STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults
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LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ABC/3TC	fixed dose combination of abacavir (ABC) 600 mg / lamivudine (3TC) 300 mg
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under curve
BIC	bictegravir
B/F/TAF	fixed dose combination of bictegravir (BIC; B) 50 mg / emtricitabine (FTC) 200 mg / tenofovir alafenamide (TAF) 25 mg
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COBI	cobicistat
CSR	clinical study report
DC	premature study drug discontinuation
DNA	deoxyribonucleic acid
DRV	darunavir
E/C/F/TAF	fixed dose combination of elvitegravir (EVG) 150 mg / cobicistat (COBI) 150 mg / emtricitabine (FTC) 200 mg / tenofovir alafenamide (TAF) 10 mg
E/C/F/TDF	fixed dose combination of elvitegravir (EVG) 150 mg / cobicistat (COBI) 150 mg / emtricitabine (FTC) 200 mg / tenofovir disoproxil fumarate (TDF) 300 mg
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
FTC/TDF	fixed dose combination of emtricitabine (FTC) 200 mg / tenofovir disoproxil fumarate (TDF) 300 mg
GEN	Genvoya, E/C/F/TAF
GFR	glomerular filtration rate

GGT	gamma-glutamyl transferase
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	human immunodeficiency virus
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
ID	Identification
IDMC	independent data monitoring committee
INSTI	integrase strand transfer inhibitor
KM	Kaplan-Meier
LDL	low density lipoprotein
LLOQ	lower limit of quantitation
LLT	lowest level term
INR	International normalized ratio
LOCF	last observation carried forward
M = E	missing = excluded
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
PK	pharmacokinetic
PT	preferred term
PT	prothrombin time
PVE	Pharmacovigilance and Epidemiology
Q1	first quartile
Q3	third quartile
RBP	retinol binding protein
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBR	stay on baseline regimen

SD	standard deviation
SE	standard error
SMQ	Standardised MedDRA Query
SOC	system organ class
STB	Stribild, E/C/F/TDF
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TFV	tenofovir
TSH	thyroid stimulating hormone; thyrotropin
UACR	urine albumin to creatinine ratio
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the final analysis for Study GS-US-380-1878, which will be performed when all subjects have completed the study or prematurely discontinued from the study drug. This SAP is based on the study protocol amendment 2 dated 19 October 2016 and the electronic case report form (eCRF). The SAP will be finalized before data finalization for the final analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching to a fixed dose combination (FDC) of bictegravir (GS-9883; BIC; B)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) versus continuing on a regimen consisting of boosted atazanavir (ATV) or darunavir (DRV) plus either emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC) in HIV-infected adult subjects who are virologically suppressed as determined by the proportion of subjects with HIV-1 ribonucleic acid (RNA) ≥ 50 copies/mL at Week 48.

The secondary objective of this study is:

- To evaluate the safety and tolerability of the 2 treatment groups through Week 48.

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1.2. Study Design

Design Configuration and Subject Population

GS-US-380-1878 is a randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to a FDC of B/F/TAF in HIV-infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a regimen consisting of boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months prior to screening and who are integrase strand transfer inhibitor (INSTI) naive.

Treatment Groups

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

- **Treatment Group 1:** Switch to a FDC of bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily without regard to food (n 260)

- **Treatment Group 2:** Remain on current antiretroviral regimen consisting of ritonavir (RTV) or cobicistat (COBI) boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally, once daily with food (n 260)

From this point on, this document will refer Treatment Group 2 as SBR (ie, Stay on baseline regimen) for simplicity.

Key Eligibility Criteria

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

- Currently receiving a once daily antiretroviral regimen consisting of RTV or COBI boosted ATV or DRV plus either FTC/TDF or ABC/3TC for ≥ 6 months preceding the Screening visit

- Currently on a stable regimen for ≥ 6 months preceding the Screening visit with documented plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the Screening visit
  (note: prior changes in antiretroviral regimen are only allowed due to tolerability issues or for regimen simplification; unconfirmed virologic elevation of ≥ 50 copies/mL [transient detectable viremia, or "blip"] prior to screening is acceptable)

- HIV-1 RNA levels < 50 copies/mL at Screening visit

- No previous use of any approved or experimental INSTI

- No documented or suspected resistance to FTC, TFV, ABC, or 3TC, including but not limited to the reverse transcriptase resistance mutations K65R and M184V/I

- Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance

- No chronic Hepatitis B Virus (HBV) infection in subjects not on a TDF containing regimen

Study Periods / Phases

Subjects will be treated for at least 48 weeks. CCI [redacted]

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

Note: After the Week 48 visit, subjects in the UK will continue to take their assigned regimen and attend visits every 12 weeks.

Schedule of Assessments

After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 48 weeks. Following the Day 1 visit, subjects will be required to return for study visits at Weeks 4, 8, and 12, and then every 12 weeks through Week 48. After 48 weeks, subjects who continue participation in the study will receive B/F/TAF for additional 96 weeks and attend study visits every 12 weeks.

For all eligible subjects, blood will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through Week 48. Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, and complete or symptom directed physical examinations will be performed at Screening, Day 1 and all subsequent visits. Urine will be collected for evaluations of renal function including urine albumin, urine creatinine, urine protein, retinol binding protein (RBP), and beta-2 microglobulin.

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

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

Pharmacokinetics

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For all subjects who are randomized in to the B/F/TAF group and who are on study drug, a single anytime pre- or post-dose PK blood sample will be collected at Weeks 8, 24, and 36.

For all subjects who are randomized into the B/F/TAF group and who are on study drug, a trough PK blood sample will be obtained 20-28 hours following the last dose at Weeks 4 and 12. Following an observed dose, one post-dose PK blood sample will be collected between 1 and 4 hours post-dose.

Randomization

Subjects will be randomized in a 1:1 ratio to 1 of 2 Treatment Groups (Treatment Group 1: Treatment Group 2). Randomization will be stratified by the prior treatment regimen group (ie, TDF containing regimens [RTV or COBI boosted ATV or DRV plus FTC/TDF] and non-TDF containing regimens [RTV or COBI boosted ATV or DRV plus ABC/3TC]) at screening.

Site and/or Stratum Enrollment Limits

Approximately 150 study sites in North America, Europe, Asia Pacific, and Latin America participated. There was no enrollment limit for individual sites.

Study Duration

The randomization phase of this study is at least 48 weeks in duration.

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1.3. Sample Size and Power

A total of approximately 520 HIV-infected subjects, randomized in a 1:1 ratio to 2 treatment groups (260 subjects per treatment group), achieves at least 90% power to detect a noninferiority margin of 4% in Week 48 response rate (HIV-1 RNA $\geq$ 50 copies/mL as determined by the United States [US] Food and Drug Administration [FDA]-defined snapshot algorithm) difference between the 2 treatment groups. For sample size and power computation, it is assumed that both treatment groups have 2% of subjects with HIV-1 RNA $\geq$ 50 copies/mL (based on Gilead Genvoya [GEN; E/C/F/TAF] and Stribild [STB; E/C/F/TDF] studies) and that the significance level of the test is at a 1-sided 0.025 level. Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 6.0).

The actual number of randomized and treated subjects is 577. A total of 577 subjects increased the statistical power from 90% to 93% for evaluation of noninferiority of the primary efficacy endpoint.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

The Week 12 Independent Data Monitoring Committee (IDMC) analysis was conducted after approximately the first 30% subjects enrolled completed their Week 12 visit or prematurely discontinued the study drug. The Week 24 IDMC analysis was conducted after all subjects enrolled completed their Week 24 visit or prematurely discontinued the study drug. The purpose of these interim analyses was to provide the IDMC with a statistical report for review. More details are documented in the IDMC charter.

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

2.2. Interim Analyses

2.2.1. Week 48 Analysis

The Week 48 analysis was conducted after all subjects had completed the Week 48 visit or prematurely discontinued study drug. This is the primary analysis of this study.

2.3. Final Analysis

The final statistical analysis for the study will be conducted after all subjects either complete the study or prematurely discontinue from the study. This analysis will include all data collected from the randomized and the extension phases of the study.

This SAP describes the analysis plan for the final analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The final analysis will include two sets of analysis: the randomized phase analysis and the all B/F/TAF analysis.

Randomized Phase Analysis:

- The randomized phase analysis will include all available data for subjects who are never treated in the extension phase of the study including those who prematurely discontinue the randomized study drug or who complete the randomized study drug and do not receive any dose of B/F/TAF in the extension phase.

- The randomized phase analysis will include (1) all available adverse event (AE), concomitant medication, pregnancy, and death data collected **prior to** the extension phase first dose date; (2) all available other data, such as laboratory, vital sign, ECG, and PK data, collected **on or prior to** the extension phase first dose date for subjects who receive at least 1 dose of B/F/TAF in the extension phase.

All B/F/TAF Analysis:

- For the all B/F/TAF analysis, all available data for subjects who actually receive B/F/TAF in the randomized phase will be included.

- The all B/F/TAF analysis will include (1) all available AE, concomitant medication, pregnancy, and death data with start date **on or after** the extension phase first dose date and (2) all available other data, such as laboratory, vital sign, and ECG data, collected **after** the extension phase first dose date for subjects who actually receive SBR in the randomized phase and receive at least 1 dose of B/F/TAF in the extension phase. Except that the data collected **on or prior to** the first dose date of B/F/TAF will be used to derive the baseline value for the all B/F/TAF analysis.

Note: All data for subjects who actually receive SBR in the randomized phase and do not receive any dose of B/F/TAF in the extension phase will be excluded. In addition, 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.

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 identification (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 in the randomized phase will be used in the listings.

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

In general, permanent discontinuation of the randomized study drug refers to premature discontinuation of the randomized study drug or completion of the randomized study drug. Similarly, permanent discontinuation of the extension phase study drug refers to premature discontinuation of the extension phase study drug or completion of the extension phase study drug. More specifically, for randomized phase analysis, study drug refers to the randomized study drugs (B/F/TAF or SBR); for all B/F/TAF analysis, study drug refers to B/F/TAF.

3.1. Analysis Sets

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

3.1.1. Analysis Sets Used for the Randomized Phase Analysis

3.1.1.1. All Randomized Analysis Set

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

3.1.1.2. Full Analysis Set

The **Full Analysis Set (FAS)** will include all subjects who (1) are randomized into the randomized phase of the study and (2) have received at least 1 dose of randomized study drug. Subjects will be grouped according to the treatment to which they were randomized. For the FAS, all efficacy data collected in the randomized phase, including data collected after the last dose date of the randomized study drug and on or prior to the first dose date of the extension study drug (if applicable), will be included, unless specified otherwise. This is the primary analysis set for efficacy analyses.

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

Adverse event (AE), concomitant medication, pregnancy, and death data collected up to 30 days after permanent discontinuation of the randomized phase study drug and **prior to** the first dose date of extension phase study drug (if applicable) will be included in the safety summaries, unless specified otherwise.

Laboratory data (eg, hematology, chemistry, and urine analysis), vital sign, ECG data collected up to 30 days after permanent discontinuation of the randomized phase study drug and **on or prior** to the first dose date of extension phase study drug (if applicable) will be included in the safety summaries, unless specified otherwise.

3.1.2. Analysis Set Used for the All B/F/TAF Analysis

3.1.2.1. All B/F/TAF Analysis Set

The **All B/F/TAF Analysis Set** will include all subjects who (1) are randomized into the randomized phase of the study and (2) have received at least 1 dose of the B/F/TAF in the randomized phase or in the extension phase. This is the primary analysis set for the all B/F/TAF efficacy and safety analyses.

For efficacy analyses, all efficacy data collected for the all B/F/TAF analysis will be included.

For safety analyses, all safety data collected up to 30 days after permanent discontinuation of the B/F/TAF will be included in the safety summaries, unless specified otherwise.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or the FAS in the randomized phase analysis, subjects will be grouped by the randomized treatment (labeled as B/F/TAF vs. SBR). For all other analyses in the randomized phase analysis, subjects will be grouped by the 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.

For all analyses included in the all B/F/TAF analysis, subjects will be grouped into the following

3 groups:

- B/F/TAF group: This group includes all subjects who actually received B/F/TAF in the randomized phase of this study, regardless whether subjects receive any B/F/TAF in the extension phase or not.

- SBR to B/F/TAF group: This group includes all subjects who actually received the SBR regimen in the randomized phase of this study and then receive at least 1 dose of B/F/TAF in the extension phase.

- All B/F/TAF group: This group includes all subjects who actually received at least 1 dose of B/F/TAF in either phase. This group includes the B/F/TAF group and the SBR to B/F/TAF group. Only data collected on and after the first dose date of B/F/TAF may be included.

Treatment comparisons will only be made between B/F/TAF and SBR for the randomized phase analysis.

3.3. Strata and Covariates

Randomization was stratified by the prior treatment regimen group (ie, TDF containing regimens [RTV or COBI boosted ATV or DRV plus FTC/TDF] and non-TDF containing regimens [RTV or COBI boosted ATV or DRV plus ABC/3TC]) at screening. However, no stratified analysis is planned for the final analysis.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Safety Analyses

Selected safety endpoints may be analyzed for the following subject subgroups (see Section 9.1 and Section 9.2 for details):

- Subjects with HIV/ hepatitis C virus (HCV) coinfection at baseline (if any)

- Subjects with HIV/ hepatitis B virus (HBV) coinfection at baseline (if any)

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

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

3.5. Multiple Comparisons

Not applicable for this analysis, as no treatment comparison is planned for the final analysis. All analyses are exploratory in nature.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

- A visit occurring in the window but data were not collected or were unusable

- A visit not occurring in the window

- A subject prematurely discontinuing from the study before reaching the window

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

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for concomitant non-antiretroviral (ARV) medications in Section 7.4.3.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

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

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

- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.

- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitation).

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

Logarithmic (base 10) transformations will be applied to HBV deoxyribonucleic acid (DNA) data for efficacy analysis. HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes. 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

Study Day 1 for the Randomized Phase Analysis is defined as the day when the first dose of randomized study drug (ie, B/F/TAF or SBR) was taken. For subjects randomized to the B/F/TAF group, the first dose date is recorded on the "Randomized Phase" Study Drug Administration eCRF. For subjects randomized to the SBR group, the first dose date is defined as Day 1 visit date on the Visit Date eCRF.

Last Dose Date for the Randomized Phase Analysis is defined as follows:

- For subjects randomized to the B/F/TAF group, the last dose date is defined as the latest of the randomized study drug end dates recorded on the "Randomized Phase" Study Drug Administration eCRF.

- For subjects randomized to the SBR group, the last dose date is the earliest of the latest end dates from each baseline regimen component (ie, protease inhibitor [PI] and nucleoside reverse transcriptase inhibitors [NRTIs] as defined in Section 7.4.2) recorded on the "Current" ARV eCRF for the randomized phase of the study.

If the last dose date for randomized phase is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up), the latest of nonmissing randomized study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates, excluding the date of 30-day follow-up visit, from the randomized phase data, will be used to impute the randomized phase last dose date. For other partial missing last dose date, please see programming specification for imputation rule details.

Study Day 1 for the all B/F/TAF analysis is defined as the day when the first dose of B/F/TAF (in the randomized phase for B/F/TAF group, and in the extension phase for SBR to B/F/TAF treatment group) was taken, as recorded on the Study Drug Administration eCRF form.

Last Dose Date for the All B/F/TAF Analysis is defined as the latest of B/F/TAF (including both phases) recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked.

If the last dose date for the all B/F/TAF analysis is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up), the latest B/F/TAF start dates and end dates, the latest clinical and laboratory visit dates, excluding the 30-day follow-up visit date, will be used to impute the last dose date.

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

Last Study Date is the latest of the randomized or extension phase (if available) study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date.

Baseline Value is defined as the last nonmissing value obtained on or prior to Study Day 1 for either the randomized phase analysis or the all B/F/TAF analysis, as appropriate. Subjects who actually received SBR in the randomized phase and received at least 1 dose of extension B/F/TAF will have a new baseline value for the all B/F/TAF analysis.

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 two different analysis windows based on the following tables: the analysis windows for the randomized phase analysis are derived relative to the Study Day 1 for the randomized phase analysis, while the analysis windows for the all B/F/TAF analysis are derived relative to the study day 1 for the all B/F/TAF analysis.

The analysis windows for HIV-1 RNA, CD4+ cell count, CCI HBV DNA, hematology, chemistry, urinalysis, urine pregnancy laboratory tests, $eGFR_{CG}$, vital signs, and weight are presented in Table 3-1 and Table 3-2 for randomized phase analysis and all B/F/TAF analysis, respectively.

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

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

Note: HBV DNA collection schedules are as follows: (1) For subjects who meet the definition of HBV infection at screening, HBV DNA will be collected at baseline, Weeks 4, 8, 12, 24, 36, and 48. (2) For subjects who meet the definition of HBV infection at any postbaseline visit, HBV DNA test will be performed at all subsequent visits. (3) For subjects who do not meet the definition of HBV infection at any visit, HBV DNA will be collected at baseline and Week 48.

Table 3-2. Analysis Windows for HIV-1 RNA, CD4+ cell count, CCI HBV DNA, Hematology, Chemistry, Urinalysis, and Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, and Weight for All B/F/TAF Analysis

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

NA Not applicable
Note: For the B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the randomized phase;
Note: For the SBR to B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the extension phase.

The analysis windows for metabolic assessments (including fasting glucose and lipid panel: total cholesterol, high density lipoprotein [HDL], direct low density lipoprotein [LDL], triglycerides, and total cholesterol to HDL ratio) and HBV serology (including hepatitis B surface antibody [HBsAb], hepatitis B surface antigen [HBsAg], hepatitis B e-antigen [HBeAg], hepatitis B e-antibody [HBeAb], and hepatitis B core antibody [HBcAb]) are presented in Table 3-3 and Table 3-4 for randomized phase analysis and all B/F/TAF analysis, respectively.

Table 3-3. Analysis Windows for Metabolic Assessments and HBV Serology for Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 12	84	2	126
Week 24	168	127	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Week k (k is every 24 weeks after previous visit)	k*7	(k-12)*7+1	(k+12)*7

Note: HBV serology collection schedules are as follows: (1) For subjects who meet the definition of HBV infection at screening, HBV serology will be collected at Weeks 12, 24, and Week 48. (2) For subjects who meet the definition of HBV infection at any postbaseline visit, HBV serology will be performed at all subsequent visits. (3) For subjects who do not meet the definition of HBV infection at any visit, HBV serology will be collected at baseline and Week 48.

Table 3-4. Analysis Windows for Metabolic Assessments and HBV Serology for all B/F/TAF Analysis

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

NA Not applicable
Note: For the B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the randomized phase;
Note: For the SBR to B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the extension phase.

The analysis windows for thyroid stimulating hormone (TSH; thyrotropin), renal function (including: urine albumin, urine creatinine, urine RBP, and urine beta-2 microglobulin, and derived ratios), and safety electrocardiogram (ECG) are presented in Table 3-5 and Table 3-6.

Table 3-5. Analysis Windows for TSH, Renal Function, and Safety ECG for Randomized Phase Analysis

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

Table 3-6. Analysis Windows for TSH, Renal Function, and Safety ECG for all B/F/TAF Analysis

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

NA Not applicable
Note: For the B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the randomized phase;
Note: For the SBR to B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the extension phase.

The analysis windows for HCV serology (including HBsAb, HBsAg, hepatitis B e-antigen [HBeAg], hepatitis B e-antibody [HBeAb], HBcAb, HCV antibody [HCVAb]), and HCV RNA assessments are presented in Table 3-7 and Table 3-8.

Table 3-7. Analysis Windows for HCV Serology and HCV RNA Assessments for Randomized Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	504
Week 96	672	505	840
Week k (k is every 48 weeks after previous visit)	k*7	(k-24)*7+1	(k+24)*7

Table 3-8. Analysis Windows for HCV Serology and HCV RNA Assessments for all B/F/TAF Analysis

	B/F/TAF Group			SBR to B/F/TAF		
Visit ID	Nominal Day	Lower Limit	Upper Limit	Nominal Day	Lower Limit	Upper Limit
Baseline			1			1
Week 48	336	2	504	336	2	504
Week 96	672	505	840	672	505	840
Week k (k is every 48 weeks after previous visit)	k*7	(k-24)*7+1	(k+24)*7	k*7	(k-24)*7+1	(k+24)*7

NA Not applicable
Note: For the B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the randomized phase;
Note: For the SBR to B/F/TAF group, Study Day 1 is the first dose date of the B/F/TAF received in the extension phase.

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, records will be chosen as follows:

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

- For postbaseline visits:

  For CD4+ cell count, 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-1 RNA, if there are multiple records on the selected day, the arithmetic mean will be used.

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

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

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

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group and overall for all Randomized subjects. This summary will include the number of subjects randomized, subjects randomized but never treated, subjects in the Safety Analysis Set, and subjects in the FAS.

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

- Subjects completing study drug in the randomized phase
- Prematurely discontinuing study drug in the randomized phase (with summary of reasons for discontinuing study drug)
- Subjects completing study in the randomized phase
- Prematurely discontinuing from study in the randomized phase (with summary of reasons for discontinuing study).
- Subjects completing study drug in the randomized phase and not entering the extension phase
- Subjects completing study drug in the randomized phase and entering the extension phase
- Subjects discontinuing study drug in the randomized phase but entering the extension phase
- Subjects entering in the extension phase
- Subjects treated in the extension phase
- Subjects completing study drug in the extension phase
- Prematurely discontinuing study drug in the extension phase (with summary of reasons for discontinuing study drug in the extension phase)
- Subjects completing the study in the extension phase
- Prematurely discontinuing from study in the extension phase (with summary of reasons for discontinuing from study in the extension phase)

The denominator for the percentages of subjects in each category in the randomized phase, including "Subjects entering in the extension phase", will be the number of subjects in the safety analysis set. The denominator for the percentages of subjects in each category in the extension phase will be the number of subjects who were treated in extension phase.

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 to study drug will be defined for both the randomized phase analysis and the all B/F/TAF analysis. For the randomized phase analysis, the terms "first dose date" and "last dose date" in the text below refer to the first dose date and last dose date defined for the randomized phase analysis. For the all B/F/TAF analysis, the terms "first dose date" and "last dose date" in the text below refer to the first dose date and last dose date defined for the all B/F/TAF phase analysis. Duration of exposure is defined as (last dose date 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).

Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, eg, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days), ≥ 84 weeks (588 days), ≥ 96 weeks (672 days), ≥ 108 weeks (756days), ≥ 120 weeks (840 days), ≥ 132 weeks (924 days), ≥ 144 weeks (1008 days), etc.

Summaries will be provided by treatment group for subjects in the Safety Analysis Set and All B/F/TAF Analysis Set for the randomized phase analysis and all B/F/TAF analysis, respectively. No inferential statistics will be provided.

Time to premature discontinuation of randomized study drug will be analyzed using the Kaplan-Meier (KM) method by treatment group based on the safety analysis set and the all B/F/TAF analysis set, respectively. The log rank test will be used to compare the difference in study drug exposure between the 2 randomized treatment groups for the safety analysis set only. A plot of KM estimates for the time to permanent discontinuation of study drug by treatment group will be generated for the safety analysis set only. Subjects who completed study drug will be censored at the last dose date.

4.2.2. Adherence to Study Drug Regimen

Adherence to study drug regimen will be defined for both the randomized phase analysis and the all B/F/TAF analysis. For randomized phase analysis, study drug accountability (ie, numbers of pills of B/F/TAF dispensed and returned) is only captured for subjects randomized into the B/F/TAF group. Therefore, adherence will only be computed for Treatment Group 1 in the randomized phase of the study. For all B/F/TAF analysis, adherence will be computed for both treatment groups as defined in Section 3.1.2.

Study drug regimen adherence will be computed based on pill counts for B/F/TAF only. The numbers of pills of each study drug dispensed and returned are captured on study drug accountability forms.

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

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

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

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

[2] Number of pills prescribed at a distinct dispensing period for B/F/TAF is calculated as the daily number of pills prescribed multiplied by the duration of treatment at the dispensing period. Total number of pills prescribed is determined by summing the number of pills prescribed from all evaluable dispensing periods.

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

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

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

Overall adherence will be calculated for both the randomized phase analysis and the all B/F/TAF analysis. Overall adherence for the randomized analysis will use all data from the entire dosing period up to the date of permanent discontinuation of the randomized study drug. Overall adherence for the all B/F/TAF analysis will use all available data for subjects who actually received B/F/TAF in the randomized phase, and data on or after the first dose date of extension B/F/TAF for subjects who actually received SBR in the randomized phase and received at least 1 dose of B/F/TAF in the extension phase.

Descriptive statistics for B/F/TAF adherence (sample size, 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 subjects who return at least 1 bottle of randomized study drug, and who have calculable adherence for the randomized phase analysis and the all B/F/TAF analysis, respectively. No inferential statistics will be provided.

4.3. Protocol Deviations

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

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

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

For the randomized phase analysis using safety analysis set, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data) will be used to compare the 2 treatment groups for categorical data, and the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups for continuous data. No statistical comparisons will be made for the all B/F/TAF analysis.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for subjects in the safety analysis set and all B/F/TAF analysis set, respectively:

- 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
- [redacted]
- Mode of infection (HIV risk factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)
- HIV/HBV co-infection status (Yes/No/Missing, only for all B/F/TAF analysis, see Section 9.1 for definition)
- HIV/HCV co-infection status (Yes/No/Missing, only for all B/F/TAF analysis, see Section 9.2 for definition)

For the randomized phase analysis using Safety Analysis Set, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data) will be used to compare the 2 treatment groups for categorical data, and the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups for continuous data. No statistical comparisons will be made for the all B/F/TAF analysis.

5.3. Medical History

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

6. EFFICACY ANALYSES

Analyses for all the primary and secondary efficacy endpoints have been performed in the Week 48 analysis and will not be repeated in the final analysis. CCI [redacted]

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US Food and Drug Administration (FDA)-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}.

The statistical analysis methods for the primary efficacy endpoint were described in the Week 48 SAP and the analysis was performed in the Week 48 analyses.

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 change from baseline in CD4+ cell count at Week 48

All the secondary efficacy endpoints indicated above have been performed in the Week 48 analyses. Endpoints based on the snapshot algorithm will not be repeated in the final analysis. However, change from baseline in CD4 cell counts at each visit will be performed for both randomized phase analysis and all B/F/TAF analysis in this final analysis.

6.2.2. Analysis of CD4+ Cell Count

The analysis of CD4 cell count will be based on on-treatment data (ie, up to 1 day after the last dose date of study drug) using the FAS for the randomized phase analysis and the All B/F/TAF Analysis Set for the all B/F/TAF analysis.

The changes from baseline in CD4+ cell count at each visit including visit past Week 48 will be summarized by treatment group using descriptive statistics. For the randomized phase analysis, 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. No statistical comparisons will be made for the all B/F/TAF analysis.

The mean and 95% CI of change from baseline in CD4+ cell count over time will be plotted for the FAS in the randomized phase analysis.

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

6.4. Changes From Protocol-Specified Efficacy Analyses

No change from protocol-specified efficacy analysis is planned.

7. SAFETY ANALYSES

Safety data will be summarized for the subjects in the Safety Analysis Set for the randomized phase analysis and the All B/F/TAF Analysis Set for the all B/F/TAF analysis, unless specified otherwise. For randomized phase, only the following analysis will be done:
(1) Treatment-Emergent Adverse Events: Overall Summary; (2) Treatment-Emergent Adverse Events by Preferred Term;(3) Treatment-Emergent Laboratory Abnormalities. No treatment comparison will be performed for all B/F/TAF analysis. All safety data from both phases of the study will be included in data listings.

For the randomized phase analysis, the terms “study drug start date (ie, the first dose date)”, “study drug stop date (ie, the last dose date)”, and “baseline” in the text below refer to the first dose date, the last dose date, and baseline defined for the randomized phase analysis; the term “study drug” in the text below refer to the randomized study drugs.

For the all B/F/TAF analysis, the terms “study drug start date (ie, the first dose date)”, “study drug stop date (ie, the last dose date)”, and “baseline” in the text below refer to the first dose date, the last dose date, and baseline defined for the all B/F/TAF phase analysis; the term “study drug” in the text below refer to B/F/TAF.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (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” in the data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

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

For the randomized phase analysis, the AE onset date will be compared with the first and last dose dates for the randomized phase analysis. For the all B/F/TAF analysis, the AE onset date will be compared with the first and last dose dates for the All B/F/TAF phase analysis.

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, 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 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 using both Safety Analysis Set and All B/F/TAF Analysis Set, respectively. For other AEs described below, summaries will be provided by SOC, PT, and treatment group using the All B/F/TAF Analysis Set only:

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

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs using both the Safety Analysis Set and All B/F/TAF Analysis Set, respectively. 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. Treatment-emergent AEs 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 Treatment-emergent AEs that occurred more than once in an individual subject during the study.

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

In addition, data listings for all AEs regardless of the study phases will be provided for the following:

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

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Stage 3 Opportunistic Illnesses in HIV

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

7.1.7.2. Cardiovascular or Cerebrovascular Events

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

The number and percentage of subjects with treatment-emergent cardiovascular or cerebrovascular events and serious cardiovascular or cerebrovascular events by PT will be provided by treatment group based on the All B/F/TAF Analysis Set. Statistical comparisons of the subject incidence rates between the 2 treatment groups will not be performed. A data listing of cardiovascular or cerebrovascular events will be provided.

7.1.7.3. Hepatic Events

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

The number and percentage of subjects with treatment-emergent hepatic events and serious hepatic events by PT will be summarized by treatment group based on the All B/F/TAF Analysis Set. Statistical comparisons of the subject incidence rates between the 2 treatment groups will not be performed. 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 All B/F/TAF Analysis Set, except that the summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided for subjects in the Safety Analysis Set and All B/F/TAF Analysis Set, respectively. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

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

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

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

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

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date of first dose of 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 0.

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.

Estimate GFR

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

- $eGFR_{CG}$ (mL/min) [(140 age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72), where weight is total body mass in kilograms 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, protocol-specified toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to 30 days after permanent discontinuation of the study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

Fasting glucose and nonfasting glucose (including glucose results without a known fasting status) are graded based on different grading scales as specified in the protocol. Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Maximum postbaseline grade, instead of treatment-emergent grade, for nonfasting glucose (including glucose results without a known fasting status) will be summarized, as nonfasting glucose was not assessed at baseline visit for most of the subjects; therefore, an abnormality is treatment-emergent or not cannot be determined for these subjects.

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

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

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. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Metabolic Laboratory Evaluations

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

In addition, the number and percentage of subjects who took lipid-modifying medication at the first dose of B/F/TAF and subjects who initiated the lipid modifying medication while receiving B/F/TAF will be provided.

A lipid modifying medication is defined as a medication with ATC2 term "LIPID MODIFYING AGENTS" and CMDECOD containing the wording of "STATIN".

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

7.2.4. Liver-Related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

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

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

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

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

7.2.5. Renal-Related Laboratory Evaluations

7.2.5.1. Serum Creatinine and $eGFR_{CG}$

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

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

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

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

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

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

7.2.5.3. Albuminuria by Quantitative Assessment

The baseline, postbaseline, changes from baseline, and percentage change from baseline in urine albumin to creatinine ratio (UACR) will be summarized by treatment group and visit using descriptive statistics.

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

Median (Q1, Q3) percentage change from baseline in UACR over time will be plotted by treatment group.

7.3. Body Weight, Height, and Vital Signs

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

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline 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 0. No formal statistical testing is planned.

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

7.4. Prior and Concomitant Medications

7.4.1. Antiretroviral Medications

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

7.4.2. Prior Antiretroviral Medications

Prior ARV medications are defined as ARV medications taken on or up to 2 days prior to the first dose date of randomized study drug based on ARVs reported on ARV eCRF (see Appendix 5 for details). For summary purposes, prior ARV medications will be classified into one of the following regimens. The number and percentage of subjects in each prior ARV regimen will be summarized as part of baseline disease characteristics table.

- Boosted ATV + ABC/3TC
- Boosted DRV + ABC/3TC
- Boosted ATV + FTC/TDF
- Boosted DRV + FTC/TDF

7.4.3. Concomitant Non-Antiretroviral Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications from the Study Day 1 up to the last dose date of the study drug will be summarized (number and percentage of subjects) by treatment group, WHO drug class and preferred name for the All B/F/TAF Analysis Set. Multiple drug use (by preferred drug name) will be counted only once per subject. The summary will be sorted alphabetically by decreasing total frequency of preferred drug name. For drug with the same frequency, sorting will be done alphabetically.

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 (or year alone) of start of the medication is after the last dose date of the study drug
- The month and year (or year alone) of stop of the medication is before the first dose date of the study drug

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

Subjects with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

7.5. Electrocardiogram Results

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

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

7.6. Other Safety Measures

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

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.4.1 using the All B/F/TAF Analysis Set.

7.8. Changes from Protocol-Specified Safety Analyses

No change from protocol-specified safety analysis is planned.

8. PHARMACOKINETIC ANALYSES

All necessary summaries on PK analyses have been performed as part of Week 48 CSR, and will not be repeated in the final analysis.

9. SPECIAL POPULATION ANALYSES

Special population analyses will be performed using all B/F/TAF analyses set only.

9.1. Analyses for HIV/HBV Coinfected Subjects

Subjects with HIV/HBV coinfection at baseline are defined as subjects meet any of the following two criteria **on or prior to** the first dose date of B/F/TAF:

- Positive HBsAg on or prior to the first dose date of B/F/TAF, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 29 IU/mL) on or prior to the first dose date of B/F/TAF

The following analyses will be provided by treatment and overall for subjects with HIV/HBV coinfection at baseline:

- The proportion of subjects with HBV DNA < 29 IU/mL at baseline and Week 48 by M E approach
- The change from baseline in $\log_{10}$ HBV DNA ($\log_{10}$ IU/mL)
- 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, gamma-glutamyl transferase (GGT), total bilirubin, direct and indirect bilirubin
- Listing of AEs
- Listing of liver-related laboratory tests and HBV DNA results

HBV DNA will be analyzed using observed, on-treatment data (ie, data collected up to the 1 day after the last dose date of B/F/TAF) for subject in the all B/F/TAF analysis set with HIV/HBV coinfection at baseline.

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

- Positive HBsAg after the first dose date of B/F/TAF and on or prior to the last dose date of B/F/TAF plus 1 day, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 29 IU/mL) after the first dose date of B/F/TAF and on or prior to the last dose date of B/F/TAF plus 1 day, or

- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") after the first dose date of B/F/TAF and on or prior to the last 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 (if any):

- Listing of AEs
- Listing of liver-related laboratory tests and HBV DNA results

9.2. Analyses for HIV/HCV Coinfected Subjects

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

- Treatment-emergent AEs overall summary
- Treatment-emergent AEs by SOC, HLT, and PT
- Treatment-emergent laboratory abnormalities
- Listing of AEs
- 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:

- Positive HCVAb after the first dose date of B/F/TAF and on or prior to the last dose date of B/F/TAF plus 1 day with baseline HCVAb Negative or missing, or
- Quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) after the first dose date of B/F/TAF and on or prior to the last dose date of B/F/TAF plus 1 day, or
- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") after the first dose date of B/F/TAF and on or prior to the last dose date of B/F/TAF plus 1 day: 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 AEs
- Listing of liver-related laboratory tests and HCV RNA results

10. REFERENCES

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

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. Revision 1. 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.

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

Phoenix WinNonlin® Version 6.4 (Certara USA, Inc., Princeton, NJ, USA.) is to be used for all PK analyses.

12. SAP REVISION

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

13. APPENDICES

Appendix 1. Study Procedures Table
Appendix 2. Region Definition
Appendix 3. Cardiovascular or Cerebrovascular Events
Appendix 4. Hepatic Events
Appendix 5. Programming Specification

Appendix 1. Study Procedures Table

Study Procedures	Screening[a]	Day 1[b]	End of Week[e,v]						Post-Week 48[e,w]	30-Day Follow-up[u]	Early Study Drugs DC[c]
			4	8	12	24	36	48	Every 12 Weeks[x]		
Informed Consent	X										
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Complete/Symptom-Directed Physical Exam	**X**	**X**	X[d]	X[d]	X[d]	**X**	X[d]	**X**	X[d,aa]	X[d,f]	**X**[f]
12-Lead ECG (performed supine)	X	X				X		X	X[m]		X[bb]
SF-36, HIV Symptoms Distress Module, WPAI, and UCLA SCTC GIT 2.0 Questionnaires		X	X		X			X			
VAS Adherence Questionnaire		X	X	X	X	X	X	X			X
Height	X										
Vital signs (blood pressure, pulse, respiration rate, and temperature), including Weight	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Urine Pregnancy Test[g]		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X										
Chemistry Profile[h]	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Metabolic Assessments[i]		X			X	X		X	X[j]		
Estimated Glomerular Filtration Rate (eGFR)	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile[k]	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X
Evaluation of renal tubular function[l]		X				X		X	X[j]		

Study Procedures	Screening[a]	Day 1[b]	End of Week[e,v]						Post-Week 48[e,w]	30-Day Follow-up[u]	Early Study Drugs DC[c]
			4	8	12	24	36	48	Every 12 Weeks[x]		
Plasma and Urine Storage Sample		X	X	X	X	X	X	X	X		X
Whole Blood sample for potential HIV DNA genotyping		X									
HCV Serology	X							X	X[m]		
HIV-1 Genotype/Phenotype [e]											X[e]
Single PK Sample[n]				X		X	X				
Trough and post dose PK Sample[o]			X		X						
CCI											
Randomization[y]		X									
Provide subject dosing diary to Treatment Group 1 subjects		X	X	X	X	X					
CCI											
HBV blood panel	X[q]				X[s]	X[s]		X[s,z]	X[s,z]		
Plasma HBV DNA[r]		X	X	X	X	X	X	X	X		X
Study Drug Dispensation[t]		X	X	X	X	X	X	X	X		
Study Drug Accountability			X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Day 1.
b Initiation of the first dose of study drug is to take place in clinic following completion of study procedures on the Day 1 visit.
c Early Study Drugs Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 48 Visit even if the subject discontinues study drug.
d Symptom directed physical examination as needed.
e HIV 1 genotype and phenotype testing for subjects with virologic failure. Following virologic rebound, subjects will be asked to return to the clinic (2 3 weeks later) prior to the next scheduled visit or at the next scheduled study visit, for a HIV 1 RNA and HIV 1 genotype and phenotype (reverse transcriptase, protease and integrase genotype and phenotype) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema.
f Any adverse event or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
g Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
h Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN) At Day 1, Weeks 12, 24, 48 and every 24 weeks post Week 48, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of

the chemistry profile. Additionally, TSH will be analyzed at Screening, Day 1, Weeks 24, 48, followed by every 24 weeks post Week 48, and Early Study Drugs Discontinuation visit. PT/INR will be performed at Day 1.

i 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 subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

j Every 24 weeks post Week 48 Visit

k CBC with differential and platelet count.

l Evaluation of renal tubular function includes analyses of urine albumin, urine creatinine, urine protein, retinol binding protein and beta 2 microglobulin

m To be performed every 48 weeks post Week 48 Visit

n A single PK blood sample will be collected at any time pre or post dose from subjects in Treatment Group 1.

o A trough PK blood sample will be collected between 20 28 hours following the last dose from subjects in Treatment Group 1. Following an observed dose, a single post dose blood sample will be collected between 1 and 4 hours post dose.

[redacted]

q HBV blood panel will be performed at Screening (Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb)).

r To be performed for subjects who meet the definition of HBV infection

s At Weeks 12, 24, 48, 72, 96, and 120, for subjects who meet the definition of HBV infection at any visit, the following will be performed by the central laboratory: HBsAb, HBsAg (qualitative and quantitative) and HBeAg (if negative reflex, HBeAb).

t Study drug GS 9883/F/TAF to be dispensed to Treatment Group 1 subjects.

u For the purpose of scheduling a 30 Day Follow Up Visit, a ± 6 days window may be used. Those subjects who prematurely discontinue study drug and continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit will not be required to complete the 30 Day Follow Up Visit.

v Study visits are to be completed within ± 2 days of the protocol specified visit date based on the Day 1 visit through Week 12 and completed within ± 6 days through to Week 36, unless otherwise specified. The visit window at Weeks 48 will be ± 6 weeks of the protocol specified visit date.

w Visit window of ± 6 days for study visits post Week 48.

x GS 9883/F/TAF FDC will be dispensed to subjects participating in the study post Week 48 visit.

y 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 subject eligibility has been confirmed.

z At Weeks 48, 96 and 144, for subjects who do **NOT** meet the definition of HBV infection at any visit, the following will be performed by the central laboratory: HBsAg, HBsAb, and HBcAb. Subjects who are HBsAg and/or HBcAb positive will have a reflex test for HBV DNA (viral load).

aa A complete physical exam should be done every 48 weeks post Week 48 Visit.

bb Only to be completed for Early Study Drugs Discontinuation Visits up to Week 48.

Appendix 2. Region Definition

Region	Country Name	State	No. of Subjects in Safety Analysis Set or FAS (N=577)	Total No. of Subjects by Region in Safety Analysis Set or FAS (N=577)
Region 1	AUSTRALIA (AUS)		31	64
	CANADA (CAN)		33	
Region 2	BELGIUM (BEL)		5	172
	FRANCE (FRA)		34	
	GERMANY (DEU)		61	
	ITALY (ITA)		8	
	SPAIN (ESP)		10	
	UNITED KINGDOM (GBR)		54	
Region 3	UNITED STATES (USA)	CA	53	68
	UNITED STATES	WA	9	
	UNITED STATES	HI	6	
Region 4	UNITED STATES	TX	39	53
	UNITED STATES	CO	4	
	UNITED STATES	AZ	5	
	UNITED STATES	KS	5	
Region 5	UNITED STATES	MO	14	48
	UNITED STATES	MI	7	
	UNITED STATES	MN	5	
	UNITED STATES	IL	18	
	UNITED STATES	KY	4	
Region 6	UNITED STATES	NY	5	31
	UNITED STATES	MA	9	
	UNITED STATES	DC	14	
	UNITED STATES	VA	3	
Region 7	UNITED STATES	GA	21	52
	UNITED STATES	SC	7	
	UNITED STATES	NC	16	
	UNITED STATES	LA	1	
	UNITED STATES	TN	7	
Region 8	UNITED STATES	FL	60	89
	UNITED STATES	PR*	18	
	DOMINICAN REPUBLIC (DOM)		11	

* PR Puerto Rico.

Note: In general, a region is defined as multiple sites combined based on geographical locations. For example, for international studies, sites from each country or multiple neighboring counties were combined; and for US studies, sites from each state or multiple neighboring states were combined.

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 **22.1** provided by Gilead PVE and reviewed by Gilead medical monitors.

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

Appendix 4. Hepatic Events

An adverse event record will be flagged as a hepatic event if its MedDRA PT included in the prespecified PT list, which includes all PTs from the broad search of the following 15 SMQs under MedDRA **22.1** provided by Gilead PVE and reviewed by Gilead medical monitors.

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

Appendix 5. Programming Specification

1) AGE calculated as follows: two AGE variables will be derived, one is for randomized phase analysis, and one is for all B/F/TAF analysis.

   I. AGE (years) for randomized phase analysis is calculated from the number of days between the date of birth (DOB) and Day 1 (randomized phase first dose date);

   II. AGE (years) for all B/F/TAF phase analysis is calculated from the number of days between the date of birth (DOB) and Day 1 (first dose date of B/F/TAF);

      a) 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),

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

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

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

   For subjects randomized and never dosed with study drug, age will be calculated from the date of randomization.

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

3) Randomized treatment (ie, TRT01P in ADSL) are 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 randomized study drug and assigned as blank if subject never dosed.

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

5) For disposition table, please follow the following specification to classify subjects into different categories:

		Q2: "Did subject complete study drug dosing as specified per protocol?" during Randomized phase in "Study Drug Completion" eCRF form	Q3: "Did subject complete study drug dosing as specified per protocol?" during Extension study phase in "Study Drug Completion" eCRF form	Q4: "Did the subject complete the protocol planned duration of the study?" in "Study Completion" eCRF form	Case ID
Q1: "Do subject participate in the extension phase of the study?" in "Extension Entry" eCRF	Blank or no Record / No	No	Blank or no Record	No	1
	No	No	Blank or no Record	Yes	2
		Yes	Blank or no Record	Yes	3
	Yes	Yes	No	No	4
		Yes	Yes	Yes	5
		No	No	No	6
		No	Yes	Yes	7

- Subjects completing study drug in the randomized phase are subjects with Case ID 3, 4, and 5.
- Subjects prematurely discontinuing study drug in the randomized phase are subjects with Case ID 1, 2, 6, and 7.
- Subjects completing study in the randomized phase are subjects with Case ID 2, 3, 4, and 5.
- Subjects prematurely discontinuing from study in the randomized phase are subjects with Case ID 1.
- Subjects completing study in the randomized phase and not entering the extension phase are subjects with Case ID 2 and 3
- Subjects who entered extension phase of the study are subjects with Case ID 4, 5, 6, and 7.
- Subjects who entered extension phase of the study and prematurely discontinuing study drug in the extension phase are subjects with Case ID 4 and 6.
- Subjects who entered extension phase of the study and completing study in the extension phase are subjects with Case ID 5 and 7.
- Subjects who prematurely discontinuing study drug in the randomized phase and entered the extension phase are subjects with CaseID 6 and 7.
- Subjects who prematurely discontinuing study drug in the randomized phase and entered and completed in the extension phase are subjects with CaseID 7.
- Data query will be issued for other cases not listed in above table.

6) Body mass index (BMI)

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

- BMI (weight [kg]) / (height [meters]^2)

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

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

a) 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;
```

b) 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;
```

c) 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;
```

Note: “Not Permitted”, “Unknown”, or missing categories will be excluded for percentage calculation and also be 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. For this variable, percentage may add up to be more than 100% and no p-value will be generated.

Subjects with Race “Not Permitted” will also be excluded to define Race subgroup (ie, back vs. nonblack) for efficacy subgroup analysis.

8) SAS code for the treatment comparison for duration of exposure. The p-value from log rank test should be used.

```
proc lifetest data=adsl method=km;
   time TRTDURD*ESDD (0); /*Derived ESDD from COMT01FL, where ESDD
   = 0 indicates censored observation (ie, subject is still on
   study drug)*/
   strata TRT01AN;
   label TRTDURD = "Duration of Exposure (Days)";
run;
```

9) Last Dose Date and Last Study Date

Last Dose Date (ie, TR01EDTC and TR01EDT for randomized phase last dose date, and TR02EDTC and TR02EDT for extension phase last dose date) in ADSL.

Randomized Phase Last Dose Date:

For **B/F/TAF** subjects with a partial last dosing date (ie, month and year of last dose are known), the minimum of {(extension phase first dose date 1 day, if available), (the latest of the dispensing dates of study drug bottles, study drug start dates and end dates (based on EX dataset with Study Phase “Randomized Treatment”), and the imputed last dose date [day imputed as 15])} will be used as the final imputed last dose date. However, if dispensing date’s month is after last dose date’s month, data query is needed. If 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 **SBR** subject with a partial last dosing date (ie, month and year of last dose are known), the minimum of {(extension phase first dose date 1 day, if available), (the latest of the study drug start dates and end dates (based on ARV dataset) and the imputed last dose date [day imputed as 15])} will be used as the final imputed last dose date. However, if dispensing date's month is after last dose date's month, data query is needed. If 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.

Please note the follows:

- When defining randomized phase last dose date for **SBR** subjects, please only include records on "Current" ARV eCRF for the randomized phase of the study, defined as "Current" ARV records with start date prior to the extension phase 1st dose date for subjects entering the extension phase of the study or all "Current" ARV records for subjects not entering the extension phase of the study.
- When defining randomized phase last dose date for **SBR** subjects, subjects might have baseline regimen switched from 1 pill of ATV or DRV to 1 pill of ATV/COBI or DRV/COBI. Such change is not considered as an ARV switch. The randomized phase last dose date will be defined based on the end date of ATV/COBI or DRV/COBI.

Extension Phase Last Dose Date:

For subjects with a partial last dosing date (ie, month and year of last dose are known), the minimum of { (the latest of the dispensing dates of study drug bottles, study drug start dates and end dates (based on EX dataset with Study Phase "Extension Treatment"), and the imputed last dose date [day imputed as 15])} will be used as the final imputed last dose date. However, if dispensing date's month is after last dose date's month, data query is needed. If subject died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date.

Last Study Date is the latest of the randomized or extension phase (if available) study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date. If study drug start dates or end dates is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

10) Toxicity Grades:

Two toxicity grades variables will be derived, one is for randomized phase analysis, and one is for all B/F/TAF analysis. For toxicity grade variable for all B/F/TAF analysis, the baseline will be adjusted based on the first dose of B/F/TAF, as specified in SAP Section 7.2.2.1. As a result, treatment-emergent laboratory abnormalities will be summarized for both randomized phase analysis and all B/F/TAF analysis, respectively, following the same rule bellows.

a) For toxicity grade summaries, include all postbaseline graded results up to 30 days after the last dose of study drug, not just those used in by-visit summaries.

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

12) Graded Laboratory Abnormalities Summary

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

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

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
	Prothrombin Intl. Normalized Ratio (INR)	Increase	N/A
	Prothrombin Time (PT)	Increase	N/A
Urinalysis	Urine Blood	Increase	N/A
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC	Increase	Urine RBC (Hematuria, Quantitative)

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

13) Renal related laboratory evaluation

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

- Urine RBP (ug/L) to creatinine (mg/dL) ratio: 1 (ug/L) / (mg/dL) 100 × ug/g
- Urine Beta-2-microglobulin (mg/L) to creatinine (mg/dL) ratio: 1 (mg/L) / (mg/dL) 10^5 ug/g
- Urine Albumin (mg/dL) to creatinine (mg/dL) ratio: 1 (mg/dL) / (mg/dL) 1000 × mg/g

b) Calculation of ratios:

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

14) Non-study drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Antiviral Medication" listing. Please note that for ARVs recorded on the "Prior ARV" eCRF will NOT be considered as ARVs taken during study. All Prior ARVs with missing end date will be queried to confirm the ARVs were stopped before the randomized phase 1st dose date.

15) Lipid modifying medication analyses:

- Lipid modifying medication is defined to be the concomitant medication with ATC2 term "LIPID MODIFYING AGENTS" and CMDECOD contains wording of "STATIN" in the ADCM dataset.

- Subjects who took lipid modifying medications at first dose of B/F/TAF refer to the subjects who use of the lipid modifying agents at study day 1 of all B/F/TAF analysis. More specifically, subjects with "Lipid Modifying Agent Use at First Dose of B/F/TAF" include those subjects in all B/F/TAF analysis set with: 1) any selected CM record with the start date ≤ the first dose date of B/F/TAF, and 2) the end date of the selected CM record is ongoing or the end date of the selected CM record ≥ the first dose date of B/F/TAF.

- Subjects who initiated lipid modifying medications while subject receiving B/F/TAF includes the following subjects in the all B/F/TAF analysis set: (1) for subjects who permanently discontinued study drug with any selected CM record started after the first dose date of B/F/TAF and on or prior to last dose of B/F/TAF. (2)for subjects who meet criteria (1) above, if they took lipid modification medications before first dose of B/F/TAF, they will NOT be considered initiated lipid modifications while receiving B/F/TAF for the all B/F/TAF analysis.

- For lipid modifying medications with start date completely unknown, we assume the start date is on or before the first dose date of B/F/TAF, lipid modifying medication was considered as being taken at first dose of B/F/TAF if the end date is not prior to the first dose date of B/F/TAF (ie, the end date is on or after the first dose date of B/F/TAF, completely unknown, or ongoing).

- Lipid modifying medications with the start date on or prior to the first dose date of B/F/TAF and the end date completely unknown were considered as being taken at first dose of B/F/TAF.

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

17) Prior ARV regimen

    All subjects will have one of the following prior ARV regimen identified based on ARVs entered in the ARV eCRF.

    - Boosted ATV + ABC/3TC
    - Boosted DRV + ABC/3TC
    - Boosted ATV + FTC/TDF
    - Boosted DRV + FTC/TDF

    Boosted agent is RTV or COBI taken as a separate pill or as a single tablet with protease inhibitor (DRV or ATV). For analysis purpose, we are not interested in type of boosting agent. We would only like to identify PI (ATV or DRV) and NRTI (ABC/3TC or FTC/TDF) used at baseline.

Definition of Prior (Baseline) Regimen: please use ARV dataset and include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT 'Prior ARV" or "Current ARV") with taken on or up to 2 days prior to the randomized phase first dose date excluding ARV.INGRED 'COBI' or "RTV". For subjects with missing prior ARV regimen based on above logics, please apply the ARV start date window up to 14 days prior to the randomized phase first dose date to account for subjects with potential ARV interruption around Study Day 1. Please use the following table to define baseline regimen:

If INGRED contains ONLY the specified ARVs:	Re-code as follows for baseline regimen
ABC 3TC ATV	Boosted ATV + ABC/3TC
ABC 3TC ATV COBI	Boosted ATV + ABC/3TC
ABC 3TC ATV	Boosted ATV + ABC/3TC
ABC 3TC ATV COBI	Boosted ATV + ABC/3TC
3TC ABC DRV	Boosted DRV + ABC/3TC
3TC ABC DRV COBI	Boosted DRV + ABC/3TC
ABC 3TC DRV	Boosted DRV + ABC/3TC
ABC 3TC DRV COBI	Boosted DRV + ABC/3TC
FTC TDF ATV	Boosted ATV + FTC/TDF
FTC TDF ATV COBI	Boosted ATV + FTC/TDF
FTC TDF ATV	Boosted ATV + FTC/TDF
FTC TDF ATV COBI	Boosted ATV + FTC/TDF
FTC TDF DRV	Boosted DRV + FTC/TDF
FTC TDF DRV COBI	Boosted DRV + FTC/TDF
FTC TDF DRV	Boosted DRV + FTC/TDF
FTC TDF DRV COBI	Boosted DRV + FTC/TDF

Note: if subject has ARVs other than specified in the first column above, please leave baseline regimen blank and query for data issues.

18) 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	CNT63	Hep B Surface Ag	"Positive"*, "Positive, Confirmed"*,"Negative"
HBsAg	ATT2	Hep. B Surf. Ag Qual(70) PS	"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 when < 29 IU/mL, NUMERICAL VALUE when ≥ 29 IU/nL**
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**

- 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

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

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 adverse events, the start date must be after the first dose date and on or prior to the last dose date in the randomized phase

  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".

19) 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", 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. If reflexive test is not available, HBV DNA level will be determined based on lab test code GET1883.

20) Clarification for AE

  The TEAE definitions will be applied to the randomized phase data and the extension phase data, separately. When randomized phase data are used, AEs onset date will be compared with the randomized phase first dose date and last dose date and premature discontinuation of study drug refers to study drug discontinuation in the randomized phase. An AE meeting the TEAE criteria will be considered as a TEAE in the randomized phase. When extension phase data are used, AEs onset date will be compared with the extension phase first dose date and last dose date and premature discontinuation of study drug refers to study drug discontinuation in the extension phase. AE meeting the TEAE criteria will be considered as a TEAE in the extension phase.

One AE will be included either in the randomized phase or extension phase, but not both, except that an AE is treatment-emergent in the randomized phase, but continuing into extension phase which will be counted as treatment-emergent for both phases.

When an AE with missing onset date and according to the following rules for incomplete dates, an AE is treatment emergent in the extension phase, then the AE will be included in extension phase and considered treatment emergent in extension phase only.

Events with Missing Onset Day and/or Month

An AE is 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:
    a. The (complete) end date is on or after the first dose date, or
    b. 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
    c. 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.

21) 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 0.10 → round to 3 decimal places
    c) values 0.10 and greater → round to 2 decimal places

22) TSH: Conversions between 2nd and 3rd generations

TSH was analyzed by 2 different assays in the study: 2nd generation (Beckman Coulter, Reference # 33820) and 3rd generation (Beckman Coulter, Reference # B63284). Samples collected before October 14th, 2019 were using TSH 2nd generation assay. Samples collected on or after October 14th, 2019 were using 3rd generation assay. Comparative studies demonstrated that the 2nd and 3rd generations are comparable and the results are showed in the following table. For this analysis, we do not request any conversion and display collected results.

TSH	2nd generation (µIU/mL) (HYPERSensitive TSH) Beckman Material Number 33820	3rd generation(µIU/mL) (TSH 3rd IS) Beckman Material Number 100T; B63284
LLOQ	0.02	0.01
AMR	0.02- 100.0	0.01 – 46.0
ULOQ	3200	3220
RR	Male and Female: 0.34- 5.60	Male and Female* (non-pregnant): 0.45- 5.33
	Serum	
Correlation	Deming Regression	Y= 0.942X +0.1515
	Correlation Coefficient	0.9951
	Bias (% Bias)	-0.327 (-4.059%)

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

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

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

For this analysis, since LDL samples were analyzed by 2nd generation assay at Baseline, we only requested conversion from 3rd generation to 2nd generation.

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

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

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Project Team Leader eSigned	22-Apr-2020 23:33:13
PPD	Biostatistics eSigned	23-Apr-2020 00:30:39