STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults
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CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 4
LIST OF ABBREVIATIONS 5
1. INTRODUCTION 8
1.1. Study Objectives 8
1.2. Study Design 8
1.3. Sample Size and Power 11
2. TYPE OF PLANNED ANALYSIS 12
2.1. Data Monitoring Committee Analyses 12
2.2. Interim Analyses 12
2.2.1. Week 48 Analysis 12
2.2.2. Week 96 Analysis 12
2.2.3. Week 144 Analysis 12
2.3. Final Analysis 12
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 13
3.1. Analysis Sets 13
3.1.1. All Randomized Analysis Set 13
3.1.2. Full Analysis Set 13
3.1.3. Per Protocol Analysis Set 14
3.1.4. Safety Analysis Set 15
3.1.5. DXA Analysis Set 15
3.2. Subject Grouping 15
3.3. Strata and Covariates 15
3.4. Examination of Subject Subgroups 16
3.4.1. Subject Subgroups for Efficacy Analyses 16
3.4.2. Subject Subgroups for Safety Analyses 16
3.5. Multiple Comparisons 16
3.6. Missing Data and Outliers 16
3.6.1. Missing Data 16
3.6.2. Outliers 17
3.7. Data Handling Conventions and Transformations 17
3.8. Analysis Windows 18
3.8.1. Definition of Study Day 18
3.8.2. Analysis Windows 18
3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Window 22
4. SUBJECT DISPOSITION 23
4.1. Subject Enrollment and Disposition 23
4.1.1. Subject Enrollment 23
4.1.2. Subject Disposition 23
4.2. Extent of Study Drug Exposure and Adherence 23
4.2.1. Duration of Exposure to Study Drug 23
4.2.2. Adherence to Study Drug Regimen 24
4.3. Protocol Deviations 25
5. BASELINE CHARACTERISTICS 26
5.1. Demographics and Baseline Characteristics 26

5.2. Baseline Disease Characteristics 26
5.3. Medical History 27
6. EFFICACY ANALYSES 28
6.1. Primary Efficacy Endpoint 28
6.2. Secondary Efficacy Endpoints 28
6.2.1. Definition of the Secondary Efficacy Endpoints 28
6.2.2. Analysis of the Secondary Efficacy Endpoints 29
6.3. Tertiary Efficacy Endpoints 32
6.3.1. Definition of the Tertiary Efficacy Endpoints 32
6.3.2. Analysis of the Tertiary Efficacy Endpoints 32
6.4. Changes From Protocol-Specified Efficacy Analyses 33
7. SAFETY ANALYSES 34
7.1. Adverse Events and Deaths 34
7.1.1. Adverse Event Dictionary 34
7.1.2. Adverse Event Severity 34
7.1.3. Relationship of Adverse Events to Study Drug 34
7.1.4. Serious Adverse Events 34
7.1.5. Treatment-Emergent Adverse Events 34
7.1.6. Summaries of Adverse Events and Death 35
7.1.7. Additional Analysis of Adverse Events 36
7.2. Laboratory Evaluations 37
7.2.1. Summaries of Numeric Laboratory Results 37
7.2.2. Graded Laboratory Values 38
7.2.3. Metabolic Laboratory Evaluations 39
7.2.4. Liver-Related Laboratory Evaluations 40
7.2.5. Renal-Related Laboratory Evaluations 41
7.3. Bone Safety Analyses 42
7.3.1. Bone Mineral Density 42
7.4. Body Weight, Height, and Vital Signs 43
7.5. Prior and Concomitant Medications 43
7.5.1. Nonstudy Drug Antiretroviral Medications 43
7.5.2. Concomitant Non-ARV Medications 44
7.6. Electrocardiogram Results 44
7.7. Other Safety Measures 44
7.8. Changes From Protocol-Specified Safety Analyses 45
8. PHARMACOKINETIC ANALYSES 46
9. SPECIAL POPULATION ANALYSES 47
9.1. Analyses for HIV/HBV Coinfected Subjects 47
9.2. Analyses for HIV/HCV Coinfected Subjects 47
10. REFERENCES 49
11. SOFTWARE 50
12. SAP REVISION 51
13. APPENDICES 52

Appendix 1. Study Procedures Table 53
Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Naïve Trial) 59
Appendix 3. Stratum-Adjusted Mantel-Haenszel Proportion Analysis 60
Appendix 4. Region Definition 61

Appendix 5. Cardiovascular or Cerebrovascular Events 62
Appendix 6. Hepatic Events 63
Appendix 7. Programming Specification 64

LIST OF IN-TEXT TABLES

Table 3-1. Subjects Included or Excluded from Week 144 PP Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 144 Analysis Window 14
Table 3-2. Analysis Windows for HIV-1 RNA, CD4+ cell count, CD4 %, Hematology, Chemistry, Urinalysis, Urine Pregnancy Laboratory Tests, $eGFR_{CG}$, Vital Signs, and Weight 19
Table 3-3. Analysis Windows for Metabolic Assessments 20
Table 3-4. Analysis Windows for TSH and Renal Function 20
Table 3-5. Analysis Windows for HBV and HCV Serology, HBV DNA, and HCV RNA Assessments 21
Table 3-6. Analysis Windows for Safety ECG 21
Table 3-7. Analysis Windows for DXA BMD 21
Table 7-1. Normal, Osteopenia, and Osteoporosis as Defined by T-score 42

LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ABC/DTG/3TC	fixed dose combination of abacavir (ABC) 600 mg / dolutegravir (DTG) 50 mg / lamivudine (3TC) 300 mg
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARV	antiretroviral
ART	antiretroviral treatment
AST	aspartate aminotransferase
BIC	bictegravir
B/F/TAF	fixed dose combination of bictegravir (BIC; B) 50 mg / emtricitabine (FTC; F) 200 mg / tenofovir alafenamide (TAF) 25 mg
BLQ	below limit of quantitation
BMD	bone mineral density
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CG	Cockcroft-Gault
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DC	premature study drug discontinuation
DNA	deoxyribonucleic acid
DTG	dolutegravir, tivicay
DXA	dual energy x-ray absorptiometry
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
F/TAF	fixed dose combination of emtricitabine (FTC; F)/ tenofovir alafenamide (TAF)
FTC, F	emtricitabine
GEN	Genvoya, E/C/F/TAF
GFR	glomerular filtration rate

Gilead	Gilead Sciences, Inc.
GS-9883	bictegravir
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e-antibody
HBeAg	hepatitis B e-antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identification
IDMC	independent data monitoring committee
IWRS	interactive web response system
LDL	low density lipoprotein
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PK	pharmacokinetic
PP	per protocol
PT	preferred term
PVE	Pharmacovigilance and Epidemiology
Q	quartile
Q1	first quartile
Q3	third quartile
QD	once daily
RBP	retinol binding protein
RNA	ribonucleic acid
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class

TAF	tenofovir alafenamide
TFL	tables, figures, and listings
TFV	tenofovir
TSH	thyroid stimulating hormone; thyrotropin
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the Week 144 interim analysis for Study GS-US-380-1489, which will be performed when all subjects have completed their Week 144 visit 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 database finalization for the interim 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 a fixed dose combination (FDC) containing bictegravir (GS-9883; BIC; B) /emtricitabine (FTC; F) /tenofovir alafenamide (TAF) versus a FDC containing abacavir /dolutegravir /lamivudine (ABC/DTG/3TC) in HIV-1 infected, antiretroviral treatment (ART)-naïve adult subjects as determined by the achievement of HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48.

The secondary objectives of this study are:

- To evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Weeks 48, 96, and 144.

- To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Weeks 48, 96, and 144.

1.2. Study Design

Design Configuration and Subject Population

GS-US-380-1489 is a randomized, double-blinded, multicenter, active-controlled study to evaluate the safety and efficacy of B/F/TAF FDC versus ABC/DTG/3TC FDC in HIV-1 infected ART-naive adult subjects.

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:** FDC of bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) + Placebo to match FDC of abacavir 600 mg/ dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) administered orally, once daily, without regard to food (n = 300)

- **Treatment Group 2:** FDC of abacavir 600 mg/dolutegravir 50 mg/ lamivudine 300 mg (ABC/DTG/3TC) + Placebo to match FDC of bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (B/F/TAF) administered orally, once daily, without regard to food (n = 300)

Key Eligibility Criteria

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

- Plasma HIV-1 RNA levels ≥ 500 copies/mL at screening

- ART-naive (≤ 10 days of prior therapy with any antiretroviral [ARV] agent following a diagnosis of HIV-1 infection) except the use for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP), up to 1 month prior to screening.

- Screening genotype report must show sensitivity to FTC, tenofovir (TFV), 3TC, and ABC

- Negative screening test for HLA-B*5701 allele

- Estimated GFR ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance

- No chronic Hepatitis B Virus (HBV) infection, as determined by either

  — Positive HBV surface antigen (HBsAg) and negative HBV surface antibody (HBsAb), regardless of HBV core antibody (HBcAb) status, at the screening visit

  — Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit

Study Periods / Phases

Subjects will be treated for at least 144 weeks during the blinded treatment phase. After Week 144, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completes the Week 144 visit and Gilead Sciences Inc. (Gilead) completes the Week 144 analysis, all subjects

will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of B/F/TAF FDC are demonstrated following review of unblinded data, subjects in a country where B/F/TAF FDC is not available will be given the option to receive B/F/TAF FDC in an open-label (OL) extension phase for up to 48 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead elects to discontinue the study in that country, whichever occurs first.

All subjects participating in the OL extension phase, without regard to their blinded treatment regimen, will return for study visits at Week 12 OL and every 12 weeks thereafter for up to 48 weeks.

Subjects who complete the study through the End of Blinded Treatment Visit and do not continue on the OL B/F/TAF FDC extension phase will be required to return to the clinic after the End of Blinded Treatment Visit for a 30-Day Follow-Up Visit.

Treatment assignments will be provided to the investigators within 30 days of the last subject completing the End of Blinded Treatment Visit.

Schedule of Assessments

After screening procedures, eligible subjects will be randomized 1:1 to Treatment Group 1 or Treatment Group 2 and treated for 144 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 from Week 12 through Week 144. After Week 144, all subjects will continue to take their blinded study drugs and attend study visits every 12 weeks until the End of Blinded Treatment Visit.

For all eligible subjects, blood will be collected at Day 1, Weeks 4, 8, 12, and then every 12 weeks through the End of Blinded Treatment Visit. 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. In addition, blood will be collected and stored for possible evaluation of markers of inflammation and immune activation, which may include but are not limited to: cystatin-C, IL-6, hs-CRP, d-dimer, sCD14, and sCD163. Platelet function evaluations may also be assessed, including but not limited to soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand. Urine will be collected for evaluations of renal function including urine albumin, urine creatinine, urine protein, retinol binding protein (RBP), and beta-2 microglobulin.

For all subjects on study drug, except subjects located in Germany, dual energy x-ray absorptiometry (DXA) scans will be performed prior to or within 24 hours of the Day 1 Visit, and then at Weeks 24, 48, 96, 144 and at the End of Blinded Treatment Visitor Early Study Drug Discontinuation Visit, if > 12 weeks since last scan. DXA scan results will be provided to study sites when available.

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

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

Pharmacokinetics

An intensive pharmacokinetic (PK) substudy will be performed at the Week 4 or 8 visit in a subset of subjects (target n=30) at study sites able to conduct this testing.

For all subjects 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 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 HIV-1 RNA level ($\leq$ 100,000 copies/mL, > 100,000 to $\leq$ 400,000 copies/mL, or > 400,000 copies/mL) at screening, CD4+ cell count (< 50 cells/μL, 50 – 199 cells/μL, or $\geq$ 200 cells/μL) at screening, and region (US or Ex-US) at randomization.

Site and/or Stratum Enrollment Limits

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

Study Duration

The randomized, double-blind phase of this study is at least 144 weeks in duration.

1.3. Sample Size and Power

A total of approximately 600 HIV-1 infected subjects, randomized in a 1:1 ratio to 2 treatment groups (300 subjects per treatment group), achieves at least 95% power to detect a noninferiority margin of 12% in Week 48 response rate (HIV-1 RNA < 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 a response rate of 91% (based on Gilead Genvoya [GEN; E/C/F/TAF] Studies GS-US-292-0104 and GS-US-292-0111), that a noninferiority margin is 12%, and that the significance level of the test is at a one-sided 0.025 level. Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 6.0).

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

The Week 12 Independent Data Monitoring Committee (IDMC) analysis was conducted after approximately the first 50% of 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 either completed their Week 48 visit or prematurely discontinued from the study drug.

2.2.2. Week 96 Analysis

The Week 96 analysis was conducted after all subjects either completed their Week 96 visit or prematurely discontinued from the study drug.

2.2.3. Week 144 Analysis

The Week 144 analysis will be conducted after all subjects either complete their Week 144 visit or prematurely discontinue from the study drug.

This statistical analysis plan describes the analysis plan for the Week 144 interim analysis.

2.3. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

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

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 study drug refers to premature discontinuation of study drug or completion of study drug.

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 the study blind is broken for analysis. The Analysis Set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each Analysis Set will be provided by treatment group and in total.

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

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

3.1.3. Per Protocol Analysis Set

The Week 144 **Per Protocol (PP) Analysis Set** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have not committed any major protocol violation, including the violation of key entry criteria. Subjects will be grouped according to the treatment they actually received. For the PP analysis, efficacy data up to 1 day after permanent discontinuation of study drug will be included. The Week 144 PP Analysis Set is the secondary Analysis Set for efficacy analysis.

Subjects meeting any of the following criteria will be excluded from the Week 144 PP Analysis Set:

- Subjects who do not have on-treatment HIV-1 RNA in the Week 144 analysis window, except when missing is due to discontinuation of study drug for lack of efficacy. (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation in the "Blinded Treatment" study phase on the study drug completion eCRF page; Table 3-1).

Table 3-1. Subjects Included or Excluded from Week 144 PP Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 144 Analysis Window

Discontinuation from Study Drug prior to or on the Upper Bound of Week 144 Analysis Window		HIV-1 RNA Data on Randomized Treatment Available in Week 144 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Other Reasons	+	-
No		+	-

+ = Inclusion of Subjects in Week 144 PP Analysis Set; - = Exclusion of Subjects in Week 144 PP Analysis Set.

- Subjects who do not meet the inclusion criterion that the screening genotype report must show sensitivity to FTC, TFV, ABC, and 3TC

- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in Section 4.3 of the study protocol including drugs not to be used with BIC, FTC, TAF, DTG, ABC, and 3TC

- Nonadherence to study drug: subjects with adherence rate for active study drug up to the Week 144 Visit below the 2.5th percentile

3.1.4. Safety Analysis Set

The **Safety Analysis Set** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study drug. All the data collected up to 30 days after permanent discontinuation of the study drug will be included in the safety summaries, unless specified otherwise. Subjects will be grouped according to the treatment they actually received. This is the primary Analysis Set for safety analyses.

3.1.5. DXA Analysis Set

3.1.5.1. Hip DXA Analysis Set

The **Hip DXA Analysis Set** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have nonmissing baseline hip BMD values. Subjects will be grouped according to the treatment they actually received.

3.1.5.2. Spine DXA Analysis Set

The **Spine DXA Analysis Set** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have nonmissing baseline spine BMD values. Subjects will be grouped according to the treatment they actually received.

For the hip DXA and spine DXA Analysis Sets, all data, including data collected after the last dose of study drug, will be used for analysis, unless specified otherwise.

3.2. Subject Grouping

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

3.3. Strata and Covariates

Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL) at screening, CD4+ cell count (< 50 cells/μL, 50 - 199 cells/μL, or ≥ 200 cells/μL) at screening, and region (US or Ex-US) at randomization.

Efficacy analyses will include 2-level HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) at baseline and region stratum (US vs. Ex-US) at randomization as stratification factors. The CD4+ cell count stratum was excluded for the analysis due to the following reasons: (1) HIV-1 RNA level and CD4+ cell count are highly correlated; (2) a balanced CD4+ cell count distribution between treatment groups is expected since CD4+ cell count was one of the stratification factors used during the randomization; and (3) the risk of including small or missing stratum during the analysis will be reduced. The HIV-1 RNA stratum will be reclassified using baseline HIV-1 RNA level for analysis purposes. Furthermore, since the number of subjects in the HIV-1 RNA > 400,000 copies/mL stratum is small, this stratum will be combined with HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL stratum to form a 2-level HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL). This will prevent small or missing stratum during the analysis.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy Analyses

The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 144 determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be analyzed for the following subject subgroups (see Section 6.2.2.2 for details):

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack
- Baseline HIV-1 RNA level (copies/mL): (a) ≤ 100,000 and (b) > 100,000
- Baseline CD4+ cell count (/μL): (a) < 200 and (b) ≥ 200
- Region: (a) US and (b) Ex-US
- Study drug adherence (%): (a) < 95 and (b) ≥ 95 (based on adherence up to Week 144 visit)

3.4.2. Subject Subgroups for Safety Analyses

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

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

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

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

3.5. Multiple Comparisons

No alpha level adjustment is applied other than for the primary endpoint.

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 medications in Section 7.5.1.

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 HIV-1 RNA and HBV DNA data for efficacy analyses. HIV-1 RNA results of "No HIV-1 RNA detected" and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes. HBV DNA results of "<20 IU/mL HBV DNA detected" or "No HBV DNA detected" will be imputed as 19 IU/mL for analysis purposes. HCV RNA results of "<15 IU/mL HCV RNA detected" or "No HCV RNA detected" will be imputed as 14 IU/mL for analysis purposes.

3.8. Analysis Windows

3.8.1. Definition of Study Day

Study Day 1 is defined as the day when the first dose of study drug (ie, *B/F/TAF or Placebo*, *ABC/DTG/3TC or Placebo*) was taken, as recorded on the Study Drug Administration eCRF form.

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

Last Dose Date is the latest of the blinded study drug end dates recorded on the Study Drug Administration eCRF form with "Permanently Withdrawn" box checked for subjects who prematurely discontinued or completed study drug in the "Blinded Treatment" study phase according to the Study Drug Completion eCRF.

If last dose date is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up) for subjects who prematurely discontinued or completed blinded study drug at the data cut date, the latest of the study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates, excluding the date of 30-day follow-up visit, will be used to impute the last dose date. For other partial missing last dose date, please see the programming specifications for imputation rule details.

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

Baseline value is defined as the last value obtained on or prior to Study Day 1 for all assessments, except for DXA BMD. The baseline value for DXA BMD is defined as the last value obtained on or prior to Study Day 14.

3.8.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for HIV-1 RNA, CD4+ cell count, CD4 %, hematology, chemistry, urinalysis, urine pregnancy laboratory tests, $eGFR_{CG}$, vital signs, and weight are presented in Table 3-2.

Table 3-2. Analysis Windows for HIV-1 RNA, CD4+ cell count, CD4 %, Hematology, Chemistry, Urinalysis, Urine Pregnancy Laboratory Tests, eGFR$_{CG}$, Vital Signs, and Weight

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 108	756	715	798
Week 120	840	799	882
Week 132	924	883	966
Week 144	1008	967	1050
Week K (K is every 12 weeks after previous visit)	K*7	(K-6)*7+1	(K+6)*7

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

Table 3-3. Analysis Windows for Metabolic Assessments

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 120	840	757	924
Week 144	1008	925	1092
Week K (K is every 24 weeks after previous visit)	K*7	(K-12)*7+1	(K+12)*7

The analysis windows for thyroid stimulating hormone (TSH; thyrotropin) and renal function (including urine albumin, urine creatinine, urine protein, urine RBP, and urine beta-2 microglobulin, and derived ratios) are presented in Table 3-4.

Table 3-4. Analysis Windows for TSH and Renal Function

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 120	840	757	924
Week 144	1008	925	1092
Week K (K is every 24 weeks after previous visit)	K*7	(K-12)*7+1	(K+12)*7

The analysis windows for HBV or HCV serology (including HBsAb, HBsAg, hepatitis B e-antigen [HBeAg], hepatitis B e-antibody [HBeAb], HBcAb, and HCV antibody [HCVAb]), HBV DNA, and HCV RNA assessments are presented in Table 3-5.

Table 3-5. Analysis Windows for HBV and HCV Serology, HBV DNA, and HCV RNA Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	504
Week 96	672	505	840
Week 144	1008	841	1176
Week K (K is every 48 weeks after previous visit)	K*7	(K-24)*7+1	(K+24)*7

The analysis windows for safety electrocardiogram (ECG) are presented in Table 3-6.

Table 3-6. Analysis Windows for Safety ECG

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 24	168	2	252
Week 48	336	253	504
Week 96	672	505	840
Week 144	1008	841	1176
Week K (K is every 48 weeks after previous visit)	K*7	(K-24)*7+1	(K+24)*7

The analysis windows for DXA BMD are presented in Table 3-7.

Table 3-7. Analysis Windows for DXA BMD

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			14
Week 24	168	15	252
Week 48	336	253	504
Week 96	672	505	840
Week 144	1008	841	1176
Post Week 144	NA	1177	NA

NA = Not Applicable.
Note: The baseline value of DXA BMD is defined as the last value obtained on or prior to Study Day 14.

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

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

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

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

- For postbaseline visits:

  — For CD4+ cell count, CD4%, and BMD data, 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 BMD data), 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 average will be taken.

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

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

- For baseline, the last available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (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 necessary summaries on subject enrollment have been performed as part of the Week 48 CSR, and will not be repeated for the Week 144 analysis.

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group and overall for all screened subjects. This summary will include the number of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects randomized, subjects randomized but never treated, subjects in the Safety Analysis Set, and subjects in the FAS.

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

- Still on study drug up to the data cut date
- Prematurely discontinuing study drug prior to the data cut date (with summary of reasons for discontinuing study drug)
- Still on study up to the data cut date
- Prematurely discontinuing from study prior to the data cut date (with summary of reasons for discontinuing study).

The denominator for the percentages of subjects in each category will be the number of subjects in the Safety Analysis Set.

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

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be defined as (the last dose date – the first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). For the calculation of the duration of exposure to study drug, the data cut date will be used to impute the last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date.

Duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, eg, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days), ≥ 84 weeks (588 days), ≥ 96 weeks (672 days), ≥ 108 weeks (756 days), ≥ 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. No inferential statistics will be provided.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier (KM) method by treatment group based on the Safety Analysis Set. The log rank test will be used to compare the difference in study drug exposure between the 2 treatment groups. Subjects who are still on the randomized study drug will be censored on the imputed last dose date as defined in this section. A plot of KM estimates for the time to premature discontinuation of study drug by treatment group will be generated.

4.2.2. Adherence to Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts for active drug only (eg, study drug regimen in Treatment Group 1 includes 1 study drug: *B/F/TAF active*. Study drug regimen in Treatment Group 2 includes 1 study drug: *ABC/DTG/3TC active*). The numbers of pills of study drug dispensed and returned are captured on study drug accountability eCRF.

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

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

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

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

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

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

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

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

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

Adherence up to Week 144 visit will also be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who prematurely discontinued study drug or completed study drug, or the Week 144 study drug dispensing date, whichever occurs earliest.

Descriptive statistics for adherence up to the data cut date and adherence up to Week 144 visit for a study drug regimen (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided by treatment group for subjects who return at least 1 bottle and have calculable adherence during the study in the Safety Analysis Set. No inferential statistics will be provided.

4.3. Protocol Deviations

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

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 subject characteristics will be provided for the Safety Analysis Set.

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

5.2. Baseline Disease Characteristics

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

- HIV-1 RNA (log_{10} copies/mL)
- HIV-1 RNA categories (copies/mL): (a) ≤ 100,000, (b) > 100,000 to ≤ 400,000, and (c) > 400,000
- CD4+ cell count (/μL)
- CD4+ cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- Mode of infection (HIV risk factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)
- HIV/HBV coinfection status (Yes/No/Missing, see Section 9.1 for definition)
- HIV/HCV coinfection status (Yes/No/Missing, see Section 9.2 for definition)
- Smoking status: (a) Never Smoker, (b) Former Smoker, and (c) Current Smoker (see Appendix 7 for details)
- Hip BMD and Spine BMD.

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

5.3. Medical History

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

6. EFFICACY ANALYSES

All necessary summaries on the primary efficacy endpoint (at Week 48) and the secondary and tertiary efficacy endpoints at Weeks 48 and 96 have been performed as part of the Week 48 CSR or Week 96 CSR, and will not be repeated for the Week 144 analysis.

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 FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The proportions are expressed as percentages for presentation purposes.

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 analysis.

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 Weeks 96 and 144 as determined by the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 48, 96, and 144 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in log10 HIV-1 RNA and CD4+ cell count at Weeks 48, 96, and 144

The analyses for the secondary efficacy endpoints will be conducted based on the FAS, unless specified otherwise.

6.2.2. Analysis of the Secondary Efficacy Endpoints

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

The analysis window at Week 144 is defined as from Study Day 967 to Study Day 1050, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL:** this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 144 analysis window
- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects
  a. Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 144 analysis window, or
  b. Who do not have on-treatment HIV-1 RNA data in the Week 144 analysis window and
     i. Who discontinue study drug prior to or in the Week 144 analysis window due to lack of efficacy, or
     ii. Who discontinue study drug prior to or in the Week 144 analysis window due to reasons other than adverse event (AE), death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL
- **No Virologic Data in the Week 144 Window:** this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 144 analysis window because of the following:
  a. Discontinuation of study drug prior to or in the Week 144 analysis window due to AE or death (regardless of whether the last available on-treatment HIV-1 RNA < 50 copies/mL or not) or,
  b. Discontinuation of study drug prior to or in the Week 144 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,
  c. Missing data during the window but on study drug.

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

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL , HIV-1 RNA ≥ 50 copies/mL, and reasons for no virologic data at Week 144 will be summarized. The difference in proportion of subjects achieving HIV-1 RNA < 50 copies/mL at Week 144 between treatment groups and the corresponding 95% confidence interval (CI) will be calculated based on

stratum-adjusted Mantel-Haenszel (MH) proportion as described in Appendix 3, where stratification factors include baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US). P-value for comparing the proportion of subjects achieving HIV-1 RNA < 50 copies/mL between treatment groups will be calculated from the CMH test stratified by baseline HIV-1 RNA stratum and region stratum. Above analyses will be performed using both the FAS and the Week 144 PP Analysis Sets. A sensitivity analysis of above secondary endpoint will be performed by excluding the subjects without any postbaseline HIV-1 RNA assessments in the FAS.

In addition, the following analyses will be performed using the FAS to evaluate the interaction between region and treatment to assess homogeneity of treatment effect across different regions.

A region is defined as multiple sites combined based on geographical locations (see Appendix 4 for the region definition).

For each region, the difference in the proportion of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI will be calculated based upon baseline HIV-1 RNA (≤ 100,000 vs. > 100,000 copies/mL) stratum-adjusted MH proportion.

The CMH analysis will be used to estimate the odds ratio and corresponding 95% CI for each region and overall. The homogeneity of the odds ratios across different regions will be tested using a Breslow-Day test and a corresponding p-value will be reported.

As for adjusting randomization stratification for other stratified analyses, region stratum (US vs. Ex-US) will be used.

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

The analysis of virologic response (HIV-1 RNA < 50 copies/mL, US FDA-defined snapshot algorithm) at Week 144 will be performed within each subgroup specified in Section 3.4 based on the FAS.

All subgroup analyses will be conducted using the US FDA-defined snapshot algorithm described in 6.2.2, adjusting for baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. Ex-US), provided that they are not the factors defining the subgroup. For each level of subgroup factors, the proportion difference between the 2 treatment groups and 95% CIs will be computed based on the MH proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. Ex-US), provided that they are not the factor defining the subgroup.

If the sample size in a subgroup is too small to calculate the proportion difference between 2 treatment groups and 95% CIs based on the stratum-adjusted MH proportions, then they will be computed based on normal approximation without stratification.

Additionally, a logistic regression model will be performed which includes the baseline stratification factor(s), subgroup factor, treatment, and treatment by subgroup factor. The baseline stratification factor(s) will include baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) when analyzing region subgroup, region stratum (US vs. Ex-US) when analyzing baseline HIV-1 RNA subgroup, and both baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. Ex-US) when analyzing other subgroups. The odds ratio and the associated 95% CI will be estimated within each subgroup. The homogeneity of the treatment effects between subgroups will be evaluated using a Wald test based on the interaction between treatment and the subgroup factor.

A forest plot of the treatment differences in HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm) at Week 144 and their associated 95% CIs for each subgroup will be generated.

6.2.2.3. Analysis of the Proportion of Subjects with HIV-1 RNA < 20 copies/mL as Determined by US FDA-defined Snapshot Algorithm

Similarly, the proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 144 will be analyzed by the US FDA-defined snapshot algorithm based on FAS. Confidence intervals will be constructed at the 95% level.

6.2.2.4. Analysis of Log_{10} HIV-1 RNA copies/mL and CD4+ Cell Count

All log_{10} HIV-1 RNA data will be summarized using observed values (ie, missing will be excluded). CD4+ cell count will be summarized using observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug) for subjects in the FAS.

The changes from baseline in log_{10} HIV-1 RNA and CD4+ cell count at Week 144 will be summarized by treatment group using descriptive statistics. The differences in changes from baseline in log_{10} HIV-1 RNA and 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, baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL), and region stratum (US vs. Ex-US) as fixed effects. The change from baseline in log_{10} HIV-1 RNA and CD4+ cell count will also be summarized at visits other than Week 144 by treatment group.

The change from baseline in CD4+ cell counts will also be analyzed based on the Week 144 PP Analysis Set.

The mean and 95% CI of change from baseline in log_{10} HIV-1 RNA and CD4+ cell count over time will be plotted for the FAS.

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

- If a value is missing in an analysis visit window, the missing value will be replaced with the last on-treatment value (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug) observed before the analysis visit window that has the missing value.
- Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no nonmissing postbaseline observation collected prior to that visit.

6.3. Tertiary Efficacy Endpoints

6.3.1. Definition of the Tertiary Efficacy Endpoints

CCI [redacted]

6.3.2. Analysis of the Tertiary Efficacy Endpoints

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.4. Changes From Protocol-Specified Efficacy Analyses

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

7. SAFETY ANALYSES

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

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

- Any AEs with an onset date on or after the 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.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The month and year (or year) of the AE onset is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

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

7.1.6. Summaries of Adverse Events and Death

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

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

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

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

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

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

In addition, data listings will be provided for the following:

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

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Stage 3 Opportunistic Illnesses in HIV

On an ongoing basis, AEs will be reviewed for events that might meet the definition of stage 3 opportunistic illnesses in HIV that are indicative of an AIDS-defining diagnoses (see Protocol Appendix 6). The Gilead medical monitor will review the possible stage 3 opportunistic illnesses and approve the events that meet the definition. Events that meet the stage 3 opportunistic illness definition of an AIDS-Defining Diagnosis will be listed.

7.1.7.2. Cardiovascular or Cerebrovascular Events

Preferred terms for defining cardiovascular or cerebrovascular events are from relevant Standardised MedDRA Query (SMQ). The selected PT listing was provided by Gilead PVE and reviewed by Gilead medical monitors (see details in Appendix 5).

The number and percentage of subjects with treatment-emergent cardiovascular or cerebrovascular events and serious cardiovascular or cerebrovascular events by PT will be summarized by treatment group based on the Safety Analysis Set. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test. A data listing of cardiovascular or cerebrovascular events will be provided.

7.1.7.3. Hepatic Events

Preferred terms for 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 6).

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 Safety Analysis Set. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test. A data listing of hepatic events will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

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

7.2.1. Summaries of Numeric Laboratory Results

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

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

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

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

Calcium Corrected for Albumin

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

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

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

Estimated GFR

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

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

7.2.2. Graded Laboratory Values

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

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

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to 30 days after permanent discontinuation of study drug or the last available date for subjects who were still on study drug at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

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

7.2.3. Metabolic Laboratory Evaluations

For metabolic assessments, including fasting glucose and the lipid panel (ie, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized. P-values comparing the difference between the 2 treatment groups in baseline values and the change from baseline in metabolic assessment will be estimated from a 2-sided Wilcoxon rank sum test.

In addition, the number and percentage of subjects who took lipid-modifying medications at study entry and initiated the medications during the study will be provided, respectively. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test.

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

A sensitivity analysis of fasting lipid tests will be performed by excluding subjects who took lipid-modifying medications at study entry or initiated the medications during the study: baseline values, Week 144 values, and changes from baseline at Week 144 will be summarized by treatment group using descriptive statistics. Baseline and change from baseline at Week 144 will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test. Only subjects with both baseline and Week 144 postbaseline values will be included in the analysis.

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 of 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. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

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. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

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

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. Baseline and percentage change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

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. Baseline and change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

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. Baseline and percentage change from baseline will be compared between the 2 treatment groups using a 2-sided Wilcoxon rank sum test.

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, 96, 144 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) {KDIGO Guideline Development Staff 2013}.

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

7.3. Bone Safety Analyses

7.3.1. Bone Mineral Density

7.3.1.1 Percentage Change from Baseline in Hip and Spine Bone Mineral Density

The percentage change from baseline in hip BMD and spine BMD will be summarized by treatment group and visit using descriptive statistics for subjects in the hip and spine DXA Analysis Sets, respectively, and compared between the 2 treatment groups at each visit using ANOVA, which includes treatment as a fixed effect.

As a sensitivity analysis, missing values for hip BMD and spine BMD will be imputed using the LOCF imputation method for the analyses of percentage change from baseline. The algorithm for LOCF is as follows:

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

Similar to the analysis of observed data, the percentage change from baseline in hip BMD and spine BMD by LOCF will also be analyzed using the hip and spine DXA substudy Analysis Sets.

Median (Q1, Q3) and mean (95% CI) of the percentage change from baseline in observed hip BMD and spine BMD over time will be plotted by treatment group. Listings of hip and spine DXA results will be provided.

7.3.1.2 Hip and Spine BMD Clinical Status

Analysis of hip and spine BMD clinical status will based on the observed BMD values (ie, missing will be excluded).

For each subject and each visit, the BMD clinical status will be defined for hip BMD and spine BMD as follows based on the t-score:

Table 7-1. Normal, Osteopenia, and Osteoporosis as Defined by T-score

Clinical Status	BMD T-score
Normal	T-score ≥ -1.0
Osteopenia	-2.5 ≤ T-score < -1.0
Osteoporosis	T-score < -2.5

The number and percentage of subjects in each BMD clinical status (normal, osteopenia, and osteoporosis) will be summarized by visit and by baseline clinical status for both hip and spine. The distribution of the BMD clinical status will be compared between the 2 treatment groups adjusting for baseline clinical status using rank analysis of covariance {LaVange 2008}.

7.3.1.3 Gradation of the Percentage Change in Hip, Femur Neck, and Spine BMD

For each subject and each visit, percentage change from baseline in spine BMD will be classified into 6 categories: ≥ 5% decrease, ≥ 3% to < 5% decrease, > 0% to < 3% decrease, ≥ 0% to < 3% increase, ≥ 3% to < 5% increase, and ≥ 5% increase. Similarly, the percentage change from baseline in Hip BMD and Femur Neck BMD will be classified into 6 categories: ≥ 7% decrease, ≥ 3% to < 7% decrease, > 0% to < 3% decrease, ≥ 0% to < 3% increase, ≥ 3% to < 7% increase, and ≥ 7% increase. The number and percentage of subjects in each category will be summarized by visit. The difference in the distribution of these categories between the treatment groups will be compared using a CMH test (row mean scores differ statistic).

In addition, the number and percentage of subjects with percentage change from baseline in each cumulative categories (ie, ≥ 5% decrease, ≥ 3% decrease, no decrease [≥ 0% increase], ≥ 3% increase, and ≥ 5% increase for Spine BMD; ≥ 7% decrease, ≥ 3% decrease, no decrease [≥ 0% increase], ≥ 3% increase, and ≥ 7% increase for Hip and Femur Neck BMD) will be compared between treatment groups using Fisher exact test based on the dichotomized response (eg, ≥ 5% decrease vs. < 5% decrease).

7.4. 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 3.8.3. No formal statistical testing is planned.

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

7.5. Prior and Concomitant Medications

7.5.1. Nonstudy Drug Antiretroviral Medications

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

7.5.2. Concomitant Non-ARV Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred drug name and drug code will be attached to the clinical database. Use of concomitant medications from Study Day 1 up to the date of last dose of study drug will be summarized (number and percentage of subjects) by treatment group and preferred drug name. Multiple drug use (by preferred drug name) will be counted only once per subject. The summary will be sorted by decreasing total frequency. For drugs 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 of start of the medication is after the date of the last dose of study drug
- The month and year of stop of the medication is before the date of the first dose of study drug

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

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

7.6. 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. 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.

7.7. Other Safety Measures

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

7.8. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

All necessary summaries on pharmacokinetic analyses have been performed as part of Week 48 CSR, and will not be repeated in the Week 144 analysis.

9. SPECIAL POPULATION ANALYSES

9.1. Analyses for HIV/HBV Coinfected Subjects

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

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

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 and on or prior to the date of permanent discontinuation of study drug, or
- Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) after the first dose date and on or prior to the date of permanent discontinuation of study drug, or
- Experience any of the following adverse events (ie, selected MedDRA PTs from the SMQ of "Liver Infections") after the first dose date and on or prior to the date of permanent discontinuation of study drug: 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 adverse events
- 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 HCVAb and quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) on or prior to the first dose date. The following analyses will be provided for subjects with HIV/HCV coinfection at baseline:

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

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

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

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

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

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.

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

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

11. SOFTWARE

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

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

12. SAP REVISION

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

13. APPENDICES

Appendix 1. Study Procedures Table
Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Naïve Trial)
Appendix 3. Stratum-Adjusted Mantel-Haenszel Proportion Analysis
Appendix 4. Region Definition
Appendix 5. Cardiovascular or Cerebrovascular Events
Appendix 6. Hepatic Events
Appendix 7. Programming Specification

Appendix 1. Study Procedures Table

Appendix Table 1. Study Procedures Table (Blinded Phase)

Study Procedures	Screening[a]	Day 1[b]	End of Week[e,r] 4	8	12	24	36	48	60	72	84	96	108	120	132	144	Post-Week 144[e,s] Every 12 Weeks	End of Blinded Treatment Visit[y]	30-Day Follow-up[q]	Early Study Drugs DC[c]
Informed Consent	X																			
Medical History	X																			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	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]	X[d]	X[d]	X	X[d]	X[d]	X[d]	X	X[x], X[d]	X	X[d,f]	X[f]
12-Lead ECG (performed supine)	X	X				X		X				X				X	X[x]	X		X
Questionnaires		X	X		X			X												
DXA scan (spine & hip)[g]		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	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Urine Pregnancy Test[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X																			

Study Procedures	Screening[a]	Day 1[b]	End of Week[e,r] 4	8	12	24	36	48	60	72	84	96	108	120	132	144	Post-Week 144[e,s] Every 12 Weeks	End of Blinded Treatment Visit[y]	30-Day Follow-up[q]	Early Study Drugs DC[c]
Chemistry Profile[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X[f]
Metabolic Assessments[j]		X			X	X		X		X		X		X		X	X[t]	X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]	X
Hematology Profile[k]	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X
HLA-B*5701[w]	X																			
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluations of inflammation and immune activation, platelet function and renal tubular function		X				X		X		X		X		X		X	X[t]	X		
Plasma & Urine Storage Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
HBV and HCV Serology	X							X				X				X	X[X]			
HIV-1 Genotype[l]	X[l]																			
HIV-1 Genotype/ Phenotype[e]																				X[e]
Single PK Sample[m]				X		X	X													
Trough PK Samples[n]			X		X															

Study Procedures	Screening[a]	Day 1[b]	End of Week[e,r] 4	8	12	24	36	48	60	72	84	96	108	120	132	144	Post-Week 144[e,s] Every 12 Weeks	End of Blinded Treatment Visit[y]	30-Day Follow-up[q]	Early Study Drugs DC[c]
CCI																				
Randomization[v]		X																		
Provide subject dosing diary to subjects		X	X	X	X	X														
CCI																				
Study Drug Dispensation		X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[u]		
Study Drug Accountability			X	X	X	X	X	X	X	X	X	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 at the Day 1 visit, with the exception of DXA.
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 End of Blinded Treatment 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 (Protocol Section 6.14.1 and Section 6.14.2).
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 DXA scans to be performed in all eligible subjects on study drug during blinded treatment only, except for those in Germany, prior to or within 24 hours of the Day 1 Visit, Weeks 24, 48, 96, 144 (±10 days), and at the End of Blinded Treatment Visit (±10 days) and the ESDD visit (if the last scan was acquired > 12 weeks from the date of the ESDD Visit).
h Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.

i 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, 72, 96, 120, 144, and every 24 weeks post Week 144, and End of Blinded Treatment Visit, 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, 72, 96, 120, 144, and every 24 weeks post Week 144, End of Blinded Treatment Visit and Early Study Drugs Discontinuation visit.

j 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.

k CBC with differential and platelet count.

l The Investigator must have received the results from the screening genotype report before proceeding with the Day 1 visit. Screening genotype report must show sensitivity to TFV, FTC, 3TC and ABC. If genotype results from a local laboratory obtained ≤ 90 days prior to screening visit date show sensitivity to these drugs, this genotype will be acceptable to fulfill this inclusion criterion in the event that the genotype obtained at screening is not yet available and all other inclusion/exclusion criteria have been confirmed.

m A single PK blood sample will be collected at any time pre or post-dose

n A trough PK blood sample will be collected between 20-28 hours following the last dose. Following an observed dose, a single post dose blood sample will be collected between 1 and 4 hours post dose.

[redacted]

q Only required for those subjects not enrolling in the open-label rollover extension or those subjects who prematurely discontinue study drugs and do not continue in the study through at least one subsequent visit after the Early Study Drugs Discontinuation Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.

r 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 132, unless otherwise specified. The visit window at Weeks 48 and 96, 144 will be ± 6 weeks of the protocol-specified visit date.

s After Week 144, subjects will continue to take their blinded study drug and attend visits every 12 weeks until the End of Blinded Treatment Visit. Visit window of ± 6 days for study visits post Week 144.

t To be performed every 24 weeks after Week 144 until End of Blinded Treatment Visit.

u Open-label study drug, GS-9883/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover extension for up to 48 weeks.

v 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.

w The Investigator must have received a negative screening test for HLA-B*5701 allele before proceeding with the Day 1 visit. If HLA-B*5701 results are available from a local laboratory prior to screening, this report will be acceptable to fulfill this inclusion criterion in the event that the HLA-B*5701 result obtained at screening is not yet available and all other inclusion/exclusion criteria have been confirmed.

x To be performed every 48 weeks after Week 144 until the End of Blinded Treatment Visit.

y Once the last subject completes the Week 144 visit and Gilead completes the Week 144 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of GS-9883/F/TAF FDC is demonstrated following review of unblinded data, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC in an OL extension phase for up to 48 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead elects to discontinue the study in that country, whichever occurs first.

Appendix Table 2. Study Procedures Table (Open-Label Rollover Extension)

Study Procedures	End of Blinded Treatment Visit[a]	End of Week[e,l]				30-Day Follow-up[k]	Early Study Drugs DC[c]
		12 OL	24 OL	36 OL	48 OL		
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X[f]	X[f]
Complete/Symptom-Directed Physical Exam	X	X[d]	X[d]	X[d]	X	X[d,f]	X[f]
12-Lead ECG (performed supine)	X				X		
DXA scan (spine & hip)[m]	X						
Vital signs (blood pressure, pulse, respiration rate, and temperature), including Weight	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X[f]	X[f]
Urine Pregnancy Test[g]	X	X	X	X	X	X	X
Chemistry Profile[h]	X	X	X	X	X	X[f]	X[f]
Metabolic Assessments[i]	X		X		X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X[f]	X
Hematology Profile[j]	X	X	X	X	X	X[f]	X[f]
Plasma HIV-1 RNA	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X
Evaluations of inflammation and immune activation, platelet function and renal tubular function	X						
Plasma & Urine Storage Sample	X	X	X	X	X		X
HBV and HCV Serology					X		
HIV-1 Genotype/Phenotype[e]							X[e]

Study Procedures	End of Blinded Treatment Visit[a]	End of Week[e,l]				30-Day Follow-up[k]	Early Study Drugs DC[c]
		12 OL	24 OL	36 OL	48 OL		
Study Drug Dispensation	X[b]	X	X	X			
Study Drug Accountability	X	X	X	X	X		X

a Once the last subject completes the Week 144 visit and Gilead completes the Week 144 analysis, all subjects will return to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of GS-9883/F/TAF FDC is demonstrated following review of unblinded data, subjects in a country where GS-9883/F/TAF FDC is not available will be given the option to receive GS-9883/F/TAF FDC in an OL extension phase for up to 48 weeks, or until the product becomes accessible to subjects through an access program, or until Gilead elects to discontinue the study in that country, whichever occurs first.

b Open-label study drug, GS-9883/F/TAF FDC will be dispensed to subjects participating in the Open-Label Rollover extension for up to 48 weeks.

c Subjects who discontinue study drug during the OL rollover extension portion of the study will be asked to return to the clinic within 72 hours of stopping study drugs for the Early Study Drugs Discontinuation Visit followed by a 30-Day Follow-Up Visit. The subject will not continue attending the scheduled study visits.

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 (Protocol Section 6.14.1 and Section 6.14.2)

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 $> 1.5 \times$ ULN). At Week 24 OL and Week 48 OL, and End of Blinded Treatment Visit, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile. For all subjects, TSH will be done at the End of Blinded Treatment Visit, Week 24 OL, Week 48 OL, and Early Study Drug Discontinuation Visit.

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 CBC with differential and platelet count.

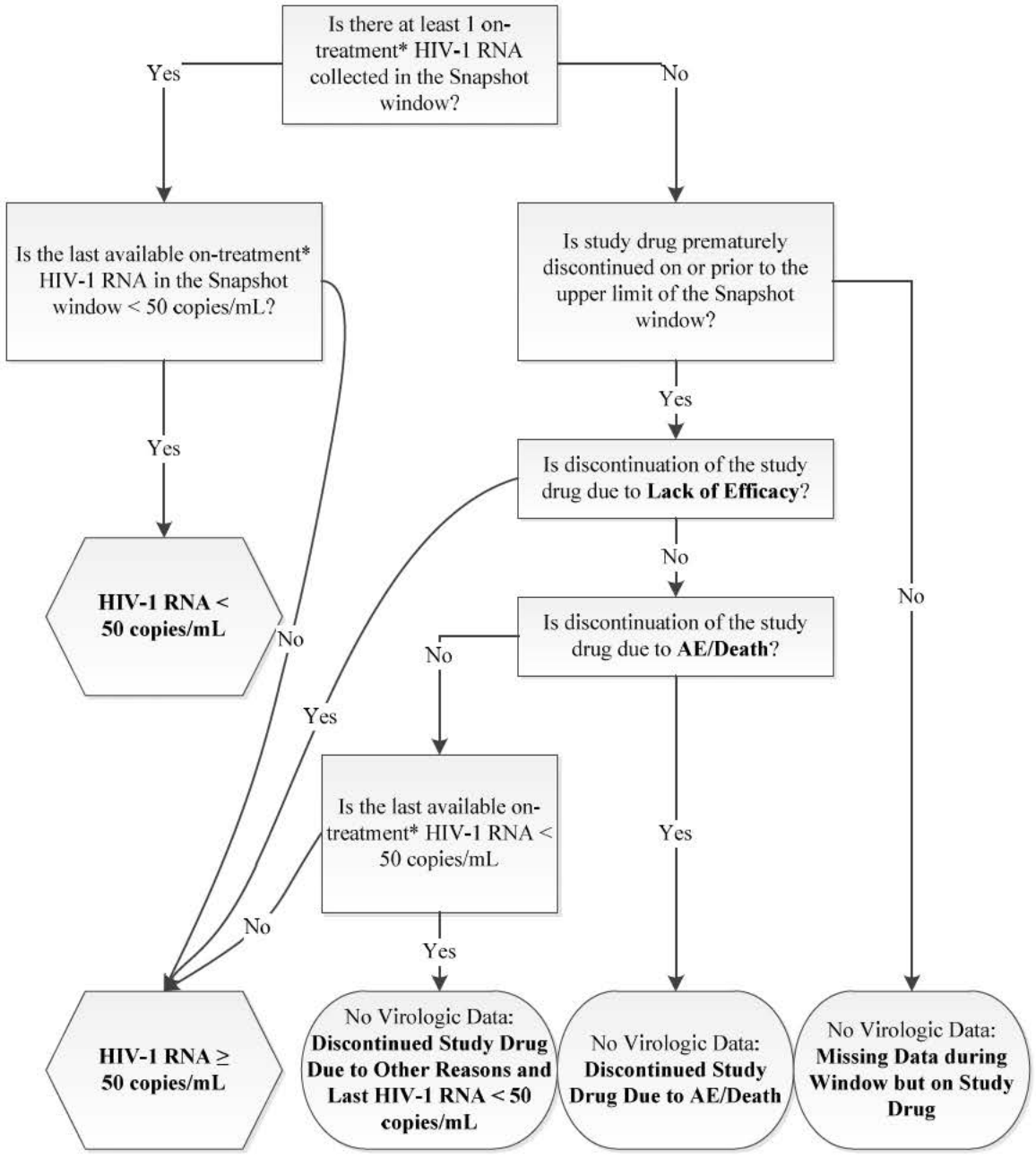
k Subjects who complete the open-label rollover extension will be required to return to the clinic 30 days after the completion of study drugs for the 30-Day Follow-Up Visit. Subjects who prematurely discontinue study drugs during the open-label rollover extension will be asked to return to the clinic 30 days after the completion of the Early Study Drugs Discontinuation Visit for the 30-Day Follow-Up Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a $\pm$ 6 days window may be used.

l Study visits are to be completed within $\pm$ 6 days of the protocol-specified visit date every 12 weeks thereafter, unless otherwise specified

m DXA scans to be performed in all eligible subjects on study drug, except for those in Germany, only at the End of Blinded Treatment Visit ($\pm$10 days).

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

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



* On-treatment data include all data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug.

Appendix 3. Stratum-Adjusted Mantel-Haenszel Proportion Analysis

The baseline stratum weighted difference in the response rate ($P_1 - P_2$) and its (1 - α/2)% CI will be calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion as described as follows {Koch 1989}, where stratification factors include baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. Ex-US):

$$P_1 - P_2 \pm Z_{(1-\alpha/2)} * SE(P_1 - P_2),$$

where

- $(P_1 - P_2) = \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h = p_{1h} - p_{2h}$ is the difference in the response rate between of the Treatment Groups 1 and 2 in stratum h (h = 1 to 4).

- $w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{1h} and n_{2h} are the sample sizes of the Treatment Groups 1 and 2 in stratum h.

- $SE(P_1 - P_2) = \sqrt{\frac{\sum w^2 \left[\frac{p^*_{1h}(1-p^*_{1h})}{n_{1h}-1} + \frac{p^*_{2h}(1-p^*_{2h})}{n_{2h}-1} \right]}{(\sum w_h)^2}}$, where $p^*_{1h} = \frac{m_{1h} + 0.5}{n_{1h} + 1}$ and $p^*_{2h} = \frac{m_{2h} + 0.5}{n_{2h} + 1}$. m_{1h} and m_{2h} are the number of subjects with HIV-1 RNA < 50 copies/mL in the Treatment Groups 1 and 2 in stratum h.

- α = 0.05 for this study

- $Z_{(1-\alpha/2)} = Z_{0.975} = 1.96$ is the 97.5th percentile of the normal distribution

Note that if the computed lower confidence bound is less than –1, the lower bound is defined as -1. If the computed upper confidence bound is greater than 1, the upper bound is defined as 1.

Appendix 4. Region Definition

Region	Country Name	State	No. of Subjects in Safety Analysis Set or FAS (N=629)	Total No. of Subjects by Region in Safety Analysis Set or FAS (N=629)
Region 1	CANADA (CAN)		33	33
Region 2	BELGIUM (BEL)		6	132
	FRANCE (FRA)		21	
	GERMANY (DEU)		13	
	ITALY (ITA)		18	
	SPAIN (ESP)		43	
	UNITED KINGDOM (GBR)		31	
Region 3	UNITED STATES (USA)	CA	56	63
	UNITED STATES (USA)	WA	7	
Region 4	UNITED STATES (USA)	AZ	15	104
	UNITED STATES (USA)	CO	6	
	UNITED STATES (USA)	NM	4	
	UNITED STATES (USA)	TX	79	
Region 5	UNITED STATES (USA)	IN	3	53
	UNITED STATES (USA)	MI	15	
	UNITED STATES (USA)	MN	6	
	UNITED STATES (USA)	MO	12	
	UNITED STATES (USA)	OH	16	
	UNITED STATES (USA)	WI	1	
Region 6	UNITED STATES (USA)	DC	13	39
	UNITED STATES (USA)	MA	3	
	UNITED STATES (USA)	NJ	5	
	UNITED STATES (USA)	NY	8	
	UNITED STATES (USA)	PA	10	
Region 7	UNITED STATES (USA)	AL	14	106
	UNITED STATES (USA)	GA	49	
	UNITED STATES (USA)	LA	3	
	UNITED STATES (USA)	NC	34	
	UNITED STATES (USA)	SC	6	
Region 8	DOMINICAN REPUBLIC (DOM)		3	99
	UNITED STATES (USA)	FL	89	
	UNITED STATES (USA)	PR*	7	

* 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 5. 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 22.0 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 6. Hepatic Events

An adverse event record will be flagged as a hepatic event if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the broad search of the following 15 SMQs under MedDRA 22.0 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 7. Programming Specification

1) AGE calculated as follows:

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

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

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

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

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

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

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

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

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

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

6) Enrollment by Stratum: using actual HIV-1 RNA or CD4+ cell count screening value, the last screening value (with visitnum < 0) prior to randomization date and time.

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

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

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

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

   Baseline height and weight will be used for this calculation.

9) 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 data=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 data=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;
```

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

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

11) 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); /*Derive 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;
```

12) Last Dose Date and Last Study Date

a) Last Dose Date (ie, TRTEDTC, TRTEDT, TR01EDT or TR01EDTC) in ADSL was defined in Section 3.8.1.

For subjects with a partial last dosing date (ie, month and year of last dose are known), the latest of the dispensing dates of study drug bottles, study drug start dates and end dates, and the imputed last dose date [day imputed as 15] will be used as the final imputed last dose date. However if 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.

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

For Week 144 interim analysis, *04/19/2019* will be the data cut date for subjects with Week 144 visits on or prior to *04/19/2019,* subjects missing Week 144 visits while on study drug, or subjects prematurely discontinued study drug. For subjects with Week 144 visit after *04/19/2019*, the last subject's Week 144 visit will be used as the data cut date as appropriate.

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

If subject died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date. Last study date is not defined for subjects still on study in SAP. However, for programing purposes, the latest of data cut date, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, will be used to impute the last study date for subjects still on study.

13) Toxicity Grades:

a) For toxicity grade summaries, include all post-baseline 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 nonfasting 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.

14) Efficacy analyses:

a) For categorical efficacy response (eg, Subjects with HIV-1 RNA < 50 copies/mL as determined by US FDA-defined snapshot algorithm, M=F, or M=E Analyses): the proportion difference between two treatment groups and its 95.002% or 95% CIs are calculated based on the MH proportion adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. Ex-US) (see Appendix 3 for details). To test superiority, the p-value from 2-sided CMH test (ie, general association test) stratified by baseline HIV-1 RNA stratum and region stratum should be used, where *brnac* is the baseline HIV-1 RNA stratum, *region* is the region stratum, *trtgrp* is the treatment, and *response* is the categorical efficacy response. The following SAS code will be used to compute cell counts and p-value.

```
proc freq data=adeff;
      tables brnac*region*trtgrp*response/cmh; /*p value from
      general association*/
run;
```

b) Homogeneity test: Homogeneity Test of Treatment Effect Across Region in HIV-1 RNA < 50 copies/mL at Week 144 (Snapshot Algorithm). For each region, the odds ratio and its 95% CI are calculated from the CMH test. For overall, the odds ratio and its 95% CI are calculated based on the common odds ratio estimate from the CMH test. The p-value for the homogeneity test is based on the Breslow-Day test of the interaction between region and treatment group as follows.

```
proc freq data=adeff;
      tables region2*trtgrp*response/all; /*p value from Breslow Day
test*/
run;
```

c) Subgroup analyses

i) For the subgroups of age, sex, race, baseline CD4+ cell count, and study drug adherence, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **baseline HIV-1 RNA stratum and region stratum** (see Appendix 3 for details). For example, for the age subgroup, the following SAS code will be used to compute cell counts.

```
proc sort data=adeff;
   by agegrp brnac region;
proc freq data=adeff;
   by agegrp;
   tables brnac*region*trtgrp*response/cmh;
run;
```

ii) For the baseline HIV-1 RNA subgroup, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **region stratum** only. The following SAS code will be used to compute the cell counts.

```
proc sort data=adeff;
   by brnac region;
proc freq data=adeff;
   by brnac;
   tables region*trtgrp*response/ cmh;
run;
```

iii) For the region subgroup, the proportion difference between two treatment groups and its 95% CIs are calculated based on the MH proportion adjusted by **baseline HIV-1 RNA stratum** only. The following SAS code will be used to compute the cell counts.

```
proc sort data=adeff;
   by region brnac;
proc freq data=adeff;
   by region;
   tables brnac*trtgrp*response/ cmh;
run;
```

d) Homogeneity test: Homogeneity Test of Treatment Effect between Subgroups in HIV-1 RNA < 50 copies/mL at Week 144 (Snapshot Algorithm)

i) For the subgroups of age, sex, race, baseline CD4+ cell count, and study drug adherence, the odds ratio and the associated 95% CIs are estimated for the response variable (response; coded as 1 for success and 0 for non-success) using a logistic regression model including treatment (trtgrp; coded as 1 for active [ie, B/F/TAF] and 2 for control), baseline HIV-1 RNA stratum (brnac; coded as 1 for < 100,000 copies/mL and 2 for >= 100,000 copies/mL), region stratum (region; coded as 1 for "US" and 2 for "Ex-US"), subgroup factor (coded as 1 for the first subgroup and 2 for the second subgroup), and treatment by subgroup factor. For example, for the age subgroup (agegrp; coded as 1 for < 50 and 2 for >= 50), the following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup:

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

```
proc genmod data=data descending; /*model for success*/
   class trtgrp brnac region agegrp;
   model response = trtgrp brnac region agegrp
trtgrp*agegrp/dist=bin     link=logit lrci;
   estimate 'Group 1' trtgrp 1 -1 trtgrp*agegrp 1 0 -1 0/exp;
   estimate 'Group 2' trtgrp 1 -1 trtgrp*agegrp 0 1 0 -1/exp;
run;
```

ii) For the baseline HIV-1 RNA subgroups, the odds ratio and the associated 95% CIs are estimated using a logistic regression model including treatment, region stratum, subgroup factor, and treatment by subgroup factor. The following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup (the same formats as described in (a) above are assumed):

```
proc genmod data=data descending;
   class trtgrp region brnac;
   model response = trtgrp region brnac trtgrp* brnac/dist=bin
   link=logit lrci;
   estimate 'Group 1' trtgrp 1 -1 trtgrp*brnac 1 0 -1 0/exp;
   estimate 'Group 2' trtgrp 1 -1 trtgrp*brnac 0 1 0 -1/exp;
run;
```

iii) For the region subgroups, the odds ratio and the associated 95% CIs are estimated using a logistic regression model including treatment, baseline HIV-1 RNA stratum, subgroup factor, and treatment by subgroup factor. The following SAS code will be used to generate the Odds Ratio and its 95% CI within the subgroup (the same formats as described in (a) above are assumed):

```
proc genmod data=data descending;
   class trtgrp brnac region;
   model response = trtgrp brnac region trtgrp*region/dist=bin
   link=logit lrci;
   estimate 'Group 1' trtgrp 1 -1 trtgrp*region 1 0 -1 0/exp;
   estimate 'Group 2' trtgrp 1 -1 trtgrp*region 0 1 0 -1/exp;
run;
```

iv) Clarification for SE(P1-P2) Calculation in Appendix 3

- if n_{1h} or $n_{2h} > 1$ the denominator $n_{1h} - 1$ or $n_{2h} - 1$ was calculated as indicated in the formula;
- if n_{1h} or $n_{2h} = 1$, the corresponding n_{1h} or n_{2h} will be adjusted to 2, then corresponding denominator $[(n_{1h} - 1)$ or $(n_{2h} - 1)]$ is 1;
- if n_{1h} or $n_{2h} = 0$ but not both n_{1h} and $n_{2h} = 0$ then not calculable;
- if both n_{1h} and $n_{2h} = 0$ then the corresponding stratum will be ignored, will not be included in the calculation, thus the proportion difference and 95% CI are still calculable.

If the sample size in a subgroup is too small to calculate the proportion difference between 2 treatment groups and its 95% CI based on the stratum-adjusted MH proportion, then a 95% CI based on the normal approximation will be used. For example, if the stratum-adjusted MH proportion cannot be calculated for sex = "Female" subgroup, the following code will be used to calculate the proportion difference and 95% CI based on the normal approximation, ie, *riskdiff* option in *tables* statement will provide the proportion difference and 95% CI estimations.

```
proc freq data = adeff;
   where sex = "F";
   tables trtgrp*response/ riskdiff(CL=(WALD));
run;
```

e) ANOVA model for continuous efficacy variable (eg, CD4+): The differences in changes from baseline in CD4+ cell count between treatment groups and the associated 95% CI will be constructed using an ANOVA, including baseline HIV-1 RNA stratum, region stratum, and treatment as fixed effects in the model.

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

f) Listing for US FDA-defined snapshot outcome:

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

i) HIV-1 RNA ≥ 50 copies/mL - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL

ii) No virologic Data - Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL

15) DXA Analysis:

a) Variable used for analysis:

i) Variable CORRBMD when Region = "SpineTotalAdequate" for spine, Region = "FemurTotal" for hip, and Region = "FemurNeck" for femur neck will be used for percentage change from baseline in BMD analysis.

ii) Variable CORRTSCR when Region = "SpineTotalAdequate" for spine and Region = "FemurTotal" for hip will be used for defining the BMD clinical status.

b) BMD clinical status comparison: Rank Analysis of covariance. *base* is the baseline BMD clinical status and *post* is the post baseline clinical status (both coded as 0 for normal, 1 for Osteopenia, 2 for Osteoporosis, . for missing). The p-value from row mean score test from the last proc freq procedure is the p-value for rank analysis of covariance.

```
proc rank data=addxa nplus1 ties=mean out=ranks1;
      var base post;
      rank baserank postrank;
run;

proc reg data=ranks1;
      model postrank=baserank;
      output out=residual1 r=resid;
run;

proc freq data=residual1;
      tables trtgrp*resid/noprint cmh2; /* row mean score test*/
run;
```

16) TEAE

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.

17) 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)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
Urinalysis	Urine Blood (Dipstick)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*

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

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

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

18) 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).

19) Smoking status at baseline

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Nonstudy-Drug Antiviral Medication" listing. The logic to define concomitant nonstudy-drug ARV is similar to concomitant non-ARV Medications (see details in Section 7.5.2)

21) 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 study entry refer to the subjects who use of the lipid-modifying agents at study day 1 (ie, the first dose date). More specifically, subjects with "Lipid Modifying Agent Use at Study Entry" include those subjects in Safety Analysis Set with: 1) any selected CM record with the start date ≤ the first dose date, 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.
- Subjects who initiated lipid-modifying medications during the study include the subjects in the Safety Analysis Set who didn't take lipid-modifying medications at study entry and met the following criteria: 1) for subjects who permanently discontinued study drug with any selected CM record started after the first dose date and on and prior to the last dose date; 2) for subjects who are still on study drug with any selected CM records started after the first dose date.
- For lipid-modifying medications with the start date completely unknown, we assume the start date is on or before the first dose date, lipid-modifying medication was considered as being taken at study entry if the end date is not prior to the first dose date (ie, the end date is on or after the first dose date, completely unknown, or ongoing).
- Lipid modifying medications with the start date prior to the first dose date and the end date completely unknown were considered as being taken at study entry.

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

23) 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**
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

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

  — 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".

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

25) 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	Clinical Research eSigned	14-May-2019 00:44:08
PPD	Biostatistics eSigned	15-May-2019 15:48:51