



STATISTICAL ANALYSIS PLAN

Study Title: A Phase 1b Randomized, Blinded, Proof-of-Concept Study to Evaluate the Safety and Efficacy of Broadly Neutralizing Antibodies (bNAbs) GS-5423 and GS-2872 in Combination with Capsid Inhibitor Lenacapavir (GS-6207) in Virologically Suppressed Adults with HIV-1 Infection

Name of Test Drug: GS-5423 and GS-2872 + Lenacapavir (LEN; GS-6207)

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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AQL	above quantitation limit
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
BE	bioequivalence
B/F/TAF	bictegravir/emtricitabine/ tenofovir alafenamide, Biktarvy®
BIC	bictegravir, B, GS-9883
BLQ	below the limit of quantitation
BMI	body mass index
bNAbs	Broadly Neutralizing Antibodies
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
ET	early termination
EVG	elvitegravir, E
FAS	Full analysis set
FDC	fixed dose combination
FTC	emtricitabine
Gilead	Gilead Sciences
GDRC	Gilead Data Review Committee
GLSM	geometric least-squares mean
Hb	hemoglobin
IV	intravenous
LA	Long-acting
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MST	Medical Surveillance Team
PK	pharmacokinetic
POC	proof of concept
PP	per protocol

PT	preferred term
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SI	International System of Units (Système International d'Unités)
SOC	system organ class
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TFV-DP	tenofovir diphosphate
ULOQ	upper limit of quantification
ULN	upper limit of normal
VF	virologic failure
VR	ventricular rate
WHO	World Health Organization

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 _{0-26wk}	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 _{1/2}	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) in the clinical study report (CSR) for the final analyses of Study GS-US-536-5816. This SAP is based on the study Protocol Amendment 2 dated 30 March 2022 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of a combination of the bNAbS GS-5423 and GS-2872 in combination with the HIV capsid inhibitor lenacapavir (LEN; GS-6207)

The secondary objectives of this study are as follows:

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

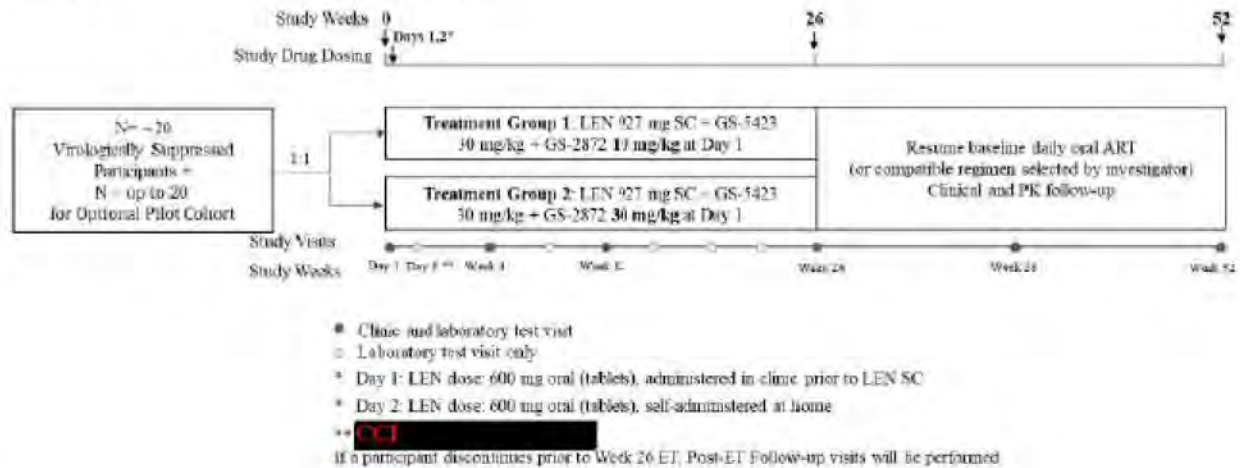
1.2. Study Design

1.2.1. Design Configuration and Participant Population

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

An overview of the study design is described below and shown in [Figure 1-1](#).

Figure 1-1. Study Schema



ART – antiretroviral therapy; ET – early termination; LEN – lenacapavir; PK – pharmacokinetic(s); SC – subcutaneous.

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Participants in the Primary Cohort and in the optional **Pilot Cohort** will be randomized in a 1:1 ratio to one of the following 2 treatment groups based on the dose of GS-2872 as in Section 1.2.2.

1.2.2. Treatment Groups

Treatment Group 1:

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

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

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

Treatment Group 2:

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

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

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

There is no stratification for randomization for the Primary Cohort. For the optional Pilot Cohort, randomization will be stratified by the antibody (GS-5423 or GS-2872) to which the participant is sensitive.

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

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

Accordingly, efficacy and safety analyses will be conducted on CCI

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Details of these two analysis periods will be addressed later in Section 3.

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

1.2.3. Key Eligibility Criteria

HIV-1 infected participants who meet the following criteria:

- Age between 18 and 65 years at screening
- On first-line ART for ≥ 2 years prior to screening. A change in ART regimen ≥ 28 days prior to screening for reasons other than virologic failure (VF) (eg, tolerability, simplification, drug-drug interaction profile) is allowed
- No documented historical resistance to the current ART regimen
- Plasma HIV-1 RNA < 50 copies/mL at screening

- Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 18 months preceding the screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL). Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or “blip”) prior to screening are acceptable.
- Proviral phenotypic sensitivity to both GS-5423 and GS-2872 at screening by the PhenoSense monoclonal antibody (mAb) Assay (Monogram Biosciences) for inclusion in the **Primary Cohort**; sensitivity at screening by the PhenoSense mAb Assay (Monogram Biosciences) to 1 mAb, either GS-5423 or GS-2872, **CC1** prior to enrollment for inclusion in the optional **Pilot Cohort**
 - In both cohorts, GS-5423 sensitivity is defined as 90% inhibitory concentration (IC_{90}) ≤ 2 μ g/mL; GS-2872 sensitivity is defined as $IC_{90} \leq 2$ μ g/mL
- CD4+ count nadir ≥ 350 cells/ μ L
- Screening CD4+ count ≥ 500 cells/ μ L
- Availability of a fully active alternative ART regimen, in the opinion of the investigator, in the event of discontinuation of the current ART regimen with development of resistance
- No comorbid condition requiring ongoing immunosuppression
- No evidence of current hepatitis B virus (HBV) infection
- No evidence of current hepatitis C virus (HCV) infection (prior infection cleared spontaneously or with treatment is acceptable)
- No history of opportunistic infection or illness indicative of Stage 3 HIV disease

1.2.4. Duration of Treatment

Duration of study drug treatment is approximately 26 weeks.

1.2.5. Study Procedures/Frequency

1.2.5.1. Screening

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

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

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

1.2.5.2. Randomization

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

There is no stratification for randomization for the Primary Cohort.

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

1.2.5.3. Schedule of Assessments

Study drug(s) will be administered in-clinic on Day 1 and self-administered on Day 2 (note: administered in-clinic on Day 2 if participating in the CCI [REDACTED]). Participants will return for study visits on Weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52 for study assessments.

Clinical and laboratory assessments including hematology, chemistry, urinalysis, pregnancy test (for women of childbearing potential), HIV-1 RNA, CD4+ cell count, CD8+ cell count, CD4/CD8 ratio, vital signs, weight, focused physical examination, eGFR, and assessment of AEs and concomitant medications will be performed at Day 1, Weeks 4, 12, 26, 38, 52, early termination (ET), and post-ET follow-up visits (note: complete physical examination will be performed at Day 1 and ET).

Thyroid will be assessed at screening, Day 1, Weeks 4, 12, 26, 38, and 52.

ECG will be performed at screening, Day 1, Weeks 26, and 52.

HIV-1 RNA will also be assessed at Weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52.

CCI [REDACTED]

CCI [REDACTED]

Plasma storage sample for virology testing at all visits except screening and Days 2 and 8.



Serum samples for immunogenicity assessment (antidrug antibody [ADA]) will be collected at Day 1 (predose) and Weeks 4, 12, 26, 38, and 52.

During the study, combination ART consisting of the baseline regimen (or a compatible regimen selected by the investigator) will be restarted in any participant who meets criteria for VF (HIV-1 RNA \geq 200 copies/mL that is confirmed upon repeat testing or has HIV-1 RNA \geq 200 copies/mL at study drug discontinuation).

Pharmacodynamic biomarkers: CCI

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CCI Fc-gamma receptor (FcγR) single nucleotide polymorphisms (SNP) will be evaluated using samples collected at the Day 1 visit (CCI analysis).

CCI If participants provide consent, a sample will be collected at the Day 1 visit but may be collected at any time during the study or at a separate study visit, if necessary.

Study procedures table can be found in [Appendix 1](#).

1.3. Sample Size and Power

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

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

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

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

VF = virologic failure.

Software: PASS® Version 14 (NCSS LLC, Kaysville, Utah, USA)

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

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

Prior to the final analysis, interim analyses have been completed. The results from these analyses may be submitted to scientific meetings and for publications and to regulatory agencies to seek guidance for the overall clinical development program.

2.1.1. Gilead Data Review Committee Analysis

The GDRC reviewed the progress, unblinded safety and efficacy data of this study. The GDRC convened after all participants enrolled in the Primary Cohort had completed their Week 12 visit or prematurely discontinued from the study.

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

2.2. Primary Analysis

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



2.4. Final Analysis

The final analysis will be performed after all participants have completed the study or prematurely discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The final analysis will include data from the Primary Cohort and the Pilot Cohort. This document describes the analysis plan for the Final Analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

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

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

Long Acting (LA) Regimen Period Analysis

Long-acting (LA) Regimen Period Analysis includes efficacy (ie, HIV-1 RNA and CD4 cell count and percentage) and safety data collected during **Long Acting Regimen Period** from participants randomized and received at least one dose of the complete long acting study drug regimen (ie, SC LEN + GS-5423 and GS-2872) up to ART restart (eg, Week 26). All data collected up to the last exposure date of LA regimen (defined in Section 3.8.1) will be summarized except for data on AEs, death and concomitant medications. For AEs, death and concomitant medications, only data collected prior to the last exposure date of LA regimen will be included. For participants who did not restart ART on or before last study date or have missing ARV restart date, all data will be included.

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

Whole Study Period Analysis

Whole Study Period Analysis includes efficacy (ie, HIV-1 RNA and CD4 cell count and percentage) and safety data collected during **Whole Study Period** from participants randomized and received at least one dose of study drug up to the end of the study (eg, Week 52). For efficacy summary, all HIV-1 RNA and CD4 data during the whole study will be included. For safety summary, all safety data collected up to the last exposure date (defined in Section 3.8.1) from participants who prematurely discontinued study or completed study will be included.

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

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized by treatment group and total.

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who have received at least one dose of the complete long acting study drug regimen (ie, SC LEN + GS-5423 and GS-2872), and do not have major protocol violation (defined as meeting exclusion criterion of having chronic hepatitis B virus (HBV) infection). This is the primary analysis set for efficacy analyses.

3.1.3. Per Protocol Analysis Set

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

- Did not have on-treatment HIV-1 RNA in the Week 26 analysis window, except when missing is due to discontinuation of study drug for lack of efficacy as in [Table 3-1](#). (Note: lack of efficacy is defined as having the check-box for Lack of Efficacy marked as the reason for premature study drug discontinuation on the study drug completion eCRF page.)
- Received partial or missed doses on Day 1 or Day 2.
- Prior receipt of any anti-HIV-1 mAbs (including ibalizumab).
- Have been treated with immunosuppressant therapies or chemotherapeutic agents (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies) within 4 weeks of study screening or have an anticipated need for such treatment during the study.

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

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

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

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

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

The Per Protocol Analysis Set is the secondary analysis set for efficacy analysis.

3.1.4. Safety Analysis Set

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

- The Safety Analysis Set includes all participants who were randomized and received at least 1 dose of study drug. This is the primary analysis set for safety analyses for whole study period. This analysis set will also be used to describe baseline information.
- The Safety Analysis Set for LA Regimen includes all randomized participants who have received at least one dose of the complete long acting study drug regimen (ie, SC LEN + GS-5423 and GS-2872). This is the primary analysis set for safety analyses for LA regimen period analysis.

3.1.5. Pharmacokinetic (PK) Substudy Analysis Set

The LEN PK Substudy Analysis Set includes all randomized participants who are enrolled in the optional PK Substudy, have received at least 1 dose of study drug, and have at least 1 nonmissing LEN concentration value reported by the PK laboratory test.

3.1.6. 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.
- GS-5423 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.
- GS-2872 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.

3.1.7. Immunogenicity Analysis Sets

The Immunogenicity analysis sets include the follows:

- Anti-GS-5423 Immunogenicity Analysis Set will include all randomized participants who have received at least 1 dose of study drug and have had at least 1 nonmissing value for anti-GS-5423 evaluation.
- Anti-GS-2872 Immunogenicity Analysis Set will include all randomized participants who have received at least 1 dose of study drug and have had at least 1 nonmissing value for anti-GS-5423 evaluation.
- Anti-GS-5423 and Anti-GS-2872 Immunogenicity Analysis Set will include all randomized participants who have received at least 1 dose of study drug and have had at least 1 nonmissing value for both anti-GS-5423 and anti-GS-2872 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 other analyses, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration. Templates of participant grouping can be found in [Appendix 6](#).

3.2.1. Grouping for Enrollment, Eligibility, Disposition, Demographics, Baseline Characteristics and Safety Analyses

For enrollment, eligibility, protocol deviation, disposition, demographics, baseline characteristics including baseline ARVs and safety analyses, participants will be grouped as follows for table summary:

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

3.2.2. Grouping for Efficacy Analyses

For efficacy analyses, participants will be grouped as follows for table summary:

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

No pooled analyses will be conducted on the efficacy.

3.2.3. Grouping for PK and Immunogenicity Analyses

For PK analysis of GS-5423 and LEN, as well as immunogenicity analysis of GS-5423 and GS-2872, participants will be grouped as follows for table summary:

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

For PK analysis of GS-2872, participants will be grouped as follows for table summary:

- Primary Cohort
 - Treatment Group 1: SC LEN + GS-5423 + GS-2872 10 mg/kg
 - Treatment Group 2: SC LEN + GS-5423 + GS-2872 30 mg/kg
- Pilot Cohort
 - Treatment Group 1: SC LEN + GS-5423 + GS-2872 10 mg/kg
 - Treatment Group 2: SC LEN + GS-5423 + GS-2872 30 mg/kg
- Pooled Cohorts
 - Treatment Group 1: SC LEN + GS-5423 + GS-2872 10 mg/kg

— Treatment Group 2: SC LEN + GS-5423 + GS-2872 30 mg/kg

PK results of GS-2872 will not be summarized across the treatment groups.

3.3. Strata and Covariates

There is no stratification for randomization for the Primary Cohort.

Regarding the optional Pilot Cohort, randomization has been stratified by the antibody (GS-5423 or GS-2872) to which the participant is sensitive, but the strata will not be used in the analyses because of the small sample size of the study.

3.4. Examination of Participant Subgroups

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

3.5. Multiple Comparisons

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

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

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.

Missing PK sampling dates may be imputed based on other visit information. Missing PK sampling times may be imputed to nominal times. Missing drug concentrations will not be imputed.

3.6.2. Outliers

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

Individual study drug concentration values may be identified as outliers by the clinical pharmacokineticist and excluded from concentration summary tables and figures and from the noncompartmental PK analysis. Outlier drug concentrations will be identified in the concentration listing along with the justification for exclusion.

3.7. Data Handling Conventions and Transformations

3.7.1. Data Handling Conventions and Transformations for Non-PK Data

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.

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.

For other non-PK data that are continuous in nature but are less than the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) will be imputed as follows:

- A value that is 1 unit less than the LLOQ will be used to calculate descriptive statistics if the datum is reported in the form of “< x” (where x is considered the LLOQ). 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 ULOQ will be used to calculate descriptive statistics if the datum is reported in the form of “> x” (where x is considered the ULOQ). Values with decimal points will follow the same logic as above.
- The limit of quantification will be used to calculate descriptive statistics if the datum is reported in the form of “≤ x” or “≥ x” (where x is considered the limit of quantification).

3.7.2. Data Handling Conventions and Transformations for PK Data

Natural logarithmic transformation will be used for non-BLQ drug concentrations and analysis of PK parameters. Concentration values that are below the limit of quantitation (BLQ) will be presented as “BLQ” in the concentration data listing.

For summary statistics, BLQ values will be treated as zero at predose and postdose time points. 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 predose concentration 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 in the summary table; otherwise, order statistics and summary statistics will be displayed in the summary table.

The following conventions will be used for the presentation of order statistics for postdose time points in the summary table:

- 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 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 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 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 values of “BLQ” for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as “BLQ”.

Similarly, for PK concentration plottings, if more than one-third of the participants have a concentration values of BLQ, then the mean and standard deviation are not displayed at that timepoint; and if more than one-half of the participants have a concentration values of BLQ, then the median and quartiles are not displayed at that timepoint.

Concentration related PK parameters (eg, C_{max} and C_{26wk}) that are BLQ will be excluded before log transformation or statistical model fitting and displayed as described above.

3.8. Analysis Visit Windows

Nominal visits will be used for the Pharmacokinetic and Immunogenicity summaries. Details for analysis visit windows used for efficacy and safety analyses in the final analysis can be found [Section 3.8.2](#).

3.8.1. Definition of Key Dates and Study Day

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

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

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

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

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

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

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

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

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

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

- the earliest date of last study day or ART restart day for participants who prematurely discontinued study or complete study, or

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

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

ART Restart Date is defined as the date when ART is resumed.

3.8.2. Analysis Visit Windows

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

The analysis windows for HIV-1 RNA, CD4+ cell count, CD8+ cell count, CD4 %, Hematology, Chemistry, Lipid Panel, Urinalysis, Urine Chemistry, Urine Pregnancy Laboratory Tests, Vital Signs, Weight and ECG are provided in [Table 3-2](#) to [Table 3-4](#).

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

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

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

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

Table 3-4. Analysis Windows for ECG

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

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, early termination (ET) data will be assigned to what would have been the next scheduled visit where the respective data were scheduled to be collected.

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

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

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

- For baseline, the last nonmissing value on or prior to the first dose date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data (except for HIV-1 RNA, see below), or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety ECG findings) for categorical data.
- For postbaseline values:
 - The record closest to the nominal day for that visit will be selected with the exception of CD4 cell counts, CD4%, and CD8 cell count in which the latest record will be selected and HIV-1 RNA level (see below).
 - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
 - If there is more than 1 record on the selected day, the average will be taken for continuous data (except for HIV-1 RNA, see below) and the worse severity will be taken for categorical data, unless otherwise specified.
- For baseline HIV-1 RNA, the latest (considering both date and time) record(s) on or prior to the first dose date and time of study drug will be selected.
- For postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected.
 - If both “HIV RNA COBAS 6800” and “HIV RNA TAQMAN 2.0” are available with the same collection time, the results from the “HIV RNA COBAS 6800” will be selected for analysis purpose.
 - 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.
 - If both “HIV RNA TAQMAN 2.0” and “HIV RNA Repeat” are available with the same collection time, the results from the “HIV RNA Repeat” will be selected for analysis purposes; otherwise, if there are multiple “HIV RNA TAQMAN 2.0” records with the same collection time, the geometric mean will be taken for analysis purposes.

If multiple valid nonmissing categorical observations exist in a window, records will be chosen as follows:

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

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A summary of participant enrollment will be provided by treatment group and total for each country, investigator within a country, and overall. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

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

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

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

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

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

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

- Reasons for premature study drug or study discontinuation

4.2. Extent of Study Drug Exposure and Administration

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

4.2.1. Duration of Exposure to Study Drug

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

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

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

Duration of exposure will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of participants exposed and remained through the following time periods: 1 day, 2 days, 4 weeks (28 days), 8 weeks (56 days), 16 weeks (112 days), 24 weeks (168 days), 26 weeks (182 days), 30 weeks (210 days), 34 weeks (238 days), 38 weeks (266 days), 42 weeks (294 days), 54 weeks (378 days), etc. Summaries will be provided based on the Safety Analysis Set for LA Regimen Period (up to 26 weeks) and for Whole Study Period separately (up to 54 weeks). No inferential statistics will be provided.

4.2.2. Study Drug Administration

Study drug administration for participants in the Primary Cohort and in the optional Pilot Cohort will be summarized by treatment groups for the following items:

- Number and percentage of participants who received oral LEN on Day 1 and Day 2, respectively
- Number and percentage of participants who received LEN SC injection on Day 1
- Number and percentage of participants who received IV infusion of GS-5423 on Day 1
- Number and percentage of participants who received IV infusion of GS-2872 on Day 1.

4.3. Protocol Deviations

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

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

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

4.4.3. Missed and Virtual Visits Due to COVID-19

A by-participant listing of participants with missed or virtual visits due to COVID-19 will be provided by participant ID number in ascending order.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in [Appendix 4](#).

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ Narrow search. A by-subject listing of AEs of COVID-19 will be provided if applicable.

4.4.5. Overall Assessment of COVID-19 Pandemic Impact

For subjects affected by COVID-19 infection and/or pandemic while participating in the study, a listing of the following individual COVID-19 related outcome categories will be provided:

- Death due to COVID-19
- Adverse event of COVID-19, as determined by COVID-19 SMQ narrow search
- Specific adverse event directly associated with the pathogen causing COVID-19, as determined by Medical Surveillance Team (MST)
- Hospitalization (using data from AE eCRF) due to adverse event of COVID-19 as defined above
- Tested positive for COVID-19
- Study drug discontinuation due to COVID-19
- Study discontinuation due to COVID-19
- Missed visits due to COVID-19
- Missed key assessments due to COVID-19, with Key assessments include the assessments contributing to primary and key secondary endpoints, including follows:
 - Missing reporting of any new treatment-emergent AE through Week 26 visit, or any update of existing treatment-emergent AE during the same period of time, could be further evaluated for missing key assessment
 - Missing HIV-1 RNA at Week 26 visit

In addition, composite broad COVID-19 impact indicator will be derived based on the following individual categories defined above: death, adverse event, hospitalization, tested positive, study drug discontinuation, study discontinuation, missed visits, and missed key assessments. Composite specific COVID-19 impact indicator will be derived based on death, specific adverse event, and tested positive.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, sex at birth, gender identity, sexual orientation, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m²]) 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_{CG} (mL/min)
- Duration of baseline ARV medication

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

5.3. Medical History

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

6. EFFICACY ANALYSES

Secondary endpoints of this study include efficacy endpoints as described below. For efficacy analyses (except for FDA-defined snapshot endpoints), two sets of analyses will be conducted unless otherwise specified: LA Regimen Period analysis and Whole Study Period analysis.

6.1. Secondary Efficacy Endpoints

6.1.1. Definition of the Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 26 as defined by the FDA-defined snapshot algorithm
- Proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 as defined by the FDA-defined snapshot algorithm
- Change from baseline in CD4+ cell counts at Weeks 26.

6.1.2. FDA-defined Snapshot Algorithm

The analysis window at Week 26 is defined as from Study Day 176 to Study Day 224, inclusive. All HIV-1 RNA data collected on-treatment (ie, data collected up to the earliest date of (196 days [28 weeks] after the dose date of complete long acting regimen, date of restarting ART) will be used in the US FDA-defined snapshot algorithm {[U. S. Department of Health and Human Services 2015](#)}. Virologic outcome will be defined as the following categories:

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

- No Virologic Data in the Week 26 Window: this includes participants who do not have on-treatment HIV-1 RNA data in the Week 26 analysis window because of the following:
 - a) Discontinuation of study drug prior to or in the Week 26 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL, or
 - b) Discontinuation of study drug prior to or in the Week 26 analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-treatment HIV-1 RNA < 50 copies/mL or,
 - c) Missing data during the window but on study drug.

The flowchart of the US FDA-defined snapshot algorithm is provided in [Appendix 2](#).

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

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

6.1.3. Analysis of Secondary Efficacy Endpoints

6.1.3.1. Analysis of the Proportion of Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 26 as determined by FDA-defined Snapshot Algorithm

The analysis of the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as determined by the US FDA-defined snapshot algorithm will be based on the FAS.

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

6.1.3.2. Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 26 as determined by FDA-defined Snapshot Algorithm

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

6.1.3.3. Analysis on CD4+ Cell Counts at Week 26

The changes from baseline in CD4+ cell count at Week 26 will be summarized by treatment group and overall for FAS using descriptive statistics. The change from baseline in CD4+ cell

count will also be summarized for other visits up to Week 26 for the LA Regimen Period Analysis, and up to Week 52 for the Whole Study Period Analysis.

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

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

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

6.2. Other Efficacy Endpoints

6.2.1. Definition of Other Efficacy Endpoints

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 26 as defined by 2 different missing data imputation methods specified in Section 6.2.2.1.
- The change from baseline in CD4 percentage (%), CD8 count, and CD4/CD8 Ratio at Week 26.

6.2.2. Analysis of Other Efficacy Endpoints

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

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

- Missing = Failure (M = F):
In this approach, missing data will be treated as virologic failure and summarized into the “missing” category (see list of HIV-RNA categories below).
- Missing = Excluded (M = E):
In this approach, missing data will be excluded in the computation of the percentages (ie, missing data points will be excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the FAS with nonmissing HIV-1 RNA value at that visit.

For both M = F and M = E analyses, the number and percentage of participants with HIV-1 RNA in the following categories will be summarized by treatment group and total for Week 26 and other visits up to Week 26 for the LA Regimen Period Analysis, and up to Week 52 for the Whole Study Period Analysis 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 secondary efficacy endpoint.

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 26 for the LA Regimen Period Analysis, and up to Week 52 for the Whole Study Period Analysis using the FAS.

6.2.2.2. Analysis of CD4 Percentage, CD8 Count, and CD4/CD8 Ratio

The change from baseline in CD4 percentage (%), CD8 count, and CD4/CD8 ratio will be based on the FAS and summarized for Week 26 and other visits up to Week 26 for the LA Regimen Period Analysis, and up to Week 52 for the Whole Study Period Analysis using descriptive statistics.

6.3. Changes from Protocol-Specified Efficacy Analyses

The definition of Full Analysis Set (FAS) is defined differently from the Protocol. Exclusion of participants who have major protocol violation (defined as meeting exclusion criterion of having chronic hepatitis B virus [HBV] infection) from the Full Analysis Set has been added in the SAP.

7. SAFETY ANALYSES

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

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

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment.” Relatedness to each study drug is justified by investigator and recorded on AE eCRF, for example, relatedness to Oral LEN is which investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment Oral LEN”. Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as follows:

- Any AEs leading to premature discontinuation of study drug, or
- Any AEs with an onset date on or after the study drug start date and
 - (i) prior to the last exposure date of LA Regimen Period for the LA Regimen Period Analysis
 - (ii) no later than the last exposure date for the Whole Study Period Analysis.

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:
 - The AE onset is the same as or after the month and year (or year) of the first dose date of study drug, and
 - The AE onset date is the same as or before the month and year (or year) of the last exposure date

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

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

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

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

7.1.6. Summaries of Adverse Events and Deaths

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

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

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

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

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

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

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

7.1.7. Additional Analysis of Adverse Events

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

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

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

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

Duration of the ISR will also be calculated and summarized. Duration of a given ISR event is defined as the ISR stop date minus the ISR onset date plus 1 day. For ISRs with ongoing stop date, stop date will be imputed as last study date or database finalization 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

Percentage of ongoing and resolved study drug related “Injection Site Induration” (one of preferred terms of ISR) will be summarized at both participant-level 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 related 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 related 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

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

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

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

Calcium Corrected for Albumin

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

Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + $0.8 \times (4.0 - \text{albumin (g/dL)})$

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

Estimated Glomerular Filtration Rate

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

$$\text{eGFR}_{\text{CG}} (\text{mL/min}) = [(140 - \text{age (yrs)}) \times \text{weight (kg)} \times (0.85 \text{ if female})] / (\text{SCr (mg/dL)} \times 72),$$

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

The analysis will be based on values reported in conventional units. When values are below the LLOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for selected laboratory test as follows:

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

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

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

7.2.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

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

If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed at any postbaseline visit will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

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

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

7.3. Body Weight and Vital Signs

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

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

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

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

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

7.4. Prior and Concomitant Medications

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

7.4.1. Nonstudy Drug Antiretroviral Medications

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

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

7.4.2. Prior and Concomitant Non-ARV Medications

Concomitant non-ARV medications are defined as non-ARV medications taken while a participant took study drug. Use of concomitant medications from Study Day 1 up to the last exposure date, will be summarized (number and percentage of participants) by treatment group and total, 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 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. Pharmacokinetic (PK) Sampling and PK Concentration

PK concentration data from serum PK samples of GS-5423 and GS-2872, as well as plasma PK samples of LEN (see Section 1.2.5.3) will be listed and summarized using the PK analysis sets. PK concentration data from PK substudy participants will be analyzed separately.

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

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

Table 8-1. Pharmacokinetic Parameters for Each Analyte

Analysis Set	Analyte	Sample Matrix	Parameters
LEN PK Substudy Analysis Set	LEN	Plasma	AUC_{0-26wk} , AUC_{last} , C_{26wk} , C_{max} , $C_{max\ day1}$, $t_{1/2}$, T_{last} , T_{max} , $T_{max\ day1}$
LEN PK Analysis Set	LEN	Plasma	C_{26wk} , $t_{1/2}$, T_{last}
GS-5423 PK Analysis Set	GS-5423	Serum	AUC_{0-26wk} , AUC_{last} , AUC_{inf} , $\%AUC_{exp}$, C_{26wk} , C_{max} , $t_{1/2}$, T_{max} , T_{last} , CL , V_{ss}
GS-2872 PK Analysis Set	GS-2872	Serum	AUC_{0-26wk} , AUC_{last} , AUC_{inf} , $\%AUC_{exp}$, C_{26wk} , C_{max} , $t_{1/2}$, T_{last} , T_{max} , CL , V_{ss}

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 group for the primary cohort, the pilot cohort, and for pooled cohorts. In addition, for LEN and GS-5423, individual participant concentration data for participants in the PK analysis set will be summarized for combined treatment groups (total) for the primary cohort, the pilot cohort, and for pooled cohorts. For the LEN PK substudy, individual participant concentration data for PK sample timepoints from Day 1 to Day 8 will be listed and summarized overall (i.e., one summary). 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 captured 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 3.7.2. Concentration values will be presented as received from the bioanalytical lab and summary statistics will be presented to three significant digits.

Participants with viral breakthrough (i.e., HIV-1 RNA \geq 50 copies/mL at Week 26 visit as defined by the FDA-defined snapshot algorithm) will be flagged in the listings.

8.3.1.1. PK Concentration Data Based on LEN PK Substudy Analysis Set

For analyses based on the LEN PK Substudy Analysis set, PK concentration will be summarized overall (i.e., one summary).

The following tables will be provided for LEN using the LEN PK Substudy Analysis Set:

- Individual participant concentration data and summary statistics

The following figures will be provided for LEN using the LEN PK Substudy Analysis Set:

- Mean (\pm 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.

8.3.1.2. PK Concentration Data Based on PK Analysis Sets

For analyses based on PK Analysis Sets, PK concentration for all analytes will be summarized for the primary cohort, the pilot cohort, and for pooled cohorts.

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

- 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:

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

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

- 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 (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 for LEN, GS-5423 and GS-2872 will be summarized as described in Section 3.2.3.

PK parameters listed in Table 8-1 will be included in the following tables.

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

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

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 (max titer of the post-baseline ADA / 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.

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.

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, and (c) Transient/Persistent ADA.

The numbers and percentages of participants within each ADA category described above will be summarized over the entire study period. In addition, the number and percentage of positive ADA 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 result, titer, and corresponding PK concentration by participant ID number and visit, as well as participant-level ADA 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 and total will be produced with ADA+ participants highlighted in red. If relevant, additional

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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 of participants in each ADA category.
- Numbers and percentages of positive ADA results by visit
- Median, Q1, Q3, minimum, maximum of titer values in positive ADA samples by visit

- Time to 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 and corresponding PK concentrations by participant ID and visit, as well as participant-level ADA status, ADA type (persistent or transient), and time to ADA onset 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 against both GS-5423 and GS-2872 will be included.

10. REFERENCES

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

11. SOFTWARE

SAS® Software Version 9.4. (SAS Institute Inc., Cary, NC, USA) is used for all programming of tables, listings, and figures.

PASS® Version 14 (NCSS, LLC; Kaysville, Utah, USA) is used for sample size and power calculation.

Phoenix WinNonlin® 8.3 (Pharsight Corporation, Princeton, NJ, USA) is used for pharmacokinetic/pharmacodynamic (PK/PD) analyses.

12. SAP REVISION

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

APPENDICES

Appendix 1.	Study Procedures Table
Appendix 2.	Flowchart of US FDA-defined Snapshot Algorithm (for Long Acting Switch Trial)
Appendix 3.	Adverse Events of COVID-19 and Suspected COVID-19 Infection
Appendix 4.	Adverse Events of COVID-19 and Suspected COVID-19 Infection
Appendix 5.	Programming Specifications
Appendix 6.	Table Shells for Participant Grouping

Appendix 1. Study Procedures Table

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

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

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

- For the Primary Cohort, screening procedures will be conducted in 2 parts: Part 2 will be performed once results of bNAb sensitivity testing from Part 1 are reviewed and participant is deemed eligible to proceed. For the optional Pilot Cohort, participants will be selected by the sponsor from the previously screened/failed participants in the Primary Cohort and will directly proceed to Screening Part 2 (no need to repeat Screening Part 1).
- Refer to Section 6.5.1 for Post-ET 30-, 90-, and 180-Day follow-up visits.
 - Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer patient to an appropriate HIV treatment facility.
- Vital signs: blood pressure, pulse, respiration rate, and temperature. On Day 1, vital signs should be recorded prior to start of study drug administration and 30 minutes (± 10 minutes) after completion of the GS-2872 infusion.
- Serum FSH test (required for female participants < 54 years of age who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure)
- HIV-1 genotype and phenotype testing for participants with virologic failure.

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- For ET visit, only single PK sample collection is required

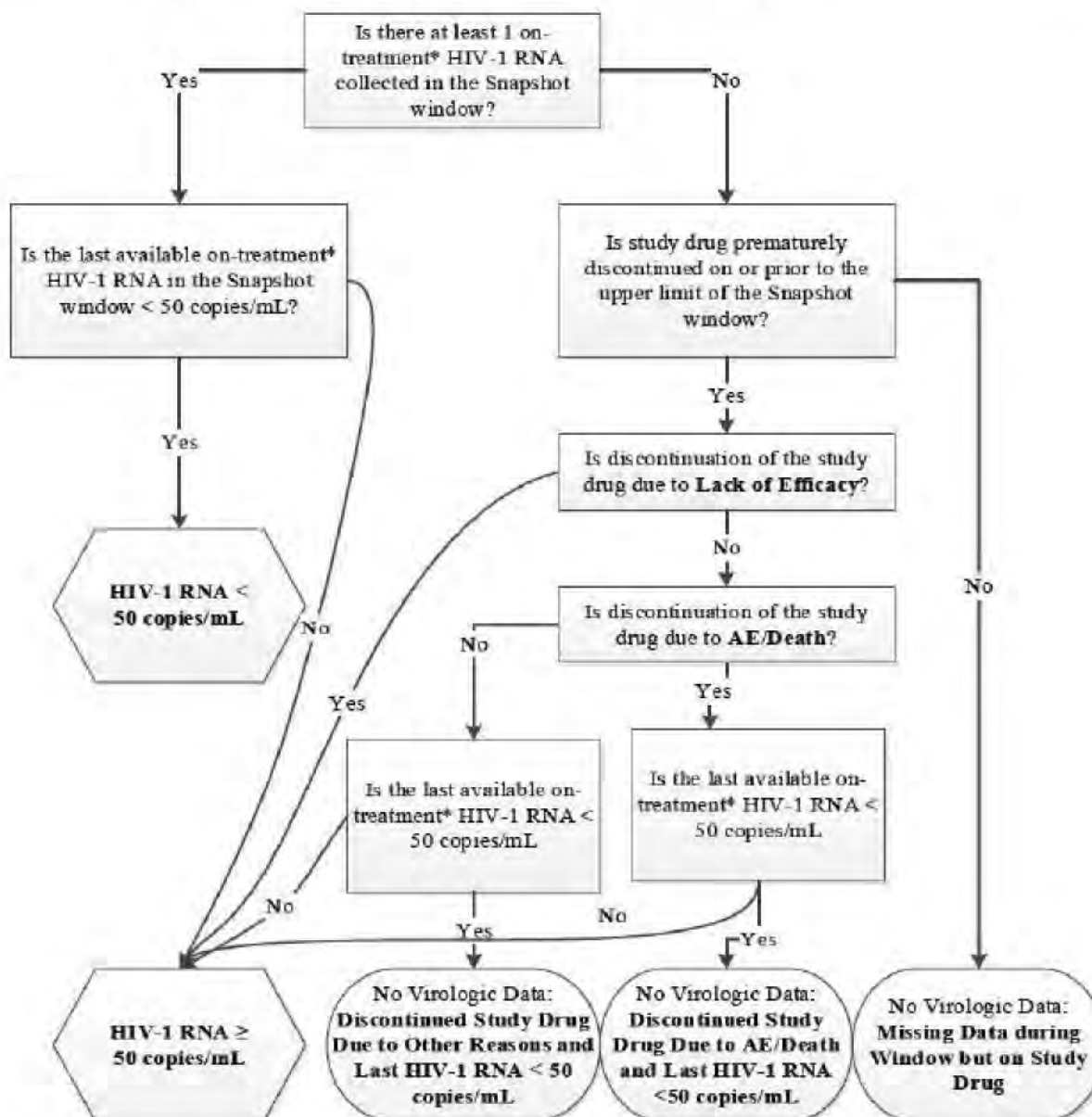
CCI

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

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

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



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

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

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

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

Appendix 3. Adverse Events of COVID-19 and Suspected COVID-19 Infection

An adverse event record will be flagged as adverse events for COVID-19 and Suspected COVID-19 infection if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the narrow search of the following COVID-19 SMQs under MedDRA v26.1 provided by Gilead GLPS (search name: COVID-19 (SMQ) – Narrow) and reviewed by Gilead medical monitors.

	SMQ Source
AEs for COVID-19 and Suspected COVID-19 infection	COVID-19 (SMQ) (Narrow Scope)

Appendix 4. Adverse Events of COVID-19 and Suspected COVID-19 Infection

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter “Visit missed due to COVID-19” and if an in-person visit was conducted virtually, sites were instructed to enter “Virtual visit due to COVID-19”.

Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of “COVID-19”, “Virtual”, or synonyms (see [Table Appendix-1](#)). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, “Missed visit” or “Virtual visit” will be assigned as follows:

- i. If COVID-19 terms are identified through NLP and the visit date is missing, then result is “Missed Visit”
- ii. If COVID-19 and Virtual terms are identified through NLP for a visit, then result is “Virtual Visit”. When there are multiple records for the same participant and the same visit, if one record could be categorized as “Virtual Visit”, all records associated with this participant and this visit will be categorized as “Virtual Visit”
- iii. Otherwise result is missing

Table Appendix-1. Examples of Searching Terms for “COVID-19” and “Virtual” Used to Identify Missed and Virtual Visits

Search Terms for “COVID-19”	Search Terms for “Virtual”
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Appendix 5. Programming Specifications

- 1) For categorical efficacy response (eg, Participants with HIV-1 RNA < 50 copies/mL or Participants with HIV-1 RNA \geq 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.

- 2) 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;
```

- 3) 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.
- 4) For figures, if at a visit where n (sample size) for any treatment group \leq 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.
- 5) 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.

- 6) 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.

- 7) Baseline ARV medication is defined as:

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

- 8) 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.

Appendix 6. Table Shells for Participant Grouping

Table Appendix-2. Participant Grouping for Enrollment, Eligibility, Disposition, Demographics, and Baseline Characteristics

Primary Cohort			Pilot Cohort			Pooled Cohorts
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	Total

Table Appendix-3. Participant Grouping for Efficacy Analyses

Primary Cohort			Pilot Cohort		
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total

Table Appendix-4. Participant Grouping for Safety Analyses

Primary Cohort			Pilot Cohort			Pooled Cohorts
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	Total

Table Appendix-5. Participant Grouping for PK Substudy Analyses of LEN

Pooled Cohort Total

Table Appendix-6. Participant Grouping for PK Analyses of GS-5423 and LEN

Primary Cohort			Pilot Cohort			Pooled Cohorts		
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total

Table Appendix-7. Participant Grouping for PK Analyses of GS-2872

Primary Cohort		Pilot Cohort		Pooled Cohorts	
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg

Table Appendix-8. Participant Grouping for Immunogenicity Analyses of Anti-GS-5423

Primary Cohort			Pilot Cohort			Pooled Cohorts		
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total

Table Appendix-9. Participant Grouping for Immunogenicity Analyses of Anti-GS-2872

Primary Cohort			Pilot Cohort			Pooled Cohorts		
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total

Table Appendix-10. Participant Grouping for Immunogenicity Analyses of Both Anti-GS-5423 and Anti-GS-2872

Primary Cohort			Pilot Cohort			Pooled Cohorts		
SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total	SC LEN + GS-5423 + GS-2872 10 mg/kg	SC LEN + GS-5423 + GS-2872 30 mg/kg	Total

GS-US-536-5816-Final-SAP v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM- yyyy hh:mm:ss)
PPD	Biostatistics eSigned	PPD
PPD	Project Team Leader eSigned	PPD