug-Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)

	B/F/TAF (N = 290)	SBR (N = 287)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	54 (18.6%)	6 (2.1%)
Headache	14 (4.8%)	0
Flatulence	7 (2.4%)	0
Nausea	7 (2.4%)	0
Diarrhea	6 (2.1%)	0
Constipation	5 (1.7%)	0
Abdominal distension	4 (1.4%)	0
Fatigue	4 (1.4%)	0
Insomnia	3 (1.0%)	0

Adverse events were coded using MedDRA 19.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-380-1878 Interim Week 48, Table 15.11.2.3.1.2

2.1.2. Deaths

Summaries of the treatment-emergent deaths reported in the Phase 3 B/F/TAF studies are provided in the individual CSRs (GS-US-380-1490 Interim Week 48, Section 11.3; GS-US-380-1844 Interim Week 48, Section 11.4; and GS-US-380-1878 Interim Week 48, Section 11.4).

ART-Naive Adult Subjects

Pooled Studies GS-US-380-1489 and GS-US-380-1490

No treatment-emergent deaths were reported in Study GS-US-380-1489, and 3 treatment-emergent deaths were reported in GS-US-380-1490 (B/F/TAF Week 48 ISS, Listing 6). One subject in the B/F/TAF group died as a result of cardiac arrest, which occurred following appendicitis and septic shock. One subject in the DTG+F/TAF group died from unknown causes; no other AEs were reported for this subject. One subject in the DTG+F/TAF group died as the result of pulmonary embolism; he had an ongoing SAE of chronic obstructive pulmonary disease. None of the deaths were considered related to study drugs.

Study GS-US-141-1475

No treatment-emergent deaths were reported in Study GS-US-141-1475.

Virologically Suppressed Adult Subjects

Study GS-US-380-1844

Two treatment-emergent deaths were reported in the B/F/TAF group in Study GS-US-380-1844. One subject died due to sudden cardiac death as a result of hypertensive and atherosclerotic cardiovascular disease, and another subject died due to unknown causes. Neither death was considered related to study drugs.

Study GS-US-380-1878

Two treatment-emergent deaths were reported in Study GS-US-380-1878 (B/F/TAF 1 subject; SBR 1 subject). One subject in the B/F/TAF group died as a result of complications from lung cancer with metastasis to the brain. One subject in the SBR group died as a result of a blunt force trauma to the head. Neither death was considered related to study drugs.

No treament-emergent deaths were reported in the extension phase of Study GS-US-380-1878.

2.1.2.1. Phase 1 Safety Population

No treatment-emergent deaths were reported in Phase 1 studies with single-agent BIC or regimens containing BIC and F/TAF.

2.1.3. Other Serious Adverse Events

A summary of SAEs reported in the Phase 2 and 3 B/F/TAF studies is provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.4; GS-US-380-1490 Interim Week 48, Section 11.4; GS-US-141-1475 Interim Week 72, Section 11.4; GS-US-380-1844 Interim Week 48, Section 11.5; and GS-US-380-1878 Interim Week 48, Section 11.5).

2.1.3.1. ART-Naive Adult Subjects

2.1.3.1.1. Studies GS-US-380-1489 and GS-US-380-1490

Serious AEs were reported for a similar percentage of subjects in each treatment group of the pooled studies GS-US-380-1489 and GS-US-380-1490 (pooled B/F/TAF 9.1%, 58 subjects; ABC/DTG/3TC 7.9%, 25 subjects; DTG+F/TAF 7.1%, 23 subjects) (B/F/TAF Week 48 ISS, Table 14.1). No individual SAEs were reported for ≥ 1% of subjects in any treatment group (B/F/TAF Week 48 ISS, Table 14.2).

The incidence of SAEs considered related to study drugs was low in each treatment group (pooled B/F/TAF 0.5%, 3 subjects; ABC/DTG/3TC 0.3%, 1 subject; DTG+F/TAF 0 subjects) (B/F/TAF Week 48 ISS, Table 15). Serious AEs considered related to study drugs (B/F/TAF Week 48 ISS, Listing 2) were as follows:

- Pooled B/F/TAF group: chest pain, suicide attempt, and generalized tonic-clonic seizure (1 subject each)
- ABC/DTG/3TC group: 1 subject with gastroenteritis, steatorrhea, and pancreatitis chronic

2.1.3.1.2. Study GS-US-141-1475

Serious AEs during the double-blinded phase of Study GS-US-141-1475 were reported as follows: BIC+F/TAF 4.6% (3 subjects), DTG+F/TAF no subjects. No SAE was reported for > 1 subject. The SAEs reported were appendicitis, psychotic disorder/suicidal ideation (in the same subject), and diabetic ketoacidosis. No SAE was considered related to study drug.

No AEs or SAEs were reported in the BIC+F/TAF to B/F/TAF group during the open-label extension phase.

2.1.3.2. Virologically Suppressed Adult Subjects

2.1.3.2.1. Study GS-US-380-1844

Serious AEs were reported for a similar percentage of subjects in each treatment group of Study GS-US-380-1844 (B/F/TAF 5.3%, 15 subjects; ABC/DTG/3TC 7.8%, 22 subjects).

The following SAEs were reported for > 1 subject in either treatment group: suicidal ideation (B/F/TAF 0.7%, 2 subjects; ABC/DTG/3TC 0.4%, 1 subject) and atrial fibrillation (B/F/TAF 0 subjects; ABC/DTG/3TC 0.7%, 2 subjects).

The incidence of SAEs considered related to study drugs was low (B/F/TAF 0.4%, 1 subject; ABC/DTG/3TC 0 subjects). A study drug related SAE of cerebrovascular accident was reported for 1 subject in the B/F/TAF group (Section 2.1.5.2.2.1).

2.1.3.2.2. Study GS-US-380-1878

Serious AEs were reported for a similar percentage of subjects in each treatment group of Study GS-US-380-1878 (B/F/TAF 5.9%, 17 subjects; SBR 7.0%, 20 subjects).

Hepatitis A was the only SAE reported for > 1 subject in either treatment group (B/F/TAF 0.7%, 2 subjects; SBR 0 subjects).

The incidence of SAEs considered related to study drugs was low (B/F/TAF 0.3%, 1 subject; SBR 0 subjects). One subject in the B/F/TAF group had a study drug-related SAE of schizophrenia, which also resulted in discontinuation of study drugs.

During open-label treatment with B/F/TAF in the extension phase, SAEs were reported in 4 additional subjects (GS-US-380-1878, Interim Week 48, Listing 16.2.7.7) as follows:

- Continue B/F/TAF: appendicitis (1 subject) and bronchitis (1 subject)
- Switch to B/F/TAF: pelvic hematoma (1 subject) and lower limb fracture (1 subject)

None of the SAEs that occurred during the extension phase were considered related to B/F/TAF, and none led to discontinuation of B/F/TAF.

2.1.3.3. Phase 1 Safety Population

No SAEs were reported in Phase 1 studies with single-agent BIC or regimens containing BIC and F/TAF.

2.1.4. Other Significant Adverse Events

A summary of the AEs that led to discontinuation of study drugs in the Phase 2 and 3 B/F/TAF studies is provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.5; GS-US-380-1490 Interim Week 48, Section 11.5; GS-US-141-1475 Interim Week 72, Section 11.5; GS-US-380-1844 Interim Week 48, Section 11.6; and GS-US-380-1878 Interim Week 48, Section 11.6).

2.1.4.1. ART-Naive Adult Subjects

2.1.4.1.1. Studies GS-US-380-1489 and GS-US-380-1490

Adverse events that led to discontinuation of study drugs were reported for a low percentage of subjects in each treatment group of the pooled studies GS-US-380-1489 and GS-US-380-1490 (pooled B/F/TAF 0.8%, 5 subjects; ABC/DTG/3TC 1.3%, 4 subjects; DTG+F/TAF 0.3%, 1 subject) (B/F/TAF Week 48 ISS, Table 16). The majority of AEs leading to discontinuation of study drugs were nonserious, and none were reported for > 1 subject in any treatment group (B/F/TAF Week 48 ISS, Listing 3).

Overall, 7 subjects had AEs leading to discontinuation of study drugs that were considered related to study drugs, as follows:

- Pooled B/F/TAF 3 subjects: chest pain, 1 subject; abdominal distension, 1 subject; and sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia, 1 subject
- ABC/DTG/3TC 4 subjects: nausea and rash generalized, 1 subject; thrombocytopenia, 1 subject; pancreatitis chronic and steatorrhea, 1 subject; and depression, 1 subject
- DTG+F/TAF 0 subjects

2.1.4.1.2. Study GS-US-141-1475

The only AE leading to premature discontinuation of study drug during the double-blinded phase of Study GS-US-141-1475 was Grade 3 urticaria for a subject in the BIC+F/TAF group who had a history of asthma, eczema, idiopathic urticaria, and peanut and shellfish allergies. This event was nonserious and considered related to study drug based on a temporal relationship.

No subjects discontinued study drug due to AEs in the BIC+F/TAF to B/F/TAF group during the open-label extension phase.

2.1.4.2. Virologically Suppressed Adult Subjects

2.1.4.2.1. Study GS-US-380-1844

Adverse events that led to discontinuation of study drugs in Study GS-US-380-1844 were reported as follows: B/F/TAF 2.1%, 6 subjects; ABC/DTG/3TC 0.7%, 2 subjects. The majority of AEs leading to discontinuation of study drugs were nonserious. Headache was the only AE leading to discontinuation of study drugs reported for > 1 subject in either treatment group (B/F/TAF 2 subjects, ABC/DTG/3TC 1 subject); all were Grade 1 or 2 with onset within the first 2 months of treatment.

All AEs leading to discontinuation of study drugs were considered related to study drugs except suicidal ideation (B/F/TAF), and were reported as follows:

- B/F/TAF group: vomiting (0.4%, 1 subject) that resulted in discontinuation after 1 dose, headache (0.7%, 2 subjects), cerebrovascular accident (0.4%, 1 subject), and abnormal dreams (0.4%, 1 subject)

- ABC/DTG/3TC group: headache (0.4%, 1 subject) and pruritus (0.4%, 1 subject)

All study drug-related AEs resulting in discontinuation of study drugs were Grade 1 or 2, with the exception of the Grade 4 SAE of cerebrovascular accident in the B/F/TAF group (Section 2.1.5.2.2.1).

2.1.4.2.2. Study GS-US-380-1878

During the randomized phase in Study GS-US-380-1878, AEs that led to discontinuation of study drugs were reported for a low percentage of subjects in each treatment group (B/F/TAF 0.7%, 2 subjects; SBR 0.3%, 1 subject). In the B/F/TAF group, 1 subject discontinued study drugs due to a Grade 2 AE of rash, and 1 subject discontinued study drugs due to a Grade 3 SAE of schizophrenia; the schizophrenia SAE was considered related to study drug. In the SBR group, the subject discontinued study drugs due to a Grade 3 SAE of acetabulum fracture and a Grade 3 AE of acute kidney injury.

During the extension phase, 1 subject receiving B/F/TAF (who switched from the SBR group) discontinued study drugs due to AEs of vomiting and diarrhea, which were considered related to study drugs.

2.1.4.3. Phase 1 Safety Population

Adverse events leading to discontinuation of study drugs were reported in 6 subjects from the Phase 1 studies with single-agent BIC or regimens containing BIC and F/TAF (Table 17).

Table 17. Phase 1 Safety Population: Discontinuations Due to Adverse Events

Study No.	No. of Subjects Who Discontinued Due to an AE	AEs Leading to Discontinuation (No. of Subjects)	Associated Treatment and Relationship
GS-US-380-1991	1	Nausea, vomiting (1)	B/F/TAF, related
GS-US-380-3908	1	Nephrolithiasis (1)	B/F/TAF, not related
GS-US-380-3909	1	Urticaria (1)	B/F/TAF, related
GS-US-141-1218	1	Hepatitis (1)	Placebo, related
GS-US-141-1485	2	Vomiting (1); Drug eruption (1)	BIC, related; BIC, related

Source: GS-US-380-1991 Final CSR, Section 11.5; GS-US-380-3908 Final CSR, Section 11.5; GS-US-380-3909 Final CSR, Section 11.2.3 and Section 11.5; GS-US-141-1218 Final CSR, Section 11.5; GS-US-141-1485 Final CSR, Section 11.5

2.1.5. Analysis of Adverse Events by Organ System or Syndrome

A summary of safety outcomes for specific organ systems in the 5 studies that comprise the Phase 2 and 3 B/F/TAF safety population are provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.2.4; GS-US-380-1490 Interim Week 48, Section 11.2.4; GS-US-141-1475 Interim Week 72, Section 11.2.4; GS-US-380-1844 Interim Week 48, Section 11.2.4; and GS-US-380-1878 Interim Week 48, Section 11.2.4).

Hepatic safety, cardiovascular and cerebrovascular events, bone safety, and renal safety are described in the sections that follow.

In nonclinical studies with BIC, the only notable adverse finding was partially reversible microscopic hepatobiliary toxicity in monkeys following 39 weeks of dosing at 1000 mg/kg/day, corresponding to BIC AUC plasma values that were 16-fold higher than clinical BIC AUC plasma values when administered as B/F/TAF (50/200/25 mg). Reversible alanine aminotransferase (ALT) elevations at 1000 mg/kg/day were not clearly associated with the hepatobiliary changes. The no observed effect level (NOEL) was 200 mg/kg/day, corresponding to BIC AUC plasma values that were at least 7.0-fold higher than clinical BIC AUC observed in the Phase 3 studies. Hepatic safety was assessed in the Phase 3 studies through analyses of clinical laboratory results and a Standardised MedDRA Query (SMQ)-based analysis of non-infectious and non-congenital hepatic AEs.

HIV-infected subjects have an increased risk of cardiovascular events {Freiberg 2013, Lichtenstein 2010}. In addition, several epidemiological studies have demonstrated an increased risk of cardiovascular and cerebrovascular events in HIV-infected subjects treated with regimens containing ABC {Choi 2011, Rasmussen 2011}. Therefore, these events were assessed in Phase 3 studies of B/F/TAF.

Regimens containing TAF or ABC have demonstrated a preferential bone and renal safety profile relative to TDF-containing products; however, few comparative data are available for non-TDF-containing NRTI backbones. Serum creatinine and $eGFR_{CG}$ were assessed in the Phase 2 and 3 B/F/TAF studies to compare the known in vitro inhibitory effects of BIC and DTG on the renal transporters, organic cation transporter 2 (OCT2) and multidrug and toxin extrusion 1 (MATE1). Albuminuria and proximal tubular proteinuria were assessed in ART-naive subjects in Study GS-US-380-1489 and in virologically suppressed subjects in Studies GS-US-380-1878 and GS-US-380-1844, and BMD was assessed in ART-naive subjects in Study GS-US-380-1489 and in virologically suppressed subjects in Study GS-US-380-1844 to evaluate the effects of different N(t)RTI backbones.

Analyses of eye disorders system organ class (SOC) AEs and potential uveitis AEs were performed across the 4 Phase 3 B/F/TAF studies due to findings of minimal mononuclear cell infiltration in the posterior uvea considered secondary to general debilitation in a nonclinical study of TAF in dogs.

Analyses of AEs based on the suicide/self-injury SMQ were performed across the 4 Phase 3 B/F/TAF studies.

2.1.5.1. Hepatic Safety

Preferred terms for defining hepatic AEs were from 15 relevant SMQs, which were identified as noninfectious and noncongenital hepatobiliary disorders, and are described in the SAPs for the individual studies. Liver-related laboratory abnormalities were summarized as described in the B/F/TAF Week 48 ISS SAP, Section 6.3. Hepatic safety was assessed in the individual Phase 2 and 3 B/F/TAF studies, and the analyses are described in the SAP for each study.

Safety and PK data are summarized for BIC in subjects with hepatic impairment in Section 5.1.7, and for B/F/TAF in HIV/HBV- or HIV/HCV-coinfected subjects in Section 5.1.8.

2.1.5.1.1. ART-Naive Adult Subjects

2.1.5.1.1.1. Studies GS-US-380-1489 and GS-US-380-1490

####### 2.1.5.1.1.1.1. Hepatic Adverse Events

Hepatic AEs were reported for similar percentages of subjects in each treatment group of the pooled studies GS-US-380-1489 and GS-US-380-1490 (pooled B/F/TAF 1.4%, 9 subjects; ABC/DTG/3TC 1.9%, 6 subjects; DTG+F/TAF 3.1%, 10 subjects (B/F/TAF Week 48 ISS, Table 18.1). No hepatic AE was reported for > 1% of subjects in any treatment group. All hepatic AEs were considered unrelated to study drugs with the exception of the following:

- Pooled B/F/TAF group (2 subjects): hyperbilirubinemia (1 subject); liver function test increased (1 subject). Each AE was Grade 1 and resolved with no changes to study drugs administration (B/F/TAF Week 48 ISS, Listing 5).

- DTG+F/TAF group (1 subject): ALT increased and aspartate aminotransferase (AST) increased. Both AEs were Grade 1 and resolved with no changes to study drugs administration (B/F/TAF Week 48 ISS, Listing 5).

No hepatic AE resulted in discontinuation of study drugs and only 1 hepatic AE resulted in a change in study drugs administration.

One hepatic SAE of Grade 3 international normalized ratio increased was reported for 1 subject in the ABC/DTG/3TC group (B/F/TAF Week 48 ISS, Table 18.2 and Listing 5). The event was a result of warfarin sodium taken to treat critical lower limb ischemia and resolved with no changes to study drugs administration.

One subject in the B/F/TAF group had Grade 3 acute hepatic failure and Grade 2 hepatic encephalopathy (B/F/TAF Week 48 ISS, Listing 5). The AE of acute hepatic failure was a consequence of an SAE of stress-induced overdose of acetaminophen, cocaine, and quetiapine. Both events were nonserious and considered unrelated to study drugs. Administration of study drugs was interrupted at the time of the events and resumed when the liver and renal laboratory parameters returned to normal. Both resolved without subsequent hepatic AEs or liver-related laboratory abnormalities.

2.1.5.1.1.1.2. Liver-Related Laboratory Parameters

No subject in any treatment group in the pooled studies GS-US-380-1489 and GS-US-380-1490 met Hy's Law criteria, defined as concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, with alkaline phosphatase (ALP) < 2 × ULN and no alternate etiology (B/F/TAF Week 48 ISS, Table 22).

There were no clinically relevant median changes from baseline for the liver-related laboratory parameters ALT, AST, ALP, and total bilirubin at Week 48 in any treatment group (Table 18).

Table 18. GS-US-380-1489 and GS-US-380-1490: Changes from Baseline in Liver-Related Laboratory Parameters at Week 48 (Safety Analysis Set)

Liver Related Parameter	Pooled B/F/TAF (N = 634)		ABC/DTG/3TC (N = 315)		DTG+F/TAF (N = 325)		Pooled B/F/TAF vs ABC/DTG/3TC p-value	Pooled B/F/TAF vs DTG+F/TAF p-value
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)		
ALT (U/L)								
Baseline	634	23 (16, 33)	315	24 (16, 35)	325	23 (17, 33)	0.40	0.36
Change at Week 48	578	−3 (−9, 3)	299	−3 (−11, 3)	304	−3 (−9, 2)	0.21	0.55
AST (U/L)								
Baseline	634	24 (20, 31)	315	24 (19, 31)	325	24 (21, 32)	0.71	0.79
Change at Week 48	577	−2 (−7, 2)	299	−3 (−9, 1)	304	−3 (−8, 1)	0.29	0.22
Alkaline phosphatase (U/L)								
Baseline	634	67 (56, 80)	315	67 (57, 84)	325	67 (55, 78)	0.66	0.49
Change at Week 48	579	3 (−3, 10)	299	2 (−5, 9)	304	3 (−5, 10)	0.16	0.71
Total bilirubin (mg/dL)								
Baseline	634	0.5 (0.3, 0.6)	315	0.5 (0.4, 0.6)	325	0.5 (0.3, 0.6)	0.32	0.45
Change at Week 48	578	0.0 (−0.1, 0.2)	299	0.0 (−0.2, 0.1)	304	0.0 (−0.1, 0.1)	< 0.001	0.11

P-values were from the 2-sided Wilcoxon rank sum test to compare the B/F/TAF group with the ABC/DTG/3TC or DTG+F/TAF treatment groups, as indicated.
Source: B/F/TAF Week 48 ISS, Table 21.1, Table 21.2, Table 21.4, and Table 21.5

Overall, the majority of subjects did not have a liver-related laboratory abnormality (B/F/TAF Week 48 ISS, Table 19).

Graded ALT abnormalities were reported for similar percentages of subjects in each treatment group (pooled B/F/TAF 11.3%, 71 subjects; ABC/DTG/3TC 14.0%, 44 subjects; DTG+F/TAF 12.0%, 39 subjects) (B/F/TAF Week 48 ISS, Table 19). The majority of ALT abnormalities were Grade 1 or 2. The percentages of subjects with Grade 3 and 4 ALT abnormalities were low and similar in each group (pooled B/F/TAF 1.4%, 9 subjects; ABC/DTG/3TC 1.3%, 4 subjects; DTG+F/TAF 0.9%, 3 subjects) (B/F/TAF Week 48 ISS, Table 20.1).

Graded AST abnormalities were reported for similar percentages of subjects in each treatment group (pooled B/F/TAF 13.1%, 82 subjects; ABC/DTG/3TC 15.2%, 48 subjects; DTG+F/TAF 11.1%, 36 subjects) (B/F/TAF Week 48 ISS, Table 19). The majority of AST abnormalities were Grade 1 or 2. The percentages of subjects with Grade 3 and 4 AST abnormalities were low and similar in each group (pooled B/F/TAF 1.6%, 10 subjects; ABC/DTG/3TC 1.3%, 4 subjects; DTG+F/TAF 2.5%, 8 subjects) (B/F/TAF Week 48 ISS, Table 20.1).

All but one of the subjects in the B/F/TAF group with Grade 3 or 4 ALT and/or AST abnormalities had alternative etiologies, as follows: medical history of steatosis and transaminase elevations (1 subject), transient transaminase elevations in the setting of concomitant transient Grade 3 or 4 creatine kinase elevations (4 subjects), HBV infection (2 subjects), HCV infection (2 subjects), elevated ALT/AST at baseline (4 subjects), AE of alcohol abuse (1 subject), and AE of hepatitis A (2 subjects). Generally the severity of Grade 3 and 4 ALT and AST abnormalities decreased or resolved through Week 48. The single subject without an alternative etiology in Study GS-US-380-1490 had normal ALT at baseline that increased to Grade 3 at Week 12 and normalized at Week 24 without changes to study drugs administration.

Graded total bilirubin abnormalities were reported for a higher percentage of subjects in the pooled B/F/TAF group than in the ABC/DTG/3TC or DTG+F/TAF groups (pooled B/F/TAF 11.6%, 73 subjects; ABC/DTG/3TC 4.1%, 13 subjects; DTG+F/TAF 5.8%, 19 subjects). Nearly all total bilirubin abnormalities were Grade 1 or 2 for each treatment group and the majority were generally not associated with other liver-related laboratory abnormalities (GS-US-380-1489 Interim Week 48, Listing 16.2.8.1.7 and GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.7). The percentages of Grade 3 total bilirubin abnormalities were low and similar in each group (pooled B/F/TAF 0.3%, 2 subjects; ABC/DTG/3TC 0.3%, 1 subject; DTG+F/TAF 0 subjects); no subject in any treatment group had a Grade 4 total bilirubin abnormality. One subject in the B/F/TAF group who had a Grade 3 total bilirubin abnormality had Grade 2 total bilirubin at baseline; both subjects in the B/F/TAF group with Grade 3 total bilirubin abnormalities had normal transaminases and alkaline phosphatases throughout the study. Increased indirect bilirubin accounted for the Grade 3 bilirubin elevations for both subjects in the B/F/TAF group; direct bilirubin was within normal limits for these subjects.

Few subjects had graded ALP abnormalities (pooled B/F/TAF 2.2%, 14 subjects; ABC/DTG/3TC 3.2%, 10 subjects; DTG+F/TAF 2.2%, 7 subjects). All ALP abnormalities were Grade 1 or 2, with the exception of 1 Grade 3 abnormality in a subject in the B/F/TAF group. This subject had Grade 2 ALP at baseline and had normal transaminases and total bilirubin throughout the study.

2.1.5.1.1.2. Study GS-US-141-1475

2.1.5.1.1.2.1. Hepatic Adverse Events

Hepatic adverse events in Study GS-US-141-1475 were reported in 2 subjects in the BIC+F/TAF group during the double-blinded phase of Study GS-US-141-1475. One hepatic disorder AE of Grade 2 hyperbilirubinemia was considered related to study drug. Details for these 3 subjects are as follows:

- One subject in the BIC+F/TAF group with a history of intermittent jaundice experienced a Grade 2 AE of study drug-related hyperbilirubinemia during the double-blinded phase. Both ALT and AST were normal from Week 8 onward. Total bilirubin was normal at Weeks 60 and 72, while continuing study drug; therefore, hyperbilirubinemia resolved while maintaining study drug.

- One subject in the BIC+F/TAF group experienced a Grade 2 AE of transaminases increased during the double-blinded phase. The subject had Grade 1 elevated AST levels at baseline. The event was ongoing, although levels were decreasing. The event was not considered to be related to study treatment.

- One subject in the BIC+F/TAF to B/F/TAF group experienced a Grade 1 AE of hepatic enzyme increased during the open-label phase. The event resolved and was not considered related to study treatment.

Among subjects switching from DTG+F/TAF to B/F/TAF, no hepatic disorder AEs were reported during the open-label extension phase.

2.1.5.1.1.2.2. Liver-Related Laboratory Parameters

No subject met criteria for Hy's Law in Study GS-US-141-1475, defined as concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, with ALP < 2 × ULN and no alternate etiology.

There were no clinically relevant changes from baseline within either treatment group or differences between the 2 groups in median values for albumin, ALP, ALT, AST, total bilirubin, direct bilirubin, or indirect bilirubin; median values were within reference ranges.

Grade 3 ALT and AST abnormalities were reported in 3.1% (2 subjects) and 4.7% (3 subjects), respectively, in the BIC+F/TAF group and in no subjects in the DTG+F/TAF group. No Grade 4 ALT or AST abnormalities were reported in either group. Grade 3 ALT and/or AST abnormalities were generally not associated with concurrent graded abnormalities in bilirubin or ALP and resolved while study drug continued, with the exception of 1 subject who acquired HCV infection during the study and had Grade 2 elevated total bilirubin. The incidence and severity of graded laboratory abnormalities in amylase and total bilirubin were similar between the 2 treatment groups during the double-blinded phase. AST and ALT results were either transient and improved or resolved with ongoing BIC+F/TAF study therapy or were attributed to other causes and not considered drug related.

No subject met criteria for Hy's Law during the open-label extension phase. There were no clinically relevant median changes from baseline within either group for albumin, ALP, ALT, AST, total bilirubin, direct bilirubin, or indirect bilirubin, and median values were within reference ranges.

Through 72 weeks of treatment with BIC+F/TAF or B/F/TAF, the hepatic safety profile was similar to that observed during the double-blinded phase. The incidence of Grade 3 or 4 laboratory abnormalities in albumin, ALP, ALT, amylase, AST, or total bilirubin was unchanged.

Among subjects switching from DTG+F/TAF to B/F/TAF, no subject met criteria for Hy's Law. There were no reports of Grade 3 or 4 laboratory abnormalities in albumin, ALP, ALT, amylase, AST, or total bilirubin.

2.1.5.1.2. Virologically Suppressed Adult Subjects

2.1.5.1.2.1. Study GS-US-380-1844

2.1.5.1.2.1.1. Hepatic Adverse Events

Hepatic AEs were reported for similar percentages of subjects in each treatment group in Study GS-US-380-1844 (B/F/TAF 1.8%, 5 subjects; ABC/DTG/3TC 0.4%, 1 subject). None of the hepatic AEs were reported for > 1 subject in either treatment group, and none were considered related to study drugs. None of the hepatic AEs resulted in discontinuation of study drugs.

One subject (ABC/DTG/3TC) had a hepatic SAE of Grade 3 bile duct stone.

2.1.5.1.2.1.2. Liver-Related Laboratory Parameters

No subject met Hy's Law criteria in Study GS-US-380-1844, defined as concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, with ALP < 2 × ULN and without an alternate etiology.

Small, statistically significant differences between treatment groups in median changes from baseline in ALT, AST, and total bilirubin values were observed at Week 48 (Table 19). The changes from baseline were not clinically relevant in either treatment group.

Table 19. GS-US-380-1844: Changes from Baseline in Liver Related Laboratory Parameters at Week 48 (Safety Analysis Set)

Liver Related Parameter	B/F/TAF (N = 282)		ABC/DTG/3TC (N = 281)		p-value
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	
Alkaline phosphatase (U/L)					
Baseline	282	69 (58, 84)	281	66 (54, 79)	0.083
Change at Week 48	264	2 (−4, 9)	267	2 (−4, 8)	0.32
ALT (U/L)					
Baseline	282	24 (17, 33)	281	22 (16, 30)	0.12
Change at Week 48	264	1 (−5, 8)	266	−1 (−5, 4)	0.017
AST (U/L)					
Baseline	282	22 (19, 28)	281	22 (18, 28)	0.48
Change at Week 48	264	0 (−3, 5)	265	0 (−5, 3)	0.012
Total bilirubin (mg/dL)					
Baseline	282	0.4 (0.3 0.5)	281	0.4 (0.3, 0.6)	0.62
Change at Week 48	264	0.1 (0.0, 0.2)	265	0.0 (−0.1, 0.1)	< 0.001

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-380-1844 Interim Week 48, Tables 15.11.6.2.8 to 15.11.6.2.10, and 15.11.6.2.13

Overall, the majority of subjects did not have any liver-related lab abnormalities.

Graded ALT abnormalities were reported for more subjects in the B/F/TAF group than the ABC/DTG/3TC group (B/F/TAF 18.4%, 52 subjects, ABC/DTG/3TC 9.6%, 27 subjects); the majority of graded ALT abnormalities were Grade 1 or 2 for both treatment groups. Grade 3 or 4 ALT abnormalities occurred in 6 subjects (2.1%) in the B/F/TAF group and 0 subjects in the ABC/DTG/3TC group (Table 31). All subjects who had Grade 3 or 4 ALT abnormalities had hepatic AEs or medical histories associated with the ALT elevation, which included the following: incident hepatitis C (3 subjects), acute hepatitis A (1 subject); suspected alcohol abuse (1 subject; data on file), and medical history of non-alcoholic steatohepatitis (1 subject).

Graded AST abnormalities were reported for more subjects in the B/F/TAF group than the ABC/DTG/3TC group (B/F/TAF 16.3%, 46 subjects, ABC/DTG/3TC 9.6%, 27 subjects); the majority of graded AST abnormalities were Grade 1 or 2 for both treatment groups. Grade 3 or 4 AST abnormalities occurred in 4 subjects (1.4%) in the B/F/TAF group and 1 subject (0.4%) in the ABC/DTG/3TC group (Table 31). All subjects in the B/F/TAF group who had Grade 3 or 4 AST abnormalities also had concurrent ALT abnormalities and alternative etiologies as described above (ie, hepatitis C or hepatitis A infection, suspected alcohol abuse, relevant medical history). The subject in the ABC/DTG/3TC group had Grade 3 AST elevation in the setting of concurrent transient Grade 4 creatinine kinase elevations.

Graded abnormalities in total bilirubin were reported for 21 subjects (7.4%) in the B/F/TAF group and 10 subjects (3.6%) in the ABC/DTG/3TC group; the majority of graded total bilirubin abnormalities were Grade 1 or 2 for both treatment groups. Two subjects in the B/F/TAF group

had Grade 3 total bilirubin abnormalities. One of the subjects had Grade 2 elevated bilirubin at baseline and a medical history of hyperbilirubinemia. The other subject had an isolated Grade 3 elevation that was not confirmed on repeat testing; the subject was receiving numerous treatments for various STIs (syphilis, herpes, chlamydia, gonorrhea) prior to the elevation. In both subjects, direct bilirubin was normal.

Few subjects had graded ALP abnormalities (B/F/TAF 2.5%, 7 subjects; ABC/DTG/3TC 0.7%, 2 subjects); all of the abnormalities were Grade 1 or 2.

No Grade 3 or 4 elevations in total bilirubin or ALP occurred in the subjects with Grade 3 or 4 ALT or AST elevations.

2.1.5.1.2.2. Study GS-US-380-1878

2.1.5.1.2.2.1. Hepatic Adverse Events

Hepatic AEs were reported for similar percentages of subjects in each treatment group of Study GS-US-380-1878 (B/F/TAF 1.4%, 4 subjects; SBR 3.5%, 10 subjects). The following hepatic AEs were reported for > 1 subject in either treatment group: hepatic steatosis (B/F/TAF 3 subjects, SBR 0 subjects), cholelithiasis (B/F/TAF 0 subjects, SBR 2 subjects), gamma-glutamyltransferase increased (B/F/TAF 0 subjects, SBR 2 subjects), and jaundice (B/F/TAF 0 subjects; SBR 2 subjects, both on a regimen containing ATV).

All hepatic AEs were considered unrelated to study drugs except for jaundice (SBR 1 subject on a regimen containing ATV).

One subject (SBR) had a serious hepatic event of acute hepatitis, with viral serologies confirming the etiology as acute hepatitis A. The SAE was Grade 3 and considered not related to study drugs. No hepatic disorder AE resulted in discontinuation of study drugs.

2.1.5.1.2.2.2. Liver-Related Laboratory Parameters

No subject met Hy's Law criteria in Study GS-US-380-1878, defined as concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, with ALP < 2 × ULN and no alternate etiology.

Overall, 5 subjects (B/F/TAF 0.7%, 2 subjects; SBR 1.1%, 3 subjects) had concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, with ALP < 2 × ULN. The alternate etiologies for these subjects were as follows:

- Two subjects in the B/F/TAF group had SAEs of hepatitis A.
- One subject in the SBR group had an SAE of acute hepatitis C.
- One subject in the SBR group had a medical history of liver disorder (chronic non-alcoholic liver disease) and Grade 2 ALT and Grade 1 AST values at baseline.
- One subject in the SBR group had a Grade 1 AE of acute hepatitis C (onset on study Day 9) and Grade 4 ALT and AST, and Grade 2 total bilirubin values at baseline.

Although the differences between treatment groups in median changes from baseline in ALP, ALT, AST, and total bilirubin were statistically significant at Week 48 (Table 20); the changes from baseline were not clinically relevant in either treatment group.

Table 20. GS-US-380-1878: Changes from Baseline in Liver Related Laboratory Parameters at Week 48 (Safety Analysis Set)

Liver Related Parameter	B/F/TAF (N = 290)		SBR (N = 287)		p-value
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	
Alkaline phosphatase (U/L)					
Baseline	290	81 (68, 101)	287	81 (65, 98)	0.29
Change at Week 48	268	−10 (−21, −2)	259	2 (−7, 10)	< 0.001
ALT (U/L)					
Baseline	290	22 (17, 33)	287	21 (16, 32)	0.69
Change at Week 48	268	2 (−4, 9)	259	0 (−5, 4)	< 0.001
AST (U/L)					
Baseline	290	22 (18, 27)	287	22 (18, 28)	0.65
Change at Week 48	266	1 (−3, 5)	258	0 (−4, 3)	0.003
Total bilirubin (mg/dL)					
Baseline	290	0.5 (0.4, 1.6)	287	0.6 (0.4, 1.7)	0.27
Change at Week 48	266	−0.1 (−1.2, 0.1)	259	0.0 (−0.2, 0.2)	< 0.001

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-380-1878 Interim Week 48, Tables 15.11.6.2.8 to 15.11.6.2.10, and 15.11.6.2.13

Overall the majority of subjects did not have liver-related lab abnormalities.

Graded ALT abnormalities were reported for more subjects in the B/F/TAF group than the SBR group (B/F/TAF 23.4%, 68 subjects, SBR 10.5%, 30 subjects). The majority of the ALT abnormalities were Grade 1 or 2 for both treatment groups. The incidences of Grade 3 and 4 ALT abnormalities were low and similar in each group (B/F/TAF 2.1%, 6 subjects; SBR 1.4%, 4 subjects) (Table 28). All subjects in the B/F/TAF group who had Grade 3 or 4 ALT abnormalities had alternative etiologies as follows: AEs of incident hepatitis A (2 subjects); alcohol poisoning, influenza A {Polakos 2006}, and incident hepatitis C during the study (1 subject each); and transient transaminase elevation in the setting of concomitant transient graded creatinine kinase elevations associated with exercise (1 subject).

Graded AST abnormalities were reported for similar proportions of subjects in each treatment group (B/F/TAF 14.8%, 43 subjects, SBR 10.2%, 29 subjects). The majority of the AST abnormalities were Grade 1 or 2 for both treatment groups. The incidences of Grade 3 and 4 AST abnormalities were low and similar in each group (B/F/TAF 1.7%, 5 subjects; SBR 1.4%, 4 subjects). Four of the subjects in the B/F/TAF group who had Grade 3 or 4 AST abnormalities also had concurrent Grade 3 or 4 ALT abnormalities and alternative etiologies as described

above (ie, hepatitis C or hepatitis A infection, influenza A, and transient transaminase elevation associated with exercise). The other subject had Grade 3 elevated AST associated with alcohol use (data on file).

Graded total bilirubin abnormalities were reported for fewer subjects in the B/F/TAF group than the SBR group (B/F/TAF 5.5%, 16 subjects; SBR 33.7%, 96 subjects). The majority of the total bilirubin abnormalities in the B/F/TAF group were Grade 1 or 2. Two subjects in the B/F/TAF group had Grade 4 total bilirubin associated with SAEs of hepatitis A, which are described above. Grade 3 and 4 total bilirubin abnormalities were reported for 15.4% of subjects in the SBR group (44 subjects); the majority (43 subjects) were on a regimen containing ATV. Hyperbilirubinemia is a known abnormality associated with ATV, which is reversible upon discontinuation {Reyataz 2016}.

Few subjects had graded ALP abnormalities (B/F/TAF 0.3%, 1 subject; SBR 3.5%, 10 subjects); all of the abnormalities were Grade 1 or 2.

2.1.5.1.3. Integrated Summary of Hepatic Laboratory Results of the Week 48 Analyses from the B/F/TAF Phase 3 Studies

An integrated evaluation of hepatic laboratory results across the 4 Phase 3 studies of B/F/TAF in HIV-infected adults does not indicate a potential for B/F/TAF to cause severe drug-induced liver injury, as evidenced by the following:

1) No subject treated with B/F/TAF met Hy's Law criteria.

No subject treated with B/F/TAF met Hy's Law criteria, defined as concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, with ALP < 2 × ULN and no alternate etiology {U.S. Department of Health & Human Services (DHHS) 2009}. The 2 subjects treated with B/F/TAF who had concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, with ALP < 2 × ULN (Study GS-US-380-1878) each had an SAE of hepatitis A, providing an alternate etiology for the concurrent hepatic laboratory parameter increases (Section 2.1.5.1.2.2).

2) There was no excess in the number of subjects with transaminase elevations > 3 × ULN, or greater frequency of unexplained transaminase elevations > 5 ×, > 10 ×, or > 20 × ULN in the subjects treated with B/F/TAF compared with subjects treated with comparator drugs.

Most subjects treated with B/F/TAF did not have an ALT or AST elevation. Across all 4 Phase 3 B/F/TAF studies, the proportion of subjects who had ALT or AST > 3 × ULN was generally balanced between the B/F/TAF and comparator groups. Elevations of ALT or AST to > 5 ×, > 10 ×, or > 20 × ULN were also generally balanced between the B/F/TAF and comparator groups.

Marked transaminase elevations (> 5 × ULN, ie, at least Grade 3) in subjects treated with B/F/TAF were explained by alternate etiologies for all but 1 subject, in whom the elevations returned to normal baseline levels with continued B/F/TAF treatment (Sections 2.1.5.1.1.1.2, 2.1.5.1.2.1.2, and 2.1.5.1.2.2.2).

3) Total bilirubin elevations to > 2 × ULN in subjects treated with B/F/TAF were explained by alternate etiologies.

Most subjects treated with B/F/TAF did not have an elevation in total bilirubin > 2 × ULN. All total bilirubin elevations to > 2 × ULN in subjects treated with B/F/TAF were explained by past medical history, coincident AEs, and/or concomitant medications (Sections 2.1.5.1.1.1.2, 2.1.5.1.2.1.2, and 2.1.5.1.2.2.2).

Total bilirubin elevations occurred in a higher proportion of subjects treated with B/F/TAF in Studies GS-US-380-1489 and GS-US-380-1490, and Study GS-US-380-1844 (Sections 2.1.5.1.1.1.2 and 2.1.5.1.2.1.2). Most total bilirubin elevations were Grade 1 or 2, did not progress beyond Grade 1 or 2, and resolved with continued treatment with B/F/TAF (GS-US-380-1489 Interim Week 48, Listings 16.2.8.1.2.4 and 16.2.5.1; GS-US-380-1490 Interim Week 48, Listings 16.2.8.1.2.4 and 16.2.5.1; GS-US-380-1844 Interim Week 48, Listings 16.2.8.1.2.4 and 16.2.5.1). Among subjects with any grade total bilirubin elevation, the changes were due to increases in indirect, not direct, bilirubin (GS-US-380-1489 Interim Week 48, Table reqs8897.5, 8897.6, and 8897.7; GS-US-380-1490 Interim Week 48, Table reqs8898.3, 8898.4, and 8898.5; GS-US-380-1844 Interim Week 48 Table reqs8901.9, 8901.10, and 8901.11).

4) Subjects treated with B/F/TAF who had total bilirubin elevations of any grade generally did not have concurrent elevations in transaminases.

The incidence of any total bilirubin elevation > 1 × ULN concurrent with any AST or ALT elevation > 1.25 × ULN was low and balanced between treatment groups as follows:

- Study GS-US-380-1489: B/F/TAF 1.0%, ABC/DTG/3TC 1.3%,
  (GS-US-380-1489 Interim Week 48, Table req8897.8)

- Study GS-US-380-1490: B/F/TAF 1.6%, DTG+F/TAF 1.2%
  (GS-US-380-1490 Interim Week 48, Table req8898.6)

- Study GS-US-380-1844: B/F/TAF 1.4%, ABC/DTG/3TC 0.4%
  (GS-US-380-1844 Interim Week 48, Table req8901.12)

Graded total bilirubin elevations occurring concurrently with transaminases elevations were generally explained by alternative etiologies, or were transient and the majority resolved while continuing B/F/TAF treatment (GS-US-380-1489 Interim Week 48, Listings 16.2.4.4, 16.2.4.7, 16.2.5.1, 16.2.7.1.1, 16.2.8.1.2.4, 16.2.8.1.9.1, 16.2.8.1.9.2, and 16.2.8.1.10; GS-US-380-1490 Interim Week 48, Listings 16.2.4.4, 16.2.4.6, 16.2.5.1, 16.2.7.1.1, 16.2.8.1.2.4, 16.2.8.1.9.1, 16.2.8.1.9.2, and 16.2.8.1.11; GS-US-380-1844 Interim Week 48, Listings 16.2.4.4, 16.2.4.5, 16.2.4.6, 16.2.4.7, 16.2.5.1, 16.2.7.1.1, 16.2.7.5, 16.2.8.1.2.4, 16.2.8.1.8, 16.2.8.1.9.1, 16.2.8.1.9.2, and 16.2.8.1.10). Graded total bilirubin elevations were also not associated with elevations of ALP or direct bilirubin (GS-US-380-1489 Interim Week 48, Listing 16.2.8.1.2.4; GS-US-380-1490 Interim Week 48, Listing 16.2.8.1.2.4; GS-US-380-1844 Interim Week 48, Listing 16.2.8.1.2.4).

Summary

Across the 4 Phase 3 B/F/TAF studies, most subjects treated with B/F/TAF did not have a hepatic laboratory abnormality. Among the subjects who did have a hepatic laboratory abnormality, most were Grade 1 and did not progress while continuing treatment with B/F/TAF. No subject discontinued study drugs due to a hepatic AE, and most hepatic laboratory abnormalities resolved with no changes in B/F/TAF administration. No hepatic AE was reported for > 1% of subjects in any treatment group across the 4 studies.

Grade 3 and 4 elevations in ALT and AST were balanced between treatment groups across the 4 Phase 3 B/F/TAF studies. All Grade 3 and 4 transaminase elevations in subjects treated with B/F/TAF were explained by alternate etiologies or returned to normal levels with continued treatment (Sections 2.1.5.1.1.1.2, 2.1.5.1.2.1.2, and 2.1.5.1.2.2.2). Grade 1 and 2 ALT and AST elevations were balanced between treatment groups in the 2 Phase 3 studies of B/F/TAF in treatment-naive subjects (GS-US-380-1489 Interim Week 48, Table 15.11.6.4.1; GS-US-380-1490 Interim Week 48, Table 15.11.6.4.1.1). Grade 1 ALT and AST elevations were reported in a higher proportion of virologically suppressed subjects who switched treatment to B/F/TAF than in subjects in the comparator groups in Studies GS-US-380-1844 and GS-US-380-1878 (GS-US-380-1844 Interim Week 48, Table 15.11.6.4.1; GS-US-380-1878 Week Interim Week 48, Table 15.11.6.4.1.1). Most Grade 1 and 2 ALT and AST elevations resolved with ongoing B/F/TAF treatment and were not associated with AEs (GS-US-380-1844 Interim Week 48, Listing 16.2.8.1.2.4 and Listing 16.2.7.1.1); GS-US-380-1878 Interim Week 48, Listing 16.2.8.1.2.4 and Listing 16.2.7.1.1).

2.1.5.2. Cardiovascular or Cerebrovascular Adverse Events

Cardiovascular and cerebrovascular events are summarized for the pooled studies GS-US-380-1489 and GS-US-380-1490 using PTs from relevant SMQs, and are described in the SAPs for the individual studies. Cardiovascular and cerebrovascular events are summarized in a similar manner for the individual Phase 3 studies GS-US-380-1844 and GS-US-380-1878.

2.1.5.2.1. ART-Naive Adult Subjects

2.1.5.2.1.1. Pooled Studies GS-US-380-1489 and GS-US-380-1490

Cardiovascular or cerebrovascular AEs were reported for similar percentages of subjects in each treatment group of the pooled studies GS-US-380-1489 and GS-US-380-1490 (pooled B/F/TAF 0.6%, 4 subjects; ABC/DTG/3TC 0.3%, 1 subject, and DTG+F/TAF 0.3% 1 subject); none of these events were considered related to study drugs (B/F/TAF Week 48 ISS, Table 17.1 and Listing 4).

The incidence of cardiovascular or cerebrovascular SAEs was as follows: pooled B/F/TAF 0.2%, 1 subject (myocardial infarction); ABC/DTG/3TC 0.3%, 1 subject (myocardial infarction), DTG+F/TAF 0.3%, 1 subject (ischaemic stroke) (B/F/TAF Week 48 ISS, Table 17.2).

2.1.5.2.2. Virologically Suppressed Adult Subjects

2.1.5.2.2.1. Study GS-US-380-1844

Cardiovascular or cerebrovascular AEs were reported for similar percentages of subjects in each treatment group in Study GS-US-380-1844 (B/F/TAF 1.1%, 3 subjects; ABC/DTG/3TC 0.4%, 1 subject).

Cardiovascular or cerebrovascular events were reported as SAEs for the 3 subjects (1.1%) in the B/F/TAF group (vertebrobasilar insufficiency [1 subject], acute coronary syndrome and acute myocardial infarction [1 subject], and cerebrovascular accident [1 subject]). The SAE of cerebrovascular accident was Grade 4, considered related to study drug, and led to discontinuation of study drugs. The event occurred on Day 100, on which day the subject's treatment assignment was unblinded, and study drugs were discontinued. The SAE resolved on Day 102. All other cardiovascular or cerebrovascular SAEs were considered not related to study drugs and did not result in discontinuation of study drugs.

2.1.5.2.2.2. Study GS-US-380-1878

Cardiovascular or cerebrovascular AEs were reported for similar percentages of subjects in each treatment group in Study GS-US-380-1878 (B/F/TAF 0.3%, 1 subject; SBR 1.7%, 5 subjects).

Cardiovascular or cerebrovascular SAEs were reported for similar percentages of subjects in each treatment group (B/F/TAF 0.3%, 1 subject [coronary artery stenosis and acute myocardial infarction]; SBR 1.4%, 4 subjects [acute myocardial infarction, coronary artery stenosis, myocardial infarction, and thrombotic stroke; 1 subject each]).

All cardiovascular or cerebrovascular AEs were considered unrelated to study drugs.

2.1.5.3. Bone Mineral Density

The percentage changes from baseline in hip or spine BMD through Week 48 and associated clinical status were compared between B/F/TAF and ABC/DTG/3TC in the individual studies GS-US-380-1489 and GS-US-380-1844. Clinical BMD status was assessed using BMD T-scores; normal bone status was defined by a BMD T-score ≥ −1, osteopenia by a T-score from < −1 to ≥ −2.5, and osteoporosis by a T-score < −2.5. The analysis methods are described in the respective SAP for each study.

2.1.5.3.1. ART-Naive Adult Subjects

2.1.5.3.1.1. Study GS-US-380-1489

Overall, mean percentage changes from baseline in BMD at the hip or spine were similar for each treatment group in Study GS-US-380-1489.

Mean (SD) percentage changes from baseline at Week 48 (observed data) were as follows:

- Hip: B/F/TAF −0.783% (2.2207%); ABC/DTG/3TC −1.021% (2.3128%)
- Spine: B/F/TAF −0.831% (3.1901%); ABC/DTG/3TC −0.596% (3.1009%)

The distribution of the clinical BMD status adjusted for baseline status was similar for each treatment group at Weeks 24 and 48 at the hip and at Week 24 at the spine.

The distribution of the clinical BMD status adjusted for baseline status was statistically significant between treatment groups at Week 48 at the spine; the numbers of subjects with a change in spine BMD clinical status from baseline (normal to osteopenia or osteopenia to osteoporosis) were as follows: B/F/TAF 15 subjects; ABC/DTG/3TC 10 subjects (p = 0.047).

2.1.5.3.2. Virologically Suppressed Adult Subjects

2.1.5.3.2.1. Study GS-US-380-1844

Mean percentage changes from baseline in BMD at the hip or spine were similar between treatment groups at Weeks 24 and 48 in Study GS-US-380-1844.

Mean (SD) percentage changes from baseline at Week 48 (observed data) were as follows:

- Hip: B/F/TAF 0.156% (2.2138%); ABC/DTG/3TC 0.299% (2.1077%)
- Spine: B/F/TAF 0.692% (3.1296%); ABC/DTG/3TC 0.416% (2.9973%)

The distribution of the clinical BMD status adjusted for baseline status was similar for each treatment group at Weeks 24 and 48 at the hip and spine.

2.1.5.4. Renal Safety

Renal safety assessments in the Phase 2 and 3 B/F/TAF clinical studies included assessments of renal-specific AEs and renal laboratory evaluations. Renal safety analyses in the pooled GS-US-380-1489 and GS-US-380-1490 studies are described in the B/F/TAF Week 48 ISS SAP, Section 6.5. Renal safety analyses in the individual Phase 2 and 3 B/F/TAF studies are described in the respective SAP for each study.

A summary of renal safety in the Phase 2 and 3 B/F/TAF studies is provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.2.4.4; GS-US-380-1490 Interim Week 48, Section 11.6.5; GS-US-141-1475 Interim Week 72, Section 11.6.5; GS-US-380-1844 Interim Week 48, Section 11.2.4.4; and GS-US-380-1878 Interim Week 48, Section 11.2.4.3).

Safety and PK data from the administration of BIC in subjects with renal impairment are summarized in Section 5.1.6.

2.1.5.4.1. ART-Naive Adult Subjects

2.1.5.4.1.1. Renal Adverse Events

Pooled Studies GS-US-380-1489 and GS-US-380-1490

No subject discontinued study drugs due to a renal and urinary disorder or associated investigation AEs in any treatment group in the pooled studies GS-US-380-1489 and GS-US-380-1490. There were no reports of proximal renal tubulopathy (including Fanconi syndrome) in any treatment group (B/F/TAF Week 48 ISS, Table 16).

Four subjects (B/F/TAF 0.3%, 2 subjects; ABC/DTG/3TC 0.3%, 1 subject; DTG+F/TAF 0.3%, 1 subject) had renal and urinary disorder or renal-associated investigation SAEs that were not considered related to study drugs and resolved with continued study drugs administration (B/F/TAF Week 48 ISS, Table 14.1), as follows:

- Grade 2 chronic kidney disease in 1 subject in the B/F/TAF group with SAEs of Grade 3 cellulitis and Grade 3 hyperglycemia. After resolution, a second SAE of Grade 4 chronic kidney disease was reported with SAEs of Grade 3 influenza and Grade 4 acute respiratory failure (GS-US-380-1490 Interim Week 48, Listing 16.2.7.7).

- Grade 2 acute kidney injury in 1 subject in the B/F/TAF group with Grade 2 SAEs of oedema peripheral and hypoglycaemia (GS-US-380-1490 Interim Week 48, Listing 16.2.7.7)

- Grade 3 chronic kidney disease in 1 subject in the ABC/DTG/3TC group with a past medical history of hypertensive nephropathy and type 2 diabetes mellitus

- Grade 1 acute kidney injury in 1 subject in the DTG+F/TAF group with a Grade 2 SAE of sepsis (GS-US-380-1490 Interim Week 48, Listing 16.2.7.7)

2.1.5.4.1.2. Renal Laboratory Parameters

Serum creatinine and eGFR were assessed in Studies GS-US-380-1489, GS-US-380-1490, and GS-US-141-1475. Albuminuria and proximal tubular proteinuria were additionally assessed in Study GS-US-380-1489.

2.1.5.4.1.2.1. Serum Creatinine and Estimated Glomerular Filtration Rate

Pooled Studies GS-US-380-1489 and GS-US-380-1490

Serum Creatinine

Increases in serum creatinine were observed by Week 4 in each treatment group in the pooled studies GS-US-380-1489 and GS-US-380-1490 that remained stable through Week 48 (B/F/TAF Week 48 ISS, Figure 3.1). Median (Q1, Q3) baseline serum creatinine values were as follows: B/F/TAF 0.90 (0.80, 1.01) mg/dL; ABC/DTG/3TC 0.91 (0.81, 0.99) mg/dL; DTG+F/TAF 0.89 (0.79, 1.00) mg/dL (B/F/TAF Week 48 ISS, Table 24.1). The median increases from baseline in serum creatinine were smaller in the pooled B/F/TAF group compared with the ABC/DTG/3TC group at Week 4 ($p = 0.029$). The median increases from baseline in serum creatinine were smaller in the pooled B/F/TAF group compared with the DTG+F/TAF group at Week 24 ($p = 0.022$) and Week 36 ($p = 0.021$). Median (Q1, Q3) changes from baseline at Week 48 were as follows: pooled B/F/TAF 0.10 (0.03, 0.17) mg/dL; ABC/DTG/3TC 0.11 (0.03, 0.18) mg/dL; DTG+F/TAF 0.11 (0.04, 0.19) mg/dL.

Graded laboratory abnormalities for serum creatinine were reported as follows: B/F/TAF 3.2%, 20 subjects; ABC/DTG/3TC 2.2%, 7 subjects; DTG+F/TAF 4.6%, 15 subjects (B/F/TAF Week 48 ISS, Table 19). The majority of these abnormalities were Grade 1. The incidence of Grade 3 or 4 laboratory abnormalities for serum creatinine was as follows: B/F/TAF 0.3%, 2 subjects; ABC/DTG/3TC 0.3%, 1 subject; DTG+F/TAF 0 subjects (B/F/TAF Week 48 ISS, Table 20.1); further details for these subjects are provided below.

One subject in the B/F/TAF group with normal serum creatinine at baseline had Grade 3 serum creatinine at Week 4. The Grade 3 serum creatinine returned to normal by Week 24 with no interruption of study drugs, and was not reported as an AE.

One subject in the B/F/TAF group had a Grade 3 serum creatinine abnormality at baseline that increased to Grade 4 at Week 36 and remained at Grade 4 at Week 48. This subject had a past medical history of poorly controlled Type 2 diabetes and hypertension leading to Stage III chronic kidney disease that continued to worsen during the study (GS-US-380-1490 Interim Week 48, Listing 16.2.4.4). He did not have evidence of proximal renal tubulopathy. Study drugs were discontinued at Week 48 at the investigator's discretion. The subject initiated treatment with ABC/DTG/3TC without a subsequent improvement in serum creatinine. The subject was subsequently transitioned to dialysis.

One subject in the ABC/DTG/3TC group had Grade 3 serum creatinine at Week 24 (GS-US-380-1489 Interim Week 48, Listings 16.2.8.1.8 and 16.2.8.1.2.3). This subject had Grade 2 serum creatinine at baseline and an SAE of Grade 3 chronic kidney disease. The serum creatinine was not reported as an AE and study drugs were continued.

Estimated Glomerular Filtration Rate

Corresponding with the results for serum creatinine, median decreases from baseline in $eGFR_{CG}$ were observed by Week 4 in each treatment group in the pooled studies GS-US-380-1489 and GS-US-380-1490 that remained stable through Week 48 (B/F/TAF Week 48 ISS, Figure 3.2). Median (Q1, Q3) baseline $eGFR_{CG}$ values were as follows: B/F/TAF 122.4 (104.1, 143.4) mL/min; ABC/DTG/3TC 123.0 (107.0, 144.3) mL/min; DTG+F/TAF 120.6 (102.8, 145.1) mL/min (B/F/TAF Week 48 ISS, Table 24.2). The median decreases from baseline in $eGFR_{CG}$ in the pooled B/F/TAF group compared with the ABC/DTG/3TC group were smaller at Week 4 ($p = 0.022$), Week 24 ($p = 0.004$), Week 36 ($p < 0.001$), and Week 48 ($p = 0.017$). The median decreases from baseline in $eGFR_{CG}$ in the pooled B/F/TAF group compared with the DTG+F/TAF group were smaller at Week 24 ($p = 0.050$) and Week 36 ($p = 0.010$). Median (Q1, Q3) changes from baseline at Week 48 were as follows: pooled B/F/TAF −8.8 (−18.4, 0.1) mL/min; ABC/DTG/3TC −10.8 (−21.6, −2.4) mL/min; DTG+F/TAF −10.8 (−20.0, −1.7) mL/min.

Study GS-US-141-1475

Increases from baseline in serum creatinine and corresponding decreases from baseline in $eGFR_{CG}$ were observed by Week 4 in both treatment groups in Study GS-US-141-1475 (GS-US-141-1475 Interim Week 72, Figures 15.11.6.1.1 and 15.11.6.2.1). After Week 4, median (Q1, Q3) serum creatinine levels remained stable through Week 60.

2.1.5.4.1.2.2. Albuminuria by Quantitative Assessment and Proximal Tubular Proteinuria

Study GS-US-380-1489

Median changes from baseline in UACR, urine RBP to creatinine ratio, and beta-2-microglobulin to creatinine ratio were similar between the treatment groups in Study GS-US-380-1489 (Table 21).

Table 21. GS-US-380-1489: Renal Biomarkers to Urine Creatinine Ratios at Week 48 (Safety Analysis Set)

Parameter	Median Percentage Change (%) (Q1, Q3)				p-value
	B/F/TAF (N = 314)		ABC/DTG/3TC (N = 315)		
UACR (mg/g)	287	0.6% (−32.0%, 48.9%)	293	6.2% (−23.6%, 57.7%)	0.11
Urine RBP to creatinine ratio (µg/g)	287	13.6% (−20.9%, 63.6%)	292	19.9% (−16.0%, 58.9%	0.34
Beta-2-microglobulin to creatinine ratio (µg/g)	286	−23.0% (−57.2%, 19.8%)	291	−18.1% (−54.2%, 17.4%))	0.40

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
For urine creatinine, value of < 1 was handled as a missing value in its summary and the calculation of related ratios.
Source: GS-US-380-1489 Interim Week 48, Tables 15.11.2.4.4.1 to 15.11.2.4.4.3

2.1.5.4.2. Virologically Suppressed Adult Subjects

2.1.5.4.2.1. Renal Adverse Events

Study GS-US-380-1844

No subject had proximal tubulopathy (including Fanconi syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE in Study GS-US-380-1844.

No renal SAEs were reported in the B/F/TAF group. In the ABC/DTG/3TC group, renal SAEs were reported for 2 subjects (hematuria and nephrolithiasis); neither SAE was considered related to study drug.

Study GS-US-380-1878

No subject had proximal tubulopathy (including Fanconi syndrome), and no subject in the B/F/TAF group discontinued study drugs due to a renal and urinary disorder or associated investigation AE in Study GS-US-380-1878. One subject in the SBR group discontinued study drugs due to acute kidney injury that was considered not related to study drugs.

Renal SAEs were reported for 3 subjects (ureterolithiasis [B/F/TAF] and acute kidney injury and ureteric stenosis [SBR]); none of the renal SAEs were considered related to study drugs.

2.1.5.4.2.2. Renal Laboratory Parameters

Serum creatinine, eGFR, albuminuria, and proximal tubular proteinuria were assessed in Studies GS-US-380-1844 and GS-US-380-1878.

2.1.5.4.2.2.1. Serum Creatinine and Estimated Glomerular Filtration Rate

Study GS-US-380-1844

Serum Creatinine

In Study GS-US-380-1844, there were generally no changes from baseline in serum creatinine values in the B/F/TAF group compared with small increases from baseline in the ABC/DTG/3TC group, which were observed by Week 4 and remained stable through Week 48 (GS-US-380-1844 Interim Week 48, Figure 15.11.2.4.4.1). The difference between the treatment groups was statistically significant at various time points between Weeks 4 to 48. Median (Q1, Q3) baseline serum creatinine values were as follows: B/F/TAF 1.05 (0.92, 1.19) mg/dL; ABC/DTG/3TC 1.06 (0.94, 1.16) mg/dL. Median (Q1, Q3) changes from baseline at Week 48 were as follows: B/F/TAF 0.00 (−0.07, 0.06) mg/dL, ABC/DTG/3TC 0.02 (–0.05, 0.09) mg/dL ($p = 0.019$).

Graded laboratory abnormalities for serum creatinine were reported as follows: B/F/TAF 7.4% (21 subjects), ABC/DTG/3TC 5.0% (14 subjects). All of these abnormalities were Grade 1, with the exception of 1 subject in the ABC/DTG/3TC group with a Grade 2 increase in serum creatinine.

Estimated Glomerular Filtration Rate

Corresponding with results for serum creatinine, small median increases or no changes from baseline in $eGFR_{CG}$ values were observed in the B/F/TAF group compared to small decreases in the ABC/DTG/3TC group in Study GS-US-380-1844 (GS-US-380-1844 Interim Week 48, Figure 15.11.2.4.4.2). Small increases were observed by Week 4 for the B/F/TAF group, and remained stable through Week 48. The difference between the treatment groups was statistically significant at all time points from Week 4 to 48 (except at Week 8). Median (Q1, Q3) baseline $eGFR_{CG}$ values were as follows: B/F/TAF 100.5 (84.5, 119.0) mL/min; ABC/DTG/3TC 100.7 (84.9, 122.4) mL/min. Median (Q1, Q3) changes from baseline at Week 48 were as follows: B/F/TAF 1.0 (−5.2, 9.4) mL/min, ABC/DTG/3TC −1.8 (−9.0, 4.8) mL/min ($p < 0.001$).

Study GS-US-380-1878

Serum Creatinine

Median increases from baseline in values for serum creatinine were observed in the B/F/TAF group compared with no change in the SBR group in Study GS-US-380-1878 (GS-US-380-1878 Interim Week 48, Figure 15.11.2.4.4.1). Increases were observed by Week 4 in the B/F/TAF group, and remained stable through Week 48. The difference between the treatment groups was statistically significant at time points from Weeks 4 to 48. Median (Q1, Q3) baseline

serum creatinine values were as follows: B/F/TAF 0.96 (0.85, 1.10) mg/dL; SBR 0.97 (0.85, 1.09) mg/dL. Median (Q1, Q3) changes from baseline in serum creatinine at Week 48 were as follows: B/F/TAF 0.06 (−0.03, 0.13) mg/dL; SBR 0.00 (−0.07, 0.07) mg/dL ($p < 0.001$).

Graded laboratory abnormalities for serum creatinine were reported as follows: B/F/TAF 2.8%, 8 subjects; SBR 1.8%, 5 subjects. All of these abnormalities were Grade 1.

Estimated Glomerular Filtration Rate

Median decreases from baseline in $eGFR_{CG}$ values were observed in the B/F/TAF group compared with minimal changes in the SBR group in Study GS-US-380-1878 (GS-US-380-1878 Interim Week 48, Figure 15.11.2.4.4.2). Decreases were observed by Week 4 in the B/F/TAF group, and remained stable through Week 48. The difference between the treatment groups was statistically significant at all time points from Weeks 4 to 48. Median (Q1, Q3) baseline $eGFR_{CG}$ values were as follows: B/F/TAF 106.7 (87.0, 124.2) mL/min; SBR 104.9 (87.1, 125.3) mL/min. Median (Q1, Q3) changes from baseline in $eGFR_{CG}$ at Week 48 were as follows: B/F/TAF −4.3 (−12.6, 4.8) mL/min; SBR 0.2 (−6.6, 7.6) mL/min ($p < 0.001$).

An AE of glomerular filtration rate decreased was reported for 1 subject in the B/F/TAF group, and AEs of creatinine renal clearance decreased were reported for 2 subjects in the B/F/TAF group. All of these events were Grade 1 or 2 in severity; none were serious or resulted in discontinuation of study drugs; and the event of glomerular filtration rate decreased was considered related to study drugs.

2.1.5.4.2.2.2. Albuminuria by Quantitative Assessment and Proximal Tubular Proteinuria

Study GS-US-380-1844

Overall, increases from baseline in UACR, urine RBP to creatinine ratio, and beta-2-microglobulin to creatinine ratio were similar between treatment groups at Week 48 in Study GS-US-380-1844 (Table 22).

Table 22. GS-US-380-1844: Renal Biomarkers at Week 48 (Safety Analysis Set)

Parameter	Median Percentage Change (%) (Q1, Q3)		p-value
	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)	
UACR (mg/g)	14.3% (-21.6%, 62.9%)	8.7% (-20.3%, 66.0%)	0.74
RBP to Creatinine Ratio (µg/g)	19.6% (-7.0%, 71.8%)	29.1% (–5.6%, 75.1%)	0.31
Beta-2-microglobulin to Creatinine Ratio (µg/g)	20.9% (-19.4%, 84.0%)	16.5% (-33.6%, 95.9%)	0.53

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
For urine creatinine, value of < 1 was handled as a missing value in its summary and the calculation of related ratios.
Source: GS-US-380-1844 Interim Week 48, Tables 15.11.2.4.4.1 to 15.11.2.4.4.3

Study GS-US-380-1878

Median changes from baseline in UACR at Week 48 were similar for each treatment group in Study GS-US-380-1878, as follows: B/F/TAF 0.0% (−34.4%, 59.6%); SBR 8.9% (−21.6%, 63.5%) (Table 23).

Urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio decreased from baseline in the B/F/TAF group and increased from baseline in the SBR group at Weeks 24 and 48 ($p < 0.001$ at each time point for the differences between the 2 groups in median percentage changes from baseline) (Table 23).

Table 23. GS-US-380-1878: Renal Biomarkers to Urine Creatinine Ratios at Week 48 (Safety Analysis Set)

	B/F/TAF (N = 290)		SBR (N = 287)		
Parameter	**N**	**Median Percentage Change (%) (Q1, Q3)**	**N**	**Median Percentage Change (%) (Q1, Q3)**	**p-value**
UACR (mg/g)	266	0.0% (−34.4%, 59.6%)	252	8.9% (−21.6%, 63.5%)	0.097
RBP to Creatinine Ratio (µg/g)	263	−14.0% (−50.6%, 23.9%)	253	33.3% (−8.6%, 113.4%)	< 0.001
Beta-2-microglobulin to Creatinine Ratio (µg/g)	265	−35.1% (−71.5%, −3.0%)	247	24.4% (−22.0%, 146.5%)	< 0.001

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
For urine creatinine, value of < 1 was handled as a missing value in its summary and the calculation of related ratios.
Source: GS-US-380-1878 Interim Week 48, Tables 15.11.2.4.4.1, 15.11.2.4.4.3, and 15.11.2.4.4.5

Median percentage change from baseline at Week 48 in renal biomarkers by prior treatment regimen (TDF- or non-TDF-containing regimen) in Study GS-US-380-1878 is presented in Table 24. Results by prior regimen show that the improvements in RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio were primarily experienced by subjects who switched from TDF-containing regimens. Subjects switching from non-TDF-containing regimens to B/F/TAF also showed an improved profile in these parameters relative to the changes for subjects in the SBR group receiving non-TDF-containing regimens.

Table 24. GS-US-380-1878: Renal Biomarkers to Urine Creatinine Ratios at Week 48 by Prior Treatment Regimen (Safety Analysis Set)

	B/F/TAF (N = 290)				SBR (N = 287)			
	TDF Containing Regimen (N = 245)		Non-TDF Containing Regimen (N = 45)		TDF Containing Regimen (N = 243)		Non-TDF Containing Regimen (N = 44)	
Parameter	N	Median Percentage Change (%) (Q1, Q3)	N	Median Percentage Change (%) (Q1, Q3)	N	Median Percentage Change (%) (Q1, Q3)	N	Median Percentage Change (%) (Q1, Q3)
UACR (mg/g)	225	−2.1% (−34.5%, 62.9%)	41	4.2% (−27.6%, 50.9%)	213	9.9% (−22.2%, 64.7%)	39	1.1% (−20.4%, 51.8%)
RBP to Creatinine Ratio (µg/g)	222	−17.7% (−54.1%, 21.7%)	41	5.4% (−19.21%, 49.7%)	214	34.9% (−7.8%, 115.2%)	39	25.8% (−14.9%, 93.1%)
Beta-2-microglobulin to Creatinine Ratio (µg/g)	224	−40.3% (−75.4%, −9.7%)	41	−19.5% (−51.5%, 16.1%)	208	31.6% (−20.1%, 156.5%)	39	7.3% (−48.5%, 58.0%)

For urine creatinine, value of < 1 was handled as a missing value in its summary and the calculation of related ratios.
Source: GS-US-380-1878 Interim Week 48, Tables 15.11.2.4.4.2, 15.11.2.4.4.4, and 15.11.2.4.4.6

2.1.5.5. Ocular Safety

Overall, the incidence of AEs in the eye disorders SOC and the incidence of AEs potentially related to uveitis were low and comparable between treatment groups in the 4 Phase 3 B/F/TAF studies (Table 25). Clinically, none of the AEs potentially related to uveitis were considered representative of an actual case of posterior uveitis.

All AEs in the eye disorders SOC were Grade 1 or 2 in severity (B/F/TAF Week 48 ISS, Table 7.1 and Table 10.1; GS-US-380-1844 Interim Week 48, Tables 15.11.2.1.2.1 and 15.11.2.2.2.1; GS-US-380-1878 Interim Week 48, Tables 15.11.2.1.2.1 and 15.11.2.2.2.1), and none resulted in discontinuation of study drugs (B/F/TAF Week 48 ISS, Table 16; GS-US-380-1844 Interim Week 48, Table 15.11.5; GS-US-380-1878 Interim Week 48, Table 15.11.5). Serious AEs in the eye disorders SOC occurred infrequently, as follows:

- Study GS-US-380-1489: keratitis in 1 subject (0.3%) in the ABC/DTG/3TC group (B/F/TAF Week 48 ISS, Table 14.1)
- Study GS-US-380-1490: iridocyclitis in 1 subject (0.3%) in the DTG+F/TAF group (B/F/TAF Week 48 ISS, Table 14.1)
- Study GS-US-380-1844: macular detachment, retinal detachment, and vitreous hemorrhage in 1 subject (0.4%) in the ABC/DTG/3TC group (GS-US-380-1844 Interim Week 48, Table 15.11.4.1.1.1)
- Study GS-US-380-1878: optic disc disorder in 1 subject (0.3%) in the B/F/TAF group (GS-US-380-1878 Interim Week 48, Table 15.11.4.1.1)

No subject had an AE in the eye disorders SOC that was considered related to study drugs, except 1 subject in the B/F/TAF group in Study GS-US-380-1844 with a medical history of myopia, who had an AE of vision blurred that resolved with continued B/F/TAF treatment (GS-US-380-1844 Interim Week 48, Table 15.11.2.3.1.1 and Listings 16.2.4.4 and 16.2.7.1.1).

Table 25. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Adverse Events in the Eye Disorders System Organ Class and Potential Uveitis Adverse Events (Safety Analysis Set)

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects			
	380-1489, 1490	380-1489	380-1490	GS-US-380-1844		GS-US-380-1878	
	Pooled B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG +F/TAF (N = 325)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Eye Disorders SOC	19 (3.0%)	10 (3.2%)	18 (5.5%)	9 (3.2%)	9 (3.2%)	7 (2.4%)	5 (1.7%)
Potential Uveitis AEs[a]	4 (0.6%)	1 (0.3%)	8 (2.5%)	3 (1.1%)	3 (1.1%)	1 (0.3%)	1 (0.3%)

a Based on the list of terms used for the GEN development program, which was reviewed and edited by an external ophthalmologist for comprehensiveness.
Source: B/F/TAF Week 48 ISS, Table 7.1 and Table req8899.3; GS-US-380-1844 Interim Week 48, Table 15.11.2.1.2.1 and Table req8901.7; GS-US-380-1878 Interim Week 48, Table 15.11.2.1.2.1 and Table req8872.3

2.1.5.6. Suicidal Ideation and Suicide Attempt

Adverse events based on the suicide/self-injury SMQ were infrequent in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878 through 48 weeks of treatment (Table 26). Most subjects with a suicide-related AE while receiving B/F/TAF had a history of depression or mental illness (GS-US-380-1489 Interim Week 48, Listing 16.2.4.4; GS-US-380-1490 Interim Week 48, Listing 16.2.4.4; GS-US-380-1844 Interim Week 48, Listing 16.2.4.4; GS-US-380-1878 Interim Week 48, Listing 16.2.4.4).

One subject in the B/F/TAF group discontinued study drugs due to an AE of suicidal ideation not considered related to study drugs (GS-US-380-1844 Interim Week 48, Listing 16.2.7.9); and an SAE of suicide attempt considered related to study drugs was reported in 1 subject in the B/F/TAF group (B/F/TAF Week 48 ISS, Listing 2). No suicide/self-injury AE was fatal (GS-US-380-1489 Interim Week 48, Listing 16.2.7.6; GS-US-380-1490 Interim Week 48, Listing 16.2.7.6; GS-US-380-1844 Interim Week 48, Listing 16.2.7.6; GS-US-380-1878 Interim Week 48, Listings 16.2.7.6.1 and 16.2.7.6.2).

Table 26. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Suicide Events by Suicide/Self-Injury SMQ (Safety Analysis Set)

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects			
	380-1489, 1490	380-1489	380-1490	GS-US-380-1844		GS-US-380-1878	
	Pooled B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG +F/TAF (N = 325)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Suicide Events	7 (1.1%)	3 (1.0%)	2 (0.6%)	3 (1.1%)	1 (0.4%)	0	1 (0.3%)
Depression suicidal	1 (0.2%)	0	0	1 (0.4%)	0	0	0
Intentional overdose	0	0	0	1 (0.4%)	0	0	0
Suicidal ideation	3 (0.5%)	3 (1.0%)	1 (0.3%)	2 (0.7%)	1 (0.4%)	0	0
Suicide attempt	3 (0.5%)	0	1 (0.3%)	1 (0.4%)	0	0	1 (0.3%)

Source: B/F/TAF Week 48 ISS, Table req8899.4; GS-US-380-1844 Interim Week 48, Table req8901.8; GS-US-380-1878 Interim Week 48, Table req8872.4

2.2. Narratives

For all Gilead-sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, and pregnancies, if applicable, are provided in the relevant CSRs.

Subjects are receiving B/F/TAF in 3 studies that are not included with this submission (Studies GS-US-380-1474, GS-US-380-1961, and GS-US-380-4017). Narratives for deaths, SAEs, discontinuations due to AEs, and pregnancies reported as of [redacted] 20[redacted] for these studies are provided in m5.3.5.1 (Study GS-US-380-1961) and m5.3.3.4 (Study GS-US-380-4017). No narratives are provided for Study GS-US-380-1474, as no deaths, SAEs, discontinuations due to AEs, or pregnancies have been reported as of [redacted] 20[redacted].

3. CLINICAL LABORATORY EVALUATIONS

In the following sections, a summary of the clinical laboratory evaluations reported in the Phase 2 and 3 B/F/TAF studies is presented. All laboratory evaluations summarized herein were treatment emergent and are referred to as laboratory abnormalities. Laboratory evaluation data from the B/F/TAF treatment groups in the 2 Phase 3 studies in ART-naive adult subjects were pooled and presented alongside laboratory data from the comparator group in each individual study (pooled B/F/TAF vs ABC/DTG/3TC or pooled B/F/TAF vs DTG+F/TAF), unless specified otherwise. Laboratory evaluation data for the 3 other Phase 2 and 3 B/F/TAF studies are presented for the individual studies.

A summary of the laboratory evaluations in the Phase 2 and 3 B/F/TAF studies is provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.6; GS-US-380-1490 Interim Week 48, Section 11.6; GS-US-141-1475 Interim Week 72, Section 11.6; GS-US-380-1844 Interim Week 48, Section 11.7; and GS-US-380-1878 Interim Week 48, Section 11.7).

Hepatic safety, including liver-related laboratory evaluations, is presented in 2.1.5.1. Renal safety, including renal laboratory evaluations, is presented in Section 2.1.5.4.

3.1. ART-Naive Adult Subjects

3.1.1. Studies GS-US-380-1489 and GS-US-380-1490

Graded Laboratory Abnormalities

In the pooled studies GS-US-380-1489 and GS-US-380-1490, the majority of subjects in each treatment group had at least 1 laboratory abnormality (pooled B/F/TAF 87.7%, 551 of 628 subjects; ABC/DTG/3TC 87.3%, 275 of 315 subjects; DTG+F/TAF 83.1%, 270 of 325 subjects) (B/F/TAF Week 48 ISS, Table 19). The majority of the reported laboratory abnormalities were Grade 1 or 2. Excluding nonfasting serum glucose abnormalities, the incidence of all graded individual laboratory abnormalities was generally similar between the pooled B/F/TAF treatment group and either comparator group, with the exception of the following parameters:

- Increased total bilirubin was more common in the pooled B/F/TAF treatment group than both comparator groups (see Section 2.1.5.1.1.1.2).

- Proteinuria (pooled B/F/TAF 21.1%, 132 subjects; ABC/DTG/3TC 34.6%, 109 subjects; DTG+F/TAF 24.6%, 80 subjects) was less common in the B/F/TAF group than the ABC/DTG/3TC group. The majority of increased urine protein was Grade 1.

- Increased lipase (pooled B/F/TAF 24.0%, 12 of 50 subjects; ABC/DTG/3TC 32.3%, 10 of 31 subjects; DTG+F/TAF 21.4%, 6 of 28 subjects) was less common in the pooled B/F/TAF treatment group than the ABC/DTG/3TC group. Lipase was only assessed in subjects with serum amylase > 1.5 × ULN. The majority of increased amylase and increased lipase were Grade 1 and 2.

Grade 3 or 4 laboratory abnormalities were reported for similar percentages of subjects in each treatment group: pooled B/F/TAF 15.6%, 98 subjects; ABC/DTG/3TC 14.6%, 46 subjects; DTG+F/TAF 13.2%, 43 subjects (Table 27). The incidence of Grade 3 or 4 individual laboratory abnormalities was similar in the B/F/TAF treatment group compared with either comparator group.

Table 27. GS-US-380-1489 and GS-US-380-1490: Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Maximum Treatment-Emergent Toxicity Grade	628	315	325
Grade 3	71 (11.3%)	32 (10.2%)	31 (9.5%)
Grade 4	27 (4.3%)	14 (4.4%)	12 (3.7%)
Grade 3 or 4	98 (15.6%)	46 (14.6%)	43 (13.2%)
Hematology			
Neutrophils (Decreased)	627	315	325
Grade 3	9 (1.4%)	6 (1.9%)	2 (0.6%)
Grade 4	2 (0.3%)	4 (1.3%)	0
Grade 3 or 4	11 (1.8%)	10 (3.2%)	2 (0.6%)
Chemistry			
ALT (Increased)	627	315	325
Grade 3	6 (1.0%)	2 (0.6%)	0
Grade 4	3 (0.5%)	2 (0.6%)	3 (0.9%)
Grade 3 or 4	9 (1.4%)	4 (1.3%)	3 (0.9%)
Amylase (Increased)	627	315	325
Grade 3	11 (1.8%)	6 (1.9%)	5 (1.5%)
Grade 4	1 (0.2%)	1 (0.3%)	1 (0.3%)
Grade 3 or 4	12 (1.9%)	7 (2.2%)	6 (1.8%)
AST (Increased)	627	315	325
Grade 3	8 (1.3%)	3 (1.0%)	6 (1.8%)
Grade 4	2 (0.3%)	1 (0.3%)	2 (0.6%)
Grade 3 or 4	10 (1.6%)	4 (1.3%)	8 (2.5%)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Creatine Kinase (Increased)	627	315	325
Grade 3	9 (1.4%)	6 (1.9%)	2 (0.6%)
Grade 4	13 (2.1%)	4 (1.3%)	5 (1.5%)
Grade 3 or 4	22 (3.5%)	10 (3.2%)	7 (2.2%)
GGT (Increased)	627	315	325
Grade 3	4 (0.6%)	2 (0.6%)	1 (0.3%)
Grade 4	1 (0.2%)	1 (0.3%)	1 (0.3%)
Grade 3 or 4	5 (0.8%)	3 (1.0%)	2 (0.6%)
Lipase (Increased)	50	31	28
Grade 3	1 (2.0%)	3 (9.7%)	2 (7.1%)
Grade 4	3 (6.0%)	0	0
Grade 3 or 4	4 (8.0%)	3 (9.7%)	2 (7.1%)
Serum Glucose (Fasting, Hyperglycemia)	625	313	325
Grade 3	2 (0.3%)	2 (0.6%)	7 (2.2%)
Grade 4	1 (0.2%)	1 (0.3%)	0
Grade 3 or 4	3 (0.5%)	3 (1.0%)	7 (2.2%)
LDL (Fasting, Increased)	613	309	317
Grade 3	16 (2.6%)	8 (2.6%)	11 (3.5%)
Grade 4	0	0	0
Grade 3 or 4	16 (2.6%)	8 (2.6%)	11 (3.5%)
Urinalysis			
Urine Glucose (Glycosuria)	627	315	325
Grade 3	6 (1.0%)	3 (1.0%)	6 (1.8%)
Urine RBC (Hematuria, Quantitative)	463	249	257
Grade 3	6 (1.3%)	3 (1.2%)	2 (0.8%)

The denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline value for the test under evaluation.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Lipase test was only performed for subjects with serum amylase > 1.5 x upper limit of normal.
For Urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.
For nonfasting serum glucose, the maximum postbaseline toxicity grades, instead of treatment-emergent abnormalities, were summarized, because nonfasting serum glucose were not available for all subjects at baseline and treatment-emergent flag cannot be derived.
Nonfasting serum glucose was not included in "Maximum Treatment-Emergent Toxicity Grade" summary as the treatment-emergent flag cannot be derived.
Nonfasting serum glucose abnormalities are not listed.
Source: B/F/TAF Week 48 ISS, Table 20.1

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline for the fasting lipid parameters total cholesterol, direct LDL, HDL, triglycerides, and total cholesterol to HDL ratio at Week 48 in any treatment group in the pooled studies GS-US-380-1489 and GS-US-380-1490 (Table 28).

Graded abnormalities in fasting lipid and glucose were reported for similar percentages of subjects in the pooled B/F/TAF treatment group compared with either comparator group (B/F/TAF Week 48 ISS, Table 19). The majority of lipid parameter abnormalities were Grade 1 or Grade 2. Grade 3 or Grade 4 abnormalities in lipid parameters were infrequent, and reported for similar percentages of subjects in each treatment group.

More subjects in the pooled B/F/TAF treatment group received lipid-modifying agents at study entry than the ABC/DTG/3TC group (pooled B/F/TAF 5.0%, 32 of 634 subjects; ABC/DTG/3TC 2.2%, 7 of 315 subjects, p = 0.038; DTG+F/TAF 5.8%, 19 of 325 subjects) (B/F/TAF Week 48 ISS, Table 23.6). Similar percentages of subjects in each treatment group initiated treatment with lipid-modifying agents during the study (pooled B/F/TAF 2.1%, 13 subjects; ABC/DTG/3TC 2.9%, 9 subjects; DTG+F/TAF 1.8%, 6 subjects) (B/F/TAF Week 48 ISS, Table 23.7).

Table 28. GS-US-380-1489, GS-US-380-1490: Changes from Baseline in Fasting Metabolic Laboratory Parameters at Week 48 (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)		ABC/DTG/3TC 380-1489 (N = 315)			DTG+F/TAF 380-1490 (N = 325)		
Metabolic Assessment	**n**	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**p-value**	**n**	**Median (Q1, Q3)**	**p-value**
Total Cholesterol (mg/dL)								
Baseline	619	157 (135, 182)	305	162 (138, 186)	0.17	321	161 (138, 186)	0.23
Change at Week 48	560	13 (−3, 30)	283	11 (-6, 28)	0.075	295	15 (1, 31)	0.11
Direct LDL (mg/dL)								
Baseline	619	99 (82, 122)	305	101 (84, 126)	0.25	321	99 (82, 124)	0.58
Change at Week 48	560	8 (−5, 23)	283	4 (-9, 18)	0.014	295	12 (−3, 25)	0.066
Triglycerides (mg/dL)								
Baseline	619	95 (70, 133)	305	96 (66, 138)	0.75	321	95 (70, 131)	0.84
Change at Week 48	560	6 (−21, 32)	283	3 (-25, 27)	0.20	295	7 (−14, 35)	0.49
HDL (mg/dL)								
Baseline	619	42 (34, 52)	305	42 (35, 51)	0.84	321	43 (35, 52)	0.67
Change at Week 48	560	5 (−1, 11)	283	5 (0, 11)	0.21	295	5 (−1, 12)	0.33
Total Cholesterol to HDL Ratio								
Baseline	619	3.7 (3.0, 4.6)	305	3.7 (3.0, 4.6)	0.81	321	3.7 (3.1, 4.5)	0.92
Change at Week 48	560	−0.1 (−0.5, 0.3)	283	-0.2 (-0.7, 0.2)	0.010	295	−0.1 (−0.6, 0.4)	0.92

Only laboratory measurements under fasting status were summarized.
P-values were from the 2-sided Wilcoxon rank sum test to compare the specific comparator group with the B/F/TAF group.
Source: B/F/TAF Week 48 ISS, Table 23.1 to Table 23.5

3.1.2. Study GS-US-141-1475

Graded Laboratory Abnormalities

Most subjects in both treatment groups had at least 1 laboratory abnormality in Study GS-US-141-1475 (BIC+F/TAF 87.5%, 56 of 64 subjects; DTG+F/TAF 87.5%, 28 of 32 subjects). Most of the reported laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 or 4 laboratory abnormalities were reported as follows: BIC+F/TAF 26.6% (17 subjects), DTG+F/TAF 28.1% (9 subjects) (Table 29).

Although a higher percentage of subjects in the BIC+F/TAF group had Grade 3 or 4 CK results than in the DTG+F/TAF group, all of these abnormalities occurred in young men, were not associated with AEs, and, with 1 exception (1 subject for whom the elevation occurred at the last visit prior to the data analysis date), were transient in nature, and resolved during study drug treatment.

Table 29. GS-US-141-1475: Grade 3 or 4 Laboratory Abnormalities Reported During the Double-Blinded Phase in Either Treatment Group (Safety Analysis Set)

	BIC+F/TAF (N = 64)	DTG+F/TAF (N = 32)
Any Grade 3 or 4 laboratory abnormality	17 (26.6%)	9 (28.1%)
Hematology		
Neutrophils (decreased)	1 (1.6%)	0
Chemistry		
Creatine kinase (increased)	6 (9.4%)	1 (3.1%)
LDL (fasting, increased)	3 (4.7%)	2 (6.3%)
AST (increased)	3 (4.7%)	0
ALT (increased)	2 (3.1%)	0
Amylase (increased)	1 (1.6%)	1 (3.1%)
Phosphate (hypophosphatemia)	1 (1.6%)	0
GGT (increased)	1 (1.6%)	0
Total bilirubin (hyperbilirubinemia)	1 (1.6%)	0
Uric acid (hyperuricemia)	1 (1.6%)	0
Serum Glucose (fasting, hyperglycemia)	0	3 (9.4%)
Lipase[a]	0	2 (50.0%)
Urinalysis[b]		
Urine glucose (glycosuria)	1 (1.6%)	2 (6.3%)
Urine RBC (hematuria, quantitative)	1 (1.6%)	1 (3.1%)

The denominator for percentages was the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value for the test under evaluation.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
a Lipase test was only performed for subjects with serum amylase > 1.5 × ULN.
b For urinalysis, the highest grade was up to Grade 3.
Source: GS-US-141-1475 Interim Week 72 CSR, Table 15.11.6.4.2.1

Metabolic Laboratory Parameters

Increases from baseline were observed for both treatment groups in fasting total cholesterol, fasting direct LDL, and fasting HDL, but not in fasting total cholesterol to HDL ratio, fasting triglycerides, or fasting glucose in Study GS-US-141-1475 (Table 30); the magnitudes of the observed changes were similar between the 2 treatment groups and were not considered clinically relevant.

Table 30. GS-US-141-1475: Changes from Baseline in Fasting Metabolic Laboratory Parameters During the Double-Blinded Phase (Safety Analysis Set)

	BIC+F/TAF (N = 65)		DTG+F/TAF (N = 33)	
	n	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**
Total cholesterol (mg/dL)				
Baseline	61	162 (136, 183)	32	166 (146, 189)
Change at Week 48	59	9 (−17, 27)	29	6 (−19, 23)
Direct LDL (mg/dL)				
Baseline	61	102 (79, 117)	32	102 (84, 125)
Change at Week 48	59	8 (−10,19)	29	8 (−10, 26)
HDL (mg/dL)				
Baseline	61	45 (36, 53)	32	45 (36, 58)
Change at Week 48	59	4 (−2, 11)	29	4 (−3, 11)
Total cholesterol to HDL ratio				
Baseline	61	3.8 (2.8, 4.6)	32	3.6 (3.2, 4.4)
Change at Week 48	59	−0.3 (−0.5, 0.2)	29	−0.1 (−0.5, 0.3)
Triglycerides (mg/dL)				
Baseline	61	85 (64, 120)	32	93 (62, 130)
Change at Week 48	59	2 (−23, 18)	29	3 (−21, 24)
Glucose (mg/dL)				
Baseline	64	92 (87, 99)	33	90 (83, 94)
Change at Week 48	62	0 (−6, 5)	31	2 (−4, 13)

Source: GS-US-141-1475 Interim Week 72 CSR, Tables 15.11.6.3.1.1 to 15.11.6.3.6.1

There were no clinically relevant median changes from baseline in values for fasting metabolic laboratory parameters for the BIC+F/TAF to B/F/TAF group through the open-label extension phase.

3.2. Virologically Suppressed Adult Subjects

3.2.1. Study GS-US-380-1844

Graded Laboratory Abnormalities

The majority of subjects in each treatment group had at least 1 laboratory abnormality in Study GS-US-380-1844 (B/F/TAF 85.1%, 240 of 282 subjects; ABC/DTG/3TC 85.8%, 241 of 281 subjects). The majority of the laboratory abnormalities were Grade 1 or 2. The incidence of all laboratory abnormalities was generally similar across the 2 treatment groups, with the exception of the following for which the difference in the incidence between treatment groups was ≥ 5%:

- Increased ALT and increased AST were more common in the B/F/TAF group than in the ABC/DTG/3TC group (Section 2.1.5.1.2.1.2).

- Fasting hyperglycemia (B/F/TAF 21.4%, 60 subjects; ABC/DTG/3TC 27.4%, 77 subjects) and proteinuria (B/F/TAF 17.0%, 48 subjects; ABC/DTG/3TC 32.0%, 90 subjects) were less common in the B/F/TAF group than in the ABC/DTG/3TC group.

Grade 3 or 4 laboratory abnormalities were reported as follows: B/F/TAF 16.7%, 47 subjects; ABC/DTG/3TC 11.4%, 32 subjects (Table 31). The most common Grade 3 or 4 laboratory abnormality was increased fasting LDL (B/F/TAF 5.1%, 14 subjects; ABC/DTG/3TC 4.7%, 13 subjects). The incidence of each individual Grade 3 and 4 laboratory abnormality was generally similar between the treatment groups with the exception of increased lipase, which was less common in the B/F/TAF group than in the ABC/DTG/3TC group and only assessed in subjects with serum amylase > 1.5 × ULN (B/F/TAF 13.3%, 2 of 15 subjects; ABC/DTG/3TC 21.4%, 3 of 14 subjects). There were no other differences in the incidence of Grade 3 or 4 laboratory abnormalities that were ≥ 5% between the 2 treatment groups.

Liver-related and renal-related laboratory abnormalities are discussed separately in Sections 2.1.5.1.2.1.2 and 2.1.5.4.2.2, respectively.

Table 31. GS-US-380-1844: Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)

	B/F/TAF (N = 282)	ABC/DTG/3TC (N = 281)
Maximum Treatment-Emergent Toxicity Grade	282	281
Grade 3 or 4	47 (16.7%)	32 (11.4%)
Chemistry		
ALT (Increased)	282	281
Grade 3 or 4	6 (2.1%)	0
AST (Increased)	282	281
Grade 3 or 4	4 (1.4%)	1 (0.4%)
Amylase (Increased)	282	281
Grade 3 or 4	7 (2.5%)	0
Creatine Kinase (Increased)	282	281
Grade 3 or 4	6 (2.1%)	6 (2.1%)
Lipase (Increased)	15	14
Grade 3 or 4	2 (13.3%)	3 (21.4%)
Serum Glucose (Fasting, Hyperglycemia)	280	281
Grade 3 or 4	6 (2.1%)	2 (0.7%)
Total Cholesterol (Fasting, Hypercholesterolemia)	277	278
Grade 3 or 4	4 (1.4%)	4 (1.4%)
Triglycerides (Fasting, Increased)	277	278
Grade 3 or 4	3 (1.1%)	2 (0.7%)
LDL (Fasting, Increased)	277	278
Grade 3 or 4	14 (5.1%)	13 (4.7%)
Urinalysis		
Urine Glucose (Glycosuria)	282	281
Grade 3	5 (1.8%)	3 (1.1%)
Urine RBC (Hematuria, Quantitative)	210	214
Grade 3	3 (1.4%)	2 (0.9%)

Nonfasting serum glucose (hyperglycemia) is not listed.
The denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline value for the test under evaluation.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Lipase test was only assessed in subjects with serum amylase > 1.5 x upper limit of normal.
For Urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.
For nonfasting serum glucose, the maximum postbaseline toxicity grades, instead of treatment-emergent abnormalities, were summarized, because nonfasting serum glucose were not available for all subjects at baseline.
Nonfasting serum glucose was not included in "Maximum Treatment-Emergent Toxicity Grade" summary as the treatment-emergent flag cannot be derived.
Source: GS-US-380-1844 Interim Week 48, Table 15.11.6.4.2

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline for the fasting lipid parameters total cholesterol, direct LDL, HDL, triglycerides, total cholesterol to HDL ratio, or glucose at Week 48 in any treatment group in Study GS-US-380-1844 (Table 32).

Graded abnormalities in fasting lipid parameters and glucose were reported for generally similar percentages of subjects in each treatment group, with the exception of fasting hyperglycemia (B/F/TAF 21.4%, 60 subjects; ABC/DTG/3TC 27.4%, 77 subjects). The majority of lipid parameter abnormalities were Grade 1 or Grade 2. Grade 3 or Grade 4 abnormalities in lipid parameters were infrequent, and reported for similar percentages of subjects in each treatment group (Table 31).

The percentages of subjects in each treatment group receiving lipid-modifying agents at study entry were as follows: B/F/TAF 19.9%, 56 subjects; ABC/DTG/3TC 13.9%, 39 subjects; p = 0.071. Fewer subjects initiated treatment with lipid-modifying agents in the B/F/TAF group than in the ABC/DTG/3TC group during the study (B/F/TAF 1.1%, 3 subjects; ABC/DTG/3TC 3.9%, 11 subjects; p = 0.033).

Table 32. GS-US-380-1844: Changes from Baseline in Fasting Metabolic Laboratory Parameters at Week 48 (Safety Analysis Set)

	B/F/TAF (N = 282)		ABC/DTG/3TC (N = 281)		
Metabolic Assessment	**n**	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**p-value**
Total cholesterol (mg/dL)					
Baseline	279	182 (162, 203)	274	186 (162, 213)	0.28
Change at Week 48	264	0 (-17, 18)	259	2 (-17, 18)	0.77
Direct LDL (mg/dL)					
Baseline	279	113 (95, 133)	275	118 (99, 141)	0.10
Change at Week 48	264	1 (-13, 18)	259	2 (-14, 14)	0.42
Triglycerides (mg/dL)					
Baseline	279	111 (76, 161)	274	111 (78, 156)	0.84
Change at Week 48	264	-5 (-34, 23)	259	3 (-23, 30)	0.028
HDL (mg/dL)					
Baseline	279	49 (40, 59)	274	48 (41, 59)	0.69
Change at Week 48	264	-1 (-6, 4)	259	0 (-4, 6)	0.13
Total cholesterol to HDL ratio					
Baseline	279	3.7 (3.0, 4.5)	274	3.8 (3.0, 4.7)	0.36
Change at Week 48	264	0.0 (-0.4, 0.4)	259	0.0 (-0.5, 0.4)	0.56
Glucose (mg/dL)					
Baseline	281	92 (85, 100)	276	92 (87, 100)	0.19
Change at Week 48	268	2 (-6, 10)	260	3 (-5, 9)	0.71

Only laboratory measurements under fasting status are summarized.
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-380-1844 Interim Week 48, Tables 15.11.6.3.1 to 15.11.6.3.6

3.2.2. Study GS-US-380-1878

Graded Laboratory Abnormalities

The majority of subjects in each treatment group had at least 1 laboratory abnormality in Study GS-US-380-1878 (B/F/TAF 84.8%, 246 of 290 subjects; SBR 90.9%, 259 of 285 subjects). The majority of the reported laboratory abnormalities were Grade 1 or 2 in the B/F/TAF group and Grade 1, 2, or 3 in the SBR group. The incidence of all graded individual laboratory abnormalities was generally similar across the 2 treatment groups, with the exception of the following parameters for which the difference in the incidence between treatment groups was ≥ 5%:

- Increased ALT and increased total bilirubin were more common in the B/F/TAF group than in the SBR group (Section 2.1.5.1.2.2.2)

- Increased urine protein (B/F/TAF 23.1%, 67 of 290 subjects; SBR 31.9%, 91 of 285 subjects) was less common in the B/F/TAF group than in the SBR group. The majority of the abnormalities were Grade 1.

- Increased lipase was less common in the B/F/TAF group than in the SBR group (B/F/TAF 25.0%, 5 of 20 subjects; SBR 30.4%, 7 of 23 subjects) and was only assessed in subjects with serum amylase > 1.5 × ULN. The majority of the abnormalities were Grade 1 and 2. No subjects with a graded amylase elevation had AEs consistent with pancreatitis.

Grade 3 or 4 laboratory abnormalities were reported as follows: B/F/TAF 15.5%, 45 subjects; SBR 29.1%, 83 subjects (Table 33). The difference was mainly in the incidence of increased total bilirubin (Section 2.1.5.1.2.2.2). There were no other differences in the incidence of Grade 3 or 4 laboratory abnormalities that were ≥ 5% between the 2 treatment groups.

Table 33. GS-US-380-1878: Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group (Safety Analysis Set)

	B/F/TAF (N = 290)	SBR (N = 287)
Maximum Treatment-Emergent Toxicity Grade, N	290	285
Grade 3 or 4, n (%)	45 (15.5%)	83 (29.1%)
Hematology		
Neutrophils (decreased), N	290	285
Grade 3 or 4, n (%)	5 (1.7%)	3 (1.1%)
Chemistry		
ALT (increased), N	290	285
Grade 3 or 4, n (%)	6 (2.1%)	4 (1.4%)
Amylase (increased) , N	290	285
Grade 3 or 4, n (%)	6 (2.1%)	6 (2.1%)
AST (increased), N	290	285
Grade 3 or 4, n (%)	5 (1.7%)	4 (1.4%)
Creatine kinase (increased) , N	290	285
Grade 3 or 4, n (%)	4 (1.4%)	4 (1.4%)
GGT (increased) , N	290	285
Grade 3 or 4, n (%)	2 (0.7%)	5 (1.8%)
Lipase (increased) , N	20	23
Grade 3 or 4, n (%)	1 (5.0%)	1 (4.3%)
Total bilirubin (hyperbilirubinemia), N	290	285
Grade 3 or 4, n (%)	2 (0.7%)	44 (15.4%)
Total cholesterol (fasting, hypercholesterolemia) , N	284	278
Grade 3 or 4, n (%)	2 (0.7%)	6 (2.2%)
Triglycerides (fasting, increased) , N	284	277
Grade 3 or 4, n (%)	4 (1.4%)	4 (1.4%)
LDL (fasting, increased) , N	284	278
Grade 3 or 4, n (%)	11 (3.9%)	11 (4.0%)
Urinalysis		
Urine glucose (glycosuria) , N	290	285
Grade 3, n (%)	6 (2.1%)	3 (1.1%)
Urine RBC (hematuria, quantitative) , N	234	224
Grade 3, n (%)	4 (1.7%)	6 (2.7%)

Nonfasting serum glucose (hyperglycemia) is not listed.
The denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline value for the test under evaluation.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Lipase test was only performed for subjects with serum amylase > 1.5 x upper limit of normal.
For Urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.
Source: GS-US-380-1878 Interim Week 48, Table 15.11.6.4.2

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline for the fasting lipid parameters total cholesterol, direct LDL, HDL, triglycerides, and glucose, or total cholesterol to HDL ratio at Week 48 in any treatment group in Study GS-US-380-1878 (Table 34).

Graded abnormalities in fasting lipid parameters and glucose were reported for similar percentages of subjects in each treatment group. The majority of lipid parameter abnormalities were Grade 1 or Grade 2. Grade 3 or 4 abnormalities in lipid parameters were infrequent, and reported for similar percentages of subjects in each treatment group (Table 33).

A similar percentage of subjects in each treatment group received lipid-modifying agents at study entry (B/F/TAF 16.2%, 47 subjects; SBR 15.7%, 45 subjects) and initiated treatment during the study (B/F/TAF 2.8%, 8 subjects; SBR 3.5%, 10 subjects).

Table 34. GS-US-380-1878: Changes from Baseline in Fasting Metabolic Laboratory Parameters at Week 48 (Safety Analysis Set)

	B/F/TAF (N = 290)		SBR (N = 287)		
Metabolic Assessment	**n**	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**p-value**
Total cholesterol (mg/dL)					
Baseline	283	188 (163, 215)	277	183 (160, 214)	0.55
Change at Week 48	261	1 (−17, 20)	248	5 (−12, 18)	0.32
Direct LDL (mg/dL)					
Baseline	283	121 (101, 148)	277	118 (98, 143)	0.41
Change at Week 48	261	0 (−16, 15)	248	3 (−14, 18)	0.47
Triglycerides (mg/dL)					
Baseline	283	122 (83, 176)	277	121 (87, 163)	0.87
Change at Week 48	260	−6 (−42, 22)	247	4 (−29, 38)	0.002
HDL (mg/dL)					
Baseline	283	47 (39, 55)	277	46 (39, 57)	0.84
Change at Week 48	261	3 (−3, 7)	247	1 (−4, 7)	0.13
Total cholesterol to HDL ratio					
Baseline	283	4.0 (3.3, 4.9)	277	3.8 (3.1, 4.9)	0.23
Change at Week 48	261	−0.2 (−0.6, 0.3)	247	0.0 (−0.5, 0.4)	0.033
Glucose (mg/dL)					
Baseline	287	91 (84, 97)	282	90 (84, 97)	0.64
Change at Week 48	269	3 (−4, 9)	258	2 (−5, 8)	0.35

Only laboratory measurements under fasting status were summarized.
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: GS-US-380-1878 Interim Week 48, Tables 15.11.6.3.1 to 15.11.6.3.6

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

A description and summary of vital signs, physical findings, and other observations related to safety in the Phase 2 and 3 B/F/TAF studies is provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.7; GS-US-380-1490 Interim Week 48, Section 11.7; GS-US-141-1475 Interim Week 72, Section 11.7; GS-US-380-1844 Interim Week 48, Section 11.8; and GS-US-380-1878 Interim Week 48, Section 11.8).

4.1. Vital Signs and Body Weight

Across the 5 Phase 2 and 3 B/F/TAF studies, there were no clinically relevant changes from baseline within any treatment group or differences between treatment groups in values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, body temperature, or body weight.

4.2. ECG Findings

4.2.1. ART-Naive Adult Subjects

4.2.1.1. Study GS-US-380-1489

Five subjects had clinically significant shifts in ECG parameters at Week 48 in Study GS-US-380-1489 (B/F/TAF 3 subjects; ABC/DTG/3TC 2 subjects). The ECG findings were reported as AEs, all of which were nonserious. One ECG-related AE (ABC/DTG/3TC group) was considered related to study drugs and led to interruption of study drugs. All other ECG-related AEs were considered not related to study drugs, and none led to discontinuation of study drugs.

4.2.1.2. Study GS-US-380-1490

There were 2 subjects in Study GS-US-380-1490, both in the DTG+F/TAF group, with clinically significant shifts in ECG parameters. Both subjects had abnormalities at baseline and/or relevant medical history.

4.2.1.3. Study GS-US-141-1475

There were no clinically significant shifts in ECG parameters in Study GS-US-141-1475.

4.2.2. Virologically Suppressed Adult Subjects

4.2.2.1. Study GS-US-380-1844

Four subjects had clinically significant shifts in ECG parameters in Study GS-US-380-1844 (B/F/TAF 3 subjects; ABC/DTG/3TC 1 subject). The ECG findings were reported as AEs, all of which were considered not related to study drug. None of the ECG-related AEs led to discontinuation of study drugs.

4.2.2.2. Study GS-US-380-1878

Six subjects had clinically significant shifts in ECG parameters in Study GS-US-380-1878 (B/F/TAF 3 subjects; SBR 3 subjects). None were reported as SAEs, resulted in discontinuation, or were considered related to study drug.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

Adverse event incidence rates in specific subgroups from the B/F/TAF treatment groups in the 2 Phase 3 studies in ART-naive adult subjects were pooled and presented alongside incidence rates from the comparator group in each individual study (pooled B/F/TAF vs ABC/DTG/3TC or pooled B/F/TAF vs DTG+F/TAF), unless specified otherwise. Subgroup analyses are also presented for the individual studies GS-US-380-1844 and GS-US-380-1878, where applicable. Supportive data are summarized for applicable Phase 1 studies in the B/F/TAF clinical development program (Table 2) and studies conducted using F/TAF, TAF, or FTC (Table 3).

A summary of AE incidence by subgroup is provided in the CSRs for the individual Phase 3 studies in virologically suppressed adult subjects (GS-US-380-1844 Interim Week 48, Section 11.3; GS-US-380-1878 Interim Week 48, Section 11.3).

Relevant PK data are also summarized herein. A summary of all covariates that were included in the population PK models for BIC, TAF, and FTC is provided in m2.7.2, Section 3.2.2. A summary of the PK effects of relevant intrinsic and extrinsic factors is provided in m2.7.2, Section 3.2.3 and Section 3.2.4, respectively.

5.1. Intrinsic Factors

5.1.1. Age

No impact of age was identified on the PK of BIC, TAF, or FTC (m2.7.2, Section 3.2.3.5.1).

ART-Naive Adult Subjects < 50 and ≥ 50 Years of Age

In the pooled studies GS-US-380-1489 and GS-US-380-1490, the incidence of AEs in subjects < 50 and ≥ 50 years of age (B/F/TAF Week 48 ISS, Table 8.1) was as follows:

- Pooled B/F/TAF group: < 50 years 83.3%, 448 of 538 subjects; ≥ 50 years 84.4%, 81 of 96 subjects
- ABC/DTG/3TC group: < 50 years 89.8%, 246 of 274 subjects; ≥ 50 years 90.2%, 37 of 41 subjects
- DTG+F/TAF group: < 50 years 84.6%, 225 of 266 subjects; ≥ 50 years 79.7%, 47 of 59 subjects

Virologically Suppressed Adult Subjects < 50 and ≥ 50 Years of Age

In Study GS-US-380-1844, the incidence of AEs in subjects < 50 and ≥ 50 years of age was as follows:

- B/F/TAF group: < 50 years 79.7%, 126 of 158 subjects; ≥ 50 years 79.8%, 99 of 124 subjects
- ABC/DTG/3TC group: < 50 years 78.0%, 138 of 177 subjects; ≥ 50 years 83.7%, 87 of 104 subjects

In Study GS-US-380-1878, the incidence of AEs in subjects < 50 and ≥ 50 years of age was as follows:

- B/F/TAF group: < 50 years 84.1%, 138 of 164 subjects; ≥ 50 years 75.4%, 95 of 126 subjects
- SBR group: < 50 years 78.9%, 138 of 175 subjects; ≥ 50 years 78.6%, 88 of 112 subjects

Subjects ≥ 65 Years of Age

Across the 4 Phase 3 B/F/TAF studies, 55 subjects were ≥ 65 years of age (B/F/TAF groups, 30 subjects; comparator groups, 25 subjects). No safety concerns for B/F/TAF were identified based on the data for these subjects (B/F/TAF Week 48 ISS, Table reqs8903.1 and 8903.2, and Listing req8903.1; GS-US-380-1844 Interim Week 48, Table reqs8920.1 and 8920.2, and Listing req8920.1; GS-US-380-1878 Interim Week 48, Table reqs8904.1 and 8904.2, and Listing req8904.1).

5.1.2. Sex

Sex did not have a clinically relevant effect of the PK of BIC, TAF, or FTC (m2.7.2, Section 3.2.3.5.4).

ART-Naive Adult Subjects

In the pooled studies GS-US-380-1489 and GS-US-380-1490, the incidence of AEs in male and female subjects (B/F/TAF Week 48 ISS, Table 8.2) was as follows:

- Pooled B/F/TAF group: male 83.4%, 471 of 565 subjects; female 84.1%, 58 of 69 subjects
- ABC/DTG/3TC group: male 89.7%, 253 of 282 subjects; female 90.9%, 30 of 33 subjects
- DTG+F/TAF group: male 84.7%, 244 of 288 subjects; female 75.7%, 28 of 37 subjects

Virologically Suppressed Adult Subjects

In Study GS-US-380-1844, the incidence of AEs in male and female subjects was as follows:

- B/F/TAF: male 80.2%, 198 of 247 subjects; female 77.1%, 27 of 35 subjects
- ABC/DTG/3TC: male 79.8%, 201 of 252 subjects; female 82.8%, 24 of 29 subjects

In Study GS-US-380-1878, the incidence of AEs in male and female subjects was as follows:

- B/F/TAF: male 79.4%, 193 of 243 subjects; female 85.1%, 40 of 47 subjects
- SBR: male 79.5%, 186 of 234 subjects; female 75.5%, 40 of 53 subjects

5.1.3. Race

No impact of race was identified on the PK of BIC, TAF, or FTC (m2.7.2, Section 3.2.3.5.3).

ART-Naive Adult Subjects

In the pooled studies GS-US-380-1489 and GS-US-380-1490, the incidence of AEs in black and nonblack subjects (B/F/TAF Week 48 ISS, Table 8.3) was as follows:

- Pooled B/F/TAF group: black 82.9%, 175 of 211 subjects; nonblack 83.8%, 353 of 421 subjects
- ABC/DTG/3TC group: black 87.5%, 98 of 112 subjects; nonblack 91.1%, 185 of 203 subjects
- DTG+F/TAF group: black 82.0%, 82 of 100 subjects; nonblack 84.4%, 190 of 225 subjects

Virologically Suppressed Adult Subjects

In Study GS-US-380-1844, the incidence of AEs in black and nonblack subjects was as follows:

- B/F/TAF: black 76.3%, 45 of 59 subjects; nonblack 80.7%, 180 of 223 subjects
- ABC/DTG/3TC: black 67.7%, 42 of 62 subjects; nonblack 83.8%, 181 of 216 subjects

In Study GS-US-380-1878, the incidence of AEs in black and nonblack subjects was as follows:

- B/F/TAF: black 74.7%, 59 of 79 subjects; nonblack 82.5%, 174 of 211 subjects
- SBR: black 77.8%, 56 of 72 subjects; nonblack 79.1%, 170 of 215 subjects

Study GS-US-380-1991

A total of 50 subjects (25 Japanese and 25 Caucasian) enrolled in Study GS-US-380-1991 and received a single oral dose of B/F/TAF 50/200/25 mg (Study GS-US-380-1991). One Caucasian subject discontinued the study due to AEs. All 50 subjects were included in the PK and Safety Analysis Sets.

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. Most AEs were Grade 1 in severity, and no clinically relevant median changes in laboratory values, vital signs, or ECGs occurred.

5.1.4. HIV-1 RNA Stratum at Baseline

In ART-naive subjects in the pooled studies GS-US-380-1489 and GS-US-380-1490, the incidence of AEs in subjects with baseline HIV-1 RNA level ≤ 100,000 copies/mL and > 100,000 copies/mL (B/F/TAF Week 48 ISS, Table 8.4) was as follows:

- Pooled B/F/TAF group: ≤ 100,000 copies/mL 82.9%, 427 of 515 subjects; > 100,000 copies/mL 85.7%, 102 of 119 subjects
- ABC/DTG/3TC group: ≤ 100,000 copies/mL 88.7%, 235 of 265 subjects; > 100,000 copies/mL 96.0%, 48 of 50 subjects
- DTG+F/TAF group: ≤ 100,000 copies/mL 82.3%, 223 of 271 subjects; > 100,000 copies/mL 90.7%, 49 of 54 subjects

5.1.5. CD4 Cell Count at Baseline

In ART-naive subjects in the pooled Studies GS-US-380-1489 and GS-US-380-1490, the incidence of AEs in subjects with baseline CD4 count < 200 cells/µL and ≥ 200 cells/µL (B/F/TAF Week 48 ISS, Table 8.5) was as follows:

- Pooled B/F/TAF group: < 200/µL 87.5%, 70 of 80 subjects; ≥ 200/µL 82.9%, 459 of 554 subjects
- ABC/DTG/3TC group: < 200/µL 93.8%, 30 of 32 subjects; ≥ 200/µL 89.4%, 253 of 283 subjects
- DTG+F/TAF group: < 200/µL 85.3%, 29 of 34 subjects; ≥ 200/µL 83.5%, 243 of 291 subjects

5.1.6. Renal Impairment

Safety of B/F/TAF in HIV-infected patients with renal impairment is supported by data from studies of BIC, FTC, TAF, and the F/TAF-containing regimen GEN. Renal safety data from the Phase 3 B/F/TAF and Phase 2 BIC+F/TAF studies, including renal AEs and renal laboratory parameters, are summarized in Section 2.1.5.4.

5.1.6.1. BIC

Study GS-US-141-1479

Study GS-US-141-1479 was a Phase 1, open-label, parallel-group, adaptive, single-dose study to evaluate the PK of BIC in subjects with impaired renal function compared with control subjects with normal renal function. A total of 10 subjects with severe renal impairment ($eGFR_{CG}$ 15-29 mL/min) and 8 matched control subjects with normal renal function ($eGFR_{CG}$ ≥ 90 mL/min) received a single oral dose of BIC 75 mg and completed the study.

The PK of BIC in subjects with severe renal impairment and healthy matched controls in Study GS-US-141-1479 are summarized in m2.7.2, Section 3.2.3.3.1. A modest decrease in BIC plasma exposure was observed in subjects in the severe renal impairment group compared with the matched control subjects in the normal renal function group that was 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.

The safety profile of BIC was similar between the 2 renal function groups. Adverse events were reported in 2 subjects with severe renal impairment and 2 subjects with normal renal function; all were Grade 1 in severity. One AE in each renal function group was considered related to study drug by the investigator (nausea in a subject with severe renal impairment and headache in a subject with normal renal function). There were no clinically meaningful median changes from baseline in values for any chemistry or hematology parameter during the study in either group. No deaths or SAEs occurred during this study, and no subject discontinued the study due to an AE. No clinically meaningful changes in vital signs or safety ECGs were observed.

5.1.6.2. FTC

Study FTC-107

Study FTC-107 was an open-label, parallel group study with 6 subjects in each of the 5 groups with varying degrees of renal impairment as determined by $eGFR_{CG}$ values (> 80 mL/min as normal function; 50–80 mL/min as mild impairment; 30–49 mL/min as moderate impairment; < 30 mL/min as severe impairment; or functional anephric requiring hemodialysis).

The percentage of dose excreted as unchanged FTC in urine for the normal and mild renal impairment groups ($eGFR_{CG}$ 50–80 mL/min) was similar to that observed with healthy subjects (FTC-106) and HIV-infected subjects with normal renal function (FTC-101). In subjects with moderate and severe impairment ($eGFR_{CG}$ < 50 mL/min), the urinary recovery was lower (approximately 30%–50% of the dose) over a 72-hour collection period, primarily due to slower excretion of FTC by the impaired kidneys, which, in the absence of clinical experience of FTC in HIV-infected subjects with $eGFR_{CG}$ < 60 mL/min, led to a dose interval adjustment recommendation.

5.1.6.3. TAF

Study GS-US-120-0108

In the Phase 1 study GS-US-120-0108, the PK of TAF was analyzed in non-HIV-infected subjects with severe renal impairment (defined as subjects with $eGFR_{CG}$ between 15 mL/min and 29 mL/min [inclusive], not on dialysis) and in age- and sex-matched non-HIV-infected subjects with normal renal function ($eGFR_{CG} \geq 90$ mL/min) following a single dose of TAF. Subjects with severe renal impairment had a 1.9-fold higher TAF systemic exposure (as assessed by AUC_{inf}) relative to age- and sex-matched subjects with normal renal function.

5.1.6.4. F/TAF

Study GS-US-292-0112

Study GS-US-292-0112 was Phase 3, open-label, multicenter, multicohort study conducted to assess the safety, tolerability, and efficacy of the F/TAF-containing regimen GEN in HIV-infected, adult subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min, inclusive). A total of 252 subjects were enrolled in the study (246 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects); 248 subjects received at least 1 dose of study drug (242 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects). Safety results through Week 144 are summarized for Cohort 1 in this section; safety data for both cohorts are presented in the CSR.

GEN was well tolerated through 144 weeks of treatment in the Cohort 1 HIV-infected adults with mild to moderate renal impairment, with low rates of treatment-related Grade 3 or 4 AEs or AEs leading to study drug discontinuations. No subject had an SAE considered related to study drug. Most subjects reported at least 1 AE. The most commonly reported AEs in Cohort 1 switch subjects were bronchitis, upper respiratory tract infection, arthralgia, and diarrhea. The majority of AEs considered related to study drug by the investigator were Grade 1 or 2; 5 subjects had Grade 3 or 4 AEs considered related to study drug (blood creatine phosphokinase increased, gastroesophageal reflux disease, hypercholesterolemia and low density lipoprotein increased, diabetes mellitus inadequate control, and chronic kidney disease).Two treatment-emergent deaths were reported (cardiopulmonary arrest and cardiac arrest). The events leading to death were considered unrelated to study drug by the investigator.

No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported through Week 144. Five subjects had renal AEs that led to discontinuation of study drug through Week 96; there were no additional subjects with renal AEs leading to discontinuation of study drug after Week 96.

Through Week 144, there were no clinically significant median changes from baseline in values for hematology or clinical chemistry parameters. Median values were generally within normal ranges. At least 1 laboratory abnormality was reported in each of the Cohort 1 switch subjects. The majority of reported laboratory abnormalities were Grade 1 or 2 in severity. The most commonly observed Grade 3 or 4 laboratory abnormalities were low-density lipoprotein (LDL; fasting) (36 subjects), total cholesterol (fasting, hypercholesterolemia) (21 subjects), serum glucose (fasting, hyperglycemia) (14 subjects), and creatine kinase (13 subjects).

The safety profile of GEN in subjects in this study was similar to that of subjects with normal renal function.

Study GS-US-292-0112 included an intensive PK substudy evaluating the PK of FTC following administration of GEN in subjects with $eGFR_{CG}$ of 30 to 69 mL/min (n = 30) and showed mean (%CV) FTC exposure AUC and C_{max} of 20,968.6 (25.5) ng*h/mL and 2645.3 (24.7) ng/mL, respectively, which were in the range of exposures where dose modification was not warranted in FTC-107. Importantly, the mean FTC AUC and C_{max} observed in GS-US-292-0112 subjects with $eGFR_{CG}$ of 30 to 69 mL/min were comparable with the AUC and C_{max} of

19,900 (6.2) ng*h/mL and 3800 (2.3) ng/mL, respectively, for subjects with $eGFR_{CG}$ of 50 to 80 mL/min receiving Emtriva, who do not require dose adjustment. Subjects with $eGFR_{CG}$ < 50 mL/min reported the same type and incidence of AEs as subjects with $eGFR_{CG}$ ≥ 50 mL/min, and the observed laboratory abnormalities were consistent between the 2 groups.

The substudy of Study GS-US-292-0112 also evaluated the PK of TAF and TFV following administration of GEN in ART-naive and ART-experienced, HIV-infected adults with stable $eGFR_{CG}$ of 30 to 69 mL/min (n = 32) and showed mean (%CV) TAF and TFV exposures (AUC) of 254.2 (54.1) ng*h/mL and 552.7 (32.0), respectively.

Complete study descriptions and results are provided in the CSRs (GS-US-292-0112 Interim Week 24 and GS-US-292-0112 Interim Week 144).

5.1.7. Hepatic Impairment

Safety of B/F/TAF in HIV-infected patients with hepatic impairment is supported by data from studies of BIC, FTC, and TAF. Hepatic safety data from the Phase 3 B/F/TAF and Phase 2 BIC+F/TAF studies, including hepatic AEs and liver-related laboratory parameters, are summarized in Section 2.1.5.1. Safety and PK data from subjects with HIV/HBV and HIV/HCV coinfection are summarized in Section 5.1.8. Safety and PK data from subjects with CHB monoinfection are summarized in Section 5.1.9.

5.1.7.1. BIC

Study GS-US-141-1478 was a Phase 1 study that evaluated the PK of a single dose of BIC 75 mg in subjects with normal or impaired hepatic function. Subjects with hepatic impairment had moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Class B). A total of 10 subjects with moderate hepatic impairment and 10 matched healthy control subjects with normal hepatic function received a single oral dose of BIC 75 mg and completed the study. All 20 subjects were included in the PK and Safety Analysis Sets. No subjects were enrolled in the mild hepatic impairment cohort.

Pharmacokinetic results from Study GS-US-141-1478 are presented in m2.7.2, Section 3.2.3.4.1. 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 versus 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. All AEs were Grade 1 in severity, and no clinically meaningful median changes in laboratory values, vital signs, or ECGs occurred.

Complete study descriptions and results are provided in the CSR (GS-US-141-1478 Final).

5.1.7.2. FTC

The PK of FTC has not been studied in hepatically impaired subjects. Renal excretion of unchanged drug is the major route of elimination of FTC in man with metabolism representing a minor pathway for the elimination (< 13% of oral dose) (Study FTC-106). Therefore, in patients with various degrees of hepatic dysfunction, minimal change in FTC clearance is expected (m2.7.2, Section 3.2.3.4.3).

5.1.7.3. TAF

Study GS-US-120-0114

Study GS-US-120-0114 evaluated 40 subjects with liver cirrhosis and mild or moderate hepatic impairment (CPT Class A or B), including age- and sex-matched subjects with normal hepatic function.

No clinically relevant changes in TAF or TFV pharmacokinetics were observed in subjects with mild or moderate hepatic impairment compared with the normal matched control subjects following administration of a single 25-mg dose of TAF. TAF was generally well tolerated in subjects with mild or moderate hepatic impairment and in subjects with normal hepatic function. No Grade 3 or 4 AEs, deaths, SAEs, or AEs leading to permanent discontinuation of study drug were reported during this study. Results from this study indicate that no dose adjustment of TAF is necessary in subjects with mild or moderate hepatic impairment.

Pharmacokinetic results from this study are presented in m2.7.2, Sections 3.1.2.2 and 3.2.3.4.2.

Complete study descriptions and results are provided in the CSR (GS-US-120-0114 Final).

Study GS-US-320-1615

Study GS-US-320-1615 evaluated 20 subjects with liver cirrhosis and severe hepatic impairment (CPT Class C), including age- and sex-matched subjects with normal hepatic function.

The total (bound and unbound) TAF exposure (AUC_{last}) was 49% lower in subjects with severe hepatic impairment relative to normal matched control subjects following a single dose of TAF 25 mg; however, given that the free fraction of TAF (as percent unbound, which is the free TAF moiety associated with therapeutic effect) is higher in subjects with severe hepatic impairment due to differences in plasma protein binding, no clinically relevant changes in free (unbound) TAF exposures were observed relative to matched healthy controls. Given this, no change in TAF therapeutic effect (efficacy or safety) is expected in patients with severe hepatic impairment. TAF was generally well tolerated in subjects with severe hepatic impairment and in subjects with normal hepatic function. No deaths, Grade 4 AEs, or AEs leading to study drug discontinuation occurred during this study. One subject in the severe hepatic impairment group had an SAE of Grade 3 hepatic failure (unrelated to study drug) during the posttreatment follow-up phase of the study. Results from this study indicate that no dose adjustment of TAF is necessary in subjects with severe hepatic impairment.

Pharmacokinetic results from this study are presented in m2.7.2, Sections 3.1.2.2 and 3.2.3.4.2.

Complete study descriptions and results are provided in the CSR (GS-US-320-1615 Final).

A summary of the safety of TAF in subjects with CHB monoinfection is provided in Section 5.1.9.2.

5.1.8. Coinfection with HIV-1 and HBV or HCV

5.1.8.1. HIV/HBV Coinfection

Studies GS-US-380-1490 and GS-US-380-1878 permitted HIV/HBV-coinfected subjects to enroll. Safety results for subjects with HIV/HBV-coinfection at baseline in these studies are summarized in Section 5.1.8.1.1. Detailed safety results for all HIV-infected adult subjects coinfected with HBV in the B/F/TAF Phase 3 studies, including any subjects meeting SAP-defined criteria for incident HBV coinfection based on HBV seropositivity, are presented in the CSRs (Study GS-US-380-1489 Interim Week 48, Section 11.2.4.1.3, Study GS-US-380-1490 Interim Week 48, Section 11.2.4.1.3.1, Study GS-US-380-1844 Interim Week 48, Section 11.2.4.1.3, and Study GS-US-380-1878 Interim Week 48, Section 11.2.4.1.3.1).

Safety of B/F/TAF in HIV/HBV coinfection is also supported by data from a study of the F/TAF-containing regimen GEN in HIV/HBV-coinfected subjects (Study GS-US-292-1249), and from studies of FTC (Study FTCB-101) and TAF (Studies GS-US-320-0101, GS-US-320-0108, and GS-US-320-0110) in CHB-monoinfected subjects. Safety results from Study GS-US-292-1249 are summarized in Section 5.1.8.1.2. Safety results from Studies GS-US-320-0101, GS-US-320-0108, and GS-US-320-0110 are presented in Section 5.1.9.2.

Hepatic safety data from the Phase 2 and 3 B/F/TAF studies, including hepatic AEs and liver-related laboratory parameters, are summarized in Section 2.1.5.1.

5.1.8.1.1. B/F/TAF

5.1.8.1.1.1. ART-naive Adult Subjects

Study GS-US-380-1490

At baseline, 14 (2.2%) subjects met SAP-defined criteria for coinfection with HBV in Study GS-US-380-1490 (B/F/TAF 2.5%, 8 subjects; DTG+F/TAF 1.9%, 6 subjects). All 14 subjects had no prior treatment for HIV or HBV infection.

The AEs reported by HIV/HBV baseline-coinfected subjects were generally similar to those reported by HIV monoinfected subjects in this study. During the study, no subjects with HIV/HBV coinfection at baseline had a hepatic AE.

One HIV/HBV baseline-coinfected subject (B/F/TAF) had a confirmed on-treatment (up to the last dose day) ALT flare (defined as ALT > 10 × ULN and ALT > 2 × baseline on 2 consecutive occasions) during the study. Baseline ALT was 118 U/L (Grade 2) and AST was 64 U/L

(Grade 1). ALT increased to 1477 U/L (Grade 4) and AST to 551 U/L (Grade 4) at Week 12. Study drug was not interrupted. Both parameters returned to normal limits at Week 24. At Week 48, ALT and AST levels were 54 U/L (Grade 1) and 40 U/L (Grade 0), respectively. HBV DNA was > 170,000,000 IU/mL at baseline, decreasing to 128,000 IU/mL at Week 12 and < 20 IU/mL at Week 48. The ALT flare was reported as a Grade 2 AE of immune reconstitution inflammatory syndrome that was not considered related to study drug. No hepatic AEs were reported for this subject. The remaining 13 subjects with HIV/HBV coinfection at baseline did not have evidence of an ALT flare during treatment with B/F/TAF or DTG+F/TAF.

One subject in the B/F/TAF group, with HIV/HBV baseline-coinfection and normal ALT (30 U/L) and AST (24 U/L) at baseline, experienced Grade 3 ALT (316 U/L) and Grade 2 AST (136 U/L) at Week 8, both of which resolved to within the normal range by Week 24.

Of the 14 HIV/HBV baseline-coinfected subjects, 1 additional subject experienced graded treatment-emergent elevation in ALT or AST. One subject in the DTG+F/TAF group experienced Grade 1 ALT and AST elevations.

5.1.8.1.1.2. Virologically Suppressed Adult Subjects

Study GS-US-380-1878

Subjects with HBV coinfection were permitted to enroll in Study GS-US-380-1878 only if TDF was part of their baseline regimen.

At baseline, 14 subjects (2.4%) in Study GS-US-380-1878 were identified as being coinfected with HIV-1 and HBV (B/F/TAF 2.8%, 8 subjects; SBR 2.1%, 6 subjects). All HIV/HBV baseline-coinfected subjects were on a TDF-containing regimen except for 1 subject in the SBR group.

The AEs reported by HIV/HBV baseline-coinfected subjects were generally similar to those reported by HIV monoinfected subjects in this study. No subjects with HIV/HBV coinfection at baseline had a hepatic AE or a confirmed on-treatment (up to the last dose day) ALT flare (defined as ALT elevation > 2 × baseline ALT and > 10 × ULN and confirmed at 2 consecutive visits).

No subjects with HIV/HBV baseline-coinfection experienced Grade 3 or 4 liver-related treatment-emergent laboratory abnormalities. In the B/F/TAF group, 3 HIV/HBV baseline-coinfected subjects experienced treatment-emergent Grade 1 ALT elevation, one of whom also experienced Grade 1 AST elevation. One HIV/HBV baseline-coinfected subject in the SBR group experienced Grade 2 total bilirubin abnormality.

5.1.8.1.2. F/TAF

Study GS-US-292-1249

Safety of B/F/TAF in HIV/HBV coinfection is supported by Study GS-US-292-1249, an open-label, single-arm, multicenter, dual-cohort study to assess the safety, efficacy, and tolerability of the F/TAF-containing regimen GEN in HIV/HBV-coinfected adult subjects who were either HIV/HBV treatment naive (Cohort 1) or HIV suppressed (with or without HBV suppression; Cohort 2). Subjects received GEN once daily with food for 48 weeks.

Because the study enrolled mostly HIV/HBV-coinfected, HIV-suppressed subjects (Cohort 2; N = 74), safety results for that population are presented here. Data from the 3 HIV/HBV-coinfected, ART-naive subjects enrolled (Cohort 1) are summarized in the CSR.

Most subjects in Study GS-US-292-1249 who were HIV-suppressed reported at least 1 AE The most commonly reported AEs in HIV-suppressed subjects were upper respiratory tract infection, nasopharyngitis, diarrhea, gastroesophageal reflux disease, and back pain. Common AEs were consistent with those expected in the subject population, the known safety profile of GEN, or with previous clinical study experience with GEN in HIV-infected subjects without HBV coinfection. GEN was well tolerated with low rates of Grade 3 or 4 AEs, SAEs, and AEs leading to drug discontinuations. No subject had an SAE considered related to study drugs. One subject discontinued study drug due to AEs (weight increased and increased appetite) that were considered related to study drug. All AEs considered related to study drug by the investigator were Grade 1 or 2. No deaths were reported.

There were no clinically significant median changes from baseline in values for hematology or clinical chemistry parameters through Week 48. Median values were generally within normal ranges. Most HIV-suppressed subjects (90.5%) had at least 1 laboratory abnormality. Most laboratory abnormalities were Grade 1 or 2 in severity. The most commonly observed Grade 3 or 4 laboratory abnormalities were related to hepatic or metabolic processes and were reported for 1 or 2 subjects for each abnormality.

No subject had a hepatic AE or confirmed on-treatment ALT flare. No Hy's Law cases were identified. One subject had elevated AST and ALT > 5 × ULN, without elevated total bilirubin > 1 × ULN, due to an AE of acute HCV infection.

The safety profile of the F/TAF-containing regimen GEN in HIV/HBV-coinfected adults in this study was similar to the safety profile in subjects with HIV-1 monoinfection.

A complete study description and detailed results are provided in the CSR (GS-US-292-1249 Interim Week 48).

5.1.8.2. HIV/HCV Coinfection

Safety of B/F/TAF in HIV/HCV-coinfection is supported by data from the 4 Phase 3 studies of B/F/TAF in adult subjects. Overall, 25 subjects in the Safety Analysis Sets of these studies had HIV/HCV coinfection at baseline (B/F/TAF group 10 subjects; comparator groups 15 subjects),

and 16 subjects met the SAP-defined criteria for incident HCV infection (B/F/TAF group 8 subjects; comparator groups 8 subjects) (GS-US-380-1489 Interim Week 48, Table 8.3.2; GS-US-380-1490 Interim Week 48, Table 8.3.2, GS-US-380-1844 Interim Week 48, Table 8.3.2, and GS-US-380-1878 Interim Week 48, Table 8.3.2). Safety results for subjects with HIV/HCV-coinfection at baseline in these studies are summarized in Sections 5.1.8.2.1 and 5.1.8.2.2. Detailed safety results for HIV/HCV coinfected subjects, including subjects with incident HCV coinfection, are presented in the CSRs (Study GS-US-380-1489 Interim Week 48, Section 11.2.4.1.3, Study GS-US-380-1490 Interim Week 48, Section 11.2.4.1.3.2, Study GS-US-380-1844 Interim Week 48, Section 11.2.4.1.3, and Study GS-US-380-1878 Interim Week 48, Section 11.2.4.1.3.2).

Hepatic safety data from the Phase 3 B/F/TAF and Phase 2 BIC+F/TAF studies, including hepatic AEs and liver-related laboratory parameters, are summarized in Section 2.1.5.1.

5.1.8.2.1. ART-naive Adult Subjects

Study GS-US-380-1489

HIV/HCV baseline-coinfection was defined in the SAP for Study GS-US-380-1489 as subjects with positive HCVAb and HCV RNA ≥ 15 IU/mL on or prior to the first dose date. At baseline, 4 subjects (1.3%) in the ABC/DTG/3TC group had HIV/HCV coinfection. The hepatic AE profile in those subjects was consistent with underlying hepatitis infection. As expected in this subject population, elevations in AST and ALT occurred more frequently than in the subjects without viral hepatitis infection.

Study GS-US-380-1490

HIV/HCV baseline-coinfection was defined in the SAP for Study GS-US-380-1490 as subjects with positive HCVAb and HCV RNA ≥ 15 IU/mL on or prior to the first dose date. At baseline, 10 (1.6%) subjects met SAP-defined criteria for coinfection with HCV at baseline (B/F/TAF 1.6%, 5 subjects; DTG+F/TAF 1.5%, 5 subjects).

Eight of the 10 subjects with HIV/HCV baseline-coinfection continued study treatment through Week 48. Subject 02191-2149 in the B/F/TAF group was lost to follow up and discontinued on Day 33. Four of these 8 subjects had available Week 48 HCV RNA assessments, of whom 2 subjects (1 in each treatment group) had detectable HCV RNA at Week 48. Neither received concomitant medications for HCV during the study. Two subjects in the DTG+F/TAF group with undetectable HCV RNA at Week 48, Subjects 02140-2351 and 11288-2413, received HCV treatment: Subject 02140-2351 received Harvoni® (LDV/SOF) from Study Days 114 to 211, and Subject 11288-2413 initiated Sovaldi® (SOF) with Daklinza® (daclatasvir) on Study Day 255 and was continuing HCV treatment at the time of the Week 48 analysis.

The AEs reported by HIV/HCV baseline-coinfected subjects were generally similar to those reported by HIV monoinfected subjects in this study. No subjects with HIV/HCV coinfection at baseline had a hepatic AE during the study.

Overall, 1 subject with HIV/HCV baseline coinfection experienced a treatment-emergent Grade 3 or 4 hepatic laboratory abnormality. Subject 02106-2023 in the B/F/TAF group, who had Grade 1 ALT (82 U/L) and Grade 2 AST (95 U/L) at baseline, had Grade 3 ALT (271 U/L) and AST (267 U/L) at Week 8. At Week 48, the subject had Grade 3 ALT (217 U/L) and Grade 2 AST (174 U/L).

As expected in HIV/HCV coinfected subjects, elevations in AST and ALT occurred more frequently than in the subjects without viral hepatitis infection. The incidence of graded AST and ALT elevations for HIV/HCV baseline-coinfected subjects was similar between the 2 treatment groups.

5.1.8.2.2. Virologically Suppressed Adult Subjects

Study GS-US-380-1844

HIV/HCV baseline-coinfection was defined in the SAP for Study GS-US-380-1844 as subjects with positive HCVAb and HCV RNA ≥ 15 IU/mL on or prior to the first dose date. At baseline, 1 subject (0.2%), in the ABC/DTG/3TC group, had HIV/HCV coinfection. The hepatic AE profile in the 1 subject coinfected with HIV-1 and HCV was consistent with underlying hepatitis infection. As expected, elevations in AST and ALT occurred more frequent for this subject than in the subjects without viral hepatitis infection.

Study GS-US-380-1878

HIV/HCV baseline-coinfection was defined in the SAP for Study GS-US-380-1878 as subjects with positive HCVAb and HCV RNA ≥ 15 IU/mL on or prior to the first dose date. At baseline, 10 subjects (1.7%) were identified as being coinfected with HIV-1 and HCV (B/F/TAF 1.7%, 5 subjects; SBR 1.7%, 5 subjects).

The AEs reported by HIV/HCV baseline-coinfected subjects were generally similar to those reported by HIV monoinfected subjects in this study. No subjects with HIV/HCV coinfection at baseline had a hepatic AE during the study.

All 10 subjects with HIV/HCV baseline-coinfection continued study treatment through Week 48. Of the 8 subjects with available HCV RNA assessment at Week 48, 7 subjects had detectable HCV RNA, of whom only 1 had a record of receiving treatment for hepatitis C during the course of the study. One subject in the B/F/TAF group, with a baseline HCV RNA of 1010 IU/mL, initiated treatment with Harvoni® (ledipasvir/sofosbuvir) on Study Day 330. The subject's HCV RNA level at Week 48 (Day 334) was 71 IU/mL. Overall, 1 subject had undetectable HCV RNA at Week 48: this subject, with a baseline HCV RNA of 2,630,000 IU/mL, was receiving RTV-boosted ATV plus ABC/3TC and initiated therapy with Epclusa® (sofosbuvir/velpatasvir) on Study Day 315, approximately 3 weeks before the Week 48 assessment.

Overall, 2 subjects with HIV/HCV baseline-coinfection (1 subject in each treatment group) experienced a treatment-emergent Grade 3 or 4 hepatic laboratory abnormality. One subject in the B/F/TAF group had elevated ALT (246 U/L, Grade 3) at the baseline visit and Grade 4 ALT (467 U/L) abnormality at Week 48. One week later, ALT decreased to 166 U/L (Grade 2).

One subject in the SBR group, who was receiving RTV-boosted ATV plus FTC/TDF, had elevated total bilirubin (2.6 mg/dL, Grade 2) at the baseline visit and a Grade 3 total bilirubin (3.2 mg/dL) abnormality at Week 24. By Week 36, the total bilirubin returned to baseline level (2.5 mg/dL, Grade 2). Direct bilirubin was not graded during the study. Both subjects completed study drug treatment in the randomized phase and continued to the extension phase of the study.

As expected in HIV/HCV coinfected subjects, elevations in AST and ALT occurred more frequently than in the subjects without viral hepatitis infection. The incidence of graded AST and ALT elevations for HIV/HCV baseline-coinfected subjects was similar between the 2 treatment groups.

5.1.9. CHB Monoinfection

Safety of B/F/TAF is supported by studies of the B/F/TAF components FTC (Study FTCB-101) and TAF (Studies GS-US-320-0101, GS-US-320-0108, and GS-US-320-0110) in HIV-negative subjects with CHB monoinfection.

The safety of B/F/TAF and its components in HIV-infected subjects with HIV/HBV coinfection is described in Section 5.1.8.1.

Hepatic safety data from the Phase 3 B/F/TAF and Phase 2 BIC+F/TAF studies, including hepatic AEs and liver-related laboratory parameters, are summarized in Section 2.1.5.1.

5.1.9.1. FTC

Study FTCB-101 was a Phase 1, open-label, dose-escalation study to evaluate the safety, tolerance, PK, and anti-HBV activity of multiple repeated doses of 5 once-daily dosage regimens (25, 50, 100, 200, and 300 mg once daily) of FTC monotherapy for 56 days (8 weeks) in subjects with CHB monoinfection. At least 8 (up to 11) subjects were enrolled in each dose cohort. Based on the steady-state data from FTCB-101, FTC PK in HBV-infected subjects are generally similar to those determined previously in healthy subjects and in HIV-infected subjects.

The data show that mean $C_{max,ss}$ and AUC_{tau} values of FTC in HBV-infected subjects (receiving 200-mg dose in capsule) appeared to be comparable with those in healthy subjects (receiving 200-mg dose in solution). The mean $C_{max,ss}$ and AUC_{tau} values of FTC in HBV-infected subjects were slightly higher than those in the HIV-infected subjects; however, the small differences are not likely to be clinically significant.

A complete study description and results are provided in the CSR (FTCB-101 Final).

5.1.9.2. TAF

The safety of B/F/TAF in HIV/HBV coinfection is supported by a Phase 1b, randomized, open-label, active controlled study that assessed the safety, viral kinetics, and anti-HBV activity of TAF in adult subjects with CHB (Study GS-US-320-0101), and 2 randomized, double-blind, active-controlled studies of TAF in HBeAg-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) subjects with CHB monoinfection. Safety of TAF 25 mg in HBV monoinfection is relevant to B/F/TAF in HIV/HBV-coinfected subjects.

Study GS-US-320-0101

A total of 51 subjects were randomized into Study GS-US-320-0101. Ten subjects received TAF 8 mg, 10 subjects received TAF 25 mg, 11 subjects received TAF 40 mg, 10 subjects received TAF 120 mg, and 10 subjects received TDF 300 mg for 28 days.

TAF was safe and well tolerated. No deaths, SAEs, Grade 3 or 4 AEs, or AEs leading to discontinuation of study drug were reported during this study. The safety profile for TAF did not differ among dose groups.

A complete study description and results are provided in the CSR (GS-US-320-0101 Final).

Studies GS-US-320-0108 and GS-US-320-0110

In Studies GS-US-320-0108 and GS-US-320-0110, eligible subjects were randomized in a 2:1 ratio to receive TAF 25 mg or TDF 300 mg once daily for 96 weeks, followed by an optional open-label extension phase during which all subjects received TAF 25 mg for up to 48 weeks. The numbers of subjects by treatment group in the Safety Analysis Set for each study were as follows:

- Study GS-US-320-0108: TAF 25 mg: 285 subjects; TDF 300 mg: 140 subjects
- Study GS-US-320-0110: TAF 25 mg: 581 subjects; TDF 300 mg: 292 subjects

Adverse Events

The rate and types of AEs were similar in the 2 treatment groups for Studies GS-US-320-0108 and GS-US-320-0110. Most AEs were Grade 1 or 2. Grade 3 AEs occurred in only 4.5% of subjects in the TAF group and 3.9% of subjects in the TDF group. No subjects had a Grade 4 AE.

The 3 most frequently reported AEs were upper respiratory tract infection (9.9%, 86 subjects), nasopharyngitis (9.9%, 86 subjects), and headache (9.5%, 82 subjects) in the TAF group and headache (8.3%, 36 subjects), upper respiratory tract infection (7.4%, 32 subjects), and nasopharyngitis (7.2%, 31 subjects) in the TDF group.

Study drug-related AEs and AEs leading to premature study drug discontinuation were infrequent. Similar percentages of subjects had an AE leading to premature discontinuation of study drugs in each treatment group: 1.0% (9 of 866 subjects) in the TAF group and 1.2% (5 of 432 subjects) in the TDF group. HCC and nausea were the only AEs leading to premature discontinuation of study drugs that occurred in > 1 subject in either treatment group.

The type, frequency, and severity of SAEs were similar in each treatment group. Similar percentages of subjects had SAEs in each treatment group: 4.2% (36 of 866 subjects) in the TAF group and 4.9% (21 of 432 subjects) in the TDF group. None of the SAEs were considered by the investigator to be related to study drugs. HCC was the only SAE reported at a frequency > 1% in either treatment group: 0.1% (1 of 866 subjects) in the TAF group and 1.2% (5 of 432 subjects) in the TDF group. The lower rate of HCC observed in the TAF group compared with the TDF group was statistically significant (p = 0.017).

No treatment-emergent deaths occurred. Two deaths occurred after study drugs were discontinued and were considered not treatment emergent. One subject, who had received TAF, contracted H1N1 influenza and died as a consequence of cardiorespiratory arrest on Day 100, 3 days after receiving the last dose of study drugs. The subject's death was preceded by complications of pneumonitis with sepsis, acute kidney injury, hepatic encephalopathy, and respiratory failure. The other subject, who had received TDF, died as a consequence of HCC on Day 392, 9 days after the last dose of study drug.

Clinical Laboratory Abnormalities

There were no clinically relevant median changes from baseline within groups or differences between the treatment groups in values for hematology or clinical chemistry parameters, and median values for these parameters were within normal ranges in Studies GS-US-320-0108 and GS-US-320-0110.

Most subjects had at least 1 laboratory abnormality: 94.8% in the TAF group and 91.1% in the TDF group. The majority of laboratory abnormalities were Grade 1 or 2. A similar percentage of subjects in each group had Grade 3 or 4 laboratory abnormalities (TAF 31.3%; TDF 29.4%). The Grade 3 or 4 chemistry laboratory abnormality that occurred in > 5% of subjects overall in both groups was increased ALT (TAF 8.1% [70 of 859 subjects]; TDF 9.3% [40 of 428 subjects]). In addition, Grade 3 or 4 increased AST also occurred in > 5% of subjects in the TDF group (TAF 3.3% [28 of 859 subjects]; TDF 5.4% [23 of 428 subjects]). No Grade 3 or 4 hematology laboratory abnormality occurred in > 1% of subjects overall in both groups.

The incidence of hepatic laboratory abnormalities was generally lower in the TAF group compared with subjects in the TDF group. Graded hepatic laboratory abnormalities included increased ALT (TAF 22.8%; TDF 30.4%), increased AST (TAF 22.2%; TDF 25.2%), increased gamma-glutamyltransferase (GGT) (TAF 7.5%; TDF 10.0%), increased ALP (TAF 2.2%; TDF 5.4%), and decreased albumin (TAF 0.9%; TDF 1.9%). The percentage of subjects with increased total bilirubin was higher in the TAF group (12.7%) compared with the TDF group (10.0%). Most hepatic laboratory abnormalities in both treatment groups were Grade 1 or 2. Grade 3 or 4 ALT abnormalities and Grade 3 or 4 AST abnormalities were observed in lower percentages of subjects in the TAF group compared with the TDF group. Grade 3 or 4 ALT abnormalities occurred in 8.1% of subjects in the TAF group and 9.3% of subjects in the TDF group, and Grade 3 or 4 AST abnormalities occurred in 3.3% of subjects in the TAF group and in 5.4% of subjects in the TDF group.

ALT elevations (defined as ALT > 2 × baseline and > 10 × ULN, with or without associated symptoms) were observed for 16 of 866 subjects (1.8%) in the TAF group and 9 of 432 subjects (2.1%) in the TDF group. With few exceptions, the events occurred at isolated time points within the first 8 weeks of dosing and resolved without recurrence while the subject remained on study drug.

Nine of 25 ALT elevations also met the protocol definition for ALT flare (ie, ALT elevation confirmed at 2 consecutive visits), which occurred in 5 of 866 subjects (0.6%) in the TAF group and 4 of 432 subjects (0.9%) in the TDF group. With the exception of 2 events, ALT flares occurred early in the dosing period (baseline to Week 8). For 7 of the 9 subjects, the ALT flares

resolved without recurrence while the subject remained on study drug. Subjects with ALT flares typically were not associated with coincident elevations in bilirubin; only 1 subject in the TDF group had a concurrent Grade 1 bilirubin elevation.

Overall, the safety profile for TAF in subjects with CHB monoinfection is similar to the safety profile for TAF in HIV-infected subjects.

Complete study descriptions and results are provided in the CSRs (GS-US-320-0108 Week 48 and GS-US-320-0110 Week 48).

5.2. Extrinsic Factors

5.2.1. Region

ART-Naive Adult Subjects

In ART-naive adult subjects in the pooled Studies GS-US-380-1489 and GS-US-380-1490, the incidence of AEs in subjects from the United States (US) and regions outside the US (ex-US) (B/F/TAF Week 48 ISS, Table 8.6) was as follows:

- Pooled B/F/TAF group: US 81.9%, 345 of 421 subjects; Ex-US 86.4%, 184 of 213 subjects
- ABC/DTG/3TC group: US 89.7%, 209 of 233 subjects; Ex-US 90.2%, 74 of 82 subjects
- DTG+F/TAF group: US 78.8%, 152 of 193 subjects; Ex-US 90.9%, 120 of 132 subjects

Virologically Suppressed Adult Subjects

In Study GS-US-380-1844, the incidence of AEs in subjects from US and ex-US regions was as follows:

- B/F/TAF: US 78.3%, 159 of 203 subjects; ex-US 83.5%, 66 of 79 subjects
- ABC/DTG/3TC: US 77.8%, 154 of 198 subjects; ex-US 85.5%, 71 of 83 subjects

In Study GS-US-380-1878, the incidence of AEs in subjects from US and ex-US regions was as follows:

- B/F/TAF: US 74.1%, 123 of 166 subjects; ex-US 88.7%, 110 of 124 subjects
- SBR: US 71.3%, 117 of 164 subjects; ex-US 88.6%, 109 of 123 subjects

5.3. Drug Interactions

The drug-drug interaction potential between B/F/TAF or the components of B/F/TAF and drugs than may be concomitantly used by patients with HIV infection has been evaluated in several clinical studies following administration of BIC, TAF, or FTC as individual agents or in combination. A detailed summary of drug interaction potential and management of known interactions is provided in m2.7.2, Section 3.2.4.2.

5.4. Use in Pregnancy and Lactation

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

In animal studies, it has been shown that TFV is excreted into milk. In animal studies, BIC was detected in the plasma of nursing rat pups, likely due to the presence of BIC in milk, without effects on nursing pups. It is not known whether BIC or TAF are excreted in human milk. In humans, samples of breast milk obtained from 5 HIV-infected mothers given Truvada® (emtricitabine/tenofovir disoproxil fumarate, coformulated; FTC/TDF) show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of FTC. Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown. Because of the potential for HIV transmission, the potential for the development of viral resistance in HIV-positive infants, and the potential for adverse reactions in nursing infants similar to those seen in adults, mothers should be instructed not to breastfeed if they are receiving the B/F/TAF FDC.

5.4.1. Phase 1 Studies with Single-agent BIC or Regimens Containing BIC and F/TAF

No pregnancies were reported in Phase 1 studies with single-agent BIC or regimens containing BIC and F/TAF.

5.4.2. Phase 2 and 3 B/F/TAF Studies

Eleven pregnancies were reported in the Phase 3 B/F/TAF studies. A summary of pregnancies is provided in the individual CSRs (GS-US-380-1489 Interim Week 48, Section 11.8; GS-US-380-1490 Interim Week 48, Section 11.8; GS-US-380-1844 Interim Week 48, Section 11.9; and GS-US-380-1878 Interim Week 48, Section 11.9). No pregnancies were reported in the Phase 2 study GS-US-141-1475.

Study GS-US-380-1489

Two confirmed pregnancies were reported during Study GS-US-380-1489 (B/F/TAF 1 subject; ABC/DTG/3TC 1 subject).

A 2[redacted]-year-old subject in the B/F/TAF group had a confirmed pregnancy on Day 294. Study drugs were discontinued, with the last dose administered on Day 297 ([redacted] 20[redacted]). The subject's pregnancy was uncomplicated as of the date of this report. Her estimated due date is [redacted] 20[redacted].

A 3[redacted]-year-old subject in the ABC/DTG/3TC group had a confirmed pregnancy on Day 427. The subject had an elective abortion on Day 439 ([redacted] 20[redacted]) and remained on study drugs. The subject recovered from the procedure without complications.

Study GS-US-380-1490

Six confirmed pregnancies were reported during Study GS-US-380-1490 for 6 subjects (B/F/TAF 3 subjects; DTG+F/TAF 3 subjects).

A 2[redacted]-year-old subject in the DTG+F/TAF group had a confirmed pregnancy on Day 247. Study drugs were interrupted from Day 247 to Day 254. The subject terminated the pregnancy.

A 3[redacted]-year-old subject in the DTG+F/TAF group had a confirmed pregnancy on Day 11. Study drugs were discontinued with the last dose administered on Day 10. She delivered a healthy baby male on [redacted] 20[redacted].

A 3[redacted]-year-old subject in the B/F/TAF group had a confirmed pregnancy on Day 302. Study drugs were discontinued with the last dose administered on Day 299. Her estimated delivery date is [redacted] 20[redacted].

A 3[redacted]-year-old subject in the B/F/TAF group had a confirmed pregnancy on Day 93. Study drugs were temporarily interrupted. The subject had a spontaneous abortion on Day 259 which was reported as Grade 2 SAE of incomplete abortion considered unrelated to study drugs. The SAE resolved the next day. The subject restarted study drugs on Day 269.

A 2[redacted]-year-old subject in the B/F/TAF group had a confirmed pregnancy on Day 93. Study drugs were discontinued with the last dose administered on Day 91. She delivered a healthy baby girl on [redacted] 20[redacted].

A 3[redacted]-year-old subject in the DTG+F/TAF group had a confirmed pregnancy on Day 58. Study drugs were discontinued with the last dose administered on Day 57. She delivered a healthy baby male on [redacted] 20[redacted].

Study GS-US-380-1844

Two confirmed pregnancies were reported during Study GS-US-380-1844 (1 subject in each treatment group).

A 2[redacted]-year-old subject in the B/F/TAF group had a confirmed pregnancy on Day 325. Study drugs were discontinued, with the last dose administered on Day 335 ([redacted] 20[redacted]). The estimated date of delivery is [redacted] 20[redacted].

A 2[redacted]-year-old subject in the ABC/DTG/3TC group had a confirmed pregnancy on Day 225. Study drugs were discontinued, with the last dose administered on Day 211 ([redacted] 20[redacted]). The pregnancy resulted in live birth at approximately 25 weeks of gestation (data on file); no other information was available at the time of this report.

Study GS-US-380-1878

One subject in the SBR group had a confirmed pregnancy in Study GS-US-380-1878.

A 3[redacted]-year-old subject in the SBR group had a positive pregnancy test on Day 315 ([redacted] 20[redacted]; first day of dosing with B/F/TAF in the extension phase of the study). Approximately 4 days earlier, the subject had presented to a hospital with heavy vaginal bleeding and was found to be pregnant by a urine pregnancy test. An ultrasound revealed fetal demise with no fetal heartbeat or yolk sac. She was re-educated regarding contraception, and continued dosing with B/F/TAF in the extension phase. The intrauterine fetal demise was considered serious, resolved (stop date of [redacted] 20[redacted]), and not related to concomitant study drugs (Truvada®, Prezista®, and Norvir®) or study procedures.

5.4.3. F/TAF

Pregnancies in clinical studies are described in individual CSRs. The safety of the use of TAF and FTC during pregnancy or breast-feeding is reflected in the respective approved drug label for Descovy®. This product should only be used in pregnancy if the potential benefit justifies the potential risk.

Cumulative Antiretroviral Pregnancy Registry (APR) interim analysis reports are produced at 6-month intervals, and the latest report was issued in [redacted] 20[redacted] (data to [redacted] 20[redacted]). The cumulative data for TAF- and FTC-containing regimens is provided below.

A total of 2326 first trimester exposure and 1080 second/third trimester exposure prospective cases of live births involving exposure to FTC were presented. There were 54 cases of birth defects following first trimester exposure and 22 cases of a birth defects following second/third trimester exposure. The prevalence of defects per 100 live births for first trimester exposures to FTC is 2.3% (95% CI: 1.7% to 3.0%) and 2.0% (95% CI: 1.3% to 3.1%) with earliest exposure to FTC in the second/third trimester.

A total of 1 first trimester exposure and 3 second/third trimester exposure prospective cases of live births involving exposure to TAF were presented. There were no cases of birth defects following first trimester or second/third trimester exposure to TAF.

The main conclusions from the latest APR report were as follows:

Primary Registry Analysis (Prospective Reports)

For FTC, sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. There are insufficient data to make similar comparisons for TAF. Measured against 17,371 live births with exposure at any time during pregnancy, there were 484 outcomes with birth defects identified, a prevalence of 2.8 birth defects per 100 live births (95% CI: 2.5-3.0). This proportion is not significantly higher than those reported in the Registry's two population based comparators, the Centers for Disease Control and Prevention

(CDC) birth defects surveillance system (Metropolitan Atlanta Congenital Defects Program [MACDP]) (2.72 per 100 live births), and the Texas Birth Defects Registry (TBDR) (4.17 per 100 live births). No increases in risk of specific defects have been detected to date when compared with observed MACDP or TBDR rates or with rates among those with earliest exposure in the second or third trimester. In analyzing individual drugs with sufficient data to warrant a separate analysis with the exception of didanosine (ddI) and nelfinavir, no increases of concern in risk have been detected.

Retrospective Reports

No pattern of defects (isolated or syndromic) associated with FTC or TAF exposure has been found in the overall evaluation of retrospective reports and registry cases of birth defects.

Reports from Clinical Studies in Pregnancy

Separate review of the available information from the clinical studies remains inconclusive. The registry will continue to examine the data as available from further studies.

Reports from the Published Literature

The registry has not identified a signal in any of the published studies reviewed to date.

5.5. Overdose

If an overdose with B/F/TAF occurs, the patient must be monitored for evidence of toxicity, and general supportive measures applied as necessary, including observation of the clinical status of the patient and monitoring of vital signs. Limited clinical experience is available at doses higher than the therapeutic doses of BIC, FTC, or TAF.

As BIC is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Up to 30% of the FTC dose may be removed by hemodialysis. TFV is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether FTC or TFV may be removed by peritoneal dialysis.

Cases of overdose are assessed within postmarketing surveillance of FTC and F/TAF are described in the periodic safety update reports (PSURs) for these products. No new safety issues have been identified regarding overdose.

5.6. Drug Abuse

No safety issues concerning the abuse or misuse of B/F/TAF tablets are anticipated from the available data.

5.7. Withdrawal and Rebound

Discontinuation of B/F/TAF therapy in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC or TAF components of B/F/TAF. Patients coinfected with HIV-1 and HBV who discontinue B/F/TAF should be closely monitored with both clinical- and laboratory-follow up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since posttreatment exacerbation of hepatitis may lead to hepatic decompensation.

5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been conducted to evaluate the effects of BIC, TAF, or FTC on the ability to drive or operate machinery.

6. POSTMARKETING DATA

B/F/TAF has not been marketed in any country at the time of this application.

7. REFERENCES

Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? Curr Med Res Opin 2014;30 (1):89-97.

Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS 2011;25 (10):1289-98.

Descovy, Gilead Sciences Ireland UC. Descovy 200 mg/10 mg film-coated tablets. Summary of Product Characteristics (SmPC). County Cork, Ireland. Revised 31 March. 2017:

DESCOVY®, Gilead Sciences Inc. DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA. Revised April. 2017:

European AIDS Clinical Society (EACS). European AIDS Clinical Society (EACS) Guidelines Version 8.2 January, 2017.

Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV Infection and the Risk of Acute Myocardial Infarction. JAMA internal medicine 2013;173 (8):1-19.

Gallant J, Thompson M, DeJesus E, Voskuhl G, Wei X, Zack J, et al. Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1–Infected Patients [Poster PW-030]. ASM Microbe; 2016 16-20 June; Boston, MA.

Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2016:191-210. vol 316).

Joint United Nations Programme on HIV/AIDS (UNAIDS). Fact Sheet 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf . 2016.

Lefebvre E, Schiffer CA. Resilience to Resistance of HIV-1 Protease Inhibitors: Profile of Darunavir. AIDS Rev 2008;10 (3):1-20.

Lichtenstein KA, Armon C, Buchacz K, Chmiel JS, Buckner K, Tedaldi EM, et al. Low $CD4^+$ T Cell Count Is a Risk Factor for Cardiovascular Disease Events in the HIV Outpatient Study. Clin Infect Dis 2010;51 (4):435-47.

Llibre JM, Imaz A, Clotet B. From TMC114 to darunavir: five years of data on efficacy. AIDS Rev 2013;15:112-21.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC) Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated 14 July. 2016.

Polakos NK, Cornejo JC, Murray DA, Wright KO, Treanor JJ, Crispe IN, et al. Kupffer Cell-Dependent Hepatitis Occurs during Influenza Infection. Am J Pathol 2006;168 (4):1169-78.

Rasmussen LD, Engsig FN, Christensen H, Gerstoft J, Kronborg G, Pedersen C, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS 2011;25 (13):1637-46.

Reyataz, Bristol Myers Squibb. Reyataz (atazanavir) highlights of prescribing information. Updated September 2016. 2016:

Sax PE, DeJesus E, Crofoot G, Ward D, Benson P, Dretler R, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. The lancet. HIV 2017.

Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. Patient preference and adherence 2012;6:427-33.

Tivicay. Tivicay 50 mg film-coated tablets Summary of Product Characteristics (SmPC). ViiV Healthcare, Middlesex, United Kingdom. Updated 19 January. 2017:

TIVICAY®, GlaxoSmithKline. TIVICAY® (dolutegravir) tablets, for oral use. US Prescribing Information. Research Triangle Park, NC. Revised March. 2017:

TRIUMEQ, GlaxoSmithKline. TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use. US Prescribing Information. Research Triangle Park, NC. Revised March. 2017a:

Triumeq, GlaxoSmithKline Pharmaceuticals S.A. Triumeq 50 mg/600 mg/300 mg film-coated tablets. Summary of Product Characteristics (SmPC). Poznan, Poland. Revised 22 February. 2017b:

U.S. Department of Health & Human Services (DHHS), Food & Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July, 2009.

Vemlidy, Gilead Sciences International Ltd. Vemlidy 25 mg film-coated tablets. Summary of Product Characteristics (SmPC). January. 2017:

VEMLIDY®. VEMLIDY® (tenofovir alafenamide) 25 mg film-coated tablets. Full Annexes. Gilead Sciences International Ltd., Cambridge, UK. Date of first authorisation 09 January. 2017:

8. APPENDIX

8.1. B/F/TAF FDC: Integrated Safety Analysis

Outputs from the integrated safety analysis of Studies GS-US-380-1489 and GS-US-380-1490 are described in the B/F/TAF Week 48 ISS SAP and are included in this submission. Additional outputs with numbering beginning with "ad hoc" present data from analyses that were not prespecified in the B/F/TAF Week 48 ISS SAP.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

LEGACY APPENDICES

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY 1

TABLE OF CONTENTS 2

1. SAFETY OF GEN 3

1.1. HIV-infected Adult Subjects with Mild to Moderate Renal Impairment 3
1.1.1. Study GS-US-292-0112 3
1.2. HIV/HBV-Coinfected Adult Subjects 4
1.2.1. Study GS-US-292-1249 5
1.3. Tabular Listing of Clinical GEN Studies 7

1. SAFETY OF GEN

Summaries of studies with Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), an emtricitabine/tenofovir alafenamide (F/TAF)-containing regimen, which provide supportive information for this bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) Summary of Clinical Safety are provided by patient population in Sections 1.1 to 1.2. A tabular listing of GEN studies is provided in Section 1.3. Further details on all of these studies are provided in the clinical study report (CSRs).

1.1. HIV-infected Adult Subjects with Mild to Moderate Renal Impairment

The principal source of supportive safety data for an F/TAF-containing regimen in adult subjects with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] calculated using the Cockcroft-Gault equation [$eGFR_{CG}$] 30 to 69 mL/min) is Study GS-US-292-0112. Pharmacokinetics (PK) was evaluated, and safety and efficacy in antiretroviral (ARV) therapy (ART)-naive and virologically suppressed adults with mild to moderate renal impairment were evaluated through Week 144.

1.1.1. Study GS-US-292-0112

Location:	GS-US-292-0112 Interim Week 24 and Interim Week 144
Title:	A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment
Objectives:	The primary objective of this study was as follows: • To evaluate the effect of GEN on renal parameters at Week 24 The secondary objectives of this study were as follows: • To evaluate the effect of GEN on renal parameters at Weeks 48, 96, and 144 • To measure the proportion of subjects achieving virologic response (HIV-1 RNA < 50 copies/mL, US Food and Drug Administration [FDA] snapshot algorithm) at Weeks 24, 48, 96, and 144 • To evaluate the safety and tolerability of GEN through 144 weeks of treatment
Study Design and Subject Population:	Subjects with a stable $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening were enrolled into Cohort 1 if they were on ART and virologically suppressed, or Cohort 2 if they were ART-naive. Subjects in Cohort 1 switched treatment from their existing ARV regimen to GEN at baseline ("switch" subjects); subjects in Cohort 2 initiated ART with GEN. For analysis purposes, Cohort 1 switch subjects were also grouped by baseline $eGFR_{CG}$ (< 50 mL/min and ≥ 50 mL/min). Of the 248 treated subjects (242 subjects in Cohort 1 and 6 subject in Cohort 2), 63.7% (158 subjects) completed study treatment up to the Week 144 data cut date, while 21.8% (54 subjects) were still on study treatment up to the data cut date (Cohort 1: 21.9% [53 subjects]; Cohort 2: 16.7% [1 subject]).

Summary of Results and Conclusions:	• Genvoya was well tolerated in subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) through Week 144. No adverse events (AEs) of proximal renal tubulopathy (or Fanconi Syndrome) were reported. • Overall, subjects with mild to moderate renal impairment who switched to GEN (containing TAF) had statistically significant improvements in eGFR at Week 144, and had rapid, persistent, and clinically significant improvements in proteinuria, albuminuria, proximal renal tubular function, and bone mineral density (BMD). — No change in actual GFR was observed through 24 weeks of treatment. — Clinically significant improvement in proteinuria, albuminuria, and tubular proteinuria were observed as soon as 1 week after switching to GEN and persisting through Week 144. There were significant decreases from baseline in the incidence of clinically significant proteinuria (from 42.3% at baseline to 15.5% at Week 144) and clinically significant albuminuria (from 48.9% at baseline to 31.6% at Week 144). — Switching to GEN generally resulted in improvements in BMD over 144 weeks. No fragility fractures were reported. • The subset of subjects with $eGFR_{CG}$ < 50 mL/min had improvements in eGFR and significant improvements in tubular function through 144 weeks after switching to once daily GEN, without dose-limiting AEs. • The subset of subjects with pre-switch TDF use showed statistically significant improvements in eGFR at Week 144, while those subjects without pre-switch tenofovir disoproxil fumarate (TDF) use had no significant changes. • Median changes from baseline in metabolic laboratory parameters at Week 144 demonstrated a trend toward increase in all parameters for subjects with pre-switch TDF use and a trend toward decrease in most parameters for subjects without pre-switch TDF use. Otherwise, no notable changes from baseline in median values for hematology, clinical chemistry, or liver-related laboratory parameters were observed through Week 144, and the majority of reported laboratory abnormalities were Grade 1 or 2. • Overall, 83.1% of subjects (Cohort 1) maintained virologic suppression (HIV-1 RNA < 50 copies/mL) through Week 144, and CD4 cell counts were stable. • The PK of the individual components of GEN in subjects with screening $eGFR_{CG}$ 30 to 69 mL/min was consistent with historical and concurrent data on these agents. • While TFV PK was higher in subjects with mild and moderate renal impairment, TFV exposures were well below those in patients with severe renal impairment and were well below the TFV exposures from TDF-containing regimens. • Despite higher emtricitabine (FTC) PK in this study, once daily administration of GEN without dose adjustment in subjects with baseline $eGFR_{CG}$ < 50 mL/min did not have a different safety profile compared with subjects with baseline $eGFR_{CG}$ < 50 mL/min and despite Emtriva® (emtricitabine; FTC) dose recommendations, GEN does not require dose adjustment in patients with $eGFR_{CG}$ ≥ 30 to < 50 mL/min.

1.2. HIV/HBV-Coinfected Adult Subjects

The principal source of supportive safety data for an F/TAF-containing regimen in HIV/hepatitis B virus (HBV)-coinfected adult subjects is Study GS-US-292-1249. Safety and efficacy data are evaluated through Week 48.

1.2.1. Study GS-US-292-1249

Location:	GS-US-292-1249 Interim Week 48
Title:	A Phase 3b Open-Label Study of the Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Single-Tablet Regimen in HIV-1/Hepatitis B Co-infected Adults
Objectives:	• To characterize the anti-HBV efficacy profile of GEN in HIV/HBV-coinfected adults as determined by the proportion of subjects with plasma HBV DNA below 29 IU/mL at Weeks 24 and 48 • To characterize the anti-HIV efficacy profile of GEN in HIV/HBV-coinfected adults by the proportion of subjects with plasma HIV-1 RNA below 50 copies/mL at Weeks 24 and 48 • To characterize the safety and tolerability profile of GEN in HIV/HBV-coinfected adults at Weeks 24 and 48 • To characterize the biochemical (alanine aminotransferase [ALT] normalization) response at Weeks 24 and 48 • To characterize serological responses (loss of hepatitis B surface antigen [HBsAg] and seroconversion to antibody against HBsAg [anti-HBs], and loss of hepatitis B e-antigen [HBeAg] and seroconversion to antibody against HBeAg [anti-HBe] [for subjects who were HBeAg positive at Day 1]) at Weeks 24 and 48 • To characterize the change in liver fibrosis as assessed by FibroTest® at Weeks 24 and 48
Study Design and Subject Population:	Eligible subjects were HIV and HBV (chronic) coinfected men and nonpregnant and nonlactating women ≥ 18 years of age with a CD4 cell count > 200 cells/μL, ALT ≤ 10 × ULN, total bilirubin ≤ 2.5 mg/dL, international normalized ratio ≤ 1.5, albumin ≥ 3 g/dL, and screening $eGFR_{CG}$ of ≥ 50 mL/min, no evidence of cirrhosis or hepatocellular carcinoma, and hepatitis C virus (HCV) and hepatitis D virus negative. Subjects in Cohort 1 (ART-naive) were required to have no current or prior anti-HIV treatment, no current or prior anti-HBV treatment, plasma HIV-1 RNA ≥ 500 copies/mL, HIV sensitive to FTC and TDF, and HBV DNA ≥ 3 log_{10} IU/mL and < 9 log_{10} IU/mL. Subjects in Cohort 2 (HIV-suppressed) must have received a current ARV regimen for at least 4 consecutive months with no current or prior regimen containing 3 active anti-HBV agents, maintained plasma HIV-1 RNA < 50 copies/mL for 6 consecutive months before screening, and had HBV DNA < 9 log_{10} IU/mL. A total of 74 HIV-suppressed subjects received at least 1 dose of study drug. Two HIV-suppressed subjects did not meet the inclusion criterion for chronic HBV infection and were excluded from the Full Analysis Set (FAS). As of the data cutoff date, 67 (90.5%) HIV-suppressed subjects were still receiving study drug. All of these subjects were participating in the extension phase. Six subjects discontinued study drug before the Week 48 visit due to withdrawn consent (3 subjects), or AE, lack of efficacy, and lost to follow up (1 subject each). One additional subject discontinued study drug in the extension phase due to noncompliance. The subject who discontinued study drug due to lack of efficacy remained in the study; the other 6 subjects also discontinued the study.

Summary of Results and Conclusions:	• In HIV-suppressed subjects, GEN effectively maintained HIV and HBV virologic suppression for subjects switching from primarily TDF-containing regimens. — At Weeks 24 and 48, 94.4% and 91.7% of subjects, respectively, had virologic success (HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm). — At Weeks 24 and 48, the overall percentage of subjects with HBV DNA < 29 IU/mL (missing = failure) was 86.1% and 91.7% of subjects, respectively. • The rates of seroconversion to anti-HBs and anti-HBe achieved at Week 48 in subjects who were HBV-antigen positive at baseline were 2.9% and 3.3%, respectively. • At Week 48, ALT normalization was achieved in 40% of subjects (4 of 10 subjects) with ALT greater than ULN at baseline. • FibroTest scores improved over the 48-week treatment period, with a median change from baseline of −0.04 at Week 48. • GEN was generally well tolerated with no on-study deaths and low incidences of SAEs and discontinuations of study drug due to AEs. • Bone turnover biomarkers (serum C-telopeptide and P1NP) improved over the 48-week treatment period, with median changes from baseline of −12.5% and −28.52% for C-telopeptide and P1NP, respectively, at Week 48. • In these subjects with normal renal function, a modest, statistically significant improvement in $eGFR_{CG}$ was observed at Week 48 (median change from baseline of 3.3 mL/min), and no subjects had an AE of proximal renal tubulopathy or discontinued study drugs due to a renal AE. • No subject had an ALT flare, and assessments of other liver-related parameters did not reveal any concerns for increased risk of hepatic clinical outcomes. • There were increases from baseline to Week 48 in total cholesterol and direct low-density lipoprotein (LDL) cholesterol (median changes from baseline of 15 and 9 mg/dL, respectively). However, no change was observed in the total cholesterol to high-density lipoprotein (HDL) ratio.

1.3. Tabular Listing of Clinical GEN Studies

Type of Study	Study Number	Study Objective(s)	Study Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects by Treatment	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	GS-US-292-0112	Evaluate the effect of the GEN on renal parameters at Week 24 Evaluate the safety and tolerability of GEN through 144 weeks of treatment	Phase 3, open-label, multicenter, multi-cohort study	GEN (E/C/F/TAF; 150/150/200/10 mg) QD PO	144 weeks Extension Phase: Subjects have option to continue study drug for another 48 weeks until GEN is commercially available, becomes available through an access program, or development is terminated	Enrolled: 252 Safety Analysis Set: Cohort 1: 242 Cohort 2: 6	HIV infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min Cohort 1: ART-experienced Cohort 2: ART-naive	Study ongoing; Interim Week 24 CSR Interim Week 144 CSR
Uncontrolled Clinical Studies	GS-US-292-1249	Assess the safety, efficacy, and tolerability of GEN in HIV/HBV-coinfected subjects	Phase 3b, open-label, multicenter, single-group, dual-cohort study	GEN (E/C/F/TAF; 150/150/200/10 mg) QD PO	48 weeks Extension Phase: Subjects have option to continue study drug until GEN is commercially available or development is terminated	Enrolled: 79 Safety Analysis Set: Cohort 1: 3 Cohort 2: 74	HIV/HBV coinfected, adult subjects Cohort 1: HIV/HBV treatment-naïve Cohort 2: HIV suppressed	Study ongoing; Interim Week 48 CSR

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.5—LITERATURE REFERENCES

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

1. LITERATURE REFERENCES

The following references are cited in the Clinical Summary documents (ie, m2.7.1 to m2.7.4). Copies of these references are available upon request if not provided with this submission.

Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? Curr Med Res Opin 2014;30 (1):89-97.

Birkus G, Hitchcock MJM, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. Antimicrob Agents Chemother 2002;46 (3):716-23.

Birkus G, Kutty N, He GX, Mulato A, Lee W, McDermott M, et al. Activation of 9-[(R)-2-[[(S)-[[(S)-1-(Isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]-methoxy]propyl]adenine (GS-7340) and other tenofovir phosphonoamidate prodrugs by human proteases. Mol Pharmacol 2008;74 (1):92-100.

Birkus G, Wang R, Liu XH, Kutty N, MacArthur H, Cihlar T, et al. Cathepsin A is the major hydrolase catalyzing the intracellular hydrolysis of the antiretroviral nucleotide phosphonoamidate prodrugs GS-7340 and GS-9131. Antimicrob Agents Chemother 2007;51 (2):543-50.

Cherrington JM, Allen SJW, Bischofberger N, Chen MS. Kinetic interaction of the diphosphates of 9-(2-phosphonylmethoxyethyl)adenine and other anti-HIV active purine congeners with HIV reverse transcriptase and human DNA polymerases α, β, and γ. Antivir Chem Chemother 1995;6 (4):217-21.

Cherrington JM, Allen SJW, McKee BH, Chen MS. Kinetic analysis of the interaction between the diphosphate of (*S*)-1-(3- hydroxy-2-phosphonylmethoxypropyl)cytosine, ddCTP, AZTTP, and FIAUTP with human DNA polymerases β and γ. Biochem Pharmacol 1994;48 (10):1986-8.

Cherrington JM, Mulato AS, Fuller MD, Chen MS. In vitro selection and characterization of HIV-1 viral isolates with reduced sensitivity to PMEA. 4th International HIV Resistance Conference; 1995 Jul; Sardinia, Italy.

Choi AI, Vittinghoff E, Deeks SG, Weekley CC, Li Y, Shlipak MG. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. AIDS 2011;25 (10):1289-98.

Delaney WE, IV, Ray AS, Yang H, Qi X, Xiong S, Zhu Y, et al. Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. Antimicrob Agents Chemother 2006;50 (7):2471-7.

Descovy, Gilead Sciences Ireland UC. Descovy 200 mg/10 mg film-coated tablets. Summary of Product Characteristics (SmPC). County Cork, Ireland. Revised 31 March. 2017:

DESCOVY®, Gilead Sciences Inc. DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA. Revised April. 2017:

Emtriva, Gilead Sciences Ltd. Emtriva 200 mg hard capsules Summary of Product Characteristics (SmPC). Gilead Sciences Ltd, High Holborn, London Updated 16 November. 2016:

EMTRIVA®, Gilead Sciences Inc. EMTRIVA® (emtricitabine) capsule, for oral use. EMTRIVA® (emtricitabine) oral solution. US Prescribing Information. Foster City, CA. Revised April. 2017:

European AIDS Clinical Society (EACS). European AIDS Clinical Society (EACS) Guidelines Version 8.2 January, 2017.

European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. [Article In Press]. J Hepatol 2017:1-29.

Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV Infection and the Risk of Acute Myocardial Infarction. JAMA internal medicine 2013;173 (8):1-19.

Frick LW, St. John L, Taylor LC, Painter GR, Furman PA, Liotta DC, et al. Pharmacokinetics, oral bioavailability, and metabolic disposition in rats of (-)-cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine, a nucleoside analog active against human immunodeficiency virus and hepatitis B virus. Antimicrob Agents Chemother 1993;37 (11):2285-92.

Furman PA, Davis M, Liotta DC, Paff M, Frick LW, Nelson DJ, et al. The anti-hepatitis B virus activities, cytotoxicities, and anabolic profiles of the (-) and (+) enantiomers of cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Antimicrob Agents Chemother 1992;36 (12):2686-92.

Gallant J, Thompson M, DeJesus E, Voskuhl G, Wei X, Zack J, et al. Novel Integrase Strand Transfer Inhibitor Bictegravir 10 Day Monotherapy in HIV-1–Infected Patients [Poster PW-030]. ASM Microbe; 2016 16-20 June; Boston, MA.

GENVOYA®, Gilead Sciences Inc. GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. Revised April. 2017:

Gilead Sciences Inc. VIREAD® (tenofovir disoproxil fumarate) tablets, for oral use. VIREAD® (tenofovir disoproxil fumarate) powder, for oral use. US Prescribing Information. Revised June 2015:

Gilead Sciences International Limited. Viread 245 mg film-coated tablets: Summary of Product Characteristics. United Kingdom. Updated December 2014:

Gilead Sciences International Ltd. Descovy 200 mg/10 mg film-coated tablets (SmPC). 2016:

GlaxoSmithKline. TIVICAY (dolutegravir) Tablets for Oral Use. U.S. Prescribing Information. Research Triangle Park, NC. Revised August. 2015:

Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2016:191-210. Vol 316).

Hill J. In vitro synergy studies of FTC in combination with MKC 442, AZT, Nelfinavir (NELF), Nevirapine (NEV) against HIV. Triangle Pharmaceuticals, Inc. Report No. Doc #470. July 31, 1997.

Inoue M, Morikawa M, Tsuboi M, Ito Y, Sugiura M. Comparative study of human intestinal and hepatic esterases as related to enzymatic properties and hydrolizing activity for ester-type drugs. Japanese journal of pharmacology 1980;30 (4):529-35.

Jeong LS, Schinazi RF, Beach JW, Kim HO, Nampalli S, Shanmuganathan K, et al. Asymmetric synthesis and biological evaluation of beta-L-(2R,5S)- and alpha-L-(2R,5R)-1,3-oxathiolane-pyrimidine and -purine nucleosides as potential anti-HIV agents. J Med Chem 1993;36 (2):181-95.

Joint United Nations Programme on HIV/AIDS (UNAIDS). Fact Sheet 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. 2016.

Kagan RM, Lee TS, Ross L, Lloyd RM, Jr., Lewinski MA, Potts SJ. Molecular basis of antagonism between K70E and K65R tenofovir-associated mutations in HIV-1 reverse transcriptase. Antiviral Res 2007;75 (3):210-8.

Kalayjian RC, Landay A, Pollard RB, Taub DD, Gross BH, Francis IR, et al. Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. J Infect Dis 2003;187 (12):1924-33.

Kramata P, Downey KM, Paborsky LR. Incorporation and excision of 9-(2-phosphonylmethoxyethyl)guanine (PMEG) by DNA polymerase delta and epsilon in vitro. J Biol Chem 1998;273 (34):21966-71.

Lee WA, He G-X, Eisenberg E, Cihlar T, Swaminathan S, Mulato A, et al. 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. Antimicrob Agents Chemother 2005;49 (5):1898-906.

Lefebvre E, Schiffer CA. Resilience to Resistance of HIV-1 Protease Inhibitors: Profile of Darunavir. AIDS Rev 2008;10 (3):1-20.

Lichtenstein KA, Armon C, Buchacz K, Chmiel JS, Buckner K, Tedaldi EM, et al. Low $CD4^+$ T Cell Count Is a Risk Factor for Cardiovascular Disease Events in the HIV Outpatient Study. Clin Infect Dis 2010;51 (4):435-47.

Liu Y, Miller MD, Kitrinos KM. Tenofovir alafenamide demonstrates broad cross-genotype activity against wild-type HBV clinical isolates and maintains susceptibility to drug-resistant HBV isolates in vitro. Antiviral Res 2017;139:25-31.

Llibre JM, Imaz A, Clotet B. From TMC114 to darunavir: five years of data on efficacy. AIDS Rev 2013;15:112-21.

Margot NA, Lu B, Cheng A, Miller MD. Resistance development over 144 weeks in treatment-naive patients receiving tenofovir disoproxil fumarate or stavudine with lamivudine and efavirenz in Study 903. HIV Med 2006;7 (7):442-50.

Margot NA, Waters JM, Miller MD. In Vitro Human Immunodeficiency Virus Type 1 Resistance Selections with Combinations of Tenofovir and Emtricitabine or Abacavir and Lamivudine. Antimicrob Agents Chemother 2006;50 (12):4087-95.

Miller MD, Anton KE, Mulato AS, Lamy PD, Cherrington JM. Human immunodeficiency virus type 1 expressing the lamivudine-associated M184V mutation in reverse transcriptase shows increased susceptibility to adefovir and decreased replication capability in vitro. J Infect Dis 1999;179 (1):92-100.

Murakami E, Wang T, Park Y, Hao J, Lepist EI, Babusis D, et al. Implications of Efficient Hepatic Delivery by Tenofovir Alafenamide (GS-7340) for Hepatitis B Virus Therapy. Antimicrob Agents Chemother 2015;59 (6):3563-9.

Odefsey, Gilead Sciences Ireland UC. Odefsey 200 mg/25 mg/25 mg film-coated tablets. Summary of Product Characteristics (SmPC). Cork, Ireland. 2017:

ODEFSEY®, Gilead Sciences Inc. ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised April. 2017:

Paff MT, Averett DR, Prus KL, Miller WH, Nelson DJ. Intracellular metabolism of (-)- and (+)-cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine in HepG2 derivative 2.2.15 (subclone P5A) cells. Antimicrob Agents Chemother 1994;38 (6):1230-8.

Painter G, St. Clair MH, Chingm S, Noblin J, Wang L, Furman PA. 524W91. Anti-HIV, Anti-Hepatitis B Virus. Drugs of the Future 1995;20 (8):761-5.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC) Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated 14 July. 2016.

Patel P, Song I, Borland J, Patel A, Lou Y, Chen S, et al. Pharmacokinetics of the HIV integrase inhibitor S/GSK1349572 co-administered with acid-reducing agents and multivitamins in healthy volunteers. J Antimicrob Chemother 2011;66 (7):1567-72.

Polakos NK, Cornejo JC, Murray DA, Wright KO, Treanor JJ, Crispe IN, et al. Kupffer Cell-Dependent Hepatitis Occurs during Influenza Infection. Am J Pathol 2006;168 (4):1169-78.

Quest Diagnostics. FSH and LH Reference Ranges. 2013:

Ramanathan S, Mathias A, Wei X, Shen G, Koziara J, Cheng A, et al. Pharmacokinetics of once-daily boosted elvitegravir when administered in combination with Acid-reducing agents. J Acquir Immune Defic Syndr 2013;64 (1):45-50.

Rasmussen LD, Engsig FN, Christensen H, Gerstoft J, Kronborg G, Pedersen C, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS 2011;25 (13):1637-46.

Reyataz, Bristol Myers Squibb. Reyataz (atazanavir) highlights of prescribing information. Updated September 2016. 2016:

Rimsky LT. In vitro synergy studies with FTC and other anti-HIV compounds. Triangle Pharmaceuticals, Inc. Report No. Doc #10804. January 12, 2001.

Robbins BL, Srinivas RV, Kim C, Bischofberger N, Fridland A. Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-*R*-(2-phosphonomethoxypropyl)adenine (PMPA), Bis(isopropyloxymethylcarbonyl) PMPA. Antimicrob Agents Chemother 1998;42 (3):612-7.

Rousseau FS, Kahn JO, Thompson M, Mildvan D, Shepp D, Sommadossi J-P, et al. Prototype trial design for rapid dose selection of antiretroviral drugs: an example using emtricitabine (Coviracil). J Antimicrob Chemother 2001;48 (4):507-13.

Ruane P, DeJesus E, Berger D, Markowitz M, Bredeek UF, Callebaut C, et al. GS-7340 25 mg and 40 mg Demonstrate Greater Antiviral Activity Compared with TDF 300 mg in a 10-Day Monotherapy Study of HIV-1 Infected Patients [Presentation]. 19th Conference on Retroviruses and Opportunistic Infections (CROI); 2012 March 7th; Seattle, WA.

Sax PE, DeJesus E, Crofoot G, Ward D, Benson P, Dretler R, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. The lancet. HIV 2017.

Schinazi RF, Boudinot FD, Ibrahim SS, Manning C, McClure HM, Liotta DC. Pharmacokinetics and metabolism of racemic 2',3'-dideoxy-5-fluoro-3'-thiacytidine in rhesus monkeys. Antimicrob Agents Chemother 1992;36 (11):2432-8.

Schinazi RF, Gosselin G, Faraj A, Korba BE, Liotta DC, Chu CK, et al. Pure nucleoside enantiomers of beta-2',3'-dideoxycytidine analogs are selective inhibitors of hepatitis B virus in vitro. Antimicrob Agents Chemother 1994;38 (9):2172-4.

Schinazi RF, McMillan A, Cannon D, Mathis R, Lloyd RM, Peck A, et al. Selective inhibition of human immunodeficiency viruses by racemates and enantiomers of cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Antimicrob Agents Chemother 1992;36 (11):2423-31.

Smith F, Hammerstrom T, Soon G, Zhou S, Chen B, Mai Y, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. Drug Information Journal 2011;45:291-300.

Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. Patient preference and adherence 2012;6:427-33.

Stray KM, Bam RA, Birkus G, Hao J, Lepist EI, Yant SR, et al. Evaluation of the effect of cobicistat on the in vitro renal transport and cytotoxicity potential of tenofovir. Antimicrob Agents Chemother 2013;57 (10):4982-9.

Stray KM, Park Y, Babusis D, Callebaut C, Cihlar T, Ray AS, et al. Tenofovir alafenamide (TAF) does not deplete mitochondrial DNA in human T-cell lines at intracellular concentrations exceeding clinically relevant drug exposures. Antiviral Res 2017;140:116-20.

Tivicay. Tivicay 50 mg film-coated tablets Summary of Product Characteristics (SmPC). ViiV Healthcare, Middlesex, United Kingdom. Updated 19 January. 2017:

Tivicay, GlaxoSmithKline. Tivicay 10 mg/25 mg/50 mg film-coated tablets. Summary of Product Characteristics (SmPC). Poznan, Poland. Revised 28 February. 2017:

TIVICAY®, GlaxoSmithKline. TIVICAY® (dolutegravir) tablets, for oral use. US Prescribing Information. Research Triangle Park, NC. Revised March. 2017:

TRIUMEQ, GlaxoSmithKline. TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use. US Prescribing Information. Research Triangle Park, NC. Revised March. 2017:

Triumeq, GlaxoSmithKline Pharmaceuticals S.A. Triumeq 50 mg/600 mg/300 mg film-coated tablets. Summary of Product Characteristics (SmPC). Poznan, Poland. Revised 22 February. 2017:

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Silver Spring, MD. November, 2015.

U.S. Department of Health & Human Services (DHHS), Food & Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July, 2009.

Van Draanen NA, Tisdale M, Parry NR, Jansen R, Dornsife RE, Tuttle JV, et al. Influence of stereochemistry on antiviral activities and resistance profiles of dideoxycytidine nucleosides. Antimicrob Agents Chemother 1994;38 (4):868-71.

Vemlidy, Gilead Sciences International Ltd. Vemlidy 25 mg film-coated tablets. Summary of Product Characteristics (SmPC). January. 2017:

VEMLIDY®. VEMLIDY® (tenofovir alafenamide) 25 mg film-coated tablets. Full Annexes. Gilead Sciences International Ltd., Cambridge, UK. Date of first authorisation 09 January. 2017:

VEMLIDY®, Gilead Sciences Inc. VEMLIDY® (tenofovir alafenamide) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. Revised November. 2016:

Wensing AM, Calvez V, Gunthard HF, Johnson VA, Paredes R, Pillay D, et al. Special Contribution: 2017 Update of the Drug Resistance Mutations in HIV-1. Topics in antiviral medicine 2017;24 (4):132-41.

Williams FM. Clinical significance of esterases in man. Clin Pharmacokinet 1985;10 (5):392-403.

Wilson JE, Martin JL, Borroto-Esoda K, Hopkins S, Painter G, Liotta DC, et al. The 5'-triphosphates of the (-) and (+) enantiomers of cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolane-5-yl]cytosine equally inhibit human immunodeficiency virus type 1 reverse transcriptase. Antimicrob Agents Chemother 1993;37 (8):1720-2.

Yokota T, Konno K, Shigeta S, Holý A, Balzarini J, De Clercq E. Inhibitory effects of acyclic nucleoside phosphonate analogues of hepatitis B virus DNA synthesis in HB611 cells. Antivir Chem Chemother 1994;5 (2):57-63.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES....1

TABLE OF CONTENTS....2

1. TABULAR LISTING OF CLINICAL STUDIES....3

1.1. B/F/TAF AND BIC....3
1.2. E/C/F/TAF....16
1.3. F/TAF....18
1.4. FTC AND FTC/TDF....21
1.5. TAF....24

1. TABULAR LISTING OF CLINICAL STUDIES

1.1. B/F/TAF AND BIC

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 ART-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
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-141-1475	Evaluate the efficacy of a regimen containing BIC + F/TAF versus DTG + F/TAF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 12, 24, and Week 48.	Phase 2, randomized, double-blind, active-controlled study	Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • BIC 75 mg + F/TAF (200/25 mg) + placebo-to-match DTG 50 mg QD without regard to food Treatment Group 2: • DTG 50 mg + F/TAF (200/25 mg) + placebo-to-match BIC 75 mg QD without regard to food	48 weeks followed by optional open-label extension in which all subjects receive B/F/TAF FDC	Randomized: 98 Completed: 92	HIV-1 infected, ART-naive adult subjects.	Study completed; Interim Week 72 CSR
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/COBI 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
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1489	Evaluate the efficacy of B/F/TAF FDC versus ABC/DTG/3TC FDC in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48	Phase 3 randomized, double-blind, multicenter, active-controlled study	Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • B/F/TAF (50/200/25 mg) FDC + placebo-to-match ABC/DTG/3TC QD, PO, without regard to food Treatment Group 2: • ABC/DTG/3TC (600/50/300 mg) FDC + placebo-to-match B/F/TAF QD, PO, without regard to food	144 weeks of randomized, double-blind treatment, followed by an optional open-label extension in which all subjects receive B/F/TAF for up to 48 weeks.	Randomized: 631 Safety Analysis Set: 629 B/F/TAF: 314 ABC/DTG/3TC: 315	HIV-infected ART-naive adults	Study ongoing; Interim Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1490	Evaluate the efficacy of B/F/TAF FDC versus DTG) + F/TAF FDC in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48	Phase 3 randomized, double-blind, multicenter, active-controlled study	Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • B/F/TAF 50/200/25 mg FDC + placebo-to-match DTG 50 mg and placebo-to-match F/TAF (200/25 mg) FDC QD, PO, without regard to food Treatment Group 2: • DTG 50 mg + F/TAF (200/25 mg) FDC+ placebo-to-match B/F/TAF FDC QD, PO, without regard to food	144 weeks of randomized, double-blind treatment, followed by optional OL extension in which all subjects receive B/F/TAF for up to 48 weeks.	Randomized: 657 Safety Analysis Set: 645 B/F/TAF: 320 DTG + F/TAF: 325	HIV-infected ART-naive adults	Study ongoing; Interim Week 48 CSR
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

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1844	Evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or ABC/DTG/3TC FDC to B/F/TAF FDC versus continuing DTG and ABC/3TC as the ABC/DTG/3TC FDC in virologically suppressed HIV-1 infected adult subjects, as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48	Phase 3, randomized, double-blind, active-control, multicenter study	Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • B/F/TAF (50/200/25 mg) FDC + placebo-to-match ABC/DTG/3TC QD, PO, without regard to food Treatment Group 2: • ABC/DTG/3TC (600/50/300 mg) FDC + placebo-to-match B/F/TAF QD, PO, without regard to food	48 weeks followed by an optional open-label extension in which all subjects will receive B/F/TAF for up to 96 weeks	Randomized: 567 Safety Analysis Set: 563 B/F/TAF: 282 ABC/DTG/3TC: 281	HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 consecutive months prior to screening	Study ongoing; Interim Week 48 CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-380-1878	Evaluate the efficacy of switching to B/F/TAF FDC versus continuing on a regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC in virologically suppressed, HIV-1-infected adult subjects, as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48	Phase 3, randomized, open-label, multicenter, active-controlled study	Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: • Switch to B/F/TAF (50/200/25 mg) FDC tablet QD, PO, without regard to food Treatment Group 2: Stay on Baseline Regimen (SBR) • Remain on RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC QD, PO, without regard to food	48 weeks followed by an optional open-label extension in which subjects in countries where B/F/TAF is not available will receive B/F/TAF for up to 96 weeks	Randomized: 578 Safety Analysis Set: 577 B/F/TAF: 290 SBR: 287	HIV-1 infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months preceding and at the screening visit	Study ongoing; Interim Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
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				
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

1.2. E/C/F/TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-292-0103	Evaluate the PK and relative bioavailability of EVG, COBI, FTC, TAF, and TFV administered as E/C/F/TAF FDC relative to the administration of the individual components	Phase 1, randomized, open-label, single-center, multiple-dose, multiple-cohort, 2-period, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatment: Cohort 1: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • EVG 150 mg + COBI 150 mg QD PO (B) Cohort 2: • E/C/F/TAF (150/150/200/10 mg) QD PO (A) • FTC 200 mg + TAF 25 mg QD PO (C)	24 days (12 days for each treatment period within a sequence)	Randomized: 34 Completed: 33 Safety Analysis Set: Cohort 1: 14 Cohort 2: 20	Healthy adult subjects	Study completed; Final CSR
Uncontrolled Clinical Studies	GS-US-292-0112	Evaluate the effect of the GEN on renal parameters at Week 24 Evaluate the safety and tolerability of GEN through 144 weeks of treatment	Phase 3, open-label, multicenter, multi-cohort study	• E/C/F/TAF (150/150/200/10 mg) QD PO	144 weeks Extension Phase: Subjects have option to continue study drug for another 48 weeks until GEN is commercially available, becomes available through an access program, or development is terminated	Enrolled: 252 Safety Analysis Set: Cohort 1: 242 Cohort 2: 6	HIV infected adult subjects with stable $eGFR_{CG}$ of 30 to 69 mL/min Cohort 1: ART-experienced Cohort 2: ART-naive	Study ongoing; Interim Week 24 CSR Interim Week 144 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	GS-US-292-1249	Assess the safety, efficacy, and tolerability of GEN in HIV/HBV-coinfected subjects	Phase 3b, open-label, multicenter, single-group, dual-cohort study	• GEN (E/C/F/TAF; 150/150/200/10 mg) QD PO	48 weeks Extension Phase: Subjects have option to continue study drug until GEN is commercially available or development is terminated	Enrolled: 79 Safety Analysis Set: Cohort 1: 3 Cohort 2: 74	HIV/HBV coinfected, adult subjects Cohort 1: HIV/HBV treatment-naïve Cohort 2: HIV suppressed	Study ongoing; Interim Week 48 CSR
Extrinsic Factor PK	GS-US-292-1316	Evaluate the PK of EVG, TAF, and SER following the coadministration of E/C/F/TAF FDC and SER relative to the administration of E/C/F/TAF or SER alone	Phase 1, open-label, 3-period, fixed-sequence, single-center study	• SER 50 mg QD PO (Day 1) (A) • E/C/F/TAF (150/150/200/10 mg) QD PO (Days 2-13) (B) • SER 50 mg + E/C/F/TAF (150/150/200/10 mg) QD PO (Day 14) (C)	14 days	Enrolled: 20 Completed: 19 Safety Analysis Set: 20	Healthy adult subjects	Study completed; Final CSR

1.3. F/TAF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-311-0101	Cohort 1: Evaluate the PK of TAF, TFV, and FTC following once-daily coadministration of F/TAF FDC and EFV relative to the administration of F/TAF FDC alone Cohorts 2 and 3: Evaluate the PK of TAF, TFV, FTC, COBI, and DRV following once-daily coadministration of F/TAF FDC and DRV+COBI relative to the administration of these agents alone Cohort 4: Evaluate the PK of TAF, TFV, and COBI following once-daily coadministration of TAF+COBI relative to the administration of TAF alone	Phase 1, nonrandomized, open-label, crossover, multicohort, multiple-dose study	Cohort 1: • F/TAF (200/40 mg) QD PO (Days 1-12, fasted) (A) • F/TAF (200/40 mg) + EFV 600 mg QD PO (Days 13-26, fasted) (B) Cohort 2: • F/TAF (200/25 mg) QD PO (Days 1-12, fed) (C) • F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 13-22, fed) (D) Cohort 3: • DRV 2 × 400 mg + COBI 150 mg QD PO (Days 1-10, fed) (E) • F/TAF (200/25 mg) + DRV 2 × 400 mg + COBI 150 mg QD PO (Days 11-22, fed) (F) Cohort 4: • TAF 8 mg QD PO (Days 1-12, fed) (G) • TAF 8 mg + COBI 150 mg QD PO (Days 13-22, fed) (H)	Cohort 1: 26 days Cohorts 2-4: 22 days	Enrolled:50 Completed: 48 Safety Analysis Set: A: 12 B: 12 C: 12 D: 25[a] E: 14 F: n/a G: 12 H: 12	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-311-1387	Part A: To evaluate the effect of steady-state CBZ on the PK of TAF when administered as F/TAF FDC Examine the safety and tolerability of F/TAF FDC when administered alone or with CBZ	Phase 1, open-label, adaptive, 2-part, 3-period, fixed-sequence, single-center study	Eligible subjects were administered the following treatments in Part A: Period 1: • F/TAF (200/25 mg) (Day 1) Period 2: • CBZ 100 mg BID (Days 6-8) • CBZ 200 mg BID (Days 9-11) • CBZ 300 mg BID (Days 12-25) Period 3: • CBZ 300 mg BID + F/TAF (200/25 mg) (Day 26)	26 days	Enrolled: 26 Completed: 22	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-311-1388	Evaluate the effect of ATV+COBI on the PK of TAF and its major metabolite TFV Evaluate the effect of ATV+COBI on the PK of FTC Evaluate the effect of TAF on the PK of ATV and COBI	Phase 1, open-label, fixed-sequence, single-center, 3-period, cross-over study	Subjects were administered the following treatments QD in the morning with food starting on Day 1: • F/TAF (200/10 mg) (Days 1-7) (A) • ATV 300 mg + COBI 150 mg + F/TAF (200/10 mg) (Days 8-14) (B) • ATV 300 mg + COBI 150 mg (Days 15-21) (C)	28 days	Enrolled:20 Completed: 19	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Comparative BA/BE	GS-US-311-1473	Evaluate the bioequivalence of FTC and TAF administered as F/TAF FDC, or as E/C/F/TAF FDC	Phase 1, randomized, open-label, single-dose, 2-way crossover study	Subjects were randomized to 1 of 2 treatment sequences and received the following treatments: • F/TAF 200/25 mg FDC PO (A) • E/C/F/TAF (150/150/200/10 mg) FDC PO (B)	7 days; study drug dosing: 2 days	Enrolled: 116 Completed: 116	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-311-1790	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

a Includes 11 subjects who received Treatment D and 14 subjects who received Treatment F

1.4. FTC AND FTC/TDF

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Patient PK and Initial Tolerability	FTC-101	Evaluate the safety, tolerance, PK, and antiviral activity of repeat doses of FTC	Phase 1, open-label, dose-ranging study with 14 days of repeated doses of monotherapy	Multiple escalating oral doses of FTC administered as capsules for: 25 mg BID (N=9) 100 mg BID (N=8) 200 mg BID (N=8) 100 mg QD (N=8) 200 mg QD (N=8)	14 days	Enrolled: 41 Completed: 41	HIV-infected, therapy-naive adult subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	FTC-102	Safety, antiviral activity, dose-defining, comparison with 3TC	Phase 1/2, randomized, open-label, 3TC-controlled, 3 doses of FTC, 10-day repeated doses of monotherapy in adult HIV infected, ART-naive patients	• FTC 25 mg QD PO (N = 20) (A) • FTC 100 mg QD PO (N = 21) (B) • FTC 200 mg QD PO (N = 19) (C) • 3TC 150 mg BID PO (N = 21) (D)	10 days	As treated: 81 Completed: 81 Safety Analysis Set: 81	HIV-infected adult subjects	Study completed; Final CSR
Healthy Subject PK and Tolerability	FTC-106	Evaluate ADME of [^{14}C]FTC, mass balance by urinary and fecal recovery, plasma and PBMCs (FTC-triphosphate)	Phase 1, open-label, single-dose and 8-day repeated doses of FTC (with a single [^{14}C]FTC dose) in healthy adult volunteers	• Day 1: 200 mg single dose PO (N = 6) • Days 3−11: 200 mg QD PO for 8 days, single 250 µCi [^{14}C]FTC dose PO on the last day (N = 5)	11 days	Enrolled: 6 Completed: 5 Safety Analysis Set: 6	Healthy male subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Intrinsic Factor PK	FTC-107	Assess the PK profiles in subjects with various degrees of renal insufficiency (for potential dosage adjustment) and effect of hemodialysis	Phase 1, open-label, single-dose study of FTC in adult volunteers with varying degrees of renal insufficiency without and with hemodialysis	One single dose of FTC 200 mg administered PO in capsule formulation to: • Group 1 (normal renal function, CL_{cr} > 80 mL/min, N=6) • Group 2 (mild renal impairment, CL_{cr} = 50−80 mL/min, N=6) • Group 3 (moderate renal impairment, CL_{cr} = 30−49 mL/min, N=6) • Group 4 (severe renal impairment, CL_{cr} < 30 mL/min, N=5) • Group 5 (end-stage renal disease, requiring hemodialysis, N=6) For Group 5 subjects, a second FTC 200 mg dose PO was administered ~1.5 hour before the start of a 3-hour hemodialysis	1−2 single doses	Enrolled: 29 Completed: 29	Adult subjects with varying degrees of renal insufficiency with and without hemodialysis	Study completed; Final CSR
Extrinsic Factor PK	FTC-108	Assess potential PK interactions with concomitant antiviral drug (ie, famciclovir) with extensive renal excretion	Phase 1, randomized, open-label, single-dose, 3-way crossover study	3 single crossover doses (all PO) of: • FTC 200 mg alone • FCV 500 mg alone • FTC 200 mg + FCV 500 mg 1-week washout interval between doses	Single dose	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
BA	FTC-110	Evaluate relative and absolute BA of FTC	Phase 1, open-label, randomized, 3-way crossover, single 200-mg doses administered as IV solution, oral solution, or oral capsule	• FTC 1 × 200-mg capsule, PO, fasted (A) • 20 mL of FTC 10 mg/mL solution, PO, fasted (B) • 20 mL of FTC 10 mg/mL solution, IV infused over 1 hour, fasted (C)	3 single doses	Enrolled: 12 Completed: 12 Safety Analysis Set: 12	Healthy adult subjects	Study completed; Final CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	FTC-303	Compare FTC to 3TC in HIV-infected subjects with copies/mL (HIV-1 RNA ≤400) on a stable (≥12 weeks) ART regimen containing 3TC, d4T or ZDV, and a PI or NNRTI	Phase 3, randomized (2:1) open-label, multi-center equivalence study	• Subjects switch from 3TC to FTC PO while continuing on current background therapy (A) • Subjects continue on current 3TC-containing regimen (B)	48 weeks	Randomized: 459 ITT: 440 A: 294 B: 146	HIV-infected, 3TC-experienced, adult subjects with stable HIV-1 RNA	Study completed; Final CSR and Addendum
Intrinsic Factor PK	FTCB-101	Assess the safety, tolerance, antiviral activity, and PK of FTC	Phase 1, open-label, dose-escalation, multiple repeat doses, 8 week study	• FTC 25 mg QD PO • FTC 50 mg QD PO • FTC 100 mg QD PO • FTC 200 mg QD PO • FTC 300 mg QD PO	56 days with 28 day follow up	Enrolled: 49 Completed: 45 Safety Analysis Set: 49	HBV-infected adult subjects	Study completed; Final CSR
Patient PK and Initial Tolerability	Burroughs Wellcome 143-001	Assess the safety, PK, and effect of food on the BA of FTC	Phase 1, randomized, single-blind, single-dose, placebo-controlled, escalating doses (100 to 1200 mg)	• Single escalating oral doses of FTC administered as capsules: 100, 200, 400 (± food), 800, and 1200 mg, PO • Placebo, PO	6 total doses, each given 1 week apart	Enrolled: 18 Active: 12 Placebo: 6 Completed: 17	HIV-infected adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-174-0105	Evaluate the PK interactions between FTC/TDF FDC and TCL when administered alone and together	Single-center, open-label, randomized, 3-way crossover study	Subjects received each of the following treatments: • FTC/TDF • (200/300 mg) QD PO • TCL 0.1 mg/kg/day in 2 divided doses BID PO	21 days (7 days FTC/TDF FDC, 7 days TCL, 7 days FTC/TDF FDC + TCL)	Enrolled: 31 Completed: 21 Safety Analysis Set: 31	Healthy adult subjects	Study completed; Final CSR

1.5. 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
Patient PD and PK/PD	GS-US-120-0104	Evaluate the short-term antiviral potency of TAF 8 mg, 25 mg, and 40 mg compared to placebo-to-match TAF or TDF 300 mg	Phase 1, randomized, partially-blinded, active- and placebo-controlled study	• TAF 8 mg QD PO (A) • TAF 25 mg QD PO (B) • TAF 40 mg QD PO (C) • TDF 300 mg QD PO (D) • Placebo-to-match TAF QD PO (E)	10 days	Randomized: 40 Completed: 37 Safety Analysis Set: A: 9 B: 8 C: 8 D: 6 E: 7	HIV-infected adult subjects, who had not received ART within 90 days of screening	Study completed; Final CSR
Healthy Subjects PD and PK/PD	GS-US-120-0107	Evaluate the effects of TAF (at therapeutic and supratherapeutic doses) and its metabolite TFV on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, randomized, partially-blinded, placebo- and positive-controlled, 4-period, single-dose crossover study	Subjects were randomized to 1 of 8 treatment sequences and received the following treatments: • TAF 25 mg + 4 × placebo-to-match TAF QD PO (A) • TAF 125 mg (5 × 25 mg) QD PO (B) • Placebo-to-match TAF (C) • Moxifloxacin 400 mg PO, administered open-label (D)	37 days (4 single-dose treatment days separated by 11 days of washout between doses)	Randomized: 59 Completed: 58 Safety Analysis Set: A: 58 B: 58 C: 59 D: 58	Healthy adult subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0108	Evaluate the PK of TAF and its metabolite TFV following administration of TAF in subjects with and without severe renal impairment	Phase 1, open-label, parallel-design, single-dose, PK study	• TAF 25 mg PO	Single dose	Enrolled: 27 Completed: 27 Safety Analysis Set: Subjects with severe renal impairment: 14 Age and sex matched controls: 13	Adult subjects with severe renal impairment ($eGFR_{CG}$ of 15 to ≤ 29 mL/min) or healthy matched control subjects ($eGFR_{CG}$ of ≥ 90 mL/min)	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Tolerability	GS-US-120-0109	Determine the mass balance of TAF following administration of a single, oral dose of radiolabeled [^{14}C]TAF	Phase 1, open-label, mass-balance study	• TAF 25 mg (mixture of unlabeled TAF and [^{14}C]TAF) PO	Single dose	Enrolled: 8 Completed: 8 Safety Analysis Set: 8	Healthy adult male subjects	Study completed; Final CSR
Intrinsic Factor PK	GS-US-120-0114	Evaluate the PK of TAF in subjects with normal and impaired hepatic function	Phase 1, open-label, 2-cohort, parallel-group, single-dose, multicenter study	• TAF 25 mg PO	Single dose	Enrolled: 40 Completed: 40 Safety Analysis Set: Cohort 1: Subjects with mild hepatic impairment: 10 Matched controls: 10 Cohort 2: Subjects with moderate hepatic impairment: 10 Matched controls: 10	Cohort 1: Adult subjects with mild hepatic impairment (CPT Class A) and healthy matched control subjects Cohort 2: Adult subjects with moderate hepatic impairment (CPT Class B) and healthy matched control subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-120-0117	Evaluate the PK of RPV and TAF following single-dose administration of RPV and TAF alone and in combination in healthy subjects	Phase 1, open-label, single-center, single-dose, crossover study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments: Cohort 1: • TAF 25 mg QD PO (A) • TAF 25 mg + RPV 25 mg QD PO (B) Cohort 2: • TAF 25 mg + RPV 25 mg QD PO (B) • RPV 25 mg QD PO (C)	2 days (Days 1 and 12)	Randomized: 36 Completed: 36 Safety Analysis Set: Cohort 1: 18 Cohort 2: 18	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-0118	Evaluate the effect of common boosted PIs ATV+RTV; DRV+RTV; LPV/r, or the INSTI DTG on the PK of TAF, and evaluate the PK of ATV, DRV, LPV, and DTG alone and in combination with FTC and TAF	Phase 1, open-label, DDI study	Cohort 1: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • ATV 300 mg + RTV 100 mg QD PO (Days 2-14) (B) • A + B (Day 15) Cohort 2: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • DRV 800 mg + RTV 100 mg QD PO (Days 2-14) (C) • A + C (Day 15) Cohort 3: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (A) • LPV/r (4 × 200/50 mg) QD PO (Days 2-14) (D) • A + D (Day 15) Cohort 4: • FTC 200 mg + TAF 10 mg QD PO (Day 1) (F) • DTG 50 mg QD PO (Days 2-14) (E) • F + E (Day 15)	15 days	Enrolled: 40 Completed: 39 Safety Analysis Set: Cohort 1: 10 Cohort 2: 10 Cohort 3: 10 Cohort 4: 10 (1 subject excluded from the FTC+TAF+ DTG safety analysis)	Healthy adult subjects	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-120-1538	Evaluate the PK and drug interaction potential between TAF and MDZ (Oral and IV)	Phase 1, open-label, multiple-dose, single-center study	Subjects received the following treatments in a fixed sequence under fed conditions in the morning: • Day 1: MDZ_{oral} 2.5 mg syrup (A) • Day 3: MDZ_{IV} 1 mg solution (B) • Days 4-15 and 17: TAF 25 mg PO (C) • Day 16: TAF 25 mg PO + MDZ_{oral} 2.5 mg syrup coadministered (D) • Day 18: TAF 25 mg PO + MDZ_{IV} 1 mg solution administered within 5 min of each other (E)	18 days (Day 1, washout on Day 2, and doses on Days 3-18)	Enrolled: 18 Completed: 18 Safety Analysis Set: A: 18 B: 18 C: 18 D: 18 E: 18	Healthy adult subjects	Study completed; Final CSR
Extrinsic Factor PK	GS-US-120-1554	Evaluate the PK and drug interaction potential between TAF and RPV	Phase 1, open-label, randomized, fixed-sequence, 2-cohort, 2-period, multiple-dose study	Within each cohort, subjects were randomized to 1 of 2 treatment sequences and received the following treatments under fed conditions: <u>Cohort 1:</u> • TAF 25 mg QD PO (Days 1-14) (A) • TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C) <u>Cohort 2:</u> • RPV 25 mg QD PO (Days 1-14) (B) • TAF 25 mg + RPV 25 mg QD PO (Days 15-28) (C)	28 days	Randomized: 34 Completed: 32 Safety Analysis Set: Cohort 1: 17 Cohort 2: 17	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-320-0101	Evaluate the short-term antiviral activity of TAF and compare with TDF. Characterize the viral dynamics of HBV DNA associated with the use of TAF. Investigate the PK of TFV and TAF.	Phase 1b, randomized, open-label, active-controlled study	Subjects were randomized to receive the following treatments. • TAF 8 mg QD PO • TAF 25 mg QD PO • TAF 40 mg QD PO • TAF 120 mg QD PO • TDF 300 mg QD PO	28 days	Randomized: 51 Treated: 51 Completed Study Treatment: 51 10 subjects per group (11 subjects TAF 40 mg group)	Treatment-naive adults with CHB infection	Study completed; Final CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-320-0108	Evaluate the safety and efficacy of TAF 25 mg QD vs TDF 300 mg QD for the treatment of HBeAg-negative CHB	Phase 3, randomized, double-blind, multicenter study	Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups. • TAF 25 mg tablet QD and matched placebo of TDF 300 mg QD (A) • TDF 300 mg QD and matched placebo of TAF 25 mg QD (B) This double-blind treatment period was followed by an open-label extension period where subjects received the following treatment. • TAF 25 mg QD	96 weeks of double-blind treatment followed by 48 weeks of open-label treatment	Randomized: 426 Treated: 425 TAF: Treated: 285 TDF: Treated: 140	Treatment-naive and treatment-experienced adult HBeAg-negative CHB subjects	Study ongoing; Interim Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-320-0110	Evaluate the safety and efficacy of TAF 25 mg QD vs TDF 300 mg QD for the treatment of HBeAg-positive CHB	Phase 3, randomized, double-blind, multicenter study	Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups. • TAF 25 mg tablet QD and matched placebo of TDF 300 mg QD (A) • TDF 300 mg QD and matched placebo of TAF 25 mg QD (B) This double-blind treatment period was followed by an open-label extension period where subjects received the following treatment. • TAF 25 mg QD	96 weeks of double-blind treatment followed by 48 weeks of open-label treatment	Randomized: 875 Treated: 873 TAF: Treated: 581 TDF: Treated: 292	Treatment-naive and treatment-experienced adult HBeAg-positive CHB subjects	Study ongoing; Interim Week 48 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Intrinsic Factor PK	GS-US-320-1615	Evaluate the PK of TAF and its metabolite TFV in subjects with normal hepatic function and subjects with severe hepatic impairment.	Phase 1, open-label, parallel-group, single-dose, multicenter study	Subjects were enrolled in 1 of 2 groups (normal hepatic function or severe hepatic impairment) and received the following treatment. • TAF 25 mg tablet PO	Single dose	Randomized: 20 Treated: 20 Completed Study Treatment: 20 10 subjects per group	Adult subjects with severe hepatic impairment (CPT C) and healthy matched control 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; DRV = 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