STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of GS-9620 in Antiretroviral Treated HIV-1 Infected Controllers
Name of Test Drug:	Vesatolimod (VES; GS-9620)
Study Number:	GS-US-382-3961
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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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 dru
$T_{1/2}$	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-382-3961. This SAP is based on the study protocol Amendment 4 dated 05 February 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 a 10-dose regimen of vesatolimod (VES; previously referred to as GS-9620) in HIV-1 infected controllers on antiretroviral treatment (ART) and during analytical treatment interruption (ATI) following VES dosing

The secondary objectives of this study are as follows:

Virology

To evaluate the effect of VES in reactivating the HIV-1 reservoir, as measured by changes in plasma HIV-1 RNA by Taqman 2.0

To evaluate the effect of VES in modulating time to virologic rebound and plasma viral load set-point following ATI

Immunology/Pharmacodynamics

- To evaluate the pharmacodynamics (PD) of VES as measured by changes in serum/plasma cytokines, and mRNA of interferon-stimulated genes (ISGs) in whole blood
- To evaluate effects of VES on immune cell activation in whole blood

Pharmacokinetics

- To evaluate the plasma pharmacokinetics (PK) of VES
- [redacted]

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1.2. Study Design

This is a phase 1b, randomized, double-blind, placebo-controlled study with a single cohort of HIV-1 infected controllers on ART with a history of pre-ART plasma HIV-1 RNA between 50 and ≤ 5000 copies/mL.

Randomization was stratified by pre-ART viral load (≥ 50 to < 2000 copies/mL or ≥ 2000 to ≤ 5000 copies/mL) at screening. Subjects were randomized in a 2:1 ratio to receive VES or placebo-to-match.

The study was conducted in three periods. In Period 1, up to 30 subjects were randomized 2:1 to receive VES or placebo-to-match. All subjects received up to 10 doses of their assigned study treatment administered orally every 14 days only in Period 1. Subjects continued to take their prescribed ART during Period 1.

In Period 2, all subjects discontinued ART and were monitored for rebound in HIV-1 plasma viremia for 24 weeks of close observation and follow up.

In Period 3 CCI [redacted]

If subjects restarted ART at the start of Period 3, subjects completed ART Re-Initiation Visits, and then Post ART Re-Suppression Visits monthly for 6 additional months (Post ART Re-Suppression Visits 1-6). For these subjects, the last study visit was the Post ART Re-Suppression Visit 6.

Dosing of VES occurred 14 days apart starting at Dose 1-Day 1, Dose 2-Day 1, Dose 3-Day 1, Dose 4-Day 1, Dose 5-Day 1, Dose 6-Day 1, Dose 7-Day 1, Dose 8-Day 1, Dose 9-Day 1 and Dose 10-Day 1 visits respectively. Subjects fasted for at least 2 hours (preferably overnight) before dosing. Subjects were also asked to provide information on food consumption and total fasting time prior to dosing.

Laboratory analyses (hematology, serum chemistry, and urinalysis) were performed at all dosing visits, monthly during Period 2 CCI [redacted], post ART Re-suppression Visits and Early Study Drug Discontinuation (ESDD) Visit.

Urine pregnancy test (for females of childbearing potential) was performed prior to each dose, at ATI visit 1 (ATI start visit), at every other visit thereafter during Period 2, CCI [redacted], at first ART Re-initiation visit and monthly thereafter until Post ART Re-Suppression Visit 1, post ART Re-suppression Visits and End of Study Visit.

Vital signs (blood pressure, pulse, respiration rate and temperature) were measured at all dosing visits and every other week during Period 2 CCI [redacted].

Plasma HIV-1 RNA was measured at every visit. Cell-associated HIV-1 RNA/DNA (CAVR/CAVD) from PBMCs was measured at Pre-baseline/Day -13 and within 1 hour before and 1 and 3 days after Doses 4 and 10, within 1 hour before and 3 days after Dose 6, Dose 10-Day 14, ATI Remission Visit and at Post-ART re-suppression Visit 6 (6 months post-ART virologic re-suppression). Plasma HIV-1 RNA Single Copy Assay (SCA) was collected at Pre-Baseline/Day -13, within 1 hour before, and 1 and 3 days after Doses 4 and 10, within 1 hour before and 3 days after Dose 6, Dose 10-Day 14, ATI Remission Visit and Post-ART re-suppression Visit 6 (6 months post-ART virologic re-suppression). CCI

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IV-specific antibody profiling from serum was performed at Pre-Baseline/Day -13, Dose 10-Day 14, and ATI Remission Visit. CCI

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Whole blood ISG mRNA panel was performed within 1 hour before and 1 day after Doses 1, 4, 10 of study drug. TLR7 genotyping was performed at Pre-Baseline/Day -1. CCI

Changes in the levels of serum/plasma cytokines/chemokines by immunoassays were measured within 1 hour before and 1 and 7 days after Doses 1, 4, and 10, and ATI Remission Visit.

Assessments of adverse events and concomitant medications were performed at each visit. Symptom-directed physical examination was performed at every visit during Period 1. Complete physical examination was performed once a month and symptom directed physical examination on other visits was performed every two weeks during Period 2 CCI

.

Blood samples were collected to determine plasma VES concentrations and plasma ART concentrations at the following time points relative to study drug dosing:

Plasma VES concentrations at the following time points:

Pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10, and 24 hours post dose at Dose 1-Day 1 visit.

Plasma ARV concentrations:

a single trough ARV PK sample was collected at Screening. Another single trough PK sample was collected at Dose 6 Day 4.

1.3. Sample Size and Power

No power calculation was performed because this was an exploratory study to characterize the safety and efficacy of VES.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Interim Blinded Analyses

A Safety Evaluation Committee (SEC) reviewed the progress of the study and performed 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 recommended to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warranted 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 occurred through email prior to the first dose of the study. This meeting formally established the SEC and thoroughly acquainted the SEC with the protocol and the SEC Charter. Subsequent SEC analysis was performed after half of the subjects had received four doses of VES or placebo-to-match.

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

2.1.2. Interim Unblinded Analyses

Prior to the final analysis, a few selected individuals from Gilead were unblinded to assess the interim safety and virology data of VES. This group may have consisted of at least one representative from Clinical Research, Biostatistics, Clinical Pharmacology, Pharmacovigilance/Epidemiology, Biomarkers, and Clinical Virology. Details of unblinding (eg, memberships, responsibilities, analysis schedules) were defined in an Internal Data Review Team Charter.

After at least 10 subjects completed ATI Week 24 or met criteria to restart ART, the Sponsor conducted interim unblinded analyses to review the data as described above. The results from these analyses were submitted to regulatory agencies to facilitate the clinical development program, presented externally or published to disseminate the findings.

2.2. Final Analysis

After all subjects had completed the study, outstanding data queries resolved or adjudicated as unresolvable, and the data had 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. In addition, 3 subjects rolled over from Study GS-US-382-1450 to the ATI phase of Study GS-US-382-3961. They will be included in the listings.

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.

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) 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) received at least 1 dose of study drug. For the safety analysis set, all safety data, including data collected after the last dose of study drug, will be included, 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) received at least 1 dose of active VES, and (3) have at least 1 nonmissing postbaseline concentration value 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.

The treatment groups for analysis are defined as follows:

- VES
- Placebo

However, for the overall TEAE and lab abnormality summary, the following treatment groups will be used due to dose change in protocol amendments.

- VES (4 mg)
- VES (4/6 mg)
- VES (6 mg)
- VES (6/8 mg)
- VES (8 mg)
- Placebo

3.3. Strata and Covariates

Randomization was stratified by pre-ART viral load (≥ 50 to < 2000 copies/mL or ≥ 2000 to ≤ 5000 copies/mL) at screening. 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.

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 copies/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 Visits

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 for a Visit

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. 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. 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:

- Completed study drug
- Prematurely discontinuing study drug (with summary of reasons for discontinuing study drug)
- Completed the study
- 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. The number of doses by VES dose level will be summarized using descriptive statistics.

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
- Time from HIV diagnosis to ART initiation (in years)
- Duration of ART prior to study (in years)
- Pre-ART HIV-RNA viral set point (log_{10} copies/mL)
- Pre-ART HIV-RNA categories (copies/mL): (a) ≥ 50 to < 2000, (b) ≥ 2000 to ≤ 5000, (c) > 5000
- Pre-ART CD4 cell count (/μL)
- Pre-ART 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 1 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. Definition of Efficacy Endpoints

Efficacy endpoints include the following:

- Change from baseline in plasma $\log_{10}$ HIV-1 RNA by Taqman 2.0 at any postdose timepoint
- Time to virologic rebound based on 2 different cutoff values:
  1) $\geq$ 50 copies/mL
  2) $\geq$ 200 copies/mL
- Change in plasma viral load set-point following ATI
- Peak HIV-1 viral load during ATI

6.2. Statistical Hypotheses for Efficacy Endpoints

The analysis of the efficacy endpoints is exploratory in nature and no formal hypothesis testing was planned.

6.3. Analysis of Efficacy Endpoints

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

The change from baseline in plasma $\log_{10}$ HIV-1 RNA by Taqman 2.0 at any postdose timepoint will be calculated for all subjects in the full analysis set using available on-treatment HIV-1 RNA data, and summarized by treatment group using descriptive statistics (n, mean, SD, 95% CI, median, Q1, Q3, minimum, and maximum). It will also be compared between the VES group and the placebo group using a Wilcoxon rank sum test at a two-sided 0.05 significant level.

Time to virologic rebound will be analyzed using the Kaplan-Meier method. The log rank test will be performed to compare the differences in the distribution of time to virologic rebound between the 2 treatment groups. Subjects who do not rebound will be censored at the last HIV-1 RNA collection date during ATI period.

Change in plasma viral load set-point following ATI will be summarized and analyzed in the same fashion as that of the change from baseline in plasma $\log_{10}$ HIV-1 RNA.

Peak HIV-1 viral load during ATI and change from baseline will be summarized and analyzed in the same fashion as that of the change from baseline in plasma $\log_{10}$ HIV-1 RNA.

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 VES dose level 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-dose 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

An analysis was performed to summarize flu-like adverse events. This was done by selecting a subset of PTs for flu-like symptoms, and this list of terms was reviewed by clinical. Please see below for the selected PTs:

- Influenza
- Influenza-like illness
- Fatigue
- Pyrexia
- Chills
- Myalgia
- Joint pain
- Headache

A summary (number and percentage of subjects) of flu-like AEs by PT will be provided by dose level based on the safety analysis set. A data listing of flu-like AEs will be provided.

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 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**:**

- Pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10, and 24 hours post dose at Dose 1-Day 1 visit.

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 primary PK parameters are AUC_{last}, AUC_{inf}, and C_{max} of VES.

Table 8-1. PK Parameters for VES

Analyte	Parameters
VES	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

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. 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.

9. PHARMACODYNAMIC (PD) ANALYSES

9.1. Definition of PD Endpoints

PD 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

9.2. Analysis of PD 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.

10. 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.

11. SOFTWARE

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

Phoenix WinNonlin®. Version 7.0 Certara. Princeton, NJ.

12. SAP REVISION

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

13. 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

Visit	Period 1[v,w]																											P2 P Period			P3		P2 or P3		
	Screening[a]	Day -13	Dose 1 -Day 1	Dose 1-Day 2	Dose 1-Day 8	Dose 2- Day 1	Dose 2-Day 8	Dose 3 Day 1	Dose 3-Day 8	Dose 4 Day 1	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5 Day 1	Dose 5-Day 8	Dose 6 Day 1	Dose 6-Day 4	Dose 6-Day 8	Dose 7 Day 1	Dose 7-Day 8	Dose 8 Day 1	Dose 8-Day 8	Dose 9 Day 1	Dose 9-Day 8	Dose 10 Day 1	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14	ATI Visit 1[p]	Visits 2-24[q,x]	ATI Remission[r]	CCI	End of Study[t]	ART Re-initiation Visits[s]	Post ART re-suppression Visits 1-6[s]	ESDD[u]
Informed Consent	X																																		
Medical History[b]	X	X	X																																
Pre-ART viral load set point	X																																		
HLA Class I and II type , pre-ART CD4 Nadir, historical genotype	X																																		
AE and Con Meds[o]	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	X																												X	X[h]	X				
Symptom Directed Physical Exam		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[i]			X		X	X
12-Lead ECG	X																																		
Vital Signs	X		X			X		X		X				X		X			X		X		X		X				X	X[j]	X		X	X	X
Weight	X		X			X		X		X				X		X			X		X		X		X				X	X[j]	X		X		X	X
Height	X																																		
Review of I/E criteria[c]		X																																	
Randomization		X																																	

Visit	Period 1[v,w]																											P2 P Period			P3		P2 or P3		
	Screening[a]	Day -13	Dose 1 -Day 1	Dose 1-Day 2	Dose 1-Day 8	Dose 2- Day 1	Dose 2-Day 8	Dose 3 Day 1	Dose 3-Day 8	Dose 4 Day 1	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5 Day 1	Dose 5-Day 8	Dose 6 Day 1	Dose 6-Day 4	Dose 6-Day 8	Dose 7 Day 1	Dose 7-Day 8	Dose 8 Day 1	Dose 8-Day 8	Dose 9 Day 1	Dose 9-Day 8	Dose 10 Day 1	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14	ATI Visit 1[p]	Visits 2-24[qx]	ATI Remission[r]	CCI	End of Study[t]	ART Re-initiation Visits[x]	Post ART re-suppression Visits 1-6[z]	ESDD[aa]
CCI																																			
Urine Collection for																																			
Urinalysis	X		X			X		X		X				X		X			X		X		X		X				X	X[k]			X		X	X
Urine Pregnancy Test[d]			X			X		X		X				X		X			X		X		X		X			X	X	X[l]	X		X	X[l]	X	X
Blood collection for																																			
Chemistry	X		X			X		X		X				X		X			X		X		X		X				X	X[k]			X		X	X
Hematology	X		X			X		X		X				X		X			X		X		X		X				X	X[k]			X		X	X
Metabolic assessment[e]	X																																	X			
eGFR	X		X																											X	X[k]			X			X
Serum Pregnancy Test[d]	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
HBV/HCV Serology[f]	X																																				
GS-9620 Intensive PK[g]			X	X																																	
Plasma ART PK	X																X														X[qx]						

Visit	Period 1[v,w]																										P2 P Period			P3		P2 or P3		
	Screening[a]	Day -13	Dose 1 -Day 1	Dose 1-Day 2	Dose 1-Day 8	Dose 2- Day 1	Dose 2-Day 8	Dose 3 Day 1	Dose 3-Day 8	Dose 4 Day 1	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5 Day 1	Dose 5-Day 8	Dose 6 Day 1	Dose 6-Day 4	Dose 6-Day 8	Dose 7 Day 1	Dose 7-Day 8	Dose 8 Day 1	Dose 8-Day 8	Dose 9 Day 1	Dose 9-Day 8	Dose 10 Day 1	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14	ATI Visit 1[p]	Visits 2-24[qs]	ATI Remission[r]	CCI	End of Study[t]	ART Re-initiation Visits[x]	Post ART re-suppression Visits 1-6[z]	ESDD[aa]
TLR7 genotyping		X																																	
Plasma HIV-1 RNA by Taqman 2.0	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
HIV -1 Genotype/Phenotype[bb]																																			
VAS Questionnaire			X							X											X														
Plasma HIV-1 RNA by SCA		X								X	X	X				X	X								X	X	X		X			X			X[aa]	
PBMC Associated viral RNA & DNA by CAVR/CAVD		X								X	X	X				X	X								X	X	X		X			X			X[aa]	
CCI																																			
CCI																																			
Whole blood ISG mRNA			X	X						X	X														X	X										X
Cytokines, chemokines			X	X	X					X	X		X												X	X		X				X				X
T cell ICS		X																											X			X				

Visit	Period 1[v,w]																										P2 P Period			P3		P2 or P3		
	Screening[a]	Day -13	Dose 1 -Day 1	Dose 1-Day 2	Dose 1-Day 8	Dose 2- Day 1	Dose 2-Day 8	Dose 3 Day 1	Dose 3-Day 8	Dose 4 Day 1	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5 Day 1	Dose 5-Day 8	Dose 6 Day 1	Dose 6-Day 4	Dose 6-Day 8	Dose 7 Day 1	Dose 7-Day 8	Dose 8 Day 1	Dose 8-Day 8	Dose 9 Day 1	Dose 9-Day 8	Dose 10 Day 1	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14	ATI Visit 1[p]	Visits 2-24[qs]	ATI Remission[r]	CCI	End of Study[t]	ART Re-initiation Visits[x]	Post ART re-suppression Visits 1-6[z]	ESDD[aa]
Immune cell activation, phenotyping		X								X	X																	X			X				
Serum antibody profiling assays		X																										X			X				
CCI																																			
CCI																																			
Review of DLTs						X		X		X				X		X			X		X		X		X										
In-Clinic Dosing[y]			X			X		X		X				X		X			X		X		X		X										

a Evaluations to be completed within 35 days prior to Pre Baseline/Day 13
b Medical history including route and estimated duration of HIV 1 infection, history of HIV 1 disease related events, anti retroviral treatment (ART) history for at least 6 months and prior medications within 35 days of the screening visit
c If subject's ART regimen is changed ≥ 45 days prior to Baseline/Dose 1 Day 1, plasma HIV 1 RNA <50 copies/mL at Pre baseline/Day 13 visit is required to confirm eligibility.
d Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
e Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments.
f HBV blood panel will be performed at Screening (Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb)). Hepatitis C antibody (HCVAb) will be performed.

g Intensive PK samples will be collected at Pre dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10 and 24 hours post dose at Dose 1 Day 1 visit.
h Complete physical examination at visits 5, 9,13,17, 21, 26, 28, 30, 32, 34, 36
i Symptom directed physical examination as needed at visits 3, 7, 11, 15, 19, 23, 25, 27, 29, 31, 33, 35
j Vital signs and weight at visits 3,5,7,9,11,13,15,17,19,21,23.
k Chemistry, Hematology, eGFR and Urinalysis at visits 5, 9, 13, 17, 21, 26, 28, 30, 32, 34, 36
l Urine pregnancy test at visits 3,5,7,9,11,13,15,17,19,21,23. Urine pregnancy test will also be done at first ART re initiation visit and monthly thereafter until Post ART re suppression Visits
m During the Pre Baseline/Day 13, Dose 10 Day 14, and ATI Remission visits, 110 ml of blood will be drawn. At Dose 6 Day 1 and Post ART Re Suppression Visit 6, only 20 ml of blood will be drawn
[redacted]
o Any adverse event or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.
p ATI Visit 1 to occur at Dose 10 Day 28 for subjects with HIV 1 RNA <50 copies/mL at Dose 10 Day 14 visit. For subjects with viral load >50 copies/mL at Dose 10 Day 14, the ATI Visit 1will only occur if undetectable viral load is achieved within two re test measurements. Subjects to discontinue study medication and ART from ATI Visit 1 through ATI Visit 24 CCI [redacted]
q Weekly visits 2 24
r This visit will be planned after completion of 12 weeks of ATI for subjects with plasma HIV 1 RNA <50 copies/mL in the absence of ART re initiation. If subjects have HIV 1 viral load <50 copies/mL at ATI Visit 12, the visit should occur within a week of ATI Visit 12. However, if the subject does not have HIV 1 viral load <50 copies/mL at ATI Visit 12, this visit may still occur at a later time point between ATI Visit 13 CCI [redacted] once the HIV 1 viral load <50 copies/mL.
[redacted]
t End of study visit to occur 7 days (± 1 day) after the last ATI Visit if subject has not re initiated ART during Period 2 and 3.
u Early Study Drugs Discontinuation visit is required if subject discontinues study medication prior to completion of Dose 10. The visit to occur within 30 days of last dose of study drug.
v If HIV 1 RNA viral load will be >5000 copies/mL at any visit post Dose, viral load will be observed at next scheduled visit or retested within 4 days. The next dose will be withheld and only given if viral load of ≤ 5000 copies/mL is achieved. The study procedure schedule will be reset relative to the next dose of GS 9620.
w If plasma virus HIV 1 RNA levels are > 5000 copies/mL at third retest visit during a single dosing period, then this subject will be considered to have confirmed virologic failure and blood samples from this visit will be used for HIV 1 genotype/phenotype testing with assays corresponding to the antiretroviral medications the subject is taking.
x During Visits 2 24 in Period 2 CCI [redacted], ART will be re initiated if subject meets the criteria defined in the protocol. Once ART is re initiated, weekly visits (ART Re initiation visits) will occur to measure plasma viral load and CD4+ count will be conducted until plasma viral load becomes undetectable (<50 copies/mL), and then every other week until two consecutive measures are undetectable.
y Dosing to occur in fasting state. Food not permitted 2 hours prior to and 2 hours after dosing. Overnight fasting is preferable. Aside from 240 mL water provided at dosing, water/liquid not to be permitted from 1 hour prior to until 2 hours after dosing. Subjects to provide information on food consumption and total fasting time prior to dosing.
z Post ART Re suppression visits is applicable for subject(s) who re initiates ART during ATI. The visit to occur monthly for six months after subject has achieved HIV 1 RNA of <50 copies/mL at two consecutive visits. A window of ± 6 days may be used to schedule this visit
aa To be performed at Post ART Re suppression Visit 6 only
bb HIV 1 genotype and phenotype testing for subjects with prolonged Viremia. Refer to the protocol for retesting and subject management.
cc Additional PK samples may be drawn to verify that subject continues being off ART during the ATI phase (Period 2 CCI [redacted]). Samples will be drawn upon Sponsor request depending on the subject's HIV 1 RNA levels

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
- t1/2, Tlast, Tmax, BEGHOUR, and ENDHOUR: 2 decimal places
- AUCtau, AUC0-last, AUCinf, %otAUCexp, Vz/F, CL/F, CLss/F, Cmax, Clast and Ctau: 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) Time from HIV diagnosis to ART initiation (in years) is calculated as (the date ART started - date subject was diagnosed with HIV disease)/365.25.

The duration of ART prior to study (in years) is calculated as (first dose date - date subject first start ART)/365.25.

For the date subject was diagnosed with HIV disease and date subject first start ART, 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.

16) Virologic rebound

- The virologic rebound $\geq$ 50 copies/mL is defined as two consecutive HIV-1 RNA measurement $\geq$ 50 copies/mL. The date of rebound is the first time HIV-1 RNA measurement $\geq$ 50 copies/mL.
- The virologic rebound $\geq$ 200 copies/mL is defined as two consecutive HIV-1 RNA measurement $\geq$ 200 copies/mL. The date of rebound is the first time HIV-1 RNA measurement $\geq$ 200 copies/mL.

Time to virologic rebound (in weeks) (date of rebound-date of first ATI visit +1)/7.

17) Change in plasma viral load set-point following ATI viral set-point following ATI pre-ART set point

The plasma viral set-point following ATI is calculated as the geometric mean of all the HIV-1 RNA measurements between a start date and an end date. The start date and end date will be provided by clinical based on blinded individual subject data review. For Pre-ART set point, we will use the value if only one value is recorded in the clinical database. If there are multiple values recorded, we will use the geometric mean.

18) Peak HIV-1 viral load during ATI

- For subjects who did not restart ART, the maximum value of HIV-1 RNA measurements during ATI is used as the peak value.
- For subjects who restarted ART, the maximum value of HIV-1 RNA measurements during ATI before the restart of ART is used as the peak value.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	17-Mar-2020 19:26:27
PPD	Biostatistics eSigned	17-Mar-2020 19:29:05