STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed on Regimens Containing ABC/3TC
Name of Test Drug:	Emtricitabine/Tenofovir Alafenamide (F/TAF)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATP	adult treatment panel
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
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CTx	C-type collagen sequence
CV	coefficient of variation
DC	premature study drug discontinuation
DXA	dual-energy x-ray absorptiometry
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate using Cockcroft-Gault formula
ESDD	early study drug discontinuation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
F/TAF	emtricitabine/tenofovir alafenamide (Descovy®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (Truvada®)
GFR	glomerular filtration rate

GSI	Gilead Sciences, Inc.
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high level group term
HLT	high level term
DMC	data monitoring committee
IXRS	interactive response system
LDL	low-density lipoprotein
LLT	lowest level term
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
NCEP	National Cholesterol Education Program
PI	protease inhibitor
PK	pharmacokinetic
PP	per-protocol
PT	preferred term
P1NP	procollagen type I N-terminal propeptide
Q	quartile
Q1	first quartile
Q3	third quartile
RBP	retinol binding protein
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TFL	tables, figures, and listings
TFV	tenofovir
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
WHO	World Health Organization

1. INTRODUCTION

GS-US-311-1717 is a Phase 3b, randomized, double-blind, switch study to evaluate emtricitabine/tenofovir alafenamide (F/TAF) in HIV-1 infected subjects who are virologically suppressed on regimens containing abacavir/lamivudine (ABC/3TC).

1.1. Study Objectives

The primary objective of this study is:

- To evaluate the efficacy of switching ABC/3TC to F/TAF versus maintaining ABC/3TC in HIV-1 infected subjects who are virologically suppressed on regimens containing ABC/3TC as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives of this study are:

- To evaluate the efficacy, safety and tolerability of two regimens through Week 48 and Week 96

- To evaluate the bone safety of two regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48 and Week 96

1.2. Study Design

1.2.1. Design Configuration and Subject Population

GS-US-311-1717 is a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of switching ABC/3TC fixed-dose combination (FDC) tablet to F/TAF FDC tablet versus continuing ABC/3TC in HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing ABC/3TC for ≥ 6 consecutive months prior to screening.

1.2.2. 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 two treatment arms:

- **Treatment Arm 1:** F/TAF + Placebo-to-match ABC/3TC; third antiretroviral agent remains the same (n = 250)

- **Treatment Arm 2:** ABC/3TC + Placebo-to-match F/TAF; third antiretroviral agent remains the same (n = 250)

1.2.3. Key Eligibility Criteria

HIV-1 infected adult subjects who meet the following criteria:

- Currently receiving an antiretroviral regimen containing ABC/3TC in combination with one third agent for ≥ 6 consecutive months prior to screening

- Plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay) and not experienced two consecutive HIV-1 RNA measurements above detectable levels after achieving a confirmed (two consecutive) HIV-1 RNA measurement below detectable levels on the current regimen in the past year. Plasma HIV-1 RNA should be < 50 copies/mL at the screening visit

- Estimated glomerular filtration rate ≥ 50 mL/min (Cockcroft-Gault formula).

1.2.4. Study Periods/Phases

Subjects will be treated for 96 weeks in the double-blind randomized phase. After Week 96, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded. After unblinding, in countries where F/TAF FDC is not commercially available, subjects (except in certain countries such as UK) will be given the option to receive the open-label F/TAF FDC and attend study visits every 12 weeks until it becomes commercially available, or until Gilead Sciences terminates the study in that country. Subjects who complete the study through Unblinding Visit and do not wish to receive open-label F/TAF FDC will be required to return to the clinic for a 30-Day Follow Up visit.

After the Unblinding Visit, subjects in certain countries (eg UK) per requirement must stop taking study drug and complete a 30-Day Follow Up visit.

1.2.5. Schedule of Assessments

After screening, eligible subjects will be randomized to Treatment Arm 1 or 2 and treated for 96 weeks. Following the Screening and Day 1 visits, subjects will return for study visits at Weeks 4, 8, 12, and then every 12 weeks through Unblinding Visit.

Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4 cell count, and complete or symptom directed physical examinations will be performed at the Screening, Day 1, and all subsequent study visits.

For all subjects excluding those in Germany, dual energy x-ray absorptiometry (DXA) scans will be performed prior to study drug administration at Day 1, every 24 weeks, Unblinding Visit, and the Early Study Drug Discontinuation (ESDD) visit, if > 12 weeks since last scan. Scans will cover the spine and hip to measure changes in bone mineral density. Analyzed DXA scans will be provided to study sites when available.

Blood and urine for selected evaluations of renal tubular function and bone turnover will be collected at Day 1, Weeks 4, 12, 24, 48, 72, 96 and ESDD (if applicable). In addition, blood will be collected and stored at Day 1, Weeks 4, 12, 24, 48, 72, and 96 and ESDD (if applicable) for possible evaluation of inflammation and immune activation, including cystatin-C, IL-6, hs-CRP, d-dimer, sCD14, and sCD163. Platelet function evaluations will also be assessed, including soluble glycoprotein VI (sGPVI), P-selectin, and soluble CD40 ligand.

A single PK blood sample will be collected any time pre or post-dose at Weeks 8, 12, 24, and 36. At Weeks 4 and 48, the single PK blood sample will be collected between 15 minutes and 4 hours post-dose.

CCI [redacted]

Subjects who complete the study through the Unblinding Visit and do not wish to continue to participate will be required to return to the clinic 30 days after the completion of the study drug for a 30-Day Follow-up Visit.

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

1.2.6. Randomization

Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment arms (Treatment Arm 1: Treatment Arm 2). Randomization will be stratified by the third agents (boosted protease inhibitors [LPV/r, ATV+RTV, ATV+COBI (or ATV/COBI FDC), DRV+RTV, DRV+COBI (or DRV/COBI FDC)] vs. others) in a subject's existing regimen. A block size of 4 was used for randomization.

1.2.7. Site and/or Stratum Enrollment Limits

Approximately 100 centers in North America and Europe will participate. There is no enrollment limit for individual sites.

1.2.8. Study Duration

The randomized, double-blind phase of this study is 96 weeks in duration.

1.3. Sample Size and Power

A total of approximately 500 HIV-1 infected subjects, randomized in a 1:1 ratio to two arms (250 subjects per arm), achieves at least 90% power to detect a non-inferiority margin of 10% in Week 48 response rate (HIV-1 RNA < 50 copies/mL as determined by the US FDA-defined snapshot algorithm) difference between the two groups. For sample size and power computation, it is assumed that both treatment arms have a response rate of 0.87, that a non-inferiority margin is 0.10, and that the significance level of the test is at a one-sided 0.025 level.

2. TYPE OF PLANNED ANALYSIS

2.1. Week 12 Data Monitoring Committee (DMC) Analysis

The Week 12 DMC analysis was conducted after the first 250 subjects who were enrolled completed the Week 12 visit or prematurely discontinued study drug. The purpose of this interim analysis was to provide the DMC with a statistical report for review. More details are documented in the DMC charter.

2.2. Week 24 DMC Analysis

The Week 24 DMC analysis was conducted after all subjects who were randomized and received study drug by 23 May 2016 had completed the Week 24 visit or prematurely discontinued study drug. The purpose of this interim analysis was to provide the DMC with a statistical report for review. More details are documented in the DMC charter.

2.3. Week 48 Analysis

The planned overall sample size per the protocol (Section 8.9 Sample Size) was approximately 500 subjects, CCI [redacted] CCI [redacted] leading to enrollment of 556 subjects total, CCI [redacted]

The interim Week 48 analysis was conducted when the planned sample size of subjects (n = 500) reached (or prematurely discontinued study drug prior to) the primary timepoint of interest (Week 48). The efficacy analysis using FDA snapshot algorithm included subjects who were randomized and received study drug on or before 23 May 2016 (n = 501). The safety analysis included all subjects who were randomized and received study drug ever (n = 556).

2.4. Final Analysis

The final statistical analysis for the study will be conducted after all subjects have completed the study. At the time of the final analysis, all subjects will have completed the Week 96 visit or have prematurely discontinued study drug.

This statistical analysis plan (SAP) describes the analysis plan for the final analysis.

Since there were two interim DMC analyses prior to the Week 48 analysis, an alpha penalty of 0.00001 was applied for each interim DMC meeting. Therefore, the alpha level for the primary endpoint analysis at Week 48 was adjusted to 0.04998.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The final analysis will include the double-blind phase analysis and the open-label phase analysis.

For the double-blind phase analysis, all available data from the double-blind phase (ie. data collected on or before the first dose of open-label F/TAF) will be included. Adverse events and concomitant medications with a start date on or after the first dose of the open-label F/TAF will be excluded from the double-blind phase analysis.

For the open-label phase analysis, all available data from the open-label phase will be included. Adverse events with a start date before the first dose of open-label F/TAF will be excluded from the open-label phase analysis.

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. 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 includes all subjects who are randomized into the study. This is the primary analysis set for by-subject listings, which include both double-blind phase and open-label phase data.

3.1.2. Full Analysis Set

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

3.1.3. Per-Protocol Analysis Set

The Week 96 Per-Protocol (PP) Analysis Set will include all subjects who (1) were randomized into the study, (2) received at least one dose of study medication, and (3) did not report 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 the last dose date of the randomized double-blind study drug will be included. The Week 96 PP analysis set is the secondary analysis set for the efficacy analysis.

Subjects meeting any of the following criteria will be excluded from the Week 96 PP analysis set:

- Subjects who do not have on-treatment HIV-1 RNA in the Week 96 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 on the study drug completion electronic Case Report Form [eCRF] page) (Table 3-1).

Table 3-1. Subjects Excluded from Week 96 PP Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 96 Analysis Window

Discontinuation from Study Drug Prior to or on the Upper Bound of Week 96 Analysis Window		HIV-1 RNA Data on Randomized Treatment Available in Week 96 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Other Reasons	+	-
No		+	-

+ = Inclusion of Subjects in Week 96 PP analysis set; - = Exclusion of Subjects in Week 96 PP analysis set

- Subjects who do not meet the key inclusion criterion that plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay) and not experienced 2 consecutive HIV-1 RNA above detectable levels after achieving a confirmed (2 consecutive) HIV-1 RNA below detectable levels on the current regimen in the past year

- Subjects who do not meet the key inclusion criterion that plasma HIV-1 RNA levels < 50 copies/mL at Screening Visit

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

- Subjects who do not meet the key inclusion criterion of receiving an antiretroviral regimen containing ABC/3TC FDC in combination with one third agent for ≥ 6 consecutive months prior to screening

- Nonadherence to study drug: subjects with adherence rate for the randomized active study drug (F/TAF or ABC/3TC) up to the Week 96 visit below the 2.5th percentile

- Subjects who were taking a third agent that is not allowed per protocol

3.1.4. Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who have received at least one dose of study drug. All the data collected up to 30 days after subjects permanently discontinue their study regimen during the double-blind phase will be included in the safety summaries, unless specified otherwise. Subjects will be grouped according to the treatment they actually received.

3.1.5. DXA Analysis Set

3.1.5.1. Hip DXA Analysis Set

The Hip DXA Analysis Set will include all subjects who are randomized and have received at least one dose of study drug, and 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 are randomized and have received at least one dose of study drug, and have nonmissing baseline spine BMD values. Subjects will be grouped according to the treatment they actually received.

3.1.6. Open-Label F/TAF Analysis Set

The Open-label F/TAF Analysis Set includes all subjects who received at least 1 dose of the open-label F/TAF during the open-label phase of study. This is the primary analysis set for all open-label phase analysis.

3.2. Subject Grouping

For efficacy analysis using FAS, subjects will be grouped by randomized treatment. For all other analyses, subjects will be grouped by actual treatment received.

For the double-blind phase efficacy and safety analysis, subjects will be grouped into the following:

- F/TAF group: This group includes all subjects who were randomized to F/TAF during the double-blind phase of the study.
- ABC/3TC group: This group includes all subjects who were randomized to ABC/3TC during the double-blind phase of the study.

For the open-label phase efficacy and safety analysis, subjects will be grouped into the following groups:

- F/TAF group: This group includes all subjects who were randomized to F/TAF in the double-blind phase of this study and then received open-label F/TAF in the open-label phase.
- ABC/3TC to F/TAF group: This group includes all subjects who were randomized to ABC/3TC in the double-blind phase of this study and then switched to open-label F/TAF in the open-label phase.

Treatment comparisons will only be made between F/TAF and ABC/3TC for the double-blind phase analysis.

3.3. Strata and Covariates

Randomization was stratified by the third agents (boosted protease inhibitors [PIs] vs. other agents) in a subject's existing regimen.

3.4. Examination of Subject Subgroups

The virologic outcome at Week 96 determined by the US FDA-defined snapshot algorithm will be analyzed for the following subject subgroups:

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack
- Ethnicity: (a) Hispanic or Latino and (b) not Hispanic or Latino
- Third agent stratum: (a) boosted PIs and (b) other agents
- Region: (a) US (b) ex-US
- Study drug adherence (%): (a) < 95 and (b) ≥ 95 (based on adherence up to Week 96 visit for the virologic outcome at Week 96)

3.5. Multiplicity Adjustments

The noninferiority evaluation of the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (snapshot algorithm) is the pre-specified primary comparison. However, 2 interim DMC analyses were performed prior to analysis for the primary endpoint and an alpha penalty of 0.00001 was applied for each interim DMC meeting. Therefore, the alpha level for the primary endpoint — snapshot algorithm of virologic outcome at Week 48 was adjusted to 0.04998.

No multiplicity adjustment will be 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 permanently discontinuing from the study before reaching the window

In general, values for missing data will not be imputed, unless specified otherwise.

3.6.2. Outliers

Outliers will be identified during 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 analysis.

3.7. Data Handling Conventions and Transformations

Data (eg, HIV-1 RNA) 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 one 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" (x is considered as the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9 will be used for calculation of summary statistics, respectively.

- A value that is one unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (x is considered as 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 data is reported in the form of "≤ x" or "≥ x" (x is considered as the limit of quantitation).

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

For direct bilirubin, value of "< 0.1" is imputed as 0.09.

3.8. Analysis Windows

3.8.1. Definition of Study Day 1 and Other Definitions

Study Day 1 for the Double-blind Phase is defined as the day when the first dose of the blinded study drug (ie, F/TAF or Placebo, or ABC/3TC or Placebo) was taken, as recorded on the double-blind Study Drug Administration eCRF form.

Last Dose Date for the Double-blind Phase is the earliest of the last dosing dates of the blinded study drug (ie, F/TAF or Placebo, or ABC/3TC or Placebo) and the third agent in a subject's study regimen.

For the blinded study drug, the last dosing date is the latest nonmissing end date recorded on the double-blind Study Drug Administration eCRF form with "Study Drug Permanently Withdrawn" box checked for subjects who prematurely discontinued study drug or who completed study drug according to the double-blind Study Drug Completion eCRF. If the last dose date for the blinded study drug is missing for subjects who prematurely discontinued study drug (eg, due to lost to

follow-up) or completed study drug in the double-blind phase, the latest of nonmissing blinded study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the date of 30-day follow-up visit, from the double-blind phase data, will be used to impute the last dosing date for the blinded study drug. For other partial missing last dose date, please see programming specification for imputation rule details.

The third agent in a subject's existing treatment regimen is the ARV medications (excluding ABC and 3TC) that a subject was taking immediately prior to the first dose date for the double-blind phase of the study (ie, ARV start date < the first dose date of blinded study drug and ARV end date ≥ the first dose date of blinded study drug − 1). The last dosing date of the third agent is recorded on the ARV eCRF form. For an ARV which is marked as current but not ongoing on the ARV eCRF form, if the ARV end date is missing (eg, due to lost to follow-up), the latest of all available nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates from both the double-blind phase and the open-label phase of the study excluding the date of 30-day follow-up visit will be used to impute the end date of this ARV. For the third agent, the last dose date will be the same for the double-blind phase analysis or the open-label phase analysis.

If the third agent is ongoing, then the last dose date of the study regimen for the double-blind phase will be the last dosing date of the blinded study drug (F/TAF or Placebo, or ABC/3TC or Placebo).

Study Day 1 for the Open-label Phase is defined as the day when the first dose of open-label F/TAF was taken.

Last Dose Date for the Open-label Phase is the earliest of the last dosing dates of open-label F/TAF and the third agent in a subject's study regimen.

For open-label F/TAF, the last dosing date is the maximum, nonmissing end date of study drug, recorded on the open-label Study Drug Administration eCRF form with "Study Drug Permanently Discontinued" box checked for subjects who prematurely discontinued study drug or who completed study drug according to the open-label Study Drug Completion eCRF.

If the third agent is ongoing, then the last dose date of the study regimen for the open-label phase will be the last dosing date of the open-label study drug (open-label F/TAF).

If the last dose date is missing for subjects who prematurely discontinued study drug in the open-label phase of the study, the latest of nonmissing open-label study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates, excluding the date of 30-day follow-up visit, from the open-label phase data, will be used to impute the open-label phase last dose date.

Study Days for the double-blind phase or the open-label phase are calculated relative to Study Day 1 for the double-blind phase or the open-label phase, respectively. For events that occurred on or after the Study Day 1 date, study days are calculated as (visit date minus date of the first

dose plus 1). For events that occurred prior to Study Day 1, study days are calculated as (visit date minus date of the first dose).

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

Baseline Values for the Double-blind Phase for HIV-1 RNA, CD4 cell count, CD4%, hematology, chemistry, urinalysis and urine chemistry laboratory tests, eGFRs estimated by CG and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) methods, vital signs, weight, safety electrocardiogram (ECG), renal and bone biomarkers, are defined as the last nonmissing value obtained on or prior to **Study Day 1 for the double-blind phase**. The baseline value of DXA BMD is defined as the last nonmissing value on or prior to **Study Day 14 for the double-blind phase**.

Baseline Values for the Open-label Phase for HIV-1 RNA, CD4 cell count, hematology, chemistry, urinalysis and urine chemistry laboratory tests, eGFRs estimated by CG and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) methods, are defined as the last nonmissing value obtained on or prior to **Study Day 1 for the open-label phase**. Data collected on or prior to the first dose date of the open-label F/TAF will be used to derive the open-label phase baseline values.

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. Due to different visit schedules between the double-blind phase and the open-label phase, analysis visit windows will be assigned separately for the double-blind phase analysis and the open-label phase analysis.

The analysis windows for HIV-1 RNA, CD4 cell count, CD4%, hematology, chemistry, urine chemistry laboratory tests, eGFRs (by CG and CKD-EPI), vital signs and weight are presented in Table 3-2 and Table 3-3.

Table 3-2. Analysis Windows for HIV-1 RNA, CD4 Cell Count, CD4%, Hematology, Chemistry, Urine Chemistry Laboratory Tests, eGFRs (by CG and CKD-EPI), Vital Signs and Weight for Double-Blind Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	546
Week 84	588	547	630
Week 96	672	631	714
Week 108	756	715	798
Week 120	840	799	882
Week 132	924	883	966
Week 144	1008	967	1050
Week k	k*7	(k-6)*7+1	(k+6)*7

Note: The above analysis window will also be used for urine protein to creatinine ratio (UPCR). For cystatin C, the analysis window in Table 3-6 will be applied.
Note: Week k is every 12 weeks after previous visit.

Table 3-3. Analysis Windows for HIV-1 RNA and CD4 Cell Count for Open-label Phase Analysis

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 12	84	2	126
Week 24	168	127	210
Week k	k*7	(k-6)*7+1	(k+6)*7

Note: Week k is every 12 weeks after previous visit.
Note: Nominal Day is relative to the Unblinding visit.

The analysis windows for lipid panel and BMD results from DXA are presented in Table 3-4.

Table 3-4. Analysis Windows for Lipid Panel and BMD Results from DXA for Double-Blind Phase Analysis

	Lipid Panel			BMD Results from DXA		
Visit ID	**Nominal Day**	**Lower Limit**	**Upper Limit**	**Nominal Day**	**Lower Limit**	**Upper Limit**
Baseline			1			14
Week 24	168	2	252	168	15	252
Week 48	336	253	420	336	253	420
Week 72	504	421	588	504	421	588
Week 96	672	589	756	672	589	756
Week 120	840	757	924	840	757	924
Week 144	1008	925	1092	1008	925	1092
Week k	k*7	(k-12)*7+1	(k+12)*7	k*7	(k-12)*7+1	(k+12)*7

Note: The baseline value of DXA BMD is defined as the last value on or prior to Study Day 14.
Note: Week k is every 24 weeks after previous visit.

The analysis windows for safety ECG are presented in Table 3-5.

Table 3-5. Analysis Windows for Safety ECG for Double-Blind Phase Analysis

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

Note: Week k is every 48 weeks after previous visit.

The analysis windows for renal and bone biomarkers including retinol binding protein (RBP) to creatinine ratio, beta-2-microglobulin to creatinine ratio, serum C-type collagen sequence(CTx), and serum bone procollagen type I N-terminal propeptide (P1NP) are presented in Table 3-6.

Table 3-6. Analysis Windows Renal and Bone Biomarkers for Double-Blind Phase Analysis

Visit ID	**Nominal Day**	**Lower Limit**	**Upper Limit**
Baseline			1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	252
Week 48	336	253	420
Week 72	504	421	588
Week 96	672	589	756
Post Week 96	N/A	757	N/A

Note: For renal biomarker UPCR, the analysis window in Table 3-2 will be applied.
N/A = Not applicable.

3.8.3. Selection of Data in the Event of Multiple Records in a Window

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

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

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic or geometric mean, as appropriate) will be computed for that day.

- For postdose visits:

  — For efficacy data (ie, HIV-1 RNA level, CD4 cell count, and CD4%) and BMD data, the latest record in the window will be selected.

  — For other numeric observations, the record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected.

  — If there is more than one record on the selected day, the average will be taken (geometric mean for HIV-1 RNA and arithmetic mean for others).

If multiple valid nonmissing categorical observations (eg, safety ECG results) exist in a window, records will be chosen as follows:

- For baseline, the last available record on or prior to the date of the first dose of the study drug will be selected.

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

The number and percentage of subjects randomized in each country and by each investigator will be summarized by treatment group and overall. The denominator for this calculation will be the number of subjects in the Safety Analysis Set. Similarly, the number and percentage of subjects enrolled in each randomization stratum (ie, boosted PIs vs. others) will be summarized by treatment group based on interactive response system (IXRS) data.

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

4.2. Disposition of Subjects

The summary of subject disposition will be provided by treatment group and overall.
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 not treated, subjects in the Safety Analysis Set, subjects in the FAS and subjects in the Open-label F/TAF Analysis Set.

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

- Completing the study treatment in the double-blind phase
- Prematurely discontinuing study treatment in the double-blind phase (with summary of reasons for discontinuing blinded study drug)
- Completing the study drug in the double-blind phase and not entering the open-label phase
- Entering the open label phase and treated
- Completing study drug in the open-label phase
- Prematurely discontinuing study drug in the open-label phase (with summary of reasons for discontinuing study drug)
- Completing study in the double-blind phase
- Prematurely discontinuing from the study in the double-blind phase (with summary of reasons for discontinuing study)
- Completing the study in the open-label phase
- Prematurely discontinuing from study in the open-label phase (with summary of reasons for discontinuing study)

The denominator for the percentages of subjects in each of the above categories will be the number of subjects in the safety analysis set.

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

4.3. Extent of Exposure

All data for study drug administration and accountability will be listed.

4.3.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be calculated for both the double-blind phase study drug and the open-label phase study drug.

Duration of exposure to study drug will be defined as (last dose date – first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to one decimal place, eg, 4.5 weeks).

Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, standard deviation [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), ≥ 16 (112 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), ≥ 48 weeks (336 days), ≥ 60 weeks (420 days), ≥ 72 weeks (504 days), ≥ 84 weeks (588 days), ≥ 96 weeks (672 days), ≥ 108 weeks (756 days), ≥ 120 weeks (840 days), etc.

Summaries of duration of exposure to the double-blind phase study drug will be provided by treatment group for subjects in the Safety Analysis Set. Summaries of duration of exposure to the open-label phase study drug will be provided by treatment group for subjects in the Open-label F/TAF Analysis Set. No inferential statistics will be provided.

Time to permanent discontinuation of the double-blind phase study drug will be analyzed using the Kaplan-Meier method based on the Safety Analysis Set. The log rank test will be performed to compare the differences in the distribution of time to study drug discontinuation between treatment groups. Subjects who completed the double-blind phase study drug will be censored on the last dose date for the double-blind phase as defined in this Section 3.8.1.

4.3.2. Adherence with Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts for the active double-blind drug only (ie, adherence in Treatment Arm 1 only includes double-blind F/TAF and not placebo or the third agents). The numbers of pills of each study drug dispensed and returned are captured on study drug accountability forms.

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

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

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

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

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

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

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

Overall adherence for the double-blind study drug will be calculated for each subject for 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.

Adherence for the double-blind study drug up to the Week 96 visit will also be calculated for each subject.

The number and percentage of subjects who return at least 1 bottle and have calculable adherence during the double-blind phase of the study, descriptive statistics for overall adherence and adherence up to the Week 96 visit for a study drug regimen (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided on study drug regimen adherence.

4.4. Protocol Deviations

A listing will be provided for subjects in the safety analysis set who violated at least one inclusion or exclusion criterion. The listing will include the criteria not met. A listing of subjects who received the wrong study treatment will also be provided.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

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

In addition, the following baseline characteristics and medical history will be summarized:

- Third agent in a subject's pre-existing treatment regimen
- HIV-1 RNA categories (copies/mL): (a) < 50 and (b) ≥ 50
- CD4 cell count (/μL)
- CD4 cell count categories (/μL) (a) < 50, (b) 50 to 199, (c) 200 to 349, (d) 350 to 499, and (e) ≥ 500
- CD4 percentage (%)
- Mode of infection (HIV risk factors)
- HIV disease status
- HBV Surface Antigen Status
- HCV Antibody Status
- Estimated GFR by CG and CKD-EPI creatinine methods
- Medical history: diabetes (Yes/No), hypertension (Yes/No), cardiovascular disease (Yes/No), and hyperlipidemia (Yes/No) (see Appendix 5)
- Smoking status: (a) Never Smoker, (b) Former Smoker, and (c) Current Smoker

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (general association statistic for nominal data, and row mean scores differ statistic for ordinal data) will be used to compare the 2 treatment groups (ie, F/TAF+3rd Agent vs. ABC/3TC+3rd Agent). For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

5.2. Medical History

A listing of HIV/acquired immune deficiency syndrome (AIDS)-specific medical history and general medical history (ie, conditions not specific to the disease being studied) data will be provided.

6. EFFICACY ANALYSES

This section describes the double-blind phase analyses of the efficacy data. Open-label phase analyses of the efficacy data will be conducted only when it is specified (Section 6.4).

For the double-blind phase analyses, all available data from the double-blind phase (ie. data collected on or before the first dose of open-label F/TAF) will be included. For the open-label phase analyses, all available data from the open-label phase will be included.

6.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 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 purpose.

6.1.1. US FDA-Defined Snapshot Algorithm

The analysis window at Week 48 is defined as from Study Day 295 to Study Day 378, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after the last dose date of study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome 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 48 analysis window
- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects
    1) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window, or
    2) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and
        a) Who discontinue study drug prior to or in the Week 48 analysis window due to lack of efficacy, or
        b) Who discontinue study drug prior to or in the Week 48 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL or
        c) Who discontinue study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL

- **No Virologic Data (in the Week 48 analysis window):** this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window because of the following:

  1) Discontinuation of study drug prior to or in the Week 48 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL or

  2) Discontinuation of study drug prior to or in the Week 48 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA is < 50 copies/mL, or

  3) Missing data during the window but on study drug

The flowchart of the US FDA-defined snapshot algorithm is provided in Appendix 3.

The term "Study Day" in the texts above refers to the Study Day defined for the double-blind phase; the term "study drug" in the texts above refers to the blinded phase study drug.

The Week 48 virologic outcomes for the US FDA-defined snapshot algorithm will be listed (Appendix 2, Appendix Listing 1).

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

- **Null Hypothesis:** the F/TAF+3rd Agent group (Treatment Group 1) is at least 10% lower than the ABC/3TC+3rd Agent group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL ("response rate", as determined by the US FDA-defined snapshot algorithm) at Week 48.

- **Alternative Hypothesis:** the F/TAF+3rd Agent group (Treatment Group 1) is less than 10% lower than the ABC/3TC+3rd Agent group (Treatment Group 2) with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL ("response rate", as determined by the US FDA-defined snapshot algorithm) at Week 48.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The analysis purpose of the primary efficacy endpoint is to assess the noninferiority of treatment with F/TAF+3rd Agent relative to treatment with ABC/3TC+3rd Agent. Noninferiority will be assessed using a two-sided exact 95% confidence interval (CI) approach, with a noninferiority margin of 10%. The exact confidence interval will be estimated based on unconditional exact methods using 2 inverted 1-sided tests with the standardized statistic. The primary analysis will be based on the FAS.

For each interim analyses performed by the DMC at Weeks 12 and 24, an alpha of 0.00001 has been spent. Therefore, the significance level for the 2-sided test in the primary analysis at Week 48 will be 0.04998 (corresponding to 95.002% CI).

It will be concluded that switching to F/TAF is noninferior to maintaining ABC/3TC if the lower bound of the 2-sided 95.002% CI of the difference (F/TAF+3rd Agent group – ABC/3TC+3rd Agent group) in the response rate is greater than −10%.

The number and percentage of subjects having HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL, and reasons for no virologic data at Week 48 will be summarized (Appendix 2, Appendix Table 1).

If noninferiority of F/TAF+3rd Agent versus ABC/3TC+3rd Agent is established, the same 95.002% CI used in evaluating noninferiority at Week 48 will be used to evaluate superiority. If the lower bound of the 95.002% CI is greater than 0, superiority of F/TAF+3rd Agent over ABC/3TC+3rd Agent will be established. Fisher's exact test will also be used to assess superiority as a secondary assessment.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- The proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Weeks 48 and 96 as determined by the US FDA-defined snapshot algorithm specified in Section 6.1.1 and Appendix 3
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm specified in Section 6.1.1 and Appendix 3
- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 48 and 96 as determined by the US FDA-defined snapshot algorithm specified in Section 6.1.1 and Appendix 3
- The change from baseline in CD4 cell count at Weeks 48 and 96

6.2.2. Analysis for Secondary Efficacy Endpoints

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

6.2.2.1. Snapshot Algorithm for Secondary Efficacy Endpoints

In the snapshot algorithm for the Week 96 virologic outcome, the analysis window is defined as from Study Day 631 to Study Day 714 (inclusive).

The proportion of subjects with HIV-1 RNA < 50 copies/mL or HIV-1 RNA < 20 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm will be analyzed using the same method as the primary analysis for the primary endpoint based on both the FAS

(Appendix 2, Appendix Table 1) and Week 96 PP analysis sets, except that confidence intervals will be constructed at 95% level.

The proportion of subjects with HIV-1 RNA $\geq$ 50 copies/mL at Weeks 48 and 96 will be analyzed using the same method as described for the primary endpoint (Appendix 2, Appendix Table 1), except that confidence intervals will be constructed at 95% level for the proportion of subjects with HIV-1 RNA $\geq$ 50 copies/mL at Week 96. Noninferiority of treatment with F/TAF+3rd Agent relative to treatment with ABC/3TC+3rd Agent will be assessed based on the exact CI for the failure rates, with a non-inferiority margin of 4%.

The proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm will also be analyzed using the same method as the primary analysis for the primary endpoint, except that confidence intervals will be constructed at 95% level.

6.2.2.2. Subgroup Analysis for the Virologic Outcome at Week 96

The analysis of virologic response at Week 96 (HIV-1 RNA < 50 copies/mL, US FDA-defined snapshot algorithm) will be performed within each subgroup specified in Section 3.4 using the FAS.

All subgroup analyses will be conducted using the US FDA-defined snapshot algorithm described in Section 6.1.1.

For each level of subgroup factors, the proportion difference between treatment groups and 95% CIs will be computed using the same method as described for the primary endpoint (Appendix 2, Appendix Table 2).

Additionally, a logistic regression model will be performed including the third agent stratum factor, subgroup factor, treatment, and treatment by subgroup factor. 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 Wald test based on the interaction between treatment and subgroup factor (Appendix 2, Appendix Table 3).

6.2.2.3. Analysis of CD4 Cell Count

The analysis of CD4 cell count will be based on on-treatment data (ie, up to 1 day after the last dose date of the double-blind phase study drug).

The changes from baseline in CD4 cell count at Week 96 will be summarized by treatment group using descriptive statistics based on observed data (ie, missing will be excluded). The differences in changes from baseline in CD4 cell count between treatment groups and the associated 95% CI will be constructed using analysis of variance (ANOVA) models, including treatment and the third agent stratum (boosted protease inhibitors vs. others) as fixed effects in the model.

The change from baseline in CD4 cell count will also be summarized at the visits other than Week 96 using observed data.

The change from baseline in CD4 cell counts will also be analyzed using the Week 96 PP analysis set.

The mean and 95% CI of change from baseline in CD4 cell count over time will be plotted using observed data for FAS and Week 96 PP analysis sets, respectively.

In addition, the change from baseline in CD4 cell counts with missing values imputed using last observation carried forward (LOCF) imputation method will be summarized at each visit up to Week 96 using 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, up to 1 day after the last dose date of 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 non-missing postbaseline observation prior to this visit.

6.3. Tertiary Efficacy Endpoints

6.3.1. Definition of Tertiary Efficacy Endpoints

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6.4. Open-Label Phase Analysis

The proportion of subjects with HIV-1 RNA < 50 copies/mL as defined by the M = E method will be summarized by visit and treatment group based on the Open-Label F/TAF Analysis Set. The proportion of subjects with HIV-1 RNA < 20 copies/mL and not detectable, and HIV-1 RNA < 20 copies/mL and detectable, will be summarized separately.

The analysis of CD4 cell count will be based on on-treatment data (ie, up to 1 day after the last dose date of the open-label phase study drug). The changes from baseline in CD4 cell count will be summarized by visit and treatment group using descriptive statistics based on the Open-Label F/TAF Analysis Set.

6.5. Changes From Protocol-Specified Efficacy Analyses

The following secondary endpoints were added in the SAP:

- The proportion of subjects with HIV-1 RNA $\geq$ 50 copies/mL at Weeks 48 and 96 as determined by the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 48 and 96 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4 cell count at Weeks 48 and 96.

7. SAFETY ANALYSES

This section describes the double-blind phase analyses of the safety data. For the double-blind phase analyses, all available safety data from the double-blind phase of the study (ie. data collected on or before the first dose of open-label F/TAF) will be included. All safety data collected up to 30 days after the last dose date of double-blind phase study drug will be summarized by treatment group for the subjects in the Safety Analysis Set, except for proteinuria by quantitative assessment based on on-treatment data (Section 7.4.5).

For the double-blinde phase analysis, the terms "study drug start date (ie, the first dose date)", "study drug stop date (ie, the last dose date)", and "baseline" in the text below refer to the first dose date, the last dose date, and baseline defined for the double-blinde phase analysis; the term "study drug" in the text below refer to the blinded phase study drug.

Open-label phase analyses of the safety data will be conducted only when it is specified (Section 7.9).

All safety data collected during the study including the open-label phase will be included in data listings.

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Lower Level Term (LLT) will be attached to the clinical database.

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 study protocol Appendix 4. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related adverse events are those for which the investigator selected "Related" to the question "Related to Study Treatment?" in the eCRF. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purpose. However, by-subject data listings will show relationship as missing.

7.1.4. Relationship of Adverse Events to Study Procedure

Adverse events for which 'Yes' is marked for question 'Related to Study Procedures?' in the eCRF will be identified and included in AE listing.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the eCRF, where 'Yes' was marked for 'AE serious'. 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.

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are:

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

For the double-blind phase analysis, the term "study drug" refers to the double-blind phase study drug. For the open-label phase analysis, the term "study drug" refers to the open-label phase study drug.

7.1.6.2. Incomplete Dates

If the date of onset is incomplete or completely missing, the detailed definition of TEAE is specified in Appendix 6.

7.1.7. Summaries of AEs and Deaths

A brief summary of double-blind phase AEs will show, by treatment group, the number and percentage of subjects who (1) had any treatment-emergent AE, (2) had any Grade 3 or 4 treatment-emergent AE, (3) had any Grade 2, 3, or 4 treatment-emergent AE, (4) had any treatment-emergent study-drug-related AE, (5) had any Grade 3 or 4 treatment-emergent study-drug-related AE, (6) had any Grade 2, 3, or 4 treatment-emergent study-drug-related AE, (7) had any treatment-emergent SAE, (8) had any treatment-emergent study-drug-related SAE, (9) had any treatment-emergent AE leading to premature study drug discontinuation, and (10) had treatment-emergent death.

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

Summaries (number and percentage of subjects) of AEs (by SOC, HLT [if specified below], and PT) will be provided by treatment group using the safety analysis set as follows:

- All treatment-emergent AEs summarized by SOC, HLT, and PT
- Any Grade 3 or 4 treatment-emergent AE
- Any Grade 2, 3, or 4 treatment-emergent AE
- All treatment-emergent study-drug-related AEs
- Any Grade 3 or 4 treatment-emergent study-drug-related AE
- Any Grade 2, 3, or 4 treatment-emergent study-drug-related AE
- All treatment-emergent SAEs
- All treatment-emergent study-drug-relatedSAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug

Multiple events will be counted once only per subject in each summary. For data presentation, SOC (and HLT) will be ordered alphabetically, with PT sorted by decreasing total frequency. For summaries by severity grade, the most severe event will be selected.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Deaths report
- Adverse events leading to premature discontinuation of study drug

7.1.8. 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 in HIV and approve the events that meet the definition. Events that meet the definition of stage 3 opportunistic illnesses in HIV will be listed.

7.1.9. Cardiovascular Events

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

The number and percentage of subjects with treatment-emergent cardiovascular events and serious cardiovascular 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 events will be provided.

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the safety analysis set. Analysis will be based on values reported in conventional units.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) 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 to each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

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

7.2.1.1. Metabolic Assessments

For the lipid panel and glucose, only those measurements under fasting status will be summarized. For the baseline and post-baseline values, and the change from baseline in fasting lipid and glucose data (including total cholesterol, triglycerides, low density lipoprotein [LDL], high density lipoprotein [HDL], total cholesterol to HDL ratio, and glucose), p-values will be calculated using the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

Fasting lipid data (including total cholesterol, LDL, HDL and triglycerides) will also be analyzed by using the following National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III categories {National Cholesterol Education Program (NCEP) 2001}:

- For total cholesterol (mg/dL): < 200 (desirable), 200-239 (borderline high), and ≥ 240 (high);
- For LDL (mg/dL): < 100 (optimal), 100-129 (never optimal/above optimal), 130-159 (borderline high), 160-189 (high), and ≥ 190 (very high);

- For HDL (mg/dL): < 40 (low), ≥ 40 to < 60 (normal), ≥ 60 (high);
- For triglycerides (mg/dL): < 150 (normal), 150-199 (borderline-high), 200-499 (high), and ≥ 500 (very high).

The number and proportion of subjects for the above categories of each lipid parameter will be summarized for each treatment group by its baseline category at each visit.

7.2.1.2. 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 draw 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.

Median (Q1, Q3) change from baseline in selected safety endpoints including the fasting lipid panel parameters, and fasting glucose over time will be plotted.

7.2.2. Graded Laboratory Values

The criteria specified in the protocol will be used to grade laboratory results as Grade 0, mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analysis for each direction (ie, increased, decreased) will be presented separately.

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

If any laboratory toxicity grading scales overlap with normal reference ranges (eg, Grade 1 scale overlaps with normal reference ranges), laboratory values within the normal range will not be graded except for lipid tests.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least one toxicity grade from baseline at any postbaseline up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory data are missing, any laboratory abnormality of at least Grade 1 is considered treatment-emergent.

Fasting glucose and nonfasting glucose are graded based on different grading criteria (as specified in the protocol). Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Since nonfasting glucose was not assessed at baseline, the maximum postbaseline grade will be summarized.

The treatment-emergent laboratory abnormalities will be defined for the double-blind phase analysis based on the double-blind phase baseline and for the open-label phase analysis based on the open-label phase baseline.

For the double-blind phase analysis, the term "study drug" refers to the double-blind phase study drug. For the open-label phase analysis, the term "study drug" refers to the open-label phase study drug.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) of laboratory abnormalities will be provided by treatment group (subjects categorized according to most severe abnormality grade):

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline value during the double-blind phase of the study. A listing of treatment-emergent Grade 3 or Grade 4 laboratory abnormalities will be provided.

7.2.2.3. Liver-Related Laboratory Test

The number and percentage of subjects will be summarized for the following liver-related laboratory tests and categories:

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

The summary will include data from all the postbaseline visits up to 30 days after the last dose of the double-blind study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. 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.

7.3. Bone Safety Analyses

7.3.1. Bone Mineral Density

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 postbaseline visit using ANOVA, which includes the third agent randomization stratum and treatment as fixed effects (Appendix 2, Appendix Table 6). For Baseline BMD values, comparison between the 2 treatment groups will be based on ANOVA, including treatment as a fixed effect.

Missing values for hip BMD and spine BMD will be imputed using LOCF for the analyses of percentage change from baseline. The last postbaseline observation will be carried forward to impute the missing value. Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no non-missing pastbaseline observation prior to this visit.

Percentage change from baseline in observed hip BMD and spine BMD will also be analyzed similarly.

Observed BMD values will be used for all the analyses described below.

For each subject and each visit, the clinical BMD status will be defined for hip 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 clinical BMD status (normal, osteopenia, and osteoporosis) will be summarized by visit and by baseline clinical status for both hip and spine. The distribution of the clinical BMD status will be compared between the 2 treatment groups adjusting for baseline status and the third agent randomization stratum using rank analysis of covariance {LaVange 2008}.

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

For each subject and each visit, percentage change from baseline in the hip BMD and femoral neck BMD will be classified into 7 categories: ≥ 7% decrease, ≥ 5% decrease to < 7% decrease, ≥ 3% decrease to < 5% decrease, ≥ 0 to < 3% decrease, > 0 to < 3% increase, ≥ 3% increase to < 5% increase, ≥ 5% increase. The number and percentage of subjects in each category will be summarized by visit. The distribution difference in these categories between the treatment groups will be compared using CMH test (row mean scores differ statistic) adjusting for the third agent randomization stratum.

Median (Q1, Q3) and mean (95% CI) of 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.

7.3.2. Bone Biomarkers

Bone biomarkers include serum CTX and P1NP.

Baseline, postbaseline, change from baseline, and percentage change from baseline in bone biomarkers will be summarized by treatment group and visit using descriptive statistics.

For Baseline values, comparison between the 2 treatment groups will be based on the 2-sided Wilcoxon rank sum test. At postbaseline visits, percentage change from baseline will be compared between the 2 treatment groups using rank analysis of covariance adjusting for baseline value and the third agent randomization stratum.

Median (Q1, Q3) percentage change from baseline in bone biomarkers over time will be plotted by treatment group. A listing of bone biomarker data will be provided.

7.3.3. Fracture Events

The PTs for fracture events are defined based on both Standardized MedDRA Query (SMQ) of Osteoporosis/Osteopenia Fractures and HLGT of Fractures from MedDRA. The lists of PTs selected by clinical review before database finalization from all the PT terms under SMQ of Osteoporosis/Osteopenia and HLGT of Fractures are presented in Appendix 4.

Fracture events will be summarized based on selected PTs from SMQ alone and both SMQ and HLGT combined, respectively. The number and percentage of subjects who experience fracture events will be summarized by treatment group. Statistical comparisons of the subject incidence rates between treatment groups will be performed using Fisher's exact test (Appendix 2, Appendix Table 7).

A data listing of fracture events will be provided.

7.4. Renal Safety Analyses

7.4.1. Serum Creatinine

The baseline and change from baseline in serum creatinine at each visit will be summarized using descriptive statistics. The baseline in serum creatinine will be compared between the 2 treatment groups using ANOVA, which includes treatment as a fixed effect. The change from baseline in serum creatinine at each visit will be compared between the 2 treatment groups using an analysis of covariance model (ANCOVA) including the third agent stratum and treatment as fixed effects and baseline serum creatinine as a covariate.

Median (Q1, Q3), mean, and 95% CI of change from baseline in observed serum creatinine over time will be plotted by treatment group.

7.4.2. Estimated Glomerular Filtration Rate

The following formulae will be used to calculate eGFR:

- Cockcroft-Gault

  $eGFR_{CG}$ (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.

- CKD-EPI creatinine based ($eGFR_{CKD\text{-}EPI,\ creatinine}$)

  $eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 m^2) = $141 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) × 1.159 (if black),

  where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1 {Levey 2009}.

Change from baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ at each postbaseline visit will also be calculated.

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

For Baseline values, comparison between the 2 treatment groups will be based on the 2-sided Wilcoxon rank sum test. At postbaseline visits, change from baseline will be compared between the 2 treatment groups using rank analysis of covariance adjusting for baseline value and the third agent randomization stratum.

Median (Q1, Q3) change from baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ over time will be plotted.

7.4.3. Proteinuria by Urinalysis (Dipstick)

The proteinuria by urinalysis (dipstick) toxicity grade (Grade 0 to Grade 3) at Weeks 24, 48 and 96 will be summarized by baseline proteinuria toxicity grade and treatment. In addition, the last on-treatment proteinuria toxicity grade through the data cut date will also be summarized by baseline proteinuria toxicity grade and treatment. On-treatment values include data collected up to the last dose date plus 1 day for subjects who permanently discontinued study drug or include all available data for subjects who completed study drug.

The distribution of proteinuria toxicity grade at Weeks 24, 48, 96 and at the last on-treatment value, respectively, will be compared between treatment groups adjusting for baseline proteinuria toxicity grade and third agent randomization stratum using rank analysis of covariance {LaVange 2008} (Appendix 2, Appendix Table 8).

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

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

For Baseline values, comparison between the 2 treatment groups will be based on the 2-sided Wilcoxon rank sum test. At postbaseline visits, percentage change from baseline will be compared between the 2 treatment groups using rank analysis of covariance adjusting for baseline value and the third agent randomization stratum.

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

7.4.5. Proteinuria by Quantitative Assessment

Subjects will be classified into three categories based on their urine protein (UP) and urine protein to creatinine ratio (UPCR) results: UPCR $\leq$ 200 mg/g (including subjects with UP $<$ 4.0 mg/dL), UPCR $>$ 200 mg/g, and Missing, where UPCR will only be calculated when UP $\geq$ 4.0 mg/dL. The number and percentage of subjects in each UP and UPCR category will be summarized by baseline category at Weeks 24, 48, 96, and based on the last on-treatment value (ie, data collected after the first dose date up to 1 day after permanent discontinuation of study drug or all available postbaseline data for subjects who completed study drug) {KDIGO Guideline Development Staff 2013}. The distribution of the UP and UPCR categories will be compared between the 2 treatment groups adjusting for baseline categories and the third agent randomization stratum using rank analysis of covariance {LaVange 2008}.

Covance changed the calibrator material used in the quantitative assay for the measurement of UP on and after May 27, 2016. As a result of this change, the UP values reported prior to May 27, 2016 will be adjusted in order to combine the UP results obtained from the two different assay methods for analysis purpose. The details of how to adjust the UP values reported prior to May 27, 2016 is provided in Appendix 6.

7.5. Body Weight

Body weight at each visit and change from baseline in body weight will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group for each postbaseline analysis window. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.6. Nonstudy-Drug Antiretroviral (ARV) Medications

All nonstudy-drug ARV medications used prior to, during, or after the study (if collected), will be coded using the GSI-modified WHO Drug dictionary. The WHO preferred 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.

7.7. Non-ARV Concomitant Medications

Non-ARV concomitant medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the current version of the WHO Drug dictionary. The WHO preferred name and drug code will be attached to the clinical database.

Use of concomitant medications from Study Day 1 up to the date of the last dose of study drug for the double-blind phase of the study will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group (Appendix 2, Appendix Table 10). A subject reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of subjects who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC drug class and then by preferred term in descending overall frequency within each ATC drug class. For drugs with the same frequency, sorting will be done alphabetically.

In addition, the number and percentage of subjects taking lipid modifying medications at the study entry and during the double-blind phase of the study will be summarized separately by treatment group.

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

- The month and year of start of the medication is after the date of the last dose of study drug for the double-blind phase
- The month and year of stop of the medication is before the date of the first dose of study drug for the double-blind phase

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

Summaries of non-ARV concomitant medications will be provided for the safety analysis set. Subjects with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

7.8. Electrocardiogram Results

The number and percentage of subjects in the safety analysis set with an investigator's ECG assessment of normal, abnormal but not clinically significant, or abnormal and clinically significant will be summarized by treatment group and by baseline result for each visit. No inferential statistics will be provided.

A listing of safety ECG results will be provided including treatment, assessment date and time, and ECG results.

7.9. Open-Label Phase Analysis

7.9.1. Summaries of AEs and Deaths

A brief summary of open-label phase AEs will show, by treatment group using the open-label F/TAF analysis set, the number and percentage of subjects who (1) had any treatment-emergent AE, (2) had any Grade 3 or 4 treatment-emergent AE, (3) had any Grade 2, 3, or 4 treatment-emergent AE, (4) had any treatment-emergent study-drug-related AE, (5) had any Grade 3 or 4 treatment-emergent study-drug-related AE, (6) had any Grade 2, 3, or 4 treatment-emergent study-drug-related AE, (7) had any treatment-emergent SAE, (8) had any treatment-emergent study-drug-related SAE, (9) had any treatment-emergent AE leading to premature study drug discontinuation, and (10) had treatment-emergent death.

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

In addition, all treatment-emergent AEs that occurred during the open-label phase will be summarized by SOC, HLT, and PT by treatment group using the open-label F/TAF analysis set.

7.9.2. Summaries of Laboratory Abnormalities

The summary of open-label phase treatment-emergent laboratory abnormalities (number and percentage of subjects) will be provided by treatment group (subjects categorized according to most severe abnormality grade) using the open-label F/TAF analysis set. For the summary of laboratory abnormalities, the denominator is the number of subjects with any nonmissing postbaseline value during the open-label phase.

7.10. Other Safety Analysis

A data listing will be provided for subjects experiencing pregnancy during the study.

7.11. Changes From Protocol-Specified Safety Analyses

Analyses of the inflammation biomarker data will not be conducted in the final analysis [redacted]

For change from baseline and percentage change from baseline in bone and renal biomarkers, comparisons between the 2 treatment groups will be based on the rank analysis of covariance adjusting for baseline value and the third agent randomization stratum, instead of van Elteren method.

8. PHARMACOKINETIC ANALYSES

8.1. Analysis for Anytime PK

PK samples are not analyzed in this study. No PK data analysis will be conducted.

8.2. Changes from Protocol-Specified Pharmacokinetics Analysis

PK analysis set will not be derived as no PK data analysis will be conducted.

9. PATIENT REPORTED OUTCOMES

There is no patient reported outcome in this study.

10. REFERENCES

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National Cholesterol Education Program (NCEP). Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary. National Institute of Health May, 2001.

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11. SOFTWARE

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

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

12. SAP REVISION

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

13. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

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6.3	Median (Q1, Q3) of Change from Baseline in Fasting HDL (mg/dL) by Visit	Safety Analysis Set
6.4	Median (Q1, Q3) of Change from Baseline in Fasting Total Cholesterol to HDL Ratio by Visit	Safety Analysis Set
6.5	Median (Q1, Q3) of Change from Baseline in Fasting Triglycerides (mg/dL) by Visit	Safety Analysis Set
6.6	Median (Q1, Q3) of Change from Baseline in Fasting Glucose (mg/dL) by Visit	Safety Analysis Set
7.1.1	Median (Q1, Q3) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data)	Hip DXA Analysis Set
7.1.2	Median (Q1, Q3) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data)	Spine DXA Analysis Set
7.2.1	Mean and 95% CIs of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data)	Hip DXA Analysis Set
7.2.2	Mean and 95% CIs of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data)	Spine DXA Analysis Set
8.1	Median (Q1, Q3) of Percentage Change from Baseline in Serum C-type Collagen Sequence (CTx) by Visit	Safety Analysis Set
8.2	Median (Q1, Q3) of Percentage Change from Baseline in Serum Bone Procollagen Type 1 N-terminal Propeptide (P1NP) by Visit	Safety Analysis Set

Figure Number	Title	Analysis Set
9.1	Median (Q1, Q3) of Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data)	Safety Analysis Set
9.2	Mean and 95% CIs of Change from Baseline in Serum Creatinine (mg/dL) by Visit (Observed Data)	Safety Analysis Set
10.1	Median (Q1, Q3) of Change from Baseline in Estimated GFR by Cockcroft-Gault (mL/min) by Visit	Safety Analysis Set
10.2	Median (Q1, Q3) of Change from Baseline in Estimated GFR by CKD-EPI Creatinine (mL/min/1.73 m^2) by Visit	Safety Analysis Set
11.1	Median (Q1, Q3) of Percentage Change from Baseline in Urine Retinol Binding Protein (RBP) to Creatinine Ratio by Visit	Safety Analysis Set
11.2	Median (Q1, Q3) of Percentage Change from Baseline in Urine Beta-2-Microglobulin to Creatinine Ratio by Visit	Safety Analysis Set

Listing Number	Title	Analysis Set
1	Subject Profiles	All Randomized Analysis Set
2	Study Completion	All Randomized Analysis Set
3.1	Subjects Who Were Excluded from Safety, Full, PP and DXA Analysis Sets	All Randomized Analysis Set
3.2	Subjects Who Were in the Full Analysis Set but Who Were Not in the PP Analysis Set	Full Analysis Set
4.1	Enrollment	All Randomized Analysis Set
4.2	Eligibility Criteria Not Met	All Randomized Analysis Set
4.3	Enrollment Summary	Subjects Not Enrolled
5	Third Agent Stratification Discrepancies between Third Agent Stratum Entered into IXRS and Actual Third Agent Stratum	All Randomized Analysis Set
6	Subjects Who Received the Wrong Study Drug Treatment (Other Than That They Were Randomized to)	All Randomized Analysis Set
7	Demographics and Baseline Characteristics	All Randomized Analysis Set
8	Baseline Disease Characteristics	All Randomized Analysis Set
9	HIV Disease Characteristics at Screening	All Randomized Analysis Set
10	Medical History	All Randomized Analysis Set
11	Nonstudy-Drug Antiretroviral Medications	All Randomized Analysis Set
12	Non-ARV Concomitant Medications	All Randomized Analysis Set
13.1	Study Drug Completion (Double Blind Phase)	All Randomized Analysis Set
13.2	Study Drug Completion (Open Label Phase)	All Randomized Analysis Set
14	Study Drug Administration	All Randomized Analysis Set
15	Study Drug Accountability and Adherence	All Randomized Analysis Set
16	Snapshot Virologic Outcomes, Plasma HIV-1 RNA, and CD4 Cell Count and Percentage	All Randomized Analysis Set
17	All Adverse Events	All Randomized Analysis Set
18	Grade 3 and 4 Adverse Events	All Randomized Analysis Set
19	Fracture Events	All Randomized Analysis Set
20.1	Serious Adverse Events	All Randomized Analysis Set
20.2	Study-Drug-Related Serious Adverse Events	All Randomized Analysis Set
21	Adverse Events Leading to Premature Study Drug Discontinuation	All Randomized Analysis Set
22	Stage 3 Opportunistic Illnesses in HIV	All Randomized Analysis Set
23	Death Report	All Randomized Analysis Set

Listing Number	Title	Analysis Set
24.1	Clinical Laboratory Data: Hematology (Part I)	All Randomized Analysis Set
24.2	Clinical Laboratory Data: Hematology (Part II)	All Randomized Analysis Set
24.3	Clinical Laboratory Data: Hematology (Part III)	All Randomized Analysis Set
24.4	Clinical Laboratory Data: Hematology (Part IV)	All Randomized Analysis Set
25.1	Clinical Laboratory Data: Chemistry (Part I)	All Randomized Analysis Set
25.2	Clinical Laboratory Data: Chemistry (Part II)	All Randomized Analysis Set
25.3	Clinical Laboratory Data: Chemistry (Part III)	All Randomized Analysis Set
25.4	Clinical Laboratory Data: Chemistry (Part IV, and Liver-Related Laboratory Tests)	All Randomized Analysis Set
26	Metabolic Assessment: Glucose and Lipid Panel	All Randomized Analysis Set
27.1	Clinical Laboratory Data: Urinalysis (Part I)	All Randomized Analysis Set
27.2	Clinical Laboratory Data: Urinalysis (Part II)	All Randomized Analysis Set
27.3	Clinical Laboratory Data: Urinalysis (Part III)	All Randomized Analysis Set
28.1	Clinical Laboratory Data: Urine Chemistry (Part I)	All Randomized Analysis Set
28.2	Clinical Laboratory Data: Urine Chemistry (Part II)	All Randomized Analysis Set
29	Clinical Laboratory Data: Hepatitis Tests	All Randomized Analysis Set
30	Clinical Laboratory Data: Pregnancy Test and FSH Test	All Randomized Analysis Set
31	Graded Laboratory Abnormalities	All Randomized Analysis Set
32	Grade 3 or 4 Laboratory Abnormalities	All Randomized Analysis Set
33	Subjects with AST or ALT > 3 × ULN	Safety Analysis Set
34	Pregnancy Report	All Randomized Analysis Set
35	Reference Ranges for Laboratory Tests	All Randomized Analysis Set
36.1	Hip Bone Mineral Density Results	All Randomized Analysis Set: Subjects with Any Hip DXA Data
36.2	Spine Bone Mineral Density Results	All Randomized Analysis Set: Subjects with Any Spine DXA Data
36.3	Femoral Neck Bone Mineral Density Results	All Randomized Analysis Set: Subjects with Any Hip DXA Data
37	Bone Biomarkers Results	All Randomized Analysis Set
38	Serum Creatinine and Estimated Glomerular Filtration Rate (eGFR)	All Randomized Analysis Set
39	Renal Biomarkers Results	All Randomized Analysis Set
40	Body Weight, Body Height, Body Mass Index (BMI)	All Randomized Analysis Set
41	12-Lead Electrocardiogram Results	All Randomized Analysis Set

Appendix 2. TFL Mocks

Appendix Table 1. Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm), Full Analysis Set

	F/TAF (N = xxx)	ABC/3TC (N = xxx)	F/TAF vs ABC/3TC	
			P-value	Difference in Percentages (95.002% CI)
HIV-1 RNA < 50 copies/mL	xx (xx.x%)	xx (xx.x%)	0.xx	xx.x% (xx.x% to xx.x%)
HIV-1 RNA ≥ 50 copies/mL	xx (xx.x%)	xx (xx.x%)	0.xx	xx.x% (xx.x% to xx.x%)
HIV-1 RNA ≥ 50 copies/mL in Week 48 Window	xx (xx.x%)	xx (xx.x%)		
Discontinued Study Drug Due to Lack of Efficacy	xx (xx.x%)	xx (xx.x%)		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥ 50 copies/mL	xx (xx.x%)	xx (xx.x%)		
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL	xx (xx.x%)	xx (xx.x%)		
No Virologic Data in Week 48 Window	xx (xx.x%)	xx (xx.x%)		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL	xx (xx.x%)	xx (xx.x%)		
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	xx (xx.x%)	xx (xx.x%)		
Missing Data During Window but on Study Drug	xx (xx.x%)	xx (xx.x%)		

Week 48 window is between Day 295 and 378 (inclusive).

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

Differences in percentages of subjects with HIV-1 RNA < 50 or ≥ 50 copies/mL between treatment groups and their 95.002% CI were calculated based on an exact method.

P-values for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL or ≥ 50 copies/mL between treatment groups were from the Fisher's exact test.

Appendix Table 2. Treatment Difference in HIV-1 RNA < 50 copies/mL at Week 96 (Snapshot Algorithm) by Subgroup, Full Analysis Set

Subgroup	F/TAF (N = xxx)	ABC/3TC (N = xxx)	F/TAF vs ABC/3TC Difference in Percentages (95% CI)
Overall	xx (xx.x%)	xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Age (Years)			
< 50	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
≥ 50	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Sex			
Male	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Female	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Race			
Black	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Nonblack	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Ethnicity			
Hispanic or Latino	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Not Hispanic or Latino	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Third Agent			
Boosted Protease Inhibitors	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Others	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Region			
US	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Ex-US	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
Study Drug Adherence (%)			
< 95	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)
≥ 95	xx/xx (xx.x%)	xx/xx (xx.x%)	xx.x% (xx.x% to xx.x%)

Week 96 window is between Day 631 and 714 (inclusive).
Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests with the standardized statistic.
Study drug adherence subgroups analysis is based on the adherence up to Week 96 visit for active study drug.

Appendix Table 3. Homogeneity Test of Treatment Effect Between Subgroups in HIV-1 RNA < 50 copies/mL at Week 96 (Snapshot Algorithm), Full Analysis Set

Subgroup	F/TAF (N = xxx)	ABC/3TC (N = xxx)	F/TAF vs ABC/3TC	
			P-value	Odds Ratio (95%CI)
Age (Years)				
< 50	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.xx (x.xx to x.xx)
≥ 50	xx/xx (xx.x%)	xx/xx (xx.x%)		x.xx (x.xx to x.xx)
Sex				
Male	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.xx (x.xx to x.xx)
Female	xx/xx (xx.x%)	xx/xx (xx.x%)		x.xx (x.xx to x.xx)
Race				
Black	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.xx (x.xx to x.xx)
Nonblack	xx/xx (xx.x%)	xx/xx (xx.x%)		x.xx (x.xx to x.xx)
Ethnicity				
Hispanic or Latino	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.xx (x.xx to x.xx)
Not Hispanic or Latino	xx/xx (xx.x%)	xx/xx (xx.x%)		x.xx (x.xx to x.xx)
Third Agent				
Boosted Protease Inhibitors	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.xx (x.xx to x.xx)
Others	xx/xx (xx.x%)	xx/xx (xx.x%)		x.xx (x.xx to x.xx)
Region				
US	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.xx (x.xx to x.xx)
Ex-US	xx/xx (xx.x%)	xx/xx (xx.x%)		x.xx (x.xx to x.xx)
Study Drug Adherence (%)				
< 95	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.xx (x.xx to x.xx)
≥ 95	xx/xx (xx.x%)	xx/xx (xx.x%)		x.xx (x.xx to x.xx)

Week 96 window is between Day 631 and 714 (inclusive).
Odds ratio and its 95% CIs were estimated for each subgroup from the logistic regression model including the third agents (boosted protease inhibitors vs. others) (if not the subgroup factor), subgroup, treatment, and the interaction between treatment and subgroup.
P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup.
Study drug adherence subgroups analysis is based on the adherence up to Week 96 visit for active study drug.

Appendix Table 4. Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Visit: Missing = Failure, Full Analysis Set

	F/TAF (N= xxx)	ABC/3TC (N= xxx)	F/TAF vs ABC/3TC	
			P-value	Difference in Percentages (95% CI)
HIV-1 RNA at Baseline				
< 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)		
95% CI	xx.x% to xx.x%	xx.x% to xx.x%		
< 20 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)		
< 20 Not Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)		
< 20 Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)		
20 to < 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)		
≥ 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)		
Missing	xx/xx (xx.x%)	xx/xx (xx.x%)		
HIV-1 RNA at Week X				
< 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)	0.xx	x.x% (x.x% to x.x%)
95% CI	xx.x% to xx.x%	xx.x% to xx.x%		
< 20 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)		
< 20 Not Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)		
< 20 Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)		
20 to < 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)		
≥ 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)		
Missing	xx/xx (xx.x%)	xx/xx (xx.x%)		
…	…	…	…	…

The denominator for percentages is based on the number of subjects in the full analysis set. P-values for comparing the two treatment groups were from the Fisher's exact test.
The 95% CI for percentage estimate of the percentage of subjects with HIV-1 RNA < 50 copies/mL for each treatment was obtained using Exact method.
P-value, percentage difference, and 95% CI were based on a dichotomized response: HIV-1 RNA < 50 or HIV-1 RNA ≥ 50 or missing.
Difference in percentages of subjects with HIV-1 RNA < 50 between treatment groups and its 95% CI were calculated based on the exact method.

Appendix Table 5. Liver-Related Laboratory Tests, Safety Analysis Set

	F/TAF (N = xx)	ABC/3TC (N = xx)
AST		
> 3 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 5 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 10 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 20 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
ALT		
> 3 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 5 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 10 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 20 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
AST or ALT		
> 3 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 5 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 10 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 20 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
Total Bilirubin		
> 1 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
> 2 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
Alkaline Phosphatase (ALP)		
> 1.5 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
AST or ALT > 3 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
Total Bilirubin > 1.5 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
Total Bilirubin > 2 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)
Total Bilirubin > 2 × ULN and ALP < 2 × ULN	xx/xx (xx.x%)	xx/xx (xx.x%)

ULN = upper limit of normal
Denominator for percentage for individual test is the number of subjects in the Safety Analysis Set with at least 1 postbaseline laboratory value.
The most severe postbaseline value per subject was summarized for each laboratory test. For AST, ALT, AST or ALT, and total bilirubin, subjects may be counted in multiple categories, eg, subject would be counted in > 3 × ULN, > 5 × ULN, and > 10 × ULN if the worst value was > 10 × ULN.
For the composite endpoint of AST or ALT, and total bilirubin with or without alkaline phosphatase (ALP), subjects were counted once when the criteria were met at the same postbaseline visit date. The denominator is the number of subjects in the safety analysis set with nonmissing postbaseline values of the tests in evaluation at the same postbaseline visit date.

Appendix Table 6. Percentage Change from Baseline in Spine Bone Mineral Density by Visit (LOCF Imputation), Spine DXA Analysis Set

	F/TAF (N = xx)	ABC/3TC (N = xx)	F/TAF vs. ABC/3TC	
			P-value	Diff in LSM (95% CI)
Baseline				
N	xx	xx		
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)		
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	0.xx	xx.x (xx.x, xx.x)
Median	xx.x	xx.x		
Q1, Q3	xx.x, xx.x	xx.x, xx.x		
Min, Max	xx.x, xx.x	xx.x, xx.x		
% Chg at Week 24				
N	xx	xx		
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)		
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	0.xx	xx.x (xx.x, xx.x)
Median	xx.x	xx.x		
Q1, Q3	xx.x, xx.x	xx.x, xx.x		
Min, Max	xx.x, xx.x	xx.x, xx.x		
% Chg at Week 48				
N	xx	xx		
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)		
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	0.xx	xx.x (xx.x, xx.x)
Median	xx.x	xx.x		
Q1, Q3	xx.x, xx.x	xx.x, xx.x		
Min, Max	xx.x, xx.x	xx.x, xx.x		
…	…	…	…	…

% Chg = Change from baseline at a postbaseline visit/baseline × 100%
For Baseline, p-value and difference in least squares means (Diff in LSM), and its 95% CI were from an ANOVA model including treatment as a fixed effect.
For postbaseline visits, p-values, difference in least squares means (Diff in LSM), and its 95% CI were from an ANOVA model including treatment and third agent randomization stratum as fixed effects.
Only subjects with nonmissing baseline spine BMD were included in the Spine DXA analysis set.
Missing values were imputed using last observation carried forward (LOCF) method. The last postbaseline observation was carried forward. Baseline values were carried forward if postbaseline observations were not available.

Appendix Table 7. Treatment-Emergent Fracture Events, Safety Analysis Set

	F/TAF (N = xx)	ABC/3TC (N = xx)	p-value
Fracture Events (Based on Osteoporosis/Osteopenia SMQ)	xx (x.xx%)	xx (x.xx%)	0.xx
Preferred Term 1	xx (x.xx%)	xx (x.xx%)	
Preferred Term 2	xx (x.xx%)	xx (x.xx%)	
Preferred Term 3	xx (x.xx%)	xx (x.xx%)	
…			
Fracture Events (based on Osteoporosis/Osteopenia SMQ and Fractures HLGT)	xx (x.xx%)	xx (x.xx%)	0.xx
Preferred Term 1	xx (x.xx%)	xx (x.xx%)	
Preferred Term 2	xx (x.xx%)	xx (x.xx%)	
Preferred Term 3	xx (x.xx%)	xx (x.xx%)	
…			

SMQ = Standardised MedDRA Query; HLGT = High Level Group Terms.
Adverse events were coded using MedDRA 20.1.
P-values were from the Fisher's exact test.
Notes for Programmer:

- There are 3 possible mutually exclusive values for AESELTYP: cSMQ, cHLGT, cSMQ+cHLGT
- For fracture events based on Osteoporosis/Osteopenia SMQ, please select preferred terms when AESELTYP = "cSMQ" or "cSMQ+cHLGT"
- For fracture events based on Osteoporosis/Osteopenia SMQ and Fractures HLGT, please select preferred terms when AESELTYP = "cSMQ", "cHLGT", or "cSMQ+cHLGT"

Appendix Table 8. Shift Table of Postbaseline Proteinuria Toxicity Grade by Baseline Proteinuria Toxicity Grade, Safety Analysis Set

	F/TAF					ABC/3TC					
	Baseline					Baseline					
	Grade 0 (N = xx)	Grade 1 (N = xx)	Grade 2 (N = xx)	Grade 3 (N = xx)	Missing (N = xx)	Grade 0 (N = xx)	Grade 1 (N = xx)	Grade 2 (N = xx)	Grade 3 (N = xx)	Missing (N = xx)	P-value
At Week 48											
Grade 0	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	0.xx
Grade 1	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	
Grade 2	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	
Grade 3	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	
Missing	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
Last On-treatment Value											
Grade 0	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	0.xx
Grade 1	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	
Grade 2	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	
Grade 3	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)	xx	
Missing	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	

The denominator for percentage was the number of subjects with nonmissing values at both baseline and postbaseline visits for each treatment group.
On-treatment values include data collected up to the last dose date + 1 day for subjects who permanently discontinued study drug or all available data for subjects who were ongoing.
P-values for treatment comparison were from the rank analysis of covariance adjusting for baseline toxicity grade and third agent randomization stratum.

Appendix Table 9. Shift Table of Urine Protein to Creatinine Ratio Category (≤ 200 vs. > 200 mg/g) by Baseline Category, Safety Analysis Set

	F/TAF			ABC/3TC			F/TAF vs. ABC/3TC
	Baseline			Baseline			
	≤ 200 mg/g (N = xx)	> 200 mg/g (N = xx)	Missing (N = xx)	≤ 200 mg/g (N = xx)	> 200 mg/g (N = xx)	Missing (N = xx)	p-value
Week 24							
≤ 200 mg/g	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx	0.xx
> 200 mg/g	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx	
Missing	xx	xx	xx	xx	xx	xx	
Week 48							
≤ 200 mg/g	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx	0.xx
> 200 mg/g	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx	
Missing	xx	xx	xx	xx	xx	xx	
Last Value on Treatment							
≤ 200 mg/g	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx	0.xx
> 200 mg/g	xx (x.xx%)	xx (x.xx%)	xx	xx (x.xx%)	xx (x.xx%)	xx	
Missing	xx	xx	xx	xx	xx	xx	

Urine protein to creatinine ratio (UPCR) were only calculated when corresponding urine protein (UP) >= 4.0 mg/dL.
"UPCR < = 200 mg/g" category includes both subjects with UP < 4.0 mg/dL and subjects with UPCR < = 200 mg/g.
The denominator for percentage was the number of subjects with nonmissing values at both baseline and each postbaseline visit for each baseline category.
On-treatment data include all data collected after the first dose date up to 1 day after permanent discontinuation of study drug or all available postbaseline data for subjects who were still on study drug.
P-values for treatment comparison were from the rank analysis of covariance adjusting for baseline category and third agent randomization stratum.

Appendix Table 10. Non-ARV Concomitant Medications by Drug Class and Preferred Drug Name, Safety Analysis Set

	F/TAF (N = xx)	ABC/3TC (N = xx)
Subjects Who Received at Least 1 Non-ARV Concomitant Medication	xx (x.xx%)	xx (x.xx%)
ATC Drug Class 1	xx (x.xx%)	xx (x.xx%)
Preferred Drug Name 1	xx (x.xx%)	xx (x.xx%)
Preferred Drug Name 2	xx (x.xx%)	xx (x.xx%)
Preferred Drug Name 3	xx (x.xx%)	xx (x.xx%)
…		
ATC Drug Class 2	xx (x.xx%)	xx (x.xx%)
Preferred Drug Name 4	xx (x.xx%)	xx (x.xx%)
Preferred Drug Name 5	xx (x.xx%)	xx (x.xx%)
Preferred Drug Name 6	xx (x.xx%)	xx (x.xx%)
…		
…		

ATC = Anatomical Therapeutic Chemical
Concomitant medications were those taken after the first study drug administration date up to the last dosing date of study drug during the double-blind phase.
Medications were mapped using WHODRUG dictionary Version X.
Subjects were counted only once for each drug class and preferred drug name.
Medications may be mapped to multiple ATC drug classes.
Sorted by alphabetically by ATC drug class and then by preferred drug name (within ATC drug class) in decreasing overall frequency.

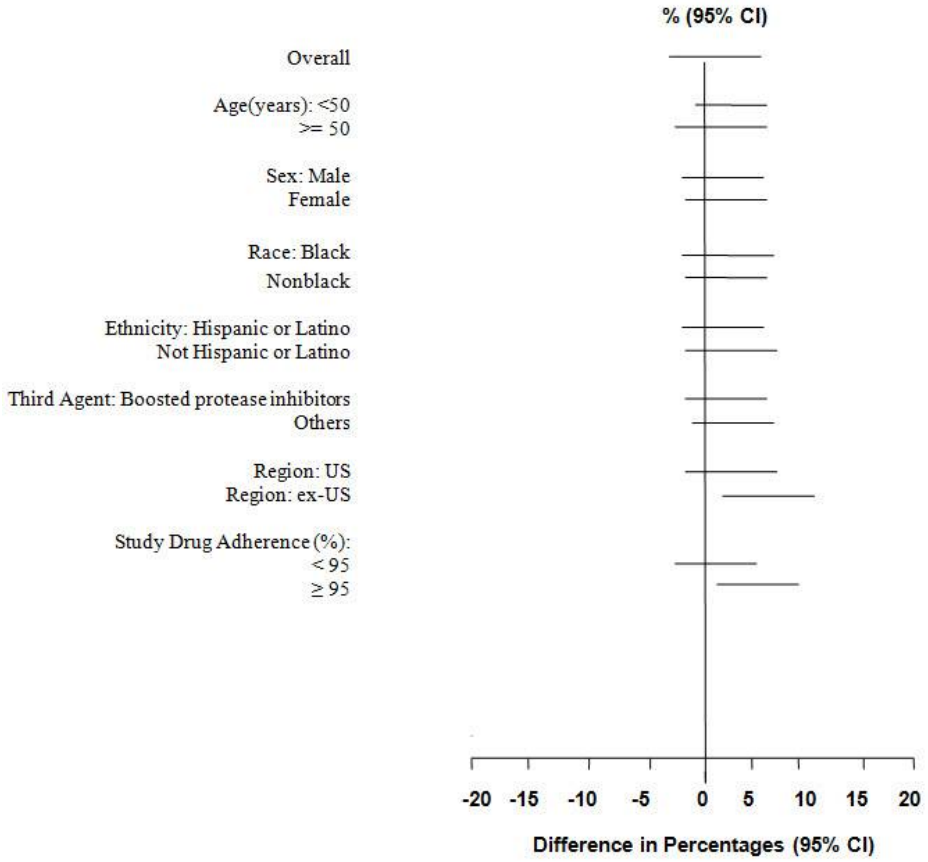
Appendix Table 11. Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Visit: Missing = Excluded, Open-Label F/TAF Analysis Set

	F/TAF (N= xxx)	ABC/3TC –> F/TAF (N= xxx)
HIV-1 RNA at Baseline		
< 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
95% CI	xx.x% to xx.x%	xx.x% to xx.x%
< 20 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
< 20 Not Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)
< 20 Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)
20 to < 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
≥ 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
Missing	xx/xx (xx.x%)	xx/xx (xx.x%)
HIV-1 RNA at Week X		
< 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
95% CI	xx.x% to xx.x%	xx.x% to xx.x%
< 20 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
< 20 Not Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)
< 20 Detectable	xx/xx (xx.x%)	xx/xx (xx.x%)
20 to < 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
≥ 50 copies/mL	xx/xx (xx.x%)	xx/xx (xx.x%)
Missing	xx/xx (xx.x%)	xx/xx (xx.x%)
…	…	…

ABC/3TC –> F/TAF refers to the ABC/3TC group subjects who received open label F/TAF during the open label phase.
The denominator for percentages is based on the number of subjects in the open-label F/TAF analysis set with nonmissing HIV-1 RNA value at each visit.

Appendix Figure 1. Forest Plot of Treatment Difference in Percentages of Subjects with HIV-1 RNA < 50 copies/mL at Week 96 (Snapshot Algorithm) by Subgroup, Full Analysis Set

(The plot will display the results from Appendix Table 2)



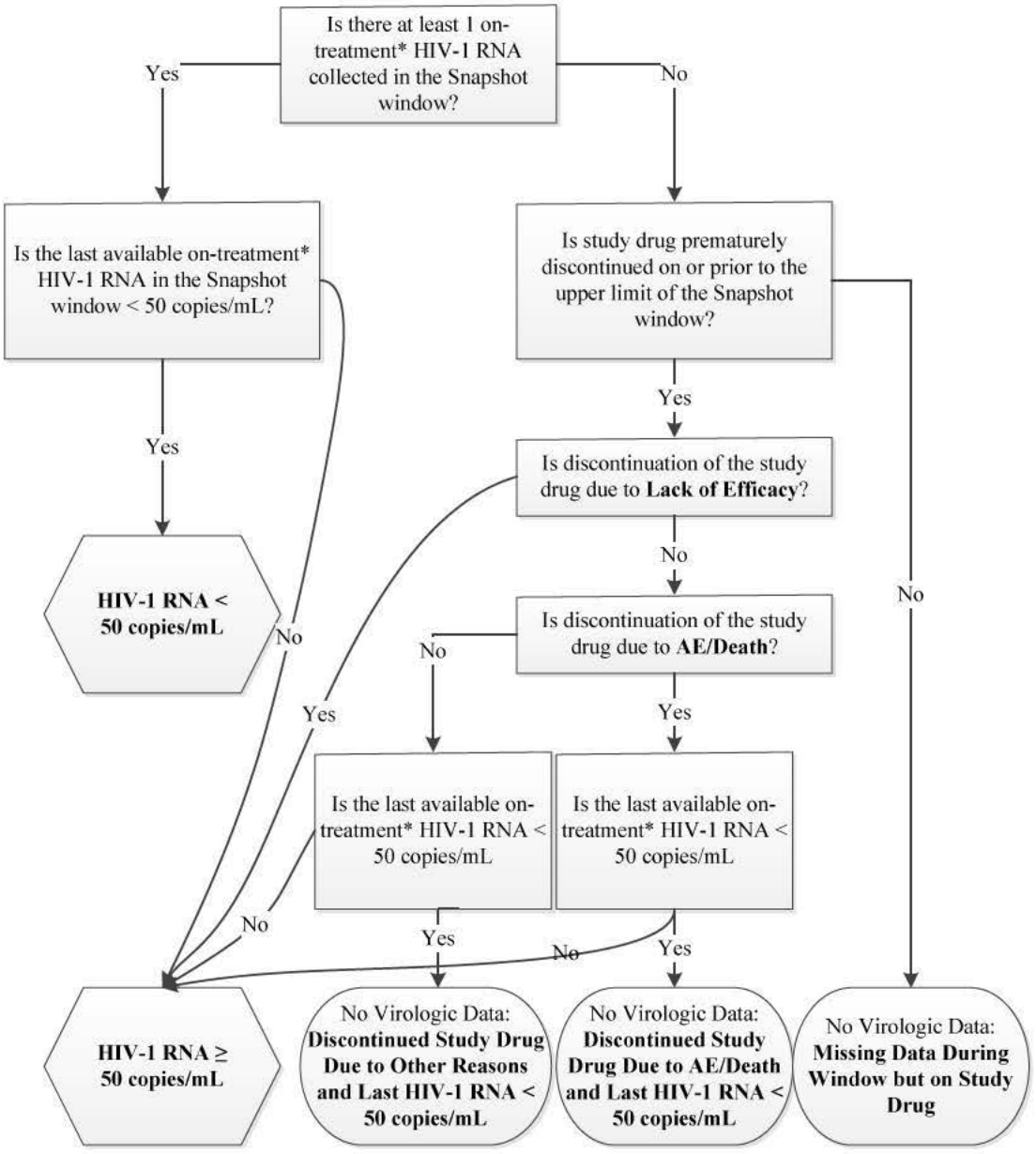
Appendix Listing 1. Snapshot Virologic Outcomes, Plasma HIV-1 RNA, and CD4 Cell Count and Percentage, All Randomized Analysis Set

Date of Collection (Study Day)	Time of Collection	Derived Visit	HIV-1 RNA (copies/mL)	In Analysis		CD4 (/uL)	CD4 (%)
				HIV-1 RNA (copies/mL)	Log_{10} HIV-1 RNA (log_{10} copies/mL)		
Subject ID: xxxxx-xxxx Third Agent: ATV/r Treatment: F/TAF Sex/Age/Race: M/22/AS Region Group: US Ethnicity: Hispanic or Latino Adherence Rate up to Week 96 Visit (%): ≥ 95 First Dose Date = xxxx-xx-xx Last Dose Date (Study Day): xxxx-xx-xx (xx) Study Drug Discontinuation Reason: Investigator's Discretion Snapshot at Wk 48 (Cutoff at 50 copies/mL) = HIV-1 RNA < 50 copies/mL Snapshot at Wk 48 (Cutoff at 20 copies/mL) = HIV-1 RNA < 20 copies/mL Snapshot at Wk 96 (Cutoff at 50 copies/mL) = HIV-1 RNA < 50 copies/mL Snapshot at Wk 96 (Cutoff at 20 copies/mL) = HIV-1 RNA < 20 copies/mL							
xxxx-xx-xx (xx)	xx:xx	Baseline	< 20 cp/mL HIV-1 RNA Detected	xx	xx	xx	xx
xxxx-xx-xx (xx)	xx:xx	Baseline	< 20 cp/mL HIV-1 RNA Detected	xx	xx	xx	xx
…	…	…	…				

Study Day was relative to the first dose date of study drug.
Age was calculated at the first dose date of study drug or enrollment date (if not dosed). For sex: F = Female; M = Male.
For snapshot virologic outcome, discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
& = Subjects who were excluded from the full analysis set. + = Subjects who were excluded from the Week 96 Per Protocol (PP) analysis set.
# = Values used for the Week 48 snapshot analysis; * = HIV-1 RNA values used in analysis based on the full analysis set (FAS).
$ = Values used for the Week 96 snapshot analysis; ^ = Missing values imputed using last observation carried forward (LOCF) method.
Note to SP:
For never dosed subjects, please display "Never Dosed" for First Dose Date.

Appendix 3. Flowchart of US FDA-Defined Snapshot Algorithm for Switch Trial

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



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

Appendix 4. Fracture Events

The selected PTs from SMQ of Osteoporosis/Osteopenia and HLGT of Fractures based on clinical review are listed as follows. AEs are coded by MedDRA 20.0.

Selected PTs based on SMQ of Osteoporosis/Osteopenia	Selected PTs based on HLGT of Fractures
Acetabulum fracture	Acetabulum fracture
Atypical femur fracture	Ankle fracture
Cervical vertebral fracture	Atypical femur fracture
Closed fracture manipulation	Atypical fracture
External fixation of fracture	Avulsion fracture
Femoral neck fracture	Bone fissure
Femur fracture	Bone fragmentation
Forearm fracture	Cervical vertebral fracture
Fracture	Chance fracture
Fracture treatment	Clavicle fracture
Fractured ischium	Comminuted fracture
Fractured sacrum	Complicated fracture
Hip fracture	Compression fracture
Ilium fracture	Craniofacial fracture
Internal fixation of fracture	Epiphyseal fracture
Lumbar vertebral fracture	Facial bones fracture
Multiple fractures	Femoral neck fracture
Open reduction of fracture	Femur fracture
Open reduction of spinal fracture	Fibula fracture
Osteoporotic fracture	Flail chest
Pathological fracture	Foot fracture
Pelvic fracture	Forearm fracture
Pubis fracture	Fracture
Radius fracture	Fracture displacement
Rib fracture	Fracture of clavicle due to birth trauma
Sacroiliac fracture	Fractured coccyx
Spinal compression fracture	Fractured ischium
Spinal fracture	Fractured sacrum
Tartrate-resistant acid phosphatase decreased	Fractured skull depressed
Thoracic vertebral fracture	Greenstick fracture
Vertebroplasty	Hand fracture
Vertebral body replacement	Hip fracture
Wrist fracture	Humerus fracture

Selected PTs based on SMQ of Osteoporosis/Osteopenia	Selected PTs based on HLGT of Fractures
	Ilium fracture
	Impacted fracture
	Jaw fracture
	Limb fracture
	Lisfranc fracture
	Lower limb fracture
	Lumbar vertebral fracture
	Multiple fractures
	Open fracture
	Osteochondral fracture
	Osteoporotic fracture
	Patella fracture
	Pathological fracture
	Pelvic fracture
	Periprosthetic fracture
	Pubis fracture
	Radius fracture
	Rib fracture
	Sacroiliac fracture
	Scapula fracture
	Scapulothoracic dissociation
	Skull fracture
	Skull fractured base
	Spinal compression fracture
	Spinal fracture
	Sternal fracture
	Stress fracture
	Thoracic vertebral fracture
	Tibia fracture
	Torus fracture
	Traumatic fracture
	Ulna fracture
	Upper limb fracture
	Wrist fracture

Appendix 5. Medical History

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

- At least 1 medical history record with MedDRA preferred term (PT; mh.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the first dose date.
- At least 1 adverse event record with MedDRA preferred term (PT; ae.MDRPT) in the following selected PT listing for the corresponding disease with start date on or prior to the first dose date.
- At least 1 concomitant medications record with ATC drug class level 2 (cm.WHOATC2) and indication (cm.CMINDC) in the following selected listing for the corresponding disease with start date on or prior to the first dose date.

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

Four variables (ie, DIABETES, HTENSION, CARDDIS, and HLIPDEM) will be added to raw Medical History and Adverse Events datasets. A medical history or an adverse event record will be flagged for a disease of interest if its MedDRA preferred term (PT) is included in the following selected PT listing for the corresponding disease of interest.

The PTs based on narrow or broad search of the pre-specified SMQ under MedDRA 21.0 are listed as follows, which was provided by Gilead PVE and reviewed by Gilead medical monitors. This list of selected PTs may be updated based on the version of MedDRA at the time of database finalization for the final analysis.

Disease of Interest	SMQ Source
Diabetes Mellitus (DIABETES)	Hyperglycaemia/new onset diabetes mellitus (SMQ) – Narrow Scope Term
Hyperlipidemia (HLIPDEM)	Dyslipidaemia (SMQ)
Hypertension (HTENSION)	Hypertension (SMQ)
Cardiovascular disease (CARDDIS)	Ischaemic central nervous system vascular conditions (SMQ) - Narrow Scope Term
	Myocardial infarction (SMQ) [20000047] - Narrow Scope Term
	Other ischaemic heart disease (SMQ) [20000168] - Narrow Scope Term

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

The selected combinations of ATC drug class and indication from the CM dataset for a subject having the medical risk factors of interest are listed as follows:

	ATC Drug Class	Indication
Hypertension		
1	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ANTIHYPERTENSIVE MEDICATION
2	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION
3	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	BENIGN ESSENTIAL HYPERTENSION
4	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION
5	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	GRADE 1 HYPERTENSION
6	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE
7	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSION
8	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSION & RIGHT EAR TINNITIS
9	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSION, WORSENING OF
10	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSIVE CRISIS
11	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	PRESTUDY HYPERTENSION
12	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	STAGE I HYPERTENSION
13	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	UNCONTROLLED HIGH BLOOD PRESSURE
14	ANTIHYPERTENSIVES	HYPERTENSION
15	ANTITHROMBOTIC AGENTS	TO THIN THE BLOOD TO TREAT THE INDICATION OF HIGH BLOOD PRESSURE
16	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION
17	BETA BLOCKING AGENTS	BENIGN HYPERTENSION
18	BETA BLOCKING AGENTS	BITEMPORAL HEADACHE; PRESTUDY HYPERTENSION
19	BETA BLOCKING AGENTS	ELEVATED BLOOD PRESSURE
20	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE
21	BETA BLOCKING AGENTS	HYPERTENSION
22	BETA BLOCKING AGENTS	HYPERTENTSION/HEART PALPATATIONS
23	BETA BLOCKING AGENTS	WORSENING HYPERTENSION
24	CALCIUM CHANNEL BLOCKERS	ANTI-HYPERTENSIVE MEDICATION
25	CALCIUM CHANNEL BLOCKERS	ANTIHYPERTENSIVE MED
26	CALCIUM CHANNEL BLOCKERS	ESSENTENTIAL HYPERTENSION
27	CALCIUM CHANNEL BLOCKERS	ESSENTILA HYPERTENSION
28	CALCIUM CHANNEL BLOCKERS	HIGH BLOOD PRESSURE
29	CALCIUM CHANNEL BLOCKERS	HYPERTENSION
30	CALCIUM CHANNEL BLOCKERS	PRESTUDY HYPERTENSION
31	DIURETICS	ARTERIAL HYPERTENSION
32	DIURETICS	ELEVATED BLOOD PRESSURE
33	DIURETICS	HIGH BLOOD PRESSURE
34	DIURETICS	HYPERTENSION
35	DIURETICS	HYPERTENSION AND EDEMA
36	DIURETICS	PRESTUDY HYPERTENSION
37	PERIPHERAL VASODILATORS	HYPERTENSION

	ATC Drug Class	Indication
	Diabetes	
1	ANALGESICS	DIABETES MELLITUS
2	ANALGESICS	DIABETIC NEUROPATHY
3	BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	DIABETES TYPE II
4	DRUGS USED IN DIABETES	ADULT ONSET DIABETES MELLITUS
5	DRUGS USED IN DIABETES	ADULT ONSET DIABETES MELLITUS (TYPE 2)
6	DRUGS USED IN DIABETES	ADULT ONSET DIABETES MELLITUS TYPE 2
7	DRUGS USED IN DIABETES	CONTROL SUGAR
8	DRUGS USED IN DIABETES	DIABETES
9	DRUGS USED IN DIABETES	DIABETES (AODM)
10	DRUGS USED IN DIABETES	DIABETES (HIPERGLICEMIA)
11	DRUGS USED IN DIABETES	DIABETES II
12	DRUGS USED IN DIABETES	DIABETES MELLITIS TYPE II
13	DRUGS USED IN DIABETES	DIABETES MELLITUS
14	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II
15	DRUGS USED IN DIABETES	DIABETES MELLITUS (ADULT ONSET/TYPE 2)
16	DRUGS USED IN DIABETES	DIABETES MELLITUS 2
17	DRUGS USED IN DIABETES	DIABETES MELLITUS BY HYSTORY
18	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE I WITH HYPERLIPIDEMIA
19	DRUGS USED IN DIABETES	DIABETES MELLITUS II
20	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE 2
21	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE II
22	DRUGS USED IN DIABETES	DIABETES MELLITUS, TYPE II
23	DRUGS USED IN DIABETES	DIABETES MILLITUS
24	DRUGS USED IN DIABETES	DIABETES TYPE 1
25	DRUGS USED IN DIABETES	DIABETES TYPE 2
26	DRUGS USED IN DIABETES	DIABETES TYPE 2 DINOVO
27	DRUGS USED IN DIABETES	DIABETES TYPE II
28	DRUGS USED IN DIABETES	DIABETIS
29	DRUGS USED IN DIABETES	DIABETTES MELLITUS
30	DRUGS USED IN DIABETES	DM
31	DRUGS USED IN DIABETES	DM2
32	DRUGS USED IN DIABETES	HYPERGLYCEMIA
33	DRUGS USED IN DIABETES	NONINSULIN-DEPENDENT DIABETES MELLITUS
34	DRUGS USED IN DIABETES	PRESTUDY DIABETES MELLITUS
35	DRUGS USED IN DIABETES	TYPE 2 DIABETES
36	DRUGS USED IN DIABETES	TYPE 2 DIABETES MELLITUS
37	DRUGS USED IN DIABETES	TYPE II DIABETES
38	DRUGS USED IN DIABETES	WORSENING OF DIABETES
39	DRUGS USED IN DIABETES	WORSENING OF DIABETES MELLITIS

	ATC Drug Class	Indication
Cardiovascular Disease		
1	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION
2	ALL OTHER THERAPEUTIC PRODUCTS	WORSENING OF CORONARY ARTERY DISEASE
3	ANALGESICS	CORONARY ARTERY DISEASE
4	ANALGESICS	INTERMITTENT CLAUDICATION OF THE LOWER EXTREMITIES
5	ANALGESICS	ISCHEMIC LEFT TOE
6	ANALGESICS	ST ELEVATION MYOCARDIAL INFARCTION
7	ANALGESICS	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
8	ANALGESICS	STROKE RELATED PAIN
9	ANALGESICS	STROKE RELATED PAIN (POST-OP)
10	ANALGESICS	WORSENING OF CORONARY ARTERY DISEASE
11	ANESTHETICS	ST ELEVATION MYOCARDIAL INFARCTION
12	ANESTHETICS	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
13	ANTIANEMIC PREPARATIONS	WORSENING OF CORONARY ARTERY DISEASE
14	ANTIBACTERIALS FOR SYSTEMIC USE	ST ELEVATION MYOCARDIAL INFARCTION
15	ANTIBACTERIALS FOR SYSTEMIC USE	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
16	ANTIEMETICS AND ANTINAUSEANTS	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
17	ANTIEPILEPTICS	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
18	ANTIHYPERTENSIVES	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
19	ANTIHYPERTENSIVES	WORSENING OF CORONARY ARTERY DISEASE
20	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	STROKE RELATED PAIN
21	ANTITHROMBOTIC AGENTS	CARDIOVASCULAR ACCIDENT PROPHYLAXIS
22	ANTITHROMBOTIC AGENTS	CARDIOVASCULAR DISEASE PROPHYLAXIS
23	ANTITHROMBOTIC AGENTS	CARDIOVASCULAR EVENT PROPHYLAXIS
24	ANTITHROMBOTIC AGENTS	CARDIOVASCULAR PROPHYLAXIS
25	ANTITHROMBOTIC AGENTS	CARDIOVASCULRAL PROPHYLAXIS
26	ANTITHROMBOTIC AGENTS	CORONARY ARTERY DISEASE
27	ANTITHROMBOTIC AGENTS	CORONARY DISEASE
28	ANTITHROMBOTIC AGENTS	CORONARY STENTS
29	ANTITHROMBOTIC AGENTS	HISTORY OF STROKE
30	ANTITHROMBOTIC AGENTS	ISCHEMIC EVENTS PREVENTION
31	ANTITHROMBOTIC AGENTS	LEFT VENTRICULAR ISCHEMIA ANTERIOIR
32	ANTITHROMBOTIC AGENTS	MILD CORONARY ATHEROSCLEROSIS

	ATC Drug Class	Indication
33	ANTITHROMBOTIC AGENTS	NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION
34	ANTITHROMBOTIC AGENTS	POST CORONARY ARTERY BYPASS GRAFT
35	ANTITHROMBOTIC AGENTS	PREVENT CARDIOVASCULAR EVENT
36	ANTITHROMBOTIC AGENTS	STROKE (BLOOD CLOT PROPHYLAXIS)
37	ANTITHROMBOTIC AGENTS	STROKE (PROPHYLAXIS)
38	ANTITHROMBOTIC AGENTS	STROKE PREVENTION
39	ANTITHROMBOTIC AGENTS	STROKE PROHYLAXIS
40	ANTITHROMBOTIC AGENTS	TO PREVENT HEART ATTACK/STROKE
41	ANTITHROMBOTIC AGENTS	VASOSPASTIC ANGINA
42	ANTITHROMBOTIC AGENTS	WORSENING OF CORONARY ARTERY DISEASE
43	BETA BLOCKING AGENTS	CARDIOVASCULAR PROTECTION POST INFERIOR WALL MYOCARDIAL INFARCTION
44	BETA BLOCKING AGENTS	CORONARY ARTERY DISEASE
45	BETA BLOCKING AGENTS	CORONARY DISEASE
46	BETA BLOCKING AGENTS	LONG TERM MANAGEMENT OF ANGINA
47	BETA BLOCKING AGENTS	NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION
48	BETA BLOCKING AGENTS	ST ELEVATION MYOCARDIAL INFARCTION
49	BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
50	BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	WORSENING OF CORONARY ARTERY DISEASE
51	CALCIUM CHANNEL BLOCKERS	ST ELEVATION MYOCARDIAL INFARCTION
52	CALCIUM CHANNEL BLOCKERS	VASOSPASTIC ANGINA
53	CARDIAC THERAPY	CORONARY ARTERY DISEASE
54	CARDIAC THERAPY	NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION
55	CARDIAC THERAPY	WORSENING OF CORONARY ARTERY DISEASE
56	DIURETICS	ST ELEVATION MYOCARDIAL INFARCTION
57	DRUGS FOR ACID RELATED DISORDERS	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
58	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	ST ELEVATION MYOCARDIAL INFARCTION (STEMI)
59	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE
60	LIPID MODIFYING AGENTS	LEFT VENTRICULAR ISCHEMIA
61	LIPID MODIFYING AGENTS	STROKE PREVENTION
62	MINERAL SUPPLEMENTS	WORSENING OF CORONARY ARTERY DISEASE
63	PERIPHERAL VASODILATORS	CORONARY ARTERY DISEASE
64	PSYCHOLEPTICS	ST ELEVATION MYOCARDIAL INFARCTION
65	PSYCHOLEPTICS	WORSENING OF CORONARY ARTERY DISEASE
66	STOMATOLOGICAL PREPARATIONS	ANGINA
67	VITAMINS	WORSENING OF CORONARY ARTERY DISEASE

	ATC Drug Class	Indication
Hyperlipidemia		
1	ANTITHROMBOTIC AGENTS	HYPERLIPIDEMIA
2	DRUGS USED IN DIABETES	DIABETES MELLITUS TYPE I WITH HYPERLIPIDEMIA
3	GENERAL NUTRIENTS	HYPERTRIGLYCERIDEMIA
4	LIPID MODIFYING AGENTS	ACUTE MIOCARDIAL INFARCTION
5	LIPID MODIFYING AGENTS	ANAL FISSURE
6	LIPID MODIFYING AGENTS	ANTIHYPERLIPIDEMIA PROPHYLAXIS
7	LIPID MODIFYING AGENTS	CHOLESTEROLEMIA
8	LIPID MODIFYING AGENTS	CORONARY ARTERY DISEASE
9	LIPID MODIFYING AGENTS	DIABETES MELLITUS TYPE I WITH HYPERLIPIDEMIA
10	LIPID MODIFYING AGENTS	DIETARY SUPPLEMENT
11	LIPID MODIFYING AGENTS	DYSLIPIDEMA
12	LIPID MODIFYING AGENTS	DYSLIPIDEMIA
13	LIPID MODIFYING AGENTS	DYSLIPIDEMIE
14	LIPID MODIFYING AGENTS	FUNCTIONAL DIARRHEA
15	LIPID MODIFYING AGENTS	GENERAL HEALTH
16	LIPID MODIFYING AGENTS	GENERAL NUTRITION
17	LIPID MODIFYING AGENTS	HEALTH MAINTENANCE
18	LIPID MODIFYING AGENTS	HEALTH SUPPLEMENT
19	LIPID MODIFYING AGENTS	HEALTH SUPPLEMENTS
20	LIPID MODIFYING AGENTS	HIGH BLOOD PRESSURE
21	LIPID MODIFYING AGENTS	HIGH CHOLESTEROL
22	LIPID MODIFYING AGENTS	HISTORY OF DYSLIPIDEMIA
23	LIPID MODIFYING AGENTS	HISTORY OF MIX HYPERLIPIDEMIA
24	LIPID MODIFYING AGENTS	HUMAN PAPILLOMAVIRUS (RECTAL)
25	LIPID MODIFYING AGENTS	HYPELIPIDEMIA
26	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLAEMIA
27	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMAIL
28	LIPID MODIFYING AGENTS	HYPERCHOLESTEROLEMIA
29	LIPID MODIFYING AGENTS	HYPERGLYCERIDEMIA
30	LIPID MODIFYING AGENTS	HYPERLIDPDEMA
31	LIPID MODIFYING AGENTS	HYPERLIPDEMIA
32	LIPID MODIFYING AGENTS	HYPERLIPEDEMIA
33	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA

	ATC Drug Class	Indication
34	LIPID MODIFYING AGENTS	HYPERLIPIDEMIA WORSENED
35	LIPID MODIFYING AGENTS	HYPERLIPIEMIA
36	LIPID MODIFYING AGENTS	HYPERTRIGLYCERICEMIA
37	LIPID MODIFYING AGENTS	HYPERTRIGLYCERIDEMIA
38	LIPID MODIFYING AGENTS	INCREASED LIPIDS
39	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA
40	LIPID MODIFYING AGENTS	NUTITIONAL SUPPLEMENT
41	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENT
42	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENTS
43	LIPID MODIFYING AGENTS	PREVENTATIVE
44	LIPID MODIFYING AGENTS	STROKE PREVENTION
45	LIPID MODIFYING AGENTS	SUPLLEMENT
46	LIPID MODIFYING AGENTS	SUPPLEMENT
47	LIPID MODIFYING AGENTS	SUPPLEMENTATION
48	LIPID MODIFYING AGENTS	TACHYARRHYTHMIA
49	LIPID MODIFYING AGENTS	WELLNESS
50	LIPID MODIFYING AGENTS	WORSENING HYPERCHOLESTEROLEMIA
51	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HYPERCHOLESTEROLEMIA

Appendix 6. Programming Specification

General Conventions

1) The standard mock tables (http://gnet/biometrics/stat/doc/Standard%20TFL_Final%20GNET%202009%2005%2015.doc) are default outputs developed based on standard CRF and standard SAP template. Changes to the CRFs or SAP may warrant changes to these outputs.

2) Italicized text in the mocks indicates that the entry is either optional or can be replaced by a more suitable term depending on the content.

3) Whenever possible, do not reference footnote by symbol within the body of the table and table title unless it greatly improves the clarity.

4) Titles should not exceed 128 characters (including the word "table," the table number, punctuation, and spaces). If a title must exceed 128 characters, key descriptive information should be presented in the first 128 characters.

5) For completeness, please always include all the possible categories on standard CRF, including those with zero counts.

6) Treatment groups will be ordered as Gilead product in the first and then the rest of active control groups in alphabetical order, and placebo in the last column. Within each treatment, dose level will be in ascending order. Separate column for total or subtotal are allowed if space permits depending on study design, eg, a subtotal column could combine dose levels within the same treatment.

7) The ordering of these mock tables is the default ordering in the TFLs, ie, enrollment, disposition, demographic, baseline data, efficacy, drug exposure, and safety.

8) Number TFLs consecutively and do not use decimal numbering for unique items.

9) A maximum of three titles and seven footnotes is allowed. Additional lines document the date of data extraction, source of SAS program, output files, and date-time of outputs generated.

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

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

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

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

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

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

    a) Values less than 0.001 → < 0.001

    b) Values 0.001 to less than 0.10 → round to 3 decimal places

    c) Values 0.10 and greater → round to 2 decimal places

12) For lab summaries, tests will be grouped as Chemistry, Hematology, and Metabolic Assessments. Disease related biomarkers, eg, bone biomarkers, will be grouped separately. Summaries will be sorted alphabetically by test within group.

13) Study day: if visit date ≥ first dose date, then study day = visit date – first dose date + 1. If visit date < first dose date, then study day = visit date – first dose date.

Other Definitions

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, 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 and have a screening number. For summarization, same subject is counted only once. DOB and other demographic information such as sex, race, ethnicity, country, and initials will be used for identifying unique screened subjects.

3) Screen failure subjects are the subjects who answered "No" to "Did the subject meet all eligibility criteria?" in Informed Consent and Eligibility Criteria electronic case report form.

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, confirmed by eCRF RAND data.

5) Enrollment by Stratum: using stratum recorded in IXRSRAND.

6) Body mass index (BMI):

   Calculated from height in meters (eg, height in cm/100) and weight in kilograms as:

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

   BMI will be calculated only at baseline. Baseline height and weight will be used for the calculation (height will be obtained from Vital Signs eCRF at screening visit, weight will be obtained from Vital Signs eCRF at baseline visit, if it's missing, weight at screening visit from Vital Signs eCRF will be used).

7) HIV Taqman Calculations:

   If a HIV-1 RNA test value is reported as "< 20 cp/mL HIV-1 RNA Detected" or "No HIV-1 RNA detected", a numeric value of 19 will be used for summary purpose. "No HIV-1 RNA detected" will be treated as < 20 cp/mL.

8) For safety ECGs at postbaseline visits, the most conservative (worst) value within the window will be selected, eg, abnormal will be selected over normal for safety ECG or clinical significant abnormal will be selected over not clinical significant abnormal if there are multiple abnormal findings.

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

   a) CMH test for nominal variable (Y):

```
proc freq order=data;
   tables treat * Y /cmh /*general association test*/
run;
```

   b) CMH test for ordinal variable (Y):

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

   c) Wilcoxon rank sum test for continuous variable (Y):

```
proc npar1way wilcoxon data=xxxx;
   class treat;
   var Y;
run;
```

10) An ARV is current if ARVTYPE_STD = “CU”.

11) Last Dose Date and Last Study Date:

a) Last Dose Date for double-blind phase and open-label phase was defined in SAP Section 3.8.1.

Double-Blind Phase Last Dose Date:

For subjects with a partial last dosing date of the blind study drug (ie, month and year of last dose are known), use the max (the dispensing dates of blinded study drug bottles, blinded study drug start dates and end dates, imputed last dose date [day imputed as 15]) as the final imputed last dose date for the blind study drug. (However if dispensing date’s month is after last dose date’s month, data query is needed.).

Open-label Phase Last Dose Date:

For subjects in the open-label F/TAF analysis set with a partial last dosing date of the open-label F/TAF (ie, month and year of last dose are known), use the max (the dispensing dates of the open-label F/TAF, open-label F/TAF study drug start dates and end dates, imputed last dose date [day imputed as 15]) as the final imputed last dose date for the open-label F/TAF. (However if dispensing date’s month is after last dose date’s month, data query is needed.)

b) Last Study Date is the latest of nonmissing study drug start dates and end dates, clinic visit and laboratory visit dates, including the 30-day follow-up visit date for subjects who prematurely discontinued study or who completed study according to study completion eCRF. Please note, if study drug start date or end date is partially missing, the imputed date (day imputed as 15) will be used.

12) Toxicity Grades:

a) With regards to Triglycerides, LDL and Hypercholesterolemia, if the fasting status is not ‘Y’, in other words it is blank or ‘U’ (for unknown), the lab result value would not be graded as nonfasting values are not interpretable.

b) For toxicity grade summary, we will include all postbaseline graded results up to 30 days after the last dose of study drug, not just those at summarized visits.

c) For hematuria grading, if the laboratory reports urine blood using the plus system (+1, +2, etc) and also provides quantitative results on reflex (ie, urine RBC), summarize only the grade of the urine RBC results, but list both grades of urine blood and urine RBC.

13) Smoking status at baseline

Smoking status at baseline (ie, never smoked, former smoker, and current smoker) will be summarized at baseline as part of the baseline disease characteristics. Specifications about how to classify a subject as prior, current, or never smoker are provided 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 used in determining subjects' smoking status.

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

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

	Selected Substance Use Records							
Former	No	No	Yes	Yes	Yes	No	No	Yes
Current	No	No	No	No	Yes	Yes	Yes	Yes
Post	No	Yes	No	Yes	No	No	Yes	Yes
Smoking History	Never	Never	Former	Former	Current	Current	Current	Current

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

a) 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 completely 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.

   i) The record will be flagged as "Former", if the stop date is before (<) the first dose date.

   ii) The record will be flagged as "Current", 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.

   iii) The record will be flagged as "Post", if the start date is after (>) the first dose date.

b) The start date of the selected record is completely missing. Assuming 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 former and current as follows.

   i) The record will be flagged as "Former", 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.

   ii) The record will be flagged as "Current", if the stop date is on or after (≥) the first dose date or the selected record is marked as ongoing.

c) 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. Assuming the start and end dates are both before the first dose date, the record will be flagged as "Former".

d) 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 may be a data issue and should be queried first. However, this record is flagged as "Current" if the start date is on the first dose; this record is flagged as "Post" if the start date is after the first dose.

14) Efficacy analyses:

a) For the percentage of subjects with HIV-1 RNA < 50 copies/mL or HIV-1 RNA ≥ 50 copies/mL (as determined by the US FDA-defined snapshot algorithm), the treatment difference and 95% CI will be calculated using the exact method. The exact CIs will be calculated using the following code:

```
proc freq data=example noprint;
   tables trtgrpn *response1/out=outp1;
   tables trtgrpn *response2/out=outp2;
run;

data snap;
   set outp1 (in=a);
   if a then grp=1;
   if b then grp=2;
   if a then event=success;
   if b then event=fail;
   keep trtgrpn grp event count;
run;

proc freq data = snap;
   table trtgrpn *event /riskdiff(CL=(exact)) alpha=0.04998;
   weight count;
   exact RISKDIFF(METHOD=SCORE);
   output out=ciexact(keep=_RDIF1_ XL_RDIF1 XU_RDIF1 grp) riskdiff;
run;
```

```
data ciexact(keep=A1 B1 Estimate LowerCL UpperCL ocharc1 sortord statord);
   set  ciexact;
   label Estimate ="Percentage Difference"
   LowerCL = "95% Lower Confidence Limit"
   UpperCL = "95% Upper Confidence Limit"
   A1 = "Percentage of Success in Treat-A"
   B1 = "Percentage of Success in Treat-B";
   Estimate=100* RDIF1 ;
   LowerCL = 100*XL_RDIF1;
   UpperCL = 100*XU_RDIF1;
   A1 = 100* RSK11;
   B1 = 100*_RSK21;
   ocharc1 = right(compress(put(Estimate,8.1)) || '% (' ||
   compress(put(LowerCL,8.1)) || '% to ' || compress(put(UpperCL,8.1))
   || '%)');
   sortord=grp;
   statord='1';
run;
```

Note: response1 and response2 are the response outcome variables. Response1 = 1 if HIV-1 RNA < 50 copies/mL; otherwise response1 = 0. Response2 = 1 if HIV-1 RNA ≥ 50 copies/mL; otherwise response2 = 0.

b) Homogeneity test: homogeneity test of treatment effect between subgroups in percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 96 (Snapshot Algorithm)

   i) For the subgroups of age, sex, race and study drug adherence, the odds ratio and the associated 95% CIs are estimated using a logistic regression model including the third agent stratum (boosted protease inhibitors vs. others), subgroup factor, treatment, and treatment by subgroup factor.

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

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

   Note: response is the response outcome variable (response = 1 if HIV-1 RNA < 50 copies/mL; otherwise response = 0); `barvstra` is the third agent stratum variable (boosted PIs vs. others); trtgrpn is the numeric treatment group variable; agegrp is the subgroup variable for age (< 50 vs ≥ 50).

ii) For the third agent subgroups, the odds ratio and the associated 95% CIs are estimated using a logistic regression model including subgroup factor, treatment, and treatment by subgroup factor.

SAS code to get odds ratio within subgroup:

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

Note: all variables are defined the same as those above in i).

c) Listing for snapshot algorithm outcome:

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

- HIV-1 RNA ≥ 50 copies/mL − Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥ 50 copies/mL
- HIV-1 RNA ≥ 50 copies/mL − Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL
- No virologic Data − Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL
- No virologic Data − Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL

Note:

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

d) 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 ANOVA, including treatment, the third agent stratum (boosted protease inhibitors vs. any other protocol-allowed third agents) as a fixed effect in the model.

SAS code is as follows:

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

Note: `barvstra` is the stratum variable of boosted protease inhibitors vs. any other protocol-allowed third agents; trtgrp is the treatment group variable.

15) Clarification of the following LOCF algorithms:

a) For CD4:

If a value is missing in an analysis visit window, replace the missing value with the last **on-treatment value** observed before the analysis visit window that has the missing value. On-treatment value refers to value up to 1 day after the date of permanent discontinuation of randomized study drug (eg, last dose date).

b) For DXA BMD:

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

Baseline values will be carried forward if there were no non-missing postbaseline observations before a specific visit window.

16) "On-treatment" HIV-1 RNA data in the SAP refer to the data up to 1 day after the date of permanent discontinuation of study drug (eg, last dose date) for the double-blind phase or the open-label phase. For subjects who completed study drug, "on-treatment" data refer to all data for the analysis.

17) For DXA analysis:

a) Variable PCHG when PARAM = "Corrected Bone Mineral Density" and PARCAT2 = "SpineTotalAdequate" for spine or PARCAT2 = "FemurTotal" for hip will be used for percentage change from baseline in BMD analysis.

b) Variable AVAL when PARAM = "Corrected T-Score" and PARCAT2 = "SpineTotalAdequate" for spine or PARCAT2 = "FemurTotal" for hip will be used for defining the clinical BMD status.

18) For TEAE:

Events with Missing Onset Day and/or Month

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

- 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
- The month and year (or year) of the onset date is the same as or before the month and year (or year) of 30th day after the date of the last dose of study drug, and
- End date is as follows:
  - The (complete) end date is on or after the first dose date, or
  - The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or
  - End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date is as follows:

- The (complete) end date is on or after the first dose date, or
- The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or
- End date is completely missing

19) Urine Protein Correction

a) The calibrator material used in the quantitative assay for the measurement of urine protein (UP) was changed globally in Covance on May 27, 2016. All samples reported prior to May 27, 2016 (ie, *RPTDTM* < 'May 27, 2016') were tested by the calibrator material manufactured by Roche Diagnostics, while the samples reported on or after May 27, 2016 were tested by the calibrator material manufactured by Quantimetrix. Covance had 3 regional lab centers to run the samples. Each regional lab center conducted its own alternate (quantitative) method comparison, all of these comparison demonstrate that calibrator materials manufactured by the Roche and Quantimetrix yield comparable results as noted in the table below:

Regional Lab Center	Accession Numbers[a]	Regular Regression for UP Correction[b]	Correlation Coef.	Bias
Indianapolis Auto Chemistry	Start with 65	Y = 1.028 X – 3.70	0.9982	-2.34 (-4.91%)
Geneva Auto Chemistry	Start with 62 or 63	Y = 0.981 X – 1.44	0.9993	-2.42 (-4.74%)
Singapore Auto Chemistry	Start with 64 or 66	Y = 0.980 X – 1.62	0.9996	-2.73 (-5.08%)
BML in China	Start with 67 or 68	NA	NA	NA

a Accession numbers specified which regional lab center tested the sample. For example, samples with accession number started with 65 were tested in Indianapolis Auto Chemistry Center.
b X and Y are the UP results using calibrator materials manufactured by Roche Diagnostics and Quantimetrix, respectively.

b) In order to combine the UP results obtained from the 2 different assay methods for summary/comparison purpose, we will convert the UP results analyzed using the calibrator from Roche (ie, results reported prior to May 27, 2016) to Quantimetrix results by using the regression equation listed in above table.

Original UP based on Reported Date	Original UP Categories	Accession Number	AVALC of Corrected UP ('UP' stands for Original UP)
UP reported on/after May 27, 2016	_ALL_	_ALL_	AVALC of UP
UP reported before May 27, 2016	UP < 4.0	_ALL_	'< 4.0'
	UP ≥ 4.0	Start with 65	1.028 × UP - 3.70; if 1.028 × UP − 3.70 ≥ 4.0 '< 4.0'; if 1.028 × UP - 3.70 < 4.0
		Start with 62 or 63	0.981 × UP − 1.44; if 0.981 × UP − 1.44 ≥ 4.0 '< 4.0'; if 0.981 × UP – 1.44 < 4.0
		Start with 64 or 66	0.980 × UP − 1.62; if 0.980 × UP − 1.62 ≥ 4.0 '< 4.0'; if 0.980 × UP – 1.62 < 4.0

c) If AVALC of the corrected UP is "< 4.0", the AVAL of the corrected UP will be imputed as 3.9 mg/dL.

d) The corrected UP results will be used for the analysis of UPCR.

20) Definition of the category of UPCR in combination with UP

a) First merge UP and UPCR based on the subject identifier and accession number.

b) At each visit, based on UP to select which pair of records should be used for the analysis. That is, once a UP record is selected for that visit, the UPCR with the same accession number (if calculated) will be selected. Please note, UPCR is missing when UP < 4.0 mg/dL.

c) Subject will be classified as "UPCR ≤ 200 mg/g" if UP < 4.0 mg/dL or UPCR ≤ 200 mg/g; Subject will be classified as "UPCR > 200 mg/g" if UPCR > 200 mg/g; Otherwise, subject will be classified as "Missing".

21) Unit conversion for some renal biomarkers derived from related tests with conventional units:

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

22) Calculation of ratios:

To calculate laboratory ratios (eg, urine RBP to creatinine ratio), 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 , the ratio is not calculable (ie, missing). For urine creatinine, a value of "< 1" is handled as a missing value in the calculation of related ratios. For urine protein, a value of "< 4.0" is handled as a missing value in the calculation of UPCR.

23) For clinical BMD status, the following codes will be used to compute the p-values for comparing the two treatment groups using rank analysis of covariance adjusting for the third agent stratum and baseline clinical BMD status:

```
proc rank data=BMD nplus1 ties=mean out=ranks;
   by stratum;
   var BMDstatus  Basestatus;
run;

proc reg data=ranks noprint;
   by stratum;
   model BMDstatus=Basestatus;
   output out=residual r=resid;
run;

proc freq data=residual;
   tables stratum * treatment * resid/noprint cmh2;
run;
```

24) For categories of percentage change from baseline in the hip BMD and spine, the distribution difference in these categories between the treatment groups will be compared using CMH test (row mean scores differ statistic) adjusting for the third agent randomization stratum. SAS codes for treatment comparison will be:

```
proc freq order=data;
   tables stratum * treatment * Y / cmh2 ; /*row mean score test*/
run;
```

25) Direct-measured LDL: conversions between the LDL data from 2nd and 3rd generation testing

LDL testing reagent that Covance uses for direct LDL test has been upversioned from "2nd generation" to "3rd generation". This study will have LDL data from both 2nd and 3rd generation testing: 2nd generation (including RCT2394, RCT2312, and RCT2811) and 3rd generation (RCT3870). A conversion factor will need to be applied to correct for an 11% negative bias in order to combine the direct LDL data from the 2 different reagents for analysis. The conversion formula is:

- 2nd Gen (mmol/L) = (3rd Gen - 0.0626)/0.882.
- 3rd Gen (mmol/L) = (0.882 × 2nd Gen) + 0.626.

For this analysis, since most of the LDL data were from 2nd generation testing, the 3rd generation to the 2nd generation conversion will be applied in the raw data.

For the analysis of change from baseline in 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 new test code (xxxx) will be generated to pool the records from both original 2nd generation (including RCT2394, RCT2312, and RCT2811) and converted 2nd generation (LIP.LDL.00.02) data to calculate the change from baseline in LDL.

For the analysis of toxicity grade for LDL: toxicity grade will be based on the Gilead grading results (ie, toxgrg) from raw values prior to conversion. During ADAM stage, a new test code (xxxx) will be generated to pool the records from both 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)
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PPD	Clinical Research eSigned	09-Jun-2018 10:09:22