STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b, Randomized, Open-Label Study to Evaluate Switching from a Tenofovir Disoproxil Fumarate (TDF) Containing Regimen to Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 60 Years
Name of Test Drug:	E/C/F/TAF FDC
Study Number:	GS-US-292-1826
Protocol Version (Date):	Amendment 1 (01 June 2016)
Analysis Type:	Final
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Analysis Plan Author(s):	PPD

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LIST OF ABBREVIATIONS

3TC	lamivudine
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ART	antiretroviral therapy
AST	aspartate aminotransferase
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
FAS	Full Analysis Set
FDC	fixed dose combination
FTC	emtricitabine
Gilead	Gilead Sciences
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B virus surface Antigen
HCVAb	hepatitis C virus antibody
HLT	high level term
IWRS	interactive web response system
LTT	lowest level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
PT	preferred term
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SBR	stay on baseline regimen
SD	standard deviation
SOC	system organ class
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for the final analysis for Study GS-US-292-1826. This SAP is based on the study protocol (Amendment 1) dated 01 June 2016 and the electronic case report form (eCRF). The SAP will be finalized prior to the data finalization date. 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 safety of E/C/F/TAF relative to unchanged current antiretroviral therapy (ART) by assessing spine and hip bone mineral density (BMD) measured at Week 48 in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years

The secondary objectives of this study are as follows:

- To evaluate spine and hip BMD at Week 24
- To evaluate maintenance of HIV-1 RNA suppression < 50 copies/mL between regimens at Weeks 24 and 48
- To evaluate the safety and tolerability of the two treatment groups through Week 48

1.2. Study Design

This is a randomized, open-label, multicenter, active-controlled study to evaluate switching from tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) or lamivudine (3TC)-containing 'backbone' (maximum of 2 nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs]) regimen plus a third agent to E/C/F/TAF fixed dose combination (FDC) in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years. Subjects with Hepatitis B co-infection will not be excluded. Eligible subjects are randomly assigned to 1 of the following treatment groups in a 2:1 ratio:

- Treatment Group 1: FDC of elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg (E/C/F/TAF) daily (n = 100);
- Treatment Group 2: Remain on current TDF and FTC or 3TC-containing 'backbone' (maximum of 2 NRTIs) regimen plus continuing third agent (SBR) (n = 50).

Central randomization is used. The randomization schedule is stratified by a bivariate cut-point of the screening spine and hip BMD T-score (< −1.00 or ≥ −1.00).

The randomized treatment duration is 48 weeks. After screening, eligible subjects will be randomized to Treatment Group 1 or 2 and treated for 48 weeks. Following the screening and Day 1 visits, subjects will return for study visits at Weeks 4, 8, 12, 24, 36, and 48.

Plasma HIV-1 RNA, laboratory analyses (CD4+ cell count, estimated glomelular filtration rate ($eGFR_{CG}$), serum chemistry, hematology, urinalysis and urine chemistry, pregnancy testing [for females of childbearing potential]), vital signs, assessment of adverse events (AEs) and concomitant medications are performed at screening, baseline, Week 4, Week 8, Week, 12, Week 24, Week 36, and Week 48/Early Discontinuation (ED) visit.

Blood and urine for evaluation of bone and renal safety, inflammation and platelet and coagulation function are performed at baseline, Week 4, Week 12, Week 24, and Week 48.

Metabolic assessments are performed at baseline, Week 24, and Week 48. Dual-energy X-ray absorptiometry (DXA) scans will be performed at screening, Week 24, and Week 48.

12-Lead ECG (Performed Supine) is collected at screening and Week 48/Early Study Drug Discontinuation (ESDD) visit only.

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

In Study GS-US-292-0109 (virologically-suppressed subjects switched from E/C/F/TDF to E/C/F/TAF) for subjects 55 or older, the mean percent change from baseline at Week 48 in hip BMD was +1.21 in the TAF group and −0.35 in the TDF group. The SD was 2.93 for the difference between the 2 groups resulting in an effect size of 0.53. The mean percent change from baseline at Week 48 in spine BMD was +1.71 in the TAF group and −1.32 in the TDF group. The SD was 4.24 for the difference between the 2 groups resulting in an effect size of 0.71. Given 150 subjects in the present study, there is at least 90% power to detect an effect size of 0.71 in spine BMD at Week 48 with a Type I error rate of $\alpha = 0.03$ and a power of 75% for hip BMD at Week 48 with $\alpha = 0.02$ (in the situation that spine BMD is not statistically significantly different) or 85% with $\alpha = 0.05$ in the situation that spine BMD is statistically significantly different) for an effect size of 0.53.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

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

2.2. Final Analysis

After all subjects 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.

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

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

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

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 by the specified treatment group.

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) will include all the subjects who (1) are randomized into the study, (2) have received at least one dose of study drug (either E/C/F/TAF or SBR on or after Day 1), and (3) did not have any major protocol violations (eg, not on a TDF and FTC or 3TC-containing ARV regimen at baseline). Unless specified otherwise, the FAS will include all efficacy data, including data collected after the last dose of study drug. The FAS is the primary analysis set for the efficacy analyses.

3.1.3. Safety Analysis Set

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

3.1.4. DXA Analyses Set

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

3.1.4.1. Spine DXA Analysis Set

The Spine DXA Analysis Set will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, (3) have nonmissing screening spine BMD values, and (4) did not have any major protocol violations (eg, not on a TDF and FTC or 3TC-containing ARV regimen at baseline). Subjects will be grouped according to the treatment they actually received.

3.1.4.2. Hip DXA Analysis Set

The Hip DXA Analysis Set will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, (3) have nonmissing screening hip BMD values, and (4) did not have any major protocol violations (eg, not on a TDF and FTC or 3TC-containing ARV regimen at baseline). Subjects will be grouped according to the treatment they actually received.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set, and FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the safety analysis set including the Hip and Spine DXA analysis sets, subjects will be grouped according to actual treatment received. The actual treatment received will be considered to be different from the randomized treatment only when the actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the the interactive web response system (IWRS) in a 2:1 allocation ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- Spine BMD T-score (< -1.00 or ≥ -1.00) at Screening
- Hip BMD T-score (< -1.00 or ≥ -1.00) at Screening

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

3.4. Examination of Subject Subgroups

The stratification factor of hip and spine BMD T-score is used only to maintain balance between the treatment groups.

3.4.1. Subject Subgroups for Efficacy

There are no prespecified subject subgroupings for efficacy analyses.

3.4.2. Subject Subgroups for Safety

There are no prespecified subject subgroupings for safety analyses.

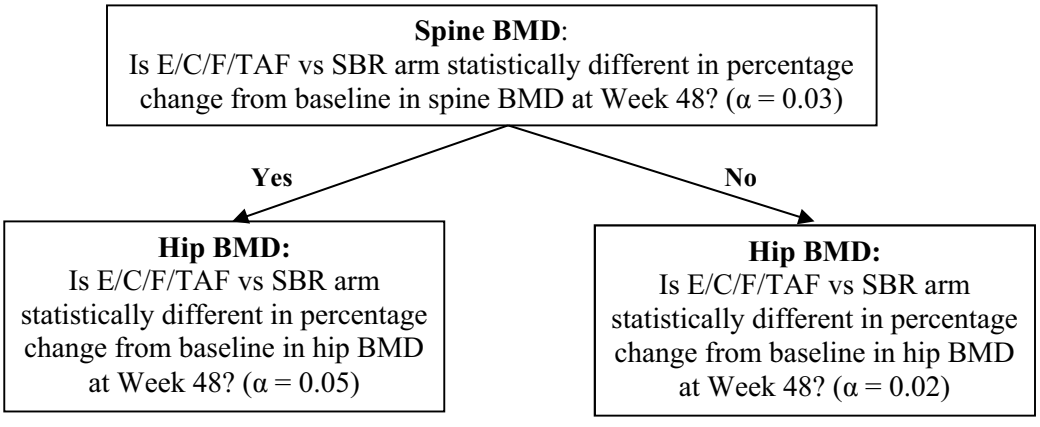
3.5. Multiple Comparisons

To control for type I error in the assessment of the primary efficacy endpoints, the hypothesis testing will be performed in a sequential order. The multiplicity adjustments with respect to the primary endpoints will follow a fallback procedure {Wiens 2005} in sequential order.

The primary hypothesis of no statistically significant difference between subjects who switched to E/C/F/TAF and subjects who continued SBR with respect to spine BMD at Week 48 will be tested first. The test will be performed at 2-sided, 0.03 alpha level. If a statistically significant difference is found, a similar hypothesis will be tested for hip BMD at a 2-sided, 0.05 alpha level; if no statistically significant difference is found, a similar hypothesis will be tested for hip BMD at a 2-sided, 0.02 alpha level.

The sequential order of hypothesis testing using the fallback procedure is shown in the following flowchart (Figure 3-1).

Figure 3-1. Flowchart of the Fallback Procedure



3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study visit window 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 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 8.1.6.2, and for concomitant non-ARV medications in Section 8.6.2.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

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

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

For urine creatinine, value of "< 1" is handled as a missing value in its summary and the calculation of related ratios. HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes. HCV RNA results of "<15 IU/mL HCV RNA detected" or "No HCV RNA detected" will be imputed as 14 IU/mL for analysis purposes.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study Day 1:

For subjects taking E/C/F/TAF, the date when the first dose of study drug was taken, as recorded on the Study Drug Administration eCRF form, will be used.

For subjects continuing SBR, the Day 1 visit date on the Visit Date eCRF will be used.

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

Last Dose Date is defined as follows:

- For subjects taking E/C/F/TAF, the last dose date is defined as the latest of the study drug end dates recorded on the Study Drug Administration eCRF with "Permanently Withdrawn" box checked for subjects who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF.

- For subjects continuing SBR, the earliest stop date of any component (ie, FTC/TDF, or 3rd Agent, etc.) of the current ARV regimen will be used as the last dose date for subjects who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF.

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

Last Study Date is the latest of 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 is defined as the last value obtained on or prior to Study Day 1 for all assessments.

3.8.2. Analysis Visit Windows

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

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

Table 3-1. Analysis Visit Windows for HIV-1 RNA, CD4+ Cell Count, CD4%, Hematology, Chemistry, Urinalysis and Urine Chemistry Laboratory Tests, $eGFR_{CG}$, Testosterone Level, VAS, 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 evaluations of bone and renal safety, inflammation and platelet and coagulation function (bone safety: parathyroid [PTH] and serum OH-25 vitamin D; inflammation: cystatin-C, IL-6, hs-CRP, sCD14, sCD163, sTNF-1R, and Lp-PLA2; platelet and coagulation function: glycoprotein VI [sGPVI], P-selectin, soluble CD40 ligand, and d-dimer; urine renal safety: retinol binding protein, and beta-2-microglobulin, and derived ratios) are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for Evaluations of Bone and Renal Safety, Inflammation and Platelet and Coagulation Function

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	28	2	56
Week 12	84	57	126
Week 24	168	127	252
Week 48	336	253	420

The analysis windows for DXA, fasting glucose and lipid panels (including total cholesterol [TC], HDL, direct LDL, triglycerides, and TC to HDL ratio), SF-36, FACIT-F, and EQ-5D-3L are provided in Table 3-3.

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

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

The analysis windows for HIVTSQs (at Day 1 Only) and HIVTSQc are provided in Table 3-4.

Table 3-4. 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

The analysis windows for ECGs are provided in Table 3-5.

Table 3-5. Analysis Visit Windows for ECGs

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 48	336	2	504

3.8.3. 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 will be used for the baseline value, except for HIV-1 RNA (see below).

- For postbaseline visits:

  — For hip and spine BMD, HIV-1 RNA, CD4+ cell count, and CD4%, the data collected on the latest day in the window will be selected for analysis.

  — For other numeric observations, the data collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

  — For any numeric observations except HIV-1 RNA, if there are multiple records on the same study day, the average will be taken.

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

If multiple valid nonmissing categorical observations (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 randomized to each stratum (screening spine BMD T-score [< -1.00 or ≥ -1.00] and hip BMD T-score [< -1.00 or ≥ -1.00]) based on actual BMD results will be summarized by treatment group and overall using the safety analysis set.

The number and percentage of subjects randomized in each country and by each investigator within a country will be summarized by treatment group and overall and using the safety analysis set.

The enrollment related data will be listed. Subjects randomized to the incorrect stratum will be included in separate listing.

4.1.2. Disposition of Subjects

A summary of subject disposition will be provided by treatment group and overall. This summary will present the number and/or percentage of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects randomized, subjects randomized but not treated, subjects in the safety analysis set, and subjects in the FAS.

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

- Completed study drug
- Prematurely discontinued study drug (with summary of reasons for discontinuing study drug)
- Completed study
- 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.

No inferential statistics will be provided. A data listing of reasons for premature study drug and study 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. Only subjects receiving E/C/F/TAF in the safety analysis set will be analyzed.

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 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], ≥ 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.

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

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method by treatment group based on the safety analysis set. The log rank test will be used to compare the difference in study drug exposure between the 2 treatment groups. A plot of KM estimates for the time to premature discontinuation of study drug by treatment group will be generated.

4.2.2. Adherence to Study Drug

Study drug regimen adherence will be computed based on pill counts for exposure to E/C/F/TAF only. 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 E/C/F/TAF will be calculated as follows:

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

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

[1] Number of pills taken at a distinct dispensing period for E/C/F/TAF 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 the study drug 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 permanent discontinuation of the study drug (if available), 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, all records for the same dispensing date for that study drug will be excluded from both denominator and numerator calculation.

Overall adherence will be calculated for each subject for the entire dosing period up to the date of permanent discontinuation of the study drug for subjects who completed or prematurely discontinued study drug.

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, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided for subjects receiving E/C/F/TAF in the safety analysis set for subjects who return at least 1 bottle and have calculable adherence during the study in the safety analysis set. No inferential statistics will be provided.

4.3. Protocol Deviations

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

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic data (age, sex, race, and ethnicity) and baseline characteristics (body weight, height, body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. The summaries of demographic data and baseline characteristics will be provided using the safety analysis set and the full analysis set.

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

5.2. Baseline Disease Characteristics

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

- 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
- HBV Surface Antigen Status (Negative/Positive)
- HCV Antibody Status (Negative/Positive)
- Estimated GFR by CG (mL/min; see Section 8.4.2.1)
- Estimated GFR by CKD-EPI (mL/min; see Section 8.4.2.2)
- Proteinuria by urinalysis (dipstick; Negative/Trace/+1/+2/+3)
- Testosterone level (ng/mL), separated by sex (Males and Females)
- Medical history: diabetes (Yes/No), hypertension (Yes/No), cardiovascular disease (Yes/No), and hyperlipidemia (Yes/No)

- Tobacco smoking history (Never Smoker/Former Smoker/Current Smoker)
- Genetic mother/father/ brother/sister with myocardial infarction/stroke before 50 years-old? (Yes/No/Unknown)
- Baseline ALT (U/L)
- Baseline AST (U/L)
- Baseline Platelet Count ($10^3/\mu L$)
- ARV Regimen at Baseline (see the programming specifications for additional details)

For categorical data (excluding HIV risk factors and ARV Regimen at Baseline), the Cochran-Mantel-Haenszel (CMH) test (general association statistic for nominal data and row means scores differ statistic for ordinal data) will be used to compare the treatment groups. For continuous data, a 2-sided Wilcoxon rank sum test will be used to compare the treatment groups.

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

5.3. Baseline Fracture Assessment

The following baseline fracture assessments (Yes/No) will be summarized by treatment group and overall, separated by sex (Males and Females):

- Has subject had a previous fragility fracture?
- Does subject have a parent with fractured hip?
- Does subject currently smoke?
- Has subject currently or previously been exposed to oral glucocorticoids?
- Has subject had a confirmed diagnosis of rheumatoid arthritis?
- Does subject exhibit secondary osteoporosis?
- Does subject consume 3 or more alcoholic drinks a day?

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

5.4. Medical History

Specific medical history such as cigarette smoking, diabetes, family cardiovascular history, history of fracture events will be listed or summarized as noted in Sections 5.2 and 5.3 above.

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

6. ANALYSES OF PRIMARY ENDPOINTS

This section describes the analysis of the primary endpoints for the study. As these are safety endpoints, these are also described in Section 8.3.1 where related secondary endpoints and further analyses are discussed.

6.1. Definition of the Primary Endpoint

The primary endpoints of this study is the percentage change from baseline in spine BMD and hip BMD at Week 48.

6.2. Statistical Hypothesis for the Primary Endpoints

- **Null hypothesis:** There is no statistically significant difference between subjects who switched to E/C/F/TAF and subjects who continued SBR with respect to spine (hip) BMD at Week 48
- **Alternative hypothesis:** There is a statistically significant difference between subjects who switched to E/C/F/TAF and subjects who continued SBR with respect to spine (hip) BMD at Week 48

6.3. Primary Analysis of the Primary Endpoints

The percentage change from baseline at Week 48 will be summarized by treatment group and visit using descriptive statistics for subjects in the spine and hip DXA analysis sets, respectively. The percentage change from baseline in spine BMD and hip BMD will be compared between the 2 treatment groups using an ANOVA model, including treatment group, baseline BMD T-score (< -1.00 vs ≥ -1.00) and sex as fixed effects in the model.

6.3.1. Analysis of Primary Endpoints Using Fallback Procedure

To control for the overall type I error rate for multiple testing, multiplicity adjustments will be performed with a fallback procedure (Figure 3-1).

A summary table for these results including analysis set used for each endpoint, the reported nominal p-values (based on results from all observed data), and pre-specified and adjusted alpha levels will be provided.

6.4. Secondary Analysis of the Primary Endpoints

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

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

Similar to the analysis of observed data, the percentage change from baseline in hip BMD and spine BMD by LOCF at Week 48 will also be analyzed using the hip and spine DXA analysis sets.

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

6.5. Changes From Protocol-Specified Primary Analyses

The Spine DXA Analysis Set and Hip DXA Analysis Set in the protocol specified that subjects must have at least one post baseline visit in addition to the other three conditions specified in Sections 3.1.4.1 and 3.1.4.2, respectively. Furthermore, the protocol specified that if the primary endpoints of spine and hip BMD measurements at Week 48 are missing, then it will be imputed with Week 24 measurement or the last post-baseline measurement available, ie, last observed carried forward (LOCF).

The requirement that postbaseline DXA data be present has been dropped and the primary analysis will be based on observed (not LOCF) data. A sensitivity analysis which will impute missing data has been specified in Section 6.4. This definition permits the baseline value to be carried forward if no postbaseline values are present.

Finally, due to potential differences between males and females, sex has been added as a covariate in the ANOVA models used.

7. EFFICACY ANALYSES

Efficacy endpoints described in this section are either secondary or additional endpoints of the study as the protocol did not define efficacy endpoints as primary study endpoints.

7.1. Efficacy Endpoints as Secondary Study Endpoints

Secondary efficacy endpoints include the following:

- Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as determined by US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}
- Proportion of subjects with HIV-1 RNA ≥ 50 copies/mL as defined by the US FDA-defined snapshot algorithm at Weeks 24 and 48.
- Change from baseline in CD4+ cell counts at Weeks 24 and 48.

The analyses for the secondary efficacy endpoints will be conducted using the FAS.

7.1.1. US FDA-Defined Snapshot Algorithm

The analysis window at Week 24 is defined as from Study Day 127 to Study Day 210, inclusive. All HIV-1 RNA data collected on-treatment will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL:** this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 24 analysis window
- **HIV-1 RNA ≥ 50 copies/mL:** this includes subjects:

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

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

     a) Who discontinue study drug prior to or in the Week 24 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

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

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

- **No Virologic Data in the Week 24 Window:** this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window because of the following:

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

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

  3) Missing data during the window but on study drug.

The flowchart of snapshot algorithm is provided in Appendix 2. A similar algorithm (replacing Week 24 with Week 48 and updating the study day range to 295 to 378) will be used to classify subjects at Week 48. Virologic outcomes at Weeks 24 and 48 for the US FDA-defined snapshot algorithm will also be listed.

Note: For switch study population, the US FDA-defined snapshot algorithm classifies subjects who discontinue study drug due to adverse event or death and have the last available on-treatment HIV-1 RNA value ≥ 50 copies/mL as HIV-1 RNA value ≥ 50 copies/mL. In the US FDA-defined snapshot algorithm for a treatment naïve study population, these subjects would be classified as having No Virologic Data in the Week 24 (Week 48) Analysis Window.

7.1.2. Primary Analysis of the Main Secondary Efficacy Endpoint

The analysis purpose of the secondary efficacy endpoint is to assess the noninferiority of switching to E/C/F/TAF relative to continuing on SBR. The two-sided exact 95% confidence interval for the difference in treatment group response rates (E/C/F/TAF minus SBR) will be constructed based on an unconditional exact method using 2 inverted 1-sided tests {Chan 1999}. A p-value from Fisher's exact test will also be calculated. The primary analysis will use the FAS.

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 24 and 48 will be summarized.

7.1.3. Analysis Methods for Other Secondary Efficacy Endpoints

7.1.3.1. Analysis of Proportion of Subjects with HIV-1 RNA ≥ 50 copies/mL as Defined by the US FDA-Defined Snapshot Algorithm at Weeks 24 and 48

The proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Weeks 24 and 48 as determined by US FDA-defined snapshot algorithm will be analyzed similarly to the main secondary efficacy endpoint.

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

The above analysis will be performed using the FAS.

7.1.3.2. Analysis of CD4+ Cell Count at Weeks 24 and 48

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

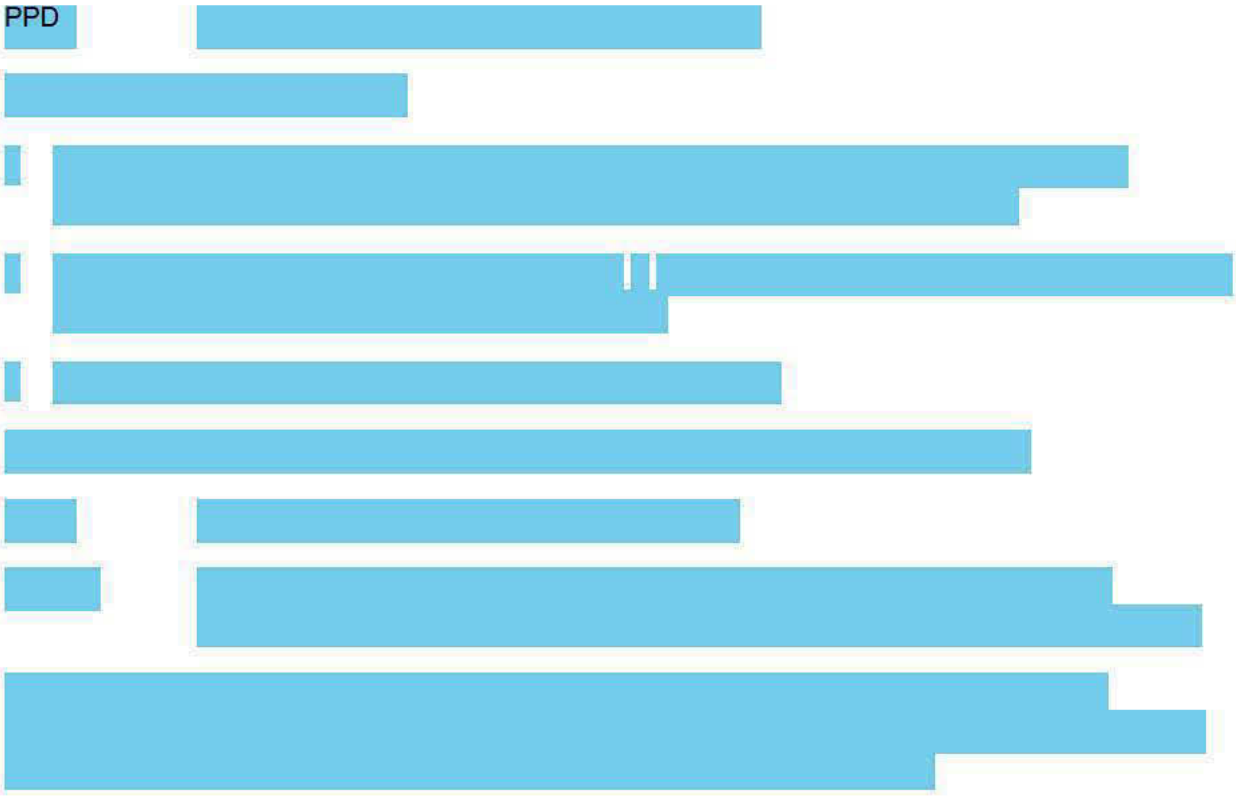
The change from baseline in CD4+ cell count at Weeks 24 and 48 (as well as all other visits) will be summarized by E/C/F/TAF and SBR using descriptive statistics.

The difference between treatment groups at baseline and change from baseline in CD4+ cell count between E/C/F/TAF and SBR and the associated 95% CI will be constructed using analysis of variance (ANOVA) models including treatment as a fixed effect in the model. P-values will be generated from the ANOVA model as well.

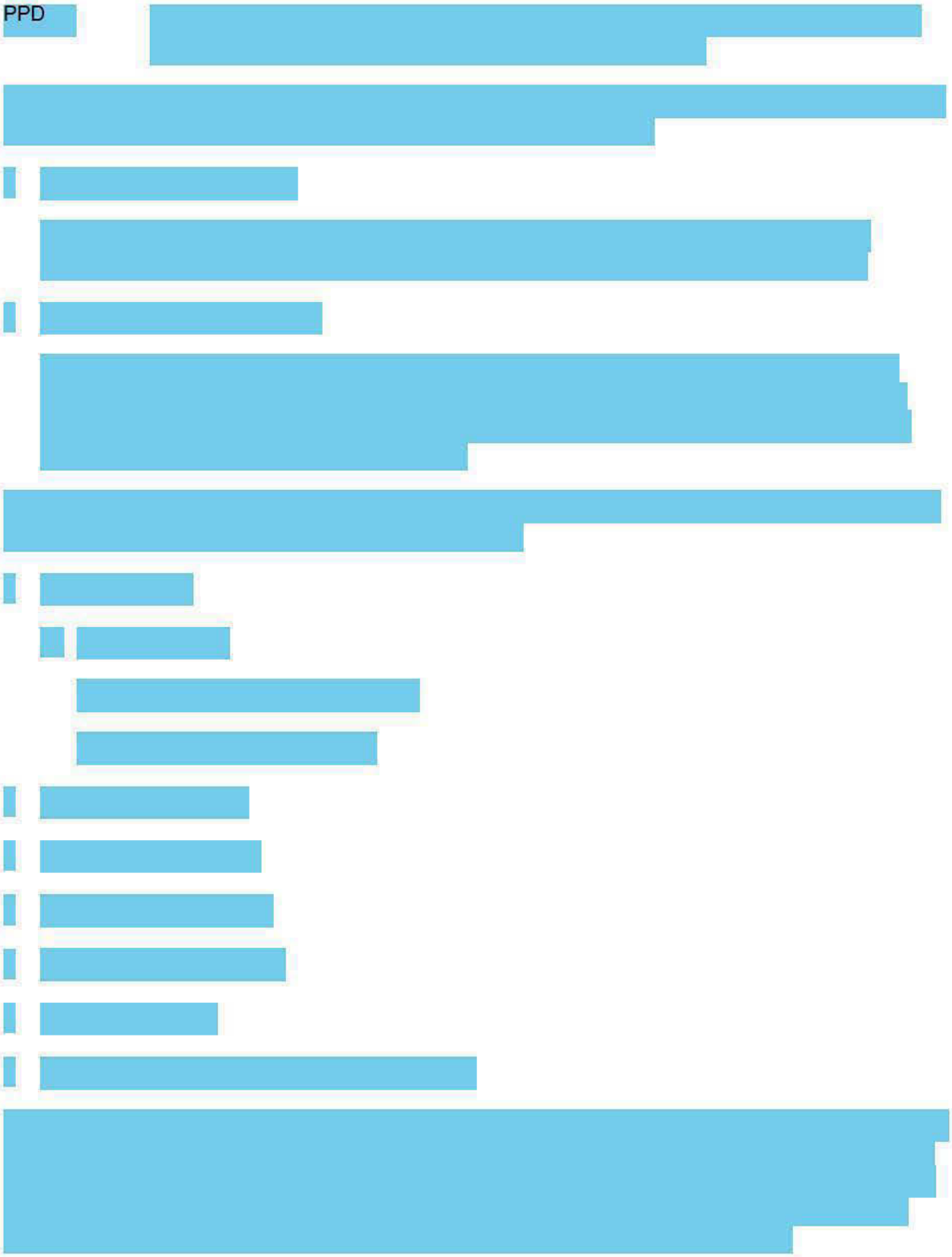
The mean and 95% CI of change from baseline in CD4+ cell count over time will be plotted for the FAS.

7.2. Tertiary Efficacy Endpoints

PPD



PPD



PPD

[redacted]

7.3. Changes From Protocol-Specified Efficacy Analyses

The proportion of subjects with HIV-1 RNA ≥ 50 copies/mL as defined by the US FDA-defined snapshot algorithm at Weeks 24 and 48 was added as a secondary endpoint.

8. SAFETY ANALYSES

The secondary objective of this study is to evaluate the safety and tolerability of the two treatment groups through Week 48. Safety data will be summarized for the subjects in the safety analysis set. All safety data collected up to 30 days after permanent discontinuation of study drug will be summarized by treatment group, unless specified otherwise. All safety data will be included in data listings.

8.1. Adverse Events and Deaths

8.1.1. Adverse Event Dictionary

AEs 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 lowest level term (LLT) will be attached to the clinical database.

8.1.2. Adverse Event Severity

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

8.1.3. 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 for summary purposes. However, by-subject data listings will show the relationship as missing.

8.1.4. 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.

8.1.5. 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 Drug Safety and Public Health (DSPH) Department before database finalization.

8.1.6. Treatment-Emergent Adverse Events

8.1.6.1. Definition of Treatment-Emergent Adverse Events

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

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

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

8.1.7. Summaries of Adverse Events and Deaths

A brief summary of AEs will show, by treatment group, the number and percentage of subjects who (1) had any treatment-emergent AE, (2) had any Grade 3 or 4 treatment-emergent AE, (3) had any Grade 2, 3, or 4 treatment-emergent AE, (4) had any treatment-emergent study drug-related AE, (5) had any Grade 3 or 4 treatment-emergent study drug-related AE, (6) had any Grade 2, 3, or 4 treatment-emergent study drug-related AE, (7) had any treatment-emergent SAE, (8) had any treatment-emergent study drug-related SAE, (9) had any treatment-emergent AE leading to premature study drug discontinuation, and (10) had treatment-emergent death. Treatment-emergent death refers to 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, HLT [if specified below], and PT) will be provided by treatment group using the safety analysis set as follows:

- All TEAEs summarized by SOC, HLT, and PT
- Any Grade 3 or 4 TEAEs

- Any Grade 2, 3, or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- All Grade 3 or 4 treatment-emergent study drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- All treatment-emergent serious AEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs leading to premature discontinuation of study drug

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

In addition to the above summary tables, all TEAEs and TE study drug-related AEs will be summarized by PT only, in descending order of total frequency.

Data listings will be provided for the following:

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

8.1.8. Stage 3 Opportunistic Illnesses in HIV

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

8.1.9. Potential Cardiovascular or Cerebrovascular Events

Potential cardiovascular or Cerebrovascular events are defined as events with PT in the selected PT listing, which was provided by Gilead Drug Safety and Public Health (DSPH) and reviewed by Gilead medical monitors (see Appendix 4).

A summary (number and percentage of subjects) of potential treatment-emergent cardiovascular or cerebrovascular events and serious cardiovascular or cerebrovascular events by PT will be provided by treatment group based on the safety analysis set. Statistical comparisons of the subject incidence rates between the 2 treatment groups will be performed using Fisher's exact test. A data listing of potential cardiovascular or cerebrovascular events will be provided.

8.2. Laboratory Evaluations

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

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the 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.

8.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) will be provided by treatment group for each laboratory test specified in the study protocol as follows:

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

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

8.2.1.1. 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 by treatment group. P-values for the

difference between E/C/F/TAF and SBR in baseline values and the change from baseline in metabolic assessment will be estimated from the 2-sided Wilcoxon rank sum test to compare E/C/F/TAF and SBR.

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. Statistical comparisons of the subject incidence rates between E/C/F/TAF and SBR will be performed using Fisher's exact test.

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 and change from baseline at Week 48 will be summarized by E/C/F/TAF and SBR and p-values for the difference between E/C/F/TAF and SBR will be estimated from a 2-sided Wilcoxon rank sum test. Only subjects with both baseline and Week 48 values will be included in the analysis.

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

8.2.1.2. Calcium Corrected for Albumin

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

Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 × (4.0 – albumin (g/dL)). Toxicity grading for calcium will be applied based on the corrected values.

8.2.1.3. Testosterone Levels

Descriptive statistics will summarize testosterone by treatment group and sex. No comparative statistics are planned to be generated.

8.2.2. 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.

8.2.2.1. 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 30 days after permanent discontinuation of 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 (including glucose results without a known fasting status) 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 by treatment group.

8.2.2.2. Summaries of Laboratory Abnormalities

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

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing post-baseline values for the lab test, obtained up to 30 days after permanent discontinuation of study drug. A listing of all graded laboratory abnormalities and all Grade 3 or Grade 4 laboratory abnormalities will be provided.

8.2.3. Liver-Related Laboratory Evaluations

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

- Aspartate aminotransferase (AST): (a) > 3 × Upper limit of normal (ULN), (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Alanine aminotransferase (ALT): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN

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

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the safety analysis set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date.

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

8.3. Bone Safety Evaluations

8.3.1. Bone Mineral Density

The primary endpoints of the study are the percentage change from baseline in spine BMD and hip BMD at Week 48, as discussed in Section 6. This section discusses secondary endpoints of the study that are based on BMD as well as additional analyses of BMD that are not protocol-defined endpoints.

8.3.1.1. Percentage Change from Baseline in Spine BMD and Hip BMD at Week 24

The percentage change from baseline in spine BMD and hip BMD at Week 24 are secondary endpoints of the study. The percentage change from baseline in spine BMD and hip BMD at Week 24 will be analyzed using the same method as the percentage change from baseline at Week 48 as described in Section 6.3. Furthermore, the secondary analyses described in Section 6.3.1 will also be performed.

8.3.1.2. Hip and Spine BMD Clinical Status

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

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

Table 8-1. Normal, Osteopenia, and Osteoporosis as Defined by T-score

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

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

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

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

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

8.3.2. Bone Biomarkers

Bone safety evaluations include parathyroid (PTH) and serum OH-25 vitamin D.

Baseline, postbaseline, change from baseline, and percentage change from baseline in bone safety evaluations at each visit will be summarized by treatment group using descriptive statistics. The difference between treatment groups at baseline and percentage change from baseline in these parameters between E/C/F/TAF and SBR will be tested using a 2-sided Wilcoxon rank sum test.

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

8.3.3. Fracture Events

The PTs for fracture events were defined based on Standardised MedDRA Query (SMQ) of Osteoporosis/Osteopenia. Fracture events will be summarized based on the identified PTs from SMQ. The number and percentage of subjects who experienced fracture events will be summarized by treatment group. Statistical comparisons of the subject incidence rates between E/C/F/TAF and SBR will be performed using Fisher's exact test.

A data listing of fracture events will be provided.

8.4. Renal Safety Analyses

8.4.1. Serum Creatinine

The baseline, postbaseline and change from baseline in serum creatinine at each visit will be summarized by treatment group using descriptive statistics. Differences in baseline and change from baseline between E/C/F/TAF and SBR at each study visit will be assessed using a 2-sided Wilcoxon rank-sum test.

Median (Q1, Q3) change from baseline in observed serum creatinine over time will be plotted by treatment group.

8.4.2. Estimated Glomerular Filtration Rate

8.4.2.1. Estimated Glomerular Filtration Rate: Cockcroft-Gault

The Cockcroft-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 $eGFR_{CG}$ at each visit will be provided by treatment group. Differences in baseline and change from baseline between E/C/F/TAF and SBR at each study visit will be assessed using a 2-sided Wilcoxon rank-sum test.

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

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

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

$eGFR_{CKD\text{-}EPI}$ (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/0.8 or 1, and max (Scys/0.8,1) indicates the maximum of Scys/0.8 or 1.

Only baseline values will be summarized. See Section 5.2 for details. Differences at baseline between E/C/F/TAF and SBR will be assessed using a 2-sided Wilcoxon rank-sum test.

8.4.3. Proteinuria by Urinalysis (Dipstick)

The proteinuria by urinalysis (dipstick) toxicity grade (Grade 0 to Grade 3) at Weeks 24 and 48, will be summarized by baseline proteinuria toxicity grade and treatment group. In addition, the last on-treatment (ie, data collected up to 1 day after permanent discontinuation the last dose date of study drug) proteinuria toxicity grade will also be summarized by baseline proteinuria toxicity grade and treatment group.

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

8.4.4. 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) at each visit will be summarized by treatment group using descriptive statistics. Baseline and percent change from baseline between E/C/F/TAF and SBR at each study visit will be assessed using a 2-sided Wilcoxon rank-sum test.

The number and percentage of subjects with UPCR $\leq$ 200 mg/g versus > 200 mg/g will be summarized by treatment group and baseline category at Weeks 24 and 48, and based on the last on-treatment value.

The number and percentage of subjects with UACR < 30 mg/g versus $\geq$ 30 mg/g will be summarized by treatment group and baseline category at Weeks 24 and 48, and the last on-treatment value.

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

8.4.5. Renal Safety Evaluations

Renal safety evaluations include urine retinol binding protein (RBP) to creatinine ratio and beta-2-microglobulin to creatinine ratio.

Baseline, postbaseline, change from baseline, and percentage change from baseline in renal safety evaluations at each visit will be summarized using descriptive statistics. Differences in baseline and percent change from baseline between E/C/F/TAF and SBR at each study visit will be assessed using a 2-sided Wilcoxon rank-sum test.

Median (Q1, Q3) percent change from baseline in renal safety evaluations over time will be plotted by treatment group.

A listing of renal safety evaluation data will be provided.

8.5. Vital Signs and Body Weight

Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) at each visit will be summarized by treatment group as follows:

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

A baseline value will be defined as the last nonmissing value obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

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

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

8.6. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

8.6.1. Nonstudy-Drug Antiretroviral Medications

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

8.6.2. Concomitant Non-Antiretroviral Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last

dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned

8.7. Electrocardiogram Results

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

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

8.8. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy during the study. Physical examination data were not collected in the eCRF, therefore there is no analysis for these data.

8.9. Changes From Protocol-Specified Safety Analyses

No change from protocol-specified safety analyses is planned.

9. PATIENT REPORTED 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) HIVTSQ (Status version at Day 1 only and Change version for other visits); (4) FACIT-F; (5) EQ-5D-3L.

PRO data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries will be provided for the safety analysis set.

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. All reported data will be listed.

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

The visual analogue scale (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.

9.1.1. VAS Statistical Method

The VAS (%) absolute value and its change from baseline at each visit will be summarized by treatment group using descriptive statistics. The 2-sided Wilcoxon rank-sum test will be used to compare the difference between E/C/F/TAF and SBR at baseline and the change from baseline at each visit.

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.

9.2. 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.

9.2.1. 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.

9.2.2. SF-36 Statistical Analysis Method

Scores for each domain, PCS, and MCS will be summarized at each visit by treatment group using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum). Baseline and change from baseline between E/C/F/TAF and SBR at each study visit for each domain, PCS, and MCS will be assessed using a 2-sided Wilcoxon rank-sum test.

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.

9.3. HIV Treatment Satisfaction Questionnaire

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

9.3.1. Scoring the 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 range from 0 to 30 on the HIVTSQs form and from -15 to 15 on the HIVTSQc form.

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

Table 9-1. List of Items on the HIVTSQ

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

9.3.2. HIV Treatment Satisfaction Questionnaire Statistical Analysis Method

The HIVTSQs scale and subscale totals at baseline, and the HIVTSQc scale and subscale totals at each visit will be summarized by treatment group using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum). The number and percent of subjects with responses to each question will be provided at each visit.

Comparison between E/C/F/TAF and SBR in HIVTSQc scale total scores will use an ANCOVA model adjusting for HIVTSQs scale total at Baseline. A similar analysis will be performed on the two subscale scores as well.

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

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

9.4. 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 inital 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 chroninc 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).

9.4.1. 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 9-2. 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 6 → 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	
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	

Three aggregate scores can be computed as shown Table 9-3, subject to the requirements listed:

Table 9-3. Compuation 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)

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

Scores for each subscale and aggregate score at each visit will be summarized by treatment group using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum). Baseline and change from baseline between E/C/F/TAF and SBR for each subscale and aggregate score will be assessed at each study visit using a 2-sided Wilcoxon rank-sum test.

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.

9.5. 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}.

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

The scores of EQ-5D-3L descriptive system are described in the following Table 9-4.

Table 9-4. 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.

9.5.2. 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 5). 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 5 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.

9.5.3. 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.

9.5.4. 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 by treatment group and by baseline result for each visit. No inferential statistics will be provided.

For the index score and VAS score, baseline, postbaseline, and change from baseline at each visit will be summarized by treatment group. Baseline and change from baseline between E/C/F/TAF and SBR for the index score and VAS score will be assessed at each study visit using a 2-sided Wilcoxon rank-sum test.

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, 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. The distribution difference in these categories between E/C/F/TAF and SBR will be compared using CMH test (row mean scores differ statistic).

Table 9-5. 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

10. REFERENCES

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11. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

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

12. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

Appendix 1. Study Procedures Table

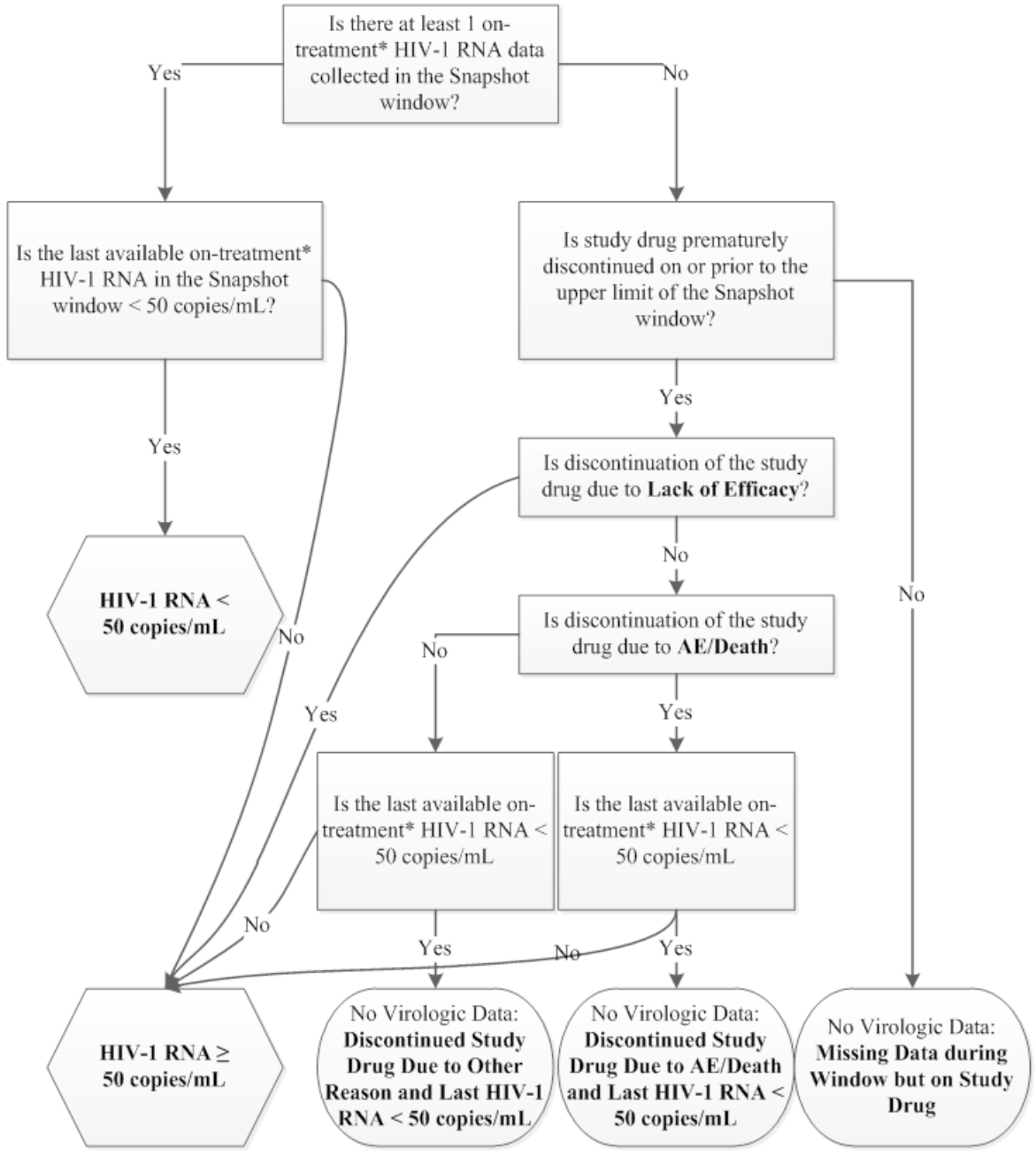
Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						30 Day Follow-up	Early Study Drug Discontinuation[d] (ESDD)
			4	8	12	24	36	48		
Informed Consent	X									
Medical History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Complete Physical Exam[e]	X	X				X		X		X
Symptom-Directed Physical Exam[f]			X	X	X		X		X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X
Height	X									
12-lead ECG	X							X		X
Urinalysis and Urine Chemistry	X	X	X	X	X	X	X	X	X[s]	X
Urine Storage Sample		X	X	X	X	X	X	X		X
Chemistry Profile[g]	X	X	X	X	X	X	X	X	X	X
Hematology Profile[h]	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA[i]	X	X	X	X	X	X	X	X	X	X
HBV and HCV Serologies[j]	X									
Cystatin-C		X								
Estimated GFR_{CG}[k]	X	X	X	X	X	X	X	X		X
Whole Blood Sample[l]	X									
Testosterone Level		X	X	X	X	X	X	X		
Metabolic Assessments[m]		X				X		X		
Evaluations of Bone & Renal Safety, Inflammation, and Platelet & Coagulation Function[n]		X	X		X	X		X		
Plasma Storage Sample[o]		X	X	X	X	X	X	X		X
PPD										
DXA Scan[p]	X					X		X		
Questionnaires: VAS,HIVTSQs, HIVTSQc, EQ-5D, SF-36, and FACIT-F[q]		X	X	X	X	X	X	X		X

Study Procedure	Screening[a]	Day 1[b]	End of Week[c]						30 Day Follow-up	Early Study Drug Discontinuation[d] (ESDD)
			4	8	12	24	36	48		
HIV-1 Genotype/Phenotype[r]								X		X
Randomization		X								
Study Drug Dispensation and Accountability		X	X	X	X	X	X	X[t]		X[t]

a Evaluations to be completed within 42 days prior to Day 1 visit.
b Subjects will be dispensed study drug at 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 will be provided to subjects randomized to Treatment Group 1.
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 12, ± 6 days of the protocol specified date for Weeks 24 & 36. The Week 48 visit window is ± 6 weeks of the visit date. Unless notified by Gilead, the Week 48 visit should be completed within ± 6 days of the visit date.
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 the Week 48 visit even as the subject discontinues study drug.
e Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator).
f Symptom-directed physical examination as needed at Weeks 4, 8, 12, and 36
g 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 Day 1, Weeks 24 and 48 analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile.
h CBC with differential and platelet count
i 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 in the protocol.
j Hepatitis B 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)
k Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
l Whole blood sample for virology analysis (if historical plasma genotype report prior to first ART is not available or subject has 3 or more ART regimens)
m Metabolic Assessments: Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state.
n Blood for bone safety, parathyroid (PTH) and serum OH-25 vitamin D; Inflammation may include cystatin-C, IL-6, hs-CRP, sCD14, sCD163, sTNF-1R, and Lp-PLA2; Platelet and coagulation function may include soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and d-dimer will be collected. Urine for renal safety, including retinol binding protein, and beta-2-microglobulin, will be collected. Samples for bone and renal safety will be collected fasted. 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.
o Plasma storage sample for safety and/or virology (Day 1, Weeks 4-48, and ESDD). PPD
p DXA scan to be performed on all eligible subjects prior to study randomization. Screening BMD results via T-score must be available to randomize subject at Day 1. At Weeks 24 and 48, DXA may be performed ≤ 10 days before study visit.
q VAS will be administered at Day 1, Week 4-48, and ESDD. EQ-5D, SF-36, and FACIT-F will be administered at Day 1, Weeks 24 and 48. HIVTSQs will be administered on Day 1. HIVTSQc will be administered at Weeks 4, 24, 48 and ESDD.
r HIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 50 copies/mL
s Urinalysis only
t Drug accountability only; study drug will not be dispensed at this visit.

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. Fracture Events

The selected PTs from SMQ of Osteoporosis/Osteopenia and HLGT of fractures based on clinical review are listed as follows.

	Selected PTs Based on SMQ of Osteoporosis/Osteopenia	Selected PTs Based on HLGT of Fractures
1	Acetabulum fracture	Acetabulum fracture
2	Atypical femur fracture	Ankle fracture
3	Cervical vertebral fracture	Atypical femur fracture
4	Closed fracture manipulation	Atypical fracture
5	External fixation of fracture	Avulsion fracture
6	Femoral neck fracture	Bone fissure
7	Femur fracture	Bone fragmentation
8	Forearm fracture	Cervical vertebral fracture
9	Fracture	Chance fracture
10	Fracture treatment	Clavicle fracture
11	Fractured ischium	Comminuted fracture
12	Fractured sacrum	Complicated fracture
13	Hip fracture	Compression fracture
14	Ilium fracture	Craniofacial fracture
15	Internal fixation of fracture	Epiphyseal fracture
16	Lumbar vertebral fracture	Facial bones fracture
17	Multiple fractures	Femoral neck fracture
18	Open reduction of fracture	Femur fracture
19	Open reduction of spinal fracture	Fibula fracture
20	Osteoporotic fracture	Flail chest
21	Pathological fracture	Foot fracture
22	Pelvic fracture	Forearm fracture
23	Pubis fracture	Fracture
24	Radius fracture	Fracture displacement
25	Rib fracture	Fracture of clavicle due to birth trauma
26	Sacroiliac fracture	Fractured coccyx
27	Spinal compression fracture	Fractured ischium
28	Spinal fracture	Fractured sacrum
29	Tartrate-resistant acid phosphatase decreased	Fractured skull depressed
30	Thoracic vertebral fracture	Greenstick fracture
31	Vertebroplasty	Hand fracture
32	Wrist fracture	Hip fracture

	Selected PTs Based on SMQ of Osteoporosis/Osteopenia	Selected PTs Based on HLGT of Fractures
33	Vertebral body replacement	Humerus fracture
34		Ilium fracture
35		Impacted fracture
36		Jaw fracture
37		Limb fracture
38		Lisfranc fracture
39		Lower limb fracture
40		Lumbar vertebral fracture
41		Multiple fractures
42		Open fracture
43		Osteochondral fracture
44		Osteoporotic fracture
45		Patella fracture
46		Pathological fracture
47		Pelvic fracture
48		Periprosthetic fracture
49		Pubis fracture
50		Radius fracture
51		Rib fracture
52		Sacroiliac fracture
53		Scapula fracture
54		Scapulothoracic dissociation
55		Skull fracture
56		Skull fractured base
57		Spinal compression fracture
58		Spinal fracture
59		Sternal fracture
60		Stress fracture
61		Thoracic vertebral fracture
62		Tibia fracture
63		Torus fracture
64		Traumatic fracture
65		Ulna fracture
66		Upper limb fracture
67		Wrist fracture

Note: AEs are coded by MedDRA 20.1.

Appendix 4. Potential Cardiovascular or Cerebrovascular Events

The selected PTs of potential cardiovascular or cerebrovascular events based on clinical review are listed as follows.

	Selected PTs Based on Clinical Review		Selected PTs Based on Clinical Review
1	Acute coronary syndrome	93	Coronary endarterectomy
2	Acute myocardial infarction	94	Coronary no-reflow phenomenon
3	Amaurosis fugax	95	Coronary ostial stenosis
4	Angina pectoris	96	Coronary revascularisation
5	Angina unstable	97	Coronary vascular graft occlusion
6	Anginal equivalent	98	Coronary vascular graft stenosis
7	Arteriogram coronary abnormal	99	Delayed ischaemic neurological deficit
8	Arteriosclerosis coronary artery	100	Dissecting coronary artery aneurysm
9	Arteriospasm coronary	101	ECG electrically inactive area
10	Basal ganglia infarction	102	ECG signs of myocardial infarction
11	Basal ganglia stroke	103	ECG signs of myocardial ischaemia
12	Basilar artery occlusion	104	Electrocardiogram Q wave abnormal
13	Basilar artery stenosis	105	Electrocardiogram ST segment abnormal
14	Basilar artery thrombosis	106	Electrocardiogram ST segment depression
15	Blood creatine phosphokinase abnormal	107	Electrocardiogram ST segment elevation
16	Blood creatine phosphokinase increased	108	Electrocardiogram ST-T segment abnormal
17	Blood creatine phosphokinase MB abnormal	109	Electrocardiogram ST-T segment depression
18	Blood creatine phosphokinase MB increased	110	Electrocardiogram ST-T segment elevation
19	Brachiocephalic arteriosclerosis	111	Electrocardiogram T wave abnormal
20	Brachiocephalic artery occlusion	112	Electrocardiogram T wave inversion
21	Brachiocephalic artery stenosis	113	Electrocardiogram U wave inversion
22	Brain hypoxia	114	Embolic cerebral infarction
23	Brain stem embolism	115	Embolic stroke
24	Brain stem infarction	116	Exercise electrocardiogram abnormal
25	Brain stem ischaemia	117	Exercise test abnormal
26	Brain stem stroke	118	External counterpulsation
27	Brain stem thrombosis	119	Haemorrhage coronary artery
28	Capsular warning syndrome	120	Hypoxic-ischaemic encephalopathy
29	Cardiac stress test abnormal	121	Infarction

	Selected PTs Based on Clinical Review		Selected PTs Based on Clinical Review
30	Cardiac ventricular scarring	122	Inner ear infarction
31	Cardiopulmonary exercise test abnormal	123	Ischaemic cardiomyopathy
32	Carotid angioplasty	124	Ischaemic cerebral infarction
33	Carotid arterial embolus	125	Ischaemic mitral regurgitation
34	Carotid arteriosclerosis	126	Ischaemic stroke
35	Carotid artery bypass	127	Kounis syndrome
36	Carotid artery calcification	128	Lacunar infarction
37	Carotid artery disease	129	Lacunar stroke
38	Carotid artery insufficiency	130	Lateral medullary syndrome
39	Carotid artery occlusion	131	Microvascular coronary artery disease
40	Carotid artery restenosis	132	Migrainous infarction
41	Carotid artery stenosis	133	Millard-Gubler syndrome
42	Carotid artery stent insertion	134	Moyamoya disease
43	Carotid artery stent removal	135	Myocardial hypoxia
44	Carotid artery thrombosis	136	Myocardial infarction
45	Carotid endarterectomy	137	Myocardial ischaemia
46	Carotid revascularisation	138	Myocardial necrosis
47	Cerebellar artery occlusion	139	Myocardial necrosis marker increased
48	Cerebellar artery thrombosis	140	Myocardial reperfusion injury
49	Cerebellar embolism	141	Myocardial stunning
50	Cerebellar infarction	142	Papillary muscle infarction
51	Cerebellar ischaemia	143	Percutaneous coronary intervention
52	Cerebellar stroke	144	Perinatal stroke
53	Cerebral arteriosclerosis	145	Periprocedural myocardial infarction
54	Cerebral artery embolism	146	Post angioplasty restenosis
55	Cerebral artery occlusion	147	Post cardiac arrest syndrome
56	Cerebral artery restenosis	148	Post procedural myocardial infarction
57	Cerebral artery stenosis	149	Post procedural stroke
58	Cerebral artery thrombosis	150	Postinfarction angina
59	Cerebral gas embolism	151	Precerebral arteriosclerosis
60	Cerebral infarction	152	Precerebral artery occlusion
61	Cerebral infarction foetal	153	Prinzmetal angina
62	Cerebral ischaemia	154	Reversible cerebral vasoconstriction syndrome

	Selected PTs Based on Clinical Review		Selected PTs Based on Clinical Review
63	Cerebral microembolism	155	Reversible ischaemic neurological deficit
64	Cerebral revascularisation	156	Scan myocardial perfusion abnormal
65	Cerebral septic infarct	157	Silent myocardial infarction
66	Cerebral small vessel ischaemic disease	158	Spinal artery embolism
67	Cerebral thrombosis	159	Spinal artery thrombosis
68	Cerebral vascular occlusion	160	Stress cardiomyopathy
69	Cerebral vasoconstriction	161	Stress echocardiogram abnormal
70	Cerebral venous thrombosis	162	Stroke in evolution
71	Cerebrovascular accident	163	Subclavian coronary steal syndrome
72	Cerebrovascular disorder	164	Subclavian steal syndrome
73	Cerebrovascular insufficiency	165	Subendocardial ischaemia
74	Cerebrovascular stenosis	166	Thalamic infarction
75	Computerised tomogram coronary artery abnormal	167	Thrombotic cerebral infarction
76	Coronary angioplasty	168	Thrombotic stroke
77	Coronary arterial stent insertion	169	Transient ischaemic attack
78	Coronary artery bypass	170	Troponin I increased
79	Coronary artery compression	171	Troponin increased
80	Coronary artery disease	172	Troponin T increased
81	Coronary artery dissection	173	Vascular encephalopathy
82	Coronary artery embolism	174	Vascular graft occlusion
83	Coronary artery insufficiency	175	Vascular stent occlusion
84	Coronary artery occlusion	176	Vascular stent restenosis
85	Coronary artery reocclusion	177	Vascular stent stenosis
86	Coronary artery restenosis	178	Vascular stent thrombosis
87	Coronary artery stenosis	179	Vertebral artery occlusion
88	Coronary artery surgery	180	Vertebral artery stenosis
89	Coronary artery thrombosis	181	Vertebral artery thrombosis
90	Coronary brachytherapy	182	Vertebrobasilar insufficiency
91	Coronary bypass stenosis	183	Wall motion score index abnormal
92	Coronary bypass thrombosis		

Note: AEs are coded by MedDRA 20.1.

Appendix 5. 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
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
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 6. Medical History

The following medical history will be summarized.

- **Diabetes Mellitus (Yes/No):** "Yes" includes subjects with at least one of the following medical condition terms: diabetes, diabetes mellitus, diabetes 1, diabetes 2, Type 1 Diabetes, Type 2 Diabetes.

- **Hypertension (Yes/No):** "Yes" includes subjects with at least one of the following medical conditions: hypertension, blood pressure, high blood pressure, elevated blood pressure.

- **Cardiovascular Disease (Yes/No):** "Yes" includes subjects with at least one of the following medical conditions: cardiovascular disease, coronary artery disease, myocardial infarction, angina, cardiac ischemia, transient ischemic attack, stroke, claudication, peripheral vascular disease.

- **Hyperlipidemia (Yes/No):** "Yes" includes subjects with at least one of the following medical conditions: hyperlipidemia, lipids elevated, hypercholesterolemia, cholesterol elevated, LDL elevated, hypertriglyceridemia, triglycerides elevated.

The selected medical condition terms from the MH dataset or preferred terms from the AE dataset for a subject having the medical risk factors of interest are listed as follows:

	Medical Conditions from MH Dataset			
	Hypertension	**Diabetes**	**Cardiovascular Disease**	**Hyperlipidemia**
1	ARTERIAL HYPERTENSION	ADULT ONSET DIABETES MELLITUS	ACUTE MYOCARDIAL INFARCTION	CHRONIC HYPERCHOLESTEROLEMIA
2	BENIGN ESSENTIAL HYPERTENSION	ADULT ONSET DIABETES MELLITUS (TYPE 2)	ANGINA	DIABETES MELLITUS TYPE I WITH HYPERLIPIDEMIA
3	BENIGN HYPERTENSION	BORDERLINE DIABETES MELLITUS TYPE II	CORONARY ARTERY BYPASS GRAFT	DYSLIPIDEMAIA
4	BORDERLINE HYPERTENSION	DIABETES	CORONARY ARTERY DISEASE	DYSLIPIDEMIA
5	ELEVATED BLOOD PRESSURE	DIABETES INSULIN DEPENDENT	CORONARY DISEASE	DYSLIPIDEMIE
6	ELEVATED BLOOD PRESSURE READING WITHOUT DIAGNOSIS OF HYPERTENSION	DIABETES - TYPE 2	CORONARY HEART DISEASE	ELEVATED CHOLESTEROL
7	ELEVATED BLOOD PRESSURE WITHOUT DIAGNOSIS	DIABETES MELISTUS TYPE II	CORONARY STENTS	ELEVATED TRIGLYCERIDES
8	ELEVATED BLOOD PRESSURE WITHOUT DIAGNOSIS OF HYPERTENSION	DIABETES MELLITIS TYPE 1	CORONARY TRIPLE BYPASS	FAMILIAL HYPER-CHOLESTEROLAEMIA

	Medical Conditions from MH Dataset			
	Hypertension	**Diabetes**	**Cardiovascular Disease**	**Hyperlipidemia**
9	ESSENTIAL HYPERTENSION	DIABETES MELLITIS TYPE II	CORONNARY ARTERY DISEASE	HIGH CHOLESTEROL
10	ESSENTIAL HYPERTENSION, BENIGN	DIABETES MELLITUS	HYPERTENSVE CARDIOPATHY	HIGH TRIGLYCERIDES
11	HIGH BLOOD PRESSURE	DIABETES MELLITUS TYPE II	INFERIOR WALL MYOCARDIAL INFARCTION	HYLERLIPIDEMIA
12	HIGH BLOOD PRESSURE (WHEN AT MD OFFICE - NO DIAGNOSIS OF HYPERTENSION	DIABETES MELLITUS (ADULT ONSET/TYPE 2)	INTERMITTENT CLAUDICATION OF THE LOWER EXTREMITIES	HYPER-CHOLESTERALEMIA
13	HYPER TENSION	DIABETES MELLITUS (TYPE 2)	ISCHEMIC LEFT GREAT TOE	HYPERCHOLESTEREMIA
14	HYPERTENSION	DIABETES MELLITUS 2	LEFT MIDDLE CEREBRAL ARTERY STROKE	HYPERCHOLESTEROL
15	HYPERTENSION (DIAGNOSED BY COMPUTERIZED MONITORING)	DIABETES MELLITUS II	MILD CORONARY ATHEROSCLEROSIS	HYPER-CHOLESTEROLEMIA
16	HYPERTENSION (SELF REPORTED)	DIABETES MELLITUS TYP II	MYOCARDIAL INFARCTION	HYPER-CHOLESTERONEMIA
17	HYPERTENSION ARTERIAL	DIABETES MELLITUS TYPE 2	MYOCARDIAL INFARCTION,PCI AND STENT	HYPERLIMIDEMIA
18	HYPERTENSION IN TREATMENT	DIABETES MELLITUS TYPE I WITH HYPERLIPIDEMIA	NON-ISCHEMIC CARDIOMYOPATHY	HYPERLIPDEMIA
19	HYPERTENSION RELATED TO EMOTIONS	DIABETES MELLITUS TYPE II	OLD MYOCARDIAL INFARCTION	HYPERLIPEDEMIA
20	HYPERTENSION, BENIGN ESSENTIAL	DIABETES MELLITUS TYPE II, WITHOUT RETINOPATHY	POSSIBLE CEREBROVASCULAR ACCIDENT HISTORY	HYPERLIPIDEMIA
21	HYPERTENSIVE	DIABETES MELLITUS, TYPE II	POSSIBLE MYOCARDIAL INFARCTION HISTORY	HYPERLIPIDEMIA (COMBINED)
22	HYPERTENSVE CARDIOPATHY	DIABETES MILLITUS II	TRANSIENT ISCHAEMIC ATTACK	HYPERLIPIMIA
23	HYPERTENTION	DIABETES TYPE 1	TRANSIENT ISCHEMIC ATTACK	HYPER-SCHOLESTERALEMIA
24	INCREASED BLOOD PRESSURE	DIABETES TYPE 2	VASOSPASTIC ANGINA WITH NON ST ELEVATION MI	HYPERTRIGLICEREMIA

	Medical Conditions from MH Dataset			
	Hypertension	**Diabetes**	**Cardiovascular Disease**	**Hyperlipidemia**
25	INTERMITTENT INCREASED BLOOD PRESSURE	DIABETES TYPE II		HYPERTRIGLYCERIDEMIA
26	INTERMKTTENT INCREASED BLOOD PRESSURE	DIABETES, TYPE II		MIXED HYPERLIPIDEMIA
27	ISOLATED HIGH BLOOD PRESSURE EPISODE	DIABETIC COMA		RAISED CHOLESTEROL
28	STRESS INDUCED HYPERTENSION	DIABETIC ERECTILE DYSFUNCTION		
29		DIABETIC FOOT		
30		DIABETIC NEUROPATHIC		
31		DIABETIC NEUROPATHY		
32		DIABETIC PERIPHERAL NEUROPATHY		
33		DIABETIC RETINOPATHY		
34		DIABETIES		
34		FAMILIARITY FOR DIABETES MELLITUS TYPE II		
36		FAMILY HISTORY FOR DIABETES		
37		GESTATIMEL DIABETES		
38		HYPERGLYCEMIA		
39		MELLITUS DIABETES IN TREATMENT		
40		NON INSULIN DEPENDENT DIABETES MELLITUS		
41		NONINSULIN-DEPENDENT DIABETES MELLITUS		
42		PROTEINURIA (RELATED TO DIABETES PER NEPHROLOGIST PER SUBJECT)		
43		TYPE 2 DIABETE		
44		TYPE 2 DIABETES		
45		TYPE 2 DIABETES MELLITUS		
46		TYPE II DIABETES		

	MedDRA Preferred Terms from AE Dataset			
	Hypertension	**Diabetes**	**Cardiovascular Disease**	**Hyperlipidemia**
1	Blood pressure inadequately controlled	Diabetes mellitus	Acute myocardial infarction	Hyperlipidemia
2	Blood pressure increased	Type 2 diabetes mellitus	Cardiac arrest	Blood cholesterol increased
3	Hypertension		Cerebral infarction	Dyslipidaemia
4	Hypertensive crisis		Cerebrovascular accident	Hypercholesterolaemia
5			Coronary artery disease	Hyperlipidaemia
6			Electrocardiogram abnormal	Hypertriglyceridaemia
7			Enlarged uvula	Lipids abnormal
8			Haemorrhagic transformation stroke	Type V hyperlipidaemia
9			Left ventricular dysfunction	
10			Myocardial ischaemia	
11			Peripheral ischaemia	

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

	Medication Class	**Indication**
	Hypertension	
1	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ANTIHYPERTENSIVE MEDICATION
2	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ARTERIAL HYPERTENSION
3	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	BENIGN ESSENTIAL HYPERTENSION
4	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	ESSENTIAL HYPERTENSION
5	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	GRADE 1 HYPERTENSION
6	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HIGH BLOOD PRESSURE
7	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSION
8	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSION & RIGHT EAR TINNITIS
9	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSION, WORSENING OF

	Medication Class	Indication
10	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	HYPERTENSIVE CRISIS
11	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	PRESTUDY HYPERTENSION
12	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	STAGE I HYPERTENSION
13	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	UNCONTROLLED HIGH BLOOD PRESSURE
14	ANTIHYPERTENSIVES	HYPERTENSION
15	ANTITHROMBOTIC AGENTS	TO THIN THE BLOOD TO TREAT THE INDICATION OF HIGH BLOOD PRESSURE
16	BETA BLOCKING AGENTS	ARTERIAL HYPERTENSION
17	BETA BLOCKING AGENTS	BENIGN HYPERTENSION
18	BETA BLOCKING AGENTS	BITEMPORAL HEADACHE; PRESTUDY HYPERTENSION
19	BETA BLOCKING AGENTS	ELEVATED BLOOD PRESSURE
20	BETA BLOCKING AGENTS	HIGH BLOOD PRESSURE
21	BETA BLOCKING AGENTS	HYPERTENSION
22	BETA BLOCKING AGENTS	HYPERTENTSION/HEART PALPATATIONS
23	BETA BLOCKING AGENTS	WORSENING HYPERTENSION
24	CALCIUM CHANNEL BLOCKERS	ANTI-HYPERTENSIVE MEDICATION
25	CALCIUM CHANNEL BLOCKERS	ANTIHYPERTENSIVE MED
26	CALCIUM CHANNEL BLOCKERS	ESSENTENTIAL HYPERTENSION
27	CALCIUM CHANNEL BLOCKERS	ESSENTILA HYPERTENSION
28	CALCIUM CHANNEL BLOCKERS	HIGH BLOOD PRESSURE
29	CALCIUM CHANNEL BLOCKERS	HYPERTENSION
30	CALCIUM CHANNEL BLOCKERS	PRESTUDY HYPERTENSION
31	DIURETICS	ARTERIAL HYPERTENSION
32	DIURETICS	ELEVATED BLOOD PRESSURE
33	DIURETICS	HIGH BLOOD PRESSURE
34	DIURETICS	HYPERTENSION
34	DIURETICS	HYPERTENSION AND EDEMA
36	DIURETICS	PRESTUDY HYPERTENSION
37	PERIPHERAL VASODILATORS	HYPERTENSION

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

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

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

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

	Medication Class	Indication
38	LIPID MODIFYING AGENTS	INCREASED LIPIDS
39	LIPID MODIFYING AGENTS	MIXED HYPERLIPIDEMIA
40	LIPID MODIFYING AGENTS	NUTITIONAL SUPPLEMENT
41	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENT
42	LIPID MODIFYING AGENTS	NUTRITIONAL SUPPLEMENTS
43	LIPID MODIFYING AGENTS	PREVENTATIVE
44	LIPID MODIFYING AGENTS	STROKE PREVENTION
45	LIPID MODIFYING AGENTS	SUPLLEMENT
46	LIPID MODIFYING AGENTS	SUPPLEMENT
47	LIPID MODIFYING AGENTS	SUPPLEMENTATION
48	LIPID MODIFYING AGENTS	TACHYARRHYTHMIA
49	LIPID MODIFYING AGENTS	WELLNESS
50	LIPID MODIFYING AGENTS	WORSENING HYPERCHOLESTEROLEMIA
51	UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	HYPERCHOLESTEROLEMIA

Appendix 7. 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

1) AGE calculated as follows:

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

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

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

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

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

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

2) All screened subjects refer to all subjects who are screened (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.

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

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

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

6) 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).

7) 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).

8) 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.

9) 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.

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

    a) CMH test for nominal variable (Y):

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

    b) CMH test for ordinal variable (Y):

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

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

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

11) SAS codes for treatment comparison using Fisher's exact test

```
proc freq order=adsl;
   tables trtgrp * Y /fisher riskdiff;
run;
```

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

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

13) 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.

14) 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 8.2.2.1, 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.

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

16) For DXA analysis,

a) Variables used for analysis:

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

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

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

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

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

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

17) Primary and Efficacy analyses:

a) ANOVA model for continuous primary endpoint (eg, Spine BMD):

The percentage change from baseline in spine BMD and hip BMD will be compared between the 2 treatment groups using an ANOVA model, including treatment group and baseline BMD T-score (< –1.00 vs ≥ –1.00) and sex as a fixed effects in the model

SAS code is as follows:

```
proc glm data=adeff;
   class blspcat trtgrp sex;
   model w48spdxa = blspcat trtgrp sex;
   lsmeans trtgrp /alpha=0.05 cl pdiff ;
run;
```

Note: blspcat is the baseline Spine DXA variable (< –1.00 or ≥ –1.00), trtgrp is the treatment group variable, sex is the gender variable (male or female), and w48spdxa is the percentage change from baseline in spine BMD at week 48.

b) Exact method for difference in primary endpoint or other efficacy endpoints with proportion of HIV-1 RNA <50 c/mL between treatment group: the code below provides exact CIs (on an unconditional exact method using 2 inverted 1-sided tests) in SAS v9.3 or above:

```
data example;
   input  trt01a $  outcome $ count ;
   datalines;
Treat-A        2-Fail        1
Treat-A        1-Succ      189
Treat-B        2-Fail        4
Treat-B        1-Succ       88
run;

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

data final(keep=Estimate LowerCL UpperCL ocharc1);
   set ciexact;
   label Estimate ="Percentage Difference"
        LowerCL = "95% Lower Confidence Limit"
        UpperCL = "95% Upper Confidence Limit";
   Estimate=100*_RDIF1_;
   LowerCL = 100*XL_RDIF1;
   UpperCL = 100*XU_RDIF1;
   ocharc1 = right(compress(put(Estimate,8.1)) || '% (' ||
   compress(put(LowerCL,8.1)) || '% to ' ||
   compress(put(UpperCL,8.1)) || '%)');
run;
```

c) Listing for snapshot algorithm outcome:

In addition to flagging the values of HIV-1 RNA < 50 or ≥ 50 for snapshot algorithm virologic outcomes, flag the last available HIV-1 RNA value 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.

d) 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.

e) ANOVA model for continuous efficacy variable (eg, CD4):

The differences in changes from baseline in CD4 cell count between treatment groups and the associated 95% CI will be constructed using ANOVA, including treatment as a fixed effect in the model.

SAS code is as follows:

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

18) Treatment-emergent proteinuria analyses with rank analysis of covariance

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

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

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

19) 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

20) 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.

21) 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

22) 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.

23) 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".

24) Prior ARV

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

25) 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.

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

27) 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.

28) 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.

29) 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:

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

30) SAS codes for ANOVA model for analyzing treatment satisfaction questionnaire (HIVTSQc) with baseline status questionnaire (HIVTSQs) as a covariate

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

31) 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;
```

32) Defining ARV Regimen at Baseline

All subjects are expected to enter the study on TDF and FTC or 3TC + 3rd Agent, where the 3rd Agent can consist of a drug (possibly with a booster) that is not in the nucleos(t)ide reverse transcriptase inhibitor (NRTI) class. However, all subjects entered on the fixed dose cominbation FTC/TDF + 3rd Agent.

Using the ARV rawdataset, include all prior and/or current ARVs (ARV.INGRED where ARV.CMSCAT ='Prior ARV" or "Current ARV"), taken on or up to 2 day prior to first dose date as defined in Section 3.8.1.

When determining the baseline ARV regimen, please use the following rules:

- The baseline ARV will be recorded as 3rd Agent + FTC/TDF (note the reversed order, as this is due to clinical trials evaluating novel 3rd agents). When ordering the 3rd Agent medications, use the following order to assign priority:

INGRED	Priority	INGRED	Priority
DTG_ABC_3TC	1.1	DTG	3.1
EFV_FTC_TDF	1.2	RAL	3.2
EVG_COBI_FTC_TDF	1.3	EFV	4.1
FTC_ RPV_TDF	1.4	ETR	4.2
ATV_COBI	2.1	NVP	4.3
DRV_COBI	2.2	RPV	4.4
LPV_RTV	2.3	ABC_3TC	5.1
ATV	2.4	FTC_TDF	5.2
DRV	2.5	ABC	5.3
COBI	2.6	FTC	5.4
RTV	2.7	3TC	5.5
		TDF	5.6

- For all ingredients, replace "_" with "/"
- Make the following replacements to the ingredients:
  - Replace "DTG/ABC/3TC" with "ABC/DTG/3TC"
  - Replace "ATV/COBI" with "ATV/co"
  - Replace "DRV/COBI" with "DRV/co"
  - Replace "LPV/RTV" with "LPV/r"
- Once the ingredients have been updated and assigned an appropriate priority, transpose the ingredients (by subject) and concatenate each column with a "+" following the priority specified above

To illustrate these rules, suppose a subject is on ATV, RTV, and FTC_TDF. This would translate into "ATV+RTV+FTC/TDF". If, instead, the subject was on LPV_RTV and FTC_TDF, their regimen would be presented as "LPV/r+FTC/TDF".

Note: The following data issues should be queried:

- If the subject does not have FTC/TDF in their baseline regimen
- If a subject does not have a 3rd agent (eg, is only identified as being on FTC/TDF)
- If a subject is on RTV but is not *also* on ATV or DRV
- If an ARV medication that starts within 30 days of the first dose date (this represents a change in the baseline regimen and would represent an eligibility criteria violation)

33) 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:

a) the start and stop dates of the selected record are not completely missing (ie, at least year is known) or the start date is not 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;

b) 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.

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

d) the start date of the selected record is on or after the first dose date, but the stop date is completely missing and the record is not marked as ongoing. This 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.