STATISTICAL ANALYSIS PLAN

Study Title:	An Umbrella Phase 1b, Open-label, Multi-Cohort Study to Evaluate Safety, Pharmacokinetics, and Antiviral Activity of Novel Antiretrovirals in Participants With HIV-1 Sub study 03: GS-6212
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
BLQ	below the limit of quantitation
BMI	body mass index
BVY	Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide)
CCG	eCRF completion guidelines
CD4	cluster of differentiation type 4
CI	confidence interval
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
$eGFR_{CG}$	estimated glomerular filtration rate (Cockcroft Gault formula)
ET	early termination
FAS	full analysis set
FIH	first-in-human
Hb	hemoglobin
HIV-1	human immunodeficiency virus type 1
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification
INSTI	integrase strand-transfer inhibitor
LLT	lower-level term
LOQ	limit of quantitation
mAbs	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MST	MedDRA search term
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitors
PD	pharmacodynamic
PEP	post-exposure prophylaxis
PI	protease inhibitor
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
PT	preferred term
PWH	people with HIV
Q1, Q3	first quartile, third quartile
RNA	ribonucleic acid

SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
SRT	safety review team
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
%CV	coefficient of variation, defined as ratio of standard deviation to the mean

PHARMACOKINETIC ABBREVIATIONS

AUC	area under the plasma/serum concentration versus time curve
AUC_{0-t}	partial area under the concentration versus time curve from time "0" to time "t"
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
AUC_{inf}	area under the concentration versus time curve from time zero to infinity
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_t	concentration at time t
C_{tau}	observed drug concentration at the end of the dosing interval
C_{trough}	concentration at the end of the dosing interval
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
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 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-544-5905-03 (Master Protocol GS-US-544-5905, Substudy 03). This SAP is based on the study GS-US-544-5905 master protocol Amendment 2 dated 24 February 2023, substudy GS-US-544-5905-03 protocol Amendment 1 dated 18 August 2023, and the electronic case report form (eCRF) for study GS-US-544-5905-03. The SAP will be finalized before study GS-US-544-5905-03 database finalization. Any changes made after the finalization of the SAP will be documented in the study GS-US-544-5905-03 CSR.

1.1. Study Objectives

The primary objective of this substudy is to evaluate the short-term antiviral activity of GS-6212 with respect to the change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) on Day 11 in people with HIV-1 (PWH) who are antiretroviral (ARV) treatment naive or treatment experienced but naive to the integrase strand-transfer inhibitor (INSTI) class, and have not received any antiretroviral therapy (ART) within 12 weeks of screening including medications received for pre-exposure prophylaxis (PrEP) or postexposure prophylaxis (PEP).

The secondary objectives of this substudy are as follows:

- To evaluate the short-term antiviral activity of GS-6212 in reducing plasma HIV-1 RNA (log_{10} copies/mL)
- To investigate the safety and tolerability of GS-6212 by dose cohort
- To characterize the plasma pharmacokinetics (PK) of GS-6212
- To characterize the PK/pharmacodynamic (PD) relationship between the exposure of GS-6212 and the viral dynamics of HIV-1
- To determine the number and percentage of participants who achieve HIV-1 RNA < 50 copies/mL of the HIV-1 RNA assay by Day 11 at each dose level
- To examine the emergence of resistance to the INSTI drug class

1.2. Study Design

This is an open-label Phase 1b, multiple dose, multicohort, substudy to an umbrella study designed to evaluate safety, PK, and antiviral activity of GS-6212 given as monotherapy in PWH who are either treatment-naive or treatment experienced but naive to the study drug class, and have not received any ART within 12 weeks of screening, including medications received for preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP). Any current or prior receipt of long-acting parenteral ARVs including: monoclonal antibodies (mAbs) targeting HIV-1, injectable cabotegravir, or injectable rilpivirine, is exclusionary.

This umbrella study will consist of a master protocol describing information relevant to all substudies; and each novel compound will have its own substudy. GS-US-544-5905-03 will be the third substudy with GS-6212 as the compound. This flexible clinical study design allows for opening new substudies as new agents become available and closing substudies with study drugs that demonstrate minimal clinical activity and/or unacceptable toxicity.

After screening and meeting all eligibility criteria, study drug dosing will be initiated on Day 1 in the clinic for each participant. Participants will be required to return to the clinic for visits on Days 2, 3, 4, 7, 8, 9, 10, and 11 (primary endpoint assessment). Doses of GS-6212 will be administered orally at the clinic under observation by site staff on clinic visit days/times and at home by the participant on nonclinic visit days/times at approximately the same time each day. In cohorts where GS-6212 is administered more than once daily, in-clinic observation of dosing will be conducted for the morning dose only. Participants will record at-home dosing details in a dosing log.

After assessments on Day 11 or upon early termination (ET), participants will initiate a regimen of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide; BVY) provided by the sponsor or an alternative standard-of-care (SOC) ART regimen selected by the investigator. If participants are switching to BVY, a sufficient supply will be given to provide coverage for the remainder of the study. Participants will be required to return to the clinic for a follow-up visit on Day 25.

Overnight fasting (≥ 6 hours prior to dosing) is required for laboratory and/or PK analyses on Days 1 and 11 (see Section 5.3). On all other days (Days 2 through 10), the AM doses should be taken on an empty stomach.

Following study completion, the participant's care will be transferred to a primary health care provider who will determine the participant's HIV long-term treatment plan.

This substudy will enroll up to 5 cohorts with at least 6 participants in each cohort. Participants will be enrolled in Cohort 1 initially and then dosing in subsequent cohorts will proceed as appropriate after safety review team (SRT) review of emerging data from Cohort 1 and available data from the Phase 1a SAD/MAD Study GS-US-469-6401.

The dose level and dosing regimen for study drug in each cohort will be selected based on a review of available PK, cumulative safety, and HIV-1 RNA data through the primary endpoint (Day 11) for this substudy, and/or relevant and available safety and PK data from the ongoing Phase 1a first-in-human (FIH) study for GS-6212.

Assessments will be conducted per the schedule of assessment table (see Schedule of Assessments, Appendix 1).

1.3. Sample Size and Power

A sample size of 6 to 8 participants in each dose cohort will provide 83% to 94% power to detect a treatment difference of 1.0 $\log_{10}$ copies/mL in change from baseline in HIV-1 RNA on Day 11 between at least one of the study drug dose groups and the historical placebo group (N = 21). In this power analysis, it is assumed that a standard deviation (SD) for the change from baseline in

HIV-1 RNA on Day 11 is 0.662 $\log_{10}$ copies/mL for each study drug dose group and 0.359 $\log_{10}$ copies/mL for the placebo group, and a 2-sided t-test is conducted at an alpha level of 0.05. Standard deviations were estimated from historical Phase 1b studies conducted by the sponsor (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072). The maximum SD from treatment groups was used for the study drug dose group and SD from the pooled placebo group was used for the placebo group.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

Before the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program of GS-6212.

2.2. Dose Escalation Analysis

A safety review team (SRT) will review the data from this substudy after all participants from Cohort 1 complete their Day 11 visit. The SRT review will include cumulative safety and HIV-1 RNA data through the primary endpoint (Day 11) and available PK data from Cohort 1 of this substudy; and/or relevant and available safety and PK data from the Phase 1a FIH study for GS-6212 (as appropriate). This initial SRT review will facilitate decision-making for dose level, dosing regimen (including whether GS-6212 study drug will be taken in a fasted state, or with a low-fat or high-fat meal) and timing of dosing for Cohorts 2 to 5. Following SRT review of Cohort 1, no additional cohorts were required. Cohorts 2-5 were not enrolled.

2.3. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint (change from baseline in HIV-1 RNA [$\log_{10}$ copies/mL] on Day 11) will be conducted at the time of the final analysis and will be tested at the 0.05 significance level (2-sided test).

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

By-participant listings will be presented for all participants in the All Enrolled Analysis Set and will be sorted by participant identification (ID) number, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within participants. The treatment group to which participants were initially assigned 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 participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion as well as the number and percentage of participants who were excluded and the reasons for their exclusion will be summarized in the disposition table as detailed in Section 4. A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all participants who received a study participant ID number in the study after screening.

All Enrolled Analysis Set is the primary analysis set for by-participant listings.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all participants who were enrolled and received at least one dose of GS-6212 study drug in this substudy. Participants will be grouped according to the GS-6212 cohort assigned at enrollment.

Participants who were randomized and assigned to receive placebo from 3 historical Gilead Phase 1b studies (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072) will be used as a historical control through Study Day 11 for only the HIV-1 RNA endpoints.

The Full Analysis Set will be the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of GS-6212 in this study. Participants who received treatment other than that assigned at enrollment will be analyzed according to the treatment that they received.

All data collected on/after first dose date of GS-6212 during the study will be included in the safety summaries.

The Safety Analysis Set is the primary analysis set for safety analyses.

3.1.4. Pharmacokinetic Analysis Set

The PK Analysis Set includes all participants who were enrolled in the study, received any dose of GS-6212 in this study, and have at least 1 nonmissing post baseline concentration value for GS-6212.

The PK Analysis Set is the primary analysis set for all PK analyses.

3.2. Participant Grouping

For analyses based on the FAS, participants will be grouped according to the GS-6212 cohort to which they were enrolled. Data from participants who were randomized and assigned to receive placebo from 3 historical Gilead Phase 1b studies (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072) will be pooled to form a historical placebo group for HIV-1 RNA endpoints through Day 11. For all other analyses, participants will be grouped according to the actual GS-6212 treatment received in this study.

3.3. Strata and Covariates

No covariates will be included in efficacy analyses.

3.4. Examination of Participant Subgroups

There are no prespecified participant subgroups for efficacy or safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made in this proof-of-concept study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

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

3.6.2. Outliers

Outliers of non-PK will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

Outliers of PK data may be identified during review of data by the PK scientist, and if necessary, appropriate sensitivity analyses may be conducted.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed.

In general, age collected on Day 1 (in years) will be used for analyses and presented in listings. If age on Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For participant without an enrollment date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower 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 upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.
- The lower or upper 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 lower or upper LOQ, respectively).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, change from baseline in HIV-1 RNA will be performed on the $\log_{10}$ transformed data) or nonparametric analysis methods may be used, as appropriate.

Data Handling for PK Summaries

Natural logarithm transformation will be used for analyzing non-BLQ concentrations and PK parameters in intensive PK samples. Concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose and postdose time points for summary purposes. The number of samples will be summarized to reflect the actual number of samples assessed at that time point

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the participants have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of order statistics for intensive PK concentrations:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the participants 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 participants 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 participants 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 participants 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."

Concentration related PK parameters (eg, C_{last}, C_{max}, and C_{tau}) that are BLQ will be excluded before log transformation or statistical model fitting and displayed as described above.

3.8. Analysis Visit Windows

3.8.1. Definition of Predose, Postdose, Study Day

Study day will be calculated from the first dosing date of study drug (or first dose date of placebo for placebo historical control group [HIV-1 RNA data only]) 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.

Baseline is defined as the last available value collected on or prior to the first dose date (and time, where applicable) of study drug (ie, prior to taking first dose of study drug). Postbaseline is defined as any value collected after the first dose of study drug. Last Study Date is the latest of clinic visit dates and laboratory visit dates, including all follow-up visits for participants who prematurely discontinued study or who completed study according to the Study Completion eCRF.

3.8.2. Analysis Visit Windows

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

The analysis windows for HIV-1 RNA are provided in Table 3-1; for hematology, chemistry, urinalysis, and $eGFR_{CG}$ in Table 3-2; for vital signs and weight in Table 3-3; for ECGs and coagulation in Table 3-4; and CD4 cell count and percentage in Table 3-5.

Table 3-1. Analysis Visit Windows for HIV-1 RNA

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 2	2	2	2
Day 3	3	3	3
Day 4	4	4	5
Day 7	7	6	7
Day 8	8	8	8
Day 9	9	9	9
Day 10	10	10	10
Day 11	11	11	11
Day 25	25	12	(none)

Cohort GS-6212 will be compared to the historical placebo control group through Study Day 11.

The percentage of participants with HIV-1 RNA < 50 copies/mL will be displayed on Day 11 (last value prior to starting standard of care) and on Days 25.

Table 3-2. Analysis Visit Windows for Hematology, Chemistry (including Thyrotropin), Urinalysis and $eGFR_{CG}$

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 3	3	2	5
Day 7	7	6	9
Day 11	11	10	11
Day 25	25	12	(none)

Table 3-3. Analysis Visit Windows for Vital Signs and Weight

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 2*	2	2	2
Day 3	3	3	3
Day 4*	4	4	5
Day 7	7	6	9
Day 11	11	10	11
Day 25	25	12	(none)

*Weight is not scheduled to be collected on Day 2 and Day 4 per protocol, so any weight collected on Day 2 will be considered for Day 3, any weight collected during Day 4 period will be considered for Day 7.

Table 3-4. Analysis Visit Windows for ECGs and Coagulation Tests

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 7	7	2	9
Day 11	11	10	11
Day 25	25	12	(none)

Table 3-5. Analysis Visit Windows for CD4 Cell Count and Percentage

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Day 11	11	2	11
Day 25	25	12	(none)

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dose of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data (except for HIV-1 RNA, see below), or the measurement with the lowest severity (ie, normal will be selected over abnormal for safety ECG findings) for categorical data.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected (with the exception of CD4+ cell count and CD4% in which the latest record will be selected and HIV-1 RNA level [see below]).
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken for continuous data (except for HIV-1 RNA, see below) and the worst severity will be taken for categorical data, unless otherwise specified.
- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both “Roche COBAS 6800” and “Roche COBAS 6800 Repeat” (ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the “Roche COBAS 6800 Repeat” will be selected for analysis purposes; otherwise, if there are multiple “Roche COBAS 6800” records with the same collection time, the geometric mean will be taken for analysis purposes.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A summary of key study dates will present the dates for: 1) first participant screened 2) first participant enrolled 3) last participant enrolled 4) last participant last visit for primary endpoint [Day 11], and 5) last participant last visit for clinical study report.

A summary of participant enrollment in this substudy will be provided for each country, and investigator within country. This summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants enrolled for that column.

A summary of participant disposition will present the number of participants screened for this substudy (denoted by an "C" contained within the participant screening number under the master protocol) and the number of participants who met all eligibility criteria but were not enrolled with the reasons that participants were not enrolled. An additional summary of participant disposition for participants in the All Enrolled Analysis Set will be provided. The number and percentage of participants in each of the categories listed below will be summarized:

- All Enrolled Analysis Set
- Safety Analysis Set
- Full Analysis Set
- PK Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column.

In addition, the total number of participants who were enrolled, and the number of participants in each of the disposition categories listed above will be displayed in a flowchart.

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

The following by-participant listings will be provided by participant ID number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Analysis set status (participants excluded from any of the analysis sets)

4.2. Extent of Study Drug Exposure and Adherence

A participant's extent of exposure to study drug data will be examined by assessing the total duration of exposure to study drug. Study drug administration was performed at the study site; adherence will not be summarized.

4.2.1. Study Drug Exposure and Duration on Study

Dose of GS-6212 will be CCI [redacted] on Days 1 through 10 for Cohort 1. Cohorts 2-5 were not initiated. The first AM dose (on Day 1) should be taken following overnight fasting (≥ 6 hours). All other AM doses (on Days 2 through 10) should be taken around the same time every morning on an empty stomach (fasting for ≥ 2 hours). Each PM dose should be taken around the same time every evening with or without food. Participants are required to keep the pattern of study drug intake consistent throughout the 10 days of dosing as much as possible. Study drug exposure will be summarized based on data collected on the Study Drug Administration eCRF.

Duration on sponsor-provided Biktarvy® (BVY) as standard of care or alternative SOC will be summarized using descriptive statistics, and will be calculated as: (last dose date BVY or alternative SOC – first dose date of BVY or alternative SOC) + 1. The start and stop dates for BVY administered as standard of care are collected on the ARV eCRF with subcategory of "CURRENT". Records with a BVY or alternative SOC start date on or after the last date in study will be excluded from calculations.

The number (ie, cumulative counts) and percentage of participants on BVY or alternative SOC for at least the following number of days will be summarized: 7 days, 14 days. For the final analysis, a ± 2 day window will be applied for the 14 days category (allows for the Day 25 [on Study] protocol specified visit window and participants starting BVY or alternative SOC on Day 11).

Duration on study (in days) will be defined as last date in study minus first dosing date plus 1. Last Study Date is the latest of clinic visit dates and laboratory visit dates, including all follow-up visits for participants who prematurely discontinued study or who completed study according to the Study Completion eCRF.

Duration on study (in days) will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of participants still on study through each study visit: ≥ 1 day, ≥ 2 days, ≥ 3 days, ≥ 4 days, ≥ 7 days, ≥ 8 days, ≥ 9 days, ≥ 10 days, ≥ 11 days, and ≥ 25 days. For the final analysis, a ± 2 day window will be applied for the ≥ 25 days category to allow for the Day 25 protocol specified visit window.

Summaries will be provided for the Safety Analysis Set. Exposure data for GS-6212 study drug will be listed.

No formal statistical testing is planned.

BVY will be provided as standard of care by the Sponsor during the follow-up period and dispensing information will be recorded on the Accountability eCRF.

Drug accountability data for study drug, BVY will be listed. Drug accountability data of alternative standard of care is not available.

4.3. Protocol Deviations

A by participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criteria. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that the participant did not meet and related comments, if collected.

Important protocol deviations occurring after participants entered the study are documented during routine monitoring. Any important deviation identified will be included in a by-participant listing. The number and percentage of participants with important protocol deviations by deviation category (eg, eligibility criteria, informed consent) will be summarized for the Safety Analysis Set.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include HIV-1 RNA (log_{10} copies/mL), CD4 cell count (/μL), CD4 percentage (%), mode of infection (HIV risk factors), HIV disease status (AIDS, asymptomatic, or symptomatic HIV infection), years since HIV-1 diagnosis, years since starting HIV-1 treatment, resistance to any of the 4 ARV classes (yes, no) with a count of the number of subjects with resistance to each ARV class [NRTI, NNRTI, PI, and/or INSTI]), and ART status (ART-experienced or ART-naïve). These baseline characteristics will be summarized and for all GS-6212 participants using descriptive statistics for continuous variables, and using number and percentage of participants for categorical variables. The summary of these baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

Note: If only the month and year are collected for “date of HIV-1 diagnosis” and/or “start date of HIV-1 treatment”, the day will be set to ‘01’ when imputing the full date. If both the day and month are missing, then ‘01 July’ will be used for the day and month unless the full imputed date is after the first dose date of GS-6212 study drug. If HIV-1 diagnosis date or HIV-1 treatment start date is imputed to be after the first dose date of GS-6212 study drug, set the imputed HIV-1 diagnosis date or treatment start date to the date of first dose of GS-6212 to avoid having a negative duration.

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

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 MedDRA dictionary.

A by-participant listing of general medical history will be provided by participant ID number in ascending order. The listing will include relevant medical condition or procedure reported term, onset date, ongoing status, and resolution date (if applicable).

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) on Day 11.

Historical HIV-1 RNA data for placebo participants from 3 sponsor Phase 1b studies (GS-US-120-0104, GS-US-141-1219, and GS-US-200-4072) will be combined to form a single placebo group for the purpose of HIV-1 RNA analysis through Study Day 11. For Study GS-US-200-4072, HIV-1 RNA (log_{10} copies/mL) collected on Day 10 will be used for "Day 11" since HIV-1 RNA was not collected on Day 11 for this study. GS-6212 cohort will be compared to the pooled placebo group with respect to the primary efficacy endpoint, the change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) on Day 11, using the 2-sided t-test conducted at an alpha level of 0.05. The analysis will be conducted using the FAS.

6.2. Secondary Efficacy Endpoints

6.2.1. Change from Baseline in Plasma HIV-1 RNA (log_{10} copies/mL) on Day 8

The secondary efficacy endpoint change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) on Day 8 will be analyzed using the same methods used for the primary endpoint. For study GS-US-120-0104, HIV-1 RNA (log_{10} copies/mL) collected on Day 7 will be used for "Day 8" since HIV-1 RNA was not collected on Day 8 for this study.

6.2.2. Percentage of Participants Ever Achieving HIV-1 RNA < 50 copies/mL Postbaseline up to Day 11

The number and percentage of participants ever achieving HIV-1 RNA < 50 copies/mL postbaseline up to Day 11 will be summarized by GS-6212 cohort and for the placebo control group (using the FAS). For historical placebo control participants in study GS-US-120-0104 with HIV-1 RNA values analyzed using the HIV PCR Stand, 1.5 Cobas-CL assay with a LLOQ of 400 copies/mL, a value less than LLOQ (ie, < 400 copies/mL) was counted as meeting the endpoint (HIV-1 RNA < 50 copies/mL). A Fisher's exact test will be used to compare each GS-6212 cohort to the historical placebo group if at least 1 participant has HIV-1 RNA < 50 copies/mL postbaseline up to Day 11.

6.3. Other Efficacy Endpoints

Maximum Reduction in Plasma HIV-1 RNA Postbaseline to Day 11

The maximum postbaseline reduction in plasma HIV-1 RNA (log_{10} copies/mL) from Day 2 through Day 11 will be analyzed using the same statistical methods used for the primary endpoint analysis. Baseline value, lowest post-baseline HIV-1 RNA value from Day 2 to Day 11, and the lowest change from baseline in HIV-1 RNA (log_{10} copies/mL) from Day 2 to Day 11 for each participant will be summarized for GS-6212 cohort and for the historical placebo group.

Change from Baseline in HIV-1 RNA by Visit

Baseline value, HIV-1 RNA (log_{10} copies/mL), and change from baseline in HIV-1 RNA (log_{10} copies/mL) will be summarized descriptively by visit for GS-6212 cohort and for the historical placebo control group through Day 11.

Mean ± 95% confidence interval (CI) and median (Q1, Q3) of the change from baseline in HIV-1 RNA (log_{10} copies/mL) at each visit will be plotted through Day 11 using a line plot with a separate line displayed for GS-6212 cohort and for the historical placebo group. Placebo data will be displayed for participants with a measurement collected in the analysis visit window.

Change from Baseline in CD4 by Visit

Baseline values, values at postbaseline visit Day 11 and Day 25), and the change from baseline in CD4 cell count (/μL) and CD4 percentage by visit will be summarized.

Percentage of Participants with HIV-1 RNA < 50 copies/mL by Visit from Day 11 to Day 25

The number and percentage of participants with HIV1 RNA < 50 copies/mL (split into categories "< 20 copies/mL" [with subcategories "< 20 copies/mL Detectable", "< 20 copies/mL Not Detectable"] and "20 to < 50 copies/mL") by visit using the Cobas 6800 assay will be displayed for GS-6212 cohort and overall using the missing = excluded method at the last visit prior to adding SOC (Day 11) and at visits after adding SOC (Days 25).

For participants who did not meet the criteria HIV-1 RNA < 50 copies/mL at the visit, the number and percentage of participants with HIV-1 RNA in the following categories will be summarized:

- 50 to < 200 copies/mL
- ≥ 200 copies/mL

Missing data will be excluded in the computation of percentages (ie, missing data points will be excluded from both numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the FAS with nonmissing HIV-1 RNA value at that visit. No statistical testing is planned.

All efficacy endpoints will include participants in the FAS.

6.4. Sensitivity Analyses

Sensitivity analyses will be performed among participants who took the study drug with correct amount of dose at each intake and completed the study drug as planned per protocol. Participants who were under dosed, or early terminated study drug will be excluded from the sensitivity analyses. Sensitivity analyses will include following analyses:

- Change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) on Day 11 using the same statistical methods used for the primary endpoint analysis;

- Maximum postbaseline reduction in plasma HIV-1 RNA (log_{10} copies/mL) from Day 2 through Day 11 using the same statistical methods used for the primary endpoint analysis;

- Change from baseline in HIV-1 RNA (log_{10} copies/mL) by visit.

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 version 27.0. 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 were graded by the investigator as Grade 1, 2, 3, or 4 according to toxicity criteria specified in the protocol. A Grade 5 event indicates death. 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

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-participant 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 considered related to study procedure for summary purposes. However, by-participant data listings will show the relationship as missing from that captured on the CRF.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AE met the definition of an SAE that was specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with those in the Gilead Patient Safety database before data 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 any AEs with an onset date on or after the study drug start date. If the AE onset date is the same as the date of study drug start date then the AE onset time must be on or after the study drug start time. If the AE onset time is missing when the start dates are the same the AE will be considered treatment emergent.

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

7.1.7. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.7.1. Summaries of AE Incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided for events with an onset date up to Day 11 (prior to adding SOC) and for the entire study.

- TEAEs
- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE procedure-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE treatment-related AEs with Grade 2 or higher

- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to premature discontinuation of study
- TEAEs leading to death (ie, outcome of death)

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT:

- TEAEs, by maximum severity
- TEAEs up to Day 11, by maximum severity
- TEAEs with Grade 3 or higher, by maximum severity
- TE treatment-related AEs, by maximum severity
- TE procedure-related AEs, by maximum severity
- TE treatment-related AEs with Grade 3 or higher, by maximum severity
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

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

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths

- All AEs with severity of Grade 3 or higher
- All AEs leading to premature discontinuation of study drug or study

7.2. Laboratory Evaluations

Laboratory data collected during the substudy 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 all data collected after the first dose date of study drug unless stated otherwise. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, coagulation, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the DAIDS Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided for selected laboratory tests specified in the study protocol as follows:

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

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 DAIDS Toxicity 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.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed postbaseline 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 participants in the study with the given response at baseline and each scheduled postbaseline visit.

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

- Graded laboratory abnormalities
- Graded laboratory abnormalities collected up to Study Day 11 (prior to the participant initiating standard of care therapy on Day 11)
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with ≥ 1 nonmissing postbaseline value.

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

7.3. Body Weight, Height, and Vital Signs

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

- Baseline value
- Value at each postbaseline time point [visit]
- Change from baseline at each postbaseline time point [visit]

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

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

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight, height, and BMI will be included in the vital signs listing if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications and Disease Specific Medications

Prior and concomitant medications (ie, non-antiretroviral [non-ARV] medications) collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug Dictionary.

Disease-specific medications (ie, nonstudy drug ARV) used prior to, during, or after the study (if collected) will be coded using the Gilead-modified WHO Drug Dictionary.

7.4.1. Prior and Disease-Specific Prior Medications

Prior and disease-specific prior medications are defined as any medications taken before a participant took their first dose of study drug.

A summary of prior or disease-specific prior medications will not be provided.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken on or after first dose date of study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for GS-6212 cohort. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

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

All prior and concomitant medications (other than per-protocol study drugs) and all nonstudy drug ARV medications will be provided in by-participant listings sorted by participant ID number and administration date in chronological order.

7.5. Electrocardiogram Results

Summaries of investigator assessment of ECG readings will be provided for the Safety Analysis Set for each scheduled visit. No formal statistical testing is planned.

7.5.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. If all participants have a baseline value then no missing category will be presented at baseline. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

No formal statistical testing is planned.

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

7.6. Other Safety Measures

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

Although not necessarily related to safety, a by-participant listing of all comments received during the study on the comments eCRF will be provided by participant ID number, and eCRF 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 (PK) ANALYSES

8.1. PK Sample Collection and Analyses

Intensive PK samples are planned to be collected on Study Day 1 and Day 10 at the following timepoints for all cohorts (as applicable): predose (≤ 30 minutes before dose), 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose (12 hour postdose sample is optional) on respective days of dosing. Additionally, single trough PK samples will be drawn prior to AM drug dosing on Study Days 2, 3, 4, 7, 8, 9, and 11. Concentrations of GS-6212 in plasma will be determined using validated bioanalytical assays.

8.1.1. Estimation of PK Parameters

PK parameters will be estimated by leveraging relevant PK data (ie, intensive PK data) using Phoenix WinNonlin® software (version 8.2.0) with standard noncompartmental methods. The linear up/log down 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. If the PK scientist identifies that another method is more appropriate, the reasons for this decision should be documented.

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

Area under the curve (AUC) will be calculated, as appropriate, by the PK scientist. For AUC calculation, samples that are BLQ occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero 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_{tau}, λ_z and $t_{1/2}$ (as applicable) 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.

8.1.2. PK Parameters

PK parameters will be generated for all participants for whom parameters can be derived in the PK Analysis Set. The analyte presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analyte

GS-6212 Cohort	Treatment	Analyte
All GS-6212 Cohorts	GS-6212	GS-6212

The analyte and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study, as appropriate. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
GS-6212	For intensive PK sampling up to 12 hours postdose on Day 1 and Day 10, following parameters will be calculated (as applicable): AUC_{0-t}, AUC_{last}, AUC_{tau}, C_{max}, C_t, C_{last}, C_{tau}, C_{avg}, T_{max}, T_{last}, and additionally λ_z, CL/F, $t_{1/2}$, and V_z/F if applicable; accumulation ratio (Day 10 / Day 1) for Ct, C_{max}, AUC_{0-t}, and AUC_{last}; C_{trough} on Day 11; $C_{trough,avg}$ (average C_{trough} based on all predose trough sampling done across several days- D2, D3, D4, D7, D8, D9, D10, and D11)

8.2. Statistical Analysis Methods

8.2.1. General considerations

Individual participant concentration data and individual participant PK parameters for GS-6212 will be listed and summarized using descriptive statistics. Summary statistics (number of participants, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual participant concentration data by visit/time point and individual participant PK parameters (as applicable). Moreover, the geometric mean, 95% CI, %Geometric CV [%GCV], and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number and percentage of participants with concentration BLQ, as well as an indicator if more than one-third of the participants are BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at predose and postdose time points. If more than one-third of the values at a postdose time point are BLQ then the mean and SD will not be presented at that time point Concentration values will be presented as received from the bioanalytical lab and summary statistics will be presented to three significant digits.

8.2.2. PK Analyses

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter. Data and summary statistics will be presented to three significant digits.

The following tables will be provided for GS-6212:

- Individual estimates and summary statistics of plasma pharmacokinetic parameters on Day 1 and Day 10
- Individual data and summary statistics of plasma concentration (ng/mL) at protocol-specified sampling times
- Statistical comparisons of plasma pharmacokinetic parameter estimates on Day 10 vs Day 1 for the accumulation analysis

Accumulation analysis of analyte GS-6212 will be evaluated by comparing the relevant Day 10 PK parameters to Day 1 PK parameters within cohort 1. The analytes and parameters are presented in Table 8-3.

A mixed effects model with the natural log-transformed PK parameter as the dependent variable, a fixed effect for day, and a random effect for participant, will be used to estimate the difference between Day 10 and Day 1. A 90% CI for the true difference on the log-scale across all participants will be estimated. The estimate and associated 90% CI will be exponentiated to obtain an estimate of the GLSM ratio and its associated 90% CI.

The following SAS® PROC MIXED code will provide assessment for accumulation ratio for natural-log transformed parameters.

```
proc mixed;
  where analyte='GS-6212 and paramcd ='parameter';
  class subjid day;
  random subjid;
  model lnest = day / ddfm=kr;
  lsmeans day / diff cl alpha = 0.1;
  estimate 'Test (Day 10) versus Reference (Day 1)' day -1 1 / cl alpha = 0.10;
  ods output Estimates = LS_Diffs LSMeans = LS_Means CovParms = MSE;
run;
```

Table 8-3. Analytes and PK Parameters for Estimation of Accumulation Ratios

Analytes	PK Parameters on Day 1	PK Parameters on Day 10
GS-6212	$AUC_{0\text{-}8h}$, AUC_{last}, C_{8h}, C_{max}	$AUC_{0\text{-}8h}$, AUC_{last}, C_{8h}, C_{max}

The following figures will be provided for GS-6212:

- Mean (± SD) concentration data on Day 1 (on linear and semilogarithmic scales).
- Mean (± SD) concentration data on Day 10 (on linear and semilogarithmic scales).

- Mean (± SD) concentration data from Day 1 through Day 11 (on linear and semilogarithmic scales).

If more than one-third of the values at a postdose time point are BLQ, then the mean and SD will not be presented at that time point and remaining points connected. If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.

- Median (Q1, Q3) concentration data on Day 1 (on linear and semilogarithmic scales).

- Median (Q1, Q3) concentration data on Day 10 (on linear and semilogarithmic scales).

- Median (Q1, Q3) concentration data Day 1 through Day 11 (on linear and semilogarithmic scales).

If more than one-third of the values at a postdose time point are BLQ then the median, Q1 and Q3 will not be presented at that time point and remaining points connected. If lower error bar (Q1) is BLQ at a timepoint then it will be presented as LLOQ at that timepoint.

- Individual participant concentration data versus time (on linear and semilogarithmic scales). Values of BLQ will be displayed as 0 on the linear scale and missing on the semi-logarithmic scale.

The following listings may be provided, as applicable:

- Plasma PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age

8.2.3. PK/PD Analyses

No formal PK/PD analysis is planned due to small number of participants in this study.

8.3. Sensitivity Analysis

Sensitivity analysis may be conducted for the key PK analyses if the PK scientist identifies PK data as questionable. The sensitivity analysis will exclude specific data from analyses, if appropriate. If a sensitivity analysis is deemed necessary, a listing of the PK parameter(s) data being excluded, with associated reason(s) provided by the PK scientist, will be generated.

9. REFERENCES

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1), July 2017, https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

10. SOFTWARE

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

nQuery, Statsols, Cork, Ireland.

Phoenix WinNonlin® software, Certara, Radnor, PA, USA

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table

Study Procedure	Screening[a]	D1[b]	D2	D3	D4	D7	D8	D9	D10	D11[b]	D25	ET[c]
Visit Window											±2D	
Written informed consent	X											
Medical history and demography	X											
Complete physical examination	X	X									X	X
Symptom-driven physical examination[d]			X		X	X				X		
Height	X											
Weight	X	X		X		X				X	X	X
Vital signs[e]	X	X	X	X	X	X				X	X	X
HBV blood panel and HCV serology[f]	X											
CD4 cell count[f]	X	X								X	X	X
Plasma sample for HIV-1 genotyping/phenotyping[f,g]	X	X								X		
Plasma HIV-1 RNA[f]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[f]	X	X		X		X				X	X	X
Coagulation panel[f]	X	X				X				X	X	X
Chemistry[f]	X	X		X		X				X	X	X
Urinalysis[f]	X	X		X		X				X	X	X
Serum pregnancy test[f,h]	X											
Urine pregnancy test[f,h,i]		X									X	X
Serum FSH[f,j]	X											
12-Lead ECG	X	X				X				X	X	X
Intensive plasma PK[k]		X							X			
Single trough plasma PK[l]			X	X	X	X	X	X		X		X
Review AEs and concomitant medications[m]	X	X	X	X	X	X	X	X	X	X	X	X
Study drug (GS-6212) dispensation[n]		X										
Study drug (GS-6212) dosing[o, p]		X	X	X	X	X	X	X	X			
BVY dispensation, as applicable										X		

Study Procedure	Screening[a]	D1[b]	D2	D3	D4	D7	D8	D9	D10	D11[b]	D25	ET[c]
Visit Window											±2D	
BVY or an alternative SOC administration										X[q]	→	

AE = adverse event; AM = before noon; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy®); CD4 = clusters of differentiation 4; D = Day; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus type 1; PK = pharmacokinetic(s); RNA = ribonucleic acid; SAE = serious adverse event; SOC = standard of care

a Prospective participants should be screened no more than 28 days prior to administration of the first dose of study drug.
b Overnight fasting (≥ 6 hours prior to dosing) is required.
c ET assessments will be performed within 72 hours of prematurely discontinuing from the study or study drug, as applicable.
d Symptom-driven physical examinations will be performed as needed, based on reported signs and symptoms.
e Vital signs include blood pressure, heart rate, respiration rate, and body temperature. Participants should be sitting down for 5 minutes before vital sign measurements are obtained.
f See detailed list of laboratory assessments in Section 6.3.7 of the master protocol.
g Participants who meet the criteria for virologic failure at Day 11 will be tested for the potential development of resistance against all components of the treatment regimen, including the study drug. See Section 6.3.9.1.3 of the master protocol for management of virologic failure.
h Participants assigned female at birth and of childbearing potential only.
i A negative urine pregnancy test is required prior to study drug dosing on Day 1. Positive urine pregnancy tests will be confirmed with a serum test.
j A serum FSH test is required for participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.
k Intensive PK samples should be collected at these time points for all cohorts (relative to AM dosing): predose (≤ 30 minutes before dose), 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose [redacted] on respective days of dosing (ie, Days 1 and 10). Please note that the 12-hour postdose sample (if collected) on Days 1 and 10 should be sampled prior to the administration of the PM dose, as applicable.
l Single trough PK sample should be drawn prior to AM drug dosing (as applicable) on the indicated dosing days (ie, Days 2, 3, 4, 7, 8, 9, and 11).
m From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol-mandated procedures, on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management, for additional details.
n Study drug bottles of GS-6212 will be dispensed on Day 1 (see Section 5.2.4).
o For Cohort 1, a 100-mg dose of GS-6212 will be administered twice daily (ie, once every 12 hours ± 1 hour) on Days 1 through 10 (for further details on dosing and meal requirements, see Section 5.2.4). Subsequent cohort doses, dosing regimens, meal requirements (fasted or fed), and progression between cohorts will be adaptive and determined as summarized in Section 3.1.1.
p Participants will take their study drug doses at home on Days 5 and 6.
q After assessments on Day 11 or upon ET, participants will initiate a regimen of BVY provided by the sponsor or an alternative SOC ART regimen selected by the investigator. Participants who discontinue study drug before Day 11 should start this regimen at the time of discontinuation (see Section 6.4.1 of the master protocol).

Appendix 2. Details for Statistical Programming

For continuous HIV-1 RNA endpoints change from baseline on Day 11, and maximum change from Day 2 to Day 11, pairwise comparisons between GS-6212 cohort and historical placebo group will be performed and p-values will be presented.

The following SAS code will be used to generate p-values:

```
**Assign treatment groups for testing**;
data trtgrp;
set trtgrp;
    if dose =’100 mg’ and meal=’Fasted’ then trt=1;
    else if treatment=’Placebo’ then trt2;
run;

ods output estimates=estimate;
proc mixed data = trtgrp;
class trt;
model chg  = trt / ddfm=kr;

/*least squares means*/
lsmeans trt / diff e;

/* p-values */
estimate 'Cohort 1 vs Placebo' trt  1 -1 / cl alpha=0.05;
run;
```

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	28-Aug-2024 03:56:43
PPD	Project Team Leader eSigned	28-Aug-2024 16:23:03
PPD	Clinical Pharmacology eSigned	28-Aug-2024 16:42:19