STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children
Name of Test Drug:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) STR
Study Number:	GS-US-292-0106
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ARV	antiretroviral
BLQ	below limit of quantitation
BMD	bone mineral density
BMI	body mass index
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CI	confidence interval
COBI	cobicistat (GS-9350)
CPK	creatine phosphokinase
CRF	case report form
CV	coefficient of variation
DC	study drug discontinuation
DEXA	dual-energy x-ray absorptiometry
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EVG	elvitegravir
EVG/COBI/FTC/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
FDA	Food and Drug Administration
FEPO4	urine fractional excretion of phosphate
FTC	emtricitabine
GFR	glomerular filtration rate
GSI	Gilead Sciences, Inc.
HIV-1	human immunodeficiency virus (Type 1)
HLGT	high-level group term
IDMC	independent data monitoring committee
MedDRA	Medical Dictionary for Regulatory Activities
NCEP	National Cholesterol Education Program
PBMC	peripheral blood mononuclear cell
PT	preferred term
PK	pharmacokinetic
PR	pulse rate
PVF	pure virologic failure
Q	Quartile
QD	once daily

RNA	ribonucleic acid
SAP	statistical analysis plan
SD	standard deviation
SMQ	standardized MedDRA query
SOC	system organ class
STB	Stribild®
STR	single-tablet regimen
TDF	tenofovir disoproxil fumarate, Viread®
TFL	tables, figures, and listings
TFV	tenofovir
WHO	World Health Organization

1. INTRODUCTION

GS-US-292-0106 is a Phase 2/3, open-label, multicenter, multicohort, single-arm study of the pharmacokinetics (PK), safety, tolerability, and antiviral activity of elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (E/C/F/TAF) single-tablet regimen (STR) in HIV-1 infected, antiretroviral (ARV) treatment-naive adolescents and virologically suppressed children.

This document describes the statistical analysis methods and data presentations to be used in the summary and analysis of data for Study GS-US-292-0106 Interim 4 Analysis. This analysis will include data collected from Cohort 1 (treatment-naïve adolescents 12 to < 18 years of age and weight ≥ 35 kg) and Cohort 2 (virologically suppressed children 6 to < 12 years of age and weight ≥ 25 kg) of the study.

1.1. Study Objectives of Cohorts 1 and 2

Cohort 1

The primary objectives of Cohort 1 are:

Part A:

- To evaluate the steady state pharmacokinetics (PK) for elvitegravir (EVG) and tenofovir alafenamide (TAF) and confirm the dose of the elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected, antiretroviral (ARV) treatment-naive adolescents

Part B:

- To evaluate the safety and tolerability of the E/C/F/TAF STR through Week 24 in HIV-1 infected, ARV treatment-naive adolescents

The secondary objectives of Cohort 1 are:

- To evaluate the safety and tolerability of the E/C/F/TAF STR through Week 48 in HIV-1 infected, ARV treatment-naive adolescents

- To evaluate the antiviral activity of the E/C/F/TAF STR through Week 48 in HIV-1 infected, ARV treatment-naive adolescents

Cohort 2

The primary objectives of Cohort 2 are:

Part A:

- To evaluate the PK of EVG and TAF in virologically suppressed HIV-1 infected children 6 to < 12 years of age weighing ≥ 25 kg administered E/C/F/TAF STR

Part B:

- To evaluate the safety and tolerability of E/C/F/TAF STR through Week 24 in virologically suppressed HIV-1 infected children 6 to < 12 years of age weighing ≥ 25 kg

The secondary objectives of Cohort 2 are:

- To evaluate the antiviral activity of switching to E/C/F/TAF STR through Week 48 in virologically suppressed HIV-1 infected children 6 to < 12 years of age weighing ≥ 25 kg

- To evaluate the safety and tolerability of E/C/F/TAF STR through Week 48 in virologically suppressed HIV-1 infected children 6 to < 12 years of age, weighing ≥ 25 kg

1.2. Study Design of Cohorts 1 and 2

1.2.1. Design Configuration

Each cohort contains 2 parts (Part A and Part B) and 2 phases (main phase CCI [redacted]). The "main phase" in this document refers the safety and efficacy evaluation phase through Week 48. For each cohort, 18 to 24 eligible subjects will be enrolled into Part A to evaluate the EVG and TAF plasma PK and confirm the dose of EVG and TAF. The Week 4 intensive PK samples will be analyzed after 18 subjects (regardless of age distribution) complete the Week 4 intensive PK portion of the study. Following completion of the intensive PK visit, subjects will continue to receive the E/C/F/TAF STR and return for scheduled study visits through Week 48.

Screening will be initiated into Part B following confirmation of EVG and TAF exposure in at least 18 subjects from Part A. An additional 26 to 32 subjects will be enrolled in Part B to evaluate the safety, tolerability and antiviral activity of the E/C/F/TAF STR in at least 50 subjects, including all subjects enrolled in Parts A and B combined.

1.2.2. Subject Population

Cohort 1

Antiretroviral treatment-naive, HIV-1 infected adolescents (12 to < 18 years of age) of either sex with plasma HIV-1 RNA levels ≥ 1,000 copies/mL

Cohort 2

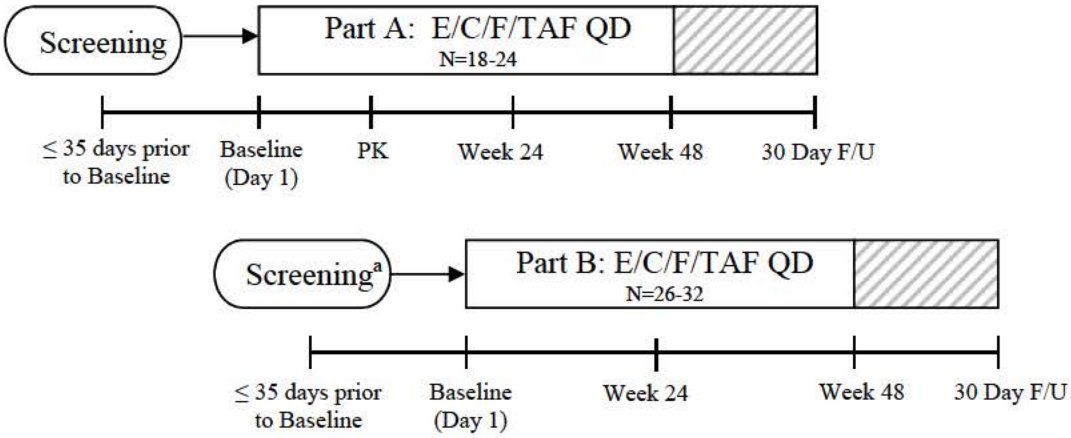
Virologically suppressed, HIV-1 infected children (6 to < 12 years of age and screening weight ≥ 25 kg) of either sex with plasma HIV-1 RNA levels < 50 copies/mL) for ≥ 6 consecutive months prior to screening on a stable antiretroviral regimen, with no documented history of resistance to any component of E/C/F/TAF STR.

1.2.3. Treatment Group

This is an open-label, single-arm study. All subjects in Cohorts 1 and 2 will be enrolled and treated with the E/C/F/TAF 150/150/200/10 mg STR.

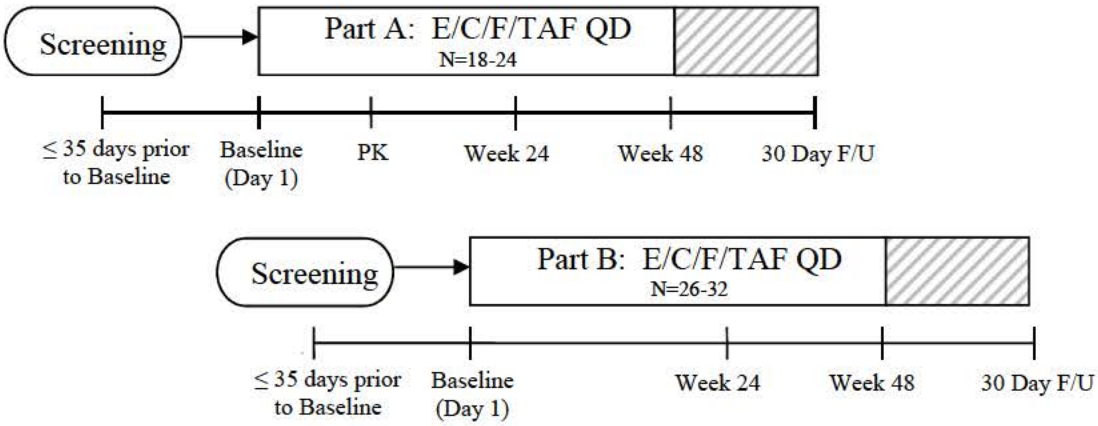
1.2.4. Study Schema (Main Phase)

Cohort 1 (N = 50):



a Screening for Part B will commence after the PK data from Part A confirms the adolescent dose of the E/C/F/TAF STR

Cohort 2 (N = 50):



1.2.5. Key Eligibility Criteria

HIV-1 infected subjects who meet the following criteria:

Cohort 1

- Age at Baseline: 12 to < 18 years old
- Weight at Screening: ≥ 35 kg (77 lbs)
- Plasma HIV-1 RNA ≥ 1,000 copies/mL at Screening (Roche COBAS TaqMan v2.0)
- Screening genotype report shows sensitivity to EVG, FTC and TFV (Monogram Biosciences, Inc.)
  - Subjects with HIV subtype AE who meet all inclusion/exclusion criteria and who have a non-reportable integrase genotype result may proceed with study enrollment. (For Thailand only)
- No prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission)

Cohort 2

- Age at Baseline: 6 to < 12 years old
- Weight at Screening: ≥ 25 kg (55 lbs)
- Plasma HIV-1 RNA: < 50 copies/mL for (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is > 50 copies/mL) ≥ 6 months prior to screening on a stable antiretroviral regimen, without prior history of resistance to any component of E/C/F/TAF STR
  - Unconfirmed HIV-1 RNA ≥ 50 copies/mL after previously reaching virologic suppression (transient detectable viremia, or "blip") and prior to screening is acceptable
- Currently receiving an antiretroviral regimen that has been stable for at least 6 months or has been newly initiated within 6 months for reasons other than virologic failure.

1.2.6. Study Periods/Phases and Duration

Intensive PK evaluation occurs at Week 4 for subjects in Part A, a 48-week safety and efficacy evaluation phase occurs for all subjects, and a 30-day follow up phase occurs for subjects who are permanently discontinued from the study before Week 48 and for subjects who do not choose to continue on the study after completing Week 48.

CCI [redacted]

1.2.7. Pharmacokinetic Evaluation

Subjects enrolled in Part A will participate in an intensive PK evaluation at Week 4. Samples will be collected at 0 (predose, ≤ 30 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 4, 5, 8, and 24 hours postdose.

A trough PK sample (20 to 24 hours postdose) will be collected at Weeks 1, 2, and 24.

A random single plasma PK sample will be collected between 0.25 to 4 hours postdose at Week 12, and another random single plasma will be collected anytime in relationship to last dose of study drug between Weeks 8 and 16.

The PK of EVG, COBI, FTC, TAF, and tenofovir (TFV) will be evaluated.

CCI [redacted]

[redacted]

1.2.9. Schedule of Assessments

Study procedures at screening, baseline, and during the study are outlined in the protocol and presented in Appendix 1 of the Statistical Analysis Plan (SAP).

1.3. Sample Size and Power of Cohorts 1 and 2

A minimum of 18 Part A subjects from each cohort will receive E/C/F/TAF STR in this study. PK data from these subjects will have 92% power to conclude exposure equivalence of TAF AUC_{last} in adolescents and children, respectively vs. 51 HIV-1 infected and HIV-negative adults (GS-US-292-0102 and GS-US-292-0103 combined) using two one-sided tests with each performed at an alpha level of 0.05. In this power analysis, it is assumed that the expected geometric mean ratios of TAF AUC_{last} between adolescent group and adult group are equal to 1, and the inter-subject standard deviation (natural log scale) of TAF AUC_{last} is 0.37 ng•hr/mL, and the equivalency boundary is 70% to 143%.

A minimum of 18 Part A subjects from each cohort will also provide > 99% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of apparent CL and Vz of TAF respectively, assuming a coefficient of variation (CV) of 38% for CL and 42% for Vz (GS-US-292-0102 and GS-US-292-0103 combined).

After protocol Amendment 2 was finalized, adult data included in Genvoya label became available. This data will be used as historical control for Cohort 2 (ie, intensive PK data from 19 HIV-1 infected adults in Study GS-US-292-0102 for EVG AUC_{tau} and population PK data from 539 HIV-1 infected adults in Studies GS-US-292 0104 and GS-US-292-0111 combined for TAF AUC_{last}) as comparison for Cohort 1 has been performed. The actual enrolled number of subjects in Cohort 2 Part A is 23, which will provide 90% power for EVG AUC_{tau} and 88% power for TAF AUC_{last} to conclude exposure equivalence between adults and children. In this power analysis, it is assumed that the expected geometric mean ratios are equal to 1, the intersubject standard deviation (natural log scale) of EVG AUC_{tau} and TAF AUC_{last} is 0.34 ng•hr/mL and 0.52 ng•hr/mL, respectively, 2 one-sided statistical tests are done at an alpha level of 0.05, and the equivalency boundary is 70% to 143%.

The total of 23 subjects enrolled in Cohort 2 Part A also provides > 86% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of CL and V_z of TAF respectively, assuming a coefficient of variation (CV) of 53% for CL and 76% for V_z (based on population PK data from GS-US-292-0104 and GS-US-292-0111 combined).

Sample size and power calculations were made using the software package nQuery Advisor (Version 6.0) and R.

2. PLANNED ANALYSES

2.1. Cohort 1 Part A Week 4 Independent Data Monitoring Committee Analysis

Analyses of safety, PK, and efficacy data were performed after 18 subjects (regardless of age distribution) from Cohort 1 Part A completed the Week 4 intensive PK portion of the study. The purpose of this interim analysis was to provide the Independent Data Monitoring Committee (IDMC) with a statistical report for review and to determine whether screening for Cohort 1 Part B would be initiated. More details are documented in the IDMC charter.

2.2. Cohort 1 Part A Final PK Analysis

A Cohort 1 Part A final PK analysis was scheduled to be performed after all subjects in Cohort 1 Part A either completed the Week 4 intensive PK portion of the study or permanently discontinued the study. This analysis was performed as part of the Cohort 1 Interim Week 24 Analysis (see the next section) and the results were included in the Interim 1 clinical study report (CSR).

2.3. Cohort 1 Interim Week 24 Analysis

An unplanned Cohort 1 interim Week 24 analysis was conducted after 23 subjects enrolled by 11 February 2014 from both Part A and Part B of Cohort 1 completed the Week 24 visit or prematurely discontinued study drug. The date of 11 February 2014 was selected for the purpose of ensuring all subjects enrolled by that date would have the chance to reach Week 24 visit by the data cut date. Results of this analysis were included in the interim 1 CSR.

2.4. Cohort 1 Week 24 Analysis (All Subjects Included)

A Cohort 1 Week 24 analysis was conducted after all subjects from both Part A and Part B of Cohort 1 completed their Week 24 visit or prematurely discontinued study drug.

The Cohort 1 Week 24 analysis was the primary analysis for the study objectives in Cohort 1 Part B. The purpose of this interim analysis was to provide the IDMC with a statistical report for review.

2.5. Cohort 1 Week 48 Analysis

A Cohort 1 Week 48 analysis was conducted after all subjects from both Part A and Part B of Cohort 1 completed their Week 48 visit or prematurely discontinued study drug. Results of this analysis were included in the interim 2 CSR.

2.6. Cohort 2 Part A Week 4 Independent Data Monitoring Committee Analysis

Analyses of safety, PK, and efficacy data were performed after 18 subjects (regardless of age distribution) from Cohort 2 Part A completed the Week 4 intensive PK portion of the study. The purpose of this interim analysis was to provide the IDMC with a statistical report for review. More details are documented in the IDMC charter.

2.7. Cohort 2 Part A Week 24 Analysis

A Cohort 2 Part A Week 24 analysis was conducted after all subjects in Cohort 2 Part A completed their Week 24 visit or prematurely discontinued study drug. Results of this analysis were included in the interim 3 CSR.

2.8. Interim 4 Analysis

An Interim 4 Analysis will be conducted after all subjects in Cohort CCI 2 have completed their CCI [redacted] or Week 48 visit (for Cohort 2), or prematurely discontinued study drug. This SAP describes the analysis plan for the Interim 4 Analysis. Results of this analysis will be included in the interim 4 CSR.

2.9. Final Analysis

A final statistical analysis will be conducted after all subjects have completed the study.

2.10. Changes from Protocol-Specified Analysis

The Cohort 1 Interim Week 24 analysis and Cohort 2 Part A Week 24 analysis were added. The rationale for performing these analysis was to include the most current Week 24 data from treatment-naïve adolescents and virologically suppressed children in the supplemental E/C/F/TAF marketing application.

A Cohort 1 Week 12 IDMC analysis was planned after the first 18 subjects from Cohort 1 Part A have either completed the Week 12 visit or prematurely discontinued study drug. This analysis was not done, as the Cohort 1 Interim Week 24 analysis results were presented to the IDMC instead.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Only Cohorts 1 and 2 data will be included for this Interim 4 Analysis.

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. A summary of the number and percentage of subjects in each analysis set will be provided. A listing will be provided for each analysis set.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set will include all subjects who are enrolled in this study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who are enrolled in the study and have received at least 1 dose of study drug. For FAS analysis, all efficacy data, including data collected after the last dose date of study drug, will be included, unless specified otherwise. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set will include all subjects who have received at least 1 dose of study drug. All data collected from the first dose date up to 30 days after subjects permanently discontinue their study drug will be included in the safety summaries**.** This is the primary analysis set for safety analyses.

3.1.4. DXA Analysis Set

3.1.4.1. Spine DXA Analysis Set

The Spine DXA Analysis Set will include all subjects who are enrolled in the study, have received at least 1 dose of study drug, and have a nonmissing baseline and at least 1 postbaseline spine bone mineral density (BMD) value.

3.1.4.2. Total Body Less Head DXA Analysis Set

The Total Body Less Head DXA analysis set will include all subjects who are enrolled in the study, have received at least 1 dose of study drug, and have a nonmissing baseline and at least one postbaseline total body less head BMD value.

3.1.5. PK Analysis Sets

3.1.5.1. PK Analysis Set

A PK analysis set will be defined separately for each of the 5 analytes (EVG, COBI, FTC, TAF, and TFV). The 5 PK analysis sets will include all enrolled and treated subjects from both Part A and Part B who have at least one observed concentration data of the respective analyte. The PK analysis sets will be used for analysis of single and trough blood concentrations.

CCI [redacted]

[redacted]

3.2. Subject Grouping

The subjects will be grouped by cohort (ie, Cohort 1 and Cohort 2) for efficacy and safety analyses.

3.3. Strata and Covariates

Not applicable.

3.4. Multiple Comparisons

Not applicable.

3.5. Missing Data and Outliers

3.5.1. 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 specified otherwise.

3.5.2. Outliers

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

3.6. Data Handling Conventions and Transformed Data

Logarithm (base 10) will be used to transform HIV-1 RNA data. Natural logarithm transformation will be applied to the PK concentrations for the PK analysis.

The PK concentration values below the lower limit of quantitation (BLQ) will be treated as zero for the determination of summary and order statistics. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing. For the presentation of summary and order statistics, if at least one subject has a concentration value of BLQ for the time point, then the minimum value will be displayed as "BLQ". If more than 50% of the subjects have a concentration data value of BLQ for the time point, then the minimum and median values will be displayed as "BLQ". If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum) will be displayed as "BLQ".

Data (eg, HIV-1 RNA 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:

- A value that is 1 unit less than the limit of quantification will be used for calculation of descriptive statistics if the datum is reported in the form of "< x". For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively.

- 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 direct bilirubin, a value of "< 0.1" is imputed as 0.09. For urine creatinine, a value of "< 1" is handled as a missing value in the calculation of related ratios.

3.7. Visit Windows

3.7.1. Key Definitions

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

Study Day is calculated relative to Study Day 1. For events that occurred on or after Study Day 1, Study Day is calculated as (visit date minus date of the first dose plus 1). For events that occurred prior to Study Day 1, Study Day is calculated as (visit date minus date of the first dose).

Last Dose Date is defined as the maximum and nonmissing end date of study drug E/C/F/TAF on the study drug administration eCRF form with "Study Drug Permanently Discontinued" box checked for subjects a) who prematurely discontinued study drug from main phase, b) completed study drug in the main phase CCI [redacted]

If the date of last dose is incomplete or missing (eg, due to lost to follow-up), the last dose date will be imputed using the instruction described in Appendix 4.

Last Study Date is the maximum of the nonmissing study drug start dates, study drug end dates, and the clinic visit and laboratory visit dates, including the 30-day follow-up visit date for subjects who a) prematurely discontinued study from main phase or b) completed study in the main phase CCI [redacted]

Baseline Value is defined as the last nonmissing value obtained on or prior to Study Day 1. The baseline BMD value and Tanner Stage is defined as the last nonmissing value obtained prior to or up to Study Day 21 (inclusive).

3.7.2. Analysis Windows

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

The analysis windows for vital signs, weight, height, laboratory tests, and urine chemistry are presented in Table 3-1.

Table 3-1. Analysis Windows for Vital Signs, Weight, Height, and Laboratory Tests[a]

	Nominal Day	Visit Window
Baseline		≤ 1
Week 1	7	[2,9] (NP[a])
Week 2	14	[10, 20] ([2,20][a])
Week 4	28	[21, 41]
Week 8	56	[42, 69]
Week 12	84	[70, 97]
Week 16	112	[98, 139]
Week 24	168	[140, 195]
Week 32	224	[196, 251]
Week 40	280	[252, 307]
Week 48	336	[308, 377]
CCI		

NP = Not planned by the protocol.
a Laboratory tests include HIV-1 RNA, CD4 cell counts, CD4%, hematology and chemistry. For CD4 cell count and CD4 %, Week 1 is not applicable and the study day range for Week 2 is [2, 20].

The analysis windows for metabolic assessments are presented in Table 3-2.

Table 3-2. Analysis Windows for Metabolic Assessments[a]

	Nominal Day	Visit Window
Baseline		≤ 1
Week 24	168	[2, 251]
Week 48	336	[252, 503]
CCI		

a Metabolic assessments include lipid panel (total cholesterol, high-density lipoprotein [HDL], direct low-density lipoprotein [LDL], and triglycerides).

The analysis windows for fasting glucose are presented in Table 3-3.

Table 3-3. Analysis Windows for Fasting Glucose

	Nominal Day	Visit Window
Baseline		≤ 1
Week 8	56	[2, 69]
Week 12	84	[70, 125]
Week 24	168	[126, 251]
Week 48	336	[252, 503]
CCI		

The analysis windows for tanner stage and BMD assessments are presented in Table 3-4.

Table 3-4. Analysis Windows for Tanner Stage and BMD Assessments

	Nominal Day	Visit Window
Baseline		≤ 21
Week 24	168	[22, 251]
Week 48	336	[252, 503]
CCI		

The analysis windows for serum bone safety assessments are presented in Table 3-5.

Table 3-5. Analysis Windows for Bone Safety Assessments[a]

	Nominal Day	Visit Window
Baseline		≤ 1
Week 12	84	[2, 125]
Week 24	168	[126, 251]
Week 24*k, k = 2, CCI	168*k	[168*k-84, 168*k+83]

a Bone safety assessments include N-Telopeptide, CTx, bone specific alkaline phosphatase, P1NP, PTH, 25-hydroxy vitamin D, 1,25-dihydroxyvitamin D. Urine bone assessments include bicarbonate, N-telopeptide.

The analysis windows for cystatin C are presented in Table 3-6.

Table 3-6. Analysis Windows for Cystatin C[a]

	Nominal Day	Visit Window
Baseline		≤ 1
Week 4	28	[2, 97]
Week 24	168	[98, 251]
Week 48	336	[252, 419]

a Only collected up to Week 48.

The analysis windows for urine renal safety assessments are presented in Table 3-7.

Table 3-7. Analysis Windows for Urine Renal Safety Assessments[a,b]

	Nominal Day	Visit Window
Baseline		≤ 1
Week 8	56	[2, 69]
Week 12	84	[70, 125]
Week 24	168	[126, 251]
Week 48	336	[252, 503]

a Urine Renal Safety including: retinol binding protein, and beta-2-microglobulin.
b Only collected up to Week 48.

3.7.3. Selection of Data in the Event of Multiple Records in a 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 multiple valid and nonmissing observations fall within the bounds of a visit window and a single value is needed, the following rule(s) will be used.

3.7.3.1. Numeric Observations

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

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

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

3.7.3.2. Categorical Observations

- For baseline, the last available record prior to the date of the first dose of the study drug will be selected. If there are multiple values recorded on the same day with the same time or missing time, select the value with the lowest severity.

- For postdose visits, the most conservative value (eg, abnormal will be selected over normal, or the value with the highest severity) within the window will be selected.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

The number and percentage of subjects enrolled will be summarized by each country and by each investigator within a country. The denominator for this calculation will be the number of all enrolled subjects.

A listing of enrollment, including informed consent date, enrollment status for the main phase CCI [redacted] will be provided.

Screen failure subjects will be listed, including screening number, inclusion criteria not met, and exclusion criteria met.

4.2. Disposition of Subjects

A summary of subject disposition will be provided for all screened subjects. This summary will include the number of subjects screened, screened subjects who were not enrolled, screen failure subjects who were not enrolled, subjects enrolled, subjects in the Safety Analysis Set, and subjects in the FAS.

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

a) Prematurely discontinued study treatment in the main phase (with summary of reasons for discontinuing treatment)

b) Completed study treatment in the main phase

c) Prematurely discontinued study in the main phase (with summary of reasons for discontinuing study).

d) Completed study in the main phase

CCI [redacted]

CCI [redacted]

The denominator for the percentages of subjects in each category will be the number of subjects in the safety analysis set for items a) through CCI [redacted]

No inferential statistics will be generated. Subject dispositions will also be listed. Data listings of reasons for premature study drug/study discontinuation will be provided.

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drug

Duration of exposure will be calculated in the Safety Analysis Set for exposure during the entire study for all subjects.

Duration of exposure during the entire study will be expressed in weeks (recorded to 1 decimal place for week, eg, 4.5 weeks), and calculated as (Date of last dose – Date of first dose + 1) / 7, regardless of temporary interruptions in study drug administration. If subjects are still on study drug, the last dose date will be imputed for the calculation of study drug exposure using instructions provided in Appendix 4.

Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, eg, ≥ 1 week (7 days), ≥ 2 weeks (14 days), ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days).

Summaries will be provided using the Safety Analysis set.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method using the Safety Analysis Set. Subjects who are still on study drug, CCI [redacted] will be censored on the imputed last dose date.

4.3.2. Adherence with Study Drug

Study drug adherence will be computed based on pill counts. The numbers of pills of study drug dispensed and returned are captured on the study drug accountability eCRF.

Adherence (%) to the study drug will be calculated as follows:

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

$$= 100 \times \frac{\text{Sum of Number of pills taken at each dispensing period [1]}}{\text{Sum of Number of pills prescribed at each dispensing period [2]}}$$

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

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

The duration of treatment at each dispensing period is calculated as the minimum of (the last returned date of the same dispensing period, the date of permanent discontinuation of study drug, and next pill dispensing date) minus the dispensing date. The next pill dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of pills returned was missing (with "Yes" answered for "Was Bottle returned?" question), it is assumed the number of pills returned was 0. If the number of pills dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, all records for the same dispensing date will be excluded from both denominator and numerator calculations.

Overall adherence will be calculated for each subject either up to the date of permanent discontinuation of the study drug for subjects who permanently discontinued study drug or completed study drug or using all data available for subjects ongoing on study drug.

Descriptive statistics for overall adherence with the study drug (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) together with the number and percentage of subjects in adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided for the Safety Analysis Set. No inferential statistics will be provided.

Drug accountability and adherence data will be listed.

4.4. Protocol Deviations

A listing will be provided for subjects in the Safety Analysis Set who violate at least 1 inclusion or exclusion criteria. The listing will include the eligibility criteria not met.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex, race, and ethnicity) and baseline characteristics (eg, body weight, weight Z-score, height, height Z-score, body surface area [BSA], body mass index [BMI], and Tanner Stage) will be summarized using descriptive statistics for all subjects in the safety analysis set. The BSA will be calculated using the formula, BSA (m^2) = SQRT([Height(cm) × Weight(kg)] / 3600). The percentage of subjects who reach Tanner Stage 4 or 5 (defined as the maximum stage of public hair and genitalia/breasts) will also be summarized. The sample size, mean, SD, median, Q1, Q3, minimum, and maximum will be provided for continuous data, and the number and percentage of subjects will be provided for categorical data. Age is calculated as age in years at first dose of study drug. The definition of baseline value is provided in Section 3.7.1.

In addition, the following baseline disease characteristics will be summarized:

- HIV-1 RNA (log_{10} copies/mL)
- HIV-1 RNA categories (copies/mL): ≤ 100,000 and > 100,000
- HIV-1 RNA categories (copies/mL): ≤ 50 and > 50
- CD4 cell count (cells/μL)
- CD4 cell count categories (cells/μL): a) ≤ 199, b) 200 to ≤ 349, c) 350 to ≤ 499, and d) ≥ 500
- CD4 percentage (%)
- HIV disease status
- Mode of infection (HIV risk factor)
- Years diagnosed with HIV (to be calculated as time prior to first dose date)
- HBV surface antigen
- HCV antibody
- eGFR calculated by the Schwartz Formula (Section 7.4.2)
- eGFR calculated by the modified Schwartz Formula (Section 7.4.2)
- Proteinuria by urinalysis (dipstick)

Demographic, baseline characteristics, and baseline disease characteristics data will be listed for all enrolled subjects.

5.2. Medical History

The HIV/AIDS-specific medical history and general medical history (ie, conditions not specific to the disease being studied) data will be listed only. Medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Definition of the Efficacy Endpoints

6.1.1. Efficacy Endpoints

The efficacy endpoints include:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the United States (US) FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}
- The change from baseline in CD4 cell count (cells/µL) and percentage at Weeks 24 and 48
- The percentage of subjects with HIV-1 RNA < 50 copies/mL and < 400 copies/mL at Weeks 24 and 48 (Missing = Failure and Missing = Excluded analyses)
- The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) at Weeks 24 and 48 (Cohort 1 only)
- The percentage of subjects with plasma HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis (Cohort 1 only)

The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL and < 400 copies/mL (based on the US FDA-defined snapshot) at Weeks 24 and 48 for Cohort 1 were performed as part of the interim 2 CSR and will not be repeated in this analysis.

The change from baseline in CD4 cell counts and percentages at Weeks 24 and 48 and the percentage of subjects with HIV-1 RNA < 50 copies/mL or < 400 copies/mL at Weeks 24 and 48 (based on the Missing = Failure and Missing = Excluded analyses) were performed as part of the interim 2 CSR for Cohort 1 and will be repeated using data from this analysis.

6.1.2. US FDA-Defined Snapshot Algorithm

The analysis window at Week 24 is defined as from Study Day 140 to Study Day 195, inclusive. All HIV-1 RNA data collected on-treatment (eg, data collected from Study Day 1 up to 1 day after the last dose date of study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

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

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

The flowchart of the snapshot algorithm is provided in Appendix 2.

The snapshot algorithm for the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 will be defined similarly. The Week 48 analysis window for snapshot algorithm will be from Study Day 308 to Day 377. The analysis based on the snapshot algorithm will be performed for Cohort 2 subjects only.

6.1.3. Missing = Failure and Missing = Excluded Analyses

Virologic response, defined as HIV-1 RNA < 50 copies/mL, will also be analyzed using the following 2 methods for imputing missing HIV-1 RNA values:

- Missing = Failure (M = F)

  In this approach, all missing data will be treated as virologic failure (ie, HIV-1 RNA ≥ 50 copies/mL). This analysis will be done using the FAS.

- Missing = Excluded (M = E)

  In this approach, all missing data will be excluded in the computation of virologic response (ie, missing data points excluded from both the numerator and denominator in response rate computation).

6.2. Analysis Methods for Efficacy Endpoints

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

The numbers and percentages of subjects with HIV-1 RNA < 50 copies/mL or < 400 copies/mL based on the US FDA-defined snapshot algorithm, M = F analysis, and M = E analysis, will be summarized. The 95% CI for the percentage estimate in the snapshot algorithm analysis, M = F analysis, and M = E analysis will be constructed using the Clopper-Pearson exact method. For the snapshot algorithm, the numbers and percentages of subjects with HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL (including subcategories), and no virological data (including reasons) will be summarized. For the M = F analysis, results will be summarized for all visits up to Week 48. For the M = E analysis, results will be summarized at all visits through the data cut date for the FAS.

The $\log_{10}$ HIV-1 RNA data will be summarized for Cohort 1 only, using observed data. The CD4 cell count and CD4% data will be summarized using observed, on-treatment data (ie, up to 1 day after the last dose date of study drug). The baseline values and changes from baseline in CD4 cell count (cells/μL), and CD4% at each visit will be summarized descriptively (sample size, mean, SD, 95% CI, median, Q1, Q3, minimum, and maximum). The mean and 95% CI of change from baseline over time will be plotted.

A listing for plasma HIV-1 RNA, CD4 cell count, CD4%, and a listing for snapshot outcome will be provided.

6.3. Changes From Protocol-Specified Efficacy Analyses

For Cohort 2, the percentage of subjects with plasma HIV-1 RNA < 400 copies/mL using snapshot algorithm was removed, because Cohort 2 is comprised of suppressed subjects and this endpoint does not apply.

7. SAFETY ANALYSES

Safety data will be summarized for the subjects in the Safety Analysis Set. All safety data collected on or after the date of the first dose of study drug up to the last dose date of study drug plus 30 days will be summarized, unless specified otherwise. All safety data will be included in data listings.

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group terms (HLGT), high-level term, preferred term (PT), and lower-level term will be attached to the clinical database.

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of AEs to Study Drug

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

7.1.4. Relationship of AEs to Study Procedure

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

7.1.5. Serious AEs

Serious AEs are those identified in the eCRF, where "Yes" was marked for "AE serious". The clinical database will be reconciled with the SAE database (from the Pharmacovigilance and Epidemiology Department) before database finalization.

7.1.6. Treatment Emergent AEs

7.1.6.1. Definition of Treatment Emergent

Treatment-emergent AEs (TEAEs) are events that meet one of the following criteria up to 30 days after the permanent discontinuation of the study drug:

- Events with onset dates on or after the first dose date of study drug
- Events that result in permanent study drug discontinuation

7.1.6.2. Incomplete Dates

If the date of onset is incomplete or completely missing, the detailed definition of TEAE is specified in Appendix 4.

7.1.7. Summaries of AEs and Deaths

A brief summary of AEs will show the number and percentage of subjects who a) had any treatment-emergent AE, b) had any Grade 3 or 4 treatment-emergent AE, c) had any Grade 2, 3, or 4 treatment-emergent AE, d) had any treatment-emergent study-drug-related AE, e) had any Grade 3 or 4 treatment-emergent study-drug-related AE, f) had any Grade 2, 3, or 4 treatment-emergent study-drug-related AE, g) had any treatment-emergent SAE, h) had any treatment-emergent study-drug-related SAE, i) had any treatment-emergent AE leading to premature study-drug discontinuation, and j) had treatment-emergent death.

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

Summaries (number and percentage of subjects) of AEs (by SOC and PT) will be provided using the safety analysis set as follows:

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

Multiple events will be counted once only per subject in each summary. For data presentation, SOC 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 summaries, data listings will be provided for the following:

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Study-drug related SAEs
- Death report
- Pregnancy report
- AEs leading to premature discontinuation of study drug

7.1.8. Stage 3 Opportunistic Illnesses in HIV

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

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the Safety Analysis Set. Analysis will be based on values reported in conventional units.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided 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 3.7.3.

7.2.1.1. Metabolic Assessments

For the lipid panel and glucose, only those measurements under fasting status will be summarized.

7.2.1.2. Calcium Corrected for Albumin

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

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

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

7.2.2. Graded Laboratory Values

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

Maximum postbaseline grade, instead of treatment-emergent grade, for nonfasting glucose will be summarized, as nonfasting glucose was not assessed at the baseline visit.

For triglycerides and cholesterol, the protocol-specified toxicity grading 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 not be graded, except lipid tests.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values in the given study period. Listings will be provided for treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or Grade 4 laboratory abnormalities.

7.2.2.3. Liver-Related Laboratory Test

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

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

The summary will use data from all the postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For 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 values of the tests in evaluation at the same postbaseline visit date.

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

7.3. Bone Safety Analyses

7.3.1. Bone Mineral Density

The BMD will be evaluated in 2 body sites: spine and total body less head. BMD standard Z-score will be computed based on the chronological age-matched population of the same sex and ethnicity. BMD height-age Z-score will be generated by substituting height-age for chronological age, where height-age will be determined as the age at which the child's height is the median on the stature-for-age Centers for Disease Control (CDC) Year 2000 growth chart published on the following CDC website:

http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/index.htm

If a subject's height was greater than the median height for a 20-year-old according to the growth chart, both height-age and height-age Z-score will not be calculated. The BMD Z-scores (standard Z-score and height-age Z-score) will be calculated for the 2 body sites (ie, spine and total body less head).

Percentage change from baseline in spine and total body less head BMD will be summarized by visit using descriptive statistics for subjects in the spine and total body less head DXA analysis sets, respectively.

Descriptive summaries for the BMD Z-scores (standard Z-score and height-age Z-score) and the change from baseline in Z-scores (standard Z-score and height-age Z-score) will be presented by visit for the spine and total body less head DXA Analysis Sets.

Shift tables of the clinical BMD status at baseline versus postbaseline visits will be presented for both spine and total body less head BMD. Clinical BMD status will be classified into 2 categories using the BMD Z-scores (standard Z-score and height-age Z-score): Z-scores > -2 versus Z-scores ≤ -2 {Gordon et al 2008}. The number and percentages of subjects with at least 4% decline in BMD from baseline to each postbaseline visit will be summarized by visit for the spine and total body less head DXA Analysis Sets.

A listing of subjects with at least 4% decline from baseline in BMD from at least one of the body sites (ie, spine and total body less head) at any postbaseline visit will be provided. The BMD values, standard BMD Z-score, height-age BMD Z-score, and height-age will be listed. Listings of subjects with baseline BMD Z-score > -2 and BMD Z-score ≤ -2 at any postbaseline visit in spine and/or total body less head BMD based on standard Z-scores and height-age Z-scores, respectively, will also be provided.

7.3.2. Bone Safety Assessments

Bone safety assessments include the following in serum: bicarbonate, N-telopeptide, C-telopeptide, osteocalcin, bone-specific alkaline phosphatase, procollagen type 1 N-terminal propeptide [P1NP], parathyroid hormone [PTH], 25-OH vitamin D, and 1, 25-OH vitamin D; and in urine: bicarbonate and N-telopeptide.

Baseline, postbaseline, changes from baseline, and percentage change from baseline in bone safety assessments will be summarized by visit using descriptive statistics.

7.3.3. Fracture Events

The preferred terms included in analysis for fracture events are defined based on the Standardized MedDRA Query (SMQ) of osteoporosis/osteopenia of fractures and HLGT of fractures from MedDRA. The lists of PTs selected by clinical review from all the PT terms under SMQ of osteoporosis/osteopenia fractures and HLGT of fractures are presented in Appendix 3. Fracture events will be listed only.

7.4. Renal Safety Analyses

7.4.1. Serum Creatinine

The baseline and change from baseline in serum creatinine will be summarized by visit using descriptive statistics.

7.4.2. Estimated Glomerular Filtration Rate

The following formulae will be used to calculate eGFR:

Schwartz Formula:

$$\text{eGFR (ml/min/1.73m}^2) = \text{k} \times \text{L/SCr},$$

where

k is the proportionality constant (0.55 for children [6-11 years old] or adolescent girls ≥ 12 years old; 0.70 for adolescent boys ≥ 12 years old)
L is height (cm)
SCr is serum creatinine (mg/dL)

Modified Schwartz Formula:

$$\begin{aligned}\text{eGFR (ml/min/1.73m}^2) &= 39.1[\text{height (m) / SCr (mg/dl)}]^{0.516} \\ &\times [1.8 / \text{cystatin C (mg/L)}]^{0.294} [30 / \text{BUN (mg/dl)}]^{0.169} \times [1.099]^{\text{male}} \\ &\times [\text{height (m)} / 1.4]^{0.188}\end{aligned}$$

where BUN is the blood urea nitrogen. The modified Schwartz formula incorporates additional laboratory assessments of renal function, specifically BUN and cystatin C, and may, therefore, offer an alternative method of assessment of postbaseline changes in eGFR that is not as strongly affected by the changes in serum creatinine assay method {Schwartz et al 2009}.

Change from baseline in eGFR at each postbaseline visit will be provided.

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

Baseline, postbaseline, change from baseline, and percentage change from baseline in urine retinol binding protein (RBP) to creatinine ratio and beta-2-microglobulin to creatinine ratio will be summarized by visit using descriptive statistics.

7.4.4. Proteinuria by Quantitative Assessment

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

7.5. Tanner Stage Assessment

The Tanner Stages will be used to evaluate the onset and progression of pubertal changes. Females will be rated for pubic hair growth and breast development, and males will be rated for pubic hair growth and genitalia development. The Tanner Stages (Pubic Hair and Breasts for female; Pubic Hair and Genitalia for male) at each postbaseline visit will be summarized by baseline Tanner Stages using frequency count and percentage.

Tanner Stage results at screening and during the study will be listed.

7.6. Palatability/Acceptability Assessment

Palatability and acceptability assessments were collected once (at a postbaseline visit) for Cohort 1 subjects, and were collected at baseline and Week 4 for Cohort 2 subjects. These assessments will be summarized using frequency count and percentage, as one group (for Cohort 1) or by visit (for Cohort 2).

Palatability and acceptability assessments will also be listed.

7.7. Body Weight, Height, and Vital Signs

Body weight and height at each visit and change from baseline in body weight and height at each visit will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by visit.

An age- and sex-specific Z-score will be derived for each weight and height measurement according to the downloadable SAS program available on the Centers for Disease Control (CDC) website using the year 2000 growth charts. The methods and SAS program published on the following CDC websites will be applied to calculate the Z-score:

http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/index.htm

http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

Z-scores for body weight and height at each visit and change from baseline in Z-scores for postbaseline body weight and height will be summarized by visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

Body weight, weight Z-score, height, height Z-score, BMI, and BSA will be listed. Vital signs will be presented in data listings only.

7.8. Nonstudy-Drug Antiretroviral Medications

Nonstudy-drug ARV medications used prior to the study (expected for Cohort 2 only), during study, and after study (if collected), will be coded using the GSI-modified World Health Organization (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.

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

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

7.9. Concomitant Non-ARV Medications

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

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

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

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

Subjects with any non-ARV concomitant medications will be listed.

7.10. Electrocardiogram Results

The ECG data collected at screening and early study drug discontinuation will be listed.

7.11. Other Safety Measures

Hepatitis test results will be listed. A data listing will be provided for subjects experiencing pregnancy during the study.

7.12. Changes from Protocol-Specified Safety Analysis

There is no change from protocol-specified safety analyses.

8. PHARMACOKINETICS ANALYSIS

All necessary summary statistics on intensive PK data for both Cohorts 1 and 2 CCI [redacted] have been performed as part of the interim 1 and interim 3 CSRs. Only the trough/single PK concentrations CCI [redacted] will be included in this analysis.

8.1. Analysis Methods for Anytime PK

Plasma concentration data for will be listed for all subjects. EVG, COBI, FTC, TFV trough samples, defined as the sampling time within a range of [20.0, 28.0] hours after observed dosing time, will be marked and included for summary statistics. Spare samples may be used for population PK assessment. Plasma concentrations for TAF will be listed only and will not be summarized.

The following TFLs will be provided for the trough PK sampling:

- Table with individual subject concentration data for EVG, COBI, FTC, TFV
- Listing of PK sampling details
- Listing of study drug administration record for PK dosing.

CCI [redacted]

8.2.1. Statistical Comparative Analysis

No statistical comparative analyses will be performed.

8.3. Changes from Protocol-Specified PK Analysis

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

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U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revision 1). March, 2003.

10. SOFTWARE

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

SAS® (SAS Institute Inc., Version 9.2, Cary, NC) will be used for generating all TFLs.

WinNonlin® (Pharsight Corporation Version 6.3, Mountain View, CA) will be used for all PK analyses.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedure Table

Study Procedures	Screening[a]	Baseline (Day 1)	Week 1 (Day 7)	Week 2[b]	Intensive PK[c]	End of Week[b]								CCI	30-Day Follow-up[d]	ESDD[e]
						4	8	12	16	24	32	40	48			
Assent/Informed Consent	X															
Medical History	X															
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Complete Physical Exam	X	X								X			X			X
Symptom-Directed Physical Exam[g]			X	X	X	X	X	X	X		X	X			X	
Height	X	X	X	X		X	X	X	X	X	X	X	X		X	X
Weight	X	X	X	X		X	X	X	X	X	X	X	X		X	X
Tanner Stage Evaluations[h]		X								X			X			
12-lead ECG – Performed Supine	X															
HIV-1 Genotype[i]	X															
Hematology Profile[j]	X	X	X	X		X	X	X	X	X	X	X	X		X	X
Chemistry Profile[k]	X	X	X	X		X	X	X	X	X	X	X	X		X	X
CD4+ Cell Count and Percentage	X	X		X		X	X	X	X	X	X	X	X		X	X
Metabolic Assessments[l]		X								X			X			
Plasma HIV-1 RNA[m]	X	X	X	X		X	X	X	X	X	X	X	X		X	X
CCI CCI																
HBV and HCV Serologies	X															
Urinalysis	X	X	X	X		X	X	X	X	X	X	X	X		X	X
Estimated Glomerular Filtration Rate[o]	X	X	X	X		X	X	X	X	X	X	X	X		X	X

Study Procedures	Screening[a]	Baseline (Day 1)	Week 1 (Day 7)	Week 2[b]	Intensive PK[c]	End of Week[b]								CCI	30-Day Follow-up[d]	ESDD[e]
						4	8	12	16	24	32	40	48			
CCI																
Serum Pregnancy Test[q]	X															
Urine Pregnancy Test[q]		X	X	X		X	X	X	X	X	X	X	X		X	X
Dispense Dosing Diary (for Part A Subjects)				X												
Review Dosing Diary (For Part A subjects)					X											
Single PK Sampling[r]						X[z]	X	X	X		X[dd]	X[dd]				X
Trough PK Sample[s]			X	X						X			X			
Intensive PK Sampling[t]					X											
CCI																
DXA Scan (Lumbar Spine & Total Body)[v]		X								X			X			
Bone Safety		X					X	X		X			X			
Urine Renal Safety[x]		X					X	X		X			X			
Study Drug Dispensation		X				X	X	X	X	X	X	X	X			
In-clinic Dosing[y]		X	X	X		X		X		X			X			
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X			X
Palatability and Acceptability Assessment		X[bb]				X[bb]				X[aa]	X[aa]	X[aa]	X[aa]		X[cc]	X[cc]

a Evaluations to be completed within 35 days prior to Baseline (or 42 days for subjects who require repeat testing of the HIV-1 genotype).
b All study visits are to be scheduled relative to the Baseline/Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Week 8, ± 4 days of the protocol specified date through Week 48, CCI [redacted], unless otherwise specified.
c Part A subjects only. The Intensive PK evaluation will occur at the Week 4 visit. For the purpose of scheduling the Intensive PK visit, a + 7 days window may be used. If the subject has already dosed prior to the Intensive PK evaluation visit or is not in a fasted state, the Intensive PK assessments must not be completed. The subject should be instructed to return in a fasted state anytime but not later than Week 4 + 7 days for the Intensive PK visit.
d Only required for those subjects not enrolling in the CCI [redacted] phase of the study or those subjects who permanently discontinue study drug and do not continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.
e ESDD visit should occur within 72 hours of last dose of study drug.
f Vital signs include blood pressure, pulse, respiration rate and temperature.
g Symptom-directed physical examinations performed as needed.

h Tanner assessments will no longer be performed once a subject has been documented as Tanner Stage 5. Tanner stage assessments will be performed CCI [redacted] until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.

i Analysis for reverse transcriptase, protease and integrase resistance will be done at Screening. The investigator must have received the results from the Screening genotype before proceeding with the Baseline visit. (Cohort 1 only).

j CBC with differential and platelet count

k Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, cystatin C (Baseline, Weeks 2 (Cohort 1 only), 4, 24, and 48), total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, CPK and uric acid

l Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). CCI [redacted]
If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.

m For, Part A subjects, back-up samples not be collected at Week 1, 2 and 4 visits for Cohort 1 and at Week 1- Week 16 for Cohort 2. For Part B subjects, back-up samples will be collected at all visits.

n [redacted]

o Estimated Glomerular Filtration Rate (GFR) using Schwartz Formula (mL/min/1.73m^2) = k × L/Scr [(k is a proportionality constant, for females ≥ 6 years old is 0.55; and for males ≥ 6 years old is 0.70); L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)]

p [redacted]

q Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test at any visit.

r At Week 4 (Cohort 1 Part B subjects only) and Week 12 (all subjects), the random single plasma PK sample should be collected between 0.25 and 4 hours post-dose. For Cohort 1 subjects, at all other visits, and for Cohort 2, at Weeks 8 and 16 only. The random single PK sample can be taken anytime in relationship to last dose of study drug.

s Subjects must come into the clinic without taking their dose of E/C/F/TAF STR. A trough (20 to 24 hours post-dose) plasma PK sample will be collected at Weeks 1, 2, and 24 for all subjects and Week 48 for Cohort 1 only.

t Part A subjects only. Intensive PK sampling will be performed on Week 4. For the purpose of scheduling the Intensive PK visit a + 7 days window may be used. If the subject has already dosed prior to the Intensive PK visit or is not in a fasted state, the Intensive PK assessments must not be completed. The subject should be instructed to return within four days for the Intensive PK visit. If dosing non-compliance is identified on or prior to the Intensive PK visit, the Intensive PK assessments must not be completed. The subject should be counseled regarding proper dosing and asked to return for the Intensive PK visit no sooner than three days following compliant dosing and no later than Week 4 + 7 days. Please refer to the PK and PBMC manual for sample collection and processing details.

u [redacted]

v DXA scans to be performed in all eligible subjects prior to study drug administration at Baseline. DXA scan also to be performed Weeks 24 and 48 (± 10 days). CCI [redacted]

w Bone Safety including: Serum: bicarbonate, N-telopeptide, C-telopeptide (CTX), osteocalcin, bone specific alkaline phosphatase, procollagen type 1 N-terminal propeptide (P1NP), serum parathyroid hormone (PTH), 25OH Vitamin D and 1, 25OH Vitamin D. Urine: bicarbonate, N-telopeptide. Specimens for bone safety should be taken when subjects are in a fasted state. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for bone safety. CCI [redacted]

x Urine Renal Safety including: urine chemistry, retinol binding protein, and beta-2-microglobulin. Urine for selected safety should be collected when subjects are in a fasted state. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to collect urine for urine renal safety.

y All subjects will be given their dose of E/C/F/TAF STR with food.

z Cohort 1 Part B subjects only

aa To be performed for all Cohort 1 subjects currently on study at their next scheduled visit.

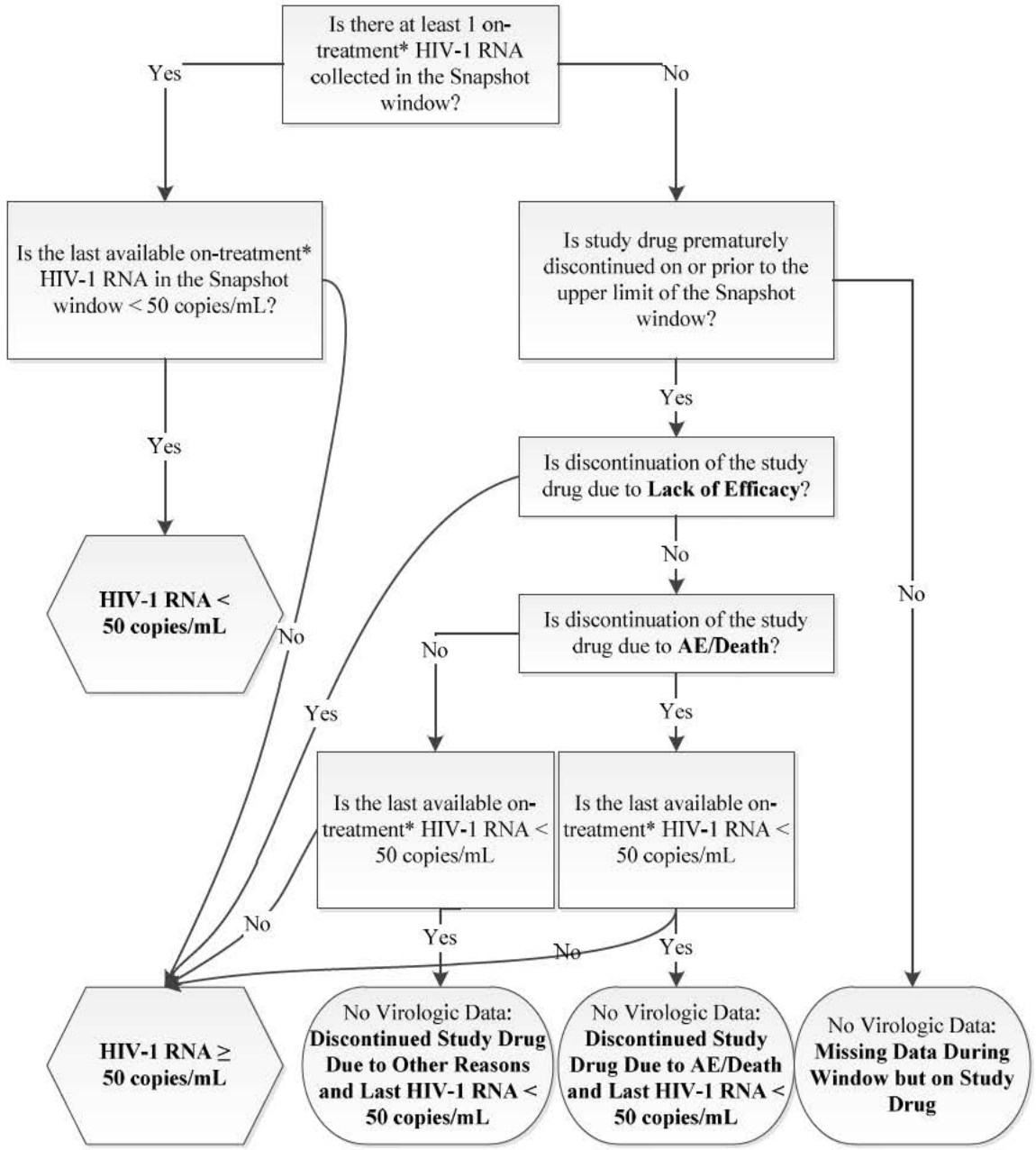
bb To be performed at Baseline and Week 4 for all Cohort 2 subjects enrolled.

cc To be performed at ESDD or 30-Day Follow-Up visit for either Cohort 1 or 2, as applicable.

dd Cohort 1 subjects only

Appendix 2. Flowchart of US FDA-Defined Snapshot Algorithm

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



* On-Treatment HIV-1 RNA data include all HIV-1 RNA data from Study Day 1 for subjects who are on-going and HIV-1 RNA data from Study Day 1 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 the SMQ of osteoporosis/osteopenia and HLGT of fractures based on clinical review are listed as follows.

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

Selected PTs Based on SMQ of Osteoporosis/Osteopenia and HLGT of Fractures
Fractured ischium
Fractured sacrum
Fractured skull depressed
Greenstick fracture
Hand fracture
Hip fracture
Humerus fracture
Ilium fracture
Impacted fracture
Internal fixation of fracture
Jaw fracture
Limb fracture
Lisfranc fracture
Lower limb fracture
Lumbar vertebral fracture
Multiple fractures
Open fracture
Open reduction of fracture
Open reduction of spinal fracture
Osteochondral fracture
Osteoporotic fracture
Patella fracture
Pathological fracture
Pelvic fracture
Periprosthetic fracture
Pubis fracture
Radius fracture
Rib fracture
Sacroiliac fracture
Scapula fracture
Scapulothoracic dissociation
Skull fracture
Skull fractured base

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

Note: AEs are coded by MedDRA 20.1.

Appendix 4. Programming Specifications

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 Urinalysis. Disease related biomarkers, eg, bone biomarkers, will be grouped separately. Summaries will be sorted alphabetically by test within group.

13) Study day calculation: 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 is calculated as follows:

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

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

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

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

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

    For subjects who are enrolled and never dosed with study drug, AGE is calculated based on the date of screened.

2) All screened subjects refer to all subjects who are screened and have a screening number. For summarization, same subject is counted only once. DOB and other demographic information such as gender, race, and ethnicity will be used for identifying unique screened subjects.

3) Screen failure subjects are the subjects who answered "Yes" to "Was subject a Screen Failure?" in informed consent and eligibility criteria eCRF.

4) BMI is calculated from height in meters (eg, height in cm/100) and weight in kilograms as:

$$\text{BMI} = (\text{weight [kg]}) / (\text{height [meters]}^2)$$

5) For HIV test using HIV Taqman kit, if a 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.

6) For direct bilirubin, a value of "< 0.1" will be treated as 0.09 for calculation of summary statistics {Nehls et al 1973}.

7) For serum Cystatin C test, a value of "< .10" is treated as missing in summary or in the calculation of eGFR.

8) Generally for AE summary tables, SOC and PT will be included in all treatment-emergent AE tables.

9) Last Dose Date has been defined in Section 3.7.1.

Last Dose Date Imputation for Subjects Who Prematurely Discontinued Study or Completed Study

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

- If the date of last dose is **missing** (ie, 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, clinical visit dates, and laboratory visit dates excluding the 30-day follow-up visit to impute the last dose date.

Last Dose Date Imputation for Ongoing Subjects (for the Purpose of Duration of Exposure)

If subjects are still on study drug (ie, defined as subjects who do not have study drug completion eCRF filled out), the last dose date will be estimated as follows:

- If the last record in the study drug administration eCRF has a nonmissing study drug end date, the estimated last dose date will be the last study drug end date.

- If the last record in the study drug administration eCRF has a missing end date, the estimated last dose date will be the maximum 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.

10) Last Study Date

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

11) Toxicity Grades:

a) With regards to metabolic assessment of lipids tests (triglycerides, total cholesterol, and LDL cholesterol), if the fasting status is 'N' or blank, the lab test values will not be graded as non-fasting values are not interpretable.

b) For the summary of the toxicity graded tests, all post-baseline graded results (not just those at summarized visits) up to 30 days after the last dose of study drug will be included.

c) For hematuria grading, the laboratory reports both dipstick results (urine blood test with values of 1+, 2+, etc) and quantitative results (urine RBC test with a unit of /HPF), only summarize toxicity grades of the quantitative (urine RBC) results, but list the grades from both tests.

12) In the listing for viologic outcomes using snapshot algorithm, flag all HIV-RNA records that are used in determining snapshot outcomes including the following:

- **Virologic Success** – HIV-1 RNA < 50 copies/mL for snapshot virologic outcome (ie, the last available HIV-1 RNA record for a certain analysis timepoint)
- **Virologic Failure** – HIV-1 RNA ≥ 50 copies/mL for snapshot virologic outcome
- **Virologic Failure** – the last available HIV-1 RNA value of ≥ 50 copies/mL if subjects discontinued study drug due to other reasons
- **No Virologic Data** – the last available HIV-1 RNA value of < 50 copies/mL if subjects discontinued study drug due to other reasons

13) "On-treatment" data in the SAP refer to the data on or prior to the date of permanent discontinuation of study drug (eg, last dose date). For subjects who are ongoing on study drug, "on-treatment" data refer to all data up to the data cut for the analysis.

CCI [redacted]

15) For HIV-1 RNA Missing = Failure or Missing = Excluded analysis:

Missing = Failure when

- The subject has a visit after the missing.
- The subject is missing HIV-1 RNA because he has already discontinued the study drug.
- The subject came for a lab visit for that visit but the HIV-1 RNA value is missing (e.g. sample issue).

Missing is excluded from the denominator when

- For ongoing subjects, HIV-1 RNA is missing and upcoming visit has not happened yet (excluding ongoing subjects who haven't reached the upper limit of the analysis window for corresponding visit).
- This subject has neither baseline nor postbaseline lab data.

16) 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