STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Multicenter, Open-Label Study to Evaluate Switching From a Regimen of Two Nucleos(t)ide Transcriptase Inhibitors (NRTI) plus a Third Agent to a Fixed Dose Combination (FDC) of Bictegravir/ Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in Virologically-Suppressed, HIV-1 Infected African American Participants
Name of Test Drug:	Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF; GS-9883/F/TAF)
Study Number:	GS-US-380-4580
Protocol Version (Date):	Original (27 June 2018)
Analysis Type:	Week 24
Analysis Plan Version:	Version 1
Analysis Plan Date:	30 August 2019
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARV	antiretroviral
AST	aspartate aminotransferase
BIC	bictegravir
B/F/TAF	fixed dose combination of bictegravir (BIC; B) 50 mg / emtricitabine (FTC; F) 200 mg / tenofovir alafenamide (TAF) 25 mg
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CG	Cockcroft-Gault
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DNA	deoxyribonucleic acid
DTG	dolutegravir
ECG	electrocardiogram
EFV	efavirenz
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
GFR	glomerular filtration rate
Gilead	Gilead Sciences, Inc.
GS-9883	bictegravir
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e-antibody
HBeAg	hepatitis B e-antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HDL	high density lipoprotein

HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
ID	identification
IWRS	interactive web response system
LDL	low density lipoprotein
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
NRTI	Nucleos(t)ide Transcriptase Inhibitors
PP	per protocol
PT	preferred term
PVE	pharmacovigilance and epidemiology (formerly Drug Safety and Public Health)
Q	quartile
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFL	tables, figures, and listings
ULN	upper limit of normal
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 Week 24 analysis for Study GS-US-380-4580, which will be performed when all subjects have completed their Week 24 visit or prematurely discontinued from the study. This SAP is based on the study protocol dated 27 June 2018 and the electronic case report form (eCRF). The SAP will be finalized before database finalization for the Week 24 analysis.

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching from a regimen of 2 NRTIs and a third agent to a fixed dose combination (FDC) of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) versus continuing their baseline regimen in HIV-1 infected, virologically suppressed African American participants as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24.

The secondary objectives of this study are:

- To evaluate the efficacy of switching to a FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48
- To evaluate the efficacy, safety, and tolerability of switching to FDC of B/F/TAF from a regimen of 2 NRTIs and a third agent in HIV-1 infected, virologically suppressed African American participants through Week 48

1.2. Study Design

Design Configuration and Subject Population

GS-US-380-4580 is a randomized, open-label, multicenter, active-controlled study of HIV-1 infected, virologically suppressed African American participants.

Treatment Groups

Participants who provide written consent and meet all eligibility criteria will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

- **Treatment Group 1:** FDC of B/F/TAF (50 mg/ 200 mg/ 25 mg) administered orally, once daily, without regard to food (n=320 planned)
- **Treatment Group 2:** Stay on baseline regimen (SBR) consisting of 2 NRTIs and a third agent (each taken as prescribed) from Day 1 until Week 24, with a delayed switch to a FDC of B/F/TAF (50 mg/ 200 mg/ 25 mg) administered orally, once daily, without regard to food (n=160 planned)

Key Eligibility Criteria

Medically stable HIV-infected participants who meet the following criteria:

- Self-describes as Black, African American, or mixed race, including Black
- Currently receiving an ARV regimen other than FDC of B/F/TAF that consists of any two NRTIs + allowed third agent for ≥ 6 months (see Protocol Section 4.2 for allowed agents)
- Have no documented or suspected resistance to integrase stand transfer inhibitors (INSTIs) and no history of virologic failure on an INSTI containing regimen (2 consecutive HIV-1 RNA ≥ 50 copies/mL after achieving < 50 copies/mL while on an INSTI-containing regimen)
- History of 1-2 thymidine analogue mutations (TAMs), M184V/I, and any other RT substitutions are allowed, with the following exceptions: History of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), T69-insertions, or K65R/E/N in RT will be excluded.
- Documented plasma HIV-1 RNA < 50 copies/mL during treatment with the baseline regimen for a minimum period of 6 months, and at least the last two HIV-1 RNA measurements prior to the Screening visit
- HIV-1 RNA levels < 50 copies/mL at Screening Visit
- Estimated Glomerular Filtration Rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance
- Eligible participants with chronic hepatitis C virus (HCV) infection are permitted to enroll. In addition, eligible participants with chronic hepatitis B virus (HBV) infection are permitted to enroll if their baseline regimen contains either TAF or TDF.

Study Periods / Phases

Participants will be treated for at least 48 weeks after randomization.

Following the Screening and Day 1 visits, participants will be required to return for study visits at Weeks 4, 12, 24, 36, and 48. Participants randomized to SBR will have, after their delayed switch at Week 24, an additional visit at Week 28.

Participants who complete the study through the Week 48 visit and wish to continue on B/F/TAF, will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and will attend study visits every 12 weeks followed by a 30-Day Follow-Up Visit.

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

Schedule of Assessments

After screening procedures, eligible subjects will be randomized 2:1 to Treatment Group 1 or Treatment Group 2, and treated for at least 48 weeks. Following the Day 1 visit, subjects will return for study visits at Weeks 4, 8, 12, 24, 36 and 48. Participants randomized to SBR will have, after their delayed switch at Week 24, an additional visit at Week 28.

Laboratory analyses (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 Screening, Day 1 and subsequent study visits. Whole blood for HIV-1 DNA archive testing will be collected at Day 1 for all participants and at Week 24 for all participants in Treatment Group 2.

Historical HIV-1 RNA genotypes (from resistance testing) will be collected, if available.

More details for study procedure could be found in Appendix 1.

Randomization

Participants will be randomized in a 2:1 allocation ratio to 1 of 2 Treatment Groups [Treatment Group 1 (B/F/TAF): Treatment Group 2 (SBR)]. Randomization will be stratified by the baseline 3rd agent ARV class at entry (integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or CCR5 antagonist).

Site and/or Stratum Enrollment Limits

Approximately 84 study sites in the United States participated. In order to provide all sites the opportunity to enroll subjects, the initial enrollment limit for individual sites was initially set to 6 subjects. Additional enrollment slots at an individual site were allocated on a case-by-case basis.

Study Duration

Study duration for each participant will be at least 48 weeks.

1.3. Sample Size and Power

A total of 480 HIV-1 infected subjects, randomized in a 2:1 ratio to 2 treatment groups, achieves approximately 89% power to detect a noninferiority margin difference between the group proportions of 0.06 for HIV-1 RNA ≥ 50 copies/mL at Week 24.

For sample size and power computation, it is assumed that the reference group proportion is 0.04. The treatment group proportion is assumed to be 0.10 under the hypothesis of inferiority. The power is computed for the case when the actual treatment group difference is zero (treatment = reference). The test statistic used is the one-sided Score test (Farrington & Manning) with the significance level of 0.025. Sample size and power calculations were performed using the statistical software package PASS (Version 14).

In general, a failure rate of 1% to 3% is assumed for switch studies in virologically suppressed subjects, and the noninferiority margin for treatment difference is typically set at 4%. The failure rate of 4% and noninferiority margin of 6% used for this study was based on the observation that African Americans have lower rates of virological suppression compared to other cohorts. In the US, not all communities have had equitable access to advancements in HIV treatment. African Americans remain disproportionately affected by HIV but have less access to HIV treatment and generally worse health outcomes compared to other racial groups.

The table below provides approximate power for SBR proportions ranging from 2% to 4% with noninferiority margin ranging from 0.04 to 0.06. A total of 480 HIV-1 infected subjects, randomized in a 2:1 ratio to 2 treatment groups, achieves approximately 87% power to detect a noninferiority margin difference between the group proportions of 0.04.

SBR Proportion	Noninferiority Margin	Approximate Power	Actual Alpha
4%	0.06	91%	0.026
3%	0.05	88%	0.026
2%	0.04	87%	0.024

SBR N=160; B/F/TAF N=320; alpha targeted at 0.025. The test statistic used is the one-sided Score test (Farrington &Manning). Power and actual alpha were computed using binomial enumeration of all possible outcomes.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Week 24 Analysis

The Week 24 analysis will be conducted after all subjects either complete their Week 24 visit or prematurely discontinue from the study.

This statistical analysis plan describes the analysis plan for the Week 24 analysis, the primary analysis of this study.

2.2. Final Analysis

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

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.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

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

For randomized subjects, age (in years) collected on the Day 1 visit will be used for analyses and presentation in listings. For screen failures, age calculated on the date of the informed consent was signed will be used. Because only birth year is collected on the eCRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation.

In general, permanent discontinuation of study drug refers to premature discontinuation of study drug or completion of study drug. Study drug refers to B/F/TAF for subjects randomized to the B/F/TAF treatment group. For subjects randomized to the SBR group, study drug refers to the baseline ARV regimen through Week 24 and to B/F/TAF after Week 24. For the SBR group, if the subject did not switch to B/F/TAF, the date of permanent discontinuation of study drug prior to Week 24 is defined as the earliest stop date for all components of the baseline ARV medication.

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 database finalization for the Week 24 analysis. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total.

For analysis by treatment group, subjects will be grouped using the following terminology:

- Treatment Group 1: B/F/TAF
- Treatment Group 2:
  - Up to Week 24: SBR
  - Post-Week 24: delayed switch to B/F/TAF
- All B/F/TAF: all subjects who received at least one dose of study assigned B/F/TAF (both immediate and delayed switch to B/F/TAF).

For comparative summaries of safety data, only data through the Week 24 visit will be summarized and presented by treatment group (B/F/TAF and SBR).

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

The **Full Analysis Set (FAS)** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study treatment (either B/F/TAF or baseline regimen on or after Day 1), and (3) do not have pre-existing INSTI resistance-associated mutations (based on historical data). Subjects will be grouped according to the treatment to which they were randomized. For the FAS, all efficacy data, including data collected after the last dose of study drug, will be included, unless specified otherwise. This is the primary analysis set for efficacy analyses.

3.1.3. Per Protocol Analysis Set

The Week 24 **Per Protocol (PP) Analysis Set** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study treatment (either B/F/TAF or baseline regimen on or after Day 1), and (3) have not committed any major protocol violation, including the violation of key entry criteria. Subjects will be grouped according to the treatment they actually received. The Week 24 PP analysis set is the secondary analysis set for efficacy analysis.

Subjects meeting any of the following criteria will be excluded from the Week 24 PP analysis set:

- Subjects who do not have on-treatment HIV-1 RNA in the Week 24 analysis window, except when missing due to discontinuation of study treatment for lack of efficacy. (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation in the "Randomized Treatment" study phase on the study drug completion eCRF page; Table 3-1).

Table 3-1. Subjects Excluded from Week 24 PP Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 24 Analysis Window

Discontinuation from Study Treatment prior to or on the Upper Bound of Week 24 Analysis Window		HIV-1 RNA Data on Randomized Treatment Available in Week 24 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Other Reasons	+	-
No		+	-

+ = Inclusion of Subjects in Week 24 PP analysis set; - = Exclusion of Subjects from Week 24 PP analysis set.

- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in protocol Section 4.3 including drugs not to be used with bictegravir
- Subjects who do not meet the inclusion criteria for baseline ARV regimen of any two NRTIs + allowed 3rd agent (Protocol Section 4.2)
- Subjects who meet the exclusion criterion for history of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), T69-insertions, or K65R/E/N in RT, including pre-existing mutations that are detected post-baseline
- Subjects who have INSTI resistance-associated mutations, including pre-existing mutations that are detected post-baseline)

3.1.4. Safety Analysis Set

The **Safety Analysis Set** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study treatment (either B/F/TAF or baseline regimen on or after Day 1). For subjects in Treatment Group 1 and in Treatment Group 2 while on B/F/TAF, all data collected up to 30 days after subjects permanently discontinue study drug will be included in safety summaries, unless specified otherwise. For subjects in Treatment Group 2 while on the baseline ARV medications, all data collected up to the minimum of (1) 30 days after subjects permanently discontinue the baseline ARV medications and (2) 1 day prior to the start of B/F/TAF will be included in safety summaries, unless specified otherwise.

Subjects will be grouped according to the treatment they actually received. This is the primary analysis set for safety analyses.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or the FAS, subjects will be grouped by randomized treatment. For other analyses, subjects will be grouped by actual treatment received. The actual treatment received will differ from the randomized treatment only when the actual treatment received differs from randomized treatment for the entire treatment duration.

Treatment groups include B/F/TAF, SBR, Delayed Switch to B/F/TAF, and All B/F/TAF.

For the purposes of the Week 24 comparisons, there will be 2 treatment groups (B/F/TAF and SBR). For the listings, observations that occur after a subject in the SBR group switches to B/F/TAF will be flagged.

3.3. Strata and Covariates

Randomization was stratified by the baseline third agent ARV class at entry (integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or CCR5 antagonist).

If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used to group subjects for analyses.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be analyzed for the following subject subgroups (also see Section 6.2.2.2 for details):

- Age (years): (a) < 50 and (b) ≥ 50
- Sex at birth: (a) male and (b) female
- Baseline NRTI Resistance (determined based on virology data): (a) Any NRTI Mutation (b) No NRTI Mutation
- Baseline M184 Resistance (determined based on virology data): (a) M184 Mutation (b) No M184 Mutation

The proportion of subjects with hepatitis B virus (HBV) Deoxyribonucleic Acid (DNA) < 29 IU/mL at baseline and Week 24 and the change from baseline in log10 HBV DNA by visit will be analyzed for the following subject subgroup:

- Subjects with HIV/HBV coinfection at baseline

3.4.2. Subject Subgroups for Safety Analyses

1) Incidence of all treatment-emergent AEs (TEAEs) will be analyzed for the following subject subgroups (also see Section 7.1.6):

- Age (years): (a) < 50 and (b) ≥ 50
- Sex at birth: (a) male and (b) female

2) Renal-related laboratory tests (ie, serum creatinine and $eGFR_{CG}$) will be analyzed for the following subgroups:

- Baseline ARV Medication containing any of the following: rilpivirine (RPV), dolutegravir (DTG), ritonavir (RTV), cobicistat
- Baseline ARV Medication not containing any of the following: RPV, DTG, RTV, cobicistat

3) Fasting metabolic laboratory tests will be analyzed for the following subgroups:

- Baseline ARV Medication containing TAF
- Baseline ARV Medication containing TDF

- Baseline ARV Medication not containing any of the following: TAF, TDF
- Baseline ARV Medication containing efavirenz (EFV)
- Baseline ARV Medication not containing EFV

4) Selected safety endpoints may be analyzed for the following subject subgroups (see Section 8.1 for details):

- Subjects with HIV/HBV coinfection at baseline
- Subjects with incident HIV/HBV coinfection while on study drug (if any)

5) Selected safety endpoints will be analyzed for the following subject subgroups (see Section 8.2 for details):

- Subjects with HIV/HCV coinfection at baseline
- Subjects with incident HIV/HCV coinfection while on study drug (if any)

3.5. Multiple Comparisons

Efficacy will be evaluated using the primary efficacy endpoint at the significance level of 0.05. The primary analysis will consist of a non-inferiority test of switching to FDC of B/F/TAF versus SBR, with respect to the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 24, as defined by the US FDA-defined snapshot algorithm. If non-inferiority of B/F/TAF to SBR is established, the upper bound of the 95% confidence interval (CI) will be compared to 0; if the upper bound of the 95% CI is less than 0, superiority of B/F/TAF over SBR will be established

No prespecified multiplicity adjustments are planned for confidence intervals or statistical tests.

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 adverse event onset is described in Section 7.1.5.2, and for concomitant non-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).

Logarithmic (base 10) transformations will be applied to HIV-1 RNA and HBV Deoxyribonucleic Acid (DNA) data for efficacy analyses. 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. HBV DNA results of "<20 IU/mL HBV DNA detected" or "No HBV DNA detected" will be imputed as 19 IU/mL for analysis purposes. HCV RNA results of "<15 IU/mL HCV RNA detected" or "No HCV RNA detected" will be imputed as 14 IU/mL for analysis purposes.

3.8. Analysis Windows

3.8.1. Definition of Study Day

For the purposes of the SBR treatment group, there are 2 study periods: (1) up to Week 24, SBR and (2) Post-Week 24, Delayed Switch to B/F/TAF.

Study Day 1/First Dose Date is defined as follows:

- Subjects randomized to the B/F/TAF treatment group: Study Day 1/First Dose Date is defined as the day when the first dose of B/F/TAF was taken, as recorded on the Study Drug Administration eCRF form.

- Subjects randomized to the SBR treatment group: Study Day 1/First Dose Date is defined as the Day 1 visit date recorded on the Visit Date eCRF.

Period 1 Study Day 1/First Dose Date is the same as the Study Day 1/First Dose Date.

Period 2 Study Day 1/First Dose Date is defined as follows:

- Subjects randomized to the B/F/TAF treatment group: Not Applicable

- Subjects randomized to the SBR treatment group who do not switch to B/F/TAF at Week 24: Not Applicable.

- Subjects randomized to the SBR treatment group who switch to B/F/TAF at Week 24: Period 2 Study Day 1/First Dose Date is defined as the day when the first dose of B/F/TAF was taken, as recorded on the Study Drug Administration eCRF form.

Study Days are calculated relative to Study Day 1. For events that occurred on or after the Study Day 1 date, study days are calculated as (visit date minus Study Day 1 plus 1). For events that occurred prior to Study Day 1, study days are calculated as (visit date minus Study Day 1).

- Treatment Group 1: B/F/TAF, study day is calculated based on Study Day 1

- Treatment Group 2:

  — Up to Week 24: SBR, study day is calculated based on Period 1 Study Day 1

  — Post-Week 24: delayed switch to B/F/TAF, study day is calculated based on Period 2 Study Day 1

- All B/F/TAF: all subjects who received at least one dose of study assigned B/F/TAF (both immediate and delayed switch to B/F/TAF). Study day is calculated based on the first dose of B/F/TAF; Study Day 1 for the B/F/TAF treatment group and Period 2 Study Day 1 for the SBR group who switched to B/F/TAF.

Last Dose Date is defined as follows:

- Subjects randomized to the B/F/TAF treatment group: 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 according to the Study Drug Completion eCRF.

- Subjects randomized to the SBR treatment group who do not switch to B/F/TAF at Week 24: Last Dose Date is defined as the earliest stop date of the baseline ARV medications.

- Subjects randomized to the SBR treatment group who switch to B/F/TAF at Week 24: 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 according to the Study Drug Completion eCRF.

Period 1 Last Dose Date is defined as follows:

- Subjects randomized to the B/F/TAF treatment group: the same as Last Dose Date

- Subjects randomized to the SBR treatment group who do not switch to B/F/TAF at Week 24: Period 1 Last Dose Date is defined as the earliest stop date of the baseline ARV medications.

- Subjects randomized to the SBR treatment group who switch to B/F/TAF at Week 24: Period 1 Last Dose Date is defined as the day prior to the first dose date of B/F/TAF, as recorded on the Study Drug Administration eCRF form.

Period 2 Last Dose Date is defined as follows:

- Subjects randomized to the B/F/TAF treatment group: Not applicable

- Subjects randomized to the SBR treatment group who do not switch to B/F/TAF at Week 24: Not applicable

- Subjects randomized to the SBR treatment group who switch to B/F/TAF at Week 24: the same as Last Dose Date

For partial or missing last dose dates, please refer to the programming specifications for imputation rule details.

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 according to the Study Completion eCRF.

Baseline value is defined as the last value obtained on or prior to 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.

In the description that follows, the column labelled "B/F/TAF" refers to subjects in the immediate (B/F/TAF group) and delayed switch group (SBR group) who have switched to B/F/TAF. The baseline for delayed switch subjects will be reset based on the date of first dose of B/F/TAF and the study day will be calculated relative to that date. Data collected after the date of switch to B/F/TAF will be excluded from the analysis of the SBR group.

The analysis windows for HIV-1 RNA, hematology, chemistry, urinalysis, urine pregnancy laboratory tests, $eGFR_{CG}$, vital signs, and weight are presented in Table 3-2.

Table 3-2. Analysis Windows for HIV-1 RNA, Hematology, Chemistry, Urinalysis, Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, Weight, and VAS

		B/F/TAF		SBR	
Visit ID	**Nominal Day**	**Lower Limit**	**Upper Limit**	**Lower Limit**	**Upper Limit**
Baseline			1		1
Week 4	28	2	56	2	56
Week 12	84	57	126	57	126
Week 24^	168	127	210	127	210*
Week 36	252	211	294		
Week 48	336	295	378		

^ VAS is collected for SBR group only and only through Week 24
*For SBR group, values after the first day of B/F/TAF will be excluded.

The analysis windows for the HIV Symptoms Distress Module, HIVTSQs (at Day 1 only) and HIVTSQc (Week 4 and Week 24 only) are presented in Table 3-3.

Table 3-3. Analysis Windows for HIV Symptoms Distress Module, HIVTSQs (at Day 1 only), and HIVTSQc (Week 4 and Week 24 only)

		B/F/TAF		SBR	
Visit ID	**Nominal Day**	**Lower Limit**	**Upper Limit**	**Lower Limit**	**Upper Limit**
Baseline	1		1		1
Week 4	28	2	98	2	98
Week 24	168	99	252	99	252*
Week 48	336	253	420		

*For SBR group, values after the first day of B/F/TAF will be excluded.

The analysis windows for CD4+ cell count, CD4 %, 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), and plasma HBV DNA are presented in Table 3-4.

Table 3-4. Analysis Windows for CD4+ cell count, CD4 %, Metabolic Assessments, and Plasma HBV DNA

		B/F/TAF		SBR	
Visit ID	**Nominal Day**	**Lower Limit**	**Upper Limit**	**Lower Limit**	**Upper Limit**
Baseline	1		1		1
Week 24	168	2	252	2	252*
Week 48	336	253	420		

*For SBR group, values after the first day of B/F/TAF will be excluded.

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 study drug will be selected. If there are multiple records with the same time or no 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, CD4%, and HBV DNA, the record(s) collected on the latest day in the window will be selected for analysis.
  - For other numeric observations (ie, except HIV-1 RNA, CD4+ cell count, CD4%, and HBV DNA), 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-RNA, if there are multiple records on the selected day, the average will be taken.
- For baseline and postbaseline HIV-1 RNA, the latest (considering both 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 study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected.

- For postbaseline visits, the most conservative value within the window will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of subjects randomized at each investigator site will be summarized by treatment group (B/F/TAF and SBR) and overall using the safety analysis set. The denominator for this calculation will be the number of subjects in the safety analysis set. Similarly, the number and percentage of subjects enrolled in each randomization stratum will be summarized based on reclassified strata using the baseline 3rd agent ARV class based on the Non-Study ARV Medication eCRF.

If there are discrepancies between IWRS and collected data with regard to stratum assignment, a listing of the discrepancies will be provided.

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group (B/F/TAF and SBR) and overall for all screened subjects. This summary will include the number of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects randomized, subjects randomized but never treated, subjects in the safety analysis set, subjects in the FAS, and subjects in the Week 24 PP.

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

- Completed 24 weeks on randomized drug (see programming specifications)
- Prematurely discontinuing study drug prior to 24 weeks on randomized drug (with summary of reasons for discontinuing study drug) (see programming specifications)
- Delayed Switch to B/F/TAF (only for Treatment Group 2 [SBR] subjects)
- Still on study drug up to the data cut date
- Prematurely discontinuing study drug prior to the data cut date (with summary of reasons for discontinuing study drug)
- Still on study up to the data cut date
- Prematurely discontinuing from study prior to Week 24 (with summary of reasons for discontinuing study) (see programming specifications)
- Prematurely discontinuing from study prior to the data cut date (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 generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to Study Drug

Duration of exposure will be calculated for the following groups: B/F/TAF, SBR, and Delayed Switch B/F/TAF). Duration of exposure to study drug will be defined as (the last dose date – the first dose date + 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). For the calculation of the duration of exposure to study drug, the data cut date will be used to impute the last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date. See Section 3.8.1 for description of first dose and last dose for SBR and Delayed Switch B/F/TAF.

Duration of exposure to study drug 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).

Summaries will be provided for subjects in the safety analysis set. No inferential statistics will be provided.

4.2.2. Adherence to Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts for B/F/TAF study drug only (ie, B/F/TAF and Delayed Switch B/F/TAF). The numbers of pills of study drug dispensed and returned are captured on study drug accountability eCRF.

Adherence (%) of study drug regimen will be calculated as follows:

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

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

[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, 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 taken for each study drug contained in the study drug regimen 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. Total number of pills prescribed is determined by summing the number of pills prescribed for each study drug contained in the study drug regimen 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 study drug at a dispensing period, (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, then all records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation.

Adherence up to the data cut date will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who prematurely discontinued study drug or completed study drug, or using all data available for subjects who are ongoing on study drug.

Adherence up to the Week 24 visit will be calculated for the B/F/TAF treatment group using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who prematurely discontinued study drug or completed study drug, or the Week 24 study drug dispensing date, whichever occurs earliest.

For the Delayed Switch B/F/TAF treatment group, adherence up to Week 24 on B/F/TAF will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who prematurely discontinued study drug or completed study drug, or the Week 48 study drug dispensing date, whichever occurs earliest.

Descriptive statistics for adherence up to the data cut date and adherence up to Week 24 visit for a study drug regimen (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided for Treatment Group 1 for subjects who return at least 1 bottle and have calculable adherence during the study in the safety analysis set. No inferential statistics will be provided.

4.3. Protocol Deviations

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

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 by treatment group (B/F/TAF, SBR) for the Full 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 at birth, gender identity, sexual orientation, race, and ethnicity) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group (B/F/TAF and SBR) and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of subjects for categorical data. The summaries of demographic data and baseline subject characteristics will be provided for the safety analysis set.

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4+ cell count (/μL)
- CD4+ cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- Mode of infection (HIV risk factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)
- HIV/HBV co-infection status (Yes/No/Missing, see Section 8.1 for definition)
- HIV/HCV co-infection status (Yes/No/Missing, see Section 8.2 for definition)
- Duration of HIV Diagnosis (years) (calculated as years prior to year from First Dose/Day 1 date; see programming specifications)
- Duration of HIV Treatment (Years) (calculated as years prior to year from First Dose/Day 1 date; see programming specifications)

- Duration of baseline ARV medication prior to randomization (based on the Non-Study ARV Medication eCRF, see programming specifications)

- Baseline ARV Regimen (based on the Non-Study ARV Medication eCRF, see programming specifications)

  — Baseline ARV Medication Backbone (FTC+TAF, FTC+TDF, TDF+3TC, ABC+3TC, AZT+3TC)

  — Baseline 3rd agent (INSTI, NNRTI, PI, CCR5), and further broken down by ingredient

  — Baseline ARV Medication (Backbone+3rd agent)

For categorical data, the CMH test (general association statistic for nominal data, and row means scores differ statistic for ordinal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

5.3. Medical History

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The proportions are expressed as percentages for presentation purpose.

6.1.2. US FDA-Defined Snapshot Algorithm

The analysis window at Week 24 is defined as from Study Day 127 to Study Day 210, inclusive. All HIV-1 RNA data collected on-treatment will be used in the US FDA-defined snapshot algorithm. On-treatment is defined for B/F/TAF and the Delayed Switch to B/F/TAF treatment groups as all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug. On-treatment is defined for the SBR treatment group as all data collected up to 1 day after permanent discontinuation of baseline ARV medication or all available data on or before the date of the first B/F/TAF dose for subjects who switched to B/F/TAF. Virologic outcome will be defined as 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 Week 24 analysis window
- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects

Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 24 analysis window, or

Who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window and

i) Who discontinue study drug prior to or in the Week 24 analysis window due to lack of efficacy, or

ii) Who discontinue study drug prior to or in the Week 24 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or

iii) Who discontinue study drug prior to or in the Week 24 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 the Week 24 Window:** this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window because of the following:

  a) Discontinuation of study drug prior to or in the Week 24 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

  Discontinuation of study drug prior to or in the Week 24 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,

  Missing data during the window but on study drug.

The flowchart of the US FDA-defined snapshot algorithm is provided in Appendix 2.

The Week 24 virologic outcomes for the US FDA-defined snapshot algorithm will be summarized for the B/F/TAF and SBR groups. Results will be listed for B/F/TAF, SBR, and Delayed Switch to B/F/TAF treatments.

For switch trials, the US FDA-defined snapshot algorithm classifies subjects who discontinue study drug due to AE or death and have the last available on-treatment HIV-1 RNA value ≥ 50 copies/mL in the "HIV-1 RNA ≥ 50 copies/mL" category. For treatment naïve study population, these subjects are classified in the "No Virologic Data in the Week 24 Window" category.

6.1.3. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: The B/F/TAF group (Treatment Group 1) is at least 6% higher than the SBR group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL as determined by the US FDA-defined snapshot algorithm) at Week 24.

Alternative hypothesis: The B/F/TAF group (Treatment Group 1) is less than 6% higher than the SBR group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 24.

6.1.4. Primary Analysis of the Primary Efficacy Endpoint

The analysis purpose of the primary efficacy endpoint is to assess the noninferiority of switching to B/F/TAF relative to a regimen of 2 NRTIs and a third agent (SBR). Noninferiority will be assessed using a conventional 95% CI approach, with a noninferiority margin of 6%.

The point estimate of treatment difference (B/F/TAF group – SBR group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL and the associated 2-sided 95% CI will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

It will be concluded that B/F/TAF is noninferior to SBR if the upper bound of the 2-sided 95% CI of the difference between treatment groups (B/F/TAF group – SBR group) in the percentage of subjects with HIV-1 RNA ≥ 50 copies/mL is less than 6%.

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 24 will be summarized.

If noninferiority of B/F/TAF versus SBR is established, the same 95% CI used in evaluating noninferiority at Week 24 will be used to evaluate superiority. If the upper bound of the 95% CI is less than 0, then superiority of B/F/TAF over SBR is established. The 2-sided Fisher's exact test will also be used to assess superiority as a secondary assessment.

The FAS will be used for the primary efficacy endpoint analysis and the superiority evaluation.

6.1.5. Secondary Analysis of the Primary Efficacy Endpoint

A secondary analysis based on the Week 24 PP analysis set will be performed to evaluate the robustness of the primary analysis of the primary endpoint. For this secondary analysis, 95% CI for the treatment difference in the primary efficacy endpoint will be calculated based on an unconditional exact method using 2 inverted 1-sided tests.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of the Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- The proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and Week 48 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count at Week 24 and Week 48

The analysis of secondary endpoints related to Week 48 will be described in a future SAP. The analyses for the Week 24 secondary efficacy endpoints will be conducted using both the FAS and the Week 24 PP analysis set.

6.2.2. Analysis of the Secondary Efficacy Endpoints

6.2.2.1. Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL as Determined by US FDA-defined Snapshot Algorithm

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 will also be analyzed by the US FDA-defined snapshot algorithm based on both the FAS and Week 24 PP analysis set.

Proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 as determined by US FDA-defined snapshot algorithm will be analyzed similarly to the primary efficacy endpoint. However, the noninferiority margin used for the proportion of subjects with HIV-1 RNA < 50 copies/mL will be -10%.

Similarly to the primary efficacy endpoint, noninferiority will be assessed using the conventional CI approach. The point estimate of treatment difference (B/F/TAF group – SBR group) in the percentage of subjects with HIV-1 RNA < 50 copies/mL and the associated 2-sided 95% CI will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

It will be concluded that B/F/TAF is noninferior to SBR if the lower bound of the 2-sided 95% CI of the difference between treatment groups (B/F/TAF group – SBR group) in the percentage of subjects with HIV-1 RNA < 50 copies/mL is greater than −10%.

6.2.2.2. Subgroup Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 as Determined by US FDA-defined Snapshot Algorithm

Because the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 24 as determined by the US FDA-defined snapshot algorithm (primary endpoint) is expected to be very low (around 4%), the efficacy analysis by subgroup will be conducted by assessing the proportion of subjects with HIV-1 RNA < 50 copies/mL determined by the US FDA-defined snapshot algorithm at Week 24 (a secondary efficacy endpoint) within each subgroup specified in Section 3.4.1 based on the FAS.

For each level of subgroup factors, the proportion difference between treatment groups and the associated 2-sided 95% CIs will be computed based on an unconditional exact method using 2 inverted 1-sided tests.

Additionally, a logistic regression model will be performed which will include subgroup, treatment, and treatment by subgroup interaction. The odds ratio and the associated 95% CI will be estimated within each subgroup. The homogeneity of the treatment effects between subgroups will be evaluated using a Wald test based on the interaction between treatment and the subgroup factor.

A forest plot of the treatment differences in HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm) at Week 24 and their associated 95% CIs for each subgroup will be generated.

6.2.2.3. Analysis of CD4+ Cell Count

All CD4+ cell count will be summarized for B/F/TAF and SBR treatment groups using observed, on-treatment data. On-treatment data is defined for B/F/TAF as all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug. On-treatment data is defined for SBR as all data collected up to 1 day after permanent discontinuation of baseline ARV medication or all available data on or before the date of the first B/F/TAF dose for subjects who switched to B/F/TAF.

The changes from baseline in CD4+ cell count at Week 24 will be summarized by treatment group using descriptive statistics. The differences in changes from baseline in CD4+ cell count between the 2 treatment groups and the associated 95% CI will be constructed using analysis of variance (ANOVA) models, including treatment group as a fixed effect in the model.

The change from baseline in CD4+ cell counts will also be analyzed based on the Week 24 PP analysis set.

In addition, the change from baseline in CD4+ cell counts with missing values imputed using the last observation carried forward (LOCF) method will be summarized at Week 24 based on the FAS. The algorithm for LOCF is as follows:

- If a value is missing in an analysis visit window, the missing value will be replaced with the last on-treatment value.
- Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no non-missing postbaseline observation collected prior to that visit.

6.3. Tertiary Efficacy Endpoints

6.3.1. Definition of the Tertiary Efficacy Endpoints

CCI [redacted]

6.3.2. Analysis of the Tertiary Efficacy Endpoints

CCI [redacted]

CCI

CCI [redacted]

[redacted]

[redacted]

6.4. Changes From Protocol-Specified Efficacy Analyses

The protocol specified a fourth criterion for the FAS (at least 1 post baseline HIV-1 RNA result while on study treatment); however this criterion was removed to eliminate potential bias.

The Week 24 PP analysis set definition was updated to exclude subjects who do not meet the inclusion criteria for baseline ARV regimen (Protocol Section 3.2) and to exclude subjects who have INSTI resistance-associated mutations, including pre-existing mutations that are detected post-baseline. The exclusion for adherence rate below the 2.5th percentile was removed because adherence cannot be calculated for the SBR group.

7. SAFETY ANALYSES

Safety data will be summarized for the subjects in the safety analysis set. All safety data collected up to 30 days after permanent discontinuation of study drug and all available data for subjects who were still on study drug will be summarized by treatment group, unless specified otherwise. All safety data will be included in data listings.

7.1. Adverse Events and Deaths

Summaries of AEs by treatment group (B/F/TAF, SBR, Delayed Switch to B/F/TAF, All B/F/TAF) will include data collected up to:

- For subjects in the B/F/TAF, Delayed Switch B/F/TAF, and All B/F/TAF treatment groups, AEs with onset date on or before 30 days after permanent discontinuation of study drug, or all AEs if the subject is receiving study drug

- For subjects in the SBR treatment group, AEs with onset date on or before the minimum of (1) 30 days after permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF

Summaries of AEs up to Week 24 by treatment group (B/F/TAF, SBR) will include data collected up to:

- For subjects in the B/F/TAF treatment group, AEs with onset date on or before the minimum of (1) 30 days after permanent discontinuation of study drug or (2) the day of the Week 24 visit

- For subjects in the SBR treatment group, AEs with onset date on or before the minimum of (1) 30 days after permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF

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 lowest-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 left as "missing" for data listings.

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) Department 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:

For subjects who received B/F/TAF:

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

For subjects in SBR treatment group:

- Any AEs with an onset date on or after Study Day 1 and on or before the minimum of (1) 30 days after permanent discontinuation of baseline ARV medication or (2) the day prior to the first dose date of B/F/TAF
- Any AEs leading to premature discontinuation of baseline ARV medication.

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 study drug, then 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 study drug, 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 study drug

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 study drug, will be considered to be treatment emergent. 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 study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Death

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group (B/F/TAF, SBR, Delayed Switch to B/F/TAF, and All B/F/TAF). For other AEs described below, summaries will be provided by SOC, PT, and treatment group (B/F/TAF, SBR, Delayed Switch to B/F/TAF, and All B/F/TAF) 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 treatment group (B/F/TAF, SBR, Delayed Switch to B/F/TAF, and All B/F/TAF) and by the number and percentage of subjects who experienced the above AEs. Treatment-emergent deaths observed in the study will be also 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 treatment-emergent AEs, Grade 3 or 4 treatment-emergent AEs, 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.

Summary of treatment-emergent AEs by SOC and PT will also be conducted for all subgroups listed in Section 3.4.2.

A second set of summaries will be provided that summarize only B/F/TAF and SBR through the Week 24 visit.

Data listings will be provided for the following:

- All AEs
- All AEs through Week 24
- Study-Drug-Related AEs
- Grade 3 and 4 AEs
- SAEs
- Study-Drug-Related SAEs
- Deaths report
- AEs leading to premature discontinuation of study drug

Listings will include all AEs, and AEs up to Week 24 will be flagged.

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 (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 by treatment group (B/F/TAF, SBR, Delayed Switch to B/F/TAF, and All B/F/TAF) based on the safety analysis set. A second summary will be prepared that only includes B/F/TAF and SBR treatment groups (up to Week 24). The second summary will include a statistical comparison of the subject incidence rates (up to Week 24) between the B/F/TAF and SBR treatment groups using Fisher's exact test. 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 by treatment group (B/F/TAF, SBR, Delayed Switch to B/F/TAF, and All B/F/TAF) based on the safety analysis set. A second summary will be prepared that only includes B/F/TAF and SBR treatment groups (up to Week 24). The second summary will include a statistical comparison of the subject incidence rates (up to Week 24) between the B/F/TAF and SBR treatment groups using Fisher's exact test. A data listing of hepatic events will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to:

- For subjects in the B/F/TAF or Delayed Switch to B/F/TAF treatment groups who have permanently discontinued B/F/TAF study drug, the last dose of B/F/TAF study drug plus 30 days.

- For subjects in the B/F/TAF or Delayed Switch to B/F/TAF treatment groups who are still on study drug, data through the data cut date

- For subjects in the SBR treatment group, the minimum of (1) 30 days after permanent discontinuation of baseline ARV medication, or (2) the first dose date of B/F/TAF

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. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group (B/F/TAF, SBR, and Delayed Switch to B/F/TAF) 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 study drug. 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 × (4.0 - albumin (g/dL)).

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

Estimated GFR

The following 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, and SCr is serum creatinine.

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, the protocol specified toxicity grading scale is for fasting test values, so non-fasting lipid results (or lipid results without known fasting status) will not be graded or summarized by toxicity grades.

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 the cutoffs specified at the start of Section 7.2.

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. Most subjects had a nonfasting glucose at the Screening visit and a fasting glucose at the Day 1 visit; therefore, both a baseline nonfasting glucose and a baseline fasting glucose are available for most subjects, and treatment-emergent laboratory abnormalities will be summarized for both nonfasting glucose and fasting glucose.

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 and treatment group (B/F/TAF, SBR, and Delayed Switch to B/F/TAF); 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

A second set of summaries will be produced that only includes the B/F/TAF and SBR treatment groups through the upper bound of the Week 24 analysis window.

For all summaries of laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline values for the particular laboratory test.

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. Results that are within the upper bound of the Week 24 analysis window will be flagged.

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 for the B/F/TAF, SBR, and Delayed Switch to B/F/TAF groups. P-values comparing the difference between the B/F/TAF and SBR groups in baseline values and the change from baseline in metabolic assessment will be estimated from a 2-sided Wilcoxon rank sum test.

In addition, the number and percentage of subjects who took lipid modifying medications at study entry and initiated the medications during the study (up to Week 24) will be provided for the B/F/TAF and SBR treatment groups. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test.

A lipid modifying medication is defined as a medication with drug class (based on World Health Organization [WHO] Drug ATC2 term) = "LIPID MODIFYING AGENTS" and WHO Drug preferred drug name containing the wording of "STATIN".

A sensitivity analysis of fasting lipid tests will be performed by excluding subjects who took lipid modifying medications at study entry or initiated the medications during the study (up to Week 24): baseline values, Week 24 values, and changes from baseline at Week 24 will be summarized by treatment group (B/F/TAF and SBR) using descriptive statistics. Baseline and change from baseline at Week 24 will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test. Only subjects with both baseline and Week 24 values will be included in the analysis.

Summary of baseline, postbaseline, and change from baseline in fasting metabolic laboratory tests will be repeated within each subgroup of baseline ARV medication (see Section 3.4.2). P-values comparing the difference between the 2 treatment groups in baseline values and the change from baseline in metabolic assessment will be generated from a 2-sided Wilcoxon rank sum test.

Median (Q1, Q3) of change from baseline in fasting metabolic assessments over time will be plotted by treatment group (B/F/TAF, SBR, and Delayed Switch to B/F/TAF).

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 × Upper limit of normal (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

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.

A second summary will be produced that only summarizes B/F/TAF and SBR through the upper bound of the Week 24 analysis visit window.

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

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by treatment group (B/F/TAF, SBR, and Delayed Switch to B/F/TAF and visit using descriptive statistics. Baseline and change from baseline will be compared between the B/F/TAF and SBR treatment groups using a 2-sided Wilcoxon rank sum test.

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 treatment group (B/F/TAF, SBR, and Delayed Switch to B/F/TAF) and visit using descriptive statistics. Baseline and change from baseline will be compared between the B/F/TAF and SBR treatment groups using a 2-sided Wilcoxon rank sum test.

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

Summary of baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{CG}$ will be repeated within each subgroup of baseline ARV medication (see Section 3.4.2). P-values comparing the difference between the B/F/TAF and SBR treatment groups in baseline values and the change from baseline in metabolic assessment will be generated from a 2-sided Wilcoxon rank sum test.

7.2.5.2. Proteinuria by Urinalysis (Dipstick)

The proteinuria by urinalysis (dipstick) toxicity grade (Grade 0 to Grade 3) at Week 12 and Week 24 will be summarized by baseline proteinuria toxicity grade and treatment group (B/F/TAF and SBR). In addition, the last on-treatment proteinuria toxicity grade will be summarized by baseline proteinuria toxicity grade and treatment group. On-treatment data is defined for the B/F/TAF treatment group as all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug. On-treatment data is defined for the SBR treatment group as all data collected up to 1 day after permanent discontinuation of baseline ARV medication or all available data on or before the date of the first B/F/TAF dose for subjects who switched to B/F/TAF.

The distribution of proteinuria toxicity grade at Weeks 24 and 48 and at the last on treatment value, respectively, will be compared between B/F/TAF and SBR adjusting for baseline proteinuria toxicity grade using rank analysis of covariance {LaVange 2008}.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by treatment group (B/F/TAF, SBR, and Delayed Switch to B/F/TAF) for vital signs and body weight as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to 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 study drug. 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. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug antiretroviral (ARV) medications used prior to, during, or after the study (if collected) will be coded using the Gilead-modified WHO Drug Dictionary for ARV medications. The WHO preferred drug name and drug code will be attached to the clinical database. All nonstudy drug ARV medications will be listed.

7.4.2. Concomitant Non-ARV 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 Drug preferred drug name and drug code will be attached to the clinical database. Use of concomitant medications from the date of first dose of study treatment up to the date of last dose of study treatment (as defined in Section 3.8.1) will be summarized (number and percentage of subjects) by treatment group (B/F/TAF, SBR, and Delayed Switch to B/F/TAF) and preferred drug name. Multiple drug use will be counted only once per subject for each preferred drug name. The summary will be sorted by decreasing total frequency. For drugs with the same frequency, sorting will be done alphabetically.

A second summary will be produced that summarizes concomitant medications with onset up to Week 24 for the B/F/TAF and SBR treatment groups only. Use of concomitant medications from the date of first dose of study treatment up through the earliest of (1) date of last dose of study treatment (as defined in Section 3.8.1) and (2) date of Week 24 visit will be summarized.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or not. 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 date of the last dose of study drug
- The month and year of stop of the medication is before the date of the first dose of study drug

If the start and stop date of non-ARV medications are complete, the start date is not after last dose date and the stop date is not before first dose date, or the non-ARV medications are marked as ongoing and start date is on or before 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.

7.5. Electrocardiogram Results

A by-subject listing for electrocardiogram (ECG) assessment results will be provided.

7.6. Other Safety Measures

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

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.4.2 using the safety analysis set.

7.8. Changes From Protocol-Specified Safety Analyses

No change from the protocol-specified safety analysis is planned.

8. SPECIAL POPULATION ANALYSES

8.1. Analyses for HIV/HBV Coinfected Subjects

Subjects with HIV/HBV coinfection at baseline are defined as subjects who meet any of the following two criteria:

- Positive HBsAg on or prior to the first dose date, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) on or prior to the first dose date.

The following analyses will be conducted by treatment (B/F/TAF and SBR) for subjects with HIV/HBV coinfection at baseline:

- The proportion of subjects with HBV DNA < 29 IU/mL at baseline and Week 24 by missing = excluded approach.
- The change from baseline in log10 HBV DNA (log10 IU/mL) at Week 24
- Treatment-emergent adverse events overall summary through Week 24
- Treatment-emergent adverse events by SOC, HLT, and PT through Week 24
- Treatment-emergent laboratory abnormalities through Week 24

The following analyses will be conducted by treatment (B/F/TAF, SBR, and Delayed Switch to B/F/TAF) for subjects with HIV/HBV coinfection at baseline:

- Treatment-emergent adverse events overall summary
- Treatment-emergent adverse events by SOC, HLT, and PT
- Treatment-emergent laboratory abnormalities
- The change from baseline for liver-related laboratory tests, including ALT, AST, ALP, total bilirubin, direct and indirect bilirubin.

Listings will be provided for:

- adverse events
- liver-related laboratory tests and HBV DNA results
- ALT elevation (ie, ALT > 2 x Baseline and ALT > 10 x ULN) and ALT flare (see section 7.2.4)

HBV DNA will be analyzed using observed, on-treatment data for subjects in the FAS with HIV/HBV coinfection at baseline. On-treatment is defined for Treatment Group 1 (B/F/TAF) as all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug. On-treatment is defined for Treatment Group 2 (SBR) as all data collected up to 1 day after permanent discontinuation of baseline ARV medication or all available data on or before the date of the first B/F/TAF dose for subjects who switched to B/F/TAF.

Subjects with incident HIV/HBV coinfection while on study drug are defined as subjects who are not HIV/HBV coinfected at baseline and meet any of the following criteria:

For subjects in Treatment Group 1 (B/F/TAF) or subjects in Treatment Group 2 who switched to B/F/TAF:

- Positive HBsAg after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date, or

- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) after the first B/F/TAF dose date and on or prior to the to the last B/F/TAF dose date, or

- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") with onset date after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date: Acute hepatitis B, Chronic hepatitis B, Congenital hepatitis B infection, Hepatitis B, Hepatitis B core antibody positive, Hepatitis B DNA assay positive, Hepatitis B surface antigen positive, Hepatitis B virus test positive.

For subjects in Treatment Group 2 (SBR):

- Positive HBsAg after the first dose date and on or prior to the minimum of (1) the date of permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF, or

- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) after the first dose date and on or prior to the minimum of (1) the date of permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF, or

- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") with onset date after the first dose date and on or prior to the minimum of (1) the date of permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF: Acute hepatitis B, Chronic hepatitis B, Congenital hepatitis B infection, Hepatitis B, Hepatitis B core antibody positive, Hepatitis B DNA assay positive, Hepatitis B surface antigen positive, Hepatitis B virus test positive.

The following listings will be provided for subjects with incident HIV/HBV coinfection while on study drug:

- Listing of adverse events
- Listing of liver-related laboratory tests and HBV DNA results

Adverse events with onset date after Week 24 and test results collected after Week 24 will be flagged.

8.2. Analyses for HIV/HCV Coinfected Subjects

Subjects with HIV/HCV coinfection at baseline are defined as subjects with positive HCVAb and quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) on or prior to the first dose date. The following listings will be provided for subjects with HIV/HCV coinfection at baseline:

- Listing of adverse events
- Listing of liver-related laboratory tests and HCV RNA results

Subjects with incident HIV/HCV coinfection while on study drug are defined as subjects who are not HIV/HCV coinfected at baseline and meet any of the following criteria:

For subjects in Treatment Group 1 (B/F/TAF) or subjects in Treatment Group 2 who switched to B/F/TAF:

- Positive HCVAb after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date, or
- Quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date, or
- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") with onset date after the first B/F/TAF dose date and on or prior to the last B/F/TAF dose date: Acute hepatitis C, Chronic hepatitis C, Hepatitis C, Hepatitis C antibody positive, Hepatitis C RNA positive, Hepatitis C virus test positive.

For subjects in Treatment Group 2 (SBR):

- Positive HCVAb after the first dose date and on or prior to the minimum of (1) the date of permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF, with baseline HCVAb Negative or missing, or

- Quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) after the first dose date and on or prior to the minimum of (1) the date of permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF, or

- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") with onset date after the first dose date and on or prior to the minimum of (1) the date of permanent discontinuation of baseline ARV medication, or (2) the day prior to the first dose date of B/F/TAF: Acute hepatitis C, Chronic hepatitis C, Hepatitis C, Hepatitis C antibody positive, Hepatitis C RNA positive, Hepatitis C virus test positive.

The following listings will be provided for subjects with incident HIV/HCV coinfection while on study drug:

- Listing of adverse events

- Listing of liver-related laboratory tests and HCV RNA results

9. PATIENT REPORTED OUTCOMES

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

- HIV Symptoms Distress Module [assessed at Day 1, Week 4, Week 24, Week 28 (SBR treatment group only, and Week 48)]
- HIV Treatment Satisfaction Questionnaire Status (HIV-TSQs, assessed at Day 1)
- HIV Treatment Satisfaction Questionnaire Change (HIV-TSQc, assessed at Week 4 and Week 24)
- VAS Adherence Questionnaire (assessed at Day 1, Week 4, Week 12, and Week 24 for SBR group only)

Summaries will be provided for the Safety Analysis Set and will include data collected up to:

- For subjects in the B/F/TAF treatment group who have permanently discontinued B/F/TAF study drug, the last dose of B/F/TAF study drug plus 30 days.
- For subjects in the B/F/TAF group who are still on study drug, data through the data cut date
- For subjects in the SBR treatment group, the minimum of (1) 30 days after permanent discontinuation of baseline ARV medication, or (2) the first dose date of B/F/TAF

Assessments will be listed using the Randomized Analysis set.

9.1. HIV Symptoms Distress Module

The Symptoms Distress Module is a self-completed questionnaire to evaluate symptoms and measure the presence and bothersomeness of side effects commonly seen with HIV and ARV treatment over the last 4 weeks (20 questions about all symptoms which the patient might have had during the past four weeks). Higher scores indicate the presence of more symptoms and/or a greater degree of distress related to the 20 symptoms.

There are 5 possible responses for each HIV symptom. These responses will be analyzed as both categorical response and numerical response. The mapping between the categorical response and the numerical response is listed in below.

Categorical Response	Numerical Response
I do not have this symptom	0
Doesn't bother	1
Bothers a little	2
Bothers	3
Bothers a lot	4

If multiple responses are provided for a single question, then the largest (worst) value will be chosen (eg, (4) bothers a lot will be chosen over (3) bothers). This applies regardless of how many responses are provided. That is, if (1) doesn't bother, (2) bothers a little, and (3) bothers are all marked, then (3) bothers will be used in the analysis.

Missing values will not be imputed.

For each question, the number and percentage of subjects in each category of the categorical responses will be summarized by treatment group (B/F/TAF and SBR) and visit (Baseline, Week 4, and Week 24). No inferential statistics will be generated.

For each question, the numerical responses will be summarized by treatment group at baseline using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum). The baseline and change from baseline at Week 4 and Week 24 will be compared between treatment groups will be assessed using a Wilcoxon rank-sum test.

9.2. 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). A value of "999" indicates a missing, ambiguous, or illegible response, and will be treated as a missing value for summaries. 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. A value of "99" indicates a missing, ambiguous, or illegible response, and will be treated as a missing value for summaries.

The VAS (%) absolute value and change from baseline at each study visit will be summarized for the SBR group 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.

9.3. HIV Treatment Satisfaction Questionnaires

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) has 10 questions regarding current treatment regimen. The Status form HIVTSQs is used at Baseline, and the change form HIVTSQc is used at postbaseline visits.

At baseline, a treatment satisfaction scale total will be calculated as the sum of the responses to the 10 question items on the HIVTSQs form (range from 0 to 60). At postbaseline visits, a treatment satisfaction scale total in change will be calculated as the sum of the responses to the 10 question items on the HIVTSQc form (range from -30 to 30).

Additionally, two subscale scores, one for general satisfaction/clinical and another for lifestyle/ease will be computed. Each subscale ranges from 0 to 30 on the HIVTSQs form and from -15 to 15 on the HIVTSQc form.

Table 9-1 lists the questions, possible responses for both the status and change questionnaires, as well as the subscale each question belongs to.

Table 9-1. List of Items on the HIVTSQ

Question	Response Options for Status Form	Response Options for Change Form	Subscale
How satisfied are you with your current treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to −3 much less satisfied now	General Satisfaction/Clinical
How well controlled do you feel your HIV has been recently?	Very well controlled 6 to 0 very poorly controlled	Much better controlled now 3 to −3 much worse controlled now	General Satisfaction/Clinical
How satisfied are you with any side effects of your present treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to −3 much less satisfied now	General Satisfaction/Clinical
How satisfied are you with the demands made by your current treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to −3 much less satisfied now	Lifestyle/Ease
How convenient have you been finding your treatment to be recently?	Very convenient 6 to 0 very inconvenient	Much more convenient now 3 to −3 much less convenient now	Lifestyle/Ease
How flexible have you been finding your treatment to be recently?	Very flexible 6 to 0 very inflexible	Much more flexible now 3 to −3 much less flexible now	Lifestyle/Ease
How satisfied are you with your understanding of your HIV?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to −3 much less satisfied now	Lifestyle/Ease
How satisfied are you with the extent to which the treatment fits in with your lifestyle?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to −3 much less satisfied now	Lifestyle/Ease
Would you recommend your present treatment to someone else with HIV?	Yes I would definitely recommend the treatment 6 to 0 No I would definitely not recommend the treatment	Much more likely to recommend the treatment now 3 to −3 much less likely to recommend the treatment now	General Satisfaction/Clinical
How satisfied would you be to continue with your present form of treatment?	Very satisfied 6 to 0 very dissatisfied	Much more satisfied now 3 to −3 much less satisfied now	General Satisfaction/Clinical

The HIVTSQs scale and subscale totals at baseline, and the HIVTSQc scale and subscale totals at each visit will be summarized by treatment group (B/F/TAF and SBR) using descriptive statistics.

Comparison between treatment groups in HIVTSQc scale total scores will use an analysis of covariance model adjusting for HIVTSQs scale total at Baseline. A similar analysis will be performed on the two subscale scores as well.

For each subscale, if more than 1 question is missing, then the subscale total or subscale total in change will be set to missing. Otherwise, the missing total will be imputed by taking the average of non-missing responses from the other questions in that subscale.

For the scale total or scale total in change, if more than 5 questions are missing, then the value will be set to missing. Otherwise, the missing total will be imputed by taking the average of nonmissing responses from the other questions.

If two responses are provided for a single question, and the scores are next to each other, then the midpoint will be used. If two responses are provided for a single question, and the scores are not immediately next to each other, then the response will be considered missing.

9.4. Change from Protocol Specified Analysis for Patient-Reported Outcomes

There are no changes from the protocol-specified patient-reported outcomes analyses.

10. REFERENCES

LaVange LM, Koch GG. Randomization-Based Nonparametric (ANCOVA). In: D'Agostino Sr. RB, Sullivan LM, Massaro JM, eds. Wiley Encyclopedia of Clinical Trials. John Wiley & Sons, Inc.; 2008: 31-8. vol 4).

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.) is to be used for all programming of tables, listings, and figures.

PASS Version 14 (NCSS, LLC, Kaysville, Utah) was used for planned sample size and power calculation.

12. SAP REVISION

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

13. APPENDICES

Appendix 1. Study Procedures Table
Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Switch Trial)
Appendix 3. Cardiovascular or Cerebrovascular Events
Appendix 4. Hepatic Events
Appendix 5. Programming Specifications

Appendix 1. Study Procedures Table

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[e]	30 Day Follow-Up[f]	ESDD[g]
			4	12	24	28[d]	36	48	Every 12 Weeks[cc]		
Informed Consent	X										
HIV Symptoms Distress Module		X	X		X	X		X			
HIV-TSQ[h]		X	X		X						
VAS Adherence Questionnaire[i]		X	X	X	X						
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete/Symptom-Directed Physical Exam[j]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (performed supine)	X										
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[k]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[l]		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[l]	X										
FSH Test[m]	X										
Chemistry Profile[n]	X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[o]		X			X			X	X		
Estimated GFR	X	X	X	X	X	X	X	X	X	X	X

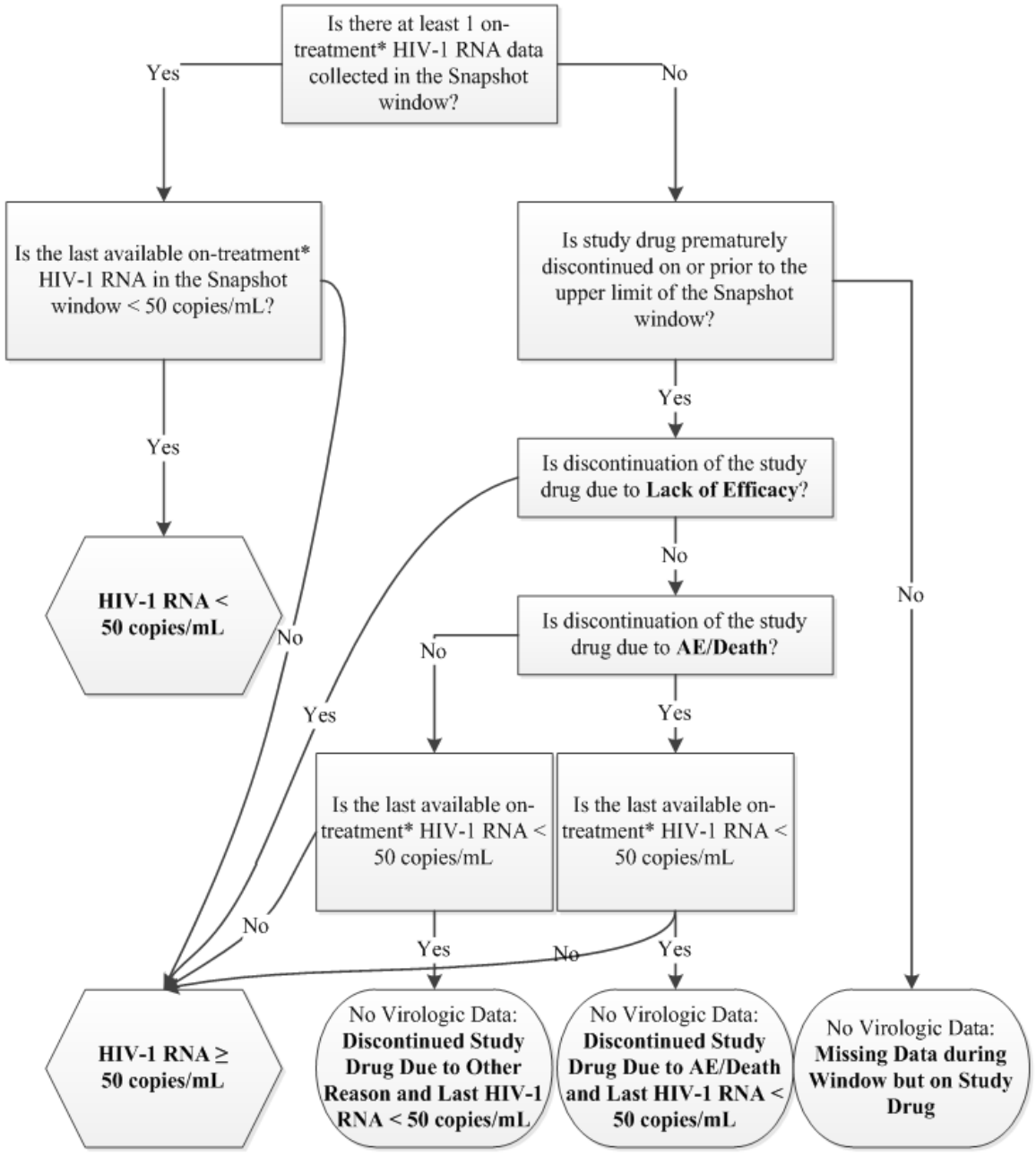
Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						Post Week 48[e]	30 Day Follow-Up[f]	ESDD[g]
			4	12	24	28[d]	36	48	Every 12 Weeks[cc]		
Hematology Profile[p]	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[q]	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count and Percentage[r]	X	X			X			X	X	X	X
HBV Blood Panel[s]	X[t]							X[t]			
Plasma HBV DNA[u]		X			X			X			X
HCV Serology[v]	X							X	X		
HIV-1 Genotype/Phenotype[q]											X[q]
Plasma, Serum, and Urine Sample Storage[w]		X	X	X	X	X	X	X	X		X
Whole Blood for HIV-1 DNA archive testing		X			X[x]						
CCI											
Obtain Screening Number	X										
Randomization[z]		X									
Study Drug Dispensation		X[bb]	X[bb]	X[bb]	X[aa]	X	X	X	X		
Study Drug Accountability			X[bb]	X[bb]	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Participants should initiate dosing of study drug on the same day as the Day 1 visit.
c All study visits are to be completed ± 6 days of the protocol-specified visit date (based on the Day 1 visit), unless otherwise specified.
d Participants randomized to continue their baseline regimen will have an additional visit at Week 28.
e At the study Week 48 Visit, participants who wish to continue on B/F/TAF will be given the option to receive FDC of B/F/TAF for up to an additional 24 weeks or until they have access to FDC of B/F/TAF, whichever occurs first, and attend study visits every 12 weeks (± 6 days of the protocol specified visit date) followed by a 30 Day Follow-Up Visit.
f Must be completed 30 days after discontinuing study drug. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used. Required for participants who permanently discontinue study drug prior to Week 48 and do not continue in the study through at least one subsequent visit after the ESDD visit. Participants who participate post Week 48 will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit.
g Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Participants will be asked to continue attending the scheduled study visits through the Week 48 Visit even if the participant discontinues study drug. Participants on Treatment 2 (SBR) who discontinue their baseline regimen due to an AE prior to Week 24 will be asked to continue attending the scheduled study visits through the Week 24 visit.

h HIV-TSQs is to be completed at Day 1. The HIV-TSQc is to be completed at Week 4 and Week 24. Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
i VAS Adherence Questionnaire will be administered at Day 1 and at all visits up to (and including) Week 24 for participants in Treatment Group 2 (SBR) only.
j Complete physical exam is required at Screening, Day 1, Week 24, 48, 72, and ESDD. Urogenital/anorectal exams will be performed at the discretion of the Investigator. Symptom-directed physical examination, as needed.
k. Vital signs measurements including blood pressure, pulse, respiratory rate, and temperature.
l All female participants will have a serum test performed at Screening. Urine pregnancy test will only be done for persons of childbearing potential. Positive urine pregnancy tests will be confirmed with a serum test.
m FSH test is required for female participants who are <54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
n Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, amylase, and Cystatin C. After Day 1, calcium, phosphorous, magnesium, and amylase (reflex lipase testing is performed in participants with total amylase > 1.5 x ULN) will not be collected. Analyses of glucose will be done as part of the fasting metabolic assessments, and not as part of the chemistry profile at Day 1, Weeks 24, 48, and 72. Cystatin C will only be collected at Day 1.
o Metabolic Assessments will be performed at Day 1, Weeks 24, 48, and 72. Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
p CBC with differential and platelet count.
q HIV-1 genotype and phenotype testing for participants with confirmed virologic failure and HIV-1 RNA >200 copies/mL. Following virologic rebound, participants will be asked to return to the clinic (2-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV-1 RNA and HIV-1 resistance analysis (reverse transcriptase, protease, and integrase genotype and phenotype) blood draw. Based on the results of this testing, participants should be managed according to the Virologic Rebound Schema.
r CD4+ Cell Count and Percentage to be collected at Screening and Day 1, and every 24 weeks thereafter, at Weeks 24, 48, and 72, in addition to the 30 Day Follow-up Visit and ESDD.
s HBV blood panel will be performed at Screening and Week 48: HBsAg, HBsAb, HBcAb.
t **For participants who are HBV co-infected (defined in Protocol Section 6.9.1):** The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBsAg (qualitative and quantitative), and HBeAg (if negative, reflex HBeAb).
For participants who are NOT HBV co-infected: The following HBV Blood panel will be conducted by the central laboratory: HBsAb, HBcAb, and HBsAg. Participants who are HBsAg or HBcAb positive will have a reflex test for HBV DNA (viral load).
u **For participants who are HBV co-infected:** Plasma HBV DNA will be collected at Day 1, Week 24, Week 48 and ESDD.
v Hepatitis C virus serology will be performed at Screening, Week 48, and Week 72. Participants who are HCVAb positive will have a HCV RNA test performed.
w Plasma, serum, and urine storage samples will be collected for safety, virology, or PK testing.
x Collect whole blood sample for participants randomized to SBR only at Week 24.
y CCI [redacted]
z Randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed.
aa At Week 24, participants randomized to continue their baseline regimen and complete 24 weeks of treatment on their baseline regimen will switch to FDC of B/F/TAF.
bb FDC of B/F/TAF will be dispensed to Treatment Group 1 only. Study drug accountability will be performed accordingly.
cc Subjects will receive study drug for dosing until Week 72.

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 v22.0 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 v22.0 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. Programming Specifications

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

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

   AGE (years) is calculated from the number of days between the DOB and Study Day 1,

   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),

   Divide the result in (b) by 12,

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

   Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened subjects refer to all subjects who are screened (ie, with non-missing screening date) and have a screening number. For summaries the same subject is counted only once. DOB and other demographic information such as sex, race, and ethnicity will be used to identify unique screened subjects.

3) Screen failure subjects are the subjects who were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the subject was consent to.

4) Subjects in the randomized analysis set are defined as subjects randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN = "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if subject took at least 1 dose of study drug and assigned as blank if the subject was never dosed.

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) and Body Surface Area (BSA)

   BMI and BSA will be calculated only at baseline as follows:

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

Baseline height and weight will be used for this calculation.

8) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

CMH test for nominal variable (Y), the p-value from general association test should be used for nominal variable:

```
proc freq order=adsl;
      tables trtgrp * Y /cmh /*general association test*/
run;
```

CMH test for ordinal variable (Y), the p-value from row mean score test should be used for ordinal variable:

```
proc freq order=adsl;
      tables trtgrp * Y / cmh2 ; /*row mean score test*/
run;
```

Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation two-sided test should be used for continuous variable:

```
proc npar1way wilcoxon data=adsl;
      class trtgrp;
      var Y;
run;
```

9) Please note, “Not Permitted”, “Unknown”, or missing categories will be excluded from percentage calculation and also excluded for p-value generation for categorical data analysis (eg, CMH test or Fisher exact test). Except for Mode of infection (HIV Risk Factors), where “Unknown” will be included for percentage calculation, since a subject may fit more than 1 HIV risk factors, therefore percentage may add to more than 100% and no p-value will be generated.

10) Defining Baseline ARV Medication

Baseline ARV Medication

All subjects are expected to enter the study on an ARV regimen other than FDC of B/F/TAF that consists of any two NRTIs + allowed 3rd agent for ≥ 6 months (see Protocol Section 4.2 for allowed agents)

Using the ARV raw dataset, for the B/F/TAF treatment group, include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT =”Prior ARV” or “Current ARV”), taken on or up to 4 days prior to first dose date as defined in Section 3.8.1 (or randomization date if not treated). For the SBR treatment group, include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT =”Prior ARV” or “Current ARV”) taken on Study Day 1.

Use the following rules to determine if the ARV medication is taken on Day 1:

- If ARV end date is before B/F/TAF first dose date -4 for B/F/TAF subjects or Day 1 date for SBR subjects then exclude. If "Ongoing" is not marked and the end date is completely missing, then exclude. See below for imputation rules for any partial dates of uncertainty.

- If ARV start date is after B/F/TAF first dose date for B/F/TAF subjects (or Day 1 visit date for SBR subjects) then exclude. See below for imputation rules for any partial dates of uncertainty.

The different categories used for the baseline ARV medication are (1) backbone, (2) third agent, and (3) third agent class.

- For subjects with more than one baseline ARV medication record, concatenate the records together using "+" to get one record for each subject. For all ingredients, replace "_" or "+" with "/".

- For each subject, search for the NRTIs: FTC, TAD, TDF, ABC, AZT, and 3TC. There should be 2 NRTIs for each subject. Create the backbone variable by concatenating the 2 NRTIs listed in the order above, and separate by a "/" as per the backbone column in the table below.

- For each subject, identify the Third Agent. These will fall into 4 categories (PI, NNRTI, INSTI, and CCR5 antagonist). Each subject should have only 1 category of third agent unless they have a protocol deviation. For each subject, create the third agent variable by selecting on the ingredients listed:

  — PIs and boosted PIs include ATV, ATV/RTV, ATV/COBI, DRV/RTV, DRV/COBI, LPV/RTV, and NFV. Create the third agent variable by concatenating the ingredients (ATV, DRV, LPV, NFV, RTV, COBI) with a "/". Change "ATV/RTV" to "ATV/r", "ATV/COBI" to "ATV/co", "DRV/RTV" to "DRV/r", "DRV/COBI" to "DRV/co", and "LPV/RTV" to "LPV/r", as per the Third Agent column in the table below.

  — NNRTIs include DOR, EFV, NVP, and RPV. ETR is not allowed, but is to be included for subjects who were not on a protocol-approved baseline ARV medication.

  — INSTIs include DTG, EVG/COBI, and RAL. Create the third agent variable by concatenating the ingredients (DTG, EVG, COBI, RAL). Change "EVG/COBI" to "EVG/co" as per the Third Agent column in the table below. RAL/RTV is a protocol violation and should be changed to "RAL/r".

  — CCR5 antagonists include MVC.

— Each subject should have PI or NNRTI or INSTI or CCR5. If a subject has more than one, then it is a protocol violation. The third agent can be listed as "DTG/RPV", and should be counted in both categories for summary purposes.

— The final Baseline ARV Medication will be presented as third agent + backbone as per the last column in the table below.

The table below provides example records for each subject with the backbone, third agent, third agent class, and final baseline ARV Medication variables.

Baseline ARV Medications from the data	Backbone	Third Agent	Third Agent Class	Baseline ARV Medication
ABC/NVP/FTC/TAF*	ABC/FTC/TAF	NVP	NNRTI	NVP+ABC/FTC/TAF
ATV/ABC/3TC	ABC/3TC	ATV	PI	ATV + ABC/3TC
ATV/RTV/ABC/3TC	ABC/3TC	ATV/r	PI	ATV/r + ABC/3TC
ATV/RTV/FTC/TAF	FTC/TAF	ATV/r	PI	ATV/r + FTC/TAF
ATV/RTV/FTC/TDF	FTC/TDF	ATV/r	PI	ATV/r + FTC/TDF
ATV/COBI/FTC/TAF	FTC/TAF	ATV/co	PI	ATV/co + FTC/TAF
DOR/FTC/TDF	FTC/TDF	DOR	NNRTI	DOR + FTC/TDF
DRV/COBI/ABC/3TC	ABC/3TC	DRV/co	PI	DRV + ABC/3TC
DRV/COBI/FTC/TAF	FTC/TAF	DRV/co	PI	DRV/co + FTC/TAF
DRV/COBI/FTC/TDF	FTC/TDF	DRV/co	PI	DRV/co + FTC/TDF
DRV/DTG/RTV/FTC/TAF*	FTC/TAF	DRV/r and DTG	DRV/r is PI DTG is INSTI	DRV/r and DTG + FTC/TAF
DTG/ABC/3TC	ABC/3TC	DTG	INSTI	DTG + ABC/3TC
DTG/FTC/TAF	FTC/TAF	DTG	INSTI	DTG + FTC/TAF
DTG/FTC/TDF	FTC/TDF	DTG	INSTI	DTG + FTC/TDF
DTG/RPV*	-	DTG and RPV	DTG is INSTI RPV is NNRTI	DTG and RPV
EFV/3TC/TDF	TDF/3TC	EFV	NNRTI	EFV + TDF/3TC
EFV/ABC/3TC	ABC/3TC	EFV	NNRTI	EFV + ABC/3TC
EFV/AZT/3TC	AZT/3TC	EFV	NNRTI	EFV + AZT/3TC
EFV/FTC/TAF	FTC/TAF	EFV	NNRTI	EFV + FTC/TAF
EFV_FTC/TDF	FTC/TDF	EFV	NNRTI	EFV + FTC/TDF
ETR/ABC/3TC*	ABC/3TC	ETR	NNRTI	ETR + ABC/3TC
EVG/COBI/FTC/TAF	FTC/TAF	EVG/co	INSTI	EVG/co + FTC/TAF
EVG/COBI/FTC/TDF	FTC/TDF	EVG/co	INSTI	EVG/co + FTC/TDF

Baseline ARV Medications from the data	Backbone	Third Agent	Third Agent Class	Baseline ARV Medication
FTC/RPV/TAF	FTC/TAF	RPV	NNRTI	RPV + FTC/TAF
FTC/RPV/TDF	FTC/TDF	RPV	NNRTI	RPV + FTC/TDF
LPV/RTV/FTC/TDF	FTC/TDF	LPV/RTV	PI	LPV/r + FTC/TDF
MVC/FTC/TDF	FTC/TDF	MVC	CCR5	MVC + FTC/TDF
NFV/FTC/TAF	FTC/TAF	NFV	PI	NFV + FTC/TAF
NVP/AZT/3TC	AZT/3TC	NVP	NNRTI	NVP + AZT/3TC
NVP/FTC/TDF	FTC/TDF	NVP	NNRTI	NVP + FTC/TDF
NVP/FTC/TAF	FTC/TAF	NVP	NNRTI	NVP + FTC/TAF
RAL/ABC/3TC	ABC/3TC	RAL	INSTI	RAL + ABC/3TC
RAL/FTC/TAF	FTC/TAF	RAL	INSTI	RAL + FTC/TAF
RAL/FTC/TDF	FTC/TDF	RAL	INSTI	RAL + FTC/TDF
RTV/DRV/ABC/3TC	ABC/3TC	DRV/r	PI	DRV/r + ABC/3TC
RTV/DRV/FTC/TAF	FTC/TAF	DRV/r	PI	DRV/r + FTC/TAF
RTV/DRV/FTC/TDF	FTC/TDF	DRV/r	PI	DRV/r + FTC/TDF
RTV/RAL*	-	RAL/r	INSTI	RAL/r
TAF/COBI/DRV/FTC	FTC/TAF	DRV/co	PI	DRV/co + FTC/TAF
TAF/DTG/FTC	FTC/TAF	DTG	INSTI	DTG + FTC/TAF

*Protocol Violation

Duration of Baseline ARV Medication

Duration of the baseline ARV medication (defined above) prior/ to the first dose date is defined as (End Date – Start Date+1). Duration will be expressed in years so that duration in days will be divided by 365.25 days.

End date is defined as the first dose date -1 or randomization date if randomized but not dosed.

Start Date: The start date of the baseline ARV medication is the latest start date of all the individual baseline ARV medications selected above

Use the following rules to handle any incomplete start dates

- If only month and year are available, day will be first imputed as 15th, then imputed as the minimum of (the start date of the ARV, first dose date-1, the stop date of the same ARV)
- If only year is available, month and day will be first imputed as July 1st of the year, then imputed as the minimum of (the start date of the ARV, first dose date-1, the stop date of the same ARV)

- No imputation applied for date missing completely

Use the following rules to handle any incomplete stop dates

- If only month and year are available, day will be first imputed as 15th, then imputed as minimum of (the first dose date-1, the stop date of the ARV)
- If only year is available, month and day will be first imputed July 1st of the year, then imputed as minimum of (first dose date-1, the stop date of the ARV)
- No imputation applied for date missing completely

11) Efficacy analyses:

For categorical efficacy response (eg, Subjects with HIV-1 RNA < 50 copies/mL or Subjects with HIV-1 RNA ≥ 50 copies/mL as determined by US FDA-defined snapshot algorithm, M=F, or M=E Analyses): the proportion difference between two treatment groups and its 95% CIs (for HIV-1 RNA < 50 at wk24 by snapshot algorithm for FAS or Week 24 PP set) or 95% CIs are calculated based on the an unconditional exact method using 2 inverted 1-sided tests in SAS v9.3 or above.

The following SAS code will be used to compute cell counts and p-values.

```
data example;
input  grp trt01a $  outcome $ count ;

datalines;
1       Treat-A        2-Fail        x
1       Treat-A        1-Succ      xxx
1       Treat-B        2-Fail        x
1       Treat-B        1-Succ      xxx
run;

proc freq data = example;
table trt01a*outcome /riskdiff(CL=(exact)) alpha=0.05;
weight count; exact RISKDIFF(METHOD=SCORE);
output out=ciexact(keep=_RDIF1_ XL_RDIF1 XU_RDIF1 _RSK11_  _RSK21) riskdiff;
run;


data final(keep=A1 B1 Estimate LowerCL UpperCL ocharc1);
set ciexact;
label Estimate ="Percentage Difference"
LowerCL = "95% Lower Confidence Limit"
UpperCL = "95% Upper Confidence Limit"
A1 = "Percentage of Success in Treat-A"
B1 = "Percentage of Success in Treat-B";
Estimate=100*_RDIF1_;
LowerCL = 100*XL_RDIF1;
UpperCL = 100*XU_RDIF1;
A1 = 100*_RSK11_;
```

```
B1 = 100*_RSK21_;
ocharc1 = right(compress(put(Estimate,8.1)) || '% (' || compress(put(LowerCL,8.1)) || '%
to ' || compress(put(UpperCL,8.1)) || '%)');
run;
```

The 95% CI for percentage estimate of HIV-1 RNA < 50 copies/mL for each treatment is calculated based on the Clopper-Pearson exact method.

Fisher's exact test for categorical efficacy response (eg, HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm), where *trtgrp* is the treatment, and *response* is the categorical efficacy response. P-value from 2-sided Fisher's exact test should be used to test superiority.

```
proc freq data=adeff;
   tables trtgrp*response/fisher; /*p value from Fisher's exact test*/
run;
```

Subgroup analyses for HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm

For the subgroups, the proportion difference between two treatment groups and its 95% CIs are calculated based on an unconditional exact method using 2 inverted 1-sided tests, similar to that for the primary efficacy endpoint.

f) Homogeneity test: Homogeneity Test of Treatment Effect (HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm) between Subgroups in HIV-1 RNA < 50 copies/mL at Week 24 (Snapshot Algorithm)

i) For the subgroups, the odds ratio and the associated 95% CIs are estimated for the response variable (response; coded as 1 for success and 0 for non-success) using a logistic regression model including subgroup factor (coded as 1 for the first subgroup and 2 for the second subgroup), treatment (trtgrp; coded as 1 for active [ie, B/F/TAF] and 2 for control), and treatment by subgroup factor.

For example, for the age subgroup (agegrp; coded as 1 for < 50 and 2 for >= 50), the following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup:

Note: For the following code, it is assumed that none of the variables have any formats applied to them. If they do, they must be removed before calling the code.

e.g. for the age subgroup, the following codes will be used to get Odds Ratio and 95% CI within subgroup:

```
proc genmod data=data descending;     /*model for success*/
    class trtgrpn agegrp;
    model response = trtgrpn agegrp trtgrpn*agegrp/dist=bin
    link=logit lrci;
    estimate 'Group 1' trtgrpn 1 -1 trtgrpn*agegrp 1 0 -1 0/exp;
```

```
    estimate 'Group 2' trtgrpn 1 -1 trtgrpn*agegrp 0 1 0 -1/exp;
run;
```

Note: trtgrpn is the numeric treatment group variable, response is the response outcome variable (1 vs 0 ('<50' vs '>=50')), agegrp is the subgroup variable for age (1:< 50 vs 2: >= 50).

(P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup. Odds ratio is from L'Beta estimate, its 95%CI is from L'Beta confidence limits for each subgroup.)

g) ANOVA model for continuous efficacy variable (eg, CD4): The differences in changes from baseline in CD4 cell count between treatment groups and the associated 95% CI will be constructed using an ANOVA, including treatment as fixed effect in the model.

```
proc glm data=adeff;
      class trtgrp;
      model CD4=trtgrp;
      lsmeans trtgrp /alpha=0.05 cl pdiff;
run;
```

h) Listing for US FDA-defined snapshot outcome:

In addition to flagging the values of HIV-1 RNA < 50 or ≥ 50 copies/mL for virologic outcomes, flag the last available HIV-1 RNA value while on treatment for the following categories:

i) HIV-1 RNA >= 50 copies/mL - Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA >= 50 copies/mL

ii) HIV-1 RNA >= 50 copies/mL - Discontinued Study Drug Due to Other reason* and Last Available HIV-1 RNA >= 50 copies/mL

iii) No virologic Data – Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL

iv) No virologic Data – Discontinued Study Drug Due to Other reason* and Last Available HIV-1 RNA < 50 copies/mL

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

12) Clarification of the following LOCF algorithms:

- Baseline values will be carried forward.
- For CD4:

  If a value is missing in an analysis visit window, replace the missing value with the last on-treatment value observed before the analysis visit window that has the missing value.

13) TEAE

Events with Missing Onset Day and/or Month

An event is considered treatment emergent if the following 3 criteria are met:

1) The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of study drug, and

2) The month and year (or year) of the onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug, and

3) End date is as follows:

   The (complete) end date is on or after the first dose date, or

   The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or

   End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date meets any of the criteria specified in 3) above.

14) Toxicity Grades:

   For toxicity grade summaries, include post-baseline graded results as defined in Section 7.2.2.1, not just those used in by-visit summaries.

15) Graded Laboratory Abnormalities Summary

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

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
Urinalysis	Urine Blood (Dipstick)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*

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 post-BL Urine Blood (Dipstick) toxicity grade to BL Urine Blood (Dipstick) toxicity grade. If post-BL toxicity is greater than BL toxicity, then treatment-emergent
No	-	Yes	No	Treatment-emergent. Use post-BL Urine Blood (Dipstick) toxicity grade.
No	-	No	-	Do not count subject in the denominator for "Urine RBC (Hematuria, Quantitative or Dipstick)"

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

16) Rank analysis of covariance for proteinuria shift table

Rank analysis of covariance:

```
proc rank data=up nplus1 ties=mean out=ranks1;
      var upbase upwk48;
run;

proc reg data=ranks1;
      model upwk48=upbase;
      output out=residual1 r=resid;
run;

proc freq data=residual1;
      tables trtgrp*resid/noprint cmh2;
run;
```

17) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Nonstudy-Drug Antiviral Medication" listing. The logic to define concomitant nonstudy-drug ARV is similar to concomitant non-ARV Medications (see details in Section 7.4.2)

18) Lipid modifying medication analyses:

- Lipid modifying medication is defined to be the concomitant medication with WHO Drug ATC2 term (drug class) = "LIPID MODIFYING AGENTS" and WHO Drug preferred drug name (CMDECOD) contains wording of "STATIN" in the ADCM dataset.

- Subjects who took lipid modifying medications at study entry refer to the subjects who have any use of the lipid modifying agents at Study Day 1.

    a) More specifically, subjects with "Lipid Modifying Agent Use at Study Entry" include those subjects in the safety analysis set meeting both of the following criteria: 1) any selected CM record with the start date ≤ the first dose date, and 2) the end date of the selected CM record ≥ the first dose date or the end date of the selected CM record is ongoing

    b) For lipid modifying medications with the start date completely unknown, assume the start date is on or before the first dose date; lipid modifying medication is considered as being taken at study entry if the end date is not prior to the first dose date (ie, the end date is on or after the first dose date, completely unknown, or ongoing).

    c) Lipid modifying medications with the start date prior to the first dose date and the end date unknown (completely missing) are considered as being taken at study entry (the unknown end date is assumed to be on or after the first dose date).

- Subjects who initiated lipid modifying medications during the study (up to Week 24) are defined as the subjects in the safety analysis set who did not take lipid modifying medications at study entry and met the following criteria: 1) for subjects who permanently discontinued study treatment with any selected CM record with start date after the first dose date and on and prior to the minimum of (a) last dose date, or (b) Week 24 visit date; 2) for subjects who are still on study treatment with any selected CM records first started after the first dose date and on or prior to the Week 24 visit date.

- Subjects who initiated lipid modifying medications during the study (at any time) are defined as the subjects in the safety analysis set who did not take lipid modifying medications at study entry and met the following criteria: 1) for subjects who permanently discontinued study treatment with any selected CM record with start date after the first dose date and on and prior to the last dose date; 2) for subjects who are still on study treatment with any selected CM records first started after the first dose date.

19) Analysis of covariance for HIVTSQc scores

```
proc mixed;
   class trtgrp;
   model change = trtgrp baseline;
   lsmeans trtgrp;
run;
```

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

21) Vital signs and weight, height, BMI will be in the same listing.

22) HIV/HBV and HIV/HCV Coinfection:

- The following table presents the HBV and HCV tests with all possible values. Values that have an asterisk after them denote a "positive" (or "quantifiable" for HBV DNA and HCV RNA) result while all others denote a "negative" result.

Label	LBTESTCD	LBTEST	Possible Values
HBsAg	ATT1	Hep.B Surf.Ag Quant(-70)CL	NUMERICAL VALUE or "<0.05" or ">124925.00" (IU/mL)
HBsAg	ATT2	Hep. B Surf. Ag Qual(-70)-CL	"Repeat reactive, confirmed"*, "Repeat Reactive Unconfirmed", "Non-Reactive"
HBsAb	CNT353	anti-Hep B Surface Ag2 Qual	"Positive"*, "Negative"
HBcAb	CNT68	Hepatitis B Core Total	"Positive"*, "Negative"
HBV DNA	GET1883	HBV DNA CAP/CTM 2.0-EDTA-CL	"No HBV DNA detected", "<20 IU/mL HBV DNA detected", ">170000000"*, NUMERICAL VALUE (IU/mL)*
HBV DNA	GET1884	HBV DNA CAP/CTM 2.0Dil-EDTA-CL	NUMERICAL VALUE (IU/mL)*
HCVAb	CNT350	Hepatitis C Virus Antibody	"Positive"*, "Indeterminate", "Negative"
HCV RNA	GET1881	HCV RNA CAP/CTM 2.0EDTA-CL	"No HCV RNA detected", "<15 IU/mL HCV RNA detected", NUMERICAL VALUE (IU/mL)*

Note: HBVDNA AMPLIPREPTAQMAN 2.0 DIL(GET1884) is for HBV DNA CAP/CTM 2.0 >170,000,000 IU/mL.
HBsAg(ATT1) test is conducted when HBsAg(ATT2) results = "Repeat reactive, confirmed", "Repeat Reactive Unconfirmed".

- For baseline coinfection, when considering the different laboratory tests, take the latest, non-missing record on or prior to the first dose date for each test (eg, HBsAg, HBsAb, HBcAb, and HBV DNA)

  — The baseline coinfection status will be one of the three values: Yes/No/Null

  — The following tables provide combinations of HBV and HCV tests and the corresponding baseline coinfection status

HBsAg	HBsAb	HBcAb	HBV DNA	Coinfection Status
Positive	-	-	-	Y
Negative	Positive	-	-	N
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
	Missing	Positive	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
Missing	Positive	-	-	Null
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	Null
			Missing	Null
		Negative	-	Null
		Missing	-	Null
	Missing	-	-	Null

HCVAb	HCV RNA	Coinfection Status
Positive	Quantifiable	Y
	Not Quantifiable	N
	Missing	Null
Negative	-	N
Missing	Quantifiable	Null
	Not Quantifiable	N
	Missing	Null

"-" means any value can be present, as it does not affect the classification

- For incident coinfection, all laboratory tests must share the same accession number and if any set of values meets the criteria, then the subject is considered to have incident coinfection

  — The incident coinfection status will be one of two values: Yes/Null

  — The following tables provide combinations of HBV and HCV tests that are considered "Y" for incident coinfection status (all others are considered Null)

HBsAg	HBsAb	HBcAb	HBV DNA	Coinfection Status
Positive	-	-	-	Y
Negative	Negative	Positive	Quantifiable	Y
Missing	Negative	Positive	Quantifiable	Y

HCVAb	HCV RNA	Coinfection Status
Positive*	-	Y
-	Quantifiable	Y

* Subjects with positive HCVAb postbaseline must also have negative or missing HCVAb at baseline in order to be considered as having incident HIV/HCV coinfection.
"-" means any value can be present, as it does not affect the classification

- For incomplete AE start dates, please follow the logic specified in Section 7.1.5.2, but modify the second criterion to read, "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 of the last dose of study drug".

23) HBV DNA test codes: If the result of the lab test code GET1883 (HBV DNA CAP/CTM 2.0-EDTA-CL) is listed as ">170000000", then a reflexive test code GET1884 (HBV DNA CAP/CTM 2.0Dil-EDTA-CL) should be performed and will share the same accession number as the original GET1883 test. In this instance, use the result from GET1884 instead of GET1883 when determining HBV DNA.

24) Reasons for Subjects who excluded from Week 24 PP Analysis Set will be summarized as follows in the table:

    a) Had Pre-existing INSTI Resistance-associated Mutations, including pre-existing mutations that were detected post-baseline

    b) Did Not Have On-Treatment HIV-1 RNA in Week 24 Window Unless due to Discontinuation of Study Drug for Lack of Efficacy

    c) Met the Exclusion Criteria for 3 or more TAMs (M41L,D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), T69-insertions, or K65R/E/N in RT, including pre-existing mutations that were detected post-baseline

    d) Did not Meet the Inclusion Criteria for Baseline ARV Regimen

    e) Took Protocol Prohibited Medications

25) The number of decimal places in reporting p-values should be as follows:

    a) values less than 0.001 → < 0.001

    b) values 0.001 to less than 1.000 → 4 decimal places (no rounding)

26) In this study, only 3rd generation LDL is collected.

27) For 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, if CM end date is completely missing and the medication is not marked "Ongoing" and the CRF indicates 'Prior ARV', the ARV will not be flagged.

28) Last Dose Date and Last Study Date

    a) Last Dose Date for subjects who permanently discontinued study drug was defined in Section 3.8.1.

       <u>For subjects in the B/F/TAF or Delayed Switch B/F/TAF groups who permanently discontinued study drug at the data cut date:</u>

       If last dose date is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up), the latest of the B/F/TAF study drug start dates and end dates, the clinic 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.

       If the last dose date is a partial date (ie, month and year of last dose are known), the latest of the dispensing dates of study drug bottles, study drug start dates and end dates, and the imputed last dose date [day imputed as 15] will be used as the final imputed last dose date. However if the dispensing date's month is after the last dose date's month, a data query is needed.

If the subject died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

For subjects in the SBR group who permanently discontinued study drug at the data cut date:

If the last dose date (as defined in Section 3.8.1) is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up) for subjects who did not switch to B/F/TAF at the data cut date, the latest of the ARV baseline medication end dates, the clinic 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.

If the last dose date is a partial date (ie, month and year of last dose are known), the latest of the ARV baseline medication end dates and the imputed last dose date [day imputed as 15] will be used as the final imputed last dose date.

If the subject died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

Last dose date is not defined for subjects still on study drug in this SAP. However, for the calculation of the duration of exposure to study drug, the data cut date will be used to impute the last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date.

For the Week 24 analysis, 07 August 2019 (last Week 24 visit date for all subjects except Subject PPD will be used as the data cut date for all subjects except for Subject PPD. For Subject PPD PPD will be used as the data cut date (corresponding to that subject's Week 24 visit date).

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 date or end date 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.

Last study date is not defined for subjects still on study in this SAP. However, for programing purposes, the latest of data cut date, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, will be used to impute the last study date for subjects still on study.

29) The precision in reporting numerical values should be as follows:

Raw measurements will be reported the same as the data captured electronically or on the CRF.

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

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

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

30) Duration of HIV Diagnosis (years) is defined as the year from the First Dose Date/Study Day 1 Date minus the year of HIV diagnosis from Disease Under Study (HIV) CRF page.

31) Duration of HIV Treatment (Years) is defined as the year from the First Dose Date/Study Day1 Date minus the year first started HIV treatment from Disease Under Study (HIV) CRF page.

32) Premature study drug discontinuation prior to Week 24 is defined as

- For SBR group: subjects with Study Drug Completion form marked "No" for "Did subject complete study drug dosing as specified per protocol?" and subject did not switch to B/F/TAF

- B/F/TAF group: subjects with Study Drug Completion eCRF marked "No" for "Did subject complete study drug dosing as specified per protocol?", permanently discontinued study drug per the Study Drug Administration eCRF, and last dose was less than the latest of 168 days or the Week 24 visit date (if non-missing).

33) Completed 24 weeks on randomized drug is defined as "Yes" if subjects did not prematurely discontinue study drug prior to Week 24

34) Premature study discontinuation prior to Week 24 is defined as

- For SBR group: subjects with Study Completion form marked "No" for "Did subject complete the protocol-planned duration of the study?" and subject did not switch to B/F/TAF

- B/F/TAF group: subjects with Study Completion eCRF marked "No" for "Did subject complete the protocol-planned duration of the study??" and there are no scheduled visit dates on or after Week 24.