STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women
Name of Test Drug:	Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF; GS-9883/F/TAF)
Study Number:	GS-US-380-1961
Protocol Version (Date):	Amendment 2 (10 November 2016)
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Analysis Plan Author(s):	PPD

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	Atazanavir
BIC	Bictegravir, GS-9883, B
B/F/TAF	single-tablet regimen of bictegravir (BIC; B) 50 mg / emtricitabine (FTC) 200 mg / tenofovir alafenamide (TAF) 25 mg; GS-9883/F/TAF
BMI	body mass index
BSA	body surface area
CG	Cockroft-Gault
CRF	case report form
CSR	clinical study report
DNA	Deoxyribonucleic Acid
DOB	date of birth
E/C/F/TAF	Elvitegravir /Cobicistat /Emtricitabine/ Tenofovir Alafenamide; Genvoya; GEN
E/C/F/TDF	Elvitegravir /Cobicistat /Emtricitabine / Tenofovir Disoproxil Fumarate; Stribild; STB
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eGFR(CG)	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC/TDF	single-tablet regimen of emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg
FTC	Emtricitabine; F
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
Gilead	Gilead Sciences, Inc.
GS-9883	Bictegravir; BIC; B
HBcAb	hepatitis B core antibody
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

HCVAb	HCV antibody
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
ID	identification
IDMC	independent data monitoring committee
INR	international normalized ratio
KM	Kaplan-Meier
LDL	low density lipoprotein
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PK	pharmacokinetic
PT	preferred term
PT	prothrombin time
PVE	pharmacovigilance and epidemiology
Q	quartile
Q1	first quartile
Q3	third quartile
RBP	retinol binding protein
RNA	ribonucleic acid
RTV	Ritonavir
SAE	serious adverse events
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
SE	standard error
SMQ	Standardised MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide
TEAE	treatment-emergent AE
TFL	tables, figures, and listings
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UACR	urine albumin to creatinine ratio
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the final analysis for Study GS-US-380-1961, which will be performed when all subjects have completed the study or prematurely discontinued from the study. This SAP is based on the study protocol amendment 2 dated 10 November 2016 and the electronic case report form (eCRF). The SAP will be finalized before data finalization for the final analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching to a fixed dose combination (FDC) of bictegravir (GS-9883; BIC; B) /emtricitabine (FTC; F) /tenofovir alafenamide (TAF) versus continuing on a regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF in virologically suppressed HIV-1 infected women as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

The secondary objective of this study is:

- To evaluate the safety and tolerability of the treatment groups through Week 48.

1.2. Study Design

Design Configuration and Subject Population

GS-US-380-1961 is a randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to an FDC of B/F/TAF in HIV-1 infected women who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF for ≥ 12 consecutive weeks prior to screening.

All subjects will be HIV-1 infected women drawn from pre-defined Gilead Sciences (Gilead) clinical studies and must be virologically suppressed. Women in Study GS-US-236-0128 who completed the Week 48 open-label extension (OLE) visit or any post Week 48 OLE visits, women in Study GS-US-292-0109 who completed the Week 96 visit or any post Week 96 visits, or women in Studies GS-US-292-0104 or GS-US-292-0111 who completed the Week 144 visit or any post Week 144 visits may be eligible to enroll in Study GS-US-380-1961.

Treatment Groups

Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to receive open-label medication as follows:

Treatment Group 1: FDC of BIC 50 mg/FTC 200 mg/TAF 25 mg (B/F/TAF) administered orally, once daily, without regard to food (approximately n = 235)

Treatment Group 2: Stay on baseline regimen (SBR), including E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF administered orally, once daily, with food (approximately n = 235)

Key Eligibility Criteria

Medically stable HIV-1 infected women who meet the following criteria:

- Currently on a stable antiretroviral regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF continuously for ≥ 12 consecutive weeks preceding the screening visit
- Documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 12 weeks preceding the Screening visit. After reaching HIV-1 RNA < 50 copies/mL, single values of HIV-1 RNA ≥ 50 copies/mL followed by re-suppression to < 50 copies/mL is allowed
- HIV-1 RNA <50 copies/mL at screening
- Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault (C-G) formula at the screening visit

Study Periods / Phases

Subjects will be treated for at least 48 weeks. At the Week 48 Visit, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC for an additional 48 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead elects to discontinue the study in that country, whichever occurs first.

Subjects who complete the study through the Week 48 Visit and do not continue participation in the study will be required to return to the clinic 30 days after the Week 48 Visit for a 30 Day Follow-Up Visit.

Schedule of Assessments

After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 48 weeks. Following the Screening and Day 1 visits, subjects will return for study visits at Weeks 4, 8, 12, and then every 12 weeks until the Week 48 visit.

For all eligible subjects, blood and urine will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through the Week 48 visit. Laboratory analyses (including hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, and complete or symptom-directed physical examinations will be performed at the Screening, Day 1, and all subsequent study visits.

Adverse events and concomitant medications will be assessed at each visit.

Pharmacokinetics

For all subjects on B/F/TAF (Treatment Group 1), a single anytime pre or post-dose PK blood sample will be collected at Weeks 8, 24, and 36.

For all subjects on B/F/TAF (Treatment Group 1), a trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4 and 12. Following an observed dose, one PK blood sample will be collected between 1 and 4 hours post-dose.

The concentration of BIC may be summarized using descriptive statistics.

Randomization

Subjects will be randomized in a 1:1 ratio to 1 of 2 Treatment Groups (Treatment Group 1: Treatment Group 2). Randomization will be stratified by the prior treatment regimen group (ie, E/C/F/TAF, E/C/F/TDF, and ATV+RTV+FTC/TDF).

Site and/or Stratum Enrollment Limits

Approximately 57 study sites in North America, Dominican Republic, Thailand, Russia, and Uganda participated. There was no enrollment limit for individual sites.

Study Duration

The randomized phase of this study is 48 weeks in duration.

1.3. Sample Size and Power

A total of approximately 470 HIV-1 infected women, randomized in a 1:1 ratio to 2 treatment groups (approximately 235 subjects per treatment group), achieves at least 87% power to detect a non-inferiority margin of 4% difference in the percentage of subjects with HIV-1 RNA $\geq$ 50 copies/mL at Week 48 between the 2 treatment groups.

For sample size and power computation, it is assumed that both treatment groups have 2% of subjects with HIV-1 RNA $\geq$ 50 copies/mL at Week 48 (based on the historical Gilead Genvoya® [GEN; E/C/F/TAF] and Stribild® [STB; E/C/F/TDF] studies), that a non-inferiority margin is 4%, and that the significance level of the test is at a one-sided 0.025 level. Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 6.0).

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analysis

The Week 24 Independent Data Monitoring Committee (IDMC) analysis was conducted after all subjects enrolled completed their Week 24 visit of the study or prematurely discontinued the study drug. The purpose of this interim analysis was to provide the IDMC with a statistical report for review. More details are documented in the IDMC charter.

Gilead does not have a prior intent to ask the IDMC to review Week 48 result or to consider early termination of the study even if there is early evidence of favorable efficacy for B/F/TAF.

2.2. Week 48 Interim Analysis

The Week 48 interim analysis was conducted after all subjects either completed their Week 48 visit or prematurely discontinued from the study drug.

2.3. Final Analysis

The final statistical analysis will be conducted after all subjects either complete the study or prematurely discontinue from the study.

This SAP describes the analysis plan for the final analysis, which will only include the all B/F/TAF analysis: safety and efficacy assessments for B/F/TAF only, not for other study drugs.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The final analysis will include only the all B/F/TAF analysis in tables and figures, unless specified otherwise. The analysis for the randomized phase data exposed to SBR group was included in the Week 48 interim analysis and will not be repeated in this final analysis. However, data collected from the entire study will be included in data listings.

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Randomized Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a subject. The actual treatment group will be used in the listings.

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. For randomized but never dosed subjects in data listings, age on the date of randomization will be used. If only birth year is collected on the eCRF, “01 January” will be used for the unknown birth day and month for the purpose of age calculation, similarly, if only birth year and month are collected on the eCRF, “01” will be used for the unknown birth day for the purpose of age calculation.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before data finalization. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total.

3.1.1. All Randomized Analysis Set

The **All Randomized Analysis Set** will include all subjects who were randomized into the study. This is the primary analysis set for by-subject listings.

3.1.2. All B/F/TAF Analysis Set

The **All B/F/TAF Analysis Set** includes all subjects who (1) were randomized to B/F/TAF and have received at least 1 dose of B/F/TAF during the randomized phase or (2) have received at least 1 dose of B/F/TAF during the extension phase. This is the primary analysis set for all B/F/TAF efficacy and safety analyses.

3.2. Subject Grouping

For the all B/F/TAF analysis including extension phase, subjects will be grouped into the following groups:

- B/F/TAF group: This group includes all subjects who were randomized to B/F/TAF in the randomized phase of this study. All data from both the randomized and extension phases (if applicable) will be included.

- Stay on Baseline Regimen (SBR) to B/F/TAF group: This group includes all subjects who were randomized to continuing pre-existing regimen in the randomized phase of this study, and who then switched to B/F/TAF in the extension phase. Only data collected on and after the extension phase first dose date of B/F/TAF will be included, except that data collected **on or prior to** the extension phase first dose date of B/F/TAF will be used to derive the baseline value for the all B/F/TAF analysis.

- All B/F/TAF group: This group includes all subjects who are in the All B/F/TAF Analysis Set, which combines the two groups above.

3.3. Strata and Covariates

There is no stratification for analysis.

3.4. Examination of Subject Subgroups

In order to explore the effect of switching from TDF to TAF on renal functions,, subgroup analysis by prior treatment regimen (ie, TDF-containing regimen versus non-TDF containing regimen) will be performed for the following endpoints:

- Urine retinal binding protein (RBP) to creatinine ratio

- beta-2 microglobulin to creatinine ratio

- Urine albumin to creatinine ratio (UACR)

3.5. Multiple Comparisons

Multiple comparisons and alpha adjustment were applied for the primary endpoint analysis conducted at Week 48. No alpha level adjustment is applied in the final analysis.

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study analysis window may be due to any of the following reasons:

- A visit occurring in the window but data were not collected or were unusable
- A visit not occurring in the window
- A subject prematurely discontinuing from the study before reaching the window

In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for concomitant non-antiretroviral (ARV) medications in Section 7.4.2.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows except for urine creatinine:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (where x is considered the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.
- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.
- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitation).

For urine creatinine, a value of "< 1" is handled as a missing value in its summary and the calculation of related ratios.

Logarithm (base 10) transformation will be applied to HIV-1 RNA data for efficacy analysis. HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purpose.

3.8. Analysis Windows

For subjects who were randomized to SBR and discontinued study drug in the randomized phase (ie, subjects who were in the All Randomized Analysis Set, but not in the All B/F/TAF Analysis Set), the definition and derivation of the necessary variables presented in the data listings (eg, first dose date, last dose date, study date, etc.) can be found in Appendix 4.

For the all B/F/TAF analysis that only evaluates the efficacy and safety of B/F/TAF, the study drug mentioned in the following only refers to B/F/TAF.

3.8.1. Definitions

Study Day 1 is defined as the day when the first dose of B/F/TAF (either in the randomized phase or extension phase) was taken. For subjects randomized to the B/F/TAF group, the first dose date is the same as the randomized phase first dose date. For subjects randomized to the SBR group, the first dose date is defined as the earliest nonmissing start date of B/F/TAF recorded on the Study Drug Administration eCRF.

Study Days are calculated relative to Study Day 1 for the all B/F/TAF analysis. For events that occur on or after the Study Day 1 date, study days are calculated as (visit date minus date of the first dose plus 1). For events that occur prior to Study Day 1, study days are calculated as (visit date minus date of the first dose).

Last Dose Date is defined as the maximum, nonmissing end date of B/F/TAF, recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Discontinued" box checked for subjects who prematurely discontinued study drug or who completed study drug according to the Study Drug Completion eCRF.

If the date of last dose is missing (eg, due to lost to follow-up) for subjects who prematurely discontinued study drug, the maximum of nonmissing study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates excluding the date of 30-day follow-up visit will be used to impute the last dose date.

Last Study Date is the maximum of nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date for subjects who prematurely discontinued or completed the study according to the Study Completion eCRF.

Baseline value is defined as the last nonmissing value obtained on or prior to the Study Day 1 for all assessments.

3.8.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis window. Since the final analysis only includes the all B/F/TAF analysis, only data included in the all B/F/TAF analysis will be assigned analysis windows.

For data listings, the observations collected from the randomized phase of the study for the subjects who were randomized to SBR group will not have analysis window assigned and will be included in listings with derived visit as blank.

The analysis windows for HIV-1 RNA, CD4+ cell count, CD4 %, hematology, chemistry, urinalysis, urine pregnancy laboratory tests, $eGFR_{CG}$, vital signs, and weight are presented in Table 3-1.

Table 3-1. Analysis Windows for HIV-1 RNA, CD4+ cell count, CD4 %, Hematology, Chemistry, Urinalysis, and Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, and Weight

	B/F/TAF			SBR to B/F/TAF		
Visit ID	**Nominal Day**	**Lower Limit**	**Upper Limit**	**Nominal Day**	**Lower Limit**	**Upper Limit**
Baseline			1			1
Week 4	28	2	42			
Week 8	56	43	70			
Week 12	84	71	126	84	2	126
Week 24	168	127	210	168	127	210
Week 36	252	211	294	252	211	294
Week 48	336	295	378	336	295	378
Week 60	420	379	462	420	379	462
Week 72	504	463	546	504	463	546
Week 84	588	547	630	588	547	630
Week 96	672	631	714	672	631	714
Week k	k*7	(k-6)*7+1	(k+6)*7	k*7	(k-6)*7+1	(k+6)*7

The analysis windows for metabolic assessments (including fasting glucose and lipid panel: total cholesterol, high density lipoprotein [HDL], direct low density lipoprotein [LDL], triglycerides, and total cholesterol to HDL ratio) are presented in Table 3-2.

Table 3-2. Analysis Windows for Metabolic Assessments

Visit ID	B/F/TAF			SBR to B/F/TAF		
	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline			1			1
Week 12	84	2	126			
Week 24	168	127	252	168	2	252
Week 48	336	253	420	336	253	420
Week 72	504	421	588	504	421	588
Week 96	672	589	756	672	589	756
Week k	k*7	(k-12)*7+1	(k+12)*7	k*7	(k-12)*7+1	(k+12)*7

The analysis windows for thyroid stimulating hormone (TSH; thyrotropin) and renal function (including urine albumin, urine creatinine, urine RBP, and urine beta-2 microglobulin, and derived ratios assessments) are presented in Table 3-3.

Table 3-3. Analysis Windows for TSH, Renal Function, and HCV RNA Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week k	k*7	(k-12)*7+1	(k+12)*7

The analysis windows for ECG assessments are presented in Table 3-4.

Table 3-4. Analysis Windows for ECG Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	504
Week 96	672	505	756
Week k	k*7	(k-12)*7+1	(k+12)*7

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Window

Depending on the statistical analysis method, single values are required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time to event analysis would not require one value per analysis window. When a single value is needed, the following rule(s) will be used.

If multiple nonmissing numeric observations exist in a window, then records will be chosen as follows:

- For baseline, the latest available record on or prior to the first dose date of B/F/TAF will be selected. If there are multiple records with the same collection time or no collection time recorded on the same day, average will be used for the baseline value, except for HIV-1 RNA (see below).

- For postbaseline visits:

  — For CD4+ cell count and CD4%, the record(s) collected on the latest day in the window will be selected for analysis.

  — For other numeric observations (eg, except HIV-1 RNA, CD4+ cell count, and CD4%), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

  — For any numeric observations except HIV-1 RNA, if there are multiple records on the selected day, the arithmetic mean will be used.

- For baseline and postbaseline HIV-1 RNA, the latest (considering both collection date and time) record(s) in the window will be selected. If both "HIV RNA Taqman 2.0" and "HIV RNA Repeat" (ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the "HIV RNA Repeat" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA Taqman 2.0" records with the same collection time, the geometric mean will be taken for analysis purposes.

If multiple valid nonmissing categorical observations exist in a window, records will be chosen as follows:

- For baseline, the last available record on or prior to the first dose date of B/F/TAF will be selected. If there are multiple records with the same collection time or no collection time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).

- For postbaseline visits, the most conservative value within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

All summaries on subject enrollment have been performed as part of the Week 48 analysis, and will not be repeated in the final analysis.

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group and overall using the All Randomized Analysis Set for all B/F/TAF analysis (Appendix 2; Appendix Table 1). This summary will include the number of subjects who were randomized, randomized but not treated, randomized and treated, subjects who prematurely discontinued study treatment in the randomized phase, subjects who completed the randomized phase but not entered the extension phase, subjects who entered the extension phase, who received B/F/TAF in either the randomized or extension phase (ie, All B/F/TAF Analysis Set).

In addition, the number and percentage of the subjects from the All B/F/TAF Analysis Set in the following categories will be summarized:

- Completed B/F/TAF
- Prematurely discontinuing B/F/TAF (with summary of reasons for discontinuing study treatment)
- Completed study
- Prematurely discontinuing (with summary of reasons for discontinuing study)

The denominator for the percentages of subjects in each category will be the number of subjects in the All B/F/TAF Analysis Set.

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation from both phases will be provided.

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to B/F/TAF

Duration of exposure to B/F/TAF is defined as (the last dose date of B/F/TAF – the first dose date of B/F/TAF + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Duration of exposure to B/F/TAF will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, eg, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks [420 days], ≥ 72 weeks [504 days], ≥ 84 weeks [588 days], ≥ 96 weeks [672 days], ≥ 108 weeks [756 days], ≥ 120 weeks [840 days], etc.

Summaries will be provided by treatment group for subjects in the All B/F/TAF Analysis Set. No inferential statistics will be provided.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method by treatment group based on the All B/F/TAF Analysis Set. No statistical comparisons will be made for the all B/F/TAF analysis. Subjects who completed study drug will be censored at the last dose date of the study.

4.2.2. Adherence to Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts for B/F/TAF only. The numbers of pills of B/F/TAF dispensed and returned are captured on Study Drug Accountability eCRF. Adherence will be summarized for B/F/TAF during the entire study (including both the randomized and extension phase if applicable).

Adherence (%) of B/F/TAF will be calculated as follows:

$$\text{Adherence}(\%) = 100 \times \frac{\text{Number of pills taken}}{\text{Number of pills prescribed}}$$

$$= 100 \times \frac{\text{Sum of No. of pills taken at each dispensing period[1]}}{\text{Sum of No. of pills prescribed at each dispensing period[2]}}$$

[1] Number of pills taken at a distinct dispensing period for a study drug is calculated as the minimum of (a) the daily number of pills prescribed for the study drug multiplied by the duration of treatment at the dispensing period of the same dispensing date, and (b) the number of pills taken for the study drug (number of pills dispensed minus the number of pills returned). Total number of pills taken is determined by summing the number of pills from all evaluable dispensing periods.

[2] Number of pills prescribed at a distinct dispensing period for a study drug is calculated as the daily number of pills prescribed for the study drug multiplied by the duration of treatment at the dispensing period of the same dispensing date. Total number of pills prescribed is determined by summing the number of pills prescribed from all evaluable dispensing periods.

The duration of treatment at a dispensing period for a study drug is calculated as the minimum of (a) the last returned date of the same dispensing period for the study drug, (b) date of premature discontinuation of the study drug, and (c) next pill dispensing date of the study drug, minus dispensing date of the study drug.

The next pill dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of pills returned was missing (with "Yes" answered for "Was Bottle returned?" question), it is assumed the number of pills returned was zero. If the number of pills dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown, all records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation.

Adherence to the study drug B/F/TAF will be calculated for each subject in the All B/F/TAF Analysis Set for the entire B/F/TAF dosing period up to the date of permanent discontinuation of B/F/TAF for subjects who prematurely discontinued B/F/TAF or using all data available for subjects completing B/F/TAF.

Descriptive statistics for overall adherence for B/F/TAF (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided by treatment group for subjects who return at least 1 bottle and have calculable adherence during the study in the All B/F/TAF Analysis Set. No inferential statistics will be provided.

4.3. Protocol Deviations

A listing will be provided for all randomized subjects who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met. A listing of subjects who received the wrong study drug will also be provided.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex, race, and ethnicity) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percentage of subjects for categorical data. Age is calculated as age in years at first dose of B/F/TAF. The summaries of demographic data and baseline subject characteristics will be provided using the All B/F/TAF Analysis Set.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4+ cell count (/μL)
- CD4+ cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- Mode of infection (HIV risk factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)

No statistical comparisons will be made for the all B/F/TAF analysis.

5.3. Medical History

Medical history data were presented in the original studies from which subjects were rolled over. Thus, medical history data will not be summarized in this study.

6. EFFICACY ANALYSES

6.1. Definition of Efficacy Endpoints

6.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with virologic failure (HIV-1 RNA ≥ 50 copies/mL) at Week 48 as defined by the modified FDA snapshot algorithm.

The analyses of the primary efficacy endpoint were performed in the Week 48 interim analyses, and will not be repeated in the final analysis.

6.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Week 48

6.1.3. Tertiary Efficacy Endpoints

CCI [redacted]

6.2. Analysis of the Efficacy Endpoints

Analyses of the proportions of subjects determined by the US FDA-defined Snapshot Algorithm (the primary efficacy endpoint at Week 48 and part of the secondary CCI [redacted] efficacy endpoints) were performed in the Week 48 interim analyses and will not be repeated in this final analysis.

6.2.1. Analysis of CD4 Cell Count and CD4%

CD4 cell count and CD4% will be summarized using observed, on-treatment data (ie, data collected up to 1 day after the last dose date of B/F/TAF) for subjects in the All B/F/TAF Analysis Set.

The changes from baseline in CD4 cell count and CD4% at each visit will be summarized by treatment group using descriptive statistics based on observed data (ie, missing will be excluded) using the All B/F/TAF Analysis Set.

The mean and 95% CI of change from baseline in CD4 cell count over time will be plotted using observed data for the All B/F/TAF Analysis Set.

6.2.2. Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL by Missing = Excluded Approach

The proportion of subjects with HIV-1 RNA < 50 copies/mL will be analyzed using the Missing = Excluded (M = E) for imputing missing HIV-1 RNA values:

In this approach, all missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of subjects in the All B/F/TAF Analysis Set with non-missing HIV-1 RNA value at that visit.

For M = E analysis, the number and percentage of subjects with HIV-1 RNA in the following categories will be summarized:

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 Not Detectable
    - < 20 Detectable
  - 20 to < 50 copies/mL
- 50 to < 200 copies/mL
- 200 to < 400 copies/mL
- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL

The 95% CI of the proportion of subjects with HIV-1 RNA < 50 copies/mL within each subject group will be provided using the Clopper-Pearson Exact method.

6.3. Changes From Protocol-Specified Efficacy Analyses

No change from protocol-specified efficacy analysis is planned.

7. SAFETY ANALYSES

Safety data for the all B/F/TAFanalysis will be summarized by treatment group and overall for the subjects in the all B/F/TAF analysis, unless specified otherwise. All safety data from the entire study including both randomized phase and extension phase will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings and will be considered the least severe for the purpose of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology (PVE) database before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the B/F/TAF start date and no later than 30 days after permanent discontinuation of B/F/TAF, or
- Any AEs leading to premature discontinuation of B/F/TAF.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of B/F/TAF, the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent.

The event is considered treatment emergent if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is **the same as or after** the month and year (or year) of the first dosing date of B/F/TAF, and
- The month and year (or year) of the AE onset is **the same as or before** the month and year (or year) of the date corresponding to 30 days after the date of the last dose of B/F/TAF

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date marked as ongoing or on or after the first dosing date of B/F/TAF, will be considered as a TEAE. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of B/F/TAF will be considered as a TEAE.

7.1.6. Summaries of Adverse Events and Death

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group using the All B/F/TAF Analysis Set:

- Any Grade 2, 3, or 4 treatment-emergent AEs
- Any Grade 3 or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- Any Grade 3 or 4 treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs. Treatment-emergent deaths observed in the all B/F/TAF phase will be also included in this summary.

Treatment-emergent death refers to deaths that occurred between the first and last dose date of B/F/TAF plus 30 days (inclusive).

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all TEAEs, Grade 3 or 4 TEAEs, treatment-emergent study drug-related AEs, Grade 2, 3, or 4 treatment-emergent study drug-related AEs, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency.

Data listings for all AEs regardless of the study phases will be provided for the following:

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Study-Drug-Related SAEs
- Deaths report
- AEs leading to premature discontinuation of study drug

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Stage 3 Opportunistic Illnesses in HIV

On an ongoing basis, AEs will be reviewed for events that might meet the definition of stage 3 opportunistic illnesses in HIV that are indicative of an AIDS-defining diagnoses (see Protocol Appendix 5). The Gilead medical monitor will review the possible stage 3 opportunistic illnesses and approve the events that meet the definition. Events that meet the stage 3 opportunistic illness definition of an AIDS-defining diagnosis will be listed.

7.1.7.2. Cardiovascular or Cerebrovascular Events

Preferred terms for defining cardiovascular or cerebrovascular events are from relevant Standardised MedDRA Query (SMQ). The selected PT listing was provided by Gilead PVE and reviewed by Gilead medical monitors (see details in Appendix 3).

The number and percentage of subjects with treatment-emergent cardiovascular or cerebrovascular events and serious cardiovascular or cerebrovascular events by PT will be provided by treatment group based on the All B/F/TAF Analysis Set. A data listing of cardiovascular or cerebrovascular events will be provided.

7.1.7.3. Hepatic Events

Preferred terms for defining hepatic events are from 15 relevant SMQs, which are identified as non-infectious and non-congenital hepatobiliary disorders. The selected PT listing was provided by Gilead PVE and reviewed by Gilead medical monitors (see details in Appendix 4).

The number and percentage of subjects with treatment-emergent hepatic events and serious hepatic events by PT will be summarized by treatment group based on the All B/F/TAF Analysis Set. A data listing of hepatic events will be provided.

7.2. Laboratory Evaluations

Laboratory data will be analyzed and summarized using both quantitative and qualitative methods using All B/F/TAF Analysis Set. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately for all data collected from both phases of the study. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date of first dose of B/F/TAF. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn are available and serum albumin value is < 4.0 g/dL.

- Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 x (4.0 - albumin (g/dL)).

Toxicity grading for calcium will be applied based on the corrected values.

Estimate GFR

The following formulae will be used to calculate $eGFR_{CG}$:

- eGFR(CG) (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72), where weight is total body mass in kilograms.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

If there is any laboratory toxicity grading scale overlapping with the normal reference ranges (eg, grade 1 scale overlaps with normal reference ranges), laboratory values that are within the normal range will be grade 0, except for lipid tests.

For triglycerides, LDL, and cholesterol, protocol-specified toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

For the international normalized ratio (INR) of prothrombin time (PT), protocol-specified toxicity grading scale depends on the upper limit of normal range (ULN). While the ULN of INR depends on whether the subject is taking anticoagulant medication or not (ie, Not taking oral anticoagulant: 0.8 – 1.2; Taking oral anticoagulant: 2.0 – 3.0), this information is not collected by the reference laboratory. As a result, INR will be graded by assuming subject is not taking an oral anticoagulant, which is a conservative approach that may lead to over-reporting of abnormalities for INR. Consequently, INR and PT will not be included in summaries of laboratory abnormalities, but will be included in listings for the following reasons: 1) INR and PT are reflexive tests; 2) only the absolute values, not the toxicity grade, are needed for subject management purposes; and 3) more importantly, the toxicity grades for INR may be over-reported.

7.2.2.1. Treatment Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to 30 days from the last dose date of B/F/TAF. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

Fasting glucose and nonfasting glucose (including glucose results without a known fasting status) are graded based on different grading scales as specified in the protocol.

Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Maximum postbaseline grade, instead of treatment-emergent grade, for nonfasting glucose (including glucose results without a known fasting status) will be summarized, as nonfasting glucose was not assessed at baseline visit for most of the subjects; therefore, an abnormality is treatment-emergent or not cannot be determined for these subjects.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent Grade 2, 3, and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline values up to 30 days after the last dose date of B/F/TAF.

A by-subject listing of all treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order.

7.2.3. Metabolic Laboratory Evaluations

For metabolite assessments, including fasting glucose and the lipid panel (ie, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized by treatment group and visit using descriptive statistics.

7.2.4. Liver-Related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements collected in the all B/F/TAF phase of this study:

- Aspartate aminotransferase (AST): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Alanine aminotransferase (ALT): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- AST or ALT: (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Total bilirubin: (a) > 1 × ULN, (b) > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN, (b) > 2 × ULN
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose date of B/F/TAF. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline value. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the All B/F/TAF Analysis Set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date.

Subjects with AST or ALT > 3 × ULN will also be listed.

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by treatment group and visit using descriptive statistics.

7.2.5. Renal-Related Laboratory Evaluations

7.2.5.1. Serum Creatinine and $eGFR_{CG}$

Baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{CG}$ will be summarized by treatment group and visit using descriptive statistics.

7.2.5.2. Urine Creatinine, Urine Retinol Binding Protein to Creatinine Ratio, and Beta-2-Microglobulin to Creatinine Ratio

Baseline, postbaseline, and change from baseline in urine creatinine will be summarized by treatment group and visit using descriptive statistics.

Baseline, postbaseline, change from baseline, and percentage change from baseline in urine RBP to creatinine ratio and beta-2 microglobulin to creatinine ratio will be summarized by treatment group and visit using descriptive statistics.

7.2.5.3. Albuminuria by Quantitative Assessment

The baseline, postbaseline, changes from baseline, and percentage change from baseline in UACR will be summarized by treatment group and visit using descriptive statistics.

The number and percentage of subjects with UACR < 30 mg/g versus ≥ 30 mg/g will be summarized by baseline category at Weeks 24, 48, 72, 96, and based on the last on-treatment value (ie, data collected after the first dose date up to 1 day after the last dose date of B/F/TAF) {KDIGO Guideline Development Staff 2013}.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by treatment group for vital signs and body weight as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window

A baseline value will be defined as the last nonmissing value obtained on or prior to the date of first dose of B/F/TAF. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. In the same listing, a by-subject listing of body weight, height, and BMI will be provided.

7.4. Prior and Concomitant Medications

7.4.1. Antiretroviral Medications

Any nonstudy ARV medications used prior to, during, or after the study (if collected) are all recorded on the ARV eCRF. All ARV medications recorded on the ARV eCRF will be coded using the Gilead-modified World Health Organization (WHO) Drug Dictionary for ARV medication. The WHO preferred name and drug code will be attached to the clinical database. All ARV medications recorded on the ARV eCRF will be listed. No inferential statistics will be provided.

7.4.2. Concomitant Non-Antiretroviral Medications

Concomitant non-ARV medications are defined as non-ARV medications taken while a subject took study drug. Use of concomitant non-ARV medications from the first dose date to the last dose date of B/F/TAF will be summarized by preferred name using the number and percentage of subjects for each treatment group. Multiple drug use (by preferred name) will be counted only once per subject. The summary will be sorted by decreasing order of total frequency.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after the last dose date of B/F/TAF
- The month and year of stop of the medication is before the first dose date of B/F/TAF

If the start and stop date of non-ARV medications are complete, the start date is not after the last dose date and the stop date is not before the first dose date, or the non-ARV medications are marked as ongoing and start date is on or before the last dose date, the non-ARV medications are concomitant for the all B/F/TAF phase of the study.

Summaries of non-ARV concomitant medications will be provided for the All B/F/TAF Analysis Set. Subjects with any non-ARV concomitant medications will be listed including Anatomical Therapeutic Chemical (ATC) drug class level 2. No inferential statistics will be provided.

7.5. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at each scheduled postbaseline visit compared with baseline values will be presented by treatment groups using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No inferential statistics will be provided.

A by-subject listing for ECG assessment results will be provided by subject ID number and visits in chronological order.

7.6. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy during the study. Physical examination was not collected in the eCRF. Therefore, it will not be included in the analysis.

7.7. Subgroup Analyses for Safety Endpoints

Subgroup analysis by prior treatment regimen (ie, TDF-containing regimen versus non-TDF containing regimen) will be performed for renal endpoints including urine RBP to creatinine ratio, beta-2 microglobulin to creatinine ratio, and UACR using All B/F/TAF Analysis Set, as described in Section 7.2.5 above.

7.8. Changes From Protocol-Specified Safety Analyses

No change from protocol-specified safety analysis is planned.

8. PHARMACOKINETIC ANALYSES

All necessary PK analyses have been performed as part of the Week 48 analysis and will not be repeated in this analysis.

9. REFERENCES

KDIGO Guideline Development Staff. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney international. Supplement 2013;3 (1):v-150.

10. SOFTWARE

SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA) is to be used for all programming of tables, listings, and figures.

nQuery Advisor® Version 6.0 (Statistical Solutions, Cork, Ireland) is to be used for sample size and power calculation.

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[d,v]	30 Day Follow-Up[e]	ESDD[f]
			4	8	12	24	36	48	Every 12 Weeks		
Informed Consent	X										
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X	X				X		X			X
Symptom-Directed Physical Exam			X	X	X		X		X	X	
12-Lead ECG	X	X				X		X			X
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Urine Chemistry[h]		X				X		X	X[w]		
Urine Pregnancy Test[i]		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[i]	X										
Chemistry Profile[j]	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[k]		X			X	X		X	X[w]		
Estimated GFR	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile[l]	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[m]	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X
HBV Blood Planel[n]	X										

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[d,v] Every 12 Weeks	30 Day Follow-Up[e]	ESDD[f]
			4	8	12	24	36	48			
Plasma HBV DNA[o]		X			X	X		X	X[w]		X
HCVAb[p]	X										
HCV RNA[p]	X					X		X	X[w]		
HIV-1 Genotype/Phenotype[q]								X[q]			X[q]
Single PK Draw[r]				X		X	X				
Trough PK Draw[s]			X		X						
PK Sample (post-dose)[s]			X		X						
Observed In-Clinic Dose[s]			X		X						
Provide Dosing Diary[u]		X	X	X	X	X					
Collect Dosing Diary[x]			X	X	X	X	X				
CCI											
CCI											
Randomization		X									
Study Drug Dispensation		X	X	X	X	X	X	X[v]	X[v]		
Study Drug Accountability			X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Subjects should initiate dosing of study drug on the same day as the Day 1 visit.
c All study visits should be ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and completed within ± 6 days at Week 24 and Week 36, unless otherwise specified. The visit window at Week 48 will be ± 6 weeks of the protocol-specified visit date.
d At the Week 48 Visit, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC for an additional 48 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead Sciences elects to discontinue the study in that country, whichever occurs first. Study visits are to be completed every 12 weeks, within ± 6 days of the protocol-specified visit date unless otherwise specified.

e Must be completed 30 days after discontinuing study drug. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. Required for subjects who permanently discontinue study drug prior to Week 48 and do not continue in the study through at least one subsequent visit after the ESDD visit. Subjects who participate post Week 48 will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit.

f Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 48 Visit even if the subject discontinues study drug.

g Vital signs measurements including blood pressure, pulse, respiratory rate, and temperature

h Urine Chemistry includes urine albumin, urine creatinine, urine protein, retinol binding protein, and beta-2 microglobulin

i Women of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.

j Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). At Day 1, Weeks 24, and 48 and every 24 weeks during the post Week 48 period, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. TSH will be collected at Screening, Day 1, Weeks 24, and 48, as well as every 24 weeks post Week 48, and ESDD if applicable.

k Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

l CBC with differential and platelet count.

m If the HIV-1 RNA value is ≥ 50 copies/mL at Week 48, a retest HIV-1 RNA value must be collected within two to three weeks of the initial test.

n Hepatitis B Virus (HBV) blood panel: Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb). If positive HBsAg, reflex testing for plasma HBV DNA, HBeAg (if negative, reflex HBeAb), and quantitative HBsAg. If positive HBcAb with negative HBsAg and negative HBsAb, reflex testing for plasma HBV DNA (if positive, reflex HBeAg). If HBeAg is performed and found to be negative, reflex HBeAb.

o For subjects who meet the definition of HBV infection, the following will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative, reflex HBeAb) at Days 1, 12, 24 and then every 24 weeks.

p Subjects who are HCVAb positive will have a HCV RNA test performed at screening and every 24 weeks.

q HIV-1 genotype/phenotype testing for subjects with HIV-1 RNA ≥ 200 copies/mL and virologic rebound, at early study drug discontinuation or Week 48. Following unconfirmed virologic rebound, subjects will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV-1 RNA and HIV-1 genotype/phenotype (reverse transcriptase, protease and integrase) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.13.1).

r All subjects on GS-9883/F/TAF (Treatment Group 1 only) will have a single anytime PK blood sample collected at Weeks 8, 24 and 36.

s Subjects on GS-9883/F/TAF (Treatment Group 1 only) will have a Trough PK blood sample collected between 20-28 hours following their last dose at Weeks 4 and 12. Subjects must be instructed to not take their study drugs on the morning of their visit for the trough sample collection. If the subject has taken their dose of study drugs prior to the visit, the visit may proceed, but the subject must return within 72 hours for the single trough PK blood sample collection. In the event a subject routinely takes their study drug in the evening, a single anytime sample may be drawn at Weeks 4 and 12 as the subject will not be instructed to change their dosing time to accommodate this trough PK draw. A post-dose PK blood sample will be collected between 1 and 4 hours post dose following an observed, in-clinic dose.

[redacted]

u A dosing diary will be dispensed for all Treatment Group 1 subjects to complete prior to each of the PK sample visits.

v Open-label GS-9883/F/TAF FDC will be dispensed to subjects participating in the study post Week 48 starting at the Week 48 Visit.

w Every 24 weeks only.

x Dosing diaries will be collected from subjects for the single anytime PK and trough PK collection (Treatment Group 1 only). If a dosing diary is not returned the site may ask the subject for the time of the last dose and if it was taken with or without food.

Appendix 2. TFL Mocks

Appendix Table 1. Subject Disposition (All Randomized Subjects)

	B/F/TAF	SBR	All B/F/TAF
Subjects Randomized	xx	xx	xx
Subjects Randomized and Never Treated	xx	xx	xx
Subjects Randomized and Treated in the Randomized Phase	xx	xx	xx
Subjects Prematurely Discontinuing Study Drug in the Randomized Phase	xx	xx	xx
Subjects Completed the Randomized Phase but not Entered into the Extension Phase	xx	xx	xx
Subjects Entering the Extension Phase and B/F/TAF Treated	xx	xx	xx
Subjects Receiving B/F/TAF in the Randomized or Extension Phase (All B/F/TAF Analysis Set)	xx	xx	xx
Subjects Completing B/F/TAF	xx (xx%)	xx (xx%)	xx (xx%)
Subjects Prematurely Discontinuing B/F/TAF	xx (xx%)	xx (xx%)	xx (xx%)
Reasons for Prematurely Discontinuing B/F/TAF			
Adverse Event	xx (xx%)	xx (xx%)	xx (xx%)
…	…	…	…
Subjects Completing Study	xx (xx%)	xx (xx%)	xx (xx%)
Subjects Prematurely Discontinuing from Study	x (x.x%)	x (x.x%)	x (x.x%)
Reasons for Prematurely Discontinuing from Study			
Adverse Event	x (x.x%)	x (x.x%)	x (x.x%)
…	…	…	…

The denominator for percentages for each category is the number of subjects in the All B/F/TAF Analysis Set.

Appendix Table 2. Summary of Laboratory Test (unit) by Visit

	All B/F/TAF Analysis Set												
	B/F/TAF (N=xxx)						SBR to B/F/TAF (N=xxx)						All B/F/TAF (N=xxx)
	N	Mean	SD	Q1	Median	Q3	N	Mean	SD	Q1	Median	Q3	…
Baseline	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	…
Week x	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	…
…	…	…	…	…	…	…	…	…	…	…	…	…	…
	xx	xx	xx	xx	xx	xx		xx	xx	xx	xx	xx	…
Change from Baseline at *Week x*	xx	xx	xx	xx	xx	xx		xx	xx	xx	xx	xx	
…	…	…	…	…	…	…	…	…	…	…	…	…	…

Note to programmer: the parameters include N, Mean, SD, Q1, Median and Q3 for each treatment group. If space is available, min and max will also be included. The format of the last column "All B/F/TAF" is the same as the other 2 columns.

Appendix 3. Cardiovascular or Cerebrovascular Events

An adverse event record will be flagged as a cardiovascular or cerebrovascular event if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the narrow search of the following 3 SMQs under MedDRA 21.1 provided by Gilead PVE and reviewed by Gilead medical monitors.

	SMQ Source
Cardiovascular or Cerebrovascular Events	Ischaemic central nervous system vascular conditions (SMQ) – Narrow Scope Term
	Myocardial infarction (SMQ) - Narrow Scope Term
	Other ischaemic heart disease (SMQ) - Narrow Scope Term

Appendix 4. Hepatic Events

An adverse event record will be flagged as a hepatic event if its MedDRA PT included in the pre-specified PT list, which includes all PTs from the broad search of the following 15 SMQs under MedDRA 21.1 provided by Gilead PVE and reviewed by Gilead medical monitors.

	SMQ Source
Hepatic Events (HEP)	Biliary neoplasms benign (incl cysts and polyps) (SMQ)
	Biliary malignant tumours (SMQ)
	Biliary tumours of unspecified malignancy (SMQ)
	Biliary system related investigations, signs and symptoms (SMQ)
	Biliary tract disorders (SMQ)
	Gallbladder related disorders (SMQ)
	Gallstone related disorders (SMQ)
	Cholestasis and jaundice of hepatic origin (SMQ)
	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
	Hepatitis, non-infectious (SMQ)
	Liver neoplasms, benign (incl cysts and polyps) (SMQ)
	Liver malignant tumours (SMQ)
	Liver tumours of unspecified malignancy (SMQ)
	Liver related investigations, signs and symptoms (SMQ)
	Liver-related coagulation and bleeding disturbances (SMQ)

Appendix 5. Programming Specification

1) For subjects who were randomized to SBR and permanently discontinued study drug in the randomized phase (subjects who were in the All Randomized Analysis Set but not in the All B/F/TAF Analysis Set), since the analysis will not include these subjects (except the disposition table and data listings), any derived variables for these subjects that will be used in the disposition table and data listings are defined as follows:

   a) Subjects in the All Randomized Analysis Set are defined as subjects randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with nonmissing RGMNDTN in the IXRSRAND dataset) and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset).

   b) **Study Day 1 (Randomized Phase)** is defined as the day when the first dose of the randomized study drug (ie, *SBR)* was taken, as recorded on the "Randomized Phase" Study Drug Administration eCRF.

   c) **Last Dose Date (Randomized Phase)** is defined as the latest of the randomized study drug end dates recorded on the "Randomized Phase" Study Drug Administration eCRF with "Permanently withdrawn" box checked for subjects who prematurely discontinued or completed the randomized study drug in the "Randomized Phase" according to the Study Drug Completion eCRF.

   d) **Last Study Date** is the latest of the study drug (SBR) start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF. If subject died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date.

2) AGE calculated as follows:

   a) AGE (years) is calculated from the number of days between the date of birth (DOB) and Day 1 (first dose date of B/F/TAF for subjects in the All B/F/TAF Analysis Set and first dose date of SBR or randomization date if never dosed for other subjects in the All Randomized Analysis Set),

   b) Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

   c) Divide the result in (b) by 12,

   d) AGE = the integer of the result in (c),

   e) If the DOB and Day 1 have the month in common and the birthday is later in the month than the date of Study Day 1, then subtract one from the AGE result above.

3) In disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

4) Body mass index (BMI) and Body Surface Area (BSA)

   BMI and BSA will be calculated as follows:

   - BMI = (weight [kg])/ (height [meters]^2)
   - BSA (m^2) = SQRT([Height(cm) x Weight(kg)]/ 3600)

   All B/F/TAF baseline height and weight of the study will be used for this calculation.

5) Last Dose Date of B/F/TAF and Last Study Date

   Last Dose Date in ADSL was defined in Section 3.8.1.

   For subjects with a partial last dosing date of B/F/TAF (ie, month and year of last dose are known), the minimum of {(death date, if available), (the latest of the dispensing dates of B/F/TAF bottles, B/F/TAF start dates and end dates (based on EX dataset), and the imputed last dose date [day imputed as 15])} will be used as the final imputed last dose date. However if dispensing date's month is after last dose date's month, data query is needed.

   Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF. If study drug start dates or end dates is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

6) Treatment Group Presented in the Listings

   In data listings, the treatment group will be presented as follows:

   B/F/TAF: subjects who were randomized into B/F/TAF group in the randomized phase, either entered into the extension phase or not;

   SBR: subjects who were randomized into SBR group in the randomized phase and did not enter into the extension phase of B/F/TAF;

   SBR to B/F/TAF: subjects who were randomized into SBR group in the randomized phase and entered into the extension phase of B/F/TAF.

7) Toxicity Grades:

   i) For toxicity grade summaries, include all postbaseline graded results up to 30 days after the last dose of B/F/TAF, not just those used in by-visit summaries.

   ii) For glucose grading, as specified in SAP Section 7.2.2.1, the treatment-emergent flag cannot be determined for nonfasting glucose (including glucose results without a known fasting status). As a result, these records will be excluded from the "Maximum Treatment-emergent Toxicity Grade" summary in the "Treatment-emergent Laboratory Abnormalities" or "Treatment-emergent Grade 3 or 4 Laboratory Abnormalities" summary tables. In addition, fasting glucose and non-fasting glucose will be listed as two separate laboratory tests in the "Laboratory Abnormalities" and "Grade 3 or 4 Laboratory Abnormalities" listings. Only a maximum postbaseline toxicity flag will be displayed and the treatment-emergent flag will not be displayed for nonfasting glucose as the treatment-emergent flag cannot be determined for nonfasting glucose.

8) Graded Laboratory Abnormalities Summary

   The following labels will be used for treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	GGT	Increase	GGT (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
	Prothrombin Intl. Normalized Ratio (INR)	Increase	N/A
	Prothrombin Time (PT)	Increase	N/A
Urinalysis	Urine Blood (Dipstick)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*

* Due to the reflexive nature of the quantitative urine RBC test, results will be combined with the dipstick test of urine blood as described below. General rule is that urine RBC (Quantitative) should always be used first (if available), no matter it is collected at the same time of Urine Blood (Dipstick) or not. The combined Urine RBC (hematuria, Quantitative or Dipstick) toxicity grade will be used for "Maximum treatment-emergent toxicity grade" summary.

Is Post-BL Urine RBC (Quant.) Result Available?	Is BL Urine RBC (Quant.) Result Available?	Is Post-BL Urine Blood (Dipstick) Result Available?	Is BL Urine Blood (Dipstick) Result Available?	How to Determine Treatment-Emergent Toxicity for "Urine RBC (Hematuria, Quantitative or Dipstick)"
Yes	Yes	-	-	Compare post-BL Urine RBC (Quant.) toxicity grade to BL Urine RBC (Quant.) toxicity grade. If post-BL toxicity is greater than BL toxicity, then treatment-emergent
Yes	No	-	-	Treatment-emergent. Use post-BL Urine RBC (Quant.) toxicity grade.
No	-	Yes	Yes	Compare post-BL Urine Blood (Dipstick) toxicity grade to BL Urine Blood (Dipstick) toxicity grade. If post-BL toxicity is greater than BL toxicity, then treatment-emergent
No	-	Yes	No	Treatment-emergent. Use post-BL Urine Blood (Dipstick) toxicity grade.
No	-	No	-	Do not count subject in the denominator for "Urine RBC (Hematuria, Quantitative or Dipstick)"

BL = Baseline. Quant = Quantitative. "-" means any value can be present (or it can be missing), as it does not affect the classification

9) Renal related laboratory evaluation

a) Unit conversion for renal safety tests derived from related tests with conventional units

i) Urine RBP (ug/L) to creatinine (mg/dL) ratio: 1 (ug/L) / (mg/dL) = 100 x ug/g

ii) Urine Beta-2-microglobulin (mg/L) to creatinine (mg/dL) ratio: 1 (mg/L) / (mg/dL) = 10^5 ug/g

iii) Urine Albumin (mg/dL) to creatinine (mg/dL) ratio: 1 (mg/dL) / (mg/dL) = 1000 x mg/g

b) Calculation of ratios:

To calculate laboratory ratios (eg, urine RBP to creatinine ratio), the lab value of each test in the ratio needs to be from the same accession number; if any test value used for the ratio calculation from the same accession number is missing , then the ratio is not calculable (ie, missing).

10) For figures, if at a visit where n (sample size) for any treatment group ≤ 5, data for that treatment group will not be displayed at the visit in figure (except the Kaplan-Meier figure), but all data will be included in the corresponding table summary.

11) Puerto Rico was combined with the United States when we evaluate the treatment effect across countries.

12) LDL: Conversions between 2nd and 3rd generations

    LDL was analyzed by 2 different assays in the study: 2nd generation (including RCT2394, RCT2312, and RCT2811) and 3rd generation (RCT3870). Samples collected at earlier visits were analyzed using LDL 2nd generation assay. Samples collected at later visits were analyzed using LDL 3rd generation assay. The conversion formulas are as follow:

    2nd Gen (mmol/L) = (3rd Gen - 0.0626)/0.882

    3rd Gen (mmol/L) = (0.882 x 2nd Gen) + 0.0626

    For this analysis, since most of the LDL tests were from the 2nd generation, we only requested conversion from 3rd generation to 2nd generation.

    For the analysis of change from baseline in fasting direct LDL: the sample analyzed by LDL 3rd generation assay will be converted to 2nd generation as a new record with test codes of LIP.LDL.00.02 in raw data. During ADaM stage, a derived parameter code (FLDL2) for "Fasting LDL Cholesterol 2ND GEN Combined" will be generated to pool the records from both original (including test codes RCT2394, RCT2312, and RCT2811) and converted (LIP.LDL.00.02) 2nd generation results to calculate the change from baseline in fasting direct LDL.

    For the analysis of toxicity grade for fasting direct LDL: toxicity grade will be based on the Gilead grading results (ie, toxgrg) from original values before conversion. In another words, during ADaM stage, a derived parameter code (FLDLTOX) for "Fasting LDL Cholesterol for Toxicity" will be generated to pool the records from 2nd generation (including RCT2394, RCT2312, and RCT2811) and 3rd generation (ie, RCT3870) to derive treatment-emergent toxicity grades, maximum postbaseline toxicity grades, etc.

SAP_Final_GS-US-380-1961_V1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	22-Dec-2018 00:00:48
PPD	Clinical Research eSigned	22-Dec-2018 00:47:59