STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b Randomized, Blinded, Proof-of-Concept Study to Evaluate the Safety and Efficacy of Broadly Neutralizing Antibodies (bNAbs) GS-5423 and GS-2872 in Combination with Capsid Inhibitor Lenacapavir (GS-6207) in Virologically Suppressed Adults with HIV-1 Infection
Name of Test Drug:	Broadly Neutralizing Antibodies (bNAbs GS-5423 and GS-2872) +Lenacapavir (LEN; GS-6207)
Study Number:	GS-US-536-5816
Protocol Version (Date):	Amendment 2 (30 March 2022)
Analysis Type:	Week 26 Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	02 August 2022
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
B/F/TAF	Bictegravir/Emtricitabine/Tenofovir Alafenamide
BIC	Bictegravir
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CK	creatine kinase
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	Electrocardiogram
$eGFR_{CG}$	estimated glomerular filtration rate using Cockcroft-Gault formula
FAS	Full Analysis Set
Hb	Hemoglobin
HLT	high-level term
ITT	intent to treat
LOQ	limit of quantitation
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
PBMC	peripheral blood mononuclear cell
POC	Proof-of-Concept
PT	preferred term
PWH	people with HIV
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SOC	system organ class
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir diphosphate
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of Week 26 primary analysis for the primary cohort of Study GS-US-536-5816. A formal primary analysis will be performed when all participants in primary cohort have completed Week 26 visit or prematurely discontinued from study.

This SAP is based on the study protocol amendment 2 dated 30 March 2022 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the Week 26 primary analysis.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of a combination of the bNAbs GS-5423 and GS-2872 in combination with the HIV capsid inhibitor LEN

The secondary objectives of this study are as follows:

- To evaluate efficacy of the study regimens determined by the proportion of participants maintaining virologic suppression (HIV-1 RNA < 50 copies/mL) at Week 26
- To evaluate the PK of GS-5423, GS-2872, and LEN
- To evaluate immunogenicity of GS-5423 and GS-2872
- To evaluate the emergence of resistance to the components of the study regimens

The exploratory objectives are as follows:

- To evaluate changes in HIV reservoir
- To evaluate changes in immune biomarkers

1.2. Study Design

Design Configuration and Participant Population

This is a randomized, blinded, Proof of Concept (POC) Phase 1b study to evaluate the safety and efficacy of a single dose each of long-acting (LA) regimen of LEN, GS-5423, and GS-2872 in adults with HIV-1 infection who are virologically suppressed on oral antiretroviral therapy (ART).

This study will enroll approximately 20 participants (Primary Cohort). After GDRC review (Section 2.1), an optional Pilot Cohort of up to 20 additional participants may be added.

Participants in the Primary Cohort and in the optional Pilot Cohort will be randomized in a 1:1 ratio to one of the following 2 treatment groups based on the dose of GS-2872 as follows:

Treatment Groups

Treatment Group 1:

Oral LEN for loading 600 mg followed by LEN 927 mg SC on Day 1; oral LEN for loading 600 mg on Day 2

GS-5423 30 mg/kg, administered via IV infusion over 60 minutes on Day 1 (after LEN SC injection)

GS-2872 10 mg/kg, administered via IV infusion over 60 minutes on Day 1 (after GS-5423 infusion)

Treatment Group 2:

Oral LEN for loading 600 mg followed by LEN 927 mg SC on Day 1; oral LEN for loading 600 mg on Day 2

GS-5423 30 mg/kg, administered via IV infusion over 60 minutes on Day 1 (after LEN SC injection)

GS-2872 30 mg/kg, administered via IV infusion over 60 minutes on Day 1 (after GS-5423 infusion)

For the optional Pilot Cohort, randomization will be stratified by the antibody (GS-5423 or GS-2872) to which the participant is sensitive.

All participants will discontinue their background oral antiretroviral (ARV) regimen 1 day prior to receiving study drugs on Day 1.

At Week 26, all participants will resume their baseline regimen of once daily oral ART (or compatible regimen selected by the investigator) and return to the clinic for visits at Weeks 38 and 52.

Unblinded treatment assignments will be provided to the investigators after all participants are back on their baseline ARVs (or compatible regimen selected by the investigator) at Week 26 or have discontinued the study, and the Week 26 analysis has been completed.

Key Eligibility Criteria

HIV-1 infected participants who meet the following criteria:

- Age between 18 and 65 years at screening
- On first-line ART for ≥ 2 years prior to screening. A change in ART regimen ≥ 28 days prior to screening for reasons other than VF (eg, tolerability, simplification, drug-drug interaction profile) is allowed
- No documented historical resistance to the current ART regimen
- Plasma HIV-1 RNA < 50 copies/mL at screening
- Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 18 months preceding the screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL). Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening are acceptable.
- Proviral phenotypic sensitivity by the PhenoSense mAb Assay DNA at Monogram Biosciences to both GS-5423 and GS-2872 at screening
- CD4+ count nadir ≥ 350 cells/μL
- Screening CD4+ count ≥ 500 cells/μL
- Availability of a fully active alternative ART regimen, in the opinion of the investigator, in the event of discontinuation of the current ART regimen with development of resistance
- No comorbid condition requiring ongoing immunosuppression
- No evidence of current hepatitis B virus (HBV) infection
- No evidence of current hepatitis C virus (HCV) infection (prior infection cleared spontaneously or with treatment is acceptable)
- No history of opportunistic infection or illness indicative of Stage 3 HIV disease

Schedule of Assessments

Due to the extended laboratory processing time for bNAb sensitivity testing, screening procedures for the Primary Cohort will be conducted in two parts. For the optional Pilot Cohort, participants will be selected from the previously screened/failed participants in the Primary Cohort and will directly proceed to Screening Part 2 (no need to repeat Screening Part 1).

Screening Part 1: Assessment of medical history, adverse events (AEs), and concomitant medications will be performed. A blood sample to assess for bNAb sensitivity will be collected and analyzed to support eligibility and entry into Screening Part 2.

Screening Part 2: Participants with proviral phenotypic sensitivity to either or both GS-5423 and GS-2872 will have the following assessments performed: changes in medical history, complete physical examination, vital signs, height, weight, electrocardiogram (ECG), and sample collection for laboratory analyses (hematology, chemistry, coagulation, thyroid function, urinalysis, serum pregnaancy test [for women of childbearing potential], serum follicle-stimulating hormone [FSH], HIV-1 RNA, CD4+ cell count, CD8+ cell count, CD4/CD8 ratio, HBV and HCV serologies, and estimated glomerular filtration rate [eGFR]). Laboratory samples for proviral DNA genotype and bulk viral outgrowth phenotype will be collected at screening for subsequent testing.

Participants in the Primary Cohort who meet all eligibility criteria will be randomized in a 1:1 ratio to Treatment Group 1 or Treatment Group 2. Participants in the Pilot Cohort who meet all eligibility criteria will be randomized in a 1:1 ratio to Treatment Group 1 or Treatment Group 2. Participants in both cohorts will return to the clinic within 28 days after the Screening Part 2 visit for the Day 1 visit.

There is no stratification for randomization for the Primary Cohort.

For the optional Pilot Cohort, randomization will be stratified by the antibody (GS-5423 or GS-2872) to which the participant is sensitive.

More details for study procedures could be found in Section 11 (Appendix 1).

Study Duration

26 weeks.

1.3. Sample Size and Power

Although the sample size in this study is determined based on practical considerations and past experience with similar types of studies, assuming the 2 treatment groups have a similar virologic suppression rate, a total of 20 participants in the Primary Cohort will provide at least 35% power to show the lower bound of 95% CI for Week 26 virologic response rate (HIV-1 RNA < 50 copies/mL as defined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}) is greater than 83%. It was assumed that the virologic response rate at Week 26 was 95% (based on Gilead studies GS-US-380-1844 and GS-US-380-4030), 12% was a clinically tolerable margin for Phase 1b studies, and a one-sided exact test with a significance level 0.025 was used. The sample size and power calculations were made using the statistical software package PASS (Version 14, NCSS, LLC; Kaysville, Utah, USA).

The estimated 95% CI for possible range of VF rate is provided in Table 1-1. For example, with 1 VF event occurrence (5% estimated VF rate), a sample size of 20 participants can provide 95% confidence that the true VF rate is unlikely to be higher than 24.9%.

Table 1-1. Estimated Virologic Failure Rate and its 95% CIs (from the Clopper-fPearson Exact CI) Based on Number of Virologic Failure Event in Each Group or in Total

Sample Size	**20**				
Number of VF Events	0	1	2	3	4
Estimate of Incidence of VF (%)	0.0	5.0	10.0	15.0	20.0
Lower Bound of 95% CI (%)	0.0	0.1	1.2	3.2	5.7
Upper Bound of 95% CI (%)	16.8	24.9	31.7	37.9	43.7

VF = virologic failure
Software: SAS® Version 9.4. (SAS Institute Inc., Cary, NC, USA)

A total of approximately 20 participants in the Primary Cohort will provide reasonable assessment of safety and the descriptive PK profile throughout the study. A total of up to 20 participants in the optional Pilot Cohort is based on practical considerations.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

Prior to the final analysis, interim analyses will be conducted. The results from these analyses may be submitted to scientific meetings and for publications and to regulatory agencies to seekguidance for the overall clinical development program.

2.1.1. Gilead Data Review Committee (GDRC) Analysis

The GDRC will review the progress, unblinded safety and efficacy data of this study while the study is ongoing. The GDRC will convene after all participants enrolled in the Primary Cohort have completed their Week 12 visit or prematurely discontinued from the study.

No formal stopping rules will be used by the GDRC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of AEs associated with a study regimen warrant the early termination of the study in the best interest of the participants. Based on safety and preliminary efficacy, the GDRC will determine whether the optional Pilot Cohort will be implemented.

In addition, the GDRC may review unblinded safety and efficacy data on an ad hoc basis when there is a need for safety or efficacy monitoring. Refer to the GDRC Charter for additional details.

2.1.2. Primary Analysis

The unblinded primary analysis will be conducted after all participants in the Primary Cohort have completed Week 26 visit or prematurely discontinued from the study.

2.2. Final Analysis

The final analysis will be performed after all participants have completed the study or prematurely discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The final analysis will include data from the Primary Cohort and may include data from the optional Pilot Cohort.

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

There are following 2 sets of analyses defined for this study. Data included in each analysis are defined as follows:

Long Acting (LA) Regimen Period Analysis

Long Acting (LA) Regimen Period Analysis includes efficacy (ie, HIV-1 RNA and CD4 cell count and percentage) and safety data collected during long acting regimen period from participants randomized and received at least one dose of the complete long acting study drug regimen (ie, SC LEN + GS-5423 and GS-2872). All data collected up to the last exposure date of LA regimen (defined in section 3.8.1) will be summarized except for data on AEs, death and concomitant medications. For AEs, death and concomitant medications, only data collected prior to the last exposure date of LA regimen will be included. For participants who did not restart ART on or before last study date or have missing ARV restart date, all data will be included.

Data included in this analysis will be used to assess the efficacy and safety data collected during the LA regimen period of the study. Results will be summarized by treatment group and overall.

Whole Study Period Analysis

Whole Study Period Analysis includes efficacy (ie, HIV-1 RNA and CD4 cell count and percentage) and safety data collected during whole study period from participants randomized and received at least one dose of study drug. For efficacy summary, all HIV-1 RNA and CD4 data during the whole study will be included. For safety summary, (1) for participants who prematurely discontinued study or complete study, all safety data collected up to the last exposure date (defined in section 3.8.1) will be included; (2) for participants who were still on study: all available data will be included.

Data included in this analysis will be used to assess the efficacy and safety data collected during the whole study period. Results will be summarized by treatment group and overall.

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 will be summarized by treatment group and total.

A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who have received at least one dose of the complete long acting study drug regimen (ie, SC LEN + GS-5423 and GS-2872). This is the primary analysis set for efficacy analyses.

3.1.3. Per Protocol Analysis Set

The **Per Protocol (PP) Analysis Set** includes all participants in the FAS excluding participants meeting any of the following criteria:

1) did not have on-treatment HIV-1 RNA in the Week 26 analysis window, except when missing is due to discontinuation of study drug for lack of efficacy as in Table 3-1. (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation on the study drug completion eCRF page.)

2) Received partial or missed doses on Day 1 or Day 2.

3) Prior receipt of any anti–HIV-1 mAbs (including ibalizumab).

4) Have been treated with immunosuppressant therapies or chemotherapeutic agents (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies) within 4 weeks of study screening or have an anticipated need for such treatment during the study.

Table 3-1. Participants Excluded from Week 26 PP Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 26 Analysis Window

Discontinuation from Study Drug prior to or on the Upper Bound of Week 26 Analysis Window		HIV-1 RNA Data on Treatment Available in Week 26 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Other Reasons	+	-
No		+	-

+ = Inclusion of Participants in Week 26 PP analysis set; - = Exclusion of Participants in Week 26 PP analysis set.
On-Treatment HIV-1 RNA data include all HIV-1 RNA data collected up to the earliest date of (196 days [28 weeks] after the dose date of complete long acting regimen, date of restarting ART).

The date of study drug premature discontinuation is the last exposure date of LA regimen for participants who prematurely discontinued study drug.

For the PP analysis, efficacy data up to the earliest date of (196 days [28 weeks] after the dose date of complete long acting regimen, date of restarting ART) will be included.

The PP Analysis Set is the secondary analysis set for efficacy analysis.

3.1.4. Safety Analysis Set

The Safety Analysis Set is the primary analysis set for safety analyses. Two safety analysis sets are defined for this study:

- The Safety Analysis Set includes all participants who were randomized and received at least 1 dose of study drug. This is the primary analysis set for safety analyses for whole study period. This analysis set will also be used to describe baseline information.

- The Safety Analysis Set for LA Regimen includes all randomized participants who have received at least one dose of the complete long acting study drug regimen (ie, SC LEN + GS-5423 and GS-2872). This is the primary analysis set for safety analyses for LA regimen period analysis.

3.2. Participant Grouping

For analyses based on the All Randomized Analysis Set or the FAS, participants will be grouped according to the treatment group to which they were randomized. For all other analyses, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

Participants will be grouped as follows for table summary:

- Treatment Group 1: SC LEN + GS-5423 + GS-2872 10 mg/kg
- Treatment Group 2: SC LEN + GS-5423 + GS-2872 30 mg/kg
- Total Group: All participants from Teatment Groups 1 and 2 (for all tables and figure summary unless specified otherwise)

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling participants in primary cohort.

3.4. Examination of Participant Subgroups

There are no prespecified participant subgroupings for efficacy and safety analyses due to small sample size.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made in this phase 1b trial.

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.

For missing last dose date of study drug, imputation rules are described in Section 3.6. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2., and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

Only year of birth is collected in this study. The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If year of birth is collected, “01 July” will be imputed as the day and month of birth
- If year of birth is missing, date of birth will not be imputed

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, age derived based on date of birth and the Day 1 visit date will be used instead. If a randomized participant was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the 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) 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 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).

HIV-1 RNA results of 'No HIV-1 RNA detected' and "<20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes.

3.8. Analysis Visit Windows

3.8.1. Definition of Key Dates and Study Day

Study Day 1 is defined as the day when the first dose of any study drug was taken, as recorded on the Study Drug Administration eCRF (ie, oral LEN, SC LEN or infusion drugs [GS-5423, GS-2872]).

Last Dose Date is defined as the latest dose date of any study drug as recorded on the Study Drug Administration eCRF (ie, oral LEN, SC LEN or infusion drugs (GS-5423, GS-2872) for participants who prematurely discontinued study drug or completed study drug according to Study Drug Completion eCRF.

Study Days are calculated relative to Study Day 1 of study drug and derived as follows:

- For postdose study days: Assessment Date – First Dose Date + 1

- For days prior to the first dose: Assessment Date – First Dose Date

Baseline Value is defined as the last value obtained on or prior to the first dose of study drug.

Last Study Date is the latest clinic visit dates, and/or the laboratory visit dates, and/or latest AE onset date and end date, whichever is latest, including the any follow-up visit dates, for participants who prematurely discontinued study or completed study according to the Study Completion eCRF.

Last Exposure Date is defined as follows for participants who prematurely discontinued study or complete study according to Study Completion eCRF (i.e. participant answered "No' or "Yes" for "Did the participant complete the protocol-planned duration of the study" on Study Completion form):

- For participants who receive any injection or infusion, last exposure date is defined as last study date.

- For participants who do not receive any injection or infusion (i.e. for those who only receive oral LEN), last exposure date is defined as the earliest of the last dose date plus 60 days and the last study date.

This date is defined considering the prolonged exposure of LEN, GS-5423, and GS-2872 after the last dose date of LEN, GS-5423, and GS-2872 through the end of study.

Last Exposure Date of LA regimen is defined as follows for participants who prematurely discontinued study drug or complete study drug according to Study Drug Completion eCRF (i.e. participant answered "No' or "Yes' for "Did participant complete study drug dosing as specified per protocol" on Study Drug Completion form):

1) the earliest (last study date or ART restart date) for participants who prematurely discontinued study or complete study;

2) the ART restart date for participants who were still on study. If the ART restart date is missing, the data cut date will be used to impute the last exposure date for participants who are still on study at the time of the data cut date.

This date is defined considering the prolonged exposure of LEN, GS-5423, and GS-2872 after the last dose date of LEN, GS-5423, and GS-2872 through the ART restart date.

ART Restart Date is defined as the date resuming baseline oral ART or compatible regimen.

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, CD4+ cell count, CD8+ cell count, CD4 %, Hematology, Chemistry, Lipid Panel, Urinalysis, Urine Chemistry, Urine Pregnancy Laboratory Tests, Vital Signs, Weight and ECG are provided in Table 3-2 to Table 3-4.

Table 3-2. Analysis Windows for HIV-1 RNA

Visit ID	Nominal Day	Lower Limit	Upper Limit
Day 1 (Baseline)			1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	175
Week 26	182	176	224
Week 38	266	225	315
Week 52	364	316	413

Table 3-3. Analysis Windows for CD4+ cell count, CD8+ cell count, Chemistry, Hematology, Urinalysis, Vital Signs, and Weight

Visit ID	Nominal Day	Lower Limit	Upper Limit
Day 1 (Baseline)			1
Week 4	28	2	56
Week 12	84	57	133
Week 26	182	134	224
Week 38	266	225	315
Week 52	364	316	413

Table 3-4. Analysis Windows for ECG

Visit ID	Nominal Day	Lower Limit	Upper Limit
Day 1 (Baseline)			1
Week 26	182	2	273
Week 52	364	274	413

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, whereas a time-to-event analysis would not require 1 value per analysis window.

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 date 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 (eg, 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 counts 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 worse severity will be taken for categorical data, unless otherwise specified.

- For baseline HIV-1 RNA, the latest (considering both date and time) record(s) on or prior to the first dose date and time of study drug will be selected. For postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both "HIV RNA Taqman 2.0" and "HIV RNA 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 "HIV RNA Repeat" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA Taqman 2.0" 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 participant enrollment will be provided by treatment group and total for each country, investigator within a country, and overall. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A summary of participant disposition will be provided by treatment group and total based on all screened participants. This summary will present the number of participants screened, the number of subjects who did not meet eligibility criteria and were not randomized, the number of participants who met all eligibility criteria but were not randomized with reasons participants not randomized, the number of participants randomized but never dosed (if applicable), number of participants in the Safety Analysis Set and the number of participants in each of the following categories as applicable:

- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Continuing study
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For summary, participants with study drug premature discontinuation are defined as participants who were answered "No" to "Did subject complete study drug dosing as specified per protocol?" and had a discontinuation reason other than "Investigator Discretion" (with comment of "Due to Clinical hold") in Study Drug Completion eCRF).

Participants who prematurely discontinued study are defined as participants who answered 'No' to "Did the subject complete the protocol-planned duration of the study?" in Study Completion eCRF)

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, a flowchart will be provided to depict the disposition.

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

4.2. Extent of Study Drug Exposure and Adherence

Study drug administration and study drug dispensing information will be collected in the Study Drug Administration and Study Drug Accountability eCRFs. Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug if applicable.

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be summarized for LA regimen period and the whole study period, respectively. Due to long acting feature of study drug, duration of follow-up to study drug will consider the prolonged exposure of LA study drug (ie, SC LEN, GS-5423, GS-2872) after the last dose date of study drug through the ART restart date or the end of study, respectively.

For long acting regimen period analysis, last exposure date of LA regimen is defined in Section 3.8.1 for participants who prematurely discontinued study drug or completed study drug.

Duration of study drug exposure for long acting regimen period is defined as (the last exposure date of LA regimen – the first dose date + 1), and duration of exposure will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

For whole study period analysis, last exposure date are defined in Section 3.8.1 for participants who prematurely discontinued study or completed study. For the calculation of the duration of exposure to study drug, the data cut date will be used to impute the last exposure date for participants who are still on study at the time of the data cut date.

Duration of study drug exposure for the whole study period will be defined as (the last exposure date – the first dose date + 1), and duration of exposure will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Duration of exposure will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of participants exposed and remained through the following time periods: 1 day, 2 days, 4 weeks (28 days), 8 weeks (56 days), 16 weeks (112 days), 24 weeks (168 days), 26 weeks (182 days), 30 weeks (210 days), 34 weeks (238 days), etc. Summaries will be provided based on the Safety Analysis Set for LA regimen period and for whole study period separately. No inferential statistics will be provided.

4.2.2. Adherence to Study Drug

4.2.2.1. Adherence to Oral Study Drug (Oral LEN)

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

Adherence (%) of oral study drug will be calculated as follows:

$$\text{Adherence (\%)} = 100 \times \frac{Total \text{ No. of pills taken}}{\text{Total No. of pills prescribed}}$$

The number of pills taken for the study drug = number of pills dispensed minus the number of pills returned. The number of pills prescribed is the number of pills dispensed.

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

Adherence will be calculated for each participant for the entire dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinued study drug or using all available data for participants ongoing by the data cut date.

Descriptive statistics for adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number will be provided for participants who return at least 1 bottle of oral study drug, and who have calculable adherence in the Safety Analysis Set. No inferential statistics will be provided.

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized. The summary will present the number and percentage of participants who did not meet at least 1 eligibility criterion and the number of participants who did not meet specific criteria based on the Safety Analysis Set. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations and number of important protocol deviations by deviation category (eg, eligibility criteria, informed consent) will be summarized by treatment group and total for the Safety Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, sex at birth, gender identity, sexual orientation, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by treatment group and overall 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.

Statistical comparison across treatment groups will be performed. For categorical data, the Cochran-Mantel-Haenszel (CMH) test will be used to compare across treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare across treatment groups.

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

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics for participants in the Safety Analysis Set:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4 cell counts (/uL)
- CD4 cell counts categories (/uL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- Mode of infection (HIV risk factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)
- Duration of baseline ARV medication

Statistical comparison across treatment groups will be conducted similarly as described for the demographic and baseline characteristics. A by-participant listing of other baseline characteristics will be provided by participant ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening. Medical history data will be coded and listed.

6. EFFICACY ANALYSES

Secondary endpoints of this study include efficacy endpoints as described below. For efficacy analysis, except for FDA-defined snapshot endpoints, two sets of analysis will be conducted unless otherwise specified: LA regimen period analysis and whole study period analysis.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint of this study is Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 26 as defined by the FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}.

6.1.2 US FDA-Defined Snapshot Algorithm

The analysis window at Week 26 is defined as from Study Day 176 to Study Day 224, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to the earliest date of (196 days [28 weeks] after the dose date of complete long acting regimen, date of restarting ART)) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL:** this includes participants who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 26 analysis window
- **HIV-1 RNA ≥ 50 copies/mL:** this includes participants
  a) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 26 analysis window, or
  b) Who do not have on-treatment HIV-1 RNA data in the Week 26 analysis window and
     i) Who discontinue study drug prior to or in the Week 26 analysis window due to lack of efficacy, or
     ii) Who discontinue study drug prior to or in the Week 26 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL, or
     iii) Who discontinue study drug prior to or in the Week 26 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL.

- **No Virologic Data in the Week 26 Window:** this includes participants who do not have on-treatment HIV-1 RNA data in the Week 26 analysis window because of the following:

  a) Discontinuation of study drug prior to or in the Week 26 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or

  b) Discontinuation of study drug prior to or in the Week 26 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,

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

The flowchart of the US FDA-defined snapshot algorithm is provided in Appendix 2.

The Week 26 virologic outcomes for the US FDA-defined snapshot algorithm will be listed.

Note, for switch trials, the US FDA-defined snapshot algorithm classifies participants who discontinue study drug due to AE or death and have the last available on-treatment HIV-1 RNA value ≥ 50 copies/mL in the "HIV-1 RNA ≥ 50 copies/mL" category. For treatment naïve study population, these participants will be classified in the "No Virologic Data in the Week 26 Window" category.

6.1.3 Analysis of the Primary Efficacy Endpoint

The Primary analysis of the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL as determined by the US FDA-defined snapshot algorithm at Week 26 will be based on the FAS. The point estimate of treatment difference in the percentage of participants with HIV-1 RNA ≥ 50 copies/mL and the associated 2-sided 95% CI will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

The 2-sided Fisher's exact test will also be used to compare the percentages of participants between treatment groups.

A secondary analysis based on the PP analysis set will also be performed. Subjects excluded from the PP analysis set will be determined before database lock.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of the Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 as defined by the FDA-defined snapshot algorithm

- Change from baseline in CD4+ cell counts at Weeks 26

6.2.2. Analysis of the Secondary Efficacy Endpoints

6.2.2.1. Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL as Determined by US FDA-defined Snapshot Algorithm

Proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 26 as determined by US FDA-defined snapshot algorithm will be analyzed based on the FAS and the PP analysis sets, similarly to the primary efficacy endpoint.

The analyses for the above endpoint will be conducted using the FAS and the PP analysis set, respectively.

6.2.2.2. Analysis of CD4+ cell counts

The changes from baseline in CD4+ cell count at Week 26 and other visits will be summarized by treatment group and overall for FAS using descriptive statistics. The change from baseline in CD4+ cell count will also be summarized up to the visits with available data for each period analysis.

The absolute values of CD4 cell counts will be also summarized by treatment group and overall similarly. The analyses of CD4 cell counts and their changes from baseline will be conducted using the FAS.

The mean and 95% CI of change from baseline in CD4+ cell count over time by treatment groups and overall will be plotted for the FAS.

CD4+ cell counts over time in individual participants will be plotted by treatment groups and overall.

6.3. Other Efficacy Endpoints

6.3.1. Definition of the Other Efficacy Endpoints

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 26 as defined by 2 different missing data imputation methods specified in Section 6.3.2.
- The change from baseline in CD4 percentage (%) at Week 26

6.3.2. Analysis of the Other Efficacy Endpoints

6.3.2.1. Analysis of Proportion of Participants with HIV-1 RNA < 50 copies/mL by Missing = Failure and Missing = Excluded Approaches

Number and percentage of participants with HIV-1 RNA < 50 copies/mL by visit will be analyzed using the following 2 methods for imputing missing HIV-1 RNA values:

- Missing = Failure (M = F):

  In this approach, missing data will be treated as virologic failure and summarized into the "missing" category (see list of HIV-RNA categories below). Results will be summarized by treatment group and total for all visits up to Week 26.

- Missing = Excluded (M = E):

  In this approach, missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the 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.

For both M = F and M = E analyses, the number and percentage of participants with HIV-1 RNA in the following categories will be summarized based on the FAS:

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 copies/mL Not Detectable
    - < 20 copies/mL Detectable
  - 20 to < 50 copies/mL
- 50 to < 200 copies/mL
- 200 to < 400 copies/mL
- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL
- Missing (only applicable to M = F analysis)

The proportion of participants with HIV-1 RNA < 50 copies/mL as defined by the 2 different missing data imputation methods will be analyzed using the same statistical method applied to the primary endpoint. In addition, the 95% CI of the proportion of participants with HIV-1 RNA < 50 copies/mL within each treatment will be provided using the Clopper-Pearson Exact method.

For the M = F analysis, results will be summarized by treatment group for all visits up to Week 26 and for LA regimen period analysis only. For the M = E analysis, results will be summarized by treatment group for all visits with available data for each period analysis.

For the M = F analysis, the proportion of subjects with HIV-1 RNA < 50 copies/mL will be

plotted by treatment group for all visits up to Week 26 using the FAS.

6.3.2.2. Analysis of CD4%

The change from baseline in CD4 percentage will be based on the FAS and summarized up to the visits with available data for each period analysis using descriptive statistics.

6.4. Changes from Protocol-Specified Efficacy Analyses

No change from protocol-specified efficacy analysis is planned.

7. SAFETY ANALYSES

The primary objective of this study is to evaluate the safety and tolerability of a combination of the bNAbs GS-5423 and GS-2872 in combination with the HIV capsid inhibitor LEN, and the primary endpoint of this study is incidence of treatment-emergent SAEs through Week 26. The second endpoint of this study includes incidence of treatment-emergent AEs through Week 26.

Safety data will be summarized for participants in the Safety Analysis Set for the whole study period analysis and for participants in the Safety Analysis Set for LA regimen for LA regimen period analysis, separately, unless otherwise specified. All collected data will be included in data listings.

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (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, 2, 3, 4, or 5 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

Related AEs are those for which the investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment.” Relatedness to each study drug is justified by investigator and recorded on AE eCRF, for example, relatedness to Oral LEN is which investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment Oral LEN”. 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. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs 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 Global Patient Safety (GLPS) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) for whole study period analysis are defined as follows:

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

For LA regimen period analysis, the definition of TEAE is the same except the last exposure date of LA regimen after permanent discontinuation of the study instead of the last exposure date after permanent discontinuation of the study will be used for defining TEAEs.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dose 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 as follows:

- Participants who receive any injection or infusion drug: the AE onset date is the same as or after the month and year (or year) of the first dose date of study drug
- Participants who do not receive any injection or infusion drug (for whole study period analysis):
  - The AE onset is the same as or after the month and year (or year) of the first dose date of study drug, and
  - The AE onset date is the same as or before the month and year (or year) of the last exposure date

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

When calculating the duration of event or time to onset, the following imputation rule will be used:

Missing start month/day: Jan 1/first day of the month will be used unless this is before the start date of study drug; in this case the study drug start date will be used;

Missing stop month/day: Dec 31/last day of the month will be used, unless this is after the last study date; in this case the last study date will be used.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set or Safety Analysis Set for LA regimen, and will be summarized separately for the whole study period analysis and LA regimen period analysis.

For each period analysis, 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 by treatment group and total. All deaths observed in the period will also be included in this summary. The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC and PT and by PT only for the following AE categories:

- TEAEs
- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-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 death (by SOC and PT only)
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to premature discontinuation of study

Multiple events will be counted only once per participant in each summary. For summaries by SOC and PT, AEs will be summarized and listed first in alphabetical order of SOC and then by PT in descending order of total frequency within each SOC. For summarizes by PT only, AEs will be summarized and listed by PT in descending order of total frequency. 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 period.

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

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

For each listing, whether the event is treatment emergent will be indicated.

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Study Drug Related Injection Site Reactions and Infusion Related Reactions

Additional analysis of AEs will be performed for injection site reaction (ISR) and infusion related reaction (IRR), respectively, as defined per eCRF (ie, AE with"Yes' answer to "Is this part of an infusion-related reaction?" or "Is this part of an injection site reaction?" in AE CRF, respectively). The following summaries will be provided for LA regimen period analysis only.

- Number of participants received any injection or infusion
- Number and percentage of participants with study drug related ISRs or IRRs
- Number and percentage of participants with study drug related ISRs or IRRs by grade
- Number and percentage of participants with study drug related ISRs or IRRs by PT

The denominator for the percentage calculation will be based on the number of participants received at least one injection or infusion in Safety Analysis Set .

Duration of the ISR will also be calculated and summarized. Duration of a given ISR event is defined as the ISR stop date minus the ISR onset date plus 1 day. For ISRs with ongoing stop date, stop date will be imputed as last study date or data cut date, whichever is the earliest. Duration of ISR events in days will be summarized by PT and overall using descriptive statistics. Duration of a given IRR event is defined as the IRR stop date minus the IRR onset date plus 1 day, and duration of IRR will be listed also.

By-participant listings for ISRs orIRRs will be provided.

7.1.7.2. Study Drug Related Injection Site Induration and Nodules

Percentage of ongoing and resolved study drug releated "Injection Site Induration" (one of preferred terms of ISR) will be summarized at both subject-level and event-level.

For the subject-level summary, if a subject had more than one injection site indurations, the subject will be counted in the "Ongoing" category unless all study drug releated injection site induration events have been resolved.

For the event-level summary, duration of the resolved events will be summarized using descriptive statistics.

Study drug related "Injection Site Nodules" (another preferred term of ISR) will be summarized in the same manner as defined for study drug releated injection site induration.

A by-subject listing for study drug related injection site induration and nodules and the corresponding duration will be provided.

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the whole study period and LA regimen period analysis, respectively. Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods.

For whole study period analysis, summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last exposure date for subjects who have permanently discontinued study, or all available data at the time of the database snapshot for subjects who were ongoing on study at the time of an interim analysis.

For LA regimen analysis, summaries of laboratory data will be provided for the Safety Analysis Set for LA regimen and will include data collected up to the last exposure date of LA regimen for subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot for subjects who were ongoing on study drug at the time of an interim analysis.

Calcium Corrected for Albumin

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

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

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

Estimated Glomerular Filtration Rate

The following formulae will be used to calculate the estimated glomerular filtration rate using Cockcroft-Gault formula ($eGFR_{CG}$):

$eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72),

where weight is total body mass in kilograms and SCr is serum creatinine.

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.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory test 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 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 Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, 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.

For triglycerides, LDL (4^{th} generation), and cholesterol, toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

For whole study period analysis, treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline visit, up to last exposure date for participants who permanently discontinued study, or the last available date in the database snapshot for participants who were still on study at the time of an interim analysis.

For LA regimen period analysis, treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline visit, up to last exposure date of LA regimen for participants who permanently discontinued study drug, or the last available date in the database snapshot for participants who were still on treatment at the time of an interim analysis.

If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed at any postbaseline visit 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, for the whole study period and LA regimen period, separately.

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

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

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

A by-participant listing of treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities, respectively, will be provided by participant 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 and abnormal flags displayed.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided for the whole study period and LA regimen period by treatment group and total for body weight, BMI and vital signs as follows:

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

A baseline value will be defined as the last available value collected on or prior to the first dose date 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

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The WHO preferred name and drug code will be attached to the clinical database.

7.4.1. Nonstudy Drug Antiretroviral Medications

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

Antiretroviral medications at baseline will be summarized by ARV category and drug name. Antiretroviral medications at baseline are defined as the ARV medications taken on or up to 2 day prior to first dose date of study drug.

7.4.2. Prior and Concomitant Non-ARV Medications

Concomitant non-ARV medications are defined as non-ARV medications taken while a subject took study drug. Use of concomitant medications from Study Day 1 up to the last exposure date for whole study period analysis and last exposure date for LA regimen for LA regimen period analysis, will be summarized (number and percentage of subjects) by treatment group and total, and by preferred name. Multiple drug use (by preferred name) will be counted only once per subject. The summary will be sorted alphabetically by preferred drug name. For drugs with the same frequency, sorting will be done alphabetically.

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-ARVs 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 exposure date (or last exposure date for LA regimen for LA regimen period analysis)

The month and year of stop of the medication is before the first dose date of study drug

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

Summaries of non-ARV concomitant medications will be based on the Safety Analysis Set. No formal statistical testing is planned. A by-subject listing for all non-ARV concomitant medications including prior medication will be listed and sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

The investigators' assessment of ECG results are collected.

A shift table of the investigators' assessment of ECG results at each scheduled postbaseline visit compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No inferential statistics will be provided.

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

7.6. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy during the study.

7.7. Changes from Protocol-Specified Safety Analyses

No change from protocol-specified safety analyses is planned.

8. REFERENCES

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

9. SOFTWARE

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

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

Phoenix WinNonlin® 7.0 Pharsigh Corporation, Princeton, NJ, USA.

10. SAP REVISION

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

11. APPENDICES

Appendix 1. Study Procedures Table

			Treatment Visits Window (± 3 Days)											Follow-up Visits Window (± 6 Days)	
Study Procedure	**Screening[a]**	**Day 1**	**Day 2**	**Day 8**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 26**	**Wk 38**	**Wk 52**	**ET**	**Post-ET 30-, 90-, and 180-Day FU[b]**
Written Informed Consent	X														
Medical History	X														
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X	X												X	
Focused Physical Examination					X		X				X	X	X		X
Height	X														
Weight	X	X			X		X				X	X	X	X	X
Vital Signs[c]	X	X			X		X				X	X	X	X	X
Proviral DNA Phenotype	X														
Bulk Viral Outgrowth Phenotype and Proviral DNA Genotype	X														
Chemistry	X	X			X		X				X	X	X	X	X
Hematology	X	X			X		X				X	X	X	X	X
Coagulation	X														
Thyroid Function	X	X			X		X				X	X	X		
CD4+, CD8+ Cell Count, CD4/CD8 Ratio	X	X			X		X				X	X	X	X	X

			Treatment Visits Window (± 3 Days)											Follow-up Visits Window (± 6 Days)	
Study Procedure	**Screening[a]**	**Day 1**	**Day 2**	**Day 8**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 26**	**Wk 38**	**Wk 52**	**ET**	**Post-ET 30-, 90-, and 180-Day FU[b]**
Serum Pregnancy Test	X				X		X					X	X	X	X
FSH[d]	X														
Urinalysis	X	X			X		X				X	X	X	X	X
Urine Pregnancy Test		X													
HBV & HCV Serology	X														
HIV-1 RNA	X	X			X	X	X	X	X	X	X	X	X	X	X
HIV-1 Genotype/Phenotype[e]															
HIV Reservoir Assay		X											X		
eGFR	X	X			X		X				X	X	X	X	X
ECG	X	X									X		X		
Immune Biomarker Collection		X			X						X	X	X		
Plasma Storage Samples for Virology Testing		X			X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Assessment Serum Sample		X			X		X				X	X	X		
PD Biomarkers: PBMC, Whole Blood, Serum, Plasma		X			X						X	X	X		
Serum PK samples (GS-5423 & GS-2872)[f]		X												X	X
Plasma PK Sample for LEN[g]		X												X	X
Single PK Sample (GS-5423 & GS-2872)					X	X	X	X	X	X	X	X	X		

			Treatment Visits Window (± 3 Days)											Follow-up Visits Window (± 6 Days)	
Study Procedure	**Screening[a]**	**Day 1**	**Day 2**	**Day 8**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 26**	**Wk 38**	**Wk 52**	**ET**	**Post-ET 30-, 90-, and 180-Day FU[b]**
Single Plasma PK Sample for LEN					X	X	X	X	X	X	X	X	X		
Optional PK Substudy Sample		X	X	X											
Randomization		X													
LEN Oral Administration[h]		X	X												
LEN SC Administration[i]		X													
GS-5423 IV Infusion Administration[i]		X													
GS-2872 IV Infusion Administration[i]		X													
Optional Pharmacogenomic Sample[j]															

a. For the Primary Cohort, screening procedures will be conducted in 2 parts: Part 2 will be performed once results of bNAb sensitivity testing from Part 1 are reviewed and participant is deemed eligible to proceed. For the optional Pilot Cohort, participants will be selected by the sponsor from the previously screened/failed participants in the Primary Cohort and will directly proceed to Screening Part 2 (no need to repeat Screening Part 1).
b. Refer to Section 6.5.1 for Post-ET 30-, 90-, and 180-Day follow-up visits.
   - Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer patient to an appropriate HIV treatment facility.
c. Vital signs: blood pressure, pulse, respiration rate, and temperature. On Day 1, vital signs should be recorded prior to start of study drug administration and 30 minutes (± 10 minutes) after completion of the GS-2872 infusion.
d. Serum FSH test (required for female participants < 54 years of age who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure; see Appendix 5)
e. HIV-1 genotype and phenotype testing for participants with virologic failure. Refer to Section 6.8.2.
f. PK serum samples will be collected in all participants for GS-5423 and GS-2872 as follows:
   - The exact time of study drug administration and the exact time points (date and time) of collection of plasma samples must be carefully recorded.
   - Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872)
   - For ET visit, only single PK sample collection is required

g. PK plasma samples for LEN will be collected in all participants as follows:
   - PK samples should be drawn from a separate catheter in the opposite arm from the one used for GS-5423 and GS-2872 IV infusion to avoid contamination.
   - Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872)
   - For ET visit, only single PK sample collection is required

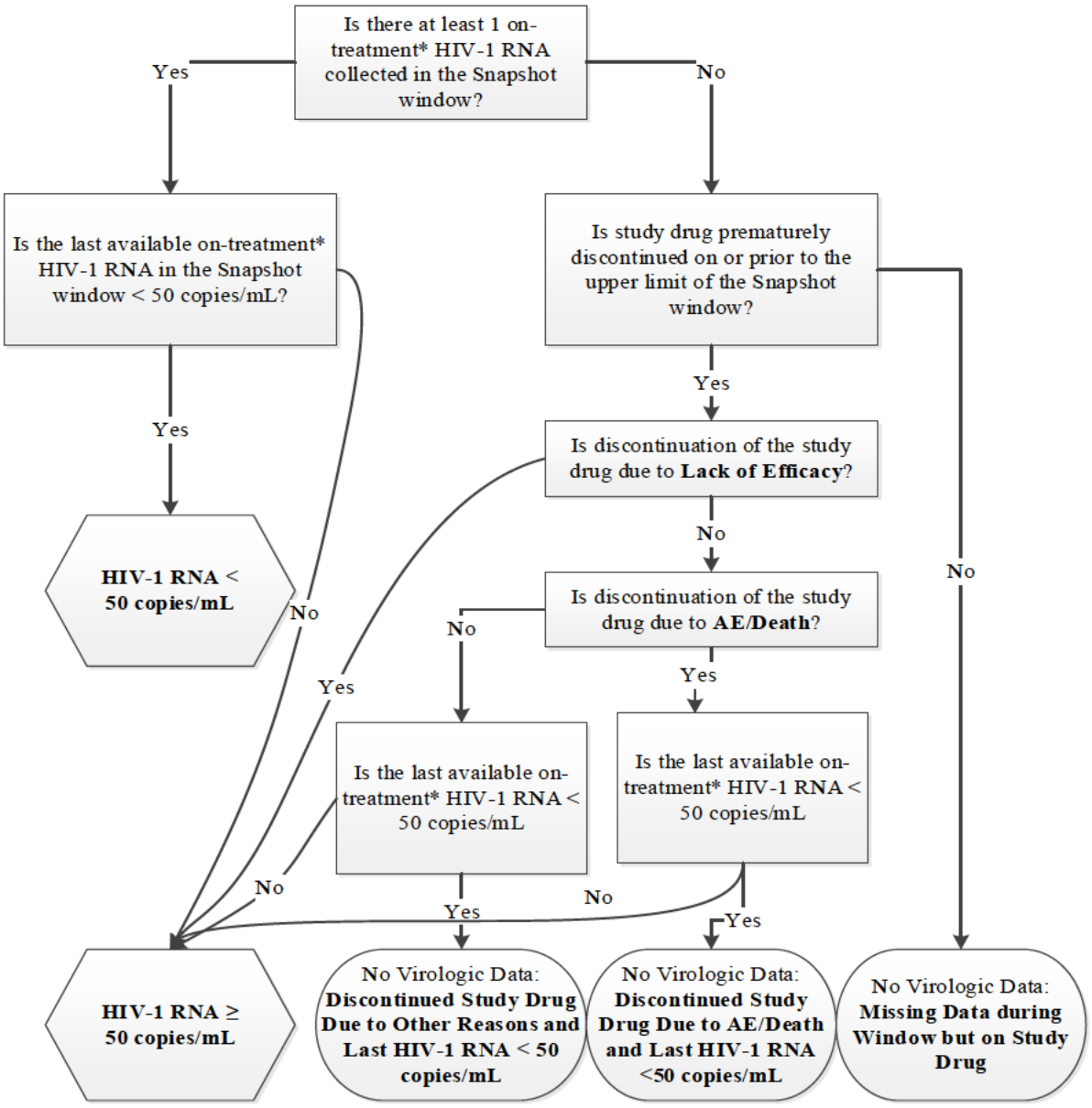
h. Participants will take oral LEN for loading on Day 1 at the clinic and self-administer on Day 2 at home, unless participating in the Optional PK Substudy.

i. On Day 1, participants will receive study treatment consisting of oral and SC LEN, followed by GS-5423, then GS-2872, each administered as separate IV infusions. Infusion of GS-2872 will begin at least 15 minutes following, and up to 1 hour after, the completion of GS-5423 IV infusion. Participants will remain in a monitored clinical setting for at least 30 minutes after completion of GS-2872 infusion, and vital signs will be recorded 30 minutes (± 10 minutes) after completion of GS-2872 infusion. For the Day 1 visit, all study drugs are to be administered on the same day. On Day 2, the participant will self-administer 2 tablets of oral LEN for loading (2 × 300 mg) at home at approximately the same time oral LEN for loading was administered on Day 1.

j. If consent for optional pharmacogenomic testing is obtained, then a sample is to be collected at the Day 1 visit, but may be collected at any time during the study or at a separate poststudy visit, if necessary.

Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Long Acting Switch Trial)

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



*On-Treatment HIV-1 RNA data include all HIV-1 RNA data collected up to the earliest date of (196 days [28 weeks] after the dose date of complete long acting regimen, date of restarting ART).

The dose date of complete long acting regimen refers to the date of dosing with complete long acting drugs (GS-5423, GS-2872, and SC LEN) (ie, Day 1).

Participants with study drug premature discontinuation are defined as participants who were answered "No" to "Did subject complete study drug dosing as specified per protocol?" and had a discontinuation reason other than "Investigator Discretion" (with comment of "Due to Clinical hold") in Study Drug Completion eCRF).

The date of study drug premature discontinuation is the last exposure date of LA regimen for participants who prematurely discontinued study drug.

Appendix 3. Programming Specifications

1) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

   CMH test for nominal variable (Y), the p-value from the general association test should be used for nominal variables:

```
proc freq;
tables trt * Y /cmh; /*general association test*/
run;
```

   CMH test for ordinal variable (Y), the p-value from the row mean score test should be used for ordinal variables:

```
proc freq;
tables trt * Y / cmh2 ; /*row mean score test*/
run;
```

   Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation two-sided test should be used for continuous variables:

```
proc npar1way wilcoxon;
class trt;
var Y;
run;
```

2) Efficacy analyses:

   a) For categorical efficacy response (eg, Participants with HIV-1 RNA < 50 copies/mL or Participants with HIV-1 RNA ≥ 50 copies/mL as determined by US FDA-defined snapshot algorithm, M=F, or M=E Analyses): the proportion difference between two treatment groups and its 95% CIs are calculated based on the an unconditional exact method using 2 inverted 1-sided tests in SAS v9.3 or above.

   b) The following SAS code will be used to compute cell counts and confidence interval.

```
data example;
input  grp trt01a $  outcome $ count ;

datalines;
1       Treat-A        2-Fail        1
1       Treat-A        1-Succ      189
1       Treat-B        2-Fail        4
1       Treat-B        1-Succ       88
run;

proc freq data = example;
table trt01a*outcome /riskdiff(CL=(exact)) alpha=0.05;
weight count; exact RISKDIFF(METHOD=SCORE);
```

```
output out=ciexact(keep=_RDIF1_ XL_RDIF1 XU_RDIF1 _RSK11_  _RSK21) riskdiff;
run;
data final(keep=A1 B1 Estimate LowerCL UpperCL ocharc1);
set ciexact;
label Estimate ="Percentage Difference"
LowerCL = "95% Lower Confidence Limit"
UpperCL = "95% Upper Confidence Limit"
A1 = "Percentage of Success in Treat-A"
B1 = "Percentage of Success in Treat-B";
Estimate=100*_RDIF1_;
LowerCL = 100*XL_RDIF1;
UpperCL = 100*XU_RDIF1;
A1 = 100*_RSK11_;
B1 = 100*_RSK21_;
ocharc1 = right(compress(put(Estimate,8.1)) || '% (' || compress(put(LowerCL,8.1)) || '%
to ' || compress(put(UpperCL,8.1)) || '%)');
run;
```

c) The 95% CI for percentage estimate of HIV-1 RNA < 50 copies/mL for each treatment is calculated based on the Clopper-Pearson exact method.

d) Fisher's exact test for categorical efficacy response (eg, HIV-1 RNA < 50 copies/mL by US FDA-defined snapshot algorithm), where *trtgrp* is the treatment, and *response* is the categorical efficacy response. P-value from 2-sided Fisher's exact test should be used

```
proc freq data=adeff;

      tables trtgrp*response/fisher; /*p value from Fisher's exact
test*/

run;
```

e) For figures, if at a visit where n (sample size) for any treatment group <= 5, data for that treatment group will not be displayed at the visit in figure (except the Kaplan-Meier figure), but all data will be included in the corresponding table summary.

f) 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.

g) Screen failure subjects are the subjects who were 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, or subjects who have missing answer to any inclusion or exclusion criteria.

h) Baseline ARV medication is defined as:

Using the ARV raw dataset, include all prior ARVs (where ARV.CMSCAT =’Prior ARV”), taken on or up to 2 day prior to first dose date (or randomization date if not treated), i.e. End date of ARV >= first dose date -2.

i) For last dose date calculation:

— For participants who receive injection or infusion, the last dose date is defined as the latest nonmissing end date of the study drug used.

— For participants who do not receive injection or infusion, the last dose date is defined as the last dose date of oral LEN.

— If the date of last dose is incomplete or missing (eg, due to lost to follow-up), the latest nonmissing study drug start dates the clinic visit dates, and the laboratory visit dates excluding the dates of any follow-up visits will be used to impute the last dose date.

GS US-536-5816-Week26-SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	PPD eSigned	04-Aug-2022 02:11:25
PPD	PPD eSigned	05-Aug-2022 00:00:34