STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2/3 Multicenter, Open-Label, Multicohort, Two-Part Study Evaluating the Pharmacokinetics (PK), Safety, and Antiviral Activity of Elvitegravir (EVG) Administered with a Background Regimen (BR) Containing a Ritonavir-Boosted Protease Inhibitor (PI/r) in HIV-1 Infected, Antiretroviral Treatment-Experienced Pediatric Subjects
Name of Test Drug:	Elvitegravir (EVG)
Study Number:	GS-US-183-0160
Protocol Version:	Original
Protocol Date:	25 April 2013
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	12 January 2018
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ANOVA	analysis of variance
ARV	antiretroviral
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below limit of quantitation
BMI	body mass index
BR	background regimen
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CPK	creatine phosphokinase
CRF	case report form
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EVG	elvitegravir
EVG/r	ritonavir-boosted elvitegravir
FAS	full analysis set
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GLSM	geometric least-squares means
GSI	Gilead Sciences, Inc.
GSS	genotypic sensitivity score
IDMC	independent data monitoring committee
HAART	highly active antiretroviral therapy
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus (type 1)
HLT	high level term
IDMC	independent data monitoring committee
LDL	direct low-density lipoprotein
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
NP	not planned in the protocol
PI	protease inhibitor

PI/r	ritonavir-boosted protease inhibitor
PT	preferred term
PK	pharmacokinetic
Q	quartile
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TFL	tables, figures, and listings
WHO	World Health Organization

1. INTRODUCTION

GS-US-183-0160 is a Phase 2/3, multicenter, open-label, multicohort, 2-part study of the pharmacokinetics (PK), safety, and antiviral activity of elvitegravir (EVG) administered with a background regimen (BR) containing a ritonavir-boosted protease inhibitor (PI/r) in HIV-1 infected, antiretroviral (ARV) treatment-experienced pediatric subjects.

This document describes the statistical analysis methods and data presentations to be used in the summary and analysis of data for Study GS-US-183-0160. This analysis will only include data collected from Cohort 1, Part B (12 to < 18 years of age) and Cohort 2, Part A (6 to < 12 years of age) as Cohort 2, Part B and Cohorts 3 and 4 were never initiated.

This statistical analysis plan (SAP) is based on the original protocol for Study GS-US-183-0160 dated 25 April 2013. Although Amendment 1 of the protocol was submitted to the FDA, it was never implemented and no patients were enrolled under the amendment.

1.1. Study Objectives of Cohort 1 Part B and Cohort 2 Part A

The primary objectives are:

- To evaluate the steady-state PK and confirm the dose of ritonavir-boosted elvitegravir (EVG/r) in HIV-1 infected, antiretroviral treatment-experienced subjects 6 to <12 years of age (Cohort 2 Part A)

- To evaluate the safety and tolerability of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 6 to <18 years of age

The secondary objective is:

- To evaluate the antiviral activity of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 6 to <18 years of age who are failing their current highly active antiretroviral therapy (HAART) regimen

1.2. Study Design

1.2.1. Design Configuration

Open-label, multicohort, 2-part study evaluating the PK, safety, and antiviral activity of EVG administered with a BR containing a PI/r in HIV-1 infected, antiretroviral treatment-experienced pediatric subjects.

1.2.1.1. Cohort 1, Part B (12 to < 18 years old)

For Cohort 1, Part B, ≥ 8 subjects who are failing a current antiretroviral regimen (HIV-1 RNA > 1,000 copies/mL) will be enrolled to evaluate the safety, tolerability, and antiviral activity of EVG.

Elvitegravir will be administered for 48 weeks concomitantly with a newly constructed BR selected by the investigator that is based on the subject's antiretroviral history and screening viral resistance results.

1.2.1.2. Cohort 2, Part A (6 to < 12 years old)

For Cohort 2, Part A, ≥ 12 subjects either with suppressed viremia (HIV-1 RNA < 50 copies/mL) or failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) will be enrolled to evaluate the steady-state PK and confirm the dose of EVG. Only subjects aged 6 to < 12 years old will be enrolled.

For subjects with HIV-1 RNA < 50 copies/mL at screening, EVG will be added to the existing BR that must include a PI/r. The dose of EVG will be dependent upon the coadministered PI/r and will be based on body weight.

For subjects with HIV-1 RNA > 1,000 copies/mL at screening, EVG will be added to a newly constructed BR selected by the investigator that is based on the subject's antiretroviral history and screening or historical viral resistance results. The BR must include at least 2 fully-active agents, one of which is a fully-active PI/r (fully active PI/r is defined by genotypic analysis).

Subjects with HIV-1 RNA < 50 copies/mL at screening are considered to have suppressed viremia and will only participate in Part A of the study. These subjects will discontinue EVG and will complete the study following the Day 10 intensive PK visit.

Subjects with HIV-1 RNA > 1,000 copies/mL at screening are considered to be failing their antiretroviral regimen and will continue to receive EVG following completion of the Day 10 intensive PK visit for scheduled study visits through Week 48.

1.2.2. Subject Population

1.2.2.1. Cohort 1, Part B

Antiretroviral treatment-experienced, HIV-1 infected subjects, aged 12 to < 18 years failing a current antiretroviral regimen (with HIV-1 RNA >1,000 copies/mL)

1.2.2.2. Cohort 2, Part A

Antiretroviral treatment-experienced, HIV-1 infected subjects, aged 6 to < 12 years, either with suppressed viremia (HIV-1 RNA < 50 copies/mL) or failing a current antiretroviral regimen (HIV-1 RNA > 1,000 copies/mL)

1.2.3. Treatment Group

This is an open-label, single-arm study.

EVG 50-mg, 85-mg, and 150-mg tablets will be administered orally, once daily with food, in combination with a BR that must include a protocol-permitted PI/r.

For subjects weighing ≥ 17 kg and receiving darunavir/r, tipranavir/r or fosamprenavir/r, the EVG dose will be as follows:

- 85 mg for subjects ≥ 17 kg to < 28 kg
- 100 mg (2 x 50 mg tablets) for subjects ≥ 28 kg to < 34 kg
- 150 mg for subjects ≥ 34 kg

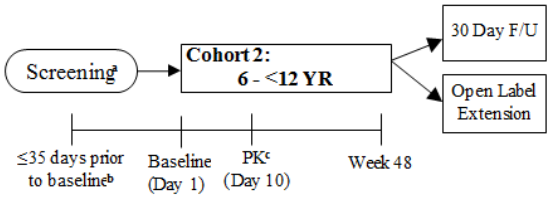
For subjects weighing ≥ 17 kg and receiving atazanavir/r or lopinavir/r, the EVG dose will be as follows:

- 50 mg for subjects ≥ 17 kg to < 30 kg
- 85 mg for subjects ≥ 30 kg

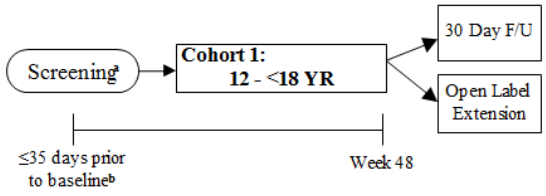
Note: All subjects in Cohort 1, Part B and Cohort 2, Part A weighed ≥ 17 kg at screening and were able to swallow tablets; therefore, only EVG 50-mg, 85-mg, and 150-mg tablets were used. No subject received EVG powder for oral suspension formulation.

1.2.4. Study Schema

Cohort 2 PART A
Subjects with Suppressed Viremia or Failing ARV Regimen



Cohort 1 PART B
Subjects Failing ARV Regimen



a. Occur concurrently
b. The screening window may be extended to 42 days for subjects who require repeat testing of HIV-1 genotype or if the screening visit is divided into multiple visits.
c. Subjects with suppressed viremia will discontinue EVG following completion of Day 10 PK and will complete the study following the Day 30 follow-up visit.

1.2.5. Key Eligibility Criteria

Inclusion Criteria:

- Antiretroviral treatment-experienced, HIV-1 infected male and female subjects 12 to < 18 years of age for Cohort 1 and 6 to < 12 years of age for Cohort 2
- Cohort 2 body weight at screening > 15 kg
- **Part A:** Evidence of suppressed viremia or failing a current antiretroviral regimen as defined below.
- **Part B:** Evidence of failing a current antiretroviral regimen as defined below.

Criteria for subjects with evidence of suppressed viremia **(Part A only)**:

- Plasma HIV-1 RNA concentration (at least 2 consecutive measurements) at an undetectable level according to the assay being used for at least 3 months prior to screening, and HIV-1 RNA < 50 copies/mL (Roche COBAS TaqMan v2.0) at screening.

- Stable antiretroviral regimen including one of the following PI/r for at least 3 months prior to screening: lopinavir/r, atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. Subjects undergoing dose modifications to their antiretroviral regimen for growth or switching medication formulations are considered to be on a stable antiretroviral regimen.

Criteria for subjects failing a current antiretroviral regimen **(Parts A and B)**:

- HIV-1 RNA > 1,000 copies/mL at screening (Roche COBAS TaqMan v2.0)

- Prior treatment for HIV-1 infection, defined as 6 months of antiretroviral treatment experience and at least 1 documented resistance mutation as defined by current IAS-USA Guidelines. These resistance mutations must be documented in a historical genotype report(s), or in the genotype report at screening provided by Gilead Sciences.

- Stable antiretroviral regimen (or no antiretroviral regimen) for at least 30 days prior to screening. Subjects undergoing dose modifications to their antiretroviral regimen for growth or switching medication formulations are considered to be on a stable antiretroviral regimen.

- Screening genotype must show full sensitivity to EVG.

- Ability to construct a BR that must contain one of the following fully active PI/r: lopinavir/r, atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. (Fully active is defined by genotypic analysis.)

- Genotypic sensitivity score (GSS) of at least 2 (including the fully active PI/r and EVG).

- No opportunistic infection within 30 days of study entry

Exclusion Criteria:

- For Cohorts 1 and 2, screening CD4 cell count < 50 cells/mm^3

- Evidence of active pulmonary or extrapulmonary tuberculosis disease within 3 months of the Screening visit

- An ongoing serious infection requiring systemic antibiotic therapy at the time of screening

- An acquired immunodeficiency syndrome (AIDS)-defining condition with onset within 30 days prior to screening

- Life expectancy of < 1 year
- For subjects with HIV-1 RNA > 1,000 copies/mL at screening, prior treatment of any duration with an integrase strand transfer inhibitor

1.2.6. Study Periods/Phases and Duration

The protocol–defined Main Phase includes treatment duration of 10 days for subjects with suppressed viremia, and treatment duration of 48 weeks for subjects failing a current antiretroviral regimen.

Subjects with suppressed viremia will have a final follow-up visit at 30 days after their last dose of study drug.

For subjects failing a current antiretroviral regimen, after Week 48, subjects receiving EVG will be given the option to participate in an extension phase of the study where Gilead will provide EVG until: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) the age appropriate EVG formulation becomes available for use in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country.

1.2.7. Pharmacokinetic Evaluation

Subjects in Cohort 2, Part A will participate in an intensive PK evaluation of EVG on Day 10. Samples will be collected at 0 (≤ 30 minutes predose), 1.5, 2.5, 3.5, 5, 8, 10, and 12 hours postdose.

Subjects failing a current antiretroviral regimen (HIV-1 RNA > 1,000 copies/mL at screening) will have trough and random single plasma PK evaluations, as follows:

- Trough plasma PK sample (20 to 24 hours postdose) will be collected at Weeks 16 and 40
- Random single plasma PK sample will be collected at Weeks 4, 8, 12, and 32, and every 12 weeks after Week 48, for descriptive PK

1.2.8. Schedule of Assessments

Study procedures at screening, baseline, and during the study are outlined in the protocol and presented in Appendix 2 of the SAP.

1.3. Sample Size and Power

A total of 12 pediatric subjects in Cohort 2, Part A compared to 334 HIV-infected historical control subjects included in the EVG population PK modeling will provide at least 90% power to conclude exposure equivalence of EVG AUC_{tau} and C_{max} in pediatric subjects vs. in historical control subjects, assuming the expected geometric mean ratio is 1, equivalency boundary is 70% to 143%, 2 one-sided tests are each performed at an alpha level of 0.05, and the standard deviation is 0.36 ng•h/mL for AUC_{tau} and 0.28 ng/mL for C_{max} (natural log scale, estimated from EVG population PK modeling).

A total of 12 subjects in Cohort 2, Part A will also provide at least 80% power to target a 95% confidence interval (CI) within 60% and 140% of the geometric mean estimate of clearance and volume of distribution of EVG respectively, assuming a coefficient of variation (CV) of 42.3% for clearance and 22.9% for volume of distribution (estimated from EVG population PK modeling).

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

2. PLANNED ANALYSES

2.1. Independent Data Monitoring Committee Analysis

Analyses of safety, PK, and efficacy data were performed after (1) subjects in Cohort 2, Part A completed the Day 10 intensive PK portion of the study and (2) the first 8 subjects with screening HIV-1 RNA > 1,000 copies/mL in Cohort 1, Part B completed the Week 12 visit or prematurely discontinued 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 3, Part A and Cohort 2, Part B would be initiated or not (see Section 2.3). More details are documented in the IDMC charter.

2.2. Final Analysis

A final statistical analysis will be conducted after all subjects have completed the study. This SAP describes the analysis plan for the Final Analysis.

2.3. Changes from Protocol-Specified Analysis

The study was discontinued after enrollment of only Cohort 1, Part B and Cohort 2, Part A. The study close-out was triggered by the voluntary withdrawal of single-agent Vitekta® (EVG 85-mg and 150-mg tablets) from sale. The decision to withdraw Vitekta was based solely on low utilization of the product, and was not a result of any ongoing or new safety issue with Vitekta.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Only Cohort 1, Part B and Cohort 2, Part A subjects were enrolled and will be included in this final 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 of subjects excluded from each analysis set will be provided.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set will include all subjects who were 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 were enrolled in the study and 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 received at least 1 dose of study drug. All data collected up to 30 days after subjects permanently discontinued their study drug will be included in the safety summaries**.** This is the primary analysis set for safety analyses.

3.1.4. Intensive PK Analysis Set

The Intensive PK Analysis Set for Part A will be defined for each analyte (EVG and metabolite GS-9200) and will include all Part A subjects who were enrolled and received at least 1 dose of study drug and for whom steady-state pharmacokinetic profiles of the analyte of interest at the Intensive PK visit are evaluable. The intensive PK Analysis Set will be used for PK analysis of EVG and GS-9200.

3.2. Subject Grouping

Subjects will be grouped into 2 groups as follows for all analyses except for endpoints specified otherwise below and for the PK analysis:

1. Age 6 to < 18 Years with Screening HIV-1 RNA > 1,000 copies/mL: this includes all subjects from Cohort 1, Part B and subjects from Cohort 2, Part A with Screening HIV-1 RNA > 1,000 copies/mL
2. Age 6 to < 12 Years with Screening HIV-1 RNA < 50 copies/mL: this includes subjects from Cohort 2, Part A with Screening HIV-1 RNA < 50 copies/mL

For the enrollment, disposition, demographics, and baseline disease characteristics tables, an additional Total column will be included.

The following endpoints will not be summarized for subjects age 6 to < 12 years with screening HIV-1 RNA < 50 copies/mL. Per protocol, data on these endpoints are either not collected at postbaseline visits or on-treatment data are not available due to short treatment duration (10-Day) required for suppressed subjects.

- Efficacy endpoints: Snapshot outcome, CD4 cell count, and CD4 percentage
- Safety endpoints: metabolic assessments, height, and Tanner stage

PK results will only be summarized for subjects age 6 to < 12 years as one group. This includes all subjects from Cohort 2, Part A (Intensive PK Analysis Set).

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 PK concentrations for the PK analysis.

Pharmacokinetic 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 1 subject has a concentration value BLQ for the time point, then the minimum value will be displayed as "BLQ". If more than 50% of 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 BLQ 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 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.

3.7. Visit Windows

3.7.1. Key Definitions

Study Day 1 is defined as the day when the first dose of study drug EVG 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 (event date minus date of the first dose plus 1). For events that occurred prior to Study Day 1, Study Day is calculated as (event date minus date of the first dose).

Last Dose Date is defined as the maximum and nonmissing end date of study drug EVG on the Study Drug Administration eCRF form with "Study Drug Permanently Discontinued" box checked.

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

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

Baseline Value is defined as the last nonmissing value obtained on or prior to Study Day 1.

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.

Due to differences in study procedures for subjects with screening HIV-1 RNA < 50 copies/mL and subjects with screening HIV-1 RNA > 1,000 copies/mL, 2 different sets of analysis windows are presented in Table 3-1 to Table 3-3 for subjects with screening HIV-1 RNA < 50 copies/mL and in Table 3-4 to Table 3-6 for subjects with screening HIV-1 RNA > 1,000 copies/mL. Analysis windows will be provided for vital signs (including blood pressure, temperature, heart rate, respiration rate), weight, laboratory tests (including HIV-1 RNA, CD4 cell count, CD4%, hematology, and chemistry), metabolic assessments (including fasting glucose and lipid panel: total cholesterol, high-density lipoprotein [HDL], direct low-density lipoprotein [LDL], and triglycerides), Tanner Stage assessments, and height. Analysis windows for metabolic assessments, Tanner stage assessments, and height will not be defined for subjects with screening HIV-1 RNA < 50 copies/mL because there were no postbaseline assessments scheduled in the protocol for these subjects.

The analysis windows for vital signs, weight, and laboratory tests (except where specified otherwise) for subjects with screening HIV-1 RNA < 50 copies/mL are presented in Table 3-1.

Table 3-1. Analysis Windows for Vital Signs, Weight, and Select Laboratory Tests for Subjects with Screening HIV-1 RNA < 50 copies/mL

	Nominal Day	Visit Window (Day)
Baseline		≤ 1
Day 10	10	[2, 25]
30-Day Follow-up	40	≥ 26

Select laboratory tests include hematology, chemistry, HIV-1 RNA, and urinalysis. Visit windows for other laboratory tests (CD4 cell count and CD4%, and eGFR) are noted in tables below.

The analysis windows for CD4 cell count and CD4% for subjects with screening HIV-1 RNA < 50 copies/mL are presented in Table 3-2.

Table 3-2. Analysis Windows for CD4 Cell Count and CD4% for Subjects with Screening HIV-1 RNA < 50 copies/mL

	Nominal Day	Visit Window (Day)
Baseline		≤ 1
30-Day Follow-up	40	≥ 2

CD4 cell count and CD4% for subjects with screening HIV-1 RNA < 50 copies/mL will be listed only.

The analysis windows for eGFR for subjects with screening HIV-1 RNA < 50 copies/mL are presented in Table 3-3.

Table 3-3. Analysis Windows for eGFR for Subjects with Screening HIV-1 RNA < 50 copies/mL

	Nominal Day	Visit Window (Day)
Baseline		≤ 1
Day 10	10	≥ 2

The analysis windows for vital signs, weight, and laboratory tests (except where specified otherwise) for subjects with screening HIV-1 RNA > 1,000 copies/mL are presented in Table 3-4.

Table 3-4. Analysis Windows for Vital Signs, Weight, and Select Laboratory Tests for Subjects with Screening HIV-1 RNA > 1,000 copies/mL

	Nominal Day	Visit Window (Day)
Baseline		≤ 1
Day 10	10	[2, 19] (NP[a])
Week 4	28	[20, 42] ([2, 42][b])
Week 8	56	[43, 70]
Week 12	84	[71, 98]
Week 16	112	[99, 140]
Week 24	168	[141, 196]
Week 32	224	[197, 252]
Week 40	280	[253, 308]
Week 48	336	[309, 378]
Week 60	420	[379, 462]
Week 72	504	[463, 546]
Week 84	588	[547, 630]

	Nominal Day	Visit Window (Day)
Week 96	672	[631, 714]
Week 108	756	[715, 798]
Week 120	840	[799, 882]
Week 132	924	[883, 966]
Week 144	1008	[967, 1050]
Week 156	1092	[1051, 1134]
Week 168	1176	[1135, 1218]
Week 180	1260	[1219, 1302]

NP = not planned for Part B subjects, nor for CD4 cell count and CD4% (neither Part A nor Part B).
Select laboratory tests include hematology, chemistry, HIV-1 RNA, CD4 cell count, CD4%, and eGFR. Visit windows for other laboratory tests (urinalysis and metabolic assessment) are noted in tables below
a Day 10 is not applicable for Part B subjects nor for CD4 cell count and CD4% (neither Part A nor Part B)
b Study day range for Week 4 is [2, 41] when Day 10 is not applicable.

The analysis windows for metabolic assessments and Tanner stage assessments for subjects with screening HIV-1 RNA > 1,000 copies/mL are presented in Table 3-5.

Table 3-5. Analysis Windows for Metabolic Assessments and Tanner Stage Assessments for Subjects with Screening HIV-1 RNA > 1,000 copies/mL

	Nominal Day	Visit Window (Day)
Baseline		≤ 1
Week 24	168	[2, 252]
Week 48	336	[253, 504]
Week 96	672	[505, 840]
Week 144	1008	[841, 1176]

The analysis windows for height for subjects with screening HIV-1 RNA > 1,000 copies/mL are presented in Table 3-6.

Table 3-6. Analysis Windows for Height for Subjects with Screening HIV-1 RNA > 1,000 copies/mL

	Nominal Day	Visit Window (Day)
Baseline		≤ 1
Week 12	84	[2, 126]
Week 24	168	[127, 252]
Week 48	336	[253, 378]

	Nominal Day	Visit Window (Day)
Week 60	420	[379, 462]
Week 72	504	[463, 546]
Week 84	588	[547, 630]
Week 96	672	[631, 714]
Week 108	756	[715, 798]
Week 120	840	[799, 882]
Week 132	924	[883, 966]
Week 144	1008	[967, 1050]
Week 156	1092	[1051, 1134]
Week 168	1176	[1135, 1218]
Week 180	1260	[1219, 1302]
Week 192	1344	[1303, 1386]

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

3.8. Changes from Protocol-Specified Analysis Conventions

Because the study was terminated after enrollment of only Cohort 1, Part B and Cohort 2, Part A (see Section 2.3), a PK Analysis Set was not defined and subject groupings were changed. PK analyses were performed only for the overall intensive PK group. Safety analyses were not performed for the intensive PK group overall or by age. Safety and efficacy analyses were not conducted by age group.

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, will be provided. Enrollment status for the main phase and extension phase (if applicable) will be provided in the disposition listing,

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, subjects enrolled, subjects in the Safety Analysis Set, and subjects in the FAS.

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

a) Prematurely discontinued study treatment (with summary of reasons for discontinuing treatment)

b) Completed study treatment

c) Prematurely discontinued study (with summary of reasons for discontinuing study)

d) Completed study

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

No inferential statistics will be generated. Subject disposition 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 for exposure during the entire study for all subjects in the Safety Analysis Set.

Duration of exposure during the entire study will be expressed in weeks (recorded to 1 decimal place for week, ie, 4.5 weeks), and calculated as (Date of last dose – Date of first dose + 1)/7, regardless of temporary interruptions in study drug administration.

Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, ie, ≥ 1 week (7 days), ≥ 2 weeks (14 days), ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 16 weeks (112 days), then for each 8 week period until Week 48, and then for each 12 week period through Week 168.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method using the Safety Analysis Set. Subjects who completed study drug will be censored at the 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 return 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 the "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 up to either the date of permanent discontinuation of the study drug for subjects who permanently discontinued study drug, or up to the date of study completion for those who completed 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 (ie, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) 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 (ie, age, sex, race, and ethnicity) and baseline characteristics (ie, 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 the Safety Analysis Set. The BSA will be calculated using the formula: BSA (m^2) = square root of ([height (cm) × weight (kg)]/3600). Sample size, mean, SD, median, Q1, Q3, minimum, and maximum will be provided for continuous data, and 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 category (copies/mL): a) < 50, b) ≥ 50 to ≤ 1,000, c) > 1,000 to ≤ 100,000, d) > 100,000
- CD4 cell count (cells/μL)
- CD4 cell count category (cells/μL): a) < 50, b) ≥ 50 to < 200, c) ≥ 200 to < 350, d) ≥ 350 to < 500, and e) ≥ 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 status
- HCV antibody status
- eGFR calculated by the Schwartz Formula (Section 7.3.2)
- Proteinuria by urinalysis (dipstick)

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

5.2. Medical History

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 are:

- 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 {Smith et al 2011}
- The percentage of subjects with plasma HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm
- The change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Weeks 24 and 48
- The change from baseline in CD4 cell count (cells/μL) and percentage at Weeks 24 and 48

6.1.2. US FDA-Defined Snapshot Algorithm

The analysis window at Week 24 is defined as from Study Day 141 to Study Day 196, inclusive. All HIV-1 RNA data collected on-treatment (ie, 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 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, 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 3.

The snapshot algorithm for the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (Study Day 309 to Study Day 378) and the percentage of subjects with HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 will be defined similarly.

6.1.3. Missing = Excluded Analyses

Virologic response, defined as achieving HIV-1 RNA < 50 and <400 copies/mL, will also be analyzed using the Missing = Excluded (M = E) method.

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

The $\log_{10}$ HIV-1 RNA data will be summarized 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 $\log_{10}$ HIV-1 RNA, 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

The analysis of the relationship between EVG exposure and virologic failure defined in the protocol was not performed due to the voluntary withdrawal of single-agent Vitekta from sale (See Section 2.3).

7. SAFETY ANALYSES

Safety data will be summarized for subjects in the Safety Analysis Set. All safety data collected 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 the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term, high-level term, preferred term (PT), and lowest-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 5 of the study protocol.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator answers 'Related' to the question 'Related to Study Treatment?' in the 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 Adverse Events 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 Adverse Events

Serious AEs (SAEs) are those identified in the eCRF for which "Yes" was marked for "AE serious?". The clinical database will be reconciled with the SAE database (from the Drug Safety and Public Health 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 1 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 had a) any TEAE, b) any Grade 3 or 4 TEAE, c) any Grade 2, 3, or 4 TEAE, d) any treatment-emergent study-drug-related AE, e) any Grade 3 or 4 treatment-emergent study-drug-related AE, f) any Grade 2, 3, or 4 treatment-emergent study-drug-related AE, g) any treatment-emergent SAE, h) any treatment-emergent study-drug-related SAE, i) any TEAE leading to premature study-drug discontinuation, and j) 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 TEAEs
- Grade 3 or 4 TEAEs
- Grade 2, 3, or 4 TEAEs
- 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 TEAEs 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 (total of Groups 1 and 2 in Section 3.2). 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. Category C Events

On an ongoing basis, AEs will be reviewed for events that might meet the definition of Category C events that are indicative of an AIDS-Defining Diagnosis (see Protocol Appendix 7). Gilead medical personnel will review the possible Category C events and confirm the events that meet the definition. Events that meet the Category C 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

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.

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 (ie, 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 1 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.

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

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) 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 laboratory abnormalities and 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 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. Renal Safety Analyses

7.3.1. Serum Creatinine

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

7.3.2. Estimated Glomerular Filtration Rate

The following formula 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); and SCr is serum creatinine (mg/dL)

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

7.4. Tanner Stage Assessment

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. Tanner Stages (pubic hair and breasts for females; pubic hair and genitalia for males) at each postbaseline visit will be summarized by baseline Tanner Stage using frequency count and percentage.

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

Age of first menses will be summarized descriptively and listed for female subjects.

7.5. Palatability Assessment

Palatability is only assessed for subjects taking EVG suspension formulation. As no subjects were dosed with the EVG oral suspension formulation, no data are available on its palatability.

7.6. 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 US 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.

7.7. Antiretroviral and Nonantiretroviral Medications

7.7.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug ARV medications used prior to, during, or after the study (if collected) will be coded using the 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. No inferential statistics will be provided.

7.7.2. Nonstudy Drug Antiretroviral Medications Received as Background Regimen

Antiretroviral medications meeting one of the following criteria will be considered as background regimen:

- Antiretroviral medications with a start date between the first dose date and the last dose date, inclusive, and without regard to the end date;
- Antiretroviral medications with a start date prior to the first dose date and the end date after the first dose date or marked as ongoing;
- Antiretroviral medications with missing start date and end date;
- Antiretroviral medications with a start date prior to the first dose date and missing end date.

If the start date or end date is incomplete, the following rules will apply to determine ARV medications received during the study:

- The month and year (or year) of the start 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 start date is the same as or before the month and year (or year) of the last dose of study drug.

Data 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. The summary will be ordered by decreasing total frequency (total of Groups 1 and 2) of use of generic name within a drug class. No inferential statistics will be provided.

7.7.3. Nonantiretroviral Concomitant Medications

Nonantiretroviral concomitant medications 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 WHO drug class and 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 (total of Groups 1 and 2 in Section 3.2) 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. 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 either of the following criteria:

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

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

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

7.8. Electrocardiogram Results

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

7.9. Other Safety Measures

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

7.10. Changes from Protocol-Specified Safety Analysis

The definition for treatment-emergent adverse events has been updated from the protocol to adopt Gilead's newer and more conservative standard which includes more cases as treatment-emergent AEs.

In the protocol it is specified that palatability of the EVG suspension formulation will be summarized. As no subjects were dosed with the EVG suspension formulation, no data are available.

8. PHARMACOKINETICS ANALYSIS

8.1. Statistical Analysis Methods

The PK parameters for each analyte (ie, EVG, GS-9200) will be estimated for all subjects in the Intensive PK Analysis Set. The pharmacokinetic parameters of GS-9202 (metabolite M1) were not calculable as all GS-9202 plasma concentration measurements were BLQ.

The PK parameters to be estimated in this study are listed and defined in Appendix 1.

In Cohort 2, Part A, the primary endpoint is the PK parameters AUC_{tau} and C_{max} for EVG. The secondary endpoints include the PK parameters C_{tau}, CL/F, and V_z/F for EVG.

8.2. Estimation of PK Parameters

The PK parameters will be estimated by application of a nonlinear model using standard noncompartmental methods (WinNonlin® software v6.3). The linear up/log down trapezoidal rule will be used in conjunction with the appropriate noncompartmental model (usually input Model 200 for oral dosing), with input values for dose, time of dose, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible.

All baseline (predose) sample times will be assigned a concentration value of 0. Samples BLQ of bioanalytical assays that occur prior to achievement of the first quantifiable concentration will be assigned a concentration of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data. The nominal time point for a key event (ie, urine collection) or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the pharmacokineticist on a profile-by-profile basis.

Accurate estimation of several PK parameters, such as λ_z and $t_{½}$, are dependent on the measured terminal elimination phase of the drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the pharmacokineticist.

A list of individual data on determination of plasma half-life and corresponding correlation coefficient will be provided, including intensive PK sampling day, number of data points in regression, start time, end time, and correlation coefficient.

8.3. Statistical Analysis Methods for Intensive PK

8.3.1. General Considerations for Statistical Analyses

Plasma concentration data will be listed for all dosed subjects and summarized by nominal time point for the Intensive PK Analysis Set.

The PK parameters of each analyte (ie, EVG, GS-9200) and the metabolite to parent ratio of AUC_{tau} and C_{max} will be listed for all dosed subjects and summarized for the Intensive PK Analysis Set. For PK parameters, values that are incalculable will be excluded from the summary statistics.

Descriptive statistics (sample size, mean, SD, coefficient of variation [%CV], minimum, median, maximum, Q1, and Q3) will be presented for PK concentration data. The number of subjects with value of BLQ will be presented at each nominal time point.

For some PK parameter data (ie, C_{max}, C_{tau}, AUC_{tau}, CL/F, V_z/F, and the metabolite to parent ratio of AUC_{tau} and C_{max}), the geometric mean, its 95% CI, and the mean and SD of the natural log-transformed values will be presented in addition to the summaries mentioned above.

Missing plasma concentrations due to missed sample collection will be excluded from the summary statistics and log-normalized data.

The following tables and listings will be provided for each analyte for the Day 10 intensive PK analysis using the Intensive PK Analysis Set:

- Table of individual subject concentration data and summary statistics at each time point
- Table of individual subject PK parameters and summary statistics
- Listing of the time points used in the calculation of the terminal elimination rate constant λ_z
- Listing of PK sampling details by subject including deviations in scheduled and actual draw times and procedures, and individual blood sampling time deviations in minutes.
- Listing of study drug administration record for intensive PK dosing

8.3.2. Statistical Comparative Analysis

To determine whether the proposed EVG dose in children 6 to < 12 years of age achieves similar systemic exposure to that in adults, statistical comparisons will be performed to compare PK data from the current study with adult data from population PK modeling in study GS-US-183-0145. More specifically, the comparisons will be carried out as follows.

A 1-way analysis of variance (ANOVA) model will be fitted to the natural log-transformed values of AUC_{tau} and C_{max} (as the primary endpoints), and C_{tau} (as the secondary endpoint), with treatment group as a fixed effect. The treatment groups are defined as:

- Test Treatment: 6 to < 12 years (Cohort 2, Part A)
- Reference Treatment: Adult subjects who took at least 1 dose of EVG/r in Study GS-US-183-0145 and who had at least 1 nonmissing EVG PK parameter (ie, AUC_{tau}, C_{max}, or C_{tau}) estimated from the population PK analysis (n=334) (Historical PK analysis sets).

The ANOVA model will be carried out using the PROC MIXED procedure in SAS. An example SAS code is provided below:

```
Proc Mixed;
   by paramcd;
   class group subjid;
   model lnest = group/ ddfm=kr;
   repeated  / group = group;
   lsmeans group / e  diff cl alpha = 0.1;
   estimate 'Test versus Reference'  group  1 -1 / cl alpha = 0.10;
Run;
```

The geometric least-squares means (GLS-means) of each treatment group, and the mean ratio (test/reference) and corresponding 90% CI for each PK parameter (ie, AUC_{tau}, C_{max}, and C_{tau}) of EVG will be reported.

The LSMEANS statement computes LS-means for each treatment group on the natural log scale. These values will then be exponentiated to produce the GLS-means on the original linear scale.

The ESTIMATE statement will produce the point estimate and 90% CI on the natural-log scale for the difference between treatments. The test/reference exposure ratio and associated 90% CIs will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI lower and upper limits.

Ninety percent CIs for the ratio of the geometric LS (GLS) means of the test (children in this study) and reference (adults from historical studies) treatments will be calculated for AUC_{tau}, C_{tau}, and C_{max} of EVG consistent with the two 1-sided tests each performed at an alpha level of 0.05 {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}, {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001}. Equivalency in PK will be concluded if the 90% CIs are within the equivalence boundaries of 70% to 143%.

In addition, the 95% CIs for the geometric mean of the apparent CL/F and VL/F of EVG will be calculated, and the ratios of the lower and upper bounds of the 95% CIs versus the point estimate of the geometric means will be compared to the interval of 60% to 140% of their respective parameters.

The effect of EVG dose on the PK of EVG will be explored. PK parameters will be analyzed separately for (1) EVG dose of 50 mg and 85mg combined, (2) EVG dose of 50 mg, and (3) EVG dose of 85 mg,

8.3.3. Analysis Methods for Anytime PK

The following listings will be provided including the EVG and 9200 analytes using the All Enrolled Analysis Set for the single PK sampling (Weeks 4, 8, and 12):

- Listing of PK sampling details and subject concentration data
- Listing of study drug administration record for PK dosing.

8.4. Changes from Protocol-Specified PK Analysis

The following protocol-specified efficacy analyses were not done:

- Plasma concentrations over time were not plotted.
- As only one age cohort (Cohort 2, Part A) was enrolled, the effect of age on the PK of EVG was not explored.
- The effect of the PI/r BR on the PK of EVG was not explored.
- The single PK sampling for Weeks 32 and every 12 weeks after Week 48, and the trough PK sampling (Weeks 16 and 40) were not listed because the samples were not analyzed.

9. REFERENCES

Gordon CM, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, et al. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. J Clin Densitom 2008;11 (1):43-58.

Nehls G, Akland G. Procedures for Handling Aerometric Data. Journal of the Air Pollution Control Association 1973;23 (3):180-4.

Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20 (3):629-37.

Smith F, Hammerstrom T, Soon G, Zhou S, Chen B, Mai Y, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. Drug Information Journal 2011;45:291-300.

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

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. January, 2001.

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) is to be used for the sample size and power calculation.

SAS® (SAS Institute Inc., Version 9.4 or higher, Cary, NC) is to be used for generating all TFLs.

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

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision
None			

12. APPENDICES

Appendix 1. PK Parameters
Appendix 2. Study Procedure Table – Cohorts 1 and 2
Appendix 3. Flowchart of US FDA-Defined Snapshot Algorithm
Appendix 4. Programming Specifications

Appendix 1. PK Parameters

PK parameters evaluated in this study are listed below.

Parameter	Description
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{max}	maximum observed concentration of drug in plasma
C_{tau}	observed drug concentration at the end of the dosing interval
CL/F	apparent oral clearance after administration of the drug: at single dose: CL/F = Dose/AUC_{inf}, where "Dose" is the dose of the drug at steady state: CL/F = Dose/AUC_{tau}, where "Dose" is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_z/F	apparent volume of distribution of the drug
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve

Appendix 2. Study Procedure Table – Cohorts 1 and 2

COHORT 1 (12 to < 18 years old);
COHORT 2 (6 to < 12 years old)

Study Procedures	Screening[a]	Baseline (Day 1)[b]	Week 1 (Day 7)[c]	Day 10[b,d]	Week 3[c]	Week 4[e]	End of Week[f] 8	12	16	24	32	40	48	Post Week 48 Every 12 weeks	30-Day Follow-up[g]	ESDD[h]
Assent/Informed Consent	X															
Medical History	X															
Adverse Events[i]	X	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	X
Vital Signs[j]	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Complete[k]/Symptom-Directed Physical Exam	**X**	**X**		X		X	X	X	X	**X**	X	X	**X**	X	X	**X**
Height/Length	X	X						X		X			X	X		X
Body Weight	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Tanner Stage Evaluations[l]		X								X			X	X		
12-lead ECG (supine)	X															X
HIV-1 Genotype[m]	X															
Hematology Profile[n]	X	X		X[b]		X	X	X	X	X	X	X	X	X	X	X
Chemistry Profile[o]	X	X		X[b]		X	X	X	X	X	X	X	X	X	X	X

COHORT 1 (12 to < 18 years old); COHORT 2 (6 to < 12 years old)

Study Procedures	Screening[a]	Baseline (Day 1)[b]	Week 1 (Day 7)[c]	Day 10[b,d]	Week 3[c]	Week 4[e]	End of Week[f]							Post Week 48	30-Day Follow-up[g]	ESDD[h]
							8	12	16	24	32	40	48	Every 12 weeks		
CD4+ Cell Count and Percentage	X	X				X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[p]		X								X			X	X		
Plasma HIV-1 RNA	X	X		X[b]		X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Sample[q]		X						X		X			X	X		X
HBV and HCV Serologies	X															
Estimated Glomerular Filtration Rate[r]	X	X		X[b]		X	X	X	X	X	X	X	X	X		X
Urinalysis	X	X		X[b]		X		X		X			X	X	X	X
Urine Storage Sample[s]		X		X[b]		X		X		X			X	X	X	X
Serum Pregnancy Test[t]	X															
Urine Pregnancy Test[t]		X		X		X	X	X	X	X	X	X	X	X	X	X
Palatability Assessments[u]		X		X						X			X			
Dispense Diary Cards[b]		X														

**COHORT 1 (12 to < 18 years old);
COHORT 2 (6 to < 12 years old)**

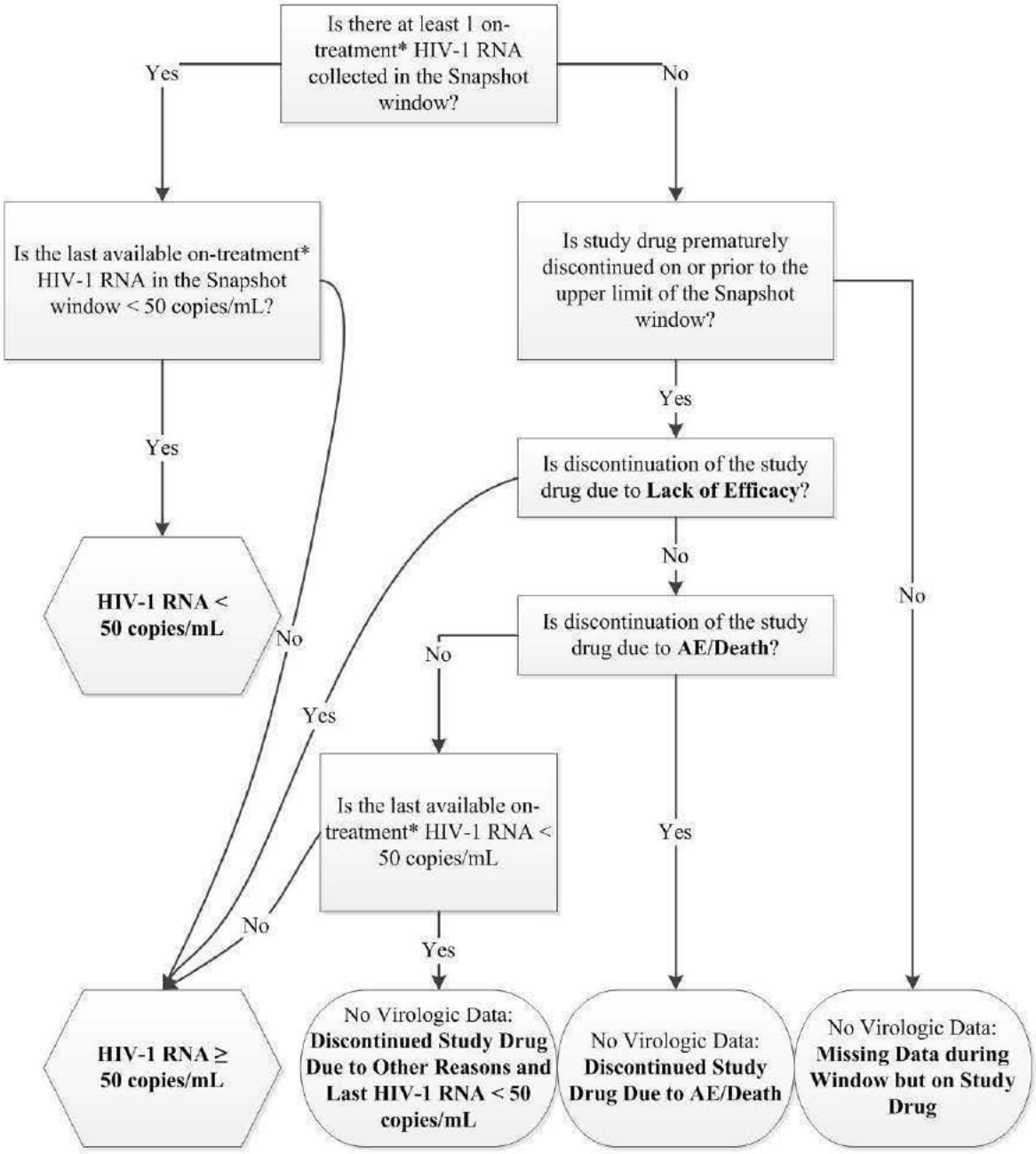
Study Procedures	Screening[a]	Baseline (Day 1)[b]	Week 1 (Day 7)[c]	Day 10[b,d]	Week 3[c]	Week 4[e]	End of Week[f]							Post Week 48	30-Day Follow-up[g]	ESDD[h]
							8	12	16	24	32	40	48	Every 12 weeks		
Review Diary Cards[b]			X	X												
Single PK Sampling[v]						X	X	X			X			X		
Trough PK Sample[w]									X			X				
Intensive PK Sampling[x]				X												
Study Drug Dispensation		X				X	X	X	X	X	X	X	X	X		
In-clinic Dosing[y]		X		X					X			X				
Drug Accountability				X		X	X	X	X	X	X	X	X	X		X

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 or if the screening visit is divided into multiple visits).
b. Part A only.
c. Week 1 (Day 7) and Week 3 are telephone visits only, to be completed ± 2 days from the protocol specified date.
d. If subject weighs <18 kg at the Baseline/Day 1 visit, the Day 10 intensive PK will be divided into separate visits. Safety and HIV-1 RNA assessments will be completed up to 3 days prior to Day 10 (ie, Day 7). Intensive PK sampling will be completed on Day 10. If the subject has already dosed prior to the Day 10 clinic visit or is not in a fasted state, the Day 10 assessments must not be completed. The subject should be instructed to return within + 4 days (Days 11, 12, 13, or 14) for the PK visit. If dosing non-compliance not related to an AE is identified on or prior to the Day 10 visit, the Day 10 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 3 days following compliant dosing and no later than Day 14 (i.e., return on Day 13 or Day 14). If dosing non-compliance due to an AE is identified on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. Consultation with the Gilead Medical Monitor is required regarding the potential of rescheduling the Day 10 intensive PK visit.
e. Week 4 visit is to be completed 31 to 33 days from the Baseline visit.
f. Study visits to be completed ± 2 days for Week 8 and ± 4 days for Week 12 through Week 48 of the protocol specified date from the Baseline visit.
g. 30-Day Follow-up visit to be completed as follows: 30 days after the last dose taken following the Day 10 PK evaluation for subjects with suppressed viremia (HIV-1 RNA <50 copies/mL at screening); 30 days after the ESDD visit for subjects who permanently discontinue study drug prior to Day 10; 30 days after the ESDD visit for subjects who permanently discontinue study drug during the 48 weeks of dosing and do not wish to continue in the study; 30 days after the Week 48 visit for subjects who complete 48 weeks on study drug and do not wish to enroll in the extension study.

h. ESDD visit should occur within 72 hours of last dose of study drug.
i. Any adverse event or test showing abnormal results that is believed to be possibly/probably related to study drug treatment will be re-evaluated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
j. Vital signs include blood pressure, temperature, heart rate, and respiration rate.
k. Perform complete physical examinations at Screening, Baseline, Weeks 24, 48 and ESDD visits.
l. Tanner Stage assessments will be performed for subjects ≥ 6 years of age at the time of the visit, until the subject has been documented as Tanner Stage 5. Tanner Stage assessments will be performed every 48 weeks in the extension phase of the study or until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.
m. Genotypic analysis for reverse transcriptase, protease, and integrase resistance will be done at screening for subjects with HIV-1 RNA >1,000 copies/mL. The investigator must have received the results from the screening genotype before proceeding with the Baseline visit. Historical genotypes should be obtained for subjects with HIV-1 RNA <50 copies/mL at screening.
n. CBC with differential and platelet count.
o. Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase
p. Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) metabolic assessments will be performed for subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) at screening and weighing ≥13 kg at the time of the visit, for the following visits: Baseline, Weeks 24, 48, ESDD, and every 48 weeks in the extension phase of the study. 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. **For Cohort 2 only**, direct LDL will be calculated if subjects weigh <15.8 kg at the time of the visit.
q. Plasma storage samples banked for possible future protocol-related testing (virology, PK analysis).
r. eGFR using Schwartz Formula (mL/min/1.73m^2) = k × L/Scr [(k is a proportionality constant, refer to SAP Section 7.3.2 for details); L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)]
s. Urine storage samples banked for possible future protocol-related testing (Urine chemistry including urine phosphorus and urine creatinine)
t. Females of childbearing potential only.
u. Palatability of EVG suspension formulation will be assessed at Baseline/Day 1, Day 10 (**Part A only**), Week 24, and Week 48, as applicable.
v. Single PK sampling at Week 12 is **only for Cohorts 1 and 2.**
w. A trough (20 to 24 hours postdose) plasma PK sample will be collected. Subjects must come into the clinic without taking their dose of EVG and the PI/r and other BR components.
x. Intensive PK sampling will be performed on Day 10 and **only applicable for subjects in Part A**. Subjects must come into the clinic without taking their dose of EVG and the PI/r and other BR components. For Cohort 2, samples will be collected at 0 (predose, ≤ 30 minutes), 1.5, 2.5, 3.5, 5, 8, 10, and 12 hours postdose. Please refer to the PK manual for details.
y. All subjects will be given their dose of EVG + PI/r and other BR components with food in the clinic at Baseline, Day 10, Weeks 16 and 40.

Appendix 3. 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 data include all data collected up to 1 day after permanent discontinuation of study drug.

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, ie, 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, and 95% CIs will be reported to the same number of decimal places as 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, ie, 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" (ie, 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 enrollment.

2) "All screened subjects" refers to all subjects who are screened and have a screening number. For summarization, a single 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 subjects who answered "Yes" to "Was subject a Screen Failure?" in the Informed Consent and Eligibility Criteria eCRF.

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

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

5) For HIV test using HIV Taqman kit, if a value is reported as "< 20 copies/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 summarystatistics {Nehls et al 1973}.

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

8) 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 date and end date, 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 date and end date, clinical visit dates, and laboratory visit dates excluding the 30-day follow-up visit to impute the last dose date.

9) 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.

10) Toxicity Grades:

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

b) For the summary of the graded toxicity tests, all postbaseline 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.

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

- **Virologic Success** – HIV-1 RNA < 50/400 copies/mL for snapshot virologic outcome (ie, the last available HIV-1 RNA record for a certain analysis timepoint)
- **Virologic Failure** – HIV-1 RNA ≥ 50/400 copies/mL for snapshot virologic outcome
- **Virologic Failure** – the last available HIV-1 RNA value of ≥ 50/400 copies/mL if subject discontinued study drug due to other reasons
- **No Virologic Data** – the last available HIV-1 RNA value of < 50/400 copies/mL if subject discontinued study drug due to other reasons

12) "On-treatment" data in the SAP refer to the data on or prior to the date of permanent discontinuation of study drug (ie, last dose date plus one day).

13) In the extension phase, if a subject filled out the extension Study Drug Completion eCRF, the subject is considered as having completed study treatment if any of the 3 following reasons is selected:

- Study terminated by the sponsor
- Subject is 18 years old and study drug is commercially available
- Study drug commercially available for adolescents

Subjects are considered as having early terminated study treatment if any of the other specified reasons is selected.

Similarly, subjects are defined as having completed or early terminated the study by using the same reasons provided in the extension Study Completion eCRF.

14) For HIV-1 RNA Missing = Excluded analysis:

Missing is excluded from the denominator when

- This subject has neither baseline nor postbaseline lab data.

15) TEAE

Events with Missing Onset Day and/or Month

An 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 the 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

16) For age of first menses, partial dates will be imputed as follows

- If only month and year are available, day will be imputed as the 15th.
- If only year is available, month and day will be imputed as July 1st.

Other dates with partially missing components will be imputed per the rules specified above if deemed necessary