STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b, Multicenter, Open Label Study to Evaluate Switching from an Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Fixed-Dose Combination Regimen or a Tenofovir Disoproxil Fumarate Containing Regimen to Fixed-Dose Combination of Bictegravir/ Emtricitabine/Tenofovir Alafenamide in Elderly, Virologically-Suppressed HIV-1 Infected Subjects Aged ≥ 65 Years
Name of Test Drug:	Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF)
Study Number:	GS-US-380-4449
Protocol Version (Date):	Amendment 2 (18 December 2018)
Analysis Type:	Final (Week 96)
Analysis Plan Version:	Version 1
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
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
CG	Cockcroft-Gault
CRF	case report form
CSR	clinical study report
DOB	date of birth
E/C/F/TAF	elvitegravir /cobicistat emtricitabine/ tenofovir alafenamide; Genvoya; GEN
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CKD\text{-}EPI,\ cysC}$	estimated glomerular filtration rate using CKD-EPI (cystatin C) formula
eGFR(CG)	estimated glomerular filtration rate using Cockcroft-Gault formula
EQ-5D	EuroQol 5D patient questionnaire
FACIT-F	functional assessment of chronic illness therapy - fatigue
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
Gilead	Gilead Sciences, Inc.
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus (Type 1)
HIVTSQc	HIV treatment satisfaction change
HIVTSQs	HIV treatment satisfaction status
HLGT	high level group term
HLT	high level term
INR	international normalized ratio
LDL	low density lipoprotein
LLT	lowest level term

MedDRA	Medical Dictionary for Regulatory Activities
NLP	natural language processing
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
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SF-36	Short Form 36 Health Survey
SOC	system organ class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent AE
TFL	tables, figures, and listings
ULN	upper limit of normal
UP	urine protein
UPCR	urine protein to urine creatinine ratio
VAS	visual analog scale
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-380-4449, which will be performed when all subjects have completed the study or prematurely discontinued from the study. The Week 24 analyses and the Week 48 analyses will not be repeated for this final analysis.

This SAP is based on the study protocol amendment 2 dated 18 December 2018 and the electronic case report form (eCRF). The SAP will be finalized before the data finalization for the final analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report.

1.1. Study Objectives

The primary objective of this study is:

- To characterize the virologic efficacy of switching virologically suppressed subjects on an Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) fixed dose combination (FDC) regimen or Tenofovir Disoproxil Fumarate (TDF)-containing regimen to bictegravir (BIC; B) /emtricitabine (FTC; F) /tenofovir alafenamide (B/F/TAF) FDC defined by HIV-1 RNA < 50 copies/mL at Week 24.

The secondary objectives of this study are:

- To characterize the safety and tolerability of switching to B/F/TAF FDC from an E/C/F/TAF FDC or TDF-containing regimen through Week 96.

- To characterize the virologic efficacy of switching to B/F/TAF FDC defined by HIV-1 RNA < 50 copies/mL at Week 48, Week 72 and Week 96.

1.2. Study Design

Design Configuration and Subject Population

GS-US-380-4449 is an open-label, multicenter, single arm study to evaluate switching from either E/C/F/TAF FDC or TDF and FTC-containing 'backbone' regimen plus a third agent to B/F/TAF FDC in virologically-suppressed (HIV-1 RNA < 50 copies/mL), HIV-1 infected subjects aged ≥ 65 years.

Eligible subjects who complete GS-US-292-1826 through Week 48 and are at least 65 years old at the screening visit will be allowed to enter. Subjects not previously participating in GS-US-292-1826 will be able to enroll as long as they meet all eligibility criteria.

Treatment Groups

There is one treatment group: FDC of BIC 50 mg/FTC 200 mg/TAF 25 mg (B/F/TAF) administered orally, once daily, without regard to food (approximate n 80).

Key Eligibility Criteria

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

- Age ≥ 65 years
- Currently receiving an antiretroviral (ARV) regimen of E/C/F/TAF FDC (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826) for ≥ 3 months
- Documented plasma HIV-1 RNA levels < 50 copies/mL during treatment with E/C/F/TAF (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826) for the last 2 visits preceding the Screening Visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL)
- Adequate renal function, an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min according to the Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$)

Study Periods / Phases

Subjects will be treated for at least 96 weeks. CCI [redacted]

Subjects who complete the study through the Week 96 Visit and do not continue participation in the study will be required to return to the clinic 30 days after the Week 96 Visit for a 30 Day Follow-Up Visit.

Schedule of Assessments

After screening procedures, study visits will occur at Day 1, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96.

Laboratory analyses (including chemistry, hematology, and urinalysis), HIV-1 RNA, CD4+ cell count, assessment of adverse events (AEs), and concomitant medications, and complete or symptom directed physical examinations will be performed at all study visits.

Blood and urine for selected evaluations of renal safety, inflammation, and platelet and coagulation function will be collected at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84, and 96. A portion of the biomarker blood sample obtained at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84, and 96 may be utilized to assess study drug pharmacokinetics (PK). This will be a random sample with the date and time of the subject's last medication dose recorded.

Site and/or Stratum Enrollment Limits

Approximately 30 study sites in Europe participated. Approximately 80 subjects who meet the eligibility criteria will be enrolled in the study.

Study Duration

The treatment duration specified in the protocol was 96 weeks CCI [redacted] However, all subjects will discontinue the study at Week 96; therefore treatment duration will be up to 96 weeks, followed by a 30 day follow-up.

1.3. Sample Size and Power

The sample size is based on feasibility of conducting a study with ≥ 65 year old subjects.

2. TYPE OF PLANNED ANALYSIS

2.1. Week 24 Analysis

The Week 24 analysis was conducted after all subjects either completed their Week 24 visit or prematurely discontinued from the study drug.

2.2. Week 48 Analysis

The Week 48 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.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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 Enrolled 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.

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 enrolled but never dosed subjects, age calculated using the date of enrollment will be used. For screen failures, age calculated using the date of the informed consent was signed will be used. Because only birth year is collected on the eCRF, and because age was not collected at Day 1 for this study, "01 January" will be used for the unknown birth day and month 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.

3.1.1. All Enrolled Analysis Set

The **All Enrolled Analysis Set** will include all subjects who were enrolled into the study. This is the primary analysis set for by-subject listings unless otherwise specified.

3.1.2. Full Analysis Set

The **Full Analysis Set** includes all subjects who (1) were enrolled and received at least 1 dose of study drug, and (2) do not have major protocol violations. This is the primary analysis set for all efficacy analyses.

The major protocol violations include

- ARV regimen at study entry other than E/C/F/TAF FDC (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826)
- ARV regimen at study entry for < 3 months

3.1.3. Safety Analysis Set

The **Safety Analysis Set** includes all subjects who were enrolled and received at least 1 dose of study drug. This is the primary analysis set for all safety analyses.

3.2. Subject Grouping

There is one subject group: B/F/TAF.

3.3. Strata and Covariates

There is no stratification for analysis.

3.4. Examination of Subject Subgroups

No subgroup analyses are planned.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

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. Urine protein to creatinine ratio (UPCR) is not calculated if the urine protein value (UP) used for the ratio calculation from the same accession number is under the lower limit of quantification (ie, < 4.0 mg/dL).

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 purposes.

3.8. Analysis Windows

3.8.1. Definitions

Study Day 1 is defined as the day when the first dose of study drug was taken. The first dose date is defined as the earliest nonmissing start date of B/F/TAF study drug recorded on the Study Drug Administration eCRF.

Study Days are calculated relative to Study Day 1. 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 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), 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.

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 windows.

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

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

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
CCI			

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	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	504
Week 96	672	505	840

The analysis windows for urine retinol binding protein (RBP), and urine beta-2 microglobulin, and related derived ratios are presented in Table 3-3.

Table 3-3. Analysis Windows for Urine RBP, Urine Beta-2 Microglobulin, and Related Ratios

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	252
Week 48	336	253	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
CCI			

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

Table 3-4. Analysis Windows for ECG

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	504
Week 96	672	505	840

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 study drug 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 study drug 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

The number and percentage of subjects enrolled for each country and investigator will be summarized for subjects using the Safety Analysis Set. The denominator for this calculation will be the number of subjects in the Safety Analysis Set.

A list of subject enrollment including date of informed consent signed and met all eligibility criteria will be provided.

4.1.2. Subject Disposition

The summary of subject disposition will be provided for all screened subjects. This summary will include the number of subjects screened, screen failure subjects who were not enrolled, subjects who met all eligibility criteria but were not enrolled, subjects enrolled, subjects enrolled but not treated, subjects in the Safety Analysis Set, Subjects in the FAS.

In addition, the number and percentage of the subjects from the Safety Analysis Set in the following categories will be summarized:

- Completed study drug
- Prematurely discontinuing study drug (with summary of reasons for discontinuing study treatment)
- Completed study
- Prematurely discontinuing study (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 Safety Analysis Set.

No inferential statistics will be provided. A data listing of reasons for study drug/study discontinuation will be provided.

4.1.3. Subjects with Missed or Virtual Visits Due To COVID-19

A listing of subjects affected by the COVID-19 pandemic will be provided for all enrolled subjects with a missed visit or virtual visit due to COVID-19.

The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 6.

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 study drug 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).

Summaries will be provided for subjects in the Safety Analysis Set. No inferential statistics will be provided.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method based on the Safety Analysis Set. Subjects who completed study drug will be censored at the last dose date.

4.2.2. Adherence to Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts. The numbers of pills of B/F/TAF dispensed and returned are captured on Study Drug Accountability eCRF.

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

$$\text{Adherence}\,(\%) \quad 100 \times \frac{\text{Total No. of pills taken}}{\text{Total No. of pills prescribed}}$$

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

[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.

Overall adherence will be calculated for each subject in the Safety analysis set using all data from the entire dosing period up to the date of permanent discontinuation of B/F/TAF.

Descriptive statistics for adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided for subjects who return at least 1 bottle and have calculable adherence in the Safety analysis set. No inferential statistics will be provided.

4.3. Protocol Deviations

A listing will be provided for all enrolled subjects who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviations.

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 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 study drug. The summaries of demographic data and baseline subject characteristics will be provided using the Safety 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
- HBV surface antigen status
- HIV/HBV coinfection at baseline, which is defined as:

  Positive HBsAg (HBV Surface Antigen) on or prior to the first dose date, or

  Negative HBsAg, negative HBsAb (HBV Surface Antibody), positive HBcAb (HBV Core Antibody), and Quantifiable HBV DNA (ie, HBV DNA >-20 IU/mL) on or prior to the first dose.

- HCV antibody status
- Medical history: diabetes (Yes/No), hypertension (Yes/No), cardiovascular disease (Yes/No), and hyperlipidemia (Yes/No) (See Appendix 5 for additional details)
- Tobacco smoking history (never smoker, former smoker, current smoker)

- Relative with myocardial infarction or stroke before 50 years-old
- $eGFR_{CG}$ (mL/min)
- estimated GFR using the CKD-EPI formula, $eGFR_{CKD\ EPI,\ cysC}$ (mL/min/1.73 m^2)
- ARV regimen at study entry (see Appendix 7 for additional details)

No inferential statistics will be provided.

5.3. Medical History

Medical history data will be collected at screening and listed only. Medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

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 HIV-1 RNA < 50 copies/mL at Week 24 as defined by the FDA snapshot algorithm.

The analyses of the primary efficacy endpoint were performed in the Week 24 analysis, and will not be repeated here.

6.1.2. Efficacy Endpoints as Secondary Endpoints

The secondary efficacy endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 48, 72, and 96 as determined by the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24, 48, 72, and 96 as defined by 2 different missing data imputation methods specified in Section 6.2.3.
- The change from baseline in CD4+ cell count and CD4 percentage (%) at Weeks 24, 48, 72, and 96

The secondary efficacy endpoints related to Week 24 and Week 48 were included in the Week 48 analyses and will not be repeated in the final analysis. However, change from baseline in CD4+ cell counts and CD4 percentage at each visit will be presented in this final analysis.

6.2. Analysis of the Efficacy Endpoints

6.2.1. US FDA-Defined Snapshot Algorithm

The analysis window at Week 96 is defined as from Study Day 631 to Study Day 714, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after the last dose date of study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome for Week 96 will be defined using the following categories:

- **HIV-1 RNA < 50 copies/mL**: this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the analysis window
- HIV-1 RNA ≥ 50 copies/mL: this includes subjects
    1) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the analysis window, or

2) Who do not have on-treatment HIV-1 RNA data in the analysis window and

   a) Who discontinue study drug prior to or in the analysis window due to lack of efficacy, or

   b) Who discontinue study drug prior to or in the analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or

   c) Who discontinue study drug prior to or in the analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL

- **No Virologic Data in Window**: this includes subjects who do not have on-treatment HIV-1 RNA data in the analysis window because of the following:

  1) Discontinuation of study drug prior to or in the analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

  2) Discontinuation of study drug prior to or in the analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA is < 50 copies/mL, or

  3) Missing data during the window but on study drug

The flowchart of the snapshot algorithm is provided in Appendix 2.

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL, and reasons for no virologic data at Week 96 will be summarized using the Full Analysis Set. The 95% confidence intervals (CIs) for percentages of subjects with HIV-1 RNA < 50 copies/mL and HIV-1 RNA ≥ 50 copies/mL will be constructed using the Exact method. The analysis will be done using the FAS. The above analysis will be repeated for Week 72.

The analysis window at Week 72 is defined as from Study Day 463 to Study Day 546, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after the last dose date of study drug) will be used in the US FDA-defined snapshot algorithm defined above.

The same analysis will be repeated for proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 72 and Week 96 as defined by US FDA-defined snapshot algorithm. The visit window was defined in Table 3-1.

The Week 72, and Week 96 virologic outcomes for the US FDA-defined snapshot algorithm will be listed.

6.2.2. 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 FAS.

The changes from baseline in CD4 cell count and CD4% at each visit will be summarized using descriptive statistics based on observed data (ie, missing will be excluded) using the FAS.

The mean and 95% CI of change from baseline in CD4 cell count over time will be plotted using observed data for the FAS.

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

The proportion of subjects with HIV-1 RNA < 50 copies/mL will also be summarized using the following 2 methods for imputing missing HIV-1 RNA values:

- Missing Failure (M F)

In this approach, all missing data will be treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for percentages is the number of subjects in the FAS. Data will be summarized through Week 96.

- Missing Excluded (M E)

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 FAS with non-missing HIV-1 RNA value at that visit.

For both M F and 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 < 1000 copies/mL
- ≥ 1000 copies/mL

The 95% CI of the proportion of subjects with HIV-1 RNA < 50 copies/mL 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 collected up to 30 days after permanent discontinuation of B/F/TAF study drug will be summarized for the subjects in the Safety Analysis Set, unless specified otherwise. All safety data 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, and PT. For other AEs described below, summaries will be provided by SOC and PT using the Safety 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 the number and percentage of subjects who experienced the above AEs. Treatment-emergent deaths will also be included in this summary.

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date 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 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 6). 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 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, which is the same PT listing used to search “Cardiovascular Disease” medical history (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 summarized based on the safety analysis set. A data listing of cardiovascular or cerebrovascular events will be provided.

7.1.7.3. Hepatic Events

Preferred terms for 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 based on the safety 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 the Safety 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. 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 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.

Estimated GFR

The Cockcroft-Gault (CG) formula 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.

Additionally, for baseline values only, the CKD-EPI (cystatin C) formula will be used to calculate $eGFR_{CKD\ EPI,\ cysC}$:

- $eGFR_{CKD\ EPI,\ cysC}$ (mL/min/1.73 m^2) $133 \times \min(Scys/0.8, 1)^{0.499} \times \max(Scys/0.8, 1)^{1.328} \times 0.996^{Age}$ [× 0.932 if female], where Scys is serum cystatin C (mg/L), min (Scys/0.8,1) indicates the minimum of Scys/0.8 or 1, and max (Scys/0.8,1) indicates the maximum of Scys/0.8 or 1.

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.

Both urine RBC based on microscopic examination, labeled as Hematuria (Quantitative), and urine blood based on a dipstick, labeled as Hematuria (Dipstick), are assessed and assigned a toxicity grade in this study. Hematuria (Quantitative) is a reflex test. Urine RBC based on microscopic examination or Dipstick will be presented in laboratory toxicity summary tables and listings.

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; 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 metabolic 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 visit using descriptive statistics. Change from baseline will be tested using the Wilcoxon signed rank test.

In addition, the number and percentage of subjects who took lipid modifying medications at study entry and he number and percentage of subjects who initiated lipid modifying medications during the study will be provided.

A lipid modifying medication is defined as a medication with drug class "LIPID MODIFYING AGENTS" and preferred drug name containing the wording of "STATIN".

A sensitivity analysis of fasting lipid tests (including total cholesterol, LDL, HDL, triglycerides, and total cholesterol to HDL ratio) will be performed by excluding subjects who took lipid modifying medications at study entry or initiated the medications during the study: baseline, Week 96 and change from baseline at Week 96 will be summarized. Only subjects with both baseline and Week 96 values will be included in the analysis.

Median (Q1, Q3) of change from baseline in fasting metabolic assessments over time will be plotted.

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:

- 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 Safety 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 visit using descriptive statistics.

In addition, ALT elevation (ie, ALT > 2 x Baseline and ALT > 10 x ULN) and ALT flare, defined as ALT elevations confirmed at two consecutive visits, will be evaluated and listed for subjects with HIV/HBV coinfection at baseline. The first occurrence of two or more consecutive ALT elevations will be identified as the ALT flare.

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 visit using descriptive statistics.

Median (Q1, Q3) of change from baseline in serum creatinine and $eGFR_{CG}$ over time will be plotted.

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

Baseline, postbaseline, and change from baseline in urine creatinine will be summarized by visit using descriptive statistics. Change from baseline will be tested using the Wilcoxon signed rank test.

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 visit using descriptive statistics. Change from baseline and percentage change from baseline will be tested using the Wilcoxon signed rank test.

Subjects will be classified into 4 categories based on their UP and UPCR results: The categories will be (1) UP < 4.0 mg/dL, (2) UPCR < 200 mg/g, (3) UPCR >200 mg/g, and (4) missing, where UPCR will only be calculated when UP ≥ 4.0 mg/dL. The number and percentage of subjects in each UP and UPCR category will be summarized by baseline category at Weeks 4, 12, 24, 48, 60, 72, 84 and 96.

Median (Q1, Q3) percentage change from baseline in urine RBP to creatinine ratio and beta-2 microglobulin to creatinine ratio over time will be plotted.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided 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 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 (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred drug name and drug code will be attached to the clinical database. Use of concomitant medications from the first dose date to the last dose date of B/F/TAF will be summarized (number and percentage of subjects) by preferred drug name. Multiple drug use (by preferred drug 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. 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.

Summaries of non-ARV concomitant medications will be provided for the Safety Analysis Set. Subjects with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

Additionally, for each subject, the number of unique chronic medications (based on preferred drug name) that the subject was receiving at baseline (ie, on the date of the first dose of study drug) will be calculated. Chronic medications are defined as those (1) given orally, and (2) given for a duration of at least 30 days. Number of chronic medications at baseline will be summarized using descriptive statistics. Additionally, chronic medications will be summarized by medication class using ATC Level 1 and ATC Level 2, separately.

7.5. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at Week 48 and Week 96 compared with baseline values will be presented 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.

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

No subgroup analyses are planned for the Week 96 analysis.

7.8. Changes From Protocol-Specified Safety Analyses

No change from protocol-specified safety analysis is planned.

8. PHARMACOKINETIC ANALYSES

There are no PK analyses planned.

9. PATIENT REPORTED OUTCOMES

The patient-reported outcomes (PROs) include the following assessments:

- Visual Analog Scale (VAS) Adherence Questionnaire (assessed at Day 1, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96)

Summaries will use the safety analysis set. Assessments will be listed using the all enrolled analysis set. Summaries will include data up to 30 days after permanent discontinuation of B/F/TAF study drug.

9.1. Medication Adherence Questionnaire

Adherence will be assessed by the medication adherence questionnaire that includes a VAS and 2 additional questions.

For the VAS, the subject is asked to describe their adherence to their ARV regimen by using a linear scale (0% 100%) to indicate what percent of medications was taken in the last 30 days (0% taken none of prescribed anti-HIV medication, and 100% taken all doses of prescribed anti-HIV medication). The 2 additional questions ask how many days the subject has missed medications in the last 30 days and how many days the subject has missed medications in the last 4 days.

9.1.1. VAS Statistical Analysis Method

The VAS (%) absolute value at each study visit will be summarized using descriptive statistics.

Number of days with missed doses in the past 30 days and past 4 days will be summarized categorically (< 2, 2 to < 4, 4 to < 6, ≥ 6 for the past 30 days; 0 and > 0 for the past 4 days) for each study visit.

10. REFERENCES

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.

11. SOFTWARE

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

12. SAP REVISION

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

13. APPENDICES

Appendix 1. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]									CCI	Early Study Drug Discontinuation (ESDD)[d]	30-Day Follow-up
			4	12	24	36	48	60	72	84	96			
Informed Consent	X													
Medical History	X													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X		X	X
Complete Physical Exam[e]	X	X					X				X		X	
Symptom Directed Physical Exam			X	X	X	X		X	X	X				X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X		X	X
Height	X													
12 lead ECG	X						X				X		X	
Urinalysis and Urine Chemistry	X	X	X	X	X	X	X	X	X	X	X		X	X[p]
Renal Safety Evaluations Urine[f]		X	X	X	X		X	X	X	X	X			
Biomarkers: inflammation, platelet, renal[g]		X	X	X	X		X	X	X	X	X			
Urine Storage Sample		X	X	X	X	X	X	X	X	X	X		X	
Chemistry Profile[h]	X	X	X	X	X	X	X	X	X	X	X		X	X
Hematology Profile[i]	X	X	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		X	
Plasma HIV 1 RNA[j]	X	X	X	X	X	X	X	X	X	X	X		X	
HBV and HCV Serologies[k]	X													
Cystatin C		X												
Estimated GFRCGl	X	X	X	X	X	X	X	X	X	X	X		X	

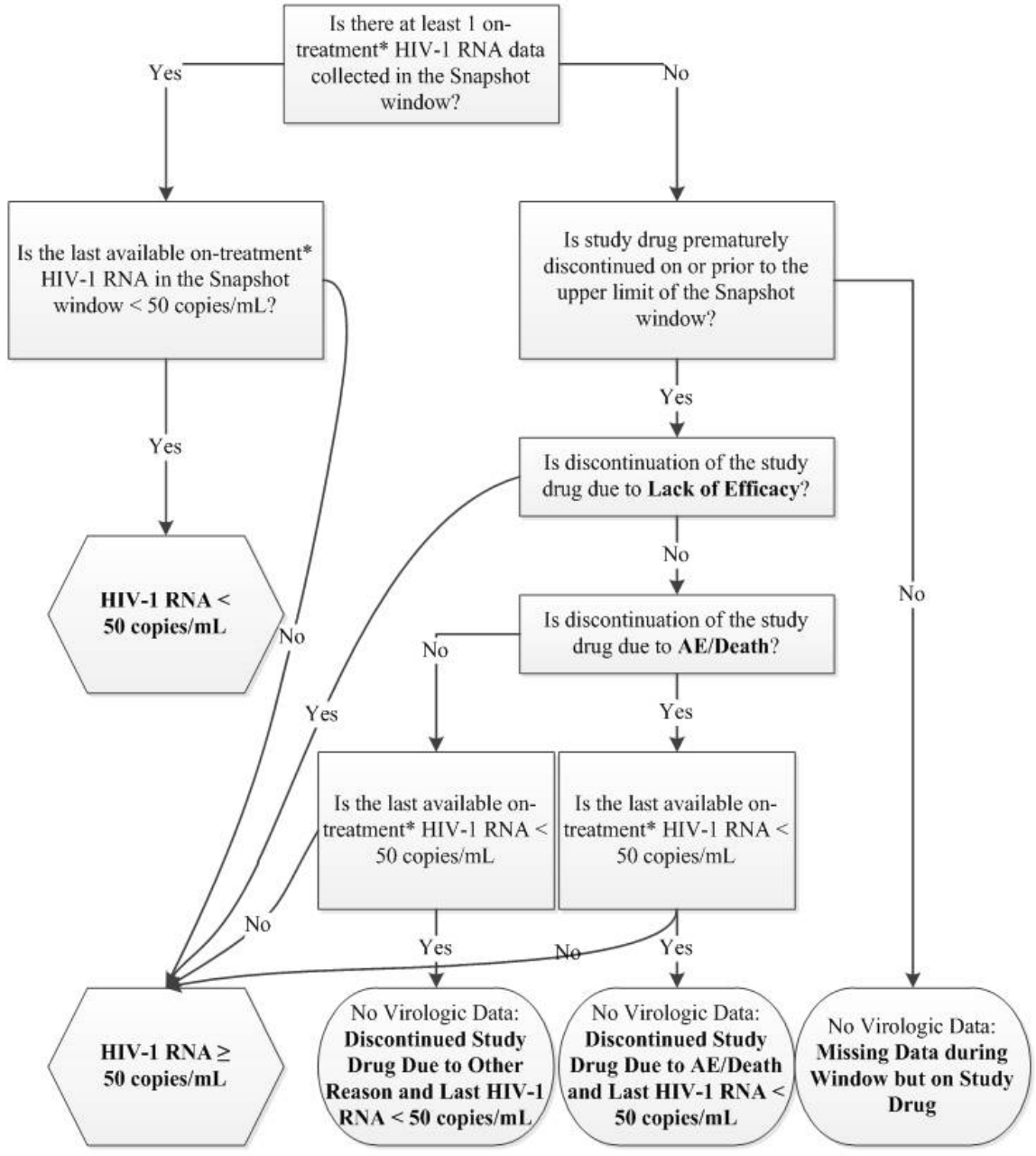
Study Procedure	Screening[a]	Day 1[b]	End of Week[c] 4	12	24	36	48	60	72	84	96	CCI	Early Study Drug Discontinuation (ESDD)[d]	30-Day Follow-up
Whole Blood Sample[m]	X	X												
Metabolic Assessments[n]		X			X		X				X			
Plasma Storage Sample[o]		X	X	X	X	X	X	X	X	X	X		X	
Patient reported outcomes: VAS		X	X	X	X	X	X	X	X	X	X		X	
Patient reported outcome: HIVTSQs		X												
Patient reported outcome: HIVTSQ[c]			X		X		X						X	
Patient reported outcome: EQ 5D		X			X		X							
Patient reported outcome: SF 36		X			X		X							
Patient reported outcome: FACIT F		X			X		X							
HIV 1 Genotype/Phenotype[q]							X		X		X		X	
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X	X	X	X		X[r]	

a Evaluations to be completed within 30 days prior to Day 1 visit.
b Subjects will be dispensed study drug at the Day 1 visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.
c All study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Week 12, ± 6 days of the protocol specified date through Week 96. The Week 24, 48 and 96 visits window is ± 6 weeks of the visit date, if notified by Gilead. Unless notified by Gilead, the Week 24, 48 and 96 visits should be completed within ± 6 days of the visit date. For the purpose of scheduling a 30 Day Follow Up Visit, a +/ 6 days window may be used. Those subjects who prematurely discontinue study drug and continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit will not be required to complete the 30 Day Follow Up Visit.
d 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 96 visit even as the subject discontinues study drug.
e Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the investigator).
f Urine for renal safety, including retinol binding protein, and beta 2 microglobulin, will be collected. Samples for renal safety will be collected fasted. 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.

g Inflammation may include cystatin C, IL 6, hs CRP, sCD14, sCD163, sTNF 1R, and Lp PLA2; Platelet and coagulation function may include soluble glycoprotein VI (sGPVI), P selectin, soluble CD40 ligand, and D dimer will be collected. Urine for renal safety, including retinol binding protein, and beta 2 microglobulin, will be collected. Samples for renal safety will be collected fasted. 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. A portion of the biomarker blood sample obtained at Day 1, Weeks 4, 12, 24, 48, 60, 72, 84 and 96 may be utilized to assess study drug PK. This will be a random sample with the date and time of the subject's last medication dose recorded.
h Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, and sodium. At Day 1, Weeks 24, 48 and 96 analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
i CBC with differential and platelet count.
j For the management of virologic rebound please refer to Protocol Section 6.12.
k Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb).
l Estimated GFR according to the Cockcroft Gault formula for creatinine clearance.
m Whole blood sample for virology analysis.
n Metabolic Assessments: 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.
o Plasma storage sample for safety and/or virology (Day 1, Weeks 4 96, and ESDD).
p Urinalysis only.
q The geno/pheno is only done if the last HIV 1 RNA is > 200 copies/mL.
r Drug accountability only; study drug will not be dispensed at this visit.

Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Switch Trial)

The following flowchart for US FDA-defined snapshot algorithm is based on the US FDA Guidance on Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for treatment {U. S. Department of Health and Human Services 2015}.



* On-Treatment HIV-1 RNA data include all HIV-1 RNA data for subjects who are on-going and HIV-1 RNA data up to 1 day after the last dose date of study drug for subjects who prematurely discontinue or complete study drug.

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 v23.0 provided by Gilead PVE (search name: Ischemic cardiac and cerebral events narrow) 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 is included in this pre-specified PT list, which includes all PTs from the broad search of the following 15 SMQs under MedDRA v23.0 provided by Gilead PVE (search name: Non-infectious, non-congenital hepatobiliary disorders) 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. Medical History

Number and percentage of subjects with selected medical history of Diabetes Mellitus, Hypertension, Cardiovascular Disease, and Hyperlipidemia will be summarized by treatment as baseline disease characteristics. A subject who had medical history of one of these diseases is a subject who experience at least one of the following events:

- At least 1 medical history record with MedDRA PT (mh.MDRPT) in the selected PT listing for the corresponding disease with start date on or prior to the first dose date.
- At least 1 adverse event record with MedDRA PT (ae.MDRPT) in the selected PT listing for the corresponding disease with start date on or prior to the first dose date.
- At least 1 concomitant medications record with medication class and indication in the following selected listing for the corresponding disease with start date on or prior to the first dose date.

If the start date is incomplete but the month and year (or year alone) of the start date is the same as or before the month and year (or year alone) of the first dosing date of study drug, then the event will be included. If the start date is completed missing, the event will be included.

Four variables (ie, DIABETES, HTENSION, CARDDIS, and HLIPDEM) will be added to raw Medical History and Adverse Events datasets. A medical history or an adverse event record will be flagged for a disease of interest if its MedDRA PT included in the pre-specified PT list for the corresponding disease of interest, which include all PTs from the narrow or broad search of the following SMQs under MedDRA 23.0 provided by Gilead DSPH and reviewed by Gilead medical monitors.

Disease of Interest	SMQ Source
Diabetes Mellitus (DIABETES)	Hyperglycaemia/new onset diabetes mellitus (SMQ) Narrow Scope Term
Hyperlipidemia (HLIPDEM)	Dyslipidaemia (SMQ)
Hypertension (HTENSION)	Hypertension (SMQ)
Cardiovascular disease (CARDDIS)	Ischaemic central nervous system vascular conditions (SMQ) Narrow Scope Term
	Myocardial infarction (SMQ) Narrow Scope Term
	Other ischaemic heart disease (SMQ) Narrow Scope Term

Similarly, four variables (ie, DIABETES, HTENSION, CARDDIS, and LIPMOD) will be added to raw Concomitant Medication dataset. A concomitant medication record will be flagged for a disease of interest if its medication preferred term and indication included in the following listing for the corresponding disease of interest.

The selected combination of medication preferred term and indication are listed as follows, which was reviewed by Gilead medical monitors.

	Indication (CMINDC)	Preferred Term
Hypertension (HTENSION)		
1	HYPERTENSION	ACETYLSALICYLATE LYSINE
2	HYPERTENSION	ACETYLSALICYLIC ACID
3	ARTERIAL HYPERTENSION	ALFUZOSIN
4	ARTERIAL HYPERTENSION	AMLODIPINE
5	HIGH BLOOD PRESSURE	AMLODIPINE
6	HYPERTENSION	AMLODIPINE
7	HYPERTENSION	AMLODIPINE BESILATE
8	HYPERTENSION	AMLODIPINE BESILATE;INDAPAMIDE;PERINDOPRIL ARGININE
9	ARTERIAL HYPERTENSION	AMLODIPINE BESILATE;PERINDOPRIL ARGININE
10	HIGH BLOOD PRESSURE	AMLODIPINE BESILATE;PERINDOPRIL ARGININE
11	HYPERTENSION	AMLODIPINE;PERINDOPRIL ARGININE
12	HYPERTENSION	BARNIDIPINE HYDROCHLORIDE
13	ARTERIAL HYPERTENSION	BISOPROLOL
14	HYPERTENSION	BISOPROLOL
15	HIGH BLOOD PRESSURE	BISOPROLOL FUMARATE
16	HYPERTENSION	BISOPROLOL FUMARATE
17	ARTERIAL HYPERTENSION	BISOPROLOL FUMARATE;HYDROCHLOROTHIAZIDE
18	HIGH BLOOD PRESSURE	CANDESARTAN
19	HYPERTENSION	CANDESARTAN
20	HYPERTENSION	CELIPROLOL HYDROCHLORIDE
21	HYPERTENSION	DOXAZOSIN MESILATE
22	ARTERIAL HYPERTENSION	EDOXABAN TOSILATE
23	ARTERIAL HYPERTENSION	ENALAPRIL
24	HIPERTENSION	ENALAPRIL
25	ARTERIAL HYPERTENSION	ENALAPRIL MALEATE;HYDROCHLOROTHIAZIDE
26	ARTERIAL HYPERTENSION	HYDRALAZINE HYDROCHLORIDE
27	ARTERIAL HYPERTENSION	HYDROCHLOROTHIAZIDE
28	HYPERTENSION	HYDROCHLOROTHIAZIDE
29	HIGH BLOOD PRESSURE	HYDROCHLOROTHIAZIDE;IRBESARTAN
30	HYPERTENSION	HYDROCHLOROTHIAZIDE;IRBESARTAN
31	HYPERTENSION	HYDROCHLOROTHIAZIDE;OLMESARTAN
32	HYPERTENSION	HYDROCHLOROTHIAZIDE;TELMISARTAN
33	HYPERTENSION	HYDROCHLOROTHIAZIDE;ZOFENOPRIL CALCIUM

	Indication (CMINDC)	Preferred Term
34	ARTERIAL HYPERTENSION	IRBESARTAN
35	HIGH BLOOD PRESSURE	IRBESARTAN
36	HYPERTENSION	IRBESARTAN
37	SYSTEMATIC BLOOD HYPERTENSION	IRBESARTAN
38	HYPERTENSION	ISOSORBIDE MONONITRATE
39	HYPERTENSION	LERCANIDIPINE
40	ARTERIAL HYPERTENSION	LISINOPRIL
41	SYSTEMIC HYPERTENSION	LISINOPRIL
42	ARTERIAL HYPERTENSION	LOSARTAN
43	HYPERTENSION	LOSARTAN
44	HYPERTENSION	NEBIVOLOL HYDROCHLORIDE
45	HYPERTENSION	OLMESARTAN
46	ARTERIAL HYPERTENSION	OLMESARTAN MEDOXOMIL
47	HYPERTENSION	OLMESARTAN MEDOXOMIL
48	ARTERIAL HYPERTENSION	PERINDOPRIL ARGININE
49	HYPERTENSION	PERINDOPRIL ERBUMINE
50	ARTERIAL HYPERTENSION	PHENPROCOUMON
51	ARTERIAL HYPERTENSION	RAMIPRIL
52	HIGH BLOOD PRESSURE	RAMIPRIL
53	HYPERTENSION	RAMIPRIL
54	ARTERIAL HYPERTENSION	TORASEMIDE
55	HIGH BLOOD PRESSURE	URAPIDIL
56	HYPERTENSION	VERAPAMIL
57	HYPERTENSION	ZOFENOPRIL

	Indication (CMINDC)	Preferred Term
Hyperlipidemia (LIPMOD)		
1	DYSLIPEMIA	ATORVASTATIN
2	DYSLIPIDEMIA	ATORVASTATIN
3	HIPERCHOLESTEROLEMIA	ATORVASTATIN
4	HIPERCOLESTEROLEMIA	ATORVASTATIN
5	HYPERCHOLESTEROLEMIA	ATORVASTATIN
6	HYPERLIPEMIA	ATORVASTATIN
7	HYPERLIPIDAEMIA	ATORVASTATIN
8	HYPERTRIGLYCERIDEMIA	ATORVASTATIN
9	MILD HYPERCHOLESTEROLEMIA	ATORVASTATIN
10	DISLIPEMIA	ATORVASTATIN CALCIUM
11	HYPER COLESTEROLEMY	ATORVASTATIN CALCIUM
12	HYPERCHOLESTEROLEMIA	ATORVASTATIN CALCIUM
13	HYPERCHOLESTEROLEMIE	ATORVASTATIN CALCIUM
14	HYPERTRIGLYCERIDEMIA	GEMFIBROZIL
15	HYPERTRIGLYCERIDEMIA	OMEGA 3 TRIGLYCERIDES
16	DISLIPEMIA MIXTA	PITAVASTATIN
17	ELEVATED LIPIS	PRAVASTATIN
18	ESSENTIAL HYPERCHOLESTEROLEMIA	PRAVASTATIN
19	HYPERLIPIDEMIA	PRAVASTATIN
20	HYPERCHOLESTEROLEMIA	PRAVASTATIN SODIUM
21	DYSLIPIDEMIA	ROSUVASTATIN
22	HYPERCHOLESTEROLEMIA	ROSUVASTATIN
23	HYPERCOLESTEROLEMIA	ROSUVASTATIN
24	SMALL FIBROUS PLATE	ROSUVASTATIN
25	CARDIOVASCULAR PREVENTION	ROSUVASTATIN CALCIUM
26	DYSLIPIDEMIA	ROSUVASTATIN CALCIUM
27	HYPERCHOLESTERIEMIA	ROSUVASTATIN CALCIUM
28	HYPERCHOLESTEROLEMIA	ROSUVASTATIN CALCIUM
29	HYPERCHOLESTEROLEMY	ROSUVASTATIN CALCIUM
30	HYPERCHOLESTEROLEMIA, CONTINUED ELEVATED LEVELS OF LDL	SIMVASTATIN
31	HYPERLIPIDEMIA	SIMVASTATIN

	Indication (CMINDC)	Preferred Term
Diabetes Mellitus (DIABETES)		
1	DIABETES MELLITUS TYPE 2	DAPAGLIFLOZIN;METFORMIN
2	MELLITUS DIABETES	EMPAGLIFLOZIN
3	DIABETES MELLITUS	GLICLAZIDE
4	DIABETES MELLITUS	INSULIN GLARGINE
5	MELLITUS DIABETES TYPE II	LINAGLIPTIN
6	DIABETES	METFORMIN
7	DIABETES MELLITUS	METFORMIN
8	DIABETES MELLITUS TYPE 2	METFORMIN
9	HYPERGLYCEMIA	METFORMIN
10	MELLITUS DIABETES	METFORMIN
11	TYPE 2 DIABETES MELLITUS	METFORMIN
12	DIABETES	METFORMIN EMBONATE
13	DIABETES	METFORMIN HYDROCHLORIDE
14	METABOLE SYNDROME (INSULIN RESISTANCE)	METFORMIN HYDROCHLORIDE
15	MELLITUS DIABETES	METFORMIN HYDROCHLORIDE;SITAGLIPTIN PHOSPHATE

	Indication (CMINDC)	Preferred Term
Cardiovascular disease (CARDDIS)		
1	AORTIC VALVE DISEASE	ACENOCOUMAROL
2	ACUTE MYOCARDIAL INFARCTION	ACETYLSALICYLATE LYSINE
3	BIFEMORAL ARTERY BYPASS SURGERY	ACETYLSALICYLATE LYSINE
4	CARDIOPATHY	ACETYLSALICYLATE LYSINE
5	STROKE	ACETYLSALICYLIC ACID
6	MYOCARDIAL INFARCTION	ACETYLSALICYLIC ACID;CLOPIDOGREL BISULFATE
7	ISCHEMIA CARDIOMYOPATHY	AMILORIDE;HYDROCHLOROTHIAZIDE
8	ARYTHMIA	AMIODARONE
9	ATRIAL FIBRILLATION	AMIODARONE
10	CARDIAC RHYTHM DISORDER	AMIODARONE
11	ANGINA	AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM
12	INFECTIOUS ENDOCARDITIS ON A PROSTHETIC VALVE WITHOUT MICROBIOLOGICAL AFFILIATION, CARDIOEMBOLISM, AND RECURRENT ACUTE CEREBRAL VASCULAR DISEASE.	AMPICILLIN
13	ATRIAL FIBRILLATION	ATENOLOL
14	HYPERTENSION	ATENOLOL
15	ISCHEMIC HEART DISEASE	ATENOLOL
16	ISCHEMIC STROKE IN THE TERRITORY OF LEFT MIDDLE CEREBRAL ARTERY	BEMIPARIN SODIUM
17	ARYTHMIA	BISOPROLOL FUMARATE
18	PROPHYLAXIS FOR MYOCARDIAL INFARCTION	BISOPROLOL FUMARATE
19	ISCHEMIA CARDIOMYOPATHY	CLOPIDOGREL
20	CARDIOPATHY	CLOPIDOGREL BISULFATE
21	INFECTIOUS ENDOCARDITIS ON A PROSTHETIC VALVE WITHOUT MICROBIOLOGICAL AFFILIATION, CARDIOEMBOLISM, AND RECURRENT ACUTE CEREBRAL VASCULAR DISEASE.	CLOXACILLIN
22	ATRIAL FIBRILLATION	DABIGATRAN
23	INFECTIOUS ENDOCARDITIS ON A PROSTHETIC VALVE WITHOUT MICROBIOLOGICAL AFFILIATION, CARDIOEMBOLISM, AND RECURRENT ACUTE CEREBRAL VASCULAR DISEASE.	DALBAVANCIN
24	INFECTIOUS ENDOCARDITIS ON A PROSTHETIC VALVE WITHOUT MICROBIOLOGICAL AFFILIATION, CARDIOEMBOLISM, AND RECURRENT ACUTE CEREBRAL VASCULAR DISEASE.	DAPTOMYCIN
25	MYOCARDIAL INFARCTION	DOXAZOSIN MESILATE

	Indication (CMINDC)	Preferred Term
26	ISCHEMIA CARDIOMYOPATHY	ENALAPRIL
27	ATRIAL FIBRILLATION	ENOXAPARIN SODIUM
28	ARRHYTHMIA	FLECAINIDE
29	ACUTE PULMONARY OEDEMA	FUROSEMIDE
30	CARDIAC ARREST	FUROSEMIDE
31	PEDAL EDEMA	FUROSEMIDE
32	INFECTIOUS ENDOCARDITIS ON A PROSTHETIC VALVE WITHOUT MICROBIOLOGICAL AFFILIATION, CARDIOEMBOLISM, AND RECURRENT ACUTE CEREBRAL VASCULAR DISEASE.	HEPARIN
33	STROKE	HEPARIN
34	ISCHEMIC HEART DISEASE	HYDROCHLOROTHIAZIDE
35	MYOCARDIAL INFARCTION	LERCANIDIPINE
36	ISCHEMIA CARDIOMYOPATHY	OMEPRAZOLE
37	CARDIOVASCULAR PREVENTION	PRASUGREL HYDROCHLORIDE
38	ARTERIOPATHY	PRAVASTATIN
39	HEART RHYTHME DISTURBANCE	PROPAFENONE
40	CARDIOVASCULAR PREVENTION	RAMIPRIL
41	LOWER LIMB OEDEMA	RAMIPRIL
42	ACUTE MYOCARDIAL INFARCTION	ROSUVASTATIN CALCIUM
43	CARDIOVASCULAR PREVENTION	ROSUVASTATIN CALCIUM
44	PROPHYLAXIS FOR MYOCARDIAL INFARCTION	ROSUVASTATIN CALCIUM
45	ATRIAL FIBRILLATION	SOTALOL HYDROCHLORIDE
46	ARYTHMIA	WARFARIN SODIUM
47	ATRIAL FIBRILLATION	WARFARIN SODIUM

Appendix 6. Determining Missing and Virtual Visits due to COVID-19

This appendix describes the site collection of COVID-19 data as it pertains to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter "Visit missed due to COVID-19." If a visit which was to be conducted in-person was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

Natural Language Processing (NLP) was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see Table X 1) and "Virtual" (or synonyms, see Table X 1). The search terms are maintained in a global lookup and can be modified and/or corrected to tune the NLP model. For each comment field the following algorithm was applied:

STEP 1: Eliminate extraneous text from each comment field, e.g. "and", "or", "for", etc. This is done using the list of extraneous terms given in Table X 2.

STEP 2: Check each of the remaining comment text strings against the "COVID-19" terms and "Virtual" terms with the Levenshtein distance, using SAS function COMPGED (Computes a generalized edit distance using the Levenshtein operations to compute/summarize the degree of difference between two text strings):

i) If Levenshtein distance < 149 for any of the "COVID-19" terms then COVIDFL 1, else COVIDFL 0

ii) If Levenshtein distance < 149 for any of the "Virtual" terms then VIRTFL 1, else VIRTFL 0

STEP 3: For any comments with COVIDFL 1, assign "Missed visit" or "Virtual visit as follows

i) IF COVIDFL 1 and the visit date is missing then result is 'Missed Visit'

ii) IF COVIDFL 1 and VIRTFL 1 then result is 'Virtual Visit'

iii) Otherwise result is missing

Examples of search terms for “COVID-19” and “Virtual” used to identify missed and virtual visits.

Table X 1.

Search terms for “COVID-19”	Search terms for “Virtual”
COVID	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTAION
QUARATINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Examples of extraneous text terms to eliminate from the comment fields.

Table X 2.

a	down	in	she'd	until
about	during	into	she'll	up
above	each	is	she's	very
after	few	it	should	was
again	for	its	so	we
against	from	it's	some	we'd
all	further	itself	such	we'll
am	had	i've	than	were
an	has	let's	that	we're
and	have	me	that's	we've
any	having	more	the	what
are	he	most	their	what's
as	he'd	my	theirs	when
at	he'll	myself	them	when's

be	her	nor	themselves	where
because	here	of	then	where's
been	here's	on	there	which
before	hers	once	there's	while
being	herself	only	these	who
below	he's	or	they	whom
between	him	other	they'd	who's
both	himself	ought	they'll	why
but	his	our	they're	why's
by	how	ours	they've	with
could	how's	ourselves	this	would
did	i	out	those	you
do	i'd	over	through	you'd
does	if	own	to	you'll
doing	i'll	same	too	your
down	i'm	she	under	you're
	you've	yourself	yourselves	yours

Appendix 7. Programming Specification

1. Subject disposition mockup table

	B/F/TAF
Subjects Screened	xx
Screen Failure Subjects Who Were Not Enrolled	x
Subjects Met All Eligibility Criteria and Not Enrolled	x
Subjects Enrolled	86
Subjects Enrolled and Never Treated	0
Subjects in Safety Analysis Set	86
Subjects in Full Analysis Set	xx
Subjects Completed Study Drug	0
Subjects Prematurely Discontinuing Study Drug	xx (x.x%)
Reason for Prematurely Discontinuing Study Drug	
Reason 1	xx (x.x%)
Reason 2	xx (x.x%)
Reason x	xx (x.x%)
Subjects Completed Study	0
Subjects Prematurely Discontinuing Study	xx (x.x%)
Reason for Prematurely Discontinuing Study	
Reason 1	xx (x.x%)
Reason 2	xx (x.x%)
Reason x	xx (x.x%)

2. Defining ARV Regimen at Study Entry

All subjects are expected to enter the study on E/C/F/TAF FDC or FTC/TDF + 3rd agent.

Using the ARV raw dataset, include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT ’Prior ARV” or “Current ARV”), taken on or up to 2 day prior to first dose date.

When determining the ARV regimen at study entry, please use the following rules:

- The ARV regimen at study entry will be recorded as 3rd Agent + FTC/TDF (note the reversed order, as this is due to clinical trials evaluating novel 3rd agents). When ordering the 3rd Agent medications, use the following order to assign priority:

INGRED	Priority	INGRED	Priority
EFV FTC TDF	1.2	RAL	3.2
EVG COBI FTC TDF	1.3	EFV	4.1
FTC RPV TDF	1.4	ETR	4.2
ATV COBI	2.1	NVP	4.3
DRV COBI	2.2	RPV	4.4
LPV RTV	2.3	ABC 3TC	5.1
ATV	2.4	FTC TDF	5.2
DRV	2.5	ABC	5.3
COBI	2.6	FTC	5.4
RTV	2.7	3TC	5.5
		TDF	5.6

- For all ingredients, replace "_" with "/"
- Make the following replacements to the ingredients:

  Replace "DTG/ABC/3TC" with "ABC/DTG/3TC"

  Replace "ATV/COBI" with "ATV/co"

  Replace "DRV/COBI" with "DRV/co"

  Replace "LPV/RTV" with "LPV/r"

- Once the ingredients have been updated and assigned an appropriate priority, transpose the ingredients (by subject) and concatenate each column with a "+" following the priority specified above

  To illustrate these rules, suppose a subject is on ATV, RTV, and FTC_TDF. This would translate into "ATV+RTV+FTC/TDF". If, instead, the subject was on LPV_RTV and FTC_TDF, their regimen would be presented as "LPV/r+FTC/TDF".

Note: The following data issues should be queried:

- If the subject does not have either EVG/COBI/FTC/TDF or FTC/TDF in their ARV regimen at study entry
- If a subject does not have a 3rd agent (eg, is only identified as being on FTC/TDF)
- If a subject is on RTV but is not *also* on ATV or DRV

The major protocol violations to be used in defining exclusion from the FAS are:

a) ARV regimen at study entry other than E/C/F/TAF FDC (or FTC/TDF + 3rd agent if currently or previously participated in GS-US-292-1826). Please see above for definition of ARV regimen at study entry.

b) ARV regimen at study entry for < 3 months. This is defined as ARV regimen starting less than 90 days prior to first dose date.

3. For the nonstudy-drug ARV listing, ARVs which were dosed between the first dose date and the last dose date (inclusive) will be flagged (eg, ^). However, please note, the ARV will not be flagged if any of the following criteria are met:

a) the medication end date is completely missing and the medication is not ongoing, and the CRF indicates 'Prior ARV'

b) the medication end date has year only and the year is equal to the year of first dose and the CRF indicates 'Prior ARV'.

4. The precision in reporting numerical values should be as follows:

a) Raw measurements will be reported the same as the data captured electronically or on the CRFs.

b) Standard deviation and standard error will be reported to one more significant decimal place than the raw measurement.

c) Mean, median, minimum, Q1, Q3, maximum, 95% CIs will be reported to the same number of decimal places of the raw measurements.

d) Exceptions may be considered; for example if more than 4 significant digits are provided for the measurement.

5. AGE is calculated as follows:

a) Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

b) AGE (years) is calculated from the number of days between the date of birth (DOB) and Day 1 (first dose date),

c) 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),

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

e) AGE the integer of the result in (c)

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

7. Body mass index (BMI)

BMI will be calculated as follows:

$$\text{BMI} \quad (\text{weight [kg]})/ (\text{height [meters]}^2)$$

Baseline height and weight of the study will be used for this calculation.

8. 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. If the 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.

9. Toxicity Grades:

1) 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.

2) 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.

10. 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)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatinine	Increase	Creatinine (Increased)
	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)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	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)
	Prothrombin Intl. Normalized Ratio (INR)	Increase	N/A
	Prothrombin Time (PT)	Increase	N/A
Urinalysis	Urine Blood	Increase	N/A
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC	Increase	Urine RBC (Hematuria, Quantitative)

Note: Prothrombin Intl. Normalized Ratio (INR) and Prothrombin Time (PT) were graded based on the protocol defined toxicity grade scale. The results and toxicity grade will be listed in listing, but not be summarized in lab toxicity summary table.

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 if 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 posy BL Urine Blood (Dipstick) toxicity grade to BL Urine Blood (Dipstick) toxicity grade. If post BL toxicity grade 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)"

11. Renal related laboratory evaluation

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

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

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

   c) UP (mg/L) to creatinine (mg/dL) ratio: 1 (mg/dL) / (mg/dL) 1000 x mg/g

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). UPCR is not calculated if the urine protein value used for the ratio calculation from the same accession number is under the lower limit of quantification (ie, < 4.0 mg/dL).

For the combined category of UP and UPCR: UP and UOCR should be merged together based on the subject identifier and accession number. At each visit, select the nonmissing UP value in the analysis window. Once the UP record is selected, then the UPCR with the same accession number is selected. If the UP value is <4.0 mg/dL then the corresponding UPCR value will be missing. Subjects will be classified as "UP < 4.0 mg/dL" if UP < 4.0 mg/dL (ie, UPCR should not be calculated for this record); Subject will be classified as "UPCR ≤ 200 mg/g" if UP ≥ 4.0 mg/dL and UPCR ≤ 200 mg/g; Subject will be classified as "UPCR > 200 mg/g" if UP ≥ 4.0 mg/dL and UPCR > 200 mg/g; Otherwise, subject will be classified as "Missing".

12. Chronic non-ARV medications at baseline

A chronic non-ARV medication at baseline is defined as

a) a concomitant medication with start date on or prior to Study Day 1 (or completely missing start date) and either "ongoing" or stop date after Study Day 1. For partial start dates, if the month and year (or year, if month is not recorded) of the start date is equal to the month and year of Study Day 1, then the medication is defined as a baseline medication. For partial stop dates, if the month and year (or year, if month is not recorded) of the stop date is equal to the month and year of Study Day 1, then the medication is defined as a baseline medication.

b) with route "ORAL" or route "RESPIRATORY (INHALATION)"

c) with a duration of >30 days. Duration is defined as stop date minus start date plus one. For partial start and stop dates, if the month and year are the same, then the duration is assumed to be < 30 days. Otherwise, if the months are different and the years are the same, then the duration is assumed to be >30 days. If both start and stop dates have year only and the years are the same, the duration is assumed to be < 30 days. If both start and stop dates have year only and the years are different, the duration is assumed to be > 30 days.

13. Smoking Status at baseline

Smoking status at baseline (ie, never smoker, former smoker, and current smoker) will be summarized as part of the baseline disease characteristics. How to classify a subject as never, former, or current smoker at baseline is specified as follows:

a) First, select only records with Type of Substance Use "Cigarettes" or "Cigars". Records with *Type of Substance Use* "Other" (including chew tobacco, e-cigarettes, etc) will not be considered as smoking.

b) Second, for each selected substance use record, flag whether it is "Prior", "Present", or "Post" relative to the first dose date according to the Algorithm below.

c) Finally, (1) the subject will be flagged as "Never smoker", if the subject has no record with Type of Substance Use "Cigarettes" or "Cigars" or all selected records have a flag of "Post"; (2) the subject will be flagged as a "Former" smoker, if any selected records has a flag of "Prior" and no record of "Present"; (3) Otherwise, the subject will be flagged as a "Current" smoker, if any selected records has a flag of "Present".

	Selected Substance Use Records							
Prior	No	No	Yes	Yes	Yes	No	No	Yes
Present	No	No	No	No	Yes	Yes	Yes	Yes
Post	No	Yes	No	Yes	No	No	Yes	Yes
Smoking Status	Never	Never	Former	Former	Current	Current	Current	Current

Algorithm to flag whether a selected record is "Prior", "Present", or "Post" relative to the first dose date:

1) the start and stop dates of the selected record are not completely missing (ie, at least year is known) or the start date is not missing and record is ongoing. The completed start or stop dates will be used to compare with the first dose date whenever possible. Otherwise, the month and year (or year alone if month is not recorded) of the start or stop dates will be used to compare with the first dose date when the start or stop date of the selected record is incomplete.

    a) The record is flagged as "Prior", if the stop date is before (<) the first dose date;

    b) The record is flagged as "Present", if the start date is on or before (≤) the first dose date and the stop date is on or after (≥) the first dose date, or the selected record is marked as ongoing and the start date is on or before (≤) the first dose date;

    c) The record is flagged as "Post", if the start date is after the first dose date;

2) the start date of the selected record is completely missing. We assume that the start date is before the first dose date, the stop date (or the month and/or year of the stop date, if stop date is incomplete) will be used to determine whether the selected record is "Prior" or "Present" as follows.

   a) The record is flagged as "Prior", if the stop date is before (<) the first dose date or the stop date is completed missing and the record is not marked as ongoing.

   b) The record is flagged as "Present", if the stop date is on or after (≥) the first dose date or the selected record is marked as ongoing.

3) the start date of the selected record is before (<) the first dose date, but the stop date is completely missing and the record is not marked as ongoing. We assume that the end date is before the first dose date, the record is flagged as "Prior".

4) The start date of the selected record is on or after the first dose date, but the stop date is completely missing and the record is not marked as ongoing. This is a data issue, should be queried first. However, this record is flagged as "Present" if the start date is on the first dose; this record is flagged as "Post" if the start date is after the first dose.

14. Figures

For figures, if at a visit where n (sample size) is < 5, data will not be displayed at that visit in the figure, but all data will be included in the corresponding table summary.

GS-US-380-4449 Final SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	20-Aug-2020 15:31:58
PPD	Medical Affairs eSigned	21-Aug-2020 23:21:05