STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Randomized, Open-label, Study to Evaluate the Safety and Efficacy of Broadly Neutralizing Antibodies (bNAbs) GS-5423 and GS-2872 in Combination With the Capsid Inhibitor Lenacapavir as Long-Acting Treatment Dosed Every 6 Months in Virologically Suppressed Adults With HIV-1 Infection
Name of Test Drug:	Lenacapavir (LEN; GS-6207), Teropavimab (TAB, GS-5423) and Zinlirvimab (ZAB, GS-2872)
Study Number:	GS-US-536-5939
Protocol Version (Date):	Amendment 3 (13 May 2024)
Analysis Type:	Week 52 Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	27 Mar 2025
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
NAb	Neutralizing antibody
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
SBR	Stay on baseline regimen
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir diphosphate

PHARMACOKINETIC ABBREVIATIONS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time
AUC_{last}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
$AUC_{0\text{-}26wk}$	area under the plasma/serum concentration versus time curve from time zero to week 26
CL	clearance
C_{26wk}	Plasma/serum concentration of drug at Week 26
C_{max}	maximum observed plasma/serum concentration of drug
$C_{max\ day1}$	maximum observed plasma/serum concentration of drug at Day 1
$t_{½}$	estimate of the apparent terminal half-life of the drug in plasma/serum, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of last observed quantifiable plasma/serum concentration of drug
T_{max}	time (observed time point) of C_{max}
$T_{max\ day1}$	time (observed time point) of $C_{max\ day1}$
V_{ss}	volume of distribution at steady state

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 52 interim analysis for the Study GS-US-536-5939. The analysis will be performed when all participants have completed Week 52 visit or have prematurely discontinued from study.

This SAP is based on the study protocol amendment 3 dated 13 May 2024 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the Week 52 primary analysis.

1.1. Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
• To evaluate the efficacy of switching to a regimen of lenacapavir (LEN, Sunlenca®), GS-5423, and GS-2872 versus continuing on baseline oral antiretroviral (ARV) therapy (ART) as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26	• Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of switching to a regimen of LEN, GS-5423, and GS-2872 versus continuing on baseline oral ART as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 • To evaluate the efficacy of switching to a regimen of LEN, GS-5423, and GS-2872 versus continuing on baseline oral ART as determined by the proportion of participants maintaining virologic suppression (HIV-1 RNA < 50 copies/mL) at Weeks 26 and 52	• Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 as determined by the US FDA-defined snapshot algorithm • Proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 and 52 as determined by the US FDA-defined snapshot algorithm • Changes from baseline in CD4+ T-cell counts at Weeks 26 and 52 • Proportion of participants experiencing treatment-emergent adverse events (TEAEs)
Secondary Objectives	**Secondary Endpoints**
• To evaluate CD4+ T-cell counts at Weeks 26 and 52 • To evaluate the safety and tolerability of the 2 treatment groups • To evaluate the pharmacokinetics (PK) of GS-5423, GS-2872, and LEN • To evaluate the immunogenicity of GS-5423 and GS-2872	• Trough concentrations at Weeks 26 and 52 and PK parameters (AUC_{0-t}, AUC_{last}, $t_{1/2}$, C_{max}, and T_{max}) for GS-5423, GS-2872, and LEN as appropriate • Incidence of anti–GS-5423 and anti–GS-2872 antibodies

1.2. Study Design

This is a Phase 2, randomized, open-label, active-controlled, multicenter study to evaluate the safety and efficacy of the long-acting regimen of LEN, TAB (ie, GS-5423), and ZAB (ie, GS-2872). The study will include approximately 75 participants with sensitivity to GS-5423 and GS-2872 by protocol-defined criteria, who meet all eligibility criteria, and who will be randomized without stratification in a 2:1 ratio to Treatment Groups 1 and 3.

1.2.1. Randomized Phase

Participants in Treatment Group 1 will receive the long-acting regimen consisting of LEN, GS-5423, and GS-2872.

Participants will discontinue their baseline oral ART following administration of the complete study drugs on Day 1 (SC LEN 927 mg, oral LEN 600 mg, and IV infusions of GS-5423 and GS-2872), and will self-administer oral LEN 600 mg at home on Day 2. Participants will also receive study drug (SC LEN and IV infusion of GS-5423 and GS-2872) at Week 26.

All participants in Treatment Group 1 will return to the study center for visits at Weeks 4, 12, 24, 26, 38, 50, and 52.

Participants in Treatment Group 3 will continue their baseline oral ART through Week 52. After Day 1, participants in Treatment Group 3 will return to the study center for visits at Weeks 12, 26, 38, 50, and 52.

Duration of treatment in the Randomized Phase is 52 weeks.

1.2.2. Extension Phase

At Week 52, participants in Treatment Group 1 who receive the study drug of LEN, GS-5423, GS-2872, and complete the study through Week 52 with HIV-1 RNA < 50 copies/mL at the preceding Week 50 visit will be given the option to participate in the study extension phase. In the study extension phase, participants will continue to receive their randomized study drugs every 26 weeks.

Participants who elect not to participate or are not eligible to participate in the extension phase will resume their baseline oral ART (or appropriate regimen selected by the investigator).

Participants in Treatment Group 3 who complete the study through Week 52 with HIV-1 RNA < 50 copies/mL at the preceding Week 50 visit and in the absence of confirmed VR (as defined in protocol section 6.3.9.2.1) throughout the randomized phase of the study will be given the option to participate in the extension phase and receive the study drugs of LEN, GS-5423, and GS-2872 every 26 weeks at the dose specified for Treatment Group 1. Treatment with LEN, GS-5423, and GS-2872 will start at Week 52 and at that time the baseline oral ART will be discontinued.

Details for study procedures could be found in Section 13 (Appendix 1).

Key Eligibility Criteria

HIV-1 infected participants who meet the following criteria:

- Between 18 and 65 years of age, inclusive, at screening.
- Body weight ≥ 40 kg at Screening Visit 2.
- On stable oral ART consisting of no more than 2 drug classes (with the exception of pharmacologic boosters cobicistat or ritonavir) for ≥ 1 year prior to Screening Visit 2. A change in ART regimen ≥ 28 days prior to Screening Visit 2 for reasons other than virologic failure (VF) (eg, tolerability, simplification, drug-drug interaction profile) is allowed.
- No clinically significant documented historical resistance to the current ART regimen with the exception of isolated nucleoside reverse transcriptase inhibitor mutations including M184V or ≤ 2 thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y, and/or K219Q).
- Plasma HIV-1 RNA < 50 copies/mL at Screening Visit 2.
- Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 12 months preceding Screening Visit 2 (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL). Virologic elevations of ≥ 50 copies/mL (transient detectable viremia or "blips") prior to screening are acceptable.
  - If HIV-1 sensitivity testing results are from > 12 months prior to screening (Inclusion Criterion 8), then documented plasma HIV-1 RNA < 50 copies/mL encompassing the time from sensitivity testing will be required.
- HIV-1 sensitivity results from screening or from the Study GS-US-536-5816 within 36 months prior to Screening Visit 2 meeting specific criteria:
  - Proviral phenotypic sensitivity to both GS-5423 and GS-2872 by the PhenoSense Assay (Monogram Biosciences). GS-5423 phenotypic sensitivity is defined as 90% inhibitory concentration (IC_{90}) ≤ 2 µg/mL; GS-2872 phenotypic sensitivity is defined as IC_{90} ≤ 2 µg/mL.
- CD4+ T-cell count ≥ 200 cells/µL at Screening Visit 2.
- 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.

1.3. Sample Size and Power

A sample size of 50 participants in Treatment Group 1 and 25 participants in Treatment Group 3 was chosen to estimate the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as determined by the US FDA-defined snapshot algorithm to allow for the planning of Phase 3 studies. This study is not formally powered for treatment comparison.

Assuming no failure (0%) in Treatment Group 3 at Week 26, the number of failures in Treatment Group 1 at Week 26 would need to be ≥ 8 (16%) for the 95% CI for the difference between treatment (Treatment Group 1 versus Treatment Group 3) in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 to exclude 0. Similarly, assuming 1 failure (4%) in Treatment Group 3 at Week 26, the number of failures in Treatment Group 1 would need to be ≥ 12 (24%) for the 95% CI for the difference between treatment (Treatment Group 1 versus Treatment Group 3) in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 to exclude 0. The 95% CI is estimated based on an exact unconditional method {Chan 1999}.

If the underlying incidence of a specific AE is 5%, there is a 92.3% chance of observing at least 1 AE among 50 participants in Treatment Group 1 and a 72.3% chance of observing at least 1 AE among 25 participants in Treatment Group 3.

2. TYPE OF PLANNED ANALYSIS

This statistical analysis plan describes the analysis planned for the Week 52 interim analysis.

2.1. Interim Analyses

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 and to support regulatory filings. Also, interim analyses may be used for publication and presentation at scientific meetings.

2.1.1. Week 52 Interim Analysis

In addition to the primary analysis, there will be 1 planned interim analysis – Week 52 interim analysis.

The Week 52 analysis will be conducted after all participants have completed their Week 52 visit or prematurely discontinued from study, outstanding data queries had been resolved or adjudicated as unresolvable, and the data had been cleaned and finalized for the analysis.

2.1.2. Data Monitoring Committee Analysis

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect participant welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will make recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

There will be 1 planned DMC analysis after approximately the first 50% of participants enrolled have completed their Week 12 visit or prematurely discontinued from the study drug. Safety data will be reviewed by the DMC without formal stopping rules. CCI [redacted]

In addition, if 4 or more participants in Treatment Group 1 experience confirmed VR (as defined in protocol section 6.3.9.2.1) before all participants reach Week 26, an ad hoc DMC meeting may be convened to assess the data.

A DMC meeting may be convened, and the supporting analyses conducted at other times during the study as deemed necessary. Further details will be provided in the DMC charter.

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

2.2. Primary Analysis

The primary analysis of the primary endpoint was conducted after all participants enrolled have completed the Week 26 visit or have prematurely discontinued study drug, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized for the analysis. This analysis of the primary endpoint will serve as the final analysis for this endpoint and will be used to evaluate the efficacy of the long-acting regimen consisting of LEN, GS-5423, and GS-2872.

2.3. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The Week 52 interim analysis will include all data collected from the randomized and the extension phases of the study. Only data collected in the randomized phase (ie, randomized phase data) will be summarized by treatment group (except that the "by-visit" summary will be up to Week 52 only), if not specified otherwise. Data collected from both phases will be included in data listings. Data included in each phase are defined as follows:

Randomized Phase Data

- For participants who do not enter the extension phase (ie, not treated in the extension phase), all available data are considered as the randomized phase data.

- For participants who enter the extension phase (ie, treated in the extension phase), randomized phase data are defined as data collected **up to** and including the first dose date of the extension phase with the exception as follows: for AEs, concomitant medications, pregnancy, and death, only data collected **prior to** the first dose date of the extension phase are included. For PK/ADA, data collected up to and including the predose timepoint on the first dose date of the extension phase is included.

Extension Phase Data

Extension phase data are only available from participants who enter the extension phase of the study. Extension phase data are defined as data collected **after** the extension phase first dose date with the exception as follows. For AEs, concomitant medications, pregnancy, and death, data collected **on or after** the extension phase first dose date are included. For PK/ADA data, data at postdose on Study Day 1 (EXT) if applicable or after Study Day 1 (EXT) is assigned to the Extension Phase.

In general, 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.

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 by treatment group.

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) or continued with their baseline ART regimen. For the FAS, all efficacy data will be included, unless specified otherwise. This is the primary analysis set for efficacy analyses.

3.1.3. Per Protocol Analysis Set

The Week 26 or Week 52 Per Protocol (PP) Analysis Set includes all participants in the FAS excluding participants who committed any major protocol violation, including the violation of key entry criteria.

Participants meeting any of the following criteria will be excluded from the Week 26 or Week 52 PP analysis set:

1) did not have on-treatment HIV-1 RNA in the Week 26 or Week 52 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 oral LEN doses on Day 1 or Day 2.

3) Any prior receipt of LEN or a bNAb for HIV-1 treatment (Exclusion criteria 1)

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 (Exclusion Criteria 3).

Table 3-1. Participants Excluded from Week 26 or Week 52 PP Analysis Set Due to Premature Discontinuation of Study Drug and/or Missing HIV-1 RNA Assessment in Week 26 or Week 52 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 or Week 52 Analysis Window	
		Yes	No
Yes	Due to Lack of Efficacy	+	+
	Due to Other Reasons	+	-
No		+	-

+ = Inclusion of Participants in Week 26 or Week 52 PP analysis set; - = Exclusion of Participants in Week 26 or Week 52 PP analysis set

The PP Analysis Sets are the secondary analysis sets for efficacy analysis.

3.1.4. Safety Analysis Set

The Safety Analysis Set includes all participants who were randomized and received at least 1 dose of any study drug (ie, study treatment, including LEN, GS-5423, GS-2872, or continued with their baseline ART regimen).

3.1.5. Pharmacokinetic (PK) Analysis Sets

The PK Analysis Sets include the follows:

- LEN PK Analysis Set includes all randomized participants who have received at least 1 dose of study drug, and have at least 1 nonmissing LEN concentration value reported by the PK laboratory test.
- TAB PK Analysis Set includes all randomized participants who have received at least 1 dose of study drug, and have at least 1 nonmissing GS-5423 concentration value reported by the PK laboratory test.
- ZAB PK Analysis Set includes all randomized participants who have received at least 1 dose of study drug, and have at least 1 nonmissing GS-2872 concentration value reported by the PK laboratory test.

3.1.6. Immunogenicity Analysis Sets

The Immunogenicity analysis sets include the follows:

- Anti-TAB Immunogenicity Analysis Set will include all randomized participants who have received at least 1 dose of study drug (GS-5423) and have had at least 1 nonmissing value for anti-GS-5423 evaluation.
- Anti-ZAB Immunogenicity Analysis Set will include all randomized participants who have received at least 1 dose of study drug (GS-2872) and have had at least 1 nonmissing value for anti-GS-ZAB evaluation.
- Anti-TAB and Anti-ZAB Immunogenicity Analysis Set will include all randomized participants who have received at least 1 dose of study drugs of GS-5423 and GS-2872 and have had at least 1 nonmissing value for both anti-TAB and anti–GS-ZAB evaluation.

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 others, 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: LEN + TAB + ZAB
- Treatment Group 3: SBR

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling participants
No covariates will be included in efficacy and safety analyses.

3.4. Examination of Participant Subgroups

The proportion of participants with HIV-1 RNA >= 50 or < 50 copies/mL at Weeks 26 and 52 as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be analyzed for the following participant subgroups (see Section 6.2.2.3 for details):

- Age (years): (a) < 50 and (b) ≥ 50
- Sex: (a) male and (b) female
- Race: (a) black and (b) nonblack
- Region: (a) US and (b) Ex-US

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made in this 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.

For missing last dose date of study drug, imputation rules are described in Appendix. 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 of non-PK data 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.

Natural logarithm transformation will be used for analyzing non-BLQ concentrations and PK parameters in intensive PK samples. Concentration values that are 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.

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 postdose time points:

- 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, Clast, Cmax, and Ctau) 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 Key Dates and Study Day

Study Day 1 (Randomized Phase) is defined as follows:

Participants randomized to treatment group 1: Study Day 1 is defined as the day when the first dose of any study drug (ie, oral LEN, SC LEN or infusion of [GS-5423, GS-2872]) is taken, as recorded on the Study Drug Administration eCRF (where study phase = "Randomized Treatment") or Study Drug Administration - Injection/Infusion eCRF.

Participants randomized to treatment group 3: Study Day 1 is defined as the Day 1 visit date recorded on the Visit Date eCRF.

Study Day 1 (Extension Phase) is defined as the day when the first dose of extension phase study drug (ie, oral LEN, SC LEN or infusion of [GS-5423, GS-2872])) is taken, i.e., the earliest of start date recorded on the Study Drug Administration eCRF (where study phase = "Extension Treatment") or Study Drug Administration - Injection/Infusion eCRF (at Week 52). This day will only be available for participants treated in the extension phase of the study.

Study Days are calculated relative to Study Day 1 of the randomized phase, and derived as follows:

- For postdose study days: Assessment Date – Study Day 1 (randomized phase) + 1
- For days prior to Study Day 1 (randomized phase): Assessment Date – Study Day 1 (randomized phase)

Last Dose Date (Randomized Phase) is defined for participants who prematurely discontinued or completed study drug according to the "Randomized Treatment" Phase of Study Drug Completion eCRF.

a) For participants randomized to treatment group 1, the last dose date is defined as the latest of the randomized study drug dose stop dates (ie, maximum of nonmissing end date of oral LEN recorded on the phase of "Randomized Treatment" in the study Drug Administration eCRF form and dose dates of GS-5423, GS-2872, and SC LEN at Day 1, Week 26 recorded in the Study Drug Administration - Injection/Infusion eCRF form).

b) For participants randomized to treatment group 3, the last dose date is defined as the latest stop date from baseline regimen component recorded on the "Current" ARV eCRF for the randomized phase of the study.

If the last dose date for randomized phase is missing for treatment group 3 (eg, only year of last dose date is known or completely missing due to lost to follow-up),

1) for participants entering extension phase, the day before study day 1 (extension)

or

2) for participants not entering extension phase, the latest of (nonmissing randomized study drug start dates and end dates, the clinical visit dates, and the laboratory visit dates, excluding the date of 30-day follow-up visit),

will be used to impute the last dose date of the randomized phase.

Last Dose Date of any LA regimen (Randomized Phase) refers to last dose date of any study drug of LA regimen (SC LEN, TAB, ZAB) administered in the randomized phase.

Last Dose Date of complete LA regimen (Randomized Phase) refers to last dose date of the complete long acting study drug regimen (ie, SC LEN + GS-5423 + GS-2872) administered in randomized phase.

Last Dose Date (Extension Phase) is defined for participants who prematurely discontinued or completed study drug according to the "Extension Treatment Phase" Study Drug Completion eCRF as the latest of the extension phase study drug end dates recorded on the "Extension Treatment Phase" Study Drug Administration eCRF or dose dates (on or after Week 52 visit) on Study Drug Administration - Injection/Infusion eCRF

This date will only be available for participants treated in the extension phase of the study.

Last Study Date is the latest of the randomized or extension phase (if available) study drug dose dates, stop dates, clinic visit dates, and/or the laboratory visit dates, including the post-study drug follow-up visit date, for participants who prematurely discontinued study or completed study according to the Study Completion eCRF.

Last Study Date (Randomized Phase) is 1) the last study date for participants who did not enter extension phase and prematurely discontinued study or completed study according to the Study Completion eCRF in the randomized phase; or 2) the Study Day 1 of extension phase for participants who entered the extension phase.

Last Exposure Date (Randomized Phase) is defined as follows for participants who prematurely discontinued or completed study drug according to Study Drug Completion eCRF. This date is defined considering the prolonged exposure of GS-5423, GS-2872 and SC LEN after the last dose date of GS-5423, GS-2872 and SC LEN. Last exposure date is utilized for summaries of extent of study drug exposure.

- Treatment Group 1:

CCI

- Treatment Group 3:

  — last exposure date is defined as the last dose date (randomized phase).

ART Restart Date is defined for treatment group 1 as the earliest ARV start date after permanent discontinuation of LA study regimen for participants who discontinued study drug.

Baseline Value is defined as the following by the treatment group that pariticipants were randomized to:

- Treatment group 1: the last value obtained on or prior to the first dose of the randomized phase.

- Treatment group 3: the last value obtained on or prior to the Study Day 1 (Randomized Phase).

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, 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 3-5.

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

Analysis Visit	Randomized Phase					
	LEN + GS-5423 + GS-2872 Group (Treatment Group 1)			SBR Group (Treatment Group 3)		
	Nominal Study Day	Visit Window Study Day		Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Baseline			1			1
Week 4	28	2	56	NA	NA	NA
Week 12	84	57	126	84	2	133
Week 24	168	127	175	NA	NA	NA
Week 26	182	176	224	182	134	224
Week 38	266	225	308	266	225	308
Week 50	350	309	357	350	309	357
Week 52	364	358	Min (406, Study Day 1 (Extension Phase))	364	358	Min (406, Study Day 1 (Extension Phase))

NA = Not applicable
For participants who entered extension phase, data after study day 1 (extension phase) are categorized under Analysis visit "Extension"; for participants who did not enter extension phase, data after the upper limit of Week 52 are categorized under "Post-Week 52".

Table 3-3. Analysis Visit Windows for Chemistry, Hematology, Urinalysis

Analysis Visit	Treatment Group 1			Treatment Group 3		
	Nominal Study Day	Visit Window Study Day		Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Baseline			1			1
Week 4	28	2	56	NA	NA	NA
Week 12	84	57	133	84	2	133
Week 26	182	134	224	182	134	224
Week 38	266	225	315	266	225	315
Week 52	364	316	Min (413, Study Day 1 (Extension Phase))	364	316	Min (413, Study Day 1 (Extension Phase))

For participants who entered extension phase, data after study day 1 (extension phase) are categorized under Analysis visit "Extension"; for participants who did not enter extension phase, data after the upper limit of Week 52 are categorized under "Post-Week 52".

Table 3-4. Analysis Visit Windows for Vital Signs, and Weight

Analysis Visit	Treatment Group 1			Treatment Group 3		
	Nominal Study Day	Visit Window Study Day		Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit
Baseline			≤ First Dose Date, if time not available ≤ First Dose Date/Time, if time vailable			1
Day 1 (0.5 h Postdose)	1	> First Dose Date/Time	1	NA	NA	NA
Week 4	28	2	56	NA	NA	NA
Week 12	84	57	133	84	2	133
Week 26	182	134	224	182	134	224
Week 38	266	225	315	266	225	315
Week 52	364	316	Min (413, Study Day 1 (Extension Phase))	364	316	Min (413, Study Day 1 (Extension Phase))

For participants who entered extension phase, data after study day 1 (extension phase) are categorized under Analysis visit "Extension"; for participants who did not enter extension phase, data after the upper limit of Week 52 are categorized under "Post-Week 52".
Vital signs: blood pressure, pulse, and temperature. On dosing days for LEN + GS-5423 + GS-2872, vital signs and weight were recorded prior to start of study drug administration (at the timepoint of "predose") and 30 minutes (± 10 minutes) after completion of both GS-5423 and GS-2872 infusion (at time point of "0.5 h postdose") if coadministered, or 30 minutes ((± 10 minutes) after the GS-2872 infusion if sequentially administered.

Table 3-5. Analysis Visit Windows for CD4+ cell count and CD4 %

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1
Week 12	84	2	133
Week 26	182	134	224
Week 38	266	225	315
Week 52	364	316	Min (413, Study Day 1 (Extension Phase))

For participants who entered extension phase, data after study day 1 (extension phase) are categorized under Analysis visit "Extension"; for participants who did not enter extension phase, data after the upper limit of Week 52 are categorized under "Post-Week 52".

Table 3-6. Analysis Visit Windows for ECG

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1
Week 26	182	2	273
Week 52	364	274	Min (413, Study Day 1 (Extension Phase))

For participants who entered extension phase, data after study day 1 (extension phase) are categorized under Analysis visit "Extension"; for participants who did not enter extension phase, data after the upper limit of Week 52 are categorized under "Post-Week 52".

Table 3-7. Analysis Visit Window for TSH

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline			1
Week 52	364	2	Min (546, Study Day 1 (Extension Phase))

For participants who entered extension phase, data after study day 1 (extension phase) are categorized under Analysis visit "Extension"; for participants who did not enter extension phase, data after the upper limit of Week 52 are categorized under "Post-Week 52".

For Pharmacokinetic and Immunogenicity analyses, the nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point and in general will not be included in by visit summaries. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- For participants who prematurely discontinue from the study drug or complete the study drug, data collected at early study drug discontinuation (ESDD) visit and post study drug follow-up visits will be summarized in the by visit tables.
- Pharmacokinetic and Immunogenicity data collected at Week 52 pre-dose timepoint for the SBR group will be excluded from the by visit summary tables.

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 up to Week 52. 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 multiple valid non-missing values in an analysis window, records will be chosen based on the following rules if a single value is needed for an analysis window (Particularly for vital signs, weight and BMI, if postbaseline multiple timepoints exist in an analysis window, single values will be required for each protocol specified timepoint of the analysis window based on the following rules):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 COBAS 6800” and “HIV RNA REPEAT COBAS” (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 COBAS” will be selected for analysis purposes; otherwise, if there are multiple “HIV 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

Key study dates (i.e., first participant screened, first participant randomized, last participant randomized, last participant last visit for the primary endpoint, and last participant last visit for the clinical study report) will be provided.

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 paricipants who were screened, the number of participants who did not meet eligibility criteria and were not randomized, and the number of participants who met all eligibility but not randomized with reason participant not randomized, the number of participants randomized, the number of participants randomized but never treated, number of participants in the Safety Analysis Set and the number of participants in each of the following categories as applicable:

- Completed study drug in the randomized phase
- Did not complete study drug in the randomized phase with reasons for premature discontinuation of study drug
- Completed study in the randomized phase
- Did not complete the study in the randomized phase with reasons for premature discontinuation of study
- Entered and treated with any component of LA regimen in the extension phase
- Entered and treated with >= 1 dose of complete LA regimen in the extension phase
- Continuing study drug in the extension phase
- Did not complete study drug in the extension phase with reasons for premature discontinuation of study drug
- Continuing study in the extension phase
- Did not complete the study in the extension phase 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, a flowchart will be provided to depict the disposition.

The following by-participant listings will be provided by participant identification (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)

4.2. Study Drug Administration

For Treatment group 1, Study drug administration and study drug dispensing information will be collected in the Study Drug Administration and Study Drug Accountability eCRFs.

Number and percentage of participants receiving oral lead-in LEN and SC LEN + TAB + ZAB at each protocol specified visit up to Week 52 (Day 1, Weeks 26, 52) for SC LEN, IV infusion GS-5423 and GS-2872 will be summarized. Number and percentage of participants receiving oral LEN before the first SC injection will also be provided.

Study drug administration and dispensing information will be listed.

4.3. Extent of Study Drug Exposure and Adherence

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 regimen specified in the protocol.

4.3.1. Duration of Exposure to Study Drug in Treatment Group 1

Total duration of exposure to study drug will be summarized. 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 end of study.

Total duration of study drug exposure during randomized phase will be defined as (the last exposure date (randomized phase) –Study Day 1 (randomized phase) + 1), and duration of exposure will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). Last exposure date are defined in Section 3.8.1 for participants who prematurely discontinuted study drug or completed study drug. For the calculation of the duration of exposure to study drug, the data cut date will be used to impute the last expoure date for participants who have not permanently discontinued study drug at the time of the data cut.

The total duration of exposure to study drug 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, >=1 day, >=2 days, >=8 days, >=15 days, >=4 weeks (28 days), >=12 weeks (84 days), >=24 weeks (168 days), >=26 weeks (182 days), >=38 weeks (266 days), >= 50 weeks (350 days) , >=52 weeks (364 days), etc. Summaries will be provided based on the Safety Analysis Set.

4.3.2. Duration of Exposure to SBR in Treatment Group 3

The exposure to SBR will be examined based on the records collected from "Non-Study ARV Medication" eCRF form with a "Current ARV" checked. The total duration of exposure of SBR during randomized phase will be defined as (the last exposure date (randomized phase) – Study Day 1 (randomized phase) + 1) for the randomized period, regardless of any temporary interruptions, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

For the calculation of the duration of exposure to SBR, the data cut date will be used to impute the last dose date for participants who are still on SBR at the time of the data cut date.

A by-participant listing of all ARV administrations will be provided by participant ID number (in ascending order) and visit (in chronological order) along with the durations of exposure during randomized period.

4.3.3. Adherence to Study Drug

The adherence to SC LEN, IV infusion TAB and/or ZAB will be assessed by adherence to the projected injection/infusion interval, which is 26 weeks (182 days) between 2 adjacent injection/infusion visits. The number of days from the projected injection/infusion visit date will be calculated for each injection/infusion visit (excluding the 1st injection visit) as the injection/infusion visit date minus the previous injection/infusion visit date plus 1 day minus 182 days. The number of days from the projected injection visit date will be classified into the following categories:

- < - 14 days
- -14 to -8 days
- -7 to -3 days
- ± 2 days
- 3 to 7 days
- 8 to 14 days
- > 14 days

The number and percentage of participants in each category will be summarized for treatment group 1 for the injection/infuision visits of interest.

4.4. Study Duration in the Randomized Phase

Due to long-acting feature of the study drug, study duration in randomized phase will be summarized by treatment group using the Safety Analysis set.

Study duration in randomized phase is calculated as the last study date in randomized phase (Section 3.8.1) minus Study Day 1 (Randomized Phase) plus 1.

For the calculation of the study duration, the data cut date will be used to impute the last study date in randomized phase for subjects who have not permanently discontinued study at the time of the data cut date.

Study duration will be expressed in days and will be summarized using descriptive statistics and using the number and percentage of participants that stayed through the following applicable time periods: >=1 day, >=2 days, >=8 days, >=15 days, >=4 weeks (28 days), >=12 weeks (84 days), >=24 weeks (168 days), >=26 weeks (182 days), >=38 weeks (266 days), >= 50 weeks (350 days), >=52 weeks (364 days), etc.

4.5. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. 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 by treatment group 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. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

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 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, region 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.

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 (mL/min/1.73m^2)
- Baseline oral ARV regimen
- Duration of baseline oral ARV regimen

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

Analysis of efficacy data for randomized phase will be conducted on the FAS, unless otherwise specified.

On-treatment data during randomized phase will be used for some efficacy analyses (eg. snapshot analysis) using FAS and all efficacy analyses using Per-Protocol analysis set. On-Treatment data during randomized phase include: 1)for treatment group 1: data collected up to the earliest date of (196 days [28 weeks] after the last dose date (randomized phase) of complete long acting regimen, date of restarting ART); 2)for treatment group 3: data collected up to 1 day after permanent discontinuation of study drug in the randomized phase.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as defined by the FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The proportions are expressed as percentages for presentation purpose.

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 for treatment group 1 and Study Day 134 to Study Day 224, inclusive for treatment group 3. All HIV-1 RNA data collected on-treatment during the randomized phase 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

   — Who discontinue study drug prior to or in the Week 26 analysis window due to lack of efficacy, or

   — 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

   — 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:

  — 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

  — 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,

  — 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.

6.1.3. Analysis of the Primary Efficacy Endpoint

The Primary analysis of the proportion of participants 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 95% CI of the proportion of participants with HIV-1 RNA >= 50 copies/mL for each treatment group will be provided using the Clopper-Pearson Exact method. 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 {Chan 1999}.

The Fisher's exact test will also be used to compare the percentages of participants between treatment groups. A secondary analysis based on the Week 26 PP analysis set will also be performed.

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 Week 52 as determined by the US FDA-defined snapshot algorithm

- Proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 and 52 as determined by the FDA-defined snapshot algorithm

- Change from baseline in CD4+ T-cell counts at Weeks 26 and 52

6.2.2. Analysis of the Secondary Efficacy Endpoints

6.2.2.1. Analysis of the Proportion of Participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 as Determined by US FDA-defined Snapshot Algorithm

The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 as determined by US FDA-defined snapshot algorithm will be analyzed similarly to the primary efficacy endpoint.

For both treatment group 1 and 3, the analysis windonw at Week 52 is defined as from Study Day 358 to Study 406 if a participant did not enter the extension phase, or to Study Day 1 (extension phase) if a patient entered the extension phase.

The analyses for the above endpoint will be conducted using the FAS and the Week 52 PP analysis set, respectively.

6.2.2.2. Analysis of the Proportion of Participants with HIV-1 RNA < 50 copies/mL at Weeks 26 and 52 as Determined by US FDA-defined Snapshot Algorithm

The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 and 52 as determined by US FDA-defined snapshot algorithm will be analyzed similarly to the primary efficacy endpoint, and be conducted using the FAS and the PP analysis set correspondingly.

6.2.2.3. Analysis of Change from Baseline in CD4+ T-cell counts

The changes from baseline in CD4+ cell count and the absolute values of CD4 cell counts at Weeks 26, 52 and other post-baseline visits will be summarized by treatment group for FAS,Week 26 PP analysis set and Week 52 PP analysis set using descriptive statistics.

The differences in changes from baseline in CD4+ T-cell count between the two treatment groups (Treatment Group 1 versus Treatment Group 3) and the associated 95% CIs and p-values will be constructed using analysis of covariance (ANCOVA) models in the FAS analysis set, including baseline CD4+ T-cell count as a covariate and treatment as a fixed-effect in the models. A secondary analysis based on the Week 26 PP and Week 52 PP analysis sets will also be performed.

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

6.3. Other Efficacy Endpoints

6.3.1. Definition of the Other Efficacy Endpoints

- Proportion of participants with HIV-1 RNA < 50 copies/mL by visit.
- The change from baseline in CD4+ percentage (%) at Weeks 26 and 52.

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 visit (Missing = Failure and Missing = Excluded Approaches).

All collected data in the randomized phase will be used for this analysis. Number and percentage of participants with HIV-1 RNA < 50 copies/mL by visit will be analyzed using the following 2 imputation methods for 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 for all visits up to Week 26.

- Missing = Excluded (M = E):

  In this approach, missing data will be excluded from 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 52 For the M = E analysis, results will be summarized by treatment group for all visits with available data.

For the M = F analysis, the proportion of participants with HIV-1 RNA < 50 copies/mL will be plotted by treatment group for all visits up to Week 52 using the FAS.

For the M = E analysis, the proportion of participants with HIV-1 RNA < 50 copies/mL will be plotted by treatment group for all available visits using the FAS.

6.3.2.2. Analysis of Change from Baseline in CD4 Percentage

The change from baseline in CD4 percentage (%) will be based on the FAS and analyzed up to the visits with available data, similarly to the change from baseline in CD4 cell count.

6.3.3. Efficacy Subgroup Analysis

The efficacy analysis by subgroup will be conducted by assessing the proportion of participants with HIV-1 RNA >= 50 copies/mL, or < 50 copies/mL at Weeks 26 and 52 determined by the US FDA-defined snapshot algorithm within each subgroup specified in Section 3.4 based on the FAS.

Results will be descriptive and the associated 95% CIs will be constructed using the Clopper-Pearson Exact method.

6.4. Changes from Protocol-Specified Efficacy Analyses

No change from protocol-specified efficacy analysis is planned.

7. SAFETY ANALYSES

Analysis of safety data will be conducted on the Safety Analysis Set for randomized phase, unless otherwise specified in the following sections.

For randomized phase, the treatment-emergent (TE) period is defined as follows:

For treatment group 1 participants who receive any long acting LEN, TAB and ZAB, the TE period is the time period from the first dose date of study drug in the randomized phase up to and including the last study date (randomized phase) (Section 3.8.1). For participants who do not receive any injection or infusion but only receive oral LEN and permanently discontinued study drug, the TE period is the time period from the first dose date of study drug in the randomized phase up to and including 60 days after the last dose of the oral LEN.

For treatment group 3 participants, the TE period is the time period from the first dose date of study drug for the randomized phase up to and including study day 1(extension phase) for participants who enter extension phase or up to and including 30 days after the last dose date of randomized phase for the participants who do not enter extension phase.

In general, safety data during the TE period will be summarized, unless otherwise specified.

7.1. Adverse Events

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 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) in the randomized phase are defined as 1 or both of the following:

- Any AEs leading to premature discontinuation of study drug during randomized phase, or
- Any AEs that start during the TE period (Section 7)

Treatment-emergent AEs (TEAEs) in extension phase are defined as 1 or both of the following:

  - Any AEs leading to premature discontinuation of study drug during extension phase, or
  - Any AEs that start on or after study day 1 (extension phase) (section 3.8.1)

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:
  - 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 day of the TE period

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.

7.1.6.1. Summaries of AE incidence

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. All deaths observed 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, HLT (if applicable), PT and and treatment group or by PT only and treatment group 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.

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

For Treatment Group 1, additional analysis of AEs will be performed for injection site reaction (ISR) (i.e., defined by high level term (HLT) of "Injection site reactions") and infusion related reaction (IRR), (ie, AE with “Yes” answer to “Is this part of an infusion-related reaction?” in AE CRF). Summaries will be provided for each SC injection visit (e.g, Day 1 SC, Week 26, and Week 52) and the overall.

- 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 for the by visit summary and the overall summary 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 or IRRs will be provided.

7.1.7.2. Study Drug Related Injection Site Induration and Nodules

For Treatment Group 1, percentage of ongoing and resolved study drug releated "Injection Site Induration" (one of preferred terms of ISR) will be summarized at both participant-level and event-level. Summaries will be provided for each SC injection visit (e.g, Day 1 SC, Week 26, and Week 52) and the overall at participant and event level.

For the participant-level summary, if a participant had more than one injection site indurations, the participant 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 participant listing for study drug related injection site induration and nodules and the corresponding duration will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. 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. Hemolyzed test results will not be included in the analysis, but they will be listed in by-participant laboratory listings.

Summaries of laboratory data will be provided for the Safety Analysis Set, and will include laboratory data collected in TE period defined at the beginning of Section 7.

A by-participant listing for laboratory test results will be provided by participant ID number and time point [visit] in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher will be flagged in the data listings, as appropriate.

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/time of first dose of study drug for treatment group 1, or the Study Day 1 for treatment group 3. 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 3.8.2.

Median (Q1, Q3) of the change from baseline values of Creatinine (mg/dL) and Glomerular Filtration Rate (mL/min/1.73m2) will be plotted by treatment group and by visit.

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.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities in randomized phase are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline visit during the TE period defined at the beginning of Section 7.

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. Treatment-Emergent Marked Laboratory Abnormalities

TE marked laboratory abnormalities in randomized phase are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point during the TE period defined at the beginning of Section 7. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered TE marked abnormalities.

7.2.2.3. 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 and treatment group; 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
- Treatment-Emergent Marked Laboratory Abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values during the TE period defined at the beginning of Section 7.

A by-participant listing of treatment-emergent laboratory abnormalities, treatment-emergent Grade 3 or 4 laboratory abnormalities, and treatment-emergent marked baboratory 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 by treatment group for body weight, BMI and vital signs as follows:

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

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 participant took study drug. Use of concomitant medications from Study Day 1 (randomized phase) up to the last exposure date (randomized phase) will be summarized (number and percentage of participants) by treatment group, and by preferred name. Multiple drug use (by preferred name) will be counted only once per participant. 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.

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-participant listing for all non-ARV concomitant medications including prior medication will be listed and sorted by participant 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 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 inferential statistics will be provided.

A by-participant listing for ECG assessment results will be provided by participant 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. PHARMACOKINETIC EVALUATION/ANALYSIS

8.1. PK Sample Collection

Blood sample for the determination of plasma LEN and serum GS-5423 and GS-2872

concentrations will be collected in all participants at scheduled time points.

8.2. PK Analyses Related to PK Sampling

8.2.1. PK Concentration

Individual participant concentration from serum PK samples of GS-5423 and GS-2872, as well as plasma PK samples of LEN will be determined using validated bioanalytical assays.

8.2.2. PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using 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, PK concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to zero for the calculation of PK parameters.

For area under the curve (AUC), samples below the limit of quantitation (BLQ) of the bioanalytical assays 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 (eg, urine collection) or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

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

The analytes and parameters presented in Table 8-1 will be used to evaluate the PK objectives of the study (as applicable).

Table 8-1. Pharmacokinetic Parameters for Each Analyte

Analysis Set	Analyte	Sample Matrix	Parameters
LEN PK Analysis Set	LEN	Plasma	Day 1 Dosing*: C_{max}, $C_{maxday1}$, T_{max}, $T_{maxday1}$, C_{trough}; Week 26 Dosing: C_{trough}
GS-5423 PK Analysis Set	GS-5423	Serum	Day 1 Dosing: AUC_{tau}, C_{trough}, C_{max}, $t_{1/2}$, T_{max}; Week 26 Dosing: AUC_{tau}, C_{trough}, C_{max}, T_{max}
GS-2872 PK Analysis Set	GS-2872	Serum	Day 1 Dosing: AUC_{tau}, C_{trough}, C_{max}, $t_{1/2}$, T_{max}; Week 26 Dosing: AUC_{tau}, C_{trough}, C_{max}, T_{max}

* $C_{maxday1}$ and $T_{maxday1}$ are derived using LEN PK data from Day 1.

8.3. Statistical Analysis Methods

8.3.1. Statistical Analysis of PK Concentration

Individual participant concentration data of LEN, GS-5423, and GS-2872 for participants in the PK analysis set will be listed and summarized using descriptive statistics by treatment periods (Day 0 to Week 26, and Week 26 to Week 52). Summary statistics (numbers of participants, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for individual participant concentration data by time point.

Individual concentration data listings and summaries will include all participants with concentration data. If a participant had quantifiable pre-dose, BLQ at end of infusion, or received incorrect dose, the related PK concentration(s) will be catpured in the table but will be excluded from the summary statistics, with reasons for exclusion identified. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. For summary statistics, BLQ values will be treated as zero at predose and postdose time points. 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. The method to handle BLQ values for PK summaries are described in Section 3.7. Concentration values will be presented as received from the bioanalytical lab and summary statistics will be presented to three significant digits.

Participants with virologic failure (i.e., HIV-1 RNA ≥ 50 copies/mL at Week 26 and 52 visit as defined by the FDA-defined snapshot algorithm) will be flagged in the listings.

8.3.1.1. PK Concentration Data

For analyses based on PK Analysis Sets, PK concentration for all analytes will be summarized by treatment periods.

The following tables will be provided for each analyte (LEN, GS-5423, and GS-2872) using the associated PK Analysis Set by treatment periods:

- Individual participant concentration data and summary statistics

The following figures will be provided for each analyte (LEN, GS-5423, and GS-2872) using the associate PK Analysis Set by treatment periods:

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales). If more than one-third of the values at a timepoint are BLQ then the mean and SD will not be presented at that timepoint 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 versus time (on linear and semilogarithmic scales). If more than one-half of the values at a timepoint are BLQ then the median and quartile values will not be presented at that timepoint and remaining points connected. If lower error bar (Q1) is BLQ at a timepoint then it will be presented as LLOQ at that timepoint.

In addition, the following listings will be provided for all analytes by treatment periods:

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

- Serum PK sampling details for GS-5423 and GS-2872 by participant, including procedures, differences in scheduled and actual draw times, and sample age.

8.3.2. Statistical Analysis of PK Parameters

Individual estimates of pharmacokinetic parameters of LEN, GS-5423, and GS-2872 will be listed and summarized using descriptive statistics by treatment periods (Day 0 to Week 26, and Week 26 to Week 52) (eg, sample size, arithmetic mean, coefficient of variation %, SD, 95% CI for the arithmetic mean, geometric mean, %CV, median, minimum, maximum, Q1, Q3, sample size of natural log-scale [LN], geometric mean, Geometric Coefficient of Variation [%GVC], 95% Confidence Interval for Geometric Mean [GCI], mean of LN, SD of LN).

PK parameters listed in Table 8-1 will be included in the following tables by treatment periods (as applicable).

- Individual estimates and summary statistics of plasma LEN PK parameters using the LEN PK Analysis Set

- Individual estimates and summary statistics of serum GS-5423 PK parameters using the GS-5423 PK Analysis Set

- Individual estimates and summary statistics of serum GS-2872 PK parameters using the GS-2872 PK Analysis Set

PK parameters could be unestimatable due to insufficient concentration data or may be estimated but marked for exclusion due to reasons such as the participant received an incorrect dose. In such cases, the PK parameters will be included in the listing (as not reported [NR] or the estimate values) but will be excluded from the summary statistics, with reasons for exclusion identified.

In addition, determination of half-life and corresponding correlation coefficient will be provided in the following listings by treatment periods:

- Individual data on determination of GS-5423 serum half-life and corresponding correlation coeffieicent using the GS-5423 PK Analysis Set
- Individual data on determination of GS-2872 serum half-life and corresponding correlation coeffieicent using the GS-2872 PK Analysis Set

8.4. Changes From Protocol-Specified PK Analyses

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

9. IMMUNOGENICITY ANALYSIS

Immunogenicity to GS-5423 and GS-2872 will be evaluated based upon the incidence of anti-GS-5423 antibody, anti–GS-2872 antibody, as well as both anti–GS-5423 and anti–GS-2872 antibody formation, respectively.

9.1. Definitions

Participants Evaluable for ADA Prevalence includes all participants who have at least one reportable ADA result at baseline or post-baseline.

Participants Evaluable for ADA Incidence includes all participants who have at least one reportable ADA result at post-baseline.

ADA Prevalence refer to the proportion of participants who have at least one positive ADA sample (baseline or post-baseline) among all participants evaluable for ADA prevalence.

ADA Incidence refer to the proportion of participants who have Treatment-Emergent ADA among all participants evaluable for ADA incidence.

Treatment-Emergent ADA: includes either Treatment-Boosted or Treatment-Induced ADAs, with details been presented in the follows:

- **Treatment-Boosted ADA** is defined as positive baseline ADA sample and at least one positive post-baseline ADA sample and the ratio of the max titer of the post-baseline ADA and the titer of baseline ADA ≥ 4. If baseline titer < 10 (10 is the minimum reportable titer value), it will be considered boosted if max titer of the post-baseline ≥ 10. The proportion of participants who have Treatment-Boosted ADA is calculated based on the total number of participants evaluable for ADA incidence as the denominator.

- **Treatment-Induced ADA** is defined as negative or missing baseline ADA sample and at least one positive post-baseline ADA sample. The proportion of participants who have Treatment-Induced ADA is calculated based on the total number of participants evaluable for ADA incidence as the denominator.

Persistent ADA is defined as (a) Treatment-Induced ADA detected at two or more sampling time points during the study, where the first and last ADA-positive sample (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer; or (b) Treatment-Induced ADA detected at the last sampling time point of the study. The proportion of participants who have persistent ADA is based on the total number of participants evaluable for ADA incidence as the denominator.

Transient ADA is defined as Treatment-Induced ADA that does not meet the definition of persistent ADA. The proportion of participants who have transient ADA is based on the total number of participants evaluable for ADA incidence as the denominator.

Neutralizing antibody (NAb) Incidence: the proportion of participants who have treatment-emergent ADA and have at least one positive post-baseline ADA sample detected positive for neutralizing antibody based on the total number of participants evaluable for ADA incidence as the denominator.

Participant-level ADA status is defined as (a) "ADA+" if the participant has Treatment-Emergent ADA; (b) "ADA-" if the participant is evaluable for ADA incidence and does not have Treatment-Emergent ADA; and (c) missing if the participant is not evaluable for ADA incidence.

Participant-level NAb status is defined as (a) "Nab+" if the participant has Treatment-Emergent NAb; (b) "Nab-" if the participant is evaluable for NAb incidence and does not have Treatment-Emergent NAb; and (c) not evaluable if the participant is negative for ADA incidence.

Time to ADA onset is defined as:

- the number of days after first dose to the day when the first positive ADA result was detected for participants with Treatment-Induced ADA
- the number of days after first dose to the day when the first boosted post-baseline positive ADA result was detected for participants with Treatment-Boosted ADA.

9.2. Evaluation of Immunogenicity Data

Based on the respective evaluable populations, the following measures of immunogenicity will be reported for (a) ADA prevalence, (b) ADA incidence, (c) Transient/Persistent ADA, and (d) NAb incidence.

The numbers and percentages of participants within each ADA/NAb category described above will be summarized over the entire study period. In addition, the number and percentage of positive ADA and NAb samples will be summarized by nominal visit. ADA titer values in positive ADA samples will be summarized by visit, including median, Q1, Q3, minimum and maximum titer values. Summary statistics for time to ADA onset in ADA+ participants (i.e. participants with Treatment-Emergent ADA) will include median, Q1, Q3, minimum and maximum onset times. Summaries will be provided for each treatment arm and all active treatment groups for the compound of interest combined.

By participant listing of ADA/NAb result, titer, and corresponding PK concentration by participant ID number and visit, as well as participant-level ADA/NAb status, ADA type (persistent or transient), and time to ADA onset will be provided for all participants in the Immunogenicity Analysis Set. A separate listing will be produced for participants with any

positive ADA results. The ADA titer values in ADA+ participants will be plotted over time by individual participant grouped by treatment. For the purpose of plotting, samples with negative ADA result or undetectable titer will have the titer value imputed to zero and connected with the adjacent time points.

In order to evaluate the impact of ADA on PK, combined individual PK concentration-time profile plots by treatment group will be produced with ADA+ participants highlighted in red [redacted]

The following ADA summary tables will be generated for (1) anti-GS-5423, (2) anti-GS-2872, and (3) both anti-GS-5423 and anti-GS-2872:

- Immunogenicity results over the entire study period, including calculation of ADA prevalence, incidence, and numbers and percentages as well as NAb incidence of participants in each ADA category.
- Numbers and percentages of positive ADA and NAb results by visit
- Median, Q1, Q3, minimum, maximum of titer values in positive ADA samples by visit
- Time to treatment-emergent ADA onset (median, Q1, Q3, minimum, maximum) in ADA+ participants

The following figures will be provided for each analyte, anti-GS-5423 and anti-GS-2872:

- Individual concentration vs. time profiles grouped by treatment, with ADA+ participants highlighted in red
- Individual ADA titer values over time grouped by treatment (ADA+ participants only)
  - ADA titer values less than the minimum reportable titer value and titer values for ADA-negative samples will be imputed to 0.

The following listings will be provided:

- Listing of ADA results, titer, NAb results and corresponding PK concentrations by participant ID and visit, as well as participant-level ADA status, ADA type (persistent or transient), time to ADA onset, and NAb status for all participants in the immunogenicity analysis set
- Same listing above in participants with any positive ADA result.

In addition, summary of immunogenicity results over the entire study period for ADA/NAb against both GS-5423 and GS-2872 will be included.

10. REFERENCES

Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55 (4):1202-9.

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.

11. 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.

12. SAP REVISION

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

13. APPENDICES

Appendix 1. Study Procedures Table
Appendix 2. Flowchart of US FDA-defined Snapshot Algorithm (for Long Acting Switch Trial)
Appendix 3. Programming Specifications

Appendix 1. Study Procedures Table

Table 13-1. Study Procedures Table (Treatment Group 1)

	Screening		Randomized Phase											Extension Phase[u]			ESDD[c]	Post Study Drug Follow up[c]	
Study Procedure	**Visit 1**	**Visit 2[a]**	**Day 1**	**Day 2[b]**	**Day 8[b]**	**Day 15[b]**	**Wk 4**	**Wk 12**	**Wk 24**	**Wk 26**	**Wk 38**	**Wk 50**	**Wk 52**	**Wk 64, 90, 116, 142**	**Wk 76, 102, 128, 154**	**Wk 78, 104, 130, 156**		**PSD Day 30, 90, 180**	**PSD Day 270, 365**
Visit Window (Days)			**Within 28 Days of Screening Visit 2**		**± 3 Days**			**± 6 Days**						**± 6 Days**				**± 6 Days**	
Written informed consent	X																		
Medical history	X	X																	
Review concomitant medications	X	X	X	X	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	X	X	X	X
Complete physical examination		X	X														X		
Focused physical examination							X	X		X	X		X	X		X		X	
Height		X																	
Weight		X	X				X	X		X	X		X	X		X	X	X	
Vital signs[d]		X	X				X	X		X	X		X	X		X	X	X	
Proviral DNA phenotype	X																		
Proviral DNA genotype	X																		
Chemistry[e]		X	X				X	X		X	X		X	X		X	X	X	
Hematology[e]		X	X				X	X		X	X		X	X		X	X	X	
TSH		X	X										X				X		

	Screening		Randomized Phase											Extension Phase[u]			ESDD[c]	Post Study Drug Follow up[c]	
Study Procedure	**Visit 1**	**Visit 2[a]**	**Day 1**	**Day 2[b]**	**Day 8[b]**	**Day 15[b]**	**Wk 4**	**Wk 12**	**Wk 24**	**Wk 26**	**Wk 38**	**Wk 50**	**Wk 52**	**Wk 64, 90, 116, 142**	**Wk 76, 102, 128, 154**	**Wk 78, 104, 130, 156**		**PSD Day 30, 90, 180**	**PSD Day 270, 365**
Visit Window (Days)			**Within 28 Days of Screening Visit 2**		**± 3 Days**			**± 6 Days**						**± 6 Days**				**± 6 Days**	
CD4+ and CD8+ T-cell count		X	X					X		X	X		X	X		X	X	X[f]	
Serum pregnancy test		X																	
FSH[g]		X																	
Urinalysis		X	X				X	X		X	X		X	X		X	X	X	
Urine pregnancy test[h]			X				X	X		X	X		X	X		X	X	X	X
HBV & HCV serology		X																	
HIV-1 RNA		X	X				X	X	X	X	X	X	X	X	X	X	X	X	
HIV-1 genotype/ phenotype[i]				X															
HIV reservoir assay (PBMC)[j]			X							X			X			X			
[redacted]																			
eGFR		X	X				X	X		X	X		X	X		X	X	X	
ECG[j]		X	X							X			X			X			
Plasma storage samples for virology testing			X				X	X	X	X	X	X	X	X	X	X	X		
Immunogenicity (ADA) serum sample[l]			X				X	X		X	X		X	X		X	X	X	X

	Screening		Randomized Phase											Extension Phase[u]				Post Study Drug Follow up[c]	
Study Procedure	**Visit 1**	**Visit 2[a]**	**Day 1**	**Day 2[b]**	**Day 8[b]**	**Day 15[b]**	**Wk 4**	**Wk 12**	**Wk 24**	**Wk 26**	**Wk 38**	**Wk 50**	**Wk 52**	**Wk 64, 90, 116, 142**	**Wk 76, 102, 128, 154**	**Wk 78, 104, 130, 156**	**ESDD[c]**	**PSD Day 30, 90, 180**	**PSD Day 270, 365**
Visit Window (Days)			**Within 28 Days of Screening Visit 2**		**± 3 Days**			**± 6 Days**						**± 6 Days**				**± 6 Days**	
Serum PK samples (GS-5423 & GS-2872)[m, n]			X				X	X	X	X	X	X	X	X		X	X	X	X
Plasma PK sample for LEN[m, o]			X				X	X	X	X	X	X	X	X		X	X	X	X
[redacted]																			
Randomization			X																
HIV Treatment Preference Questionnaire			X							X			X			X			
HIVDQoL			X							X			X			X			
HIVTSQs[q]			X				X			X			X			X			
HIVTSQc[q]										X									
LEN oral administration[r]			X	X															
LEN SC administration			X							X			X			X			
GS-5423 IV infusion administration[s]			X							X			X			X			

	Screening		Randomized Phase											Extension Phase[u]				Post Study Drug Follow up[c]	
Study Procedure	**Visit 1**	**Visit 2[a]**	**Day 1**	**Day 2[b]**	**Day 8[b]**	**Day 15[b]**	**Wk 4**	**Wk 12**	**Wk 24**	**Wk 26**	**Wk 38**	**Wk 50**	**Wk 52**	**Wk 64, 90, 116, 142**	**Wk 76, 102, 128, 154**	**Wk 78, 104, 130, 156**	**ESDD[c]**	**PSD Day 30, 90, 180**	**PSD Day 270, 365**
Visit Window (Days)			**Within 28 Days of Screening Visit 2**		**± 3 Days**			**± 6 Days**						**± 6 Days**				**± 6 Days**	
GS-2872 IV infusion administration[s]			X							X			X			X			
CCI [redacted]																			

ADA = antidrug antibody; AE = adverse event; ARV = antiretroviral; bNAb = broadly neutralizing antibody; CD4 = clusters of differentiation 4; CD8 = clusters of differentiation 8; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESDD = early study drug discontinuation; ET = early termination; FSH = follicle-stimulating hormone; Gilead = Gilead Sciences; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; HIVDQoL = HIV-dependent quality of life; HIVTSQc = HIV Treatment Satisfaction Questionnaire change version; HIVTSQs = HIV Treatment Satisfaction Questionnaire status version; IV = intravenous; LEN = lenacapavir; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); PSD = post study drug; RNA = ribonucleic acid; SC = subcutaneous; TSH = thyroid-stimulating hormone; Wk = week

a Screening Visit 2 will be performed once results of GS-5423 and GS-2872 sensitivity testing from Visit 1 are reviewed and participant is deemed eligible to proceed.

CCI [redacted]

c Refer to Section 6.3.11 for ESDD and post-ESDD 30-, 90-, 180-, 270-, and 365-day follow-up visits. Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer participant to an appropriate HIV treatment facility.

d Vital signs: blood pressure, pulse, and temperature. On dosing days for LEN + GS-5423 + GS-2872, vital signs should be recorded prior to start of study drug administration and 30 minutes (± 10 minutes) after completion of both GS-5423 and GS-2872 infusion, if coadministered or the GS-2872 infusion, if sequentially administered.

e Refer to Table 6 for specific tests that are not on a standard chemistry panel (eg, amylase/lipase, uric acid).

f CD4+ and CD8+ T-cell counts at post-ESDD 90-day follow-up visit only.

g An FSH test is required for participants assigned female at birth who are younger than 54 years, have not undergone permanent sterilization, are not on hormonal contraception, and have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure; see Appendix 11.3.

h Participants assigned female at birth of childbearing potential only. On dosing days, urine pregnancy test to be performed predose. A positive urine pregnancy test should be confirmed with a serum pregnancy test.

i HIV-1 genotype and phenotype testing for participants with confirmed virologic failure and HIV-1 RNA ≥ 200 copies/mL. Refer to Section 6.3.9.2.

j HIV reservoir sample (PBMC) and ECG to be collected at Day 1, Week 26, Week 52, Week 104, and every 12 months thereafter.

CCI [redacted]

CCI [redacted]

n Serum PK samples for GS-5423 and GS-2872 will be collected in all participants as follows:
- Day 1: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of the second antibody infusion (GS-2872).
- Week 26: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN) and within 5 minutes after the end of the second antibody infusion (GS-2872).
- Week 52 and subsequent dosing days: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN) and within 5 minutes after the end of both antibody infusions (GS-5423 and GS-2872), if coadministered or the second antibody infusion (GS-2872), if sequentially administered.
- A single any time sample at other scheduled visits.

o Plasma samples for LEN will be collected in all participants as follows:
- Day 1: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of the second antibody infusion (GS-2872).
- Week 26 and subsequent dosing days: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN).
- A single any time sample at other scheduled visits.

[redacted]

q On visits when both HIVTSQs and HIVTSQc will be completed, HIVTSQs should be completed first.

r Participants will take 2 oral LEN tablets on Day 1 at the clinic and self-administer 2 oral LEN tablets on Day 2 at home, [redacted]

s Refer to Section 5.3. If coadministered, infusion of GS-5423 and GS-2872 will begin immediately following (up to 1 hour after) the last SC LEN injection. If sequentially administered, infusion of GS-2872 will begin at least 15 minutes following (up to 1 hour after) the completion of GS-5423 IV infusion. The exact date and time of study drug administration must be carefully recorded. Participants will remain in a monitored clinical setting for at least 30 minutes after completion of GS-5423 and GS-2872 infusion, if coadministered or GS-2872 infusion if sequentially administered. For the Day 1 and Week 26 visits and all subsequent dosing visits, all study drugs are to be administered

[redacted]

u Participants may opt to continue study visits beyond Week 156 on the same schedule with study visits every 12 and 24 weeks between dosing visits (every 26 weeks) until the product becomes accessible to participants through an access program, is commercially available, or Gilead elects to discontinue the study, whichever occurs first.

Table 13-2. Study Procedures Table (Treatment Group 3)

	Screening		Randomized Phase						Extension Phase[s]				ESDD[b]	Post Study Drug Follow-up[cb]	
Study Procedure	**Visit 1**	**Visit 2[a]**	**Day 1**	**Wk 12**	**Wk 26**	**Wk 38**	**Wk 50**	**Wk 52**	**Wk 56**	**Wk 64, 90, 116, 142**	**Wk 76, 102, 128, 154**	**Wk 78, 104, 130, 156**		**PSD Day 30, 90, 180**	**PSD Day 270, 365**
Visit Window (Days)			**Within 28 Days of Screening Visit 2**	**± 6 Days**					**± 6 Days**					**± 6 Days**	
Written informed consent	X														
Medical history	X	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		X		X	
Height		X													
Weight		X	X	X	X	X		X	X	X		X	X	X	
Vital signs[c]		X	X	X	X	X		X	X	X		X	X	X	
Proviral DNA phenotype	X														
Proviral DNA genotype	X														
Chemistry[d]		X	X	X	X	X		X	X	X		X	X	X	
Hematology[d]		X	X	X	X	X		X	X	X		X	X	X	
TSH		X	X					X					X		
CD4+ and CD8+ T-cell count		X	X	X	X	X		X		X		X	X	X[e]	
Serum pregnancy test		X													

	Screening		Randomized Phase						Extension Phase[s]				ESDD[b]	Post Study Drug Follow-up[cb]	
Study Procedure	**Visit 1**	**Visit 2[a]**	**Day 1**	**Wk 12**	**Wk 26**	**Wk 38**	**Wk 50**	**Wk 52**	**Wk 56**	**Wk 64, 90, 116, 142**	**Wk 76, 102, 128, 154**	**Wk 78, 104, 130, 156**		**PSD Day 30, 90, 180**	**PSD Day 270, 365**
Visit Window (Days)			**Within 28 Days of Screening Visit 2**	**± 6 Days**					**± 6 Days**					**± 6 Days**	
FSH[f]		X													
Urinalysis		X	X	X	X	X		X	X	X		X	X	X	
Urine pregnancy test[g]			X		X			X	X	X		X	X	X	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[h]				X									X		
HIV reservoir assay (PBMC)[i]			X		X			X				X			
CCI															
eGFR		X	X	X	X	X		X	X	X		X	X	X	
ECG[i]		X	X		X			X				X			
Plasma storage samples for virology testing			X	X	X	X	X	X	X	X	X	X	X		
Immunogenicity (ADA) serum sample[k]								X		X		X	X	X	X
Serum PK samples (GS-5423 & GS-2872)[l, m]								X	X	X		X	X	X	X
Plasma PK sample for LEN[l, n]								X	X	X		X	X	X	X
Randomization			X												

	Screening		Randomized Phase						Extension Phase[s]				ESDD[b]	Post Study Drug Follow-up[cb]	
Study Procedure	**Visit 1**	**Visit 2[a]**	**Day 1**	**Wk 12**	**Wk 26**	**Wk 38**	**Wk 50**	**Wk 52**	**Wk 56**	**Wk 64, 90, 116, 142**	**Wk 76, 102, 128, 154**	**Wk 78, 104, 130, 156**		**PSD Day 30, 90, 180**	**PSD Day 270, 365**
Visit Window (Days)			**Within 28 Days of Screening Visit 2**	**± 6 Days**					**± 6 Days**					**± 6 Days**	
HIV Treatment Preference Questionnaire			X		X			X				X			
HIVDQoL			X		X			X				X			
HIVTSQs[o]			X		X			X	X			X			
HIVTSQc[o]												X			
Continue baseline oral ART			X												
LEN oral administration[p]								X							
LEN SC administration								X				X			
GS-5423 IV infusion administration[q]								X				X			
GS-2872 IV infusion administration[q]								X				X			
CCI															

ADA = antidrug antibody; AE = adverse event; ARV = antiretroviral; bNAb = broadly neutralizing antibody; CD4 = clusters of differentiation 4; CD8 = clusters of differentiation 8; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESDD = early study drug discontinuation; FSH = follicle-stimulating hormone; Gilead = Gilead Sciences; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; HIVDQoL = HIV-dependent quality of life; HIVTSQc = HIV Treatment Satisfaction Questionnaire change version; HIVTSQs = HIV Treatment Satisfaction Questionnaire status version; IV = intravenous; LEN = lenacapavir; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); PSD = post study drug; RNA = ribonucleic acid; SC = subcutaneous; TSH = thyroid-stimulating hormone; Wk = week

a Screening Visit 2 will be performed once results of GS-5423 and GS-2872 sensitivity testing from Visit 1 are reviewed and participant is deemed eligible to proceed.

b For participants who discontinue the study prior to Week 52, only a ESDD and 30-day follow-up visit is required. For participants who receive study drug in extension phase, refer to Section 6.3.11 for ESDD and post-ESDD 30-, 90-, 180-, 270-, and 365-day follow-up visits. Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer participant to an appropriate HIV treatment facility.

c Vital signs: blood pressure, pulse, and temperature. On dosing days for LEN + GS-5423 + GS-2872, vital signs should be recorded prior to start of study drug administration and 30 minutes (± 10 minutes) after completion of both GS-5423 and GS-2872 infusion, if coadministered or the GS-2872 infusion, if sequentially administered.

d Refer to Table 6 for specific tests that are not on a standard chemistry panel (eg, amylase/lipase, uric acid).

e CD4+ and CD8+ T-cell count at post-ESDD 90-day follow-up visit only.

f An FSH test is required for participants assigned female at birth who are younger than 54 years, have not undergone permanent sterilization, are not on hormonal contraception, and have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure; see Appendix 11.3.

g Participants assigned female at birth of childbearing potential only. On Week 52 and subsequent dosing days, urine pregnancy test to be performed predose. During the randomized and extension phase, a positive urine pregnancy test should be confirmed with a serum pregnancy test.

h HIV-1 genotype and phenotype testing for participants with confirmed virologic failure and HIV-1 RNA ≥ 200 copies/mL. Refer to Section 6.3.9.2.

i HIV reservoir sample (PBMC) and ECG to be collected at Day 1, Week 26, Week 52, Week 78, Week 104, and every 12 months thereafter.

CCI [redacted]

l The exact date and time of collection of PK samples must be recorded. PK samples should be drawn from a separate catheter in the opposite arm from the one used for GS-5423 and GS-2872 IV infusions to avoid contamination. Refer to Section 6.3.6 for details.

m Serum PK samples for GS-5423 and GS-2872 will be collected in all participants as follows:

- Week 52: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of both antibody infusions (GS-5423 and GS-2872), if coadministered or the second antibody infusion (GS-2872), if sequentially administered.
- Week 78 and subsequent dosing visits: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN).
- A single any time sample at other scheduled visits.

n Plasma PK samples for LEN will be collected in all participants as follows:

- Week 52: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of the infusion of both antibodies (GS-5423 and GS-2872), if coadministered or the second antibody infusion (GS-2872), if sequentially administered.
- Week 78 and subsequent dosing days: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN).
- A single any time sample at other scheduled visits.

o HIVTSQc will only be completed at Week 78. On visits when both HIVTSQs and HIVTSQc will be completed, HIVTSQs should be completed first.

p Participants will take 2 oral LEN tablets at Week 52 at the clinic and self-administer 2 oral LEN tablets the following day (Week 52 + 1 day) at home.

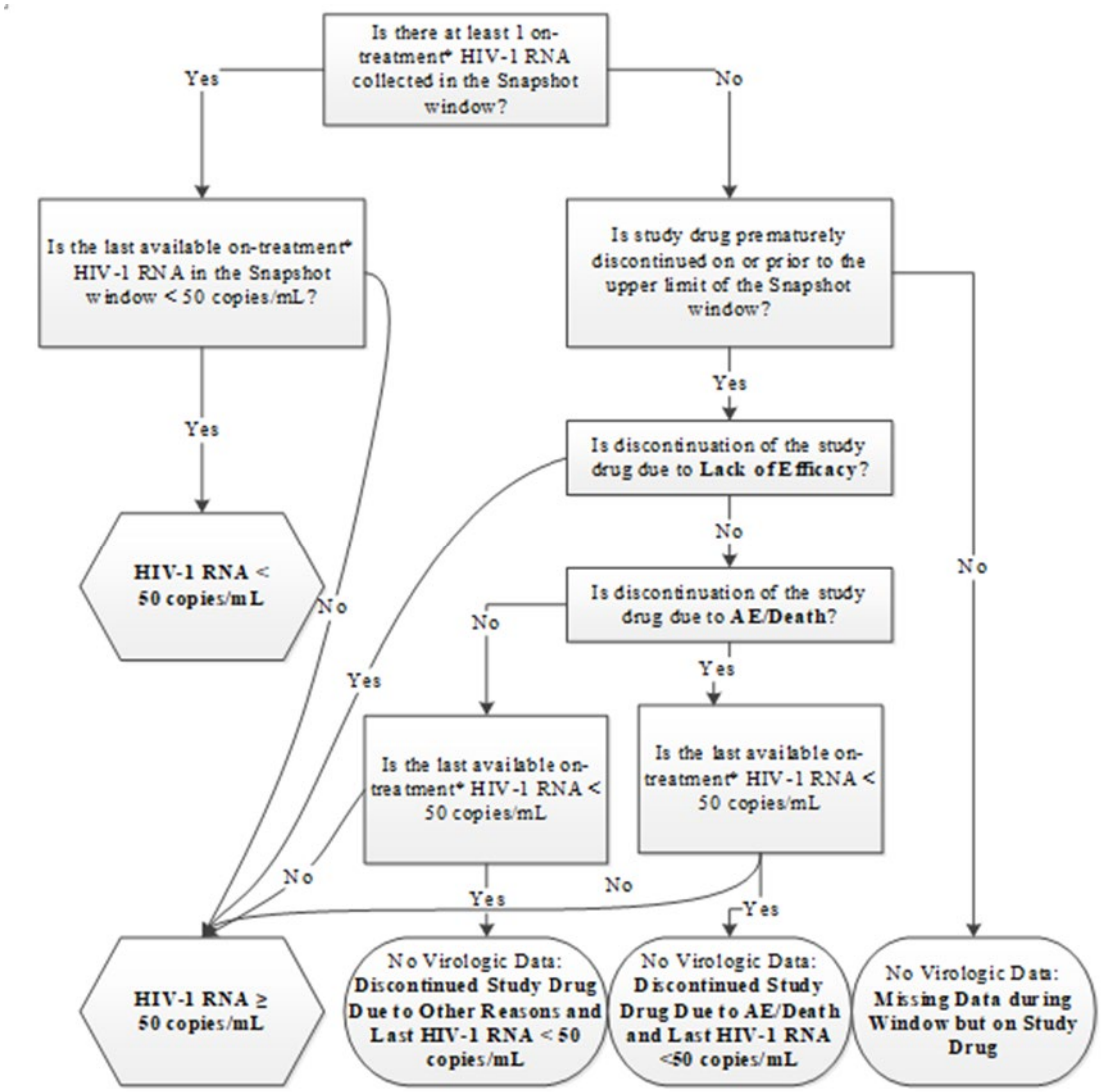
q Refer to Section 5.3. If coadministered, infusion of GS-5423 and GS-2872 will begin at least 15 minutes (up to 1 hour after) after SC LEN injection. If sequentially administered, infusion of GS-2872 will begin at least 15 minutes following (up to 1 hour after) the completion of GS-5423 IV infusion. The exact date and time of study drug administration must be carefully recorded. Participants will remain in a monitored clinical setting for at least 30 minutes after completion of GS-5423 and GS-2872 infusion, if coadministered or GS-2872 infusion, if sequentially administered. For the Week 52, 78, and 104 visits and all subsequent dosing visits, all study drugs are to be administered on the same day.

CCI [redacted]

s Participants may opt to continue study visits beyond Week 156 on the same schedule with study visits every 12 and 24 weeks between dosing visits (every 26 weeks) until the product becomes accessible to participants through an access program, is commercially available, or Gilead elects to discontinue the study, whichever occurs first.

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: 1)for treatment group 1: HIV-1 RNA data collected up to the earliest date of (196 days [28 weeks] after the last dose date of complete long acting regimen, date of restarting ART); 2)for treatment group 3: HIV-1 RNA data collected up to 1 day after permanent discontinuation of study drug.

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?” in Study Drug Completion eCRF).

The date of study drug premature discontinuation is

1) The earliest (196 days [28 weeks] after the last dose date of complete long acting regimen, ARV restart date, last study date) for participants who prematurely discontinued study drug for treatment group 1

2) The date of permanent discontinuation of baseline oral ART regimen for treatment group 3.

Appendix 3. Programming Specifications

1) All study days will be calculated from Study Day 1 of the randomization phase including observations collected from the extension phase of the study in listings.

2) 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.

3) 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;
```

4) 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.

5) 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;
```

6) 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.

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

8) Screen failure participants are the participants who were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the participant was consent to, or participants who have missing answer to any inclusion or exclusion criteria.

9) Baseline ARV medication is defined as:

- Using the ARV raw dataset, include all prior ARVs (where ARV.CMSCAT ='Prior ARV" or "Current 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 or ongoing (for ARVs with start date < firist dose date); if not treated, End date of ARV >= randomization date or ongoing (for ARVs with start date < randomization date).

- Duration of baseline ARV medication (year) = (End Date – Start Date + 1) / 365.25

  — End Date of the baseline ARV medication is defined as the first dose date (Study Day 1 (randomized phase)) -1 or randomization date if randomized but not dosed.

  — Start Date of the baseline ARV medication is the start date of the latest individual baseline ARV medications.

- For calculation of duration of baseline regimen, if the start date or stop date is missing or partially missing, the following imputation rule will be used.

  — Missing start month/day: Jan 1/first day of the month will be used.

  — Missing stop month/day: Dec 31/last day of the month will be used, unless the imputed date is on or after the first study drug dose date (randomized phase). In such case, the day before the first study drug dose date (randomized phase) will be used.

- 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.

  For actual infusion dose calculation:

  Actual dose for infusion = planned dose*[(start of infusion volume - end of infusion volume)/start of infusion volume*100%].

10) Injection site reaction (ISR)/Infusion related reaction (IRR): To summarize ISRs/IRR by injection visit, each study drug related ISR/IRR will be associated with one injection/infusion visit based on the start date of the ISR/IRR. If the start date of the ISR/IRR is on or after a given injection visit date and prior to the next injection visit date, if available, the ISR/IRR will be associated with that injection visit.

    For ISR/IRR summarized by PT: For the overall summary (ie, participants received at least one injection), multiple ISRs/IRRs with the same PT will only be counted once per participant for each PT. For by visit summary (ie, participants received injection for a given injection visit), multiple ISRs/IRRs associated with the injection visit of interest with the same PT will only be counted once per subject for each PT. For ISR/IRR summarized by grade: For the overall summary (ie, participants received at least one injection), the most severe grade based on all ISRs/IRRs will be used. For by visit summary (participants received injection for a given injection visit), the most severe grade from all ISRs/IRRs associated with the injection visit of interest will be used.

    In the listing, for postbaseline vital sign and weight, 0.5 hr post dose on Day 1 will be displayed as “Day 1 0.5 hr post dose”.

11) Date of the Last Lab Collection in the Randomized Phase: If a participant entered the extension phase, set to the date of the last available lab record up to and including the first dose date (extension phase). If a participant did not enter the extension phase, set to the date of the last available lab record.

12) Date of the Last Lab Collection in the Extension Phase: set the date to the last available lab record up to earliest of the last study day (if the participant discontinued or completed study in the extension phase) or the data cut date (if the participant is still ongoing in the extension phase.

13) Date of the Last Visit in the Randomized Phase: if a participant entered the extension phase, set to the date of the last available visit record up to and including the first dose date (extension phase). If a participant did not enter the extension phase, set to the date of the last available visit record.

14) Date of the Last Vist in the Extension Phase: set the date to the last available visit record up to earliest of the last study day (if the participant discontinued or completed study in the extension phase) or the data cut date (if the participant is still ongoing in the extension phase.)

15) If a participant completed study (Study Completion Form in eCRF) during the randomized phase, or entered and was treated in the extension phase, s/he will be considered as completed the study in the randomized phase.

16) For vital signs and body weight, only the data collected at the protocol defined timepoint will be summarized. But all collected data will be included in the listing.