STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b, Randomized, Blinded, Placebo-Controlled Dose-Escalation Study of the Safety and Biological Activity of GS-9620 in HIV-1 Infected, Virologically Suppressed Adults
Name of Test Drug:	VES (GS-9620)
Study Number:	GS-US-382-1450
Protocol Version (Date):	Amendment 7: 16 January 2019
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	15 May 2019
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
CAVR/CAVD	cell-associated HIV-1 RNA/DNA
CRF	case report form
CSR	clinical study report
DLTs	dose-limiting toxicities
DMC	data monitoring committee
ECG	electrocardiogram
ESDD	early study drug discontinuation
eCRF	electronic case report form
FU	follow-up
GLSM	geometric least-squares means
GSI	Gilead Sciences, Inc
HLT	high level term
HLGT	high level group term
ICS	intracellular cytokine staining
ISGs	interferon-stimulated genes
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantitation
LLT	lower level term
LOQ	limit of quantitation
MAD	multiple ascending dose
MedDRA	medical dictionary for regulatory activities
PBMC	peripheral blood mononuclear cell
PT	preferred term
PVE	Pharmacovigilance and Epidemiology
Q1	first quartile

Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SCA	single copy assay
SD	standard deviation
SEC	safety evaluation committee
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	Upper limit of normal
ULOQ	upper limit of quantification
VES (GS-9620)	Vesatolimod
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$
$\%AUC_{exp}$	Percentage of AUC extrapolated between $AUC_{0\text{-}last}$ and AUC_{inf}
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
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
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-382-1450. This SAP is based on the study protocol Amendment 7 dated 16 January 2019 and the electronic case report form (eCRF). The SAP will be finalized before database finalization for the final analysis. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of escalating, multiple doses of Vesatolimod (VES [GS-9620]) in HIV-1 infected virologically suppressed adults on antiretroviral therapy (ART)
- To evaluate the virologic effect of VES as measured by changes in plasma HIV-1 RNA

The secondary objectives of this study are as follows:

- To evaluate the plasma pharmacokinetics (PK) of VES
- To evaluate the pharmacodynamics (PD) of VES as measured by changes in interferon-stimulated genes (ISGs) and serum cytokines in whole blood compared to placebo
- To evaluate effects of VES on whole blood immune cell activation (CD4 and CD8 T cell, NK cell)

The exploratory objectives of this study are as follows:

- [redacted]
- [redacted]
- [redacted]

1.2. Study Design

This is a phase 1b, randomized, double-blinded, placebo-controlled, multi-cohort dose-escalation study with dose cohorts: Cohort 1 (1 mg Dose), Cohort 2 (2 mg Dose), Cohort 3 (4 mg Dose), Cohort 4 (6 mg Dose), Cohort 5 (8 mg Dose), Cohort 6 (three administrations of 10 mg Dose, followed by seven administrations of 12 mg Dose; Safety Evaluation Committee [SEC] review of the 10mg safety data will be required prior to dose escalating to 12mg), and optional Cohort 7 CCI

Two additional optional adaptive cohorts, Cohort 8 CCI and Cohort 9 CCI

HIV-1 infected male and non-pregnant, non-lactating female adults who have been virologically suppressed (HIV-1 RNA < 50 copies/mL) on ART for ≥ 12 consecutive months prior to screening may be eligible for entry (refer to the protocol for complete inclusion and exclusion criteria). Eligible subjects are randomly assigned to 1 of the following 2 treatment groups in a 6:2 ratio for each cohort. CCI .

- Cohort 1 (n = 8): Blinded VES 1 mg (n = 6) vs. Placebo (n = 2)
- Cohort 2 (n = 8): Blinded VES 2 mg (n = 6) vs. Placebo (n = 2)
- Cohort 3 (n = 8): Blinded VES 4 mg (n = 6) vs. Placebo (n = 2)
- Cohort 4 (n = 8): Blinded VES 6 mg (n = 6) vs. Placebo (n = 2)
- Cohort 5 (n = 8): Blinded VES 8 mg (n = 6) vs. Placebo (n = 2)
- Cohort 6 (n = 8): Blinded VES 10/12 mg (n = 6) vs. Placebo (n = 2)

Central randomization is used. Enrollment will initially be opened for Cohort 1 only. The SEC will review study progress, safety and virology results of enrolled subjects. After all subjects in a cohort have received at least three doses (Cohorts 1 to 3, and 6) or five doses (Cohorts 4 and 5), the SEC will review safety data from that cohort, including adverse events (AEs) and clinical laboratory results (including plasma HIV-1 RNA) before approving the next dose escalation. CCI **A cohort may be suspended** if ≥ 2 out of 6 subjects receiving VES experience one or more dose-limiting toxicities (DLTs) considered related to study drug. Subjects will receive a total of either 6 doses in Cohorts 1 to 3, 10 doses in Cohorts 4

to 6, CCI [redacted] of their assigned study treatment administered once every other week. For all subjects in Cohort 6, Dose 4 (Day 43) will occur after SEC review has been completed. If dose escalation is approved by the SEC, subjects in Cohort 6 will receive 12 mg of VES or placebo from Doses 4 to 10; if dose escalation is not approved by the SEC, subjects will continue receiving 10 mg of VES or placebo from Doses 4 to 10.

For **Cohorts 1 to 3**, dosing visits will occur at Day 1, Day 15, Day 29, Day 43, Day 57, and Day 71. For **Cohorts 4 to 9**, dosing visits will occur at Day 1, Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, Day 113 and Day 127. CCI [redacted] For **Cohorts 1 to 4**, subjects will fast for at least 2 hours before dosing. For **Cohorts 5 to 8**, subjects will fast overnight (at least 8 hours) before dosing. CCI [redacted] The Investigator will verify the subject's continued eligibility for dosing at post-Baseline dosing visits, including the absence of DLTs and (for females of childbearing potential) a negative urine pregnancy test, prior to dosing. All doses will be directly administered by blinded site staff.

Laboratory analyses (hematology, serum chemistry, and urinalysis) will be performed weekly for **Cohorts 1 to 3**. For **Cohorts 4 to 9,** these labs will be collected on dosing days, seven days post dose (starting from Dose 4), at end of study, and early study drug discontinuation (ESDD). For **Cohorts 6** CCI these labs will also be collected on Day 2 and two days post dose (starting from Dose 5). CCI [redacted] Urine pregnancy test (for females of childbearing potential) will be performed prior to each dose. Vital signs (blood pressure, pulse, respiration rate and temperature) will be measured at all dosing visits.

Plasma HIV-1 RNA will be measured at every visit except Pre-Baseline (Day -13). Cell-associated HIV-1 RNA/DNA (CAVR/CAVD), and plasma HIV-1 RNA by SCA will be collected immediately before and two days post Doses 1, 4, 6 and at end of the study (Cohort 1 to 3); immediately before and two days post Doses 1, 5, 10 and at end of the study (Cohorts 4 to 9). CCI [redacted]

Peripheral blood immune cell numbers for T/B/NK/pDC/mDC including: CD4 and CD8 populations, CD4/CD8 ratio, CD4% and lymphocyte activation (T, B and NK cells) by flow cytometry will be collected immediately before and two days post Doses 1, 3, and 6 (Cohorts 1 to 3), and immediately before and two days post Doses 1, 5, 10 and at end of the study (Cohorts 4 to 9). FoxP3+ Treg cells by flow cytometry will be collected immediately before Doses 1, 3, and 6 (Cohorts 1 to 3), and immediately before Doses 1, 5 and 10 (Cohort 4 to 9). CCI [redacted]

Changes in the levels of antiviral cytokines and inflammatory markers by chemiluminescence will be collected immediately before and 2 days and 7 days after each dose, and at the end of the study (Cohorts 1 to 3). For subjects in Cohorts 4 to 9, they will be collected immediately before, post dose days 1, 2 and 7 after Doses 1, 4 (only if Cohort 6 subjects receive 12 mg at Dose 4), 5 and 10. CCI [redacted]

PBMC intracellular cytokine staining (ICS) for Treg cells will be done immediately before and 2 days after Doses 1 and 6 for subjects in Cohorts 1 to 3. HIV-specific T-cell responses by ELISPOT will be collected at Pre-Baseline/Day -13, immediately before Dose 6 and at the end of study for subjects in **Cohorts 1 to 3**. For subjects in Cohorts 4 to 9, HIV-specific polyfunctional T cell ICS and HIV-specific T-cell responses by ELISPOT will be collected at Pre-Baseline/Day -13 and at the end of the study. CCI [redacted]

Whole blood ISG mRNA panel will be performed immediately before and 2 days and 7 days after each dose of study drug and at the end of the study (Day 101) (for Cohorts 1 to 3) and immediately before and 1, 2 and 7 days after Doses 1, 4 (only if Cohort 6 subjects receive 12 mg starting at Dose 4), 5 and 10. CCI [redacted]

Assessments of adverse events, concomitant medications and symptom-directed physical examination are performed at each visit.

Blood samples will be collected to determine plasma VES concentrations and plasma ARV concentrations at the following time points relative to study drug dosing:

Plasma VES concentrations at the following time points **for all cohorts**:

- Pre-dose (≤5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post dose at Day 1; then one sample 48 hours post dose at Day 3
- **If the SEC approves the dose escalation to 12 mg in Cohort 6, starting from Dose 4 and onwards**, plasma VES concentrations will also be collected on Day 43 (Dose 4): Pre-dose (≤5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post dose; then one sample 48 hours post dose at Day 45.

Plasma ARV concentrations: a single trough ARV PK sample will be collected at Pre-Baseline/Day -13 (**Cohorts 1 to 3)** or at Screening, Day 29, Day 57, Day 85 and Day 99 (**Cohort 5),** or at Screening, Day 57 and Day 99 **(Cohorts 6** CCI CCI [redacted]

1.3. Sample Size and Power

No power calculation was performed because this is an exploratory study to characterize the safety and efficacy of VES in HIV-1 infected patients.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Interim Blinded Analyses

SEC will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the SEC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The initial meeting of the SEC has occurred prior to the first dose of Cohort 1. This meeting formally established the SEC and thoroughly acquainted the SEC with the protocol and the SEC Charter. Subsequent SEC analyses have been performed after all subjects enrolled in each Cohort received at least three doses (Cohorts 1 to 3, and 6) or five doses (Cohorts 4 to 5) to review the safety and virology data before approving the opening of enrollment in the next Cohort or dose escalation within the same Cohort (Cohort 6).

The SEC's role and responsibilities and the scope of analysis to be provided to the SEC are provided in a mutually agreed upon charter, which defines the SEC membership, meeting logistics, and meeting frequency.

2.1.2. Interim Unblinded Analyses

Prior to the final analysis, selected individuals from Gilead were unblinded to assess the interim safety, virology, biomarker, and PK data of VES. This group may consist of at least one representative from Clinical Research, Biostatistics, Clinical Pharmacology, Pharmacovigilance/Epidemiology, Biomarkers, Clinical Virology and may include other personnel as necessary.

The access to individual unblinded data (safety, virology, biomarker and PK) was limited only to data relevant for analysis by the function representatives and was summarized at the group level for regulatory documents and external submissions without revealing individual subject identification to protect study blind at the subject level. This group reviewed data (safety, virology, biomarker and PK) to support development of new clinical protocols, regulatory documents, and conference submissions.

2.2. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

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

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total for all cohorts combined.

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis set

The Full Analysis Set (FAS) will include all subjects who (1) were randomized into the study and (2) have received at least one dose of study drug. Subjects will be grouped according to the treatment to which they were randomized. For the FAS, all efficacy data, including data collected after the last dose 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 (1) were randomized into the study and (2) have received at least 1 dose of study drug. All the data collected up to 30 days after permanent discontinuation of the study drug will be included in the safety summaries, unless specified otherwise. Subjects will be grouped according to the treatment they actually received. This is the primary analysis set for safety analyses.

3.1.4. VES Pharmacokinetic Analysis Set

The VES PK Analysis Set will include all subjects who (1) were randomized into the study, (2) have received at least 1 dose of active VES, and (3) have at least 1 nonmissing steady state PK parameter for VES. This is the primary analysis set for detailed PK analysis of intensive PK sampling.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set or the FAS, subjects will be grouped by randomized treatment. For other analyses, subjects will be grouped by actual treatment received. The actual treatment received will differ from the randomized treatment only when the actual treatment received differs from randomized treatment for the entire treatment duration.

Subjects who received placebo in different cohorts will be combined as one placebo group for analysis purposes if applicable. The treatment groups for analysis are defined as follows:

- Treatment 1: VES 1 mg (in Cohort 1)
- Treatment 2: VES 2 mg (in Cohort 2)
- Treatment 3: VES 4 mg (in Cohort 3)
- Treatment 4: VES 6 mg (in Cohort 4)
- Treatment 5: VES 8 mg (in Cohort 5)
- Treatment 6: VES 10/12 mg (in Cohort 6)
- Treatment 7: Placebo (in all Cohorts)

3.3. Strata and Covariates

This study does not use a stratified randomization schedule in enrolling subjects. No covariates will be included in analyses.

3.4. Examination of Subject Subgroups

There are no pre-specified subject subsets for efficacy or safety analyses.

3.5. Multiple Comparisons

All endpoint tests will be done at the significance level of 0.05 with no multiplicity adjustment in this proof-of-concept study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study analysis window may be due to any of the following reasons:

- A visit occurring in the window but data were not collected or were unusable
- A visit not occurring in the window
- A subject prematurely discontinuing from the study before reaching the window

In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for concomitant medications in Section 7.4.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

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

- A value that is 1 unit less than the limit of quantitation (LOQ) will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

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

Logarithmic (base 10) transformations will be applied to HIV-1 RNA data for efficacy analyses. HIV-1 RNA results of 'No HIV-1 RNA detected' and "< 20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes.

Biomarker values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing. Values that are BLQ will be treated as LLOQ at both predose and postbaseline time points.

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below BLQ will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at pre-dose time points, and one-half the value of the LLOQ at postbaseline time points.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the CRF or lab date will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point and will not be included in the summary tables, but will be included in the listings. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.
- For subjects who prematurely discontinue from the study, early termination (ET) data will be summarized as a separate visit, labeled as "Early Termination Visit".
- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

3.8.3. 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 day. For example, change from baseline by visit usually requires a single value.

If multiple valid, nonmissing, numeric measurements exist on the same nominal visit, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average (arithmetic or geometric mean, as appropriate) of these measurements (for continuous data) will be considered the baseline value.
- For postbaseline values:
  - 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), unless otherwise specified.

If multiple valid, nonmissing, categorical measurements exist on the same nominal visit, records will be chosen based on the following rule if a single value if needed:

- For baseline, the last available record on or prior to the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).
- For postbaseline visits, the value for the scheduled visit only will be used. If multiple records are available for a scheduled visit, the most conservative value within that day will be selected (eg, abnormal will be selected over normal for safety ECGs).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

A summary of subject enrollment will be provided by treatment group for each country, investigator within a country and overall for all cohorts combined. The summary will present the number and percentage of subjects enrolled. The denominator for the percentage calculation will be the total number of enrolled subjects for that column.

The randomization schedule used for the study will be provided as an appendix to the clinical CSR.

4.1.2. Subject Disposition

The summary of subject disposition will be provided by treatment group and overall for all screened subjects for all cohorts combined. This summary will include the number of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects randomized, subjects randomized but never treated, 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:

1) Completed study drug
2) Prematurely discontinuing study drug (with summary of reasons for discontinuing study drug)
3) Completed the study
4) Prematurely discontinuing from study (with summary of reasons for discontinuing study).

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

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

4.2. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration page in the eCRF. Exposure data will be listed.

4.3. Protocol Deviations

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the Full Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

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

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized:

- HIV-1 RNA (log_{10} copies/mL)
- HIV-1 RNA categories (copies/mL) (a) < 50 and (b) ≥ 50
- CD4 cell count (/μL)
- CD4+ cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- $eGFR_{CG}$ (mL/min)
- Mode of infection (HIV risk factors)
- HIV disease status
- Duration of being diagnosed with HIV disease (in years)
- Duration of ARV prior to study (in years)
- Pre-ARV HIV-RNA viral set point (log_{10} copies/mL)
- Pre-ARV HIV-RNA categories (copies/mL): (a) ≤ 100,000, (b) > 100,000 to ≤ 400,000 , and (c) > 400,000
- Pre-ARV CD4 cell count (/μL)
- Pre-ARV CD4 cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500

5.3. Medical History

General medical history data will be collected at screening and listed only. General medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

6. EFFICACY ANALYSES

As this study is still in phase I of the drug development, p-values from statistical comparisons will not be adjusted for multiplicity, so the results should be interpreted with caution.

6.1. Primary Efficacy Analysis

6.1.1. Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is the maximum change from baseline in plasma $\log_{10}$ HIV-1 RNA at any postdose timepoint up to Day 81 for Cohorts 1-3 or Day 134 for Cohorts 4-6.

6.1.2. Statistical Hypotheses for Primary Efficacy Endpoint

The analysis of maximum change from baseline in plasma $\log_{10}$ HIV-1 RNA at any postdose timepoint up to Day 81 for Cohorts 1-3 or Day 134 for Cohorts 4-6 between a VES treatment group and pooled placebo group is exploratory in nature and no formal hypothesis testing was planned.

6.1.3. Analysis of Primary Efficacy Endpoint

The maximum change from baseline in plasma $\log_{10}$ HIV-1 RNA at any postdose timepoint up to Day 81 for Cohorts 1-3 or Day 134 for Cohorts 4-6 will be calculated for all subjects in the full analysis set using available on-treatment HIV-1 RNA data up to Day 81 for Cohorts 1-3 or Day 134 for Cohorts 4-6, and summarized by treatment group using descriptive statistics (n, mean, SD, 95% CI, median, Q1, Q3, minimum, and maximum).

The primary efficacy endpoint will be compared between each active treatment group and the pooled placebo group using a Wilcoxon rank sum test at a two-sided 0.05 significant level.

6.2. Secondary Efficacy Analyses

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Change from baseline in plasma $\log_{10}$ HIV-1 RNA at postbaseline visits
- Proportion of subjects with plasma HIV-1 RNA $\geq$ 50 copies/mL at any postdose timepoint (up to 10 days after each dose for Cohorts 1-3 and 7 days after each dose for Cohorts 4-6)

6.2.2. Analysis of Secondary Efficacy Endpoints

The full analysis set will be used for secondary efficacy endpoint analysis.

Baseline and change from baseline in plasma $\log_{10}$ HIV-1 RNA at postbaseline visits will be summarized by treatment group using descriptive statistics. The change from baseline in plasma $\log_{10}$ HIV-1 RNA at postbaseline visits will be analyzed in the same fashion as that of the primary efficacy endpoint.

The number and proportion of subjects with plasma HIV-1 RNA ≥ 50 copies/mL at any postdose timepoint (up to 10 days after each dose for Cohorts 1-3 and 7 days after each dose for Cohorts 4-6) will be summarized by treatment group and compared between each active treatment group and the pooled placebo group using a Fisher's exact test at a two-sided 0.05 significant level. The number and percentage of subjects with HIV-1 RNA in the following categories will be summarized:

- ≥ 50 copies/mL
- < 50 copies/mL

6.3. Other Efficacy Analyses

6.3.1. Definition of the Other Efficacy Endpoints

Other efficacy endpoints include the following:

- Change, percentage change and fold change from baseline in the levels of serum cytokines (including IFN-α , IL-1RA, IP-10, and ITAC)
- Fold change in mRNA for ISGs including MX1, OAS1 and ISG15
- Change and percentage change from baseline in CD4/CD38/HLADR, CD8/CD38/HLADR and NK cell activation

6.3.2. Analysis of Other Efficacy Endpoints

The full analysis set will be used for other efficacy endpoint analysis.

Change percentage change and fold change from baseline (postbaseline/baseline) in the levels of serum cytokines will be summarized by treatment group using descriptive statistics and compared between each active treatment group and the pooled placebo group using a Wilcoxon rank sum test at a two-sided 0.05 significant level.

Fold change from baseline (postbaseline/baseline) in mRNA for ISGs will be analyzed similarly as above.

Change and percentage change from baseline in CD4/CD38/HLADR, CD8/CD38/HLADR and NK cell activation will also be analyzed similarly as above.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

Study drug related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Relationship of Adverse Events to Study Procedure

Study procedure related AEs are those for which the investigator selected "Yes" on the AE CRF to the question of "Related to Study Procedures." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationships to study procedure will be shown as missing from that captured on the CRF in by-subject data listings.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology (PVE) Department before database finalization.

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment-Emergent Adverse Events

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

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

7.1.6.2. Incomplete Dates

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

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

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent.

7.1.7. Summaries of Adverse Events and Deaths

A brief high-level summary of TEAEs will be provided by treatment for the number and percentage of subjects who had the following: any TEAE; any TEAE of Grade 3 or above; any serious TEAE; any study drug-related TEAE; any study drug-related serious TEAE; any TEAE that led to premature discontinuation of study drug. The treatment-emergent deaths observed during the study will also be summarized and included in this table. Treatment-emergent death refers to the death occurred between the first dose date and the last dose date plus 30 days, inclusive.

Adverse event summaries will provide the number and percentage of subjects with AEs by SOC and PT, by treatment based on the Safety Analysis Set as follows:

- All AEs
- All AEs by severity
- AEs of Grade 3 or above
- All study-drug related AEs

- All SAEs
- All study-drug related SAEs
- All AEs leading to premature discontinuation of study drug

Multiple events will be counted only once per subject per treatment in each summary. An AE that starts in one treatment period and continues into the following treatment period(s) will be counted only in the period in which the AE began. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in order of descending incidence of the pooled treatment groups within each SOC. For summaries by severity, the most severe grade will be used for those AEs that occurred more than once in an individual subject per treatment during the study.

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

- All AEs (with a variable indicating whether the event is treatment emergent)
- SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

7.1.8. Additional Analysis of Adverse Events

No additional analysis of adverse events is planned.

7.2. Laboratory Evaluations

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

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

No inferential statistics will be generated.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline time point
- Change from baseline at each postbaseline time point

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

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

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately. If there is any lab 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.

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 postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline time point.

The following summary (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment; subjects will be categorized according to the most severe postdose abnormality grade for a given lab test within a treatment:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent Grade 2, 3 and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing postbaseline values up to 30 days after last dosing date.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.3. Body Weight, Height, BMI and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

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

7.4. Prior and Concomitant Medications

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

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.4.1. Antiretroviral Medications

Any ARV medications used prior to, during, or after the study (if collected) are all recorded on the ARV eCRF. All ARV medications recorded on the ARV eCRF will be coded using the Gilead-modified World Health Organization (WHO) Drug Dictionary for ARV medication. The WHO preferred name and drug code will be attached to the clinical database. All ARV medications recorded on the ARV eCRF will be listed. No inferential statistics will be provided.

7.4.2. Prior Antiretroviral Medications

Prior ARV medications are defined as ARV medications taken on or up to 2 days prior to the first dose date of randomized study drug based on ARVs reported on ARV eCRF.

7.4.3. Concomitant Non-Antiretroviral Medications

Concomitant non-ARV medications (ie, non-ARV 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 will be summarized (number and percentage of subjects) by treatment group, WHO drug class and preferred name. Multiple drug use (by preferred name) will be counted only once 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 non-ARV medications 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 medications are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

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

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

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

7.5. Electrocardiogram Results

Electrocardiogram (ECG) data will not be presented in the CSR since ECGs were not assessed in this study other than as part of the screening process for potential new subjects.

7.6. Other Safety Measures

A by-subject listing of subject pregnancies during the study will be provided by subject ID number. No additional safety measures are specified in the protocol.

Although not necessarily related to safety, a by-subject listing of all comments received during the study on the comments form will be provided by subject ID number, and form for which the comment applies.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

Plasma VES (concentrations will be collected at the following time points **for all cohorts** relative to the Dose 1 on Day 1**:**

- Pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose at Day 1; then one sample 48 hours post dose at Day 3

Plasma VES concentrations will be collected at the following time points **for Cohort 6** relative to the Dose 4 on Day 43**:**

- Pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post dose at Day 43; then one sample 48 hours post-dose at Day 45.

8.2. PK Analyses Related to Intensive PK Sampling

VES PK parameters will be determined in subjects in the VES PK analysis set. Concentrations of VES in plasma will be determined using validated bioanalytical assays.

8.2.1. Estimation of Pharmacokinetic Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin®. The nominal time point for a key event 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 PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{inf}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2.2. PK Parameters

Pharmacokinetic parameters will be generated for all subjects for whom parameters can be derived. The analyte and parameters will be used to evaluate the PK objectives of the study. The primary PK parameters are AUC_{last}, AUC_{inf}, and C_{max} of VES.

Table 8-1. PK Parameters for VES

Analyte	Parameters
VES (Single Dose)	C_{max}, T_{max}, C_{last}, T_{last}, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, $T_{1/2}$, Vz/F, CL/F, and λ_z

8.3. Statistical Analysis Methods

8.3.1. General Considerations for Statistical Analyses

Individual subject concentration data and individual subject PK parameters of VES will be listed and summarized for subjects in the VES PK analysis set by treatment. Summary statistics (n, mean, SD, coefficient of variation [CV(%)], minimum, median, maximum, Q1, Q3) will be presented by treatment group. The number of subjects with concentration values BLQ will be presented. The geometric mean, geometric mean 95% CI, and the mean and SD of the natural log-transformed values will be presented for all PK parameters in addition to the summaries mentioned above.

Plasma concentrations over time will be plotted in the semi-logarithmic and linear scale as mean ± SD, and median (Q1, Q3) by treatment. In addition, individual subject plasma concentrations over time will be plotted by treatment group.

8.3.2. Dose Proportionality

If data are available, dose proportionality will be obtained by comparing PK parameters of VES across all dose levels for Cohorts 1-6.

Dose proportionality will be evaluated based on the power model and the ANOVA method.

The following PK parameters and dose levels will be included in both the power model and ANOVA method:

	Day	Doses (mg)	PK Parameters
VES (single dose)	1	1, 2, 4, 6, 8, 10, 12	AUC_{last}, AUC_{inf}, C_{max}

Power Model

The dose proportionality analysis will be addressed in terms of point estimates and CIs of statistical model parameters (slopes). The power model has the general equation $y = \beta_0 \times \text{dose}^{\beta_1}$ where y represents the dependent variables, eg, AUC_{last}, AUC_{inf}, and C_{max} for VES single-dose. The exponent β_1 in the model will be assessed by regressing the natural log-transformed PK parameter on the natural log-transformed dose{Smith 2000},

$$\log(y) = \log(\beta_0) + \beta_1 \log(dose)$$

The population mean slope β_1 and corresponding 90% confidence interval (CI) will be estimated.

The following SAS® PROC MIXED code will provide the analysis and the 90% CI calculations for natural log-transformed C_{max}. Similar code will be used for other natural log-transformed parameters.

```
proc mixed;
  class subjid;
  model lncmax = lndose / ddfm=kr;
  estimate "Slope of log dose" lndose 1/ cl alpha=0.10;
  make 'estimates' out=slope1;
run;
```

Due to the exploratory nature of the analysis, no dose proportionality boundaries are explicitly stated.

Analysis of Variance (ANOVA)

An ANOVA model using PROC MIXED will be used to estimate the ratio of the PK parameter at each dose level to the PK parameter at the reference dose. The parameters will be dose-normalized and natural log-transformed prior to analysis. The reference dose is 1 mg, determined by the PK scientist. Dose normalization is calculated by dividing each PK parameter value by the test dose/reference dose ratio. The ratio of geometric least-squares means (GLSM) and the corresponding 90% CI will be estimated for each PK parameter of interest.

The statistical model will include dose as a fixed effect {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}. The following SAS PROC MIXED code will provide the single dose comparison analysis and the 90% CI calculations for the natural log-transformed normalized PK parameter C_{max}. Similar code will be used for other natural log-transformed dose normalized PK parameters. The estimate statements assume that the treatment is ordered as VES 1 mg, VES 2 mg, VES 4 mg, VES 6 mg, VES 8 mg, VES 10 mg and VES 12 mg.

```
proc mixed;
  class dose;
  model lncmax = dose / ddfm=kr;
  lsmeans dose/cl alpha=0.1;
  estimate "VES 2 mg vs. 1 mg" dose -1 1 0 0 0 0 0/ cl alpha=0.10;
  estimate "VES 4 mg  vs. 1 mg" dose -1 0 1 0 0 0 0/ cl alpha=0.10;
  estimate "VES 6 mg  vs. 1 mg" dose -1 0 0 1 0 0 0/ cl alpha=0.10;
  estimate "VES 8 mg  vs. 1 mg" dose -1 0 0 0 1 0 0 / cl alpha=0.10;
  estimate "VES 10 mg  vs. 1 mg" dose -1 0 0 0 0 1 0/ cl alpha=0.10;
  estimate "VES 12 mg  vs. 1 mg" dose -1 0 0 0 0 0 1/ cl alpha=0.10;
  run;
```

The ESTIMATE statement is used to produce the point estimate and the corresponding 90% CI of the difference in PK parameters of interest on a logarithmic scale. The test-to-reference ratio and the 90% CI will be calculated by taking the exponential of the point estimate and the corresponding lower and upper limits.

9. REFERENCES

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, et al. Confidence interval criteria for assessment of dose proportionality. Pharm Res 2000;17 (10):1278-83.

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

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

WinNonlin®. Pharsight Corporation Version 6.3. Mountain View, CA.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. PK Parameters

PK parameters evaluated in this study are listed below.

Parameter	Description
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$
$\%AUC_{exp}$	Percentage of AUC extrapolated between $AUC_{0\text{-}last}$ and AUC_{inf}
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
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

The following plasma PK parameters of VES will be calculated:

C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $T_{1/2}$, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, V_z/F, and CL/F.

Appendix 2. Schedule of Assessments

Study Procedures Table (Cohorts 1 to 3)

Study Procedure	Screen[a]	Pre-Baseline	Dose 1[b]					Dose 2					Dose 3					Dose 4					Dose 5					Dose 6					End of Study	ESDD
	Post-Baseline study visits[c]																																
	Day -48	Day -13	Baseline/ Day 1	Day 3	Day 5	Day 8	Day 11	Day 15	Day 17	Day 19	Day 22	Day 25	Day 29	Day 31	Day 33	Day 36	Day 39	Day 43	Day 45	Day 47	Day 50	Day 53	Day 57	Day 59	Day 61	Day 64	Day 67	Day 71	Day 73	Day 75	Day 78	Day 81	Day 101	
Informed Consent	X																																
Review I/E Criteria		X																															
Medical History[d]	X	X	X																														
AEs and Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[e]	X																																
Symptom Directed Physical Exam[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (performed supine)	X																																
Vital Signs	X		X					X					X					X					X					X						
Weight	X		X																													X	X
Height	X																																

Study Procedure	Screen[a]	Pre-Baseline	Dose 1[b]					Dose 2					Dose 3					Dose 4					Dose 5					Dose 6					End of Study	ESDD
	Post-Baseline study visits[c]																																
	Day -48	Day -13	Baseline/ Day 1	Day 3	Day 5	Day 8	Day 11	Day 15	Day 17	Day 19	Day 22	Day 25	Day 29	Day 31	Day 33	Day 36	Day 39	Day 43	Day 45	Day 47	Day 50	Day 53	Day 57	Day 59	Day 61	Day 64	Day 67	Day 71	Day 73	Day 75	Day 78	Day 81	Day 101	
Randomization		X																															
Plasma HIV-1 RNA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ cell count	X		X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X
Chemistry profile	X		X			X		X			X		X			X		X			X		X			X		X			X		X	X
Hematology profile	X		X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X
HBV/HCV Serology	X																																		
Estimated GFR	X		X																														X	X
Urinalysis	X		X			X		X			X		X			X		X			X		X			X		X			X		X	X
Serum Pregnancy Test[g]	X																																	
Urine Pregnancy Test[g]			X					X					X					X					X					X					X	X
Plasma GS-9620 Intensive PK[h]			X	X																														
Plasma ARV Trough PK[h]		X																																

Study Procedure	Screen[a]	Pre-Baseline	Dose 1[b]					Dose 2					Dose 3					Dose 4					Dose 5					Dose 6					End of Study	ESDD
	Post-Baseline study visits[c]																																
	Day -48	Day -13	Baseline/ Day 1	Day 3	Day 5	Day 8	Day 11	Day 15	Day 17	Day 19	Day 22	Day 25	Day 29	Day 31	Day 33	Day 36	Day 39	Day 43	Day 45	Day 47	Day 50	Day 53	Day 57	Day 59	Day 61	Day 64	Day 67	Day 71	Day 73	Day 75	Day 78	Day 81	Day 101	
TLR7 genotyping		X																															
Serum for cytokine/ soluble biomarker studies[i]			X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X
Whole blood ISG mRNA[i]			X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X		X		X	X
Cell associated HIV-1 RNA/DNA with stored PBMCs[i]			X	X														X	X									X	X				X	
Plasma HIV-1 RNA Single Copy Assay with stored plasma[i]			X	X														X	X									X	X				X	
PBMC – ELISPOT[i]		X																										X					X	
Whole blood – immune cell activation[i]			X	X									X	X														X	X					

Study Procedure	Screen[a]	Pre-Baseline	Dose 1[b]					Dose 2					Dose 3					Dose 4					Dose 5					Dose 6					End of Study	ESDD
	Post-Baseline study visits[c]																																
	Day -48	Day -13	Baseline/ Day 1	Day 3	Day 5	Day 8	Day 11	Day 15	Day 17	Day 19	Day 22	Day 25	Day 29	Day 31	Day 33	Day 36	Day 39	Day 43	Day 45	Day 47	Day 50	Day 53	Day 57	Day 59	Day 61	Day 64	Day 67	Day 71	Day 73	Day 75	Day 78	Day 81	Day 101	
Whole blood - flow FoxP3+ Treg[i]			X										X															X					
PBMC ICS for Treg[i]			X	X																								X	X				
Review DLTs to confirm dosing can proceed								X					X					X					X					X					
In-Clinic Dosing[j]			X					X					X					X					X					X					

a Evaluation to be completed within 35 days prior to Pre-Baseline/Day -13
b Subjects should be administered study drug after Baseline/Day 1 visit assessments (except for post-dose intensive PK)
c All study visits are to be scheduled relative to the Baseline/Day 1 visit date.
d Collect ART history for at least 12 months; Pre-ARV viral set point, pre-ARV CD4 nadir and historical genotype will be collected if available
e Urogenital/anorectal exams may be performed at discretion of the Investigator
f Symptom-directed physical examination as needed
g Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test at any visit. At End of Study visit (Day 101), urine pregnancy test only performed if not done within past 30 days.
h Details of pharmacokinetic blood sampling procedures and sample management for all PK samples in the study will be documented in the Pharmacokinetic Sample Collection, Processing, Storage, and Shipment Manual.
i To be collected pre-dose on dosing days
j On dosing days, study drug should be taken with approximately 240 mL of water on an empty stomach. Food will not be permitted between at least 2 hours prior to and until 2 hours after dosing. Aside from the 240 mL of water provided at dosing, water/liquids will not be permitted from 1 hour prior to until 2 hours after dosing. If subjects eat prior to the 2 hour fasting period before study drug dosing, no more than a light meal should be eaten (as described in the PK Sample Collection, Processing, Storage, and Shipment Manual).

Study Procedures Table (Cohort 4)

Study Procedure	Screen[a]	Pre-Baseline	Dose 1[b]				Dose 2		Dose 3		Dose 4		Dose 5				Dose 6		Dose 7		Dose 8		Dose 9		Dose 10				End of Study	ESDD
	Post-Baseline study visits[c]																													
	Day -48	Day -13	Baseline/ Day 1	Day 2	Day 3	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 58	Day 59	Day 64	Day 71	Day 78	Day 85	Day 92	Day 99	Day 106	Day 113	Day 120	Day 127	Day 128	Day 129	Day 134	Day 157	
Informed Consent	X																													
Review I/E Criteria		X																												
Medical History[d]	X	X	X																											
AEs and Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[e]	X																													
Symptom Directed Physical Exam[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (performed supine)	X																													
Vital Signs	X		X				X		X		X		X				X		X		X		X		X					
Weight	X		X																										X	X
Height	X																													
Randomization		X																												
Plasma HIV-1 RNA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ cell count	X		X				X		X		X	X	X			X	X	X	X	X	X		X	X	X			X	X	X
Chemistry profile	X		X				X		X		X	X	X			X	X	X	X	X	X		X	X	X			X	X	X
Hematology profile	X		X				X		X		X	X	X			X	X	X	X	X	X		X	X	X			X	X	X

Study Procedure	Screen[a]	Pre-Baseline	Dose 1[b]				Dose 2		Dose 3		Dose 4		Dose 5				Dose 6		Dose 7		Dose 8		Dose 9		Dose 10				End of Study	ESDD
	Post-Baseline study visits[c]																													
	Day -48	Day -13	Baseline/ Day 1	Day 2	Day 3	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 58	Day 59	Day 64	Day 71	Day 78	Day 85	Day 92	Day 99	Day 106	Day 113	Day 120	Day 127	Day 128	Day 129	Day 134	Day 157	
HBV/HCV Serology	X																													
Estimated GFR	X		X																									X	X
Urinalysis	X		X				X		X		X	X	X			X	X	X	X	X	X		X	X	X			X	X	X
Serum Pregnancy Test[g]	X																													
Urine Pregnancy Test[g]			X				X		X		X		X				X		X		X		X		X				X	X
Plasma GS-9620 Intensive PK[h]			X		X																									
TLR7 genotyping		X																												
Serum for cytokine/ soluble biomarker studies			X[i]	X	X	X							X[i]	X	X	X									X[i]	X	X	X		X
Whole blood ISG mRNA			X[i]	X	X	X							X[i]	X	X	X									X[i]	X	X	X		X
Cell associated HIV-1 RNA/DNA with stored PBMCs			X[i]		X								X[i]		X										X[i]		X		X	
Plasma HIV-1 RNA Single Copy Assay with stored plasma			X[i]		X								X[i]		X										X[i]		X		X	
PBMC – ELISPOT		X																											X	
Whole blood – immune cell activation			X[i]	X	X								X[i]	X	X										X[i]	X	X			

Study Procedure	Screen[a]	Pre-Baseline	Dose 1[b]				Dose 2		Dose 3		Dose 4		Dose 5				Dose 6		Dose 7		Dose 8		Dose 9		Dose 10				End of Study	ESDD
	Post-Baseline study visits[c]																													
	Day -48	Day -13	Baseline/ Day 1	Day 2	Day 3	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 58	Day 59	Day 64	Day 71	Day 78	Day 85	Day 92	Day 99	Day 106	Day 113	Day 120	Day 127	Day 128	Day 129	Day 134	Day 157	
Whole blood - flow FoxP3+ Treg			X[i]										X[i]												X[i]					
T cell ICS		X																											X	
HIV reservoir measurement		X																											X	
Future Biomarker/Virology analysis Blood Sample		X																											X	
Review DLTs to confirm dosing can proceed							X		X		X		X				X		X		X		X		X					
In-Clinic Dosing[j]			X				X		X		X		X				X		X		X		X		X					

a Evaluation to be completed within 35 days prior to Pre-Baseline/Day -13
b Subjects should be administered study drug after Baseline/Day 1 visit assessments (except for post-dose intensive PK)
c All study visits are to be scheduled relative to the Baseline/Day 1 visit date
d Collect ART history for at least 12 months; Pre-ARV viral set point, pre-ARV CD4 nadir and historical genotype will be collected if available
e Urogenital/anorectal exams may be performed at discretion of the Investigator
f Symptom-directed physical examination as needed
g Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test at any visit. At End of Study visit (Day 157), urine pregnancy test only performed if not done within past 30 days.
h Details of pharmacokinetic blood sampling procedures and sample management for all PK samples in the study will be documented in the Pharmacokinetic Sample Collection, Processing, Storage, and Shipment Manual
i To be collected pre-dose on dosing days
j On dosing days, study drug should be taken with approximately 240 mL of water on an empty stomach. Food will not be permitted between at least 2 hours prior to and until 2 hours after dosing. Aside from the 240 mL of water provided at dosing, water/liquids will not be permitted from 1 hour prior to until 2 hours after dosing. If subjects eat prior to the 2 hour fasting period before study drug dosing, no more than a light meal should be eaten (as described in the PK Sample Collection, Processing, Storage, and Shipment Manual).

Study Procedures Table (Cohorts 5 to 9)[a]

Study Procedure[a]	Screen[b]	Pre-Baseline	Dose[c] 1	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 2	Day 7 Post Dose	Dose 3	Day 2 Post Dose	Day 7 Post Dose	Dose[d] 4	Day 2 Post Dose	Day 7 Post Dose	Dose 5	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 6	Day 2 Post Dose	Day 7 Post Dose	Dose 7	Day 2 Post Dose	Day 7 Post Dose	Dose 8	Day 2 Post Dose	Day 7 Post Dose	Dose 9	Day 2 Post Dose	Day 7 Post Dose	Dose 10	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	End of Study	ESDD
			Post-Baseline study visits[e]																																	
	Day -48	Day -13	Baseline/ Day 1	Day 2	Day 3	Day 8	Day 15	Day 22	Day 29	Day 31	Day 36	Day 43	Day 45	Day 50	Day 57	Day 58	Day 59	Day 64	Day 71	Day 73	Day 78	Day 85	Day 87	Day 92	Day 99	Day 101	Day 106	Day 113	Day 115	Day 120	Day 127	Day 128	Day 129	Day 134	Day 157	
Informed Consent	X																																		
Review I/E Criteria		X																																	
Medical History[f]	X	X	X																																
AEs and Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam[g]	X																																		
Symptom Directed Physical Exam[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (performed supine)	X																																		
Vital Signs	X		X				X		X			X			X				X			X			X			X			X				
Weight	X		X																															X	X
Height	X																																		
Randomization		X																																	
Stool sample for microbiome analysis[i]			X																															X	X
VAS Questionnaire			X						X						X										X						X				

Study Procedure[a]	Screen[b]	PreBaseline	Dose[c]1	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 2	Day 7 Post Dose	Dose 3	Day 2 Post Dose	Day 7 Post Dose	Dose[d]4	Day 2 Post Dose	Day 7 Post Dose	Dose 5	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 6	Day 2 Post Dose	Day 7 Post Dose	Dose 7	Day 2 Post Dose	Day 7 Post Dose	Dose 8	Day 2 Post Dose	Day 7 Post Dose	Dose 9	Day 2 Post Dose	Day 7 Post Dose	Dose 10	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	End of Study	ESDD
	Post-Baseline study visits[e]																																			
	Day48	Day43	Baseline/ Day	Day 2	Day 3	Day 8	Day 15	Day 22	Day 29	Day 31	Day 36	Day 43	Day 45	Day 50	Day 57	Day 58	Day 59	Day 64	Day 71	Day 73	Day 78	Day 85	Day 87	Day 92	Day 99	Day 101	Day 106	Day 113	Day 115	Day 120	Day 127	Day 128	Day 129	Day 134	Day 157	
Plasma HIV-1 RNA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ cell count, CD8+ cell count, CD4/CD8 ratio and CD4 %	X		X				X		X			X		X	X			X	X		X	X		X	X			X		X	X			X	X	X
Chemistry profile	X		X	X[m]			X		X			X		X	X		X[m]	X	X	X[m]	X	X	X[m]	X	X	X[m]		X	X[m]	X	X		X[m]	X	X	X
Hematology profile	X		X	X[m]			X		X			X		X	X		X[m]	X	X	X[m]	X	X	X[m]	X	X	X[m]		X	X[m]	X	X		X[m]	X	X	X
HBV/HCV Serology	X																																			
Estimated GFR	X		X																															X	X
Urinalysis	X		X	X[m]			X		X			X		X	X		X[m]	X	X[m]	X	X	X[m]	X	X	X[m]		X	X[m]	X	X		X[m]	X	X	X
Urine Pregnancy Test[j]			X				X		X			X			X				X			X			X			X			X				X	X
Serum Pregnancy Test[j]	X																																			
Plasma GS-9620 Intensive PK[k]			X		X							X[n]	X[n]																							
Plasma ART PK[p]	X								X						X							X			X											
TLR7 genotyping		X																																		
Serum for cytokine/soluble biomarker studies			X[o]	X	X							X[n]	X[n]	X[n]	X[o]	X	X	X													X[o]	X	X	X		X

Study Procedure[a]	Screen[b]	Pre-Baseline	Dose[c] 1	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 2	Day 7 Post Dose	Dose 3	Day 2 Post Dose	Day 7 Post Dose	Dose[d] 4	Day 2 Post Dose	Day 7 Post Dose	Dose 5	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 6	Day 2 Post Dose	Day 7 Post Dose	Dose 7	Day 2 Post Dose	Day 7 Post Dose	Dose 8	Day 2 Post Dose	Day 7 Post Dose	Dose 9	Day 2 Post Dose	Day 7 Post Dose	Dose 10	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	End of Study	ESDD
	Post-Baseline study visits[e]																																			
	Day 48	Day 43	Baseline/ Day 1	Day 2	Day 3	Day 8	Day 15	Day 22	Day 29	Day 31	Day 36	Day 43	Day 45	Day 50	Day 57	Day 58	Day 59	Day 64	Day 71	Day 73	Day 78	Day 85	Day 87	Day 92	Day 99	Day 101	Day 106	Day 113	Day 115	Day 120	Day 127	Day 128	Day 129	Day 134	Day 157	
Whole blood ISG mRNA			X[o]	X	X							X[n]	X[n]	X[n]	X[o]	X	X	X												X[o]	X	X	X		X
Cell associated HIV-1 RNA/DNA (CAVR/CAVD) with stored PBMCs			X[o]		X										X[o]		X													X[o]		X		X	
Plasma HIV-1 RNA Single Copy Assay with stored plasma			X[o]		X										X[o]		X													X[o]		X		X	
PBMC – ELISPOT[i]		X																																X	
Whole blood – immune cell activation			X[o]	X	X										X[o]	X	X													X[o]	X	X			
Whole blood - flow FoxP3+ Treg			X[o]												X[o]															X[o]					
T cell ICS[i]		X																																X	
HIV-1 Reservoir measurement[i]		X																																X	
CCI																																			
Review DLTs to confirm dosing can proceed							X		X			X			X				X			X			X			X			X					

Study Procedure[a]	Screen	Pre-Baseline	Dose 1	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 2	Day 7 Post Dose	Dose 3	Day 2 Post Dose	Day Post Dose	Dose 4	Day 2 Post Dose	Day 7 Post Dose	Dose 5	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	Dose 6	Day 2 Post Dose	Day 7 Post Dose	Dose 7	Day 2 Post Dose	Day 7 Post Dose	Dose 8	Day 2 Post Dose	Day 7 Post Dose	Dose 9	Day 2 Post Dose	Day 7 Post Dose	Dose 10	Day 1 Post Dose	Day 2 Post Dose	Day 7 Post Dose	End of Study	ESDD
	Post-Baseline study visits[e]																																			
	Day -48	Day -13	Baseline/ Day 1	Day 2	Day 3	Day 8	Day 15	Day 22	Day 29	Day 31	Day 36	Day 43	Day 45	Day 50	Day 57	Day 58	Day 59	Day 64	Day 71	Day 73	Day 78	Day 85	Day 87	Day 92	Day 99	Day 101	Day 106	Day 113	Day 115	Day 120	Day 127	Day 128	Day 129	Day 134	Day 157	
In-Clinic Dosing[l]			X				X		X			X			X				X			X			X			X			X					

[redacted]

b Evaluation to be completed within 35 days prior to Pre-Baseline/Day -13

c Subjects should be administered study drug after Baseline/Day 1 visit assessments (except for post-dose intensive PK)

d Dose 4 (**Cohort 6 only**) cannot occur until SEC completes review of the safety data from all subjects' first three doses (GS-9620 10 mg dose). If the GS-9620 10mg dose is found to be safe, Dose 4 and subsequent Doses (5-10) will escalate to GS-9620 12 mg. If dose escalation is not approved by the SEC, subjects will continue receiving 10 mg of GS-9620 or placebo from Doses 4 to 10

e All study visits are to be scheduled relative to the Baseline/Day 1 visit date

f Collect ART history for at least 12 months; Pre-ARV viral set point, pre-ARV CD4 nadir and historical genotype will be collected if available

g Urogenital/anorectal exams may be performed at discretion of the Investigator

h Symptom-directed physical examination as needed

[redacted]

j Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test at any visit. At End of Study visit, urine pregnancy test only performed if not done within past 30 days

k Details of pharmacokinetic blood sampling procedures and sample management for all PK samples in the study will be documented in the Pharmacokinetic Sample Collection, Processing, Storage, and Shipment Manual.

l In **Cohorts 5 and 6,** CCI the study drug will be administered following an overnight fast.

[redacted]

o **Cohorts 6** CCI

p **Cohort 6 only,** if dose escalation to 12mg is approved by SEC

q To be collected pre-dose on dosing days

Appendix 3. Programming Specification

1) AGE calculated as follows:

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

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

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

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

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

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

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

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

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

5) Randomized treatment (ie, TRT01P in ADSL) are derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if subject took at least 1 dose of study drug and assigned as blank if subject never dosed.

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

7) Body mass index (BMI) and Body Surface Area (BSA)

   BMI and BSA will be calculated only at baseline as follows:

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

   BSA (m^2) = SQRT([Height(cm) × Weight(kg)] / 3600)

   Baseline height and weight will be used for this calculation.

8) Please note, "Not Permitted", "Unknown", or missing categories will be excluded for percentage calculation. Except for Mode of infection (HIV Risk Factors), where "Unknown" will be included for percentage calculation, since a subject may fit more than 1 HIV risk factors, therefore percentage may add to more than 100% and no p-value will be generated.

   Subjects with Race = "Not Permitted" will also be excluded to define Race subgroup (ie, black vs. nonblack) for efficacy subgroup analysis.

9) Last Dose Date and Last Study Date

   a) Last Dose Date (ie, TRTEDTC, TRTEDT, TR01EDT or TR01EDTC) in ADSL was defined in Section 3.8.1.

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

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

   b) Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF. If study drug start dates or end date is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

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

10) Toxicity Grades:

a) For toxicity grade summaries, include all postbaseline graded results up to 30 days after the last dose of study drug, not just those used in by-visit summaries.

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

11) TEAE

Events with Missing Onset Day and/or Month

An AE 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:
    a. The (complete) end date is on or after the first dose date, or
    b. 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
    c. 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 meets any of the criteria specified in 3) above.

12) PK parameters at the individual subject level should be displayed with the following reported number of decimal places:

- LambdaZ, r2, r2 adj, and CORRXY: 3 decimal places
- $t_{1/2}$, T_{last}, T_{max}, BEGHOUR, and ENDHOUR: 2 decimal places
- AUC_{tau}, $AUC_{0\text{-}last}$, AUC_{inf}, $\%otAUC_{exp}$, Vz/F, CL/F, CLss/F, C_{max}, C_{last} and C_{tau}: 1 decimal place
- NPOINTS: 0 decimal place
- PK concentration data will be reported with 1 decimal place.

13) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in "Nonstudy-Drug Antiviral Medication" listing. The logic to define concomitant nonstudy-drug ARV is similar to concomitant non-ARV Medications (see details in Section 7.4.3)

14) For biomarker data, study day will be calculated from the first dosing date of study drug and derived as follows:

For postdose study days: Collection Date – First Dosing Date + 1

For days prior to the first dose: Collection Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

15) The duration of being diagnosed with HIV disease (in years) is calculated as (first dose date - date subject was diagnosed with HIV disease)/365.25. The duration of ARV prior to study (in years) is calculated as (first dose date - date subject first start ARV)/365.25. For the date subject was diagnosed with HIV disease and date subject first start ARV, missing dates will be imputed. If only the date is missing, it is imputed as 15. If both month and date are missing, it will be imputed as July 1st.

GS-382-1450 Final Analysis SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	15-May-2019 18:35:04
PPD	Biostatistics eSigned	15-May-2019 19:30:18