STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b Open-Label Pilot Study to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects Harboring the Archived Isolated NRTI Resistance Mutation M184V/M184I
Name of Test Drug:	E/C/F/TAF FDC
Study Number:	GS-US-292-1824
Protocol Version:	Amendment 1
Protocol Date:	19 August 2016
Analysis Type:	Final Analysis
Analysis Plan Version:	3.0
Analysis Plan Date:	31 January 2020
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CK	creatine kinase
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
ESDD	early study drug discontinuation
ET	early termination
FAS	Full Analysis Set
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FDC	fixed dose combination
GFR	glomerular filtration rate
Gilead	Gilead Sciences
Hb	hemoglobin
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HLGT	high level group term
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification
iDMC	Internal Data Monitoring Committee
INSTI	integrase strand transfer inhibitor
ITT	intent to treat
KM	Kaplan-Meier
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
PI	protease inhibitor
PP	per protocol
PRO	patient reported outcomes

PT	preferred term
PVF	pure virologic failure
PVR	pure virologic response
Q1, Q3	first quartile, third quartile
SAE	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SI (units)	international system of units
SOC	system organ class
TAM	thymidine analogue associated mutations
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
UACR	urine albumin to creatinine ratio
UPCR	urine protein to creatinine ratio
ULN	upper limit of normal
VAS	visual analogue scale
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-292-1824. This SAP is based on the study protocol (Amendment 1) dated 19 August 2016 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) fixed dose combination (FDC) after switching from a stable regimen consisting of emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) or abacavir (ABC)/lamivudine (3TC) plus a third antiretroviral agent in maintaining HIV-1 RNA < 50 copies/mL at Week 12 (using pure virologic response) in subjects harboring the archived nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) resistance mutation M184V and/or M184I in HIV-1 reverse transcriptase

The secondary objectives of this study are as follows:

- To determine the safety and tolerability of E/C/F/TAF FDC in subjects switching from 2 NRTI plus third antiretroviral agent regimens
- To evaluate the development of new resistance mutations in subjects who develop virologic failure after switching to E/C/F/TAF FDC
- To determine the durability of efficacy at Weeks 24 and 48 in maintaining HIV-1 RNA < 50 copies/mL using pure virologic response (PVR)

1.2. Study Design

This is an open-label, single arm, multicenter, two part study to evaluate the efficacy and safety of switching to E/C/F/TAF FDC in HIV-1 infected adult subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL) harboring an archived isolated M184V and/or M184I mutation and who have been on a stable regimen consisting of FTC/TDF or ABC/3TC plus a third antiretroviral agent for ≥ 6 consecutive months prior to screening. Eligible subjects will be assigned to E/C/F/TAF FDC.

Enrollment of subjects will proceed in 2 parts: Part 1 and Part 2. Each part will consist of subjects who have a documented presence of M184V and/or M184I mutations (mixtures are acceptable) in reverse transcriptase.

In Part 1, the subjects will have M184V and/or M184I (mixtures are acceptable) in reverse transcriptase WITHOUT any other NRTI resistance mutation (including thymidine analogue-associated mutations (TAMs) [TAMs are: M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N/R], K65R, K70E, T69 insertion, and/or Q151M mutation complex [A62V, V75I, F77L, F116Y, Q151M]. If the rate of virologic failure in Part 1 is deemed acceptable, after the internal Data Monitoring Committee (iDMC) officially completes the interim review, the study will continue to Part 2 (with the expanded entry criteria).

In Part 2, the subjects will have M184V and/or M184I (mixtures are acceptable) in reverse transcriptase WITH or WITHOUT 1 or 2 TAMs. Evidence of K65R, K70E, T69 insertion, and/or Q151M mutation complex in subjects in addition to the resistance mutations above will not be eligible for entry into the study.

The study will consist of a 42-day screening period (within 42 days before Day 1 visit), followed by a 48 week treatment period. After Day 1, subjects will return for study visits at Weeks 4, 8, 12, 16, 24, 36 and 48. End of study is defined as completion of the 48 weeks of treatment and the 30 Day Follow-Up visit.

Plasma HIV-1 RNA, assessment of adverse events (AEs) and concomitant medications are performed at screening, baseline, Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, and Week 48/Early Study Drug Discontinuation (ESDD) visit.

Laboratory analyses (CD4+ cell count, estimated glomerular filtration rate [$eGFR_{CG}$], serum chemistry, hematology, urinalysis and urine chemistry, pregnancy testing [for females of childbearing potential]), and vital signs are performed at screening, baseline, Week 4, Week 8, Week, 12, Week 24, Week 36, and Week 48/ESDD visit. Metabolic assessments are performed at baseline, Week 24, and Week 48.

12-Lead electrocardiogram (ECG) (performed supine) is collected at screening and Week 48/ESDD only.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies (ie, HBV virus surface antigen [HBsAg], hepatitis B core antibody [HBcAb], and hepatitis C virus [HBCAb] serologies [reflex HCV RNA is performed in subjects with positive HCVAb serology]) are performed at screening only. Height is collected at screening only.

For further details of assessments taken at each visit, see Schedule of Assessments, Appendix 1.

1.3. Sample Size and Power

The primary analysis will describe the point estimate and 95% confidence interval (CI) around the proportion of subjects with HIV-1 RNA < 50 copies/ mL for the primary endpoint. If the observed pure virologic response rate is 90%, then with 100 participants, the width of the 95% CI will be ± 5.9% (large sample size approximation and binomial distribution).

After the Week 12 (iDMC review for Part 1, the actual pure virologic response rate in Part 1 was determined to be 100%. Based on this, it was reasonable to assume that the observed pure virologic response rate for the study will be 95% or higher, and the sample size of the study was reduced to 64 subjects. Under this assumption, with a sample size of 64 subjects, the width of the 95% CI will be ± 5.3% or lower (large sample size approximation and binomial distribution).

2. TYPE OF PLANNED ANALYSIS

2.1. Week 12 Internal Data Monitoring Committee Analysis

An internal Data Monitoring Committee (iDMC) reviewed the progress of the study and performed interim reviews of safety and efficacy data in order to protect subject welfare.

The initial interim review was conducted after all subjects enrolled in Part 1 completed the Week 12 visit assessment or prematurely discontinued study drug.

The iDMC's role and responsibilities, including the scope of analysis to be provided to the iDMC, were provided in a mutually agreed upon charter, which defined the iDMC membership, meeting logistics, and meeting frequency.

2.2. Interim Analysis

No formal interim efficacy analysis, with the possibility of early termination for efficacy or futility, is planned.

2.3. Final Analysis

After all subjects (Part 1 and Part 2) have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set unless otherwise specified, and sorted by subject identification (ID) number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within subject. The part (e.g. Part 1 or Part 2) under which subjects were enrolled will be included in the listings.

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If a subject was not dosed with study drug, the date of enrollment will be used instead of the first dose date of study drug. For screen failures, age as calculated on the date that informed consent was signed will be used.

In general, permanent discontinuation of study drug refers to premature discontinuation of study drug or completeness of study drug.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided overall and by Parts 1 and 2.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis set includes all subjects who enrolled into the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) will include all the subjects who were enrolled and received at least one dose of study drug. For the FAS, all efficacy data will be included, unless specified otherwise. The FAS is the primary analysis set for the efficacy analyses.

Subjects meeting the following criteria will be excluded from the FAS:

- Subjects who took Stribild or Descovy as part of the baseline antiretroviral (ARV) regimen and thus violated the inclusion criterion.

3.1.3. Safety Analysis Set

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

3.2. Strata and Covariates

There is no stratification for enrollment.

3.3. Subject Subgroup Grouping

The subjects will be grouped by Part 1, Part 2 and overall.

3.4. Multiple Comparisons

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

3.5. Missing Data and Outliers

3.5.1. Missing Data

A missing data point for a given study visit may be due to any of the following reasons:

- A visit occurred in the window but data were not collected or were unusable
- A visit did not occur in the window
- A subject permanently discontinued from the study before reaching the window.

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

For missing last dosing date of study drug, imputation rules are described in Section 3.5.1 and the SAP Appendix 5. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for concomitant medications in Section 7.5.2 as well as the SAP Appendix 5.

3.5.2. Outliers

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

3.6. Data Handling Conventions and Transformations

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

- A value that is 1 unit less than the limit of quantitation (LOQ) 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 < 20 and < 5.0, values of 19 and 4.9 will be used for calculation of summary statistics, respectively. An exception to this rule is: for values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.

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

- The LOQ 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 LOQ).

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

3.7. Analysis Visit Windows

3.7.1. Definition of Study Day

Study Day 1 is defined as the day when the first dose of study drug (ie, E/C/F/TAF) was taken, as recorded on the Study Drug Administration eCRF form.

Study Days are calculated relative to Study Day 1. For events that occurred on or after 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 Dose Date is the latest nonmissing end date of study drug (E/C/F/TAF) recorded on the 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 Study Drug Completion eCRF.

If the date of last dose is missing (eg, only year of last dose is known or completely missing due to lost to follow-up) for subjects who prematurely discontinued study drug, or for subjects who completed study drug, the latest of nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the date of 30-day follow-up visit will be used to impute the last dose date. For other partial missing last dose date, please see SAP Appendix 5 for details.

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 Value for HIV-1 RNA, CD4+ cell count, CD4%, hematology, chemistry, urinalysis and urine chemistry laboratory tests, fasting glucose and lipid panels, $eGFR_{CG}$, cystatin C testing, vital signs and weight, safety electrocardiogram (ECG), Visual Analogue Scale (VAS) Adherence Questionnaire, Medical Outcome Study Short Form-36 Questionnaire (SF-36), HIV Treatment Satisfaction Questionnaire (HIVTSQ) (Status at Day 1 only), Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F), and EQ-5D is defined as the last nonmissing value obtained on or prior to Study Day 1.

3.7.2. Analysis Visit Windows

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

The analysis windows for HIV-1 RNA and VAS are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for HIV-1 RNA and VAS

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	140
Week 24	168	141	210
Week 36	252	211	294
Week 48	336	295	378

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

Table 3-2. Analysis Visit Windows for CD4+ Cell Count, CD4%, Hematology, Chemistry, Urinalysis, Urine Chemistry Laboratory Tests, eGFR$_{CG}$, Vital Signs and Weight

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	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

The analysis windows for fasting glucose, lipid panels, EQ-5D, SF-36, and FACIT-F are provided in Table 3-3.

Table 3-3. Analysis Visit Windows for Fasting Glucose, Lipid Panels, EQ-5D, SF-36, and FACIT-F

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	168	2	252
Week 48	336	253	420

Lipid panel includes total cholesterol, HDL, direct LDL and triglycerides.

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

Table 3-4. Analysis Visit Windows for ECG

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 48	336	2	671

The analysis windows for HIVTSQs (at Day 1 Only) and HIVTSQc are provided in Table 3-5.

Table 3-5. Analysis Visit Windows for HIVTSQs (at Day 1 Only) and HIVTSQc

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	98
Week 24	168	99	252
Week 48	336	253	420

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

Depending on the statistical analysis method, single values may be 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 (geometric mean for HIV-1 RNA and arithmetic mean for others) will be computed for that day.

- For postbaseline visits:

  For key efficacy and safety data (ie, HIV-1 RNA level, CD4+ cell count, and CD4%), 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 1 record on the selected day, the average will be taken (geometric mean for HIV-1 RNA and arithmetic mean for others).

If multiple 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. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of subjects enrolled in each country and by each investigator within a country will be summarized for all subjects in the Safety Analysis Set by Parts 1 and 2.

The enrollment related data will be listed.

4.1.2. Disposition of Subjects

A summary of subject disposition will be provided overall and by Parts 1 and 2. This summary will present the number and/or percentage of subjects screened, screen failure subjects who were not enrollment, subjects who met all eligibility criteria and were not enrolled, subjects enrolled, subjects enrolled but not treated, subjects in the Safety Analysis Set, subjects in the FAS.

In addition, the number and percentage of subjects meeting the following criteria will be summarized:

- Prematurely discontinued study drug (with summary of reasons for discontinuing treatment)
- Prematurely discontinued from the study (with summary of reasons for discontinuing the study).

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

A data listing of reasons for premature study drug discontinuation will be provided.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.2.1. Duration of Exposure to 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 1 decimal place, eg, 4.5 weeks).

Duration of exposure to study drug will be summarized overall and by Parts 1 and 2 using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum). The number and percentage of subjects in the following categories will also be summarized: ≥ 4 weeks [28 days], ≥ 8 weeks [56 days], ≥ 12 weeks [84 days], ≥ 16 weeks [112 days], ≥ 24 weeks [168 days], ≥ 36 weeks [252 days], and ≥ 48 weeks [336 days]. These categories start with a cumulative count thus subjects who complete the study will be counted from the first category up.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier (KM) method for all subjects in the Safety Analysis Set and by Parts 1 and 2.

A KM plot of the estimates for time to premature discontinuation will be generated.

4.2.2. Adherence to Study Drug

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

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

$$\text{Adherence (\%)} \quad 100 \times \frac{\text{Total Number of Pills Taken}}{\text{Total Number of Pills Prescribed}}$$

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

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

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

Descriptive statistics for adherence to study drug regimen (n, mean, SD, median, Q1, Q3, minimum and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided overall and by Parts 1 and 2 for subjects who return at least 1 bottle and have calculable adherence during the study in the Safety Analysis Set.

4.3. Protocol Deviations

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

5. BASELINE DATA

5.1. Demographics

Subject demographic data (age, sex, race, and ethnicity) and baseline characteristics (body weight, height, body mass index [BMI]) will be summarized overall and by Parts 1 and 2 using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. The summaries of demographic data and baseline characteristics will be provided using the Safety Analysis Set. Age is calculated as age in years at first dose of study drug.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized overall and by Parts 1 and 2:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4+ cell count (/μL)
- CD4+ cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- HIV risk factors (mode of infection): (a) Heterosexual Sex; (b) Homosexual Sex; (c) IV Drug Use; (d) Transfusion; (e) Vertical Transmission; (f) Other; (g) Unknown
- HIV disease status: (a) Asymptomatic; (b) Symptomatic HIV Infection; (c) AIDS; (d) Unknown
- HBV Surface Antigen Status (Yes, No)
- HCV Antibody Status (Yes, No)
- Estimated GFR by CG (see Section 7.3.2.1)
- Estimated GFR by CKD-EPI (see Section 7.3.2.2)
- Proteinuria by urinalysis (dipstick)
- Tobacco smoking history (Current/Former)
- Genetic mother/father/ brother/sister with myocardial infarction/stroke before 50 years-old?
- Currently using indinavir, lopinavir, or abacavir

- Baseline alanine aminotransferase (ALT) (U/L)
- Baseline aspartate aminotransferase (AST) (U/L)
- Baseline platelet count ($10^3/\mu L$)

A by-subject listing of baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

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

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 12 as defined by PVR.

6.1.1.1. Definition of Pure Virologic Response at Week 12

The following criterion is considered for classifying subjects as a pure virologic responder at Week 12:

- No confirmed rebound (ie, no instances of either HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits or last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study) by the upper limit of the Week 12 analysis window.

Note: For confirmation of virologic rebound, the first HIV-1 RNA datum must occur on or before the upper limit of the Week 12 analysis window. The confirming event (ie, the second of the 2 consecutive HIV-1 RNA values or premature study discontinuation) can occur after the upper limit of the Week 12 analysis window.

Subjects who meet the above criterion are PVRs at Week 12; otherwise subjects are pure virologic failures (PVFs) at Week 12.

6.1.1.2. Joint Distribution of Pure Virologic Failure and Study Drug Discontinuation

PVF at Week 48 is defined similary as PVF at Week 12, except that the time point is at Week 48. For subjects with PVF at Week 48, event time is defined as the day of the first occurrence of confirmed HIV-1 RNA ≥ 50 copies/mL or the collection time of last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study.

Drug discontinuation (DC) is defined as subjects who prematurely discontinued study drug on or prior to the upper limit of the Week 48 analysis window. The premature study drug discontinuation date is the last dose date defined in Section 3.7.1.

To better understand the relationship between study drug discontinuation and pure virologic failure by Week 48, subjects will be classified into the following 4 categories:

- **Success** is defined as subjects who were pure virologic responders and did not discontinue study drug prematurely.
- **PVF alone** is defined as subjects who were pure virologic failures but did not discontinue study drug prematurely.

- **DC alone** is defined as subjects who were pure virologic responders but discontinued study drug prematurely.

- **PVF and DC** is defined as subjects who were pure virologic failures and discontinued study drug prematurely.

For 'DC alone' and 'PVF and DC' categories, reasons for DC will be grouped into 3 mutually exclusively categories: (1) **DC due to drug**, including discontinuation due to lack of efficacy, death, or AE; (2) **DC due to choice**, including discontinuation due to noncompliance, withdrew consent, protocol violation, or investigator's discretion (3) **DC due to administration**, including lost to follow-up or pregnancy. For each premature study drug discontinuation group under 'PVF and DC' category, outcomes will further be broken down into 3 mutually exclusively categories based on the sequence when PVF and DC occurred:
(1) **PVF-DC** is defined as subjects who met the criteria for PVF followed by DC;
(2) **PVF/DC** is defined as subjects who met the criteria for PVF and DC at the same time;
(3) **DC-PVF** is defined as subjects who had DC first and then met the criteria for PVF.

The pure virologic response analysis will be descriptive in nature using the FAS only. No inferential statistics will be provided.

6.1.1.3. Time to Pure Virologic Failure Analysis

For subjects who do not experience a confirmed rebound (ie, HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits or the last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study) by the data cut, subjects will be censored at the last HIV-1 RNA collection date. For subjects who experience confirmed rebound, the time to PVF will be defined as the earlier time of 2 consecutive HIV-1 RNA ≥ 50 copies/mL or the last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study.

Time to PVF will be analyzed using the Kaplan-Meier method by treatment group using the FAS. The log rank test will be performed to compare the difference in time to PVF between the 2 treatment groups stratified by the prior treatment regimen (ie, STB, ATR, or ATV/boosted+TVD).

Lastly, subjects who failed according to snapshot algorithm, pure virologic failure analysis algorithms, or had premature study drug discontinuation by Week 48 will be listed.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

No formal statistical hypotheses are being tested.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The number and proportion of subjects with PVR and PVF at Week 12 will be summarized overall and by Parts 1 and 2. Two-sided 95% CIs will be constructed for the overall estimate of PVR and PVF using the normal approximation and the exact method.

6.1.4. Secondary Analysis for the Primary Efficacy Endpoint

6.1.4.1. Analysis of Pure Virologic Response at Week 12

Subjects who took Stribild or Descovy as part of the baseline ARV regiment were excluded from the FAS. A sensitivity analysis will be performed by including these subjects in the PVR analysis.

6.1.5. Subgroup Analysis for the Primary Efficacy Endpoint

No subgroup analyses will be performed.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- HIV-1 RNA< 50 copies/mL at Weeks 24 and 48 using PVR (See Section 6.2.2.2)
- HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and 48 using the Food and Drug Administration (FDA) snapshot analysis (sensitivity analysis)
- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm.
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as defined by 2 different missing data imputation methods.
- The change from baseline in CD4+ cell count at Weeks 12, 24, and 48
- The change from baseline in CD4% at Weeks 12, 24, and 48

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

6.2.2.1. Analysis of Pure Virologic Response at Weeks 24 and 48

The number and proportion of subjects with PVR at Weeks 24 and 48 will be summarized overall and by Parts 1 and 2. Two-sided 95% CIs will be constructed for the overall estimate of PVR using the normal approximation and the exact method.

6.2.2.2. Time to Pure Virologic Failure Analysis

For subjects who do not experience a confirmed rebound (ie, HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits or the last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study), subjects will be censored at the last HIV-1 RNA collection date. For subjects who experience confirmed rebound, the time to PVF will be defined as the earlier time of 2 consecutive HIV-1 RNA ≥ 50 copies/mL or the last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study.

Time to PVF will be analyzed using the KM method by Part 1 and Part 2 using the FAS.

Lastly, subjects who failed according to snapshot algorithm, pure virologic failure analysis algorithms, or had premature study drug discontinuation by Week 48 will be listed.

6.2.2.3. Analysis of proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm

The analysis windows for Weeks 12, 24, and 48 are defined in Table 3-1. All HIV-1 RNA data collected on-treatment (eg, 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 analysis window
- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects:
    a. Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the analysis window, or
    b. Who do not have on-treatment HIV-1 RNA data in the analysis window and
        1) Who discontinue study drug prior to or in the analysis window due to lack of efficacy (note: Lack of efficacy is defined as having the check-box for Lack of efficacy marked on the Study Drug Completion eCRF), or
        2) Who discontinue study drug prior to or in the analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL
        3) Who discontinue study drug prior to or in the analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL
- **No Virologic Data (in the Window):** this includes subjects who do not have on-treatment HIV-1 RNA data in the analysis window because of the following:
        1) Discontinuation of study drug prior to or in the analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
        2) Discontinuation of study drug prior to or in the analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
        3) Missing data during the window but on study drug.

Virologic outcomes for the US FDA-defined snapshot algorithm will also be listed.

Note: For switch study populations, the US FDA-defined snapshot algorithm classifies subjects who discontinue study drug due to AE or death and have the last available on-treatment HIV-1 RNA value ≥ 50 copies/mL as HIV-1 RNA value ≥ 50 copies/mL. For a treatment naïve study population, the US FDA-defined snapshot algorithm classifies these subjects as having No Virologic Data in the analysis window.

The number and percentage of subjects achieving HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL, and reasons for no virologic data at Weeks 12, 24, and 48 will be summarized overall and by Parts 1 and 2. Two-sided 95% CIs will be constructed for overall estimates using the exact method.

6.2.2.4. Analysis of proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm

The number and percentage of subjects achieving HIV-1 RNA < 20 copies/mL, HIV-1 RNA ≥ 20 copies/mL, and reasons for no virologic data at Weeks 12, 24, and 48 will be summarized overall and by Parts 1 and 2. Two-sided 95% CIs will be constructed for the overall estimate of the proportion of subjects with HIV-1 RNA < 20 copies/mL using the exact method.

6.2.2.5. Analysis of Proportion of Subjects with HIV-1 RNA < 50 copies/mL (Missing Excluded and Missing Failure Approaches)

The proportion of subjects with HIV-1 RNA < 50 copies/mL will also be analyzed using the following 2 methods for imputing missing HIV-1 RNA values, where the proportions will be expressed as percentages in all tables, listings, and figures:

- Missing Failure (M F)

  In this approach, all missing data will be treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for percentages at a visit is based on the number of subjects in the FAS.

- Missing Excluded (M E)

  In this approach, all missing data will be excluded in the computation of the proportions (ie, missing data points will be excluded from both the numerator and denominator). The denominator for percentages at a visit is based on the number of subjects in the FAS with non-missing HIV-1 RNA value at that visit.

For both M F and M E analyses, the number and percentage of subjects with HIV-1 RNA in the following categories will be summarized:

- < 50 copies/mL
- < 20 copies/mL

  < 20 copies/mL Not Detectable

  < 20 copies/mL Detectable

- 20 to < 50 copies/mL
- ≥ 50 copies/mL
- Missing (only applicable for M F analysis)

The proportion of subjects with HIV-1 RNA < 50 copies/mL as defined by the 2 different missing data imputation methods will be summarized for each visit. Two-sided 95% CIs will be constructed using the exact method.

For M F analysis, results will be summarized and plotted for visits up to and including Week 12. For M E analysis, results will be summarized for each visit.

6.2.2.6. Analysis of CD4+ cell count

Analysis of CD4+ cell count will be based on on-treatment data (ie, data collected up to 1 day after the last dose date of study drug) using observed data (ie, missing will be excluded) for subjects in the FAS.

The change from baseline in CD4+ cell count at Weeks 12, 24, and 48 will be summarized overall and by Parts 1 and 2 using descriptive statistics. The change from baseline in CD4+ cell count will be similarly summarized at the visits other than Weeks 12, 24, and 48.

6.2.2.7. Analysis of CD4%

Analysis of CD4% will be based on on-treatment data (ie, up to 1 day after the last dose date of study drug) using observed data (ie, missing will be excluded) for subjects in the FAS.

The change from baseline in CD4% at Weeks 12, 24, and 48 will be summarized overall and by Parts 1 and 2 using descriptive statistics. The change from baseline in CD4% will be similarly summarized at the visits other than Weeks 12, 24, and 48.

6.3. Changes From Protocol-Specified Efficacy Analyses

For the primary efficacy endpoint, PVR at Week 12, the protocol specifies that 95% CIs will be generated using the normal approximation method, but in the SAP, both the normal approximation and the exact methods are specified.

7. SAFETY ANALYSES

Safety data will be summarized for the subjects in the Safety Analysis Set. All safety data collected on or after the date of the first dose of study drug up to the last dose date of study drug plus 30 days for subjects who have permanently discontinued study drug, or all available data for subjects who are ongoing will be summarized overall and by Parts 1 and 2, unless specified otherwise. All safety data will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version). 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

AEs 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 AEs are those for which the investigator answers "Related" to the question "Related to Study Treatment?" in the CRF. Events for which the investigator did not record relationship to study drug will be considered related to study drug. Data listings will show relationship as missing.

7.1.4. Relationship of AEs 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 the AE listing.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the clinical database. The clinical database will be reconciled with the SAE database from the Pharmacovigilance and Epidemiology (PVE) Department before database finalization.

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment-Emergent Adverse Events

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

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

7.1.6.2. Incomplete Dates

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

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

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

7.1.7. Summaries of Adverse Events and Deaths

A brief summary of AEs will show overall and by Parts 1 and 2, the number and percentage of subjects who had:

- Any TEAE
- Any Grade 2, 3 or 4 TEAE
- Any Grade 3 or 4 TEAE
- Any study-drug-related TEAE
- Any Grade 2, 3 or 4 study-drug-related TEAE
- Any Grade 3 or 4 study-drug-related TEAE

- Any serious TEAE
- Any serious study-drug-related TEAE
- Any TEAE leading to premature study drug discontinuation
- Treatment-emergent death

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

Summaries (number and percentage of subjects) of AEs (by SOC, and PT) will be provided overall and by Parts 1 and 2 using the Safety Analysis Set as follows:

- All TEAEs
- All Grade 2, 3, or 4 TEAEs
- Grade 3 or 4 TEAEs
- All study-drug-related TEAEs
- All Grade 2, 3, or 4 study-drug-related TEAEs
- All Grade 3 or 4 study-drug-related TEAEs
- All serious TEAEs
- All study-drug-related serious TEAEs
- All TEAEs that caused premature discontinuation from study drug

Multiple events will be counted only once per subject in each summary. For data presentation, SOC will be ordered alphabetically, and then by 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
- Adverse events leading to premature discontinuation of study drug
- Deaths report

7.1.8. Additional Analysis of Adverse Events

7.1.8.1. Stage 3 Opportunistic Illnesses in HIV

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

7.1.9. Fracture Events

The preferred terms included in analysis for fracture events are defined based on the Standardized MedDRA Query (SMQ) of osteoporosis/osteopenia of fractures and HLGT of fractures from MedDRA. The lists of PTs selected by clinical review from all the PT terms under SMQ of osteoporosis/osteopenia fractures and HLGT of fractures are presented in Appendix 4. Fracture events will be listed only.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.6.

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

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided overall and by Parts 1 and 2 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

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

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

7.2.1.1. Metabolic Assessments

For the metabolic assessments (including total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], total cholesterol to HDL ratio, triglycerides, and glucose), only those measurements under fasting status will be summarized overall and by Parts 1 and 2.

In addition, the number and percentage of subjects who took lipid modifying medications at the study entry and initiated the medications during the study will be provided, respectively. A lipid modifying medication is defined as a medication with drug class "LIPID MODIFYING AGENTS" and CMDECOD containing the wording of "STATIN".

A sensitivity analysis of fasting lipid tests (including total cholesterol, LDL, HDL, triglycerides, and total cholesterol to HDL ratio) will be performed by excluding subjects who took lipid modifying medications at study entry or initiated the medications during the study: baseline, Week 48. Only subjects with both baseline and Week 48 values will be included in the analysis.

7.2.1.2. Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized overall and by Parts 1 and 2. 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 x (4.0 albumin (g/dL)). Toxicity grading for calcium will be applied based on the corrected values.

7.2.2. Graded Laboratory Values

The criteria specified in the study protocol will be used to grade laboratory results as Grade 0, mild (Grade 1), moderate (Grade 2), severe (Grade 3) or potentially 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; analyses for each direction (i.e., increased, decreased) will be presented separately.

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

If there is any laboratory toxicity grading scale overlapping with normal reference ranges (eg, Grade 1 scale overlaps with normal reference ranges), laboratory values within normal range will be grade 0, except 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 time post-baseline up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 will be considered treatment emergent.

For serum glucose, 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 instead of treatment-emergent laboratory abnormalities will be summarized.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) of laboratory abnormalities will be provided overall and by Parts 1 and 2 (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 non-missing post-baseline values. A listing of all graded laboratory abnormalities and all Grade 3 or Grade 4 laboratory abnormalities will be provided.

7.2.3. Liver-related Laboratory Evaluations

The number and percentage of subjects will be summarized overall and by Parts 1 and 2 for the following liver-related laboratory tests and categories:

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

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

7.3. Renal Safety Analyses

7.3.1. Serum Creatinine

The baseline, postbaseline and change from baseline in serum creatinine at each visit will be summarized overall and by Parts 1 and 2 for each visit using descriptive statistics.

The median (Q1, Q3) of change from baseline in observed serum creatinine over time will be plotted.

7.3.2. Estimated Glomerular Filtration Rate

7.3.2.1. Estimated Glomerular Filtration Rate: Cockroft-Gault

The Cockroft-Gault formula will be used to calculate $eGFR_{CG}$:

$eGFR_{CG}$ (mL/min) [(140 age (years)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72),

where weight is total body mass in kilograms, and SCr is serum creatinine.

Summary of baseline, post-baseline, and change from baseline in $eGFR_{CG}$ will also be provided overall and by Parts 1 and 2.

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

7.3.2.2. Estimated Glomerular Filtration Rate: CKD-EPI (cystatin C)

The CKD-EPI (cystatin C) formula will be used to calculate $eGFR_{CKD\ EPI}$:

$eGFR_{CKD\ EPI}$ (mL/min/1.73 m^2) $133 \times \min(Scys/0.8, 1)^{0.499} \times \max(Scys/0.8, 1)^{1.328} \times 0.996^{Age}$ [× 0.932 if female],

where Scys is serum cystatin C (mg/L), min (Scys/0.8,1) indicates the minimum of Scys/κ or 1, and max (Scys/0.8,1) indicates the maximum of Scys/κ or 1.

Only baseline values will be summarized. See Section 5.2 for details.

7.3.3. Proteinuria by Urinalysis (Dipstick)

The proteinuria by urinalysis (dipstick) toxicity grade (Grade 0 to Grade 3) at Weeks 12, 24, and 48 will be summarized by baseline proteinuria toxicity grade and treatment. In addition, the last on-treatment proteinuria toxicity grade will also be summarized by baseline proteinuria toxicity grade and overall and by Parts 1 and 2. On-treatment values include data collected after the last dose date up to the last dose date plus 1 day for subjects who permanently discontinued study drug.

7.3.4. Proteinuria by Quantitative Assessment

The baseline, postbaseline, changes from baseline, and percentage change from baseline in urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR) will be summarized overall and by Parts 1 and 2 for each visit using descriptive statistics.

The number and percentage of subjects with UPCR $\leq$ 200 mg/g versus > 200 mg/g will be summarized by baseline category at Weeks 12, 24, and 48, and based on the last on-treatment value (up to 1 day after the last dose date of study drug {KDIGO Guideline Development Staff 2013}).

The number and percentage of subjects with UACR < 30 mg/g versus $\geq$ 30 mg/g will be summarized by baseline category at Weeks 12, 24, and 48, and the last on-treatment value (after first dose date up to 1 day after the last dose date of study drug {KDIGO Guideline Development Staff 2013}).

Median (Q1, Q3) percentage change from baseline in UPCR and UACR over time will be plotted.

7.4. Vital Signs

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided overall and by Parts 1 and 2 for each visit and vital sign as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

A listing of weight, BMI, height, and vital signs will be provided.

7.5. Prior and Concomitant Medications

7.5.1. Nonstudy-Drug Antiretroviral Medications

Nonstudy drug ARV medications used prior to, during, or after the study (if collected), will be coded using the Gilead-modified World Health Organisation (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.

Nonstudy-drug ARV medication with an end date one day before the first dose date of study drug will be considered as nonstudy-drug ARV medication received immediately prior to the first dose date of study drug (or pre-switch ARV used).

Nonstudy-drug ARV medication received immediately prior to the first dose date of study drug will be summarized by ARV drug class and generic name for subjects in the Safety Analysis Set. Multiple drug use (by drug class or generic name) will be counted only once per subject. Drug classes were presented alphabetically and generic names within each drug class were presented by descending order of the total frequency. No inferential statistics will be provided.

7.5.2. Concomitant Non-Antiretroviral Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications from Study Day 1 up to the date of last dose of study drug will be summarized (number and percentage of subjects) overall and by Parts 1 and 2 by preferred name. Multiple drug use (by preferred name) will be counted once only per subject. The summary will be sorted alphabetically by decreasing total frequency within a class.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone if month is not recorded) of start or stop date will be used to determine whether the non-ARV medications 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 meeting any of following criteria:

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

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

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

7.6. 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 overall and by Parts 1 and 2 and by baseline ECG 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.

7.7. Other Safety Measures

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

7.8. Subject Subgroup for Safety Endpoints

Not applicable.

7.9. Changes From Protocol-Specified Safety Analyses

No change from protocol-specified safety analyses is planned.

8. PATIENT REPORT OUTCOMES

The Patient reported outcomes (PROs) include: (1) Visual Analogue Scale (VAS) adherence questionnaires; (2) Short Form-36 Version 2 Health Survey (SF-36); (3) HIVTSQs Status version (at Day 1 only)/HIVTSQc Change version (post-Day 1); (4) FACIT-F; (5) EQ-5D. Unless otherwise stated, multiple responses and out of range responses will be set to missing and missing responses will not be imputed. The Safety Analysis Set will be used in all analyses. No inferential statistics will be provided. All reported data will be listed.

8.1. Adherence – Visual Analogue Scale (VAS) Adherence Questionnaire

The VAS adherence questionnaire is a 3-item, self-reported questionnaire that assesses the degree to which ARV medication was taken in the past 30 days.

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

8.1.1. VAS Statistical Method

The VAS (%) absolute value and its change from baseline at each visit will be summarized overall and by Parts 1 and 2 using descriptive statistics. Number of days with missed doses in the past 30 days and past 4 days will be summarized categorically (eg, < 2, 2 to < 4, 4 to < 6, ≥ 6 for the past 30 days; 0 and > 0 for the past 4 days) at each visit.

8.2. SF-36 (Version 2) Health Survey

The SF-36 Version 2 is a 36-item, self-reported, generic, comprehensive, and widely used questionnaire that is designed to measure health-related quality of life in the general population, as well as in subject groups with diverse chronic diseases including HIV/AIDS. Responses from the 36 items are used to construct 8 health domains including physical functioning, social functioning, general health, vitality, bodily pain, mental health, role capacity-physical, and role capacity-emotional. Furthermore, 2 summary scores, the Physical Component Summary (PCS) score and Mental Component Summary (MCS) score, aggregate information from the 8 SF-36 domains in a way that captures 80% to 85% of the variance in the 8 domains.

8.2.1. Scoring the SF-36

The 8 domains and 2 component summary scores of the SF-36 will be calculated according to "How to Score Version 2 of the SF-36 Health Survey (Chapters 6 and 7)" {Maruish 2011} published by QualityMetric Inc *{using 2009 population norms}*. Scores for each of the 8 domain including PCS and MCS range from 0 to 100 with higher score indicating a better functioning.

8.2.2. SF-36 Statistical Analysis Method

Scores for each domain, PCS, and MCS will be summarized overall and by Parts 1 and 2 for each visit using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum).

A by-subject listing for the scores for each domain, PCS, and MCS will be provided by subject ID number and visits in chronological order.

8.3. HIV Treatment Satisfaction Questionnaire

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

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

Table 8-1 lists the questions, possible responses for both the status and change questionnaires, as well as the subscale each question belongs to.

Table 8-1. List of Items on the HIVTSQ

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

8.3.1. HIV Treatment Satisfaction Questionnaires Statistical Analysis Method

The HIVTSQs scale and subscale totals at baseline, and the HIVTSQc scale and subscale totals at each visit will be summarized using descriptive statistics.

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

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

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

8.4. Functional Assessment of Chronic Illness Therapy – Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) was adopted from the Functional Assessment of Cancer Therapy in 1997 as an instrument to measure the health related quality of life (HRQOL) of patients with chronic illnesses. FACIT-F contains 13 additional items not in the initial FACIT questionnaire under the heading “Additional Concerns” that comprise the fatigue subscale.

The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Version 4.0 is a 40 item, self-reported questionnaire which measures the HRQOL of patients with chronic illnesses over a one-week time interval. Each item takes a range of 0 4, corresponding to (0) Not at all; (1) A little bit; (2) Somewhat; (3) Quite a bit; (4) Very much. Forty individual items generate 5 subscales: (1) Physical Well-Being (PWB); (2) Social/Family Well-Being (SWB); (3) Emotional Well-Being (EWB); (4) Functional Well-Being (FWB); and (5) Fatigue Subscale (FS).

8.4.1. Scoring the Functional Assessment of Chronic Illness Therapy – Fatigue

Full details of the scoring of the FACIT-F are available in the initial publication. A brief overview appears below. Instructions for scoring each subscale are presented in the table below. If “Reverse item?” is “Yes”, then the response should be reversed by substracting the response from “4” (ie, New response 4 original response).

Missing values will not be imputed. Prorating subscale scores is acceptable as long as more than 50% of items were answered (a minimum of 4 out of 7 items, 4 of 6 items, and 7 out of 13 items). This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered.

Table 8-2. Items by Subscale and Scoring Algorithm for FACIT-F

Subscale	Item Code	Reverse item?	Scoring Algorithm
PWB	GP1	Yes	Sum individual item score → Multiply by 7 → Divide by the number of answered items *(Score range: 0 28)*
	GP2	Yes	
	GP3	Yes	
	GP4	Yes	
	GP5	Yes	
	GP6	Yes	
	GP7	Yes	
SWB	GS1	No	Sum individual item score --> Multiply by 7 ---> Divide by the number of answered items *(Score range: 0 28)*
	GS2	No	
	GS3	No	
	GS4	No	
	GS5	No	
	GS6	No	
	GS7	No	
EWB	GE1	Yes	Sum individual item score → Multiply by 7 → Divide by the number of answered items *(Score range: 0 24)*
	GE2	No	
	GE3	Yes	
	GE4	Yes	
	GE5	Yes	
	GE6	Yes	
FWB	GF1	No	Sum individual item score → Multiply by 7 → Divide by the number of answered items *(Score range: 0 28)*
	GF2	No	
	GF3	No	
	GF4	No	
	GF5	No	
	GF6	No	
	GF7	No	

Subscale	Item Code	Reverse item?	Scoring Algorithm
FS	HI7	Yes	Sum individual item score → Multiply by 13 → Divide by the number of answered items *(Score range: 0 52)*
	HI12	Yes	
	An1	Yes	
	An2	Yes	
	An3	Yes	
	An4	Yes	
	An5	No	
	An7	No	
	An8	Yes	
	An12	Yes	
	An14	Yes	
	An15	Yes	
	An16	Yes	

PWB Physical Well Being; SWB Social/Family Well Being; EWB Emotional Well Being; FWB Functional Well Being; and FS Fatigue Subscale.

Three aggregate scores can be computed as shown in Table 8-3, subject to the requirements listed:

Table 8-3. Computation of Aggregate Scores

Aggregate Score	Formula	Requirement
FACIT-F Trial Outcome Index (TOI)	PWB+FWB+FS	PWB, FWB, FS all nonmissing
FACT-G total score	PWB + SWB + EWB + FWB	At least 80% nonmissing (ie, 22 out of 27)
FACIT-F total score	PWB + SWB + EWB + FWB + FS	At least 80% nonmissing (ie, 33 out of 40)

FACIT F Functional Assessment of Chronic Illness Therapy Fatigue; PWB Physical Well Being; SWB Social/Family Well Being; EWB Emotional Well Being; FWB Functional Well Being; and FS Fatigue Subscale.

8.4.2. Functional Assessment of Chronic Illness Therapy – Fatigue Analysis Method

Scores for each subscale and aggregate score will be summarized overall and by Parts 1 and 2 for each visit using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum).

A by-subject listing for the scores for each subscale and aggregate score will be provided by subject ID number and visits in chronological order.

8.5. EQ-5D-3L

The EQ-5D-3L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state"). This information can be used as a quantitative measure of health outcomes as judged by the individual respondents {Rabin 2011}.

8.5.1. Scoring the EQ-5D-3L Descriptive System

The scores of EQ-5D-3L descriptive system are described in Table 8-4.

Table 8-4. Scores of EQ-5D-3L Descriptive System

Original Response Category	Score
No problems	1
Some problems	2
Extreme problems	3

Note: Missing values is to be coded as 9. Ambiguous values (eg, 2 boxes are ticked for a single dimension) should be treated as missing values.

8.5.2. EQ-5D Single Summary Index

EQ-5D health states, defined by the EQ-5D descriptive system, will be converted into a single summary index using the UK time trade-off (TTO) value set (Appendix 3). For example, the health state is 11111 if the response to each of the 5 dimensions of the EQ-5D system is 1. Since there are 3 possible responses (ie, 1, 2 and 3) to each of the 5 dimensions of the EQ-5D system, there are 3^5 243 health states in total.

For the UK TTO value set, the index is calculated for each of the health states (see Appendix 3 for details). Missing responses for EQ-5D-3L Questionnaire will not be imputed. If any one of the 5 dimensions is missing, the index will be missing.

8.5.3. Scoring the EQ VAS

For EQ VAS, the value is scored from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state"). Missing values is to be coded as "999". Ambiguous values (eg. the line crosses the VAS twice) should be treated as missing values.

8.5.4. EQ-5D Statistical Analysis Method

For the 5 descriptive scores, the number and percentage of subjects with a response of "No problems", "Some problems" and "Extreme problems" will be summarized overall and by Parts 1 and 2 for each visit. No inferential statistics will be provided.

For the index score and VAS score, change from baseline will be summarized overall and by Parts 1 and 2 for each visit. No inferential statistics will be provided.

In addition, responder analysis will be performed based on the index score to determine the proportion of patients with health worsening or improvement by visit. Worsening or improvement in health (see Table 8-5), as measured by the proportion of patients experiencing a decrease or an increase of ≥ 0.07, which is the minimally important difference (MID) {Walters 2005}, in the index score. No inferential statistics will be provided.

Table 8-5. Response Category for Responder Analysis

Response Category	Change from Baseline in Index Score
Worsening	≤ -0.07
No change	> -0.07 and < 0.07
Improvement	≥ 0.07

9. REFERENCES

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

Maruish ME. User's manual for the SF-36v2 Health Survey. 3rd ed. Lincoln, RI: Quality Metric Incorporated.; 2011.

Rabin R, Oemar M, Oppe M. EQ-5D-3L User Guide: Basic information on how to use the EQ-5D-3L instrument Version 4.0. EuroQol Group, 2011:

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

Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005;14 (6):1523-32.

10. SOFTWARE

SAS® Software Version 9.1. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision
06 November, 2019	List of abbreviations	List of abbreviations updated.	To update the list of abbreviations.
06 November, 2019	Section 1.2	Added K60R to list of resistance criteria for Part 1 subjects.	To be align with the protocol.
31 January, 2020	Section 5.2	Removed the summary of baseline medical history: diabetes, hypertension, cardiovascular disease, and hyperlipidemia.	Data not present in the SDTM data.
06 November, 2019	Section 7.1.7	Removed HLT from AE summaries	Removed HLT due to small sample sizes.
06 November, 2019	Appendix 3	Added Appendix 3.	To provide more details on UK TTO Value Set for EQ-5D-3L Questionnaire.
06 November, 2019	Appendix 4	Added Appendix 4.	To provide more details on baseline medical history: diabetes, hypertension, cardiovascular disease, and hyperlipidemia.
31 January, 2020	Appendix 4	Removed Appendix 4.	Data not present in the SDTM data.
06 November, 2019	Appendix 7	Added Item 41).	To provide more programming details on “currently using abacavir, indinavir or lopinavir”.

12. APPENDICES

Appendix 1. Schedule of Assessents
Appendix 2. Flowchart of US FDA-Defined Snapshot Algorithm (for Switch Study Trial)
Appendix 3. UK TTO Value Set for EQ-5D-3L Questionnaire
Appendix 4. Fracture Events
Appendix 5. Programming Specification

Appendix 1. Schedule of Assessents

Study Procedure	Screening	Day 1[b]	End of Week[c]							30 Day Follow-up	ESDD[d]
			4	8	12	16[t]	24	36	48		
Informed Consent	X										
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[e]	X	X					X		X		X
Symptom Directed Physical Exam[f]			X	X	X			X		X	
12 Lead ECG (Performed Supine)	X								X		X
Vital Signs and Weight	X	X	X	X	X		X	X	X	X	X
Height	X										
Urinalysis and Urine Chemistry	X	X	X	X	X		X	X	X	X	X
Urine Storage Sample		X	X	X	X		X	X	X		X
Urine Pregnancy Test[g]		X	X	X	X		X	X	X		X
Serum Pregnancy Test[g]	X										
Chemistry Profile[h]	X	X	X	X	X		X	X	X	X	X
Metabolic Assessments[i]		X					X		X		
Estimated GFR[j]	X	X	X	X	X		X	X	X		X
Hematology Profile[k]	X	X	X	X	X		X	X	X	X	X
Plasma HIV 1 RNA[l]	X	X	X	X	X	X	X	X	X	X	X

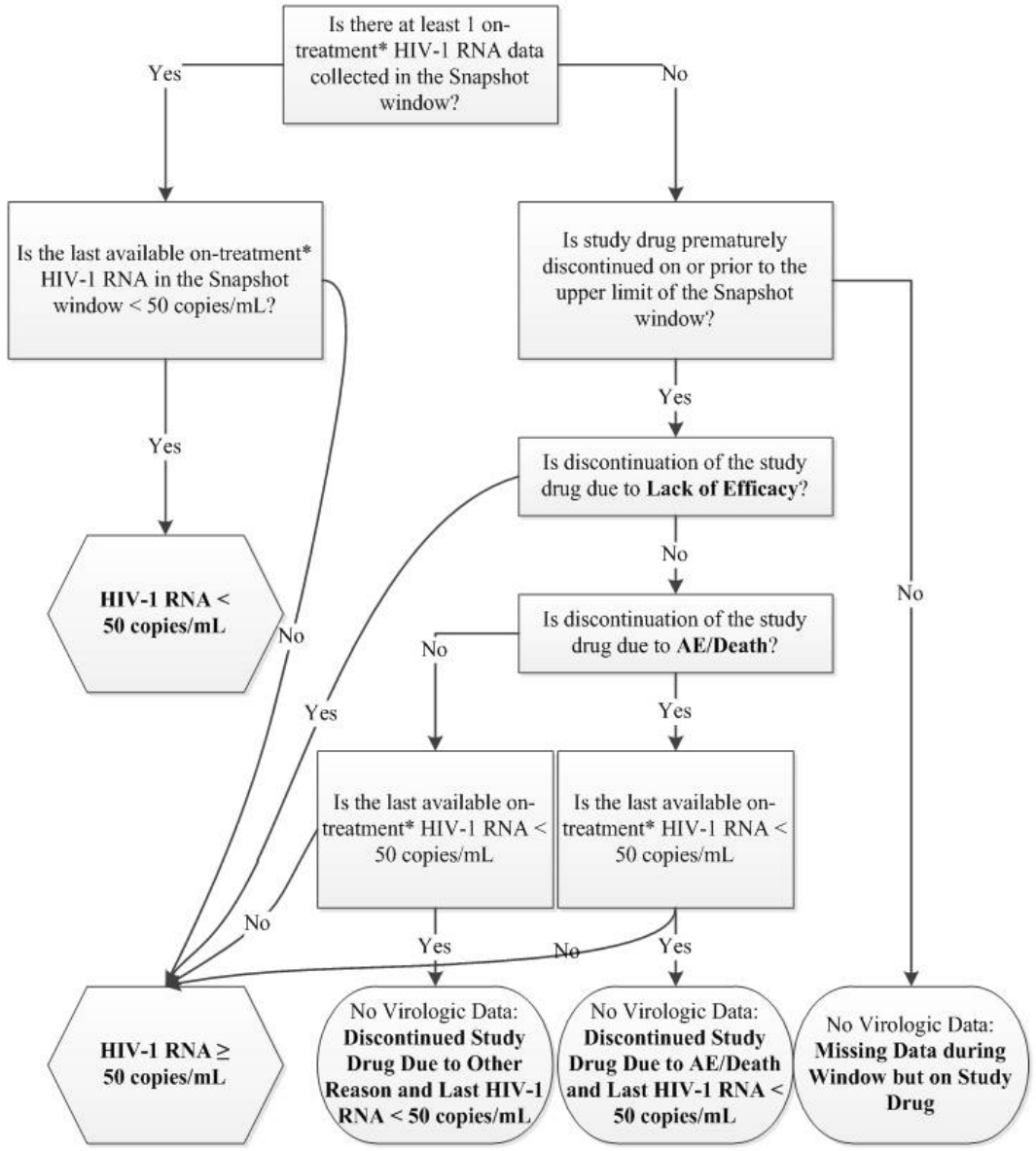
Study Procedure	Screening	Day 1[b]	End of Week[c]							30 Day Follow-up	ESDD[d]
			4	8	12	16[t]	24	36	48		
CD4+ Cell Count	X	X	X	X	X		X	X	X	X	X
HBV and HCV Serologies[m]	X										
Plasma Sample Storage[n]		X	X	X	X	X	X	X	X		X
PPD											
Whole Blood Sample[p]	X										
HIV 1 Genotype/Phenotype[q]									X		X
Cystatin C Testing[u]		X									
Questionnaires: VAS, HIVTSQ[s], HIVTSQ[c], EQ 5D, SF 36, and FACIT F[r]		X	X	X	X	X	X	X	X		X
Enrollment		X									
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X	X[s]		X[s]

a Evaluations to be completed within 42 days prior to the Day 1 visit.
b Subjects will be dispensed study drug on the Day 1 visit; initiation of treatment with the study drug must take place within 24 hours after the Day 1 Visit. E/C/F/TAF FDC will be provided by the Sponsor.
c All study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Week 16, ± 6 days of the protocol specified date through Week 36, and all other study visits except Week 48. Week 48 visit window is ± 6 weeks of the protocol specified visit date, and this clinical visit window coincides with the Week 48 statistical analysis window for HIV 1 RNA.
d Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through Week 48 visit even if the subject discontinues study drug.
e Complete physical examination every 48 weeks (urogenital/anorectal exams will be performed at the discretion of the Investigator)
f Symptom directed physical examination as needed.
g Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
h Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium and sodium. At visits in which metabolic assessments are to be performed, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.

i Metabolic Assessments: Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL and triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
j Estimated GFR according to the Cockcroft Gault formula for creatinine clearance
k CBC with differential and platelet count
l If the HIV 1 RNA value is ≥ 50 copies/mL a retest should be collected at a scheduled or unscheduled visit, 2 4 weeks after the date of the original test (except for screening and Day 1 results). HIV 1 genotype/phenotype resistance testing only conducted for subjects with confirmed virologic failure with HIV 1 RNA value ≥ 50 copies/mL. Subjects should be managed according to Figure 6 1 of the protocol, Management of Virologic Failure.
m Hepatitis B virus surface antigen serology (HBsAg) and Hepatitis C virus (HBVAb) serology (reflex HCV RNA is performed in subjects with positive HCVAb serology)
n Plasma sample storage for safety and virology testing
PPD
p Whole blood sample collected at Screening Visit for proviral genotype analysis of archived resistance
q HIV 1 genotype/phenotype resistance testing only conducted for subjects with unconfirmed virologic rebound with HIV 1 RNA value ≥ 50 copies/mL at the Week 48 and
r ESDD visit. Subjects should be managed according to Figure 6 1 of the protocol, Management of Virologic Failure. HIV 1 genotype/phenotype sample collection to occur if subjects
s HIV 1 RNA lab values meet the criteria described in this section.
EQ 5D, SF 36, and FACIT F will be administered at Day 1, Weeks 24 and 48. VAS will be administered on Day 1, Weeks 4, 8, 12, 16, 24, 36, 48 and ESDD. HIVTSQs will be administered on Day 1. HIVTSQc will be administered at Weeks 4, 24, 48 and ESDD.
t Drug accountability only; study drug will not be dispensed at this visit.
u At Week 16, subject will have only the following assessments completed: Review of AEs and changes in concomitant medications, blood sample collection for plasma
v HIV 1 RNA and plasma sample storage. Study drug dispensation and accountability will be documented.
w Estimated GFR according to CKD EPI formula for cystatin clearance will be used for Nephrotoxicity Management per Section 7.5.4 of the protocol.

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

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



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

Appendix 3. UK TTO Value Set for EQ-5D-3L Questionnaire

For the UK TTO value set, the index is calculated for each of the health states based on the following equation:

Index 1 0.081 0.069 MO2 0.314 MO3 0.104 SC2 0.214 SC3 0.036 UA2 0.094 UA3 0.123 PD2 0.386 PD3 0.071 AD2 0.236 AD3 0.269 N3

- -0.081 is a constant term for any dysfunctional state.
- MO2 is a dummy variable for level 2 of Mobility.
- MO3 is a dummy variable for level 3 of Mobility.
- SC2 is a dummy variable for level 2 of Self Care.
- SC3 is a dummy variable for level 3 of Self Care.
- UA2 is a dummy variable for level 2 of Usual Activities.
- UA3 is a dummy variable for level 3 of Usual Activities.
- PD2 is a dummy variable for level 2 of Pain/Discomfort.
- PD3 is a dummy variable for level 3 of Pain/Discomfort.
- AD2 is a dummy variable for level 2 of Anxiety/Depression.
- AD3 is a dummy variable for level 3 of Anxiety/Depression.
- N3 is a dummy variable that represents level 3 occurs within at least one dimension.

The index score is missing if any one of the 5 dimensions is missing.

UK TTO					
Health State	**Index Value**	**Health State**	**Index Value**	**Health State**	**Index Value**
11111	1.000	12233	-0.112	21132	0.124
11112	0.848	12311	0.452	21133	-0.041
11113	0.414	12312	0.381	21211	0.814
11121	0.796	12313	0.216	21212	0.743
11122	0.725	12321	0.329	21213	0.309
11123	0.291	12322	0.258	21221	0.691
11131	0.264	12323	0.093	21222	0.620
11132	0.193	12331	0.066	21223	0.186
11133	0.028	12332	-0.005	21231	0.159
11211	0.883	12333	-0.170	21232	0.088
11212	0.812	13111	0.436	21233	-0.077
11213	0.378	13112	0.365	21311	0.487
11221	0.760	13113	0.200	21312	0.416
11222	0.689	13121	0.313	21313	0.251
11223	0.255	13122	0.242	21321	0.364
11231	0.228	13123	0.077	21322	0.293
11232	0.157	13131	0.050	21323	0.128
11233	-0.008	13132	-0.021	21331	0.101
11311	0.556	13133	-0.186	21332	0.030
11312	0.485	13211	0.400	21333	-0.135
11313	0.320	13212	0.329	22111	0.746
11321	0.433	13213	0.164	22112	0.675
11322	0.362	13221	0.277	22113	0.241
11323	0.197	13222	0.206	22121	0.623
11331	0.170	13223	0.041	22122	0.552
11332	0.099	13231	0.014	22123	0.118
11333	-0.066	13232	-0.057	22131	0.091
12111	0.815	13233	-0.222	22132	0.020
12112	0.744	13311	0.342	22133	-0.145
12113	0.310	13312	0.271	22211	0.710
12121	0.692	13313	0.106	22212	0.639
12122	0.621	13321	0.219	22213	0.205

UK TTO					
Health State	**Index Value**	**Health State**	**Index Value**	**Health State**	**Index Value**
12123	0.187	13322	0.148	22221	0.587
12131	0.160	13323	-0.017	22222	0.516
12132	0.089	13331	-0.044	22223	0.082
12133	-0.076	13332	-0.115	22231	0.055
12211	0.779	13333	-0.280	22232	-0.016
12212	0.708	21111	0.850	22233	-0.181
12213	0.274	21112	0.779	22311	0.383
12221	0.656	21113	0.345	22312	0.312
12222	0.585	21121	0.727	22313	0.147
12223	0.151	21122	0.656	22321	0.260
12231	0.124	21123	0.222	22322	0.189
12232	0.053	21131	0.195	22323	0.024

UK TTO					
Health State	**Index Value**	**Health State**	**Index Value**	**Health State**	**Index Value**
22331	-0.003	31223	-0.059	33122	-0.072
22332	-0.074	31231	-0.086	33123	-0.237
22333	-0.239	31232	-0.157	33131	-0.264
23111	0.367	31233	-0.322	33132	-0.335
23112	0.296	31311	0.242	33133	-0.500
23113	0.131	31312	0.171	33211	0.086
23121	0.244	31313	0.006	33212	0.015
23122	0.173	31321	0.119	33213	-0.150
23123	0.008	31322	0.048	33221	-0.037
23131	-0.019	31323	-0.117	33222	-0.108
23132	-0.090	31331	-0.144	33223	-0.273
23133	-0.255	31332	-0.215	33231	-0.300
23211	0.331	31333	-0.380	33232	-0.371
23212	0.260	32111	0.232	33233	-0.536
23213	0.095	32112	0.161	33311	0.028
23221	0.208	32113	-0.004	33312	-0.043

UK TTO					
Health State	**Index Value**	**Health State**	**Index Value**	**Health State**	**Index Value**
23222	0.137	32121	0.109	33313	-0.208
23223	-0.028	32122	0.038	33321	-0.095
23231	-0.055	32123	-0.127	33322	-0.166
23232	-0.126	32131	-0.154	33323	-0.331
23233	-0.291	32132	-0.225	33331	-0.358
23311	0.273	32133	-0.390	33332	-0.429
23312	0.202	32211	0.196	33333	-0.594
23313	0.037	32212	0.125		
23321	0.150	32213	-0.040		
23322	0.079	32221	0.073		
23323	-0.086	32222	0.002		
23331	-0.113	32223	-0.163		
23332	-0.184	32231	-0.190		
23333	-0.349	32232	-0.261		
31111	0.336	32233	-0.426		
31112	0.265	32311	0.138		
31113	0.100	32312	0.067		
31121	0.213	32313	-0.098		
31122	0.142	32321	0.015		
31123	-0.023	32322	-0.056		
31131	-0.050	32323	-0.221		
31132	-0.121	32331	-0.248		
31133	-0.286	32332	-0.319		
31211	0.300	32333	-0.484		
31212	0.229	33111	0.122		
31213	0.064	33112	0.051		
31221	0.177	33113	-0.114		
31222	0.106	33121	-0.001		

Appendix 4. Fracture Events

The selected PTs from the SMQ of osteoporosis/osteopenia and HLGT of fractures based on clinical review are listed as follows.

Selected PTs Based on SMQ of Osteoporosis/Osteopenia and HLGT of Fractures
Acetabulum fracture
Ankle fracture
Atypical femur fracture
Atypical fracture
Avulsion fracture
Bone fissure
Bone fragmentation
Cervical vertebral fracture
Chance fracture
Clavicle fracture
Closed fracture manipulation
Comminuted fracture
Complicated fracture
Compression fracture
Craniofacial fracture
Epiphyseal fracture
External fixation of fracture
Facial bones fracture
Femoral neck fracture
Femur fracture
Fibula fracture
Flail chest
Foot fracture
Forearm fracture
Fracture
Fracture displacement
Fracture of clavicle due to birth trauma
Fracture treatment
Fractured coccyx

Selected PTs Based on SMQ of Osteoporosis/Osteopenia and HLGT of Fractures
Fractured ischium
Fractured sacrum
Fractured skull depressed
Greenstick fracture
Hand fracture
Hip fracture
Humerus fracture
Ilium fracture
Impacted fracture
Internal fixation of fracture
Jaw fracture
Limb fracture
Lisfranc fracture
Lower limb fracture
Lumbar vertebral fracture
Multiple fractures
Open fracture
Open reduction of fracture
Open reduction of spinal 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

Selected PTs Based on SMQ of Osteoporosis/Osteopenia and HLGT of Fractures
Spinal compression fracture
Spinal fracture
Sternal fracture
Stress fracture
Tartrate-resistant acid phosphatase decreased
Thoracic vertebral fracture
Tibia fracture
Torus fracture
Traumatic fracture
Ulna fracture
Upper limb fracture
Vertebroplasty
Wrist fracture
Vertebral body replacement

Note: AEs are coded by MedDRA 22.0.

Appendix 5. 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 date 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, study day visit date first dose date +1.
If visit date < first dose date, study day visit date first dose date.

Other Definitions

14) 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 enrolled and never dosed with study drug, age will be calculated from the date of enrollment.

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

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

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

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

19) Body mass index (BMI)

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

BMI will be calculated only at baseline. Baseline height and weight will be used for the BMI (weight [kg])/ (height [meters]^2) 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).

20) Please note, "Not Permitted" or missing categories will be excluded for p value generation for categorical data analysis (eg, CMH test or Fisher exact test).

21) 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.

22) 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.

23) Last Dose Date and Last Study Date

a) Last Dose Date (ie, TRTEDTC or TRTEDT in ADSL)

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

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

- If the date of last dose is missing (eg, only year of last dose is known or completely missing due to lost to follow-up), use the maximum of study drug start dates and end dates, clinic visit dates (i.e., visit dates from vital sign and ECG forms), and laboratory visit dates excluding the 30-day follow-up visit to impute the last dose date.

b) Last Study Date is the maximum of nonmissing study drug start dates and end dates, clinic visit dates (i.e., visit dates from vital sign and ECG forms) 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. If subject died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date.

24) Toxicity Grades:

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

b) 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.

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

25) "On-treatment" HIV-1 RNA data in the SAP refer to the data up to 1 day after the date of premature discontinuation of study drug (eg, last dose date).

26) Primary and Efficacy analyses:

a) 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 for the following categories:

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

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

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

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

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

b) For patients discontinued study drugs, if the last HIV-1 RNA (< 50 copies/mL) was on the same day as the start date of a new non-study ARV, the subjects was not a failure for the Snapshot outcome.

c) For a subject who completed the study drug with Week 48 HIV-1 RNA missing, snapshot outcome for such subject would be "Missing data during the windows but on study drug".

27) 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

28) 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) The corrected UP results will be used for the following analysis and referred as "UP" in following text. If AVALC of the corrected UP is "< 4.0", the AVAL of the corrected UP will be imputed as 3.9 mg/dL.

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

- Urine RPB (μg/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
- Urine Albumin (mg/dL) to creatinine (mg/dL) ratio: 1 (mg/dL) / (mg/dL) 1000 × mg/g

30) Calculation of ratios

To calculate laboratory ratios (eg, urine RPB 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.

31) Combined category of UP and UPCR

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".

32) Prior ARV

Non-study drug ARVs collected in prior ARV form with start date and stop date completely missing are considered "not concomitant".

33) Lipid modifying medication analyses:

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

- Subjects who took lipid modifying medications at study entry refer to the subjects who use of the lipid modifying agents at study day 1 (ie, the first dose date). More specifically, subjects with "Lipid Modifying Agent Use at Study Entry" include those subjects in Safety Analysis Set with: 1) any selected CM record with the start date ≤ the first dose date, and 2) the end date of the selected CM record is ongoing or the end date of the selected CM record ≥ the first dose date.

- Subjects who initiated lipid modifying medications during the study include the subjects in the Safety Analysis Set who didn't take lipid modifying medications at study entry and met the following criteria: 1) for subjects who permanently discontinued study drug with any selected CM record started after the first dose date and on and prior to the last dose date; 2) for subjects who are still on study drug with any selected CM records started after the first dose date.

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

- Lipid modifying medications with the start date prior to the first dose date and the end date completely unknown were considered as being taken at study entry.

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

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

36) For the PRO data, data up to 30 day after the last dose date for subjects who permanently discontinued of study drug will be summarized.

37) For PRO data, unless otherwise stated, multiple responses and out of range responses will be set to missing and missing responses will not be imputed.

    Out of range value is determined based on the following table for within-range response values:

    SF-36v2 Health Survey:

	Response	
Question	**Min**	**Max**
1, 2, 4a to 4d, 5a to 5c, 6, 8, 9a to 9i, 10, 11a to 11d	1	5
3a to 3j	1	3
7	1	6

VAS adherence questionnaire:

Questions	Response	
	Min	Max
1	0	100
2	0	30
3	0	4

38) Computing EQ-5D index values with SAS using the UK TTO value set

The variables for the 5 dimensions of the EQ-5D descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. The variable 'UK_TTO' contains the values of the EQ-5D index.

You can copy and paste the syntax below directly into the SAS syntax window.

```
*****************************************************************
*  SAS syntax code for the computation of index  *
*  values with the UK MVH A1 TTO value set  *
*****************************************************************;

data Euroqol.Uk_data;
set Euroqol.EQ5D_states;

UK_TTO = 1;

if (mobility = 2) then UK_TTO = UK_TTO   0.069;
if (mobility = 3) then UK_TTO = UK_TTO   0.314;

if (selfcare = 2) then UK_TTO = UK_TTO   0.104;
if (selfcare = 3) then UK_TTO = UK_TTO   0.214;

if (activity = 2) then UK_TTO = UK_TTO   0.036;
if (activity = 3) then UK_TTO = UK_TTO   0.094;

if (pain = 2) then UK_TTO = UK_TTO   0.123;
if (pain = 3) then UK_TTO = UK_TTO   0.386;

if (anxiety = 2) then UK_TTO = UK_TTO   0.071;
if (anxiety = 3) then UK_TTO = UK_TTO   0.236;

if (mobility ne 1) or (activity ne 1) or (selfcare ne 1) or (pain ne 1) or
(anxiety ne 1) then UK_TTO = UK_TTO   0.081;
if (mobility = 3) or (selfcare = 3) or (activity = 3) or (pain = 3) or
(anxiety = 3) then UK_TTO = UK_TTO   0.269;

if (mobility = .) or (selfcare = .) or (activity = .) or (pain = .) or
(anxiety = .) then UK_TTO = . ;

output;
run;
```

39) Smoking status at baseline

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

41) A subject is currently taking abacavir if the ingredient in the ARV form (variable INGRED) contains the substring “ABC” at baseline. Similarly, a subject is considered currently taking indinavir or lopinavir if the abbreviation contains the substring “IDV” or “LPV”.