CLINICAL STUDY PROTOCOL

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
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	136260
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT04811040
Indication:	HIV-1 Infection
Protocol ID:	GS-US-536-5816
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 30 October 2020 Amendment 1: 06 April 2021 Amendment 2: 30 March 2022

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312).

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

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
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	136260 Not Applicable NCT04811040
Study Centers Planned:	Approximately 15-25 centers in the United States (US)
Objectives:	The primary objective of this study is as follows: • To evaluate the safety and tolerability of a combination of the broadly neutralizing antibodies (bNAbs) GS-5423 and GS-2872 (formerly 3BNC117-LS and 10-1074-LS, respectively) in combination with the HIV capsid inhibitor lenacapavir (LEN; GS-6207) The secondary objectives of this study are as follows: • To evaluate the efficacy of the study regimens determined by the proportion of participants maintaining virologic suppression (HIV-1 RNA < 50 copies/mL) at Weeks 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 The exploratory objectives are as follows: • To evaluate changes in HIV reservoir • To evaluate changes in immune biomarkers

Study Design:	A randomized, blinded, proof-of-concept (POC) study to evaluate the safety and efficacy of a single dose each of a long-acting regimen of LEN, GS-5423, and GS-2872 in adults with HIV-1 infection who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on oral antiretroviral treatment (ART). Participants who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of 2 treatment groups based on the dose of GS-2872. Participants will discontinue their background oral antiretroviral (ARV) regimen one day prior to receiving study drugs on Day 1. At Week 26, all participants will resume their background oral ARV baseline regimen (or compatible regimen selected by the investigator) and return to the clinic for visits at Weeks 38 and 52. Unblinded treatment assignments will be provided to the investigators after all participants are back on their baseline ARVs (or compatible regimen selected by the investigator) at Week 26 or have discontinued the study, and the Week 26 analysis has been completed.
Number of Participants Planned:	Approximately 20 in the Primary Cohort, up to 20 in the optional Pilot Cohort
Target Population:	Adults with HIV-1, no history of virologic failure (VF) or antiretroviral drug resistance, a CD4 nadir ≥ 350 cells/μL, on first-line ART for at least 2 years with demonstrated virologic suppression (HIV-1 RNA < 50 copies/mL) for at least 18 months prior to screening who are willing to modify their ARV regimen for an investigational strategy.
Duration of Treatment:	26 weeks

Diagnosis and Main Eligibility Criteria:	HIV-1 infected participants who meet the following criteria: • Age between 18 and 65 years at screening • On first-line ART for ≥ 2 years prior to screening. A change in ART regimen ≥ 28 days prior to screening for reasons other than VF (eg, tolerability, simplification, drug-drug interaction profile) is allowed • No documented historical resistance to the current ART regimen • Plasma HIV-1 RNA < 50 copies/mL at screening • Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 18 months preceding the screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL). Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening are acceptable. • Proviral phenotypic sensitivity 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, within 18 months 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 µg/mL; GS-2872 sensitivity is defined as IC_{90} ≤ 2 µg/mL • CD4+ count nadir ≥ 350 cells/µL • Screening CD4+ count ≥ 500 cells/µL • Availability of a fully active alternative ART regimen, in the opinion of the investigator, in the event of discontinuation of the current ART regimen with development of resistance • No comorbid condition requiring ongoing immunosuppression • No evidence of current hepatitis B virus (HBV) infection • No evidence of current hepatitis C virus (HCV) infection (prior infection cleared spontaneously or with treatment is acceptable) • No history of opportunistic infection or illness indicative of Stage 3 HIV disease

Study Procedures/ Frequency:	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. 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. 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 Optional PK Substudy). Participants will return for study visits on Weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52 for study assessments.

	A Gilead Data Review Committee (GDRC) analysis of Primary Cohort data will be conducted after the approximately 20 participants planned to be enrolled in the Primary Cohort reach Week 12. After GDRC review, the optional Pilot Cohort of up to 20 participants may be enrolled and will have the same treatments and assessments as the Primary Cohort. 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. HIV reservoir assays will be assessed at Day 1 (predose) and Week 52. Immune biomarker will be collected at Day 1 (predose), Weeks 4, 26, 38, and 52. Plasma storage sample for virology testing at all visits except screening and Days 2 and 8. Serum PK samples for GS-5423 and GS-2872 will be collected at the following time points for all participants: • Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872) • Single anytime sample at Weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52 Plasma PK samples for LEN will be collected at the following times for all participants:

	• Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872) • Single anytime sample at Weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52 Optional PK Substudy: If participants provide specific separate consent, plasma PK samples for LEN will be collected at the following times in a subset of participants (approximately n = 14 evaluable; approximately n = 7 from each treatment group): • Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872), 4 hours post oral LEN dose for loading, and 8 hours post oral LEN dose for loading • Day 2: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading) and single anytime sample between 1 and 6 hours post oral LEN dose for loading • Day 8: single anytime sample 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 ≥ 200 copies/mL that is confirmed upon repeat testing or has HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation).
	• Pharmacodynamic biomarkers: Peripheral blood mononuclear cell (PBMC), whole blood, serum, and plasma samples will be collected at Day 1 (predose) and Weeks 4, 26, 38, and 52 for exploratory analysis, which may include HIV-1 specific T-cell response, immune cell phenotyping, gene expression, antibody profiling, and soluble proteins (eg, cytokines, chemokines, inflammatory markers, etc.). Fc-gamma receptor (FcgR) single nucleotide polymorphisms (SNP) will be evaluated using samples collected at the Day 1 visit (exploratory analysis).

<table>
<tr><td></td><td>• Optional pharmacogenomic testing: 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.</td></tr>
<tr><td>Product, Dose, and Mode of Administration:</td><td>
<table>
<tr><th>Study Day</th><th>Treatment Group 1</th><th>Treatment Group 2</th></tr>
<tr><td>Day 1</td><td>LEN 600 mg (two 300 mg tablets, PO)
LEN 927 mg (two 1.5 mL injections, SC)
GS-5423 30 mg/kg (IV infusion)
GS-2872 10 mg/kg (IV infusion)</td><td>LEN 600 mg (two 300 mg tablets, PO)
LEN 927 mg (two 1.5 mL injections, SC)
GS-5423 30 mg/kg (IV infusion)
GS-2872 30 mg/kg (IV infusion)</td></tr>
<tr><td>Day 2</td><td>LEN 600 mg (two 300 mg tablets, PO)</td><td>LEN 600 mg (two 300 mg tablets, PO)</td></tr>
</table>
</td></tr>
<tr><td>Reference Therapy, Dose, and Mode of Administration:</td><td>None</td></tr>
<tr><td>Criteria for Evaluation:</td><td></td></tr>
<tr><td>Safety:</td><td>Incidence of treatment-emergent AEs and treatment-emergent clinical laboratory abnormalities</td></tr>
<tr><td>Immunogenicity:</td><td>Proportion of participants positive with anti-GS-5423 or anti-GS-2872 antibodies</td></tr>
<tr><td>Efficacy:</td><td>• Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 26 as defined by the Food and Drug Administration (FDA)-defined snapshot algorithm
• Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as defined by the FDA-defined snapshot algorithm
• Change from baseline in CD4+ cell counts at Week 26
• Treatment-emergent resistance to study drugs</td></tr>
<tr><td>Pharmacokinetics:</td><td>PK parameters for GS-5423, GS-2872, and LEN (and metabolites, if applicable), as appropriate: AUC_{0-t}, AUC_{last}, $t_{1/2}$, C_{max}, T_{max}, T_{last}, C_t</td></tr>
<tr><td>Statistical Methods:</td><td>Study endpoints will be assessed in the Primary Cohort excluding the optional Pilot Cohort. Exploratory analysis may be conducted for the optional Pilot Cohort as applicable.</td></tr>
</table>

	Safety: Treatment-emergent AEs, serious adverse events (SAEs), and AEs leading to permanent study drug discontinuation will be summarized by treatment group, system organ class (SOC), and preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory results and change from baseline values for selected laboratory tests will be summarized by treatment group and visit. The incidence of treatment-emergent laboratory abnormalities will be summarized by treatment group. Vital signs and ECG data will be summarized by treatment group. **Immunogenicity:** The proportion of participants with detectable anti–GS-5423 or anti–GS-2872 antibodies at each specified time point will be summarized by treatment group. **Efficacy:** The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 26 as defined by the FDA-defined snapshot algorithm will be summarized by treatment group and overall using the Full Analysis Set. The 95% CIs will be constructed using the exact method. These efficacy endpoints will be compared between treatment groups by Fisher exact test.

	The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as defined by the FDA-defined snapshot algorithm will also be summarized by treatment group and overall in a similar manner. The change from baseline in CD4+ cell count at Week 26 will be summarized using descriptive statistics by treatment group. Treatment-emergent resistance to study drugs will be summarized by treatment group. **Pharmacokinetics:** Serum or plasma concentrations and PK parameters for GS-5423, GS-2872, and LEN (and metabolites, if applicable) will be listed and summarized for each analyte using descriptive statistics by treatment group or overall, as appropriate. **Sample Size:**

	Although the sample size in this study is determined based on practical considerations and past experience with similar types of studies, assuming the 2 treatment groups have a similar virologic suppression rate, a total of 20 participants in the Primary Cohort will provide at least 35% power to show the lower bound of 95% CI for Week 26 virologic response rate (HIV-1 RNA < 50 copies/mL as defined by the FDA-defined snapshot algorithm) 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). A total of approximately 20 participants in the Primary Cohort will provide reasonable assessment of safety and PK. A total of up to 20 participants in the optional Pilot Cohort is based on practical considerations.

This study will be conducted in accordance with the guidelines of Good Clinical Practice including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	antidrug antibodies
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATI	analytical treatment interruption
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{0-t}	partial area under the concentration versus time curve from time "0" to time "t"
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
BCRP	breast cancer resistance protein
BLQ	below the limit of quantitation
bNAbs	broadly neutralizing antibodies
BUN	blood urea nitrogen
CBC	complete blood count
CD4	cluster determinant 4
CD8	cluster determinant 8
CI	confidence interval
CK	creatine kinase
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C_t	concentration at a particular time (t)
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	concentration at the end of the dosing interval
CYP	cytochrome P450 enzyme
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form

eGFR	estimated glomerular filtration rate
ET	early termination
eTMF	electronic trial master file
EU	European Union
EudraCT	European Clinical Trials Database
FcRn	neonatal Fc receptor
FcgR	Fc-gamma receptor
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDRC	Gilead Data Review Committee
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GLPS	Global Patient Safety (formerly Pharmacovigilance and Epidemiology)
gp	glycoprotein
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HLGT	high-level group term
HLT	high-level term
IB	investigator's brochure
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
Ig	immunoglobulin
IQ	inhibitory quotient
IRB	institutional review board
IRT	interactive response technology
ISR	injections site reaction
IV	intravenous
LDH	lactate dehydrogenase
LEN	lenacapavir, GS-6207
LLOQ	lower limit of quantitation
LLT	lower-level term
mAbs	monoclonal antibodies

MedDRA	Medical Dictionary for Regulatory Activities
NaS	LEN injection
NaSP	LEN injection with poloxamer
NOAEL	no observed adverse effect level
$paEC_{95}$	protein-adjusted 95% effective concentration
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PLWH	people living with HIV
POC	proof of concept
PO	by mouth
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDR	source data review
SDV	source data verification
SNP	single nucleotide polymorphisms
SOC	system organ class
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TE	treatment experienced
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
TN	treatment naive
TSH	thyroid-stimulating hormone
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T3	triiodothyronine
T4	thyroxine
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
ULQ	upper limit of quantitation
URI	upper respiratory infection
US	United States

VF	virologic failure
VR	virologic rebound

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus type 1 (HIV-1) infection causes a serious life-threatening disease and remains one of the leading causes of morbidity and mortality worldwide. In the United States (US), there are approximately 1 million people living with HIV (PLWH) infection, and globally there are over 38 million {UNAIDS 2021}. Advances in antiretroviral (ARV) therapy (ART) for HIV have led to significant improvements in morbidity and mortality by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. However, current therapeutic strategies have been unable to eliminate the virus and cure HIV-1 infection.

While current combination ART for the treatment of HIV-1 infection is efficacious and well tolerated, these agents need to be taken every day and require near-perfect adherence to minimize the emergence of drug-resistant variants. As a result, "treatment fatigue" can occur, defined as "decreased desire and motivation to maintain vigilance in adhering to a treatment regimen" among patients prescribed chronic or lifelong treatment {Claborn 2015}, which can lead to nonadherence and treatment failure. As such, there remains a significant medical need for ARVs that can be administered less frequently (ie, long-acting drug products), thereby providing an alternative treatment option for HIV-1 infected individuals.

Monoclonal antibodies (mAbs) with neutralizing activity against HIV-1 envelope glycoproteins of increasing potency and breadth have been identified {Burton 2015} and the parenteral administration of broadly neutralizing mAbs produce significant reductions in plasma viremia in untreated patients and have maintained virologic suppression in virologically suppressed patients who have received broadly neutralizing antibodies (bNAbs) prior to undergoing analytic treatment interruption {Caskey 2015, Caskey 2017, Mendoza 2018}. Antibodies can be long-acting and have the potential to mitigate the challenges or lifelong adherence to daily therapy. Antibodies also engage the immune system which may contribute to a beneficial HIV-specific immune response {Niessl 2020}, including the clearance of latently infected cells, that is not achieved by ARV drugs. As biologics, bNAbs may spare patients from adverse effects associated with chronic ARV therapy. HIV-1, however, is a diverse virus whose variants have varying levels of sensitivity for any bNAb. Therefore, bNAbs identified to date have incomplete breadth when measured for their ability to neutralize a diversity of HIV-1 isolates {Nishimura 2017}. 3BNC-117 and 10-1074 are two of the most potent bNAbs that have been identified and clinically tested {Mouquet 2012, Scheid 2011}. However, viral resistance to bNAbs can occur after antibody titer wanes via mutation {Bar-On 2018}. Combination therapy of bNAbs with an ARV drug may overcome this limitation and enable a safe long-acting treatment option for PLWH.

1.2. Information About GS-5423, GS-2872, and Lenacapavir

GS-5423

GS-5423 (formerly 3BNC117-LS) is a recombinant, fully human anti–HIV-1 antibody of the immunoglobulin (Ig) G1κ isotype that targets the CD4 binding site of HIV-1 glycoprotein (gp) 120 and shows neutralization activity against > 80% of viral strains. GS-5423 is the same molecule as 3BNC117 with the exception of 2 amino acid substitutions of Met to Leu at Fc position 428 (M428L), and Asp to Ser at Fc position 434 (N434S), which enhance the antibody's affinity to the neonatal Fc receptor (FcRn) and prolong its half-life in vivo.

GS-2872

GS-2872 (formerly 10-1074-LS) is a recombinant, fully human monoclonal antibody of the IgG1λ isotype that specifically binds to the V3 loop within the HIV external membrane glycoprotein, gp120. GS-2872 is the same molecule as the original antibody 10-1074 with the exception of the 2 amino acid substitutions in the Fc domain (M248L and N434S), which were made to extend the half-life in vivo.

Lenacapavir

Lenacapavir (LEN; GS-6207) is a novel, first-in-class, selective inhibitor of HIV-1 capsid function, which has potent antiviral activity, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

The investigational regimen combines 2 potent bNAbs, GS-2872 and GS-5423, targeting nonoverlapping epitopes on HIV-1 envelope with LEN, a potent first-in-class inhibitor of HIV-1 capsid function. Each drug has established antiviral activity and safety. Their complementary mechanisms of action and compatible long half-lives allow the study regimen to be dosed only once every 6 months while maintaining therapeutic drug levels.

1.2.1. General Information

GS-5423

The HIV bNAb GS-5423 (3BNC117-LS) and the original antibody from which it is derived, 3BNC117, have been characterized in nonclinical and clinical studies, including studies in combination with the bNAb GS-2872 (in the case of GS-5423) or 10-1074 (in the case of 3BNC117). For further information, refer to the current investigator's brochure (IB) for GS-5423 (formerly 3BNC117-LS).

GS-2872

The HIV bNAb GS-2872 (10-1074-LS) and the original antibody from which it is derived, 10-1074, have been characterized in nonclinical and clinical studies. For further information, refer to the current IB for GS-2872 (formerly 10-1074-LS).

Lenacapavir

The HIV capsid inhibitor LEN has been previously characterized in nonclinical and clinical studies. For further information, refer to the current IB for LEN.

1.2.2. Preclinical Pharmacology and Toxicology

GS-5423

A Good Laboratory Practice (GLP) 25-day twice weekly intravenous (IV) and subcutaneous (SC) toxicity study with a 47-day recovery period in male and female Sprague Dawley rats was conducted with 3BNC117, the precursor antibody for GS-5423. Chronic, active inflammation with or without hemorrhage was noted at the SC injection sites but reversed after the recovery period. Antidrug antibodies (ADA) were detected in some animals in the IV and SC dose groups with no dose dependency. No 3BNC117-related adverse toxicological effects were observed in main or recovery group animals administered IV or SC doses of up to 60 mg/kg/injections, which was considered the no observed adverse effect level (NOAEL) for animals dosed twice weekly for 4 weeks with 3BNC117.

GS-5423 has the same antigen binding characteristics as 3BNC117 as evaluated in a GLP-compliant tissue cross-reactivity study with human tissues. No significant staining was observed. The physiochemical characteristics and biological efficacy showed that GS-5423 and 3BNC117 are similar in all characteristics, except for expected differences in pharmacokinetics (PK) due to amino acid substitutions in the Fc domain (M248L and N434S). The results of toxicology studies for the precursor antibody, 3BNC117 would be expected to predict the safety of GS-5423 when administered with similar drug exposures. For further information, refer to the current IB for GS-5423 (formerly 3BNC117-LS).

GS-2872

A GLP 25-day twice weekly IV and SC toxicity study with a 45-day recovery period in male and female Sprague Dawley rats was conducted with 10-1074, the precursor antibody for GS-2872. Additionally, the combination of 10-1074 with 3BNC117 (once weekly IV injections each) were assessed for toxicity at a dose level of 60 mg/kg/antibody/injection. The ADAs were detected in some animals in the IV and SC dose groups with no dose dependency. No 10-1074-related toxicological effects were observed in main or recovery group animals administered IV or SC doses of up to 60 mg/kg/injections or in the combination dosing with 10-1074 and 3BNC117. The 60 mg/kg/injection dose was considered the NOAEL for animals dosed twice weekly for 4 weeks with 10-1074 alone or dosed once weekly in combination with 3BNC117.

GS-2872 has the same antigen binding characteristics as 10-1074 as evaluated in a GLP-compliant tissue cross-reactivity study with human tissues. No significant staining was observed. The results of toxicology studies for the precursor antibody, 10-1074 would be expected to predict the safety of GS-2872 when administered with similar drug exposures. For further information, refer to the current IB for GS-2872 (formerly 10-1074-LS).

Lenacapavir

The potential systemic toxicology of LEN has been characterized through single-dose IV, repeat-dose SC, and repeat-dose oral administration of LEN. The GLP SC toxicity 6-month rat study and 9-month dog studies are completed. Reversible liver changes were observed after a large single-dose IV administration to dogs. Expected granulomatous inflammation has been observed at the SC injection sites. A second 9-month SC toxicity study in dog was initiated in January 2020. The purpose is to administer higher doses in order to evaluate higher exposure margins than in the previous studies. No adverse events (AEs) have been observed in embryo-fetal toxicity studies in rat and rabbit, or in a male and female rat fertility study.

1.2.3. Clinical Experience for GS-5423 and GS-2872

1.2.3.1. GS-5423 and GS-2872

Clinical experience with the parental antibodies 3BNC117 and with 10-1074 alone and in combination are presented in the respective IBs. In aggregate, the clinical experience with > 160 participants who have received infusions of either bNAb alone or in combination indicates that the bNAbs are generally safe and well tolerated, with the majority of AEs being transient and Grade 1. Repeat doses of both antibodies in combination have been administered over 4, 6, and 16 weeks, and 3BNC117 has been administered over 27 weeks.

These data present a summary of available data for GS-5423 and GS-2872 from a first-in-human (FIH) Phase 1 study of GS-5423 in PLWH and uninfected individuals (Study YCO-0946) and a Phase 1 dose escalation, FIH study of GS-2872 alone and in combination with GS-5423 in PLWH and uninfected individuals (Study YCO-0971).

1.2.3.2. Study YCO-0946: First-in-Human Study of GS-5423 (3BNC117-LS) in HIV-Infected and Uninfected Individuals

This was a Phase 1, dose escalation, open-label FIH study of the safety and PK of GS-5423 (3BNC117-LS) administered IV to PLWH suppressed on ART and administered either IV or SC in HIV-uninfected participants by Rockefeller University. Participants received a single dose of GS-5423 at one of the following dose levels: 3 mg/kg, 10 mg/kg, or 30 mg/kg administered IV, or a single SC injection of GS-5423 or placebo at 150 mg or 300 mg.

A total of 43 participants were enrolled (31 HIV-uninfected and 12 HIV-infected individuals on suppressive ART) from September 2017 to May 2019; 39 received GS-5423 and 4 received placebo. Two manufacturing lots were used for this study. The manufacturing process for lot 2 was the same as that for lot 1 except for the addition of a supplement to increase sialic acid content in order to increase serum half-life. Four participants were lost to follow-up. All enrolled PLWH remained on ART during study follow-up, according to protocol. Follow-up was completed on 07 April 2020. As GS-5423 was produced for the current protocol using the manufacturing process for lot 2 and will be administered 30 mg/kg IV, only the relevant preliminary PK data (following a single dose of GS-5423 at 30 mg/kg from lot 2) are presented in Table 1-1. Safety data from all cohorts are summarized.

Safety Results

The occurrence of AEs was assessed at multiple time points following administration of the study products. Four participants reported a single reactogenicity event (nausea, headache, tenderness, and malaise/fatigue), all were graded as mild (Grade 1). A single local reactogenicity event has been reported (Grade 1 tenderness) following SC administration. Serious adverse events (SAEs) were reported for 2 participants (cellulitis and transient ischemic attack); neither was judged as related to study drug. There were 44 nonreactogenicity AEs reported to date, with 79.5% of the reported AEs of Grade 1 severity (one of which was an SAE). Six reported AEs were of Grade 2 severity, 2 were of Grade 3 severity (hyperalbuminuria and cellulitis, the latter reported as an SAE), and 1 was of Grade 4 severity (hypokalemia). The Grade 1 SAEs and Grade 3 and 4 AEs were:

- SAE Grade 1 transient ischemic attack – Transient ischemic attack was reported in 1 participant whose workup revealed a vascular anatomic abnormality treated with a stent and was judged not related to study drug.

- Grade 3 hyperalbuminuria – Baseline urinalysis showed 100 mg/dL albumin prior to study drug infusion in a participant with trace proteinuria at screening and was judged not related to study drug.

- SAE Grade 3 cellulitis – Cellulitis was judged not related to study drug and resolved with treatment.

- Grade 4 hypokalemia – Serum potassium was 3.0 mEq/L 1 week after SC injection in a participant with no symptoms and no concomitant study drugs associated with hypokalemia. At Week 2, the participant's potassium level was 4.0 mEq/L.

One pregnancy was reported at Week 36 in a participant who received study drug or placebo SC. The participant reported spontaneous abortion at approximately 10 weeks gestational age. The pregnancy and miscarriage event were judged not related to study drug.

Table 1-1. Study YCO-0946: Summary of Reported Adverse Events

AEs Table	No. AEs	No. Mild (Grade 1)	No. Moderate (Grade 2)	No. Severe (Grade 3)	No. Potentially Life-Threatening (Grade 4)	No. of Participants (N = 39)	% of Participants
0-28 Days from Study Drug Dosing							
Solicited							
Nausea	1	1	—	—	—	1	2.6
Headache	1	1	—	—	—	1	2.6
Tenderness	1	1	—	—	—	1	2.6
Malaise/fatigue	1	1	—	—	—	1	2.6

AEs Table	No. AEs	No. Mild (Grade 1)	No. Moderate (Grade 2)	No. Severe (Grade 3)	No. Potentially Life-Threatening (Grade 4)	No. of Participants (N = 39)	% of Participants
Unsolicited							
URI	4	4	—	—	—	4	10.3
Dizziness	2	2	—	—	—	2	5.1
Vulvovaginal candidiasis	2	2	—	—	—	1	2.6
Abdominal pain	1	1	—	—	—	1	2.6
Borborygmus	1	1	—	—	—	1	2.6
Cellulitis	1	—	—	1	—	1	2.6
Contact dermatitis	1	1	—	—	—	1	2.6
Elevated creatinine	1	1	—	—	—	1	2.6
Gonorrhea	1	1	—	—	—	1	2.6
Hematoma	1	1	—	—	—	1	2.6
Hyperalbuminuria	1	—	—	1	—	1	2.6
Hyperbilirubinemia	1	—	1	—	—	1	2.6
Hypokalemia	1	—	—	—	1	1	2.6
Muscle twitching	1	1	—	—	—	1	2.6
Ocular pruritis	1	1	—	—	—	1	2.6
Pruritis	1	1	—	—	—	1	2.6
Pruritis at injection site	1	1	—	—	—	1	2.6
Urethral chlamydia	1	1	—	—	—	1	2.6
Worsening hypertension	1	—	1	—	—	1	2.6
Subtotal AEs	28	23	2	2	1	—	—
> 28 Days from Study Drug Dosing							
Solicited	—	—	—	—	—	—	—
Unsolicited							
URI	5	4	1	—	—	4	10.3
Decreased hemoglobin	2	2	—	—	—	2	5.1
Musculoskeletal pain	2	2	—	—	—	2	5.1
Worsening hypertension	2	1	1	—	—	2	5.1
Anemia	1	1	—	—	—	1	2.6
Chalazion	1	1	—	—	—	1	2.6
Elevated creatinine	1	—	1	—	—	1	2.6

AEs Table	No. AEs	No. Mild (Grade 1)	No. Moderate (Grade 2)	No. Severe (Grade 3)	No. Potentially Life-Threatening (Grade 4)	No. of Participants (N = 39)	% of Participants
Fatigue	1	1	—	—	—	1	2.6
Lipodystrophy	1	1	—	—	—	1	2.6
Miscarriage	1	—	1	—	—	1	2.6
Transient ischemic attack	2	2	—	—	—	1	2.6
Vomiting	1	1	—	—	—	1	2.6
Subtotal AEs	20	16	4	—	—	—	—
Total reported AEs	48	39	6	2	1	25	64.1

AE(s) = adverse event(s); URI = upper respiratory infection

Laboratory abnormalities of moderate or severe grade were uncommon and are summarized in Table 1-2. Both HIV-1 viral load and CD4 counts were monitored in ART-treated participants and have generally remained stable during follow-up.

Table 1-2. Study YCO-0946: Postinfusion Laboratory Abnormalities of Moderate or Severe Grade

Postinfusion Laboratory Results	Number of Participants with Moderate Laboratory Abnormalities	Number of Participants with Severe Laboratory Abnormalities	Number of Participants with Life-Threatening Abnormalities
Chemistry			
Total bilirubin	2	—	—
Direct bilirubin	—	1	—
Creatinine	1	—	—
AST	2	—	—
ALT	2	—	—
Potassium (decreased)	—	—	—
Hematology			
Hemoglobin (decreased)	16	—	—
Neutrophils (decreased)	3	1	—
Lymphocytes (decreased)	2	—	—

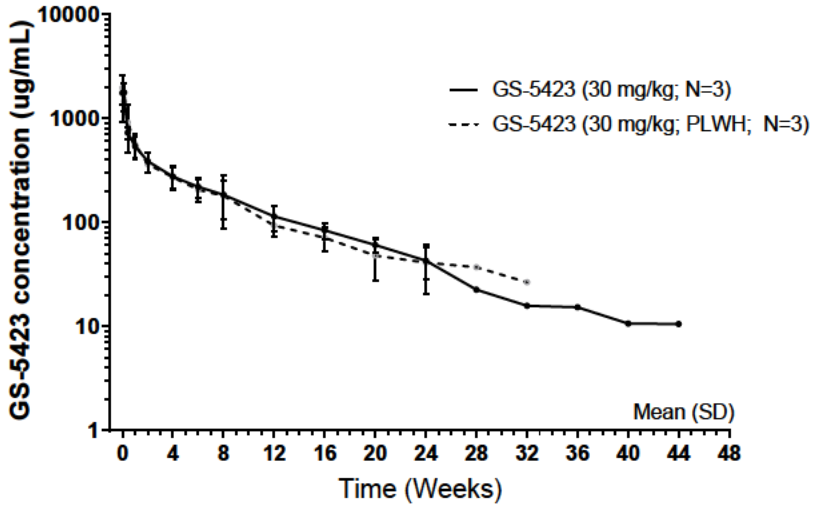
ALT = alanine aminotransferase; AST = aspartate aminotransferase

In summary, GS-5423 (3BNC117-LS) was generally well tolerated at all doses tested when administered IV or SC. The most frequently reported AEs within 28 days of study drug administration were Grade 1 upper respiratory infections (URIs; 9.7%), dizziness (4.7%), and nausea (4.7%).

Pharmacokinetics of GS-5423 (3BNC117-LS)

Preliminary concentration-time profiles of GS-5423 following a single dose of 30 mg/kg GS-5423 in healthy volunteers or in PLWH who were ART suppressed are presented in Figure 1-1. Preliminary data suggest the average half-life of GS-5423 is 62 days.

Figure 1-1. Study YCO-0946: Preliminary Concentration-Time Profiles of Serum GS-5423 (3BNC117-LS)

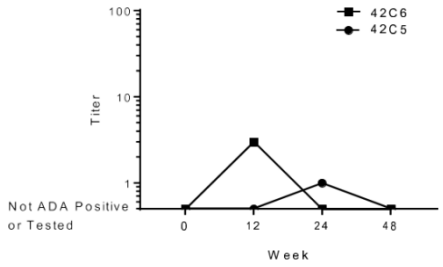


PLWH = people living with HIV

Antidrug Antibodies

Serum samples from participants enrolled in Part A of the study (Groups 1A-1C and 2A-2C) were tested for the presence of ADA. Samples from Weeks 0, 12, 24, and 48 were tested. Of 83 samples tested, 6 were found to be positive for anti-3BNC117 antibodies in the Tier 1 screening assay, and 2 of these 6 samples, deriving from 2 of the 21 tested participants, were confirmed to be specific anti-3BNC117 antibody responses in Tier 2 testing. These 2 responses were considered "treatment-induced," but returned to baseline levels at Week 48 (Figure 1-2). These transient responses were not associated with AEs or different antibody decay kinetics.

Figure 1-2. Study YCO-0946: Anti-GS-5423 (Anti-3BNC117-LS) Antibody Response Titers



ADA = antidrug antibody

Analysis of samples from participants enrolled in Part B of the study is ongoing.

1.2.3.3. Study YCO-0971: First-in-Human Study of GS-2872 (10-1074-LS) Alone and in Combination with GS-5423 (3BNC117-LS) in HIV-Infected and Uninfected Individuals

Study YCO-0971 is a Phase 1, dose escalation cohort study of GS-2872 administered IV or SC alone in HIV-uninfected individuals at SC doses of 140 or 280 mg or in combination with GS-5423 at doses ranging from 60 mg to 100 mg of GS-2872 and 200 mg to 240 mg of GS-5423 and groups that received IV infusions (HIV-uninfected and PLWH) of either GS-2872 alone at doses ranging from 3 to 30 mg/kg, or GS-2872 in combination with GS-5423 at 30 mg/kg of each antibody. Participants were followed for 48 weeks following last antibody dose.

A total of 69 participants were enrolled in the study and treated with GS-2872 or a combination of GS-2872 and GS-5423; 44 received the antibodies SC and 25 received the antibodies IV.

Safety Summary

Adverse Events

The occurrence of AEs was assessed at multiple time points following administration of the study products.

Systemic and local reactogenicity and nonreactogenicity AEs are summarized in Table 1-3. In total, there have been 101 AEs reported; 14 (13 were dosed SC) enrolled participants reported 17 reactogenicity events within 2 weeks following study drug administration and all were Grade 1. These included erythema/skin discoloration (n = 2), pain (n = 3) and induration (n = 1) at administration site, headache (n = 4), feverishness (n = 3), malaise/fatigue (n = 3), and myalgia (n = 1).

There were 84 unsolicited AEs reported by enrolled participants. Of these, 27 AEs (32.1%) occurred within 4 weeks of study drug administration. Nine AEs (10.7%) were Grade 3: nephrolithiasis (n = 1), elevated blood pressure (n = 4), decrease in hemoglobin (n = 1),

proteinuria (n = 2), and increased left-sided weakness (also reported as an SAE; n = 1). Three participants with transient Grade 3 elevation in blood pressure on the day of study drug administration had preexisting history of hypertension. Ten AEs (11.9%) were Grade 2: musculoskeletal pain (n = 3), rash (n = 1), elevated systolic blood pressure (n = 1), gastroenteritis (n = 2), abdominal pain (n = 1), abscess (n = 1), and sciatica (n = 1). All other AEs (n = 66) were Grade 1, and of these, 6 were considered possibly, probably, or definitely related to study drug administration. The most common AEs were related to URIs, musculoskeletal pain, and symptoms of gastroenteritis. Overall, no dose-limiting toxicities have occurred during study follow-up.

One SAE of worsening left-sided weakness (Grade 3) was reported in a participant receiving GS-5423 and GS-2872 or placebo. The participant had a history of ischemic stroke with residual left-sided weakness, and a workup did not reveal an etiology. The SAE and the event were not considered related to study drug.

Table 1-3. Study YCO-0971: Summary of Reported Adverse Events

Adverse Events	Severity			Total No. Participants
	Mild	Moderate	Severe	
Related AEs				
Local Injection Site Reactions				***SC Groups Only (n = 44)***
Erythema/skin discoloration	2	—	—	2
Induration	1	—	—	1
Pain	3	—	—	3
Systemic AEs Within 4 Weeks of Study Drug Administration				***All Groups (n = 69)***
Feverishness	3	—	—	3
Headache	4	—	—	3
Myalgia	1	—	—	1
Malaise/fatigue	3	—	—	3
Abdominal pain	1	—	—	1
Decrease in hemoglobin	—	—	1	1
Elevated blood pressure	—	1	1	2
Upper respiratory infection symptoms	2	—	—	2
Systemic AEs After 4 Weeks of Study Drug Administration				
Xerophthalmia	1	—	—	1
Total Reported Related AEs	21	1	2	—

Adverse Events	Severity			Total No. Participants
	Mild	Moderate	Severe	
Not-Related AEs				
Systemic AEs Within 4 Weeks of Study Drug Administration				
Bacterial vaginosis	1	—	—	1
Candida vaginitis	1	—	—	1
Chest pain	1	—	—	1
Dizziness	1	—	—	1
Dyspepsia	1	—	—	1
Elevated blood pressure	1	—	2	3
Facial edema	1	—	—	1
Gastroenteritis	1	—	—	1
Musculoskeletal pain	2	—	—	2
Rash	—	1	—	1
Upper respiratory infection	7	—	—	7
Proteinuria	—	—	1	1
Systemic AEs After 4 Weeks of Study Drug Administration				
Abdominal pain	—	1	—	1
Bacterial vaginosis	1	—	—	1
Chlamydia urethritis	1	—	—	1
Constipation	2	—	—	1
Dizziness	1	—	—	1
Elevated blood pressure	1	—	—	1
Flu-like symptoms	1	—	—	1
Folliculitis	1	—	—	1
Gastroenteritis	3	2	—	5
Hordeolum	1	—	—	1
Rash	1	—	—	1
Musculoskeletal contusions	2	—	—	2
Musculoskeletal pain	4	2	—	6
Nephrolithiasis	—	—	1	1
Proteinuria	1	1	2	4
Sciatica	1	1	—	2
Dental extraction	1	—	—	1
Toothache	1	—	—	1
Upper respiratory infection	12	—	—	14

Adverse Events	Severity			Total No. Participants
	Mild	Moderate	Severe	
Skin laceration	2	—	—	2
Syphilis	2	—	—	2
Abscess	—	1	—	1
Diarrhea	1	—	—	1
Earache	1	—	—	1
Gonorrhea	1	—	—	1
Laryngeal polyp removal	1	—	—	1
Hemiparesis	—	—	1	1
Viral syndrome	1	—	—	1
Total Reported Not-Related AEs	61	9	7	—

AE(s) = adverse event(s); SC = subcutaneous

Chemistry and hematology laboratory abnormalities of moderate or severe grade are summarized in Table 1-4. Laboratory abnormalities graded as severe were judged not related to study drug or procedures.

Thyroid function tests were also monitored following study drug administration given findings on tissue cross-reactivity studies that showed binding of GS-2872 to thyroid human tissue. No significant changes from baseline in thyroid function tests (thyroid-stimulating hormone [TSH], triiodothyronine [T3], and free thyroxine [T4]) were noted 4 weeks after study drug administration. HIV serologies were checked 2 or 4 weeks after antibody administration to determine if antibody administration might cause a transient false-positive HIV test in HIV-uninfected participants. Indeterminate HIV serologies were measured in participants in the groups receiving study drug by IV administration and less commonly in participants receiving study drug through SC administration. All participants with indeterminate HIV serologies also had an HIV viral load performed, which was negative in all participants.

Table 1-4. Study YCO-0971: Postinfusion Laboratory Abnormalities of Moderate or Severe Grade (Maximum Severity Per Volunteer)

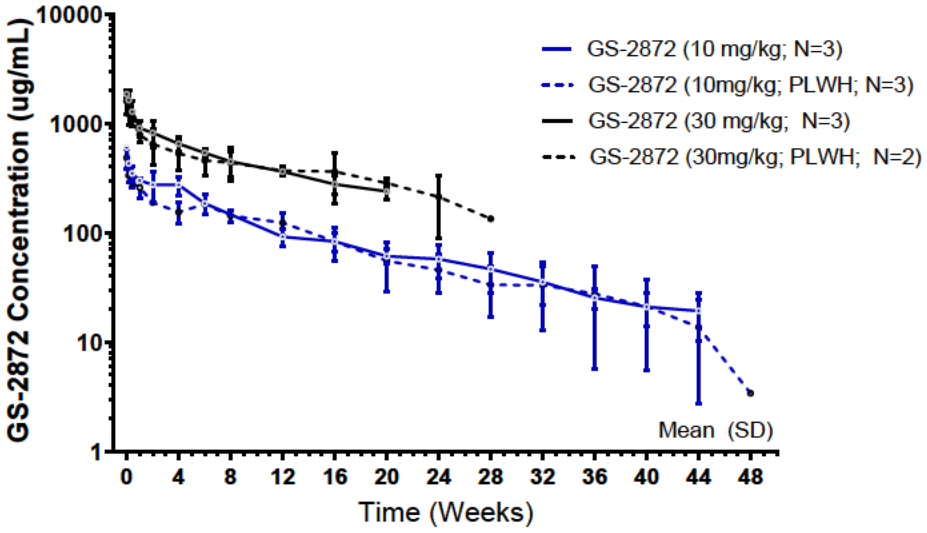
Postinfusion Laboratory Results	Number of Moderate Laboratory Abnormalities	Number of Severe Laboratory Abnormalities	Number of Life-Threatening Laboratory Abnormalities
Hematology	—	—	—
Hemoglobin	20	2	—
Total white blood cell count	1	—	—
Neutrophils	6	—	—
Lymphocytes	6	—	—
Platelets	1	—	—
Chemistry	—	—	—
Creatinine	—	—	—
AST	2	—	—
ALT	—	—	—
Total bilirubin	1	—	—
Direct bilirubin	—	—	—

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Pharmacokinetics of GS-2872 (10-1074-LS)

Preliminary concentration-time profiles of GS-2872 are presented in Figure 1-3 following a single dose of 10 or 30 mg/kg GS-2872 in healthy volunteers, or in PLWH who were ART suppressed. Preliminary analysis of GS-2872 PK in Study YCO-0971 suggests that its elimination half-life is approximately 80 days.

Figure 1-3. Study YCO-0971: Preliminary Concentration-Time Profiles of Serum GS-2872



PLWH = people living with HIV

1.2.4. Clinical Experience for LEN

A summary of the relevant available data from studies not yet included in the LEN IB is presented. These data are from two Phase 1 clinical studies in healthy volunteers (Studies GS-US-200-4538 and GS-US-200-4071) and one Phase 1b study in PLWH (Study GS-US-200-4072).

1.2.4.1. Study GS-US-200-4538

Study GS-US-200-4538 is an ongoing, blinded, Phase 1 study in healthy volunteers evaluating the safety, tolerability, and PK of single ascending SC doses of LEN solution formulations. As of 29 October 2019, 100 unique participants received single doses of either SC LEN formulations or placebo (4:1 ratio) (Table 1-5).

Table 1-5. Study GS-US-200-4538: Solution Formulations and Doses

Formulation	Dose of LEN (Volume Injected)
300 mg/mL FA	300 mg (1 × 1 mL)
309 mg/mL LEN injection	309 mg (1 × 1 mL)
	927 mg (3 × 1 mL)
	927 mg (2 × 1.5 mL)
155 mg/mL NaS	309 mg (1 × 2 mL)
	927 mg (3 × 2 mL)
300 mg/mL NaSP	900 mg (3 × 1 mL)
75 mg/mL NaSP	75 mg (1 × 1 mL)
	225 mg (2 × 1.5 mL)
50 mg/mL NaSP	50 mg (1 × 1 mL)

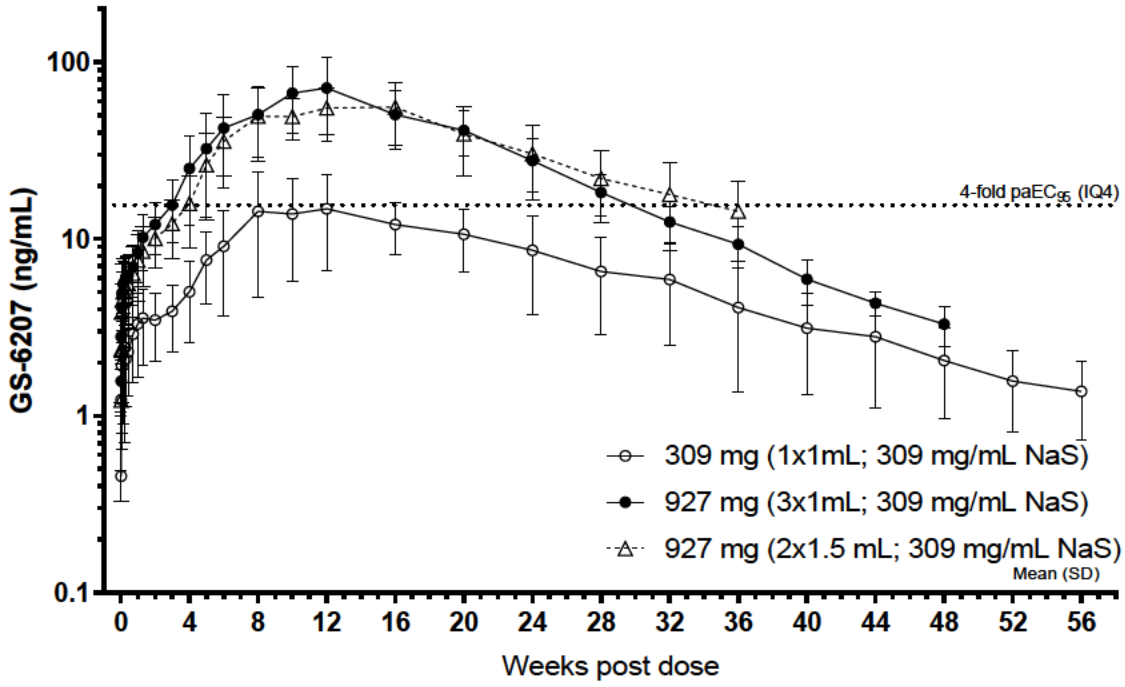
FA = free acid; LEN = lenacapavir; NaS = LEN injection; NaSP = LEN injection with poloxamer

Pharmacokinetic samples will be collected for up to 450 days; safety and PK analyses are ongoing. Data from selected formulations are presented below in Table 1-6.

Pharmacokinetic Results

Data available to date after administration of single doses of SC LEN injection, 309 mg/mL are presented in Figure 1-4. Based on available PK data, a slow initial release of LEN was observed; however, concentrations exceeding an inhibitory quotient (IQ) of 4 (4-fold higher than the protein-adjusted 95% effective concentration [paEC$_{95}$] from MT-4 cells; 3.87 ng/mL) were observed for at least 26 weeks following a single 927-mg dose (Figure 1-4). Preliminary PK data through 28 weeks postdose suggest similar PK profiles following SC administration of a 927-mg dose administered as either 3 × 1.0 mL or 2 × 1.5 mL SC injections.

Figure 1-4. **Study GS-US-200-4538: Preliminary Mean (SD) LEN Plasma Concentration-Time Profiles Following Single-Dose Administration of Subcutaneous LEN Injection, 309 mg/mL (n = 8 Per Cohort)**



IQ4 = inhibitory quotient 4; LEN = lenacapavir, GS-6207; NaS = LEN injection; $paEC_{95}$ = protein-adjusted 95% effective concentration

Table 1-6. Study GS-US-200-4538: Preliminary Pharmacokinetic Parameters for Subcutaneous LEN Injection, 309 mg/mL

PK Parameter (Mean %CV)	309 mg (1 × 1.0 mL) (n = 8)	927 mg (3 × 1.0 mL) (n = 8)	927 mg (2 × 1.5 mL) (n = 8)
AUC_{inf} (h•ng/mL)	66,400 (27.8)	225,000 (33.6)	224,000 (31.5)
AUC_{last} (h•ng/mL)	61,100 (28.8)	179,000 (53.4)	153,000 (47.6)
$\%AUC_{exp}$	8.06 (51.2)	5.79 (50.6)	21.5 (33.8)
C_{max} (ng/mL)	17.7 (50.3)	67.0 (54.8)	61.2 (43.5)
T_{max} (h) [days]	2350 (1340, 3360) [98]	1850 (1680, 2020) [77]	2020 (1510, 2690) [84.2]
T_{last} (h) [days]	8740 (8060, 8740) [364]	6720 (4030, 6720) [280]	4700 (4700, 4700) [196]
$t_{1/2}$ (h) [days]	1810 (1640, 2250) [75.4]	1190 (1120, 1420) [49.6]	1550 (1180, 1920) [64.7]

%CV = percentage coefficient of variation; LEN = lenacapavir; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
PK parameters presented to 3 significant digits as mean (%CV), except T_{max}, T_{last}, and $t_{1/2}$: median (Q1, Q3).

Safety Results

In a preliminary blinded review of safety data as of 29 October 2019, of 60 participants who received SC LEN injection, 309 mg/mL or SC LEN injection, 300 mg/mL with poloxamer or SC LEN injection, 155 mg/mL or placebo, no deaths or Grade 4 AEs have been reported.

A total of 57 of 60 participants (95%) had at least 1 AE during the study (Table 1-7).

The most frequently reported AEs were injection site induration (n = 47; 78.3%), injection site pain (n = 33; 55%), injection site erythema (n = 31; 51.7%), injection site swelling (n = 23; 38.3%), headache (n = 21; 35.0%), injection site bruising (n = 16; 26.7%), and injection site nodules (n = 8; 13.3%). Three participants experienced Grade 3 SAEs; 1 with Grade 3 hypoxemia on Day 16, 1 with Grade 3 abscess on Day 225, and 1 with Grade 3 fracture tibia on Day 121. All SAEs were not attributed to study drug.

Grade 3 and 4 treatment-emergent laboratory abnormalities were reported in 15 participants. Laboratory abnormalities reported in > 1 participant were creatine kinase (CK) (n = 4; attributed to exercise or boxes lifting), aspartate aminotransferase (AST) (n = 2 with CK elevation attributed to exercise and boxes lifting), low-density lipoprotein cholesterol (n = 2), and urine blood (n = 9). All cases were determined by the investigator to be not clinically significant.

Table 1-7. Study GS-US-200-4538: Summary of Adverse Events in > 2 Participants by Preferred Term

Preferred Term	Cohort 5 LEN 309 mg (309 mg/mL NaS)/ Placebo (n = 10)	Cohort 6 LEN 927 mg (309 mg/mL NaS)/ Placebo (3 × 1.0 mL) (n = 10)	Cohort 7 LEN 927 mg (309 mg/mL NaS)/ Placebo (2 × 1.5 mL) (n = 10)	Cohort 9 LEN 309 mg (155 mg/mL NaS)/ Placebo (1 × 2 mL) (n = 10)	Cohort 10 LEN 927 mg (155 mg/mL NaS)/ Placebo (3 × 2 mL) (n = 10)	Cohort 13 LEN 900 mg (300 mg/mL + NaSP)/ Placebo (3 × 1 mL) (n = 10	Total (n = 60)
Number (%) of Participants with Any Treatment-Emergent Adverse Event	7	10	10	10	10	10	57 (95)
Injection site induration	3 (30)	8 (80)	10 (100)	8 (80)	9 (90)	9 (90)	47 (78)
Injection site pain	—	6 (60)	8 (80)	3 (30)	8 (80)	8 (80)	33 (55)
Injection site erythema	1 (10)	5 (50)	4 (40)	6 (60)	8 (80)	7 (70)	31 (52)
Injection site swelling	—	4 (40)	4 (40)	4 (40)	6 (60)	5 (50)	23 (38)
Headache	3 (30)	4 (40)	3 (30)	3 (30)	5 (50)	3 (30)	21 (35)
Injection site bruising	—	3 (30)	1 (10)	2 (20)	5 (50)	5 (50)	16 (27)
Injection site nodule	2 (20)	3 (30)	—	3 (30)	—	—	8 (13)
Hypersensitivity	—	—	—	1 (10)	2 (20)	—	3 (5)
Injection site discoloration	—	—	—	2 (20)	1 (10)	—	3 (5)
Injection site pruritus	—	—	2 (20)	—	—	1 (10)	3 (5)
Nausea	1 (10)	1 (10)	—	1 (10)	—	—	3 (5)
Oropharyngeal pain	—	—	—	1 (10)	2 (20)	—	3 (5)
Upper respiratory tract infection	1 (10)	1 (10)	1 (10)	—	—	—	3 (5)

LEN = lenacapavir; NaS = LEN injection; NaSP = LEN injection with poloxamer

No notable changes from predose in vital signs (systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiration rate) have been observed in the study. No clinically significant electrocardiogram (ECG) abnormalities have been reported during the study.

1.2.4.2. Study GS-US-200-4072

Study GS-US-200-4072 is an ongoing, Phase 1b, randomized, double-blinded, placebo-controlled, multicohort dose-ranging study evaluating the safety, tolerability, PK, and short-term antiviral activity of monotherapy with SC doses of a LEN free-acid suspension (100 mg/mL) in PLWH who are either ART naive or ART experienced but capsid inhibitor naive.

This study will enroll 5 cohorts of approximately 8 unique participants per cohort to receive LEN or placebo. Within each cohort (n = 8), participants are randomized in a 3:1 ratio to receive active LEN (n = 6) or placebo (n = 2). A single dose of LEN or placebo is administered as an SC injection in the abdomen on Day 1.

As of 20 November 2019, 39 participants have received SC LEN or placebo (3:1 ratio) at doses of 20, 50, 150, 450, and 750 mg.

Disposition and Baseline Characteristics

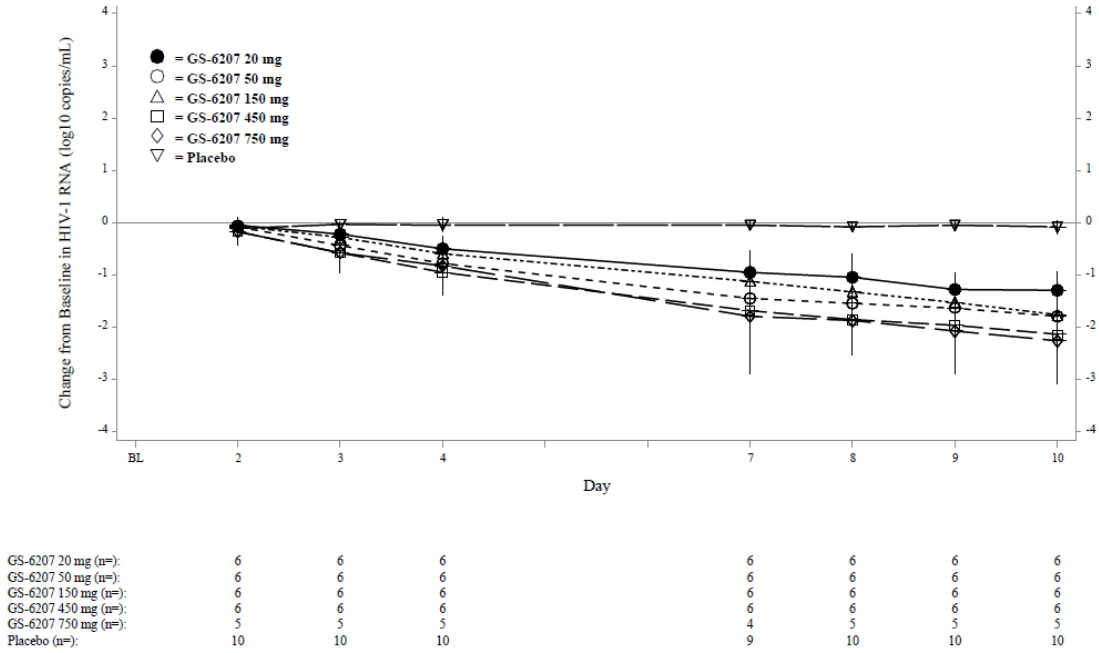
As of 20 November 2019, 39 participants were randomized and received a single dose of SC LEN or placebo. One participant who received a single dose of LEN 450 mg was lost to follow-up after Day 169. The median duration of follow-up (number of days between Day 1 and the last study date) was 225 days and ranged from 16 to 247 days across the 5 cohorts.

The majority of participants were male (89.7%; 35 participants), white (53.8%; 21 participants), and not Hispanic or Latino (84.6%; 33 participants). The median age was 33 years (range: 19 to 65 years). The median (first quartile [Q1], third quartile [Q3]) baseline HIV-1 RNA was 4.53 (4.3, 4.74) $\log_{10}$ copies/mL, and the median (Q1, Q3) CD4 cell count was 463 (359, 614) cells/µL. The majority of participants were ART-naive (82.1%; 32 participants).

Virologic Efficacy Results

HIV-1 RNA levels decreased following initiation of study drug (Figure 1-5). The mean (SD) maximum HIV-1 RNA reductions from baseline through Day 10 were 1.35 (0.318), 1.79 (0.476), 1.76 (0.203), 2.20 (0.468), and 2.26 (0.662) $\log_{10}$ copies/mL at doses of LEN 20, 50, 150, 450, and 750 mg, respectively. All participants who received ≥ 50 mg LEN had a > 1 $\log_{10}$ copies/mL reduction in their HIV-1 RNA through Day 10. Overall, antiviral activity was comparable across the dose range of 50 to 750 mg, but lower at the 20-mg dose.

Figure 1-5. Study GS-US-200-4072: Mean and 95% CIs Change From Baseline in HIV-1 RNA (log_{10} copies/mL) (Full Analysis Set)



GS-6207 20 mg (n=):	6	6	6	6	6	6	6
GS-6207 50 mg (n=):	6	6	6	6	6	6	6
GS-6207 150 mg (n=):	6	6	6	6	6	6	6
GS-6207 450 mg (n=):	6	6	6	6	6	6	6
GS-6207 750 mg (n=):	5	5	5	4	5	5	5
Placebo (n=):	10	10	10	9	10	10	10

BL = baseline; GS-6207 = lenacapavir

Pharmacokinetic Results

Preliminary PK data show that following 50-, 150-, 450-, and 750-mg doses of LEN SC suspension, mean LEN concentrations on Day 10 were 1.1- to 20.5-fold higher than the $paEC_{95}$ for wild-type HIV-1 based on the half-maximal effective concentration in MT-4 cells (IQ = 1.1, 3.3, 9.9, and 20.5 for the 50-, 150-, 450-, and 750-mg doses, respectively).

Safety Results

As of 20 November 2019, no deaths, Grade 4 AEs, or AEs leading to study drug discontinuation had been reported. One participant experienced a Grade 3 SAE of atrial fibrillation, which occurred following methamphetamine use and was not considered related to study drug by the investigator. After the data cut, the same participant, who had a history of hypertension, hyperlipidemia, and tobacco abuse, experienced Grade 4 SAEs of coronary artery disease and acute myocardial infarction, Grade 3 AEs of unstable angina and angina pectoris, and a Grade 3 SAE of noncardiac chest pain. All AEs and SAEs were considered not related to study drug by the investigator. Another participant experienced a Grade 2 SAE of small intestinal obstruction, which was considered not related to study drug by the investigator.

No other SAEs or Grade 3 AEs were reported. Most participants (33 of 39; 84.6%) reported an AE. The most frequent AEs were injection site pain (48.7%), injection site erythema (28.2%), and injection site induration (20.5%).

Eight participants (20.5%) had a Grade 3 or Grade 4 laboratory abnormality reported. The Grade 3 or 4 abnormalities reported for more than 1 participant were transient CK elevations (n = 3), attributed to recent exercise or carrying heavy bags; asymptomatic elevated amylase (n = 2); and urine blood attributed to menses (n = 2).

1.2.4.3. Study GS-US-200-4071

Study GS-US-200-4071 is a completed Phase 1 study in healthy volunteers that evaluated the safety, tolerability, and PK of single- and multiple-ascending doses of oral LEN as an oral liquid (solution)-filled capsule (50 mg/mL or 100 mg/mL) or tablet (50 mg or 300 mg). Single- and multiple-dose PK data from the 50 mg/mL solution-filled capsule, and single-dose PK data from the tablets are presented in Table 1-8. To reduce pill burden, the LEN tablet was the oral form used in this study.

This study was originally designed as a single- and multiple-ascending dose evaluation of solution in capsule formulations, with 10 days of washout between the single- and multiple-dose periods (Cohorts 1 and 2). Following receipt of PK data from these 2 cohorts suggesting the $t_{1/2}$ was longer than predicted, the study design was altered to administer a single-ascending dose.

Within each cohort, participants were randomized to receive LEN (n = 8) or placebo (n = 2); all study drugs were administered under fasted conditions unless otherwise specified. In Cohorts 1, 2, and 5, capsules containing 50 mg/mL solution were evaluated at doses of 30, 100, and 300 mg, respectively. Following development of a tablet formulation, 50-mg and 300-mg tablets were assessed, and participants were randomized to receive LEN (n = 8) or placebo (n = 2) under fasted conditions. In addition, 2 cohorts received open-label 300-mg LEN tablets (n = 8) given with a high-fat, high-calorie meal, or with a low-fat, low-calorie meal. A brief description of all cohorts is presented in Table 1-8.

Table 1-8. Study GS-US-200-4071: LEN Formulations and Doses Evaluated

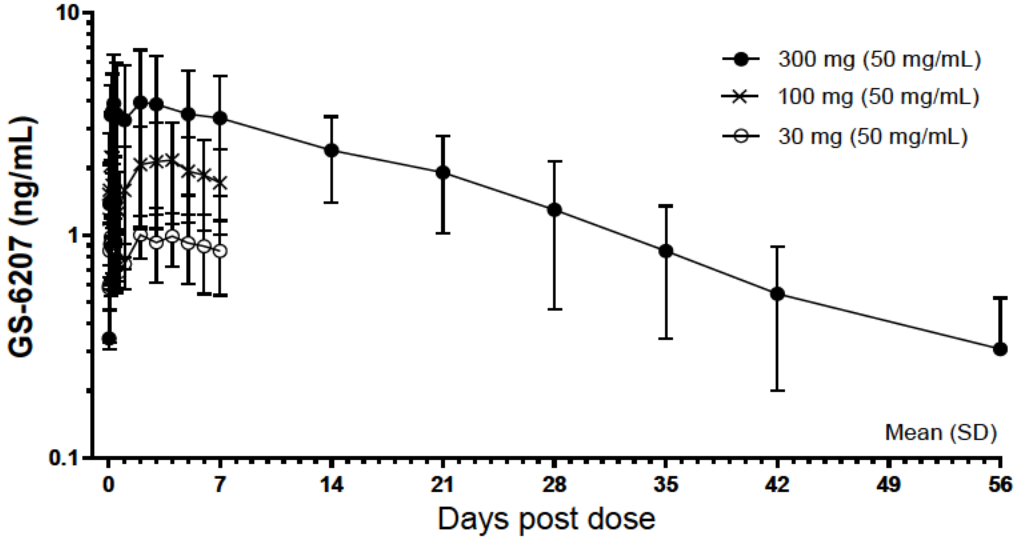
Formulation Description	Dose (No. of Capsules/Fasting Status)
Single-dose solution in capsule	
50 mg/mL	30 mg (1 capsule, fasted) 100 mg (3 capsules, fasted) 300 mg (8 capsules, fasted)
Multiple-dose solution in capsule	
50 mg/mL	30 mg (1 capsule, fasted) 100 mg (3 capsules, fasted)
Single-dose tablet	
50 mg	50 mg (1 tablet, fasted)
300 mg	300 mg (1 tablet, fasted) 900 mg (3 tablets, fasted) 1800 mg (6 tablets, fasted) 300 mg (1 tablet, high fat)[a] 300 mg (1 tablet, low fat)[a]

LEN = lenacapavir
a High-fat meal included high-calorie count (~1000 kcal, ~50% fat), low-fat meal included low-calorie count (~400 kcal, ~25% fat)

Pharmacokinetic Results

LEN concentration-time profiles and preliminary PK parameters after administration of single oral doses of LEN oral solution in capsules are presented in Figure 1-6 and Table 1-9, respectively. C_{max} of LEN occurred between 7 and 29 hours (median T_{max}), and the median $t_{1/2}$ of LEN was approximately 12 days. Within each increase in dose, the increase in C_{max} was less than dose proportional, suggesting LEN exhibits solubility-limited absorption.

Figure 1-6. Study GS-US-200-4071: Preliminary Mean (SD) LEN Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral LEN Solution in Capsule (50 mg/mL; n = 8 Per Cohort)



LEN = lenacapavir, GS-6207

Table 1-9. Study GS-US-200-4071: Preliminary LEN Plasma Pharmacokinetic Parameters Following Single-Dose Administration of Oral LEN Solution in Capsule (50 mg/mL; n = 8 Per Cohort)

Parameter	Cohort 1; 30 mg (n = 8)	Cohort 2; 100 mg (n = 8)	Cohort 5; 300 mg (n = 8)
C_{max} (ng/mL)	1.16 (23.9)	2.70 (55.4)	4.75 (52.4)
T_{max} (hr) [a]	29.0 (4.00, 90.0)	26.0 (4.00, 96.0)	7.00 (4.00, 18.00)
AUC_{last} (hr•ng/mL)[b]	147 (29.0)	319 (46.0)	1990 (52.0)
AUC_{inf} (hr•ng/mL)	ND	ND	2280 (53.1)
$\%AUC_{exp}$ (%)	ND	ND	11.6 (61.0)
AUC_{0-24} (hr•ng/mL)	17.6 (19.7)	34.8 (47.3)	75.7 (61.3)
$t_{1/2}$[a] (days)	ND	ND	12.3 (10.7, 13.8)

%CV = percentage coefficient of variation; LEN = lenacapavir; ND = not determined due to insufficient PK sampling; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
PK parameters are presented as Mean (%CV), and shown to 3 significant digits
a Median (Q1, Q3)
b AUC_{last} calculated through Day 7 postdose for Cohorts 1 and 2 and through last currently available time point for Cohort 5

LEN preliminary PK parameters after 10 daily oral doses of LEN (50 mg/mL solution in capsule) are presented in Table 1-10. Consistent with its half-life, following 10 days of multiple dosing, the mean LEN C_{max} and AUC_{0-24} were at least 10-fold higher than after a single dose (Table 1-11).

Table 1-10. Study GS-US-200-4071: Preliminary LEN Plasma Pharmacokinetic Parameters Following Multiple-Dose Oral Administration of 30 mg and 100 mg Solution in Capsule (50 mg/mL; n = 8 Per Cohort)

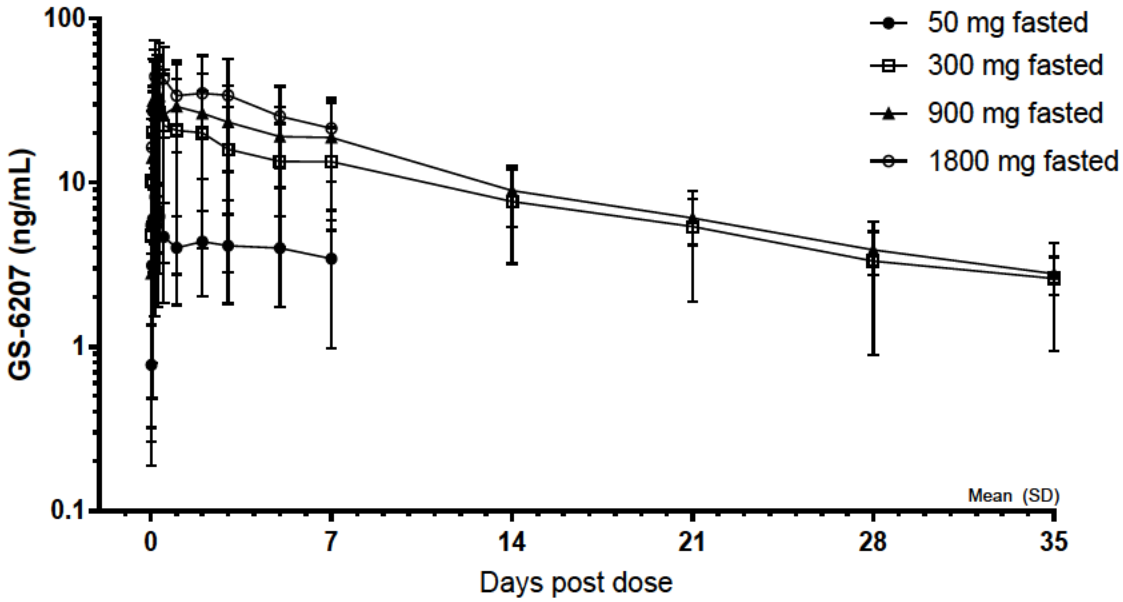
Parameter	Cohort 1; 30 mg (n = 8)	Cohort 2; 100 mg (n = 8)
	50 mg/mL solution in capsule	
C_{max} (ng/mL)	12.2 (17.1)	41.3 (53.8)
t_{max} (hr)[a]	3.50 (1.89, 10.0)	4.00 (4.00, 10.5)
AUC_{0-24hr} (hr•ng/mL)	232 (17.9)	843 (56.5)

%CV = percentage coefficient of variation; LEN = lenacapavir; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
PK parameters are presented as Mean (%CV), and shown to 3 significant digits
a Median (Q1, Q3)

LEN concentration-time profiles and preliminary PK parameters after administration of single doses of LEN oral tablets administered either under fasted conditions, or with a high-fat or low-fat meal, are presented in Figure 1-7 and Figure 1-8. Interim safety and PK data are available through at least 8 days postdose. Based on preliminary PK data, LEN exposures increased in a less than dose-proportional manner over the range of 50 to 1800 mg. Maximal concentrations (C_{max}) of LEN were achieved approximately 4 to 8 hours postdose (T_{max}), and LEN half-life ($t_{1/2}$) is estimated to be approximately 12 days (Figure 1-7).

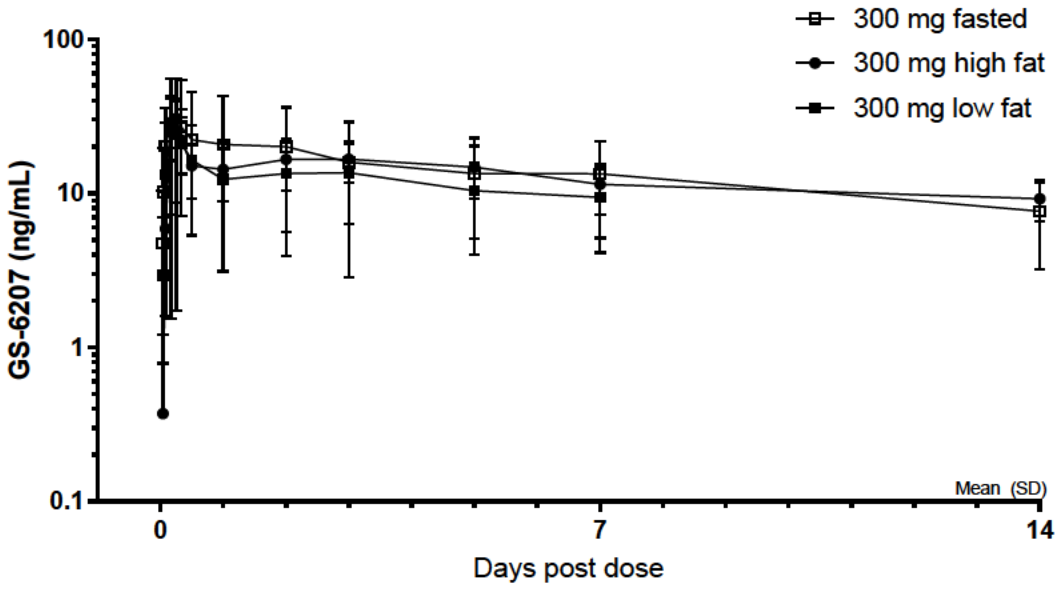
Exposure (C_{max} and $AUC_{0\text{-}D8}$) and time to maximal exposure (T_{max}) were comparable following administration of LEN 300 mg tablets under fasted conditions or with a high or low fat meal; thereby, supporting dosing of LEN tablets with or without food in future clinical studies (Table 1-11).

Figure 1-7. Study GS-US-200-4071: Preliminary Mean (SD) LEN Plasma Concentration-Time Profiles Following Single-Dose Oral Administration of LEN Tablets, Fasted (n = 8 Per Cohort)



LEN = lenacapavir, GS-6207

Figure 1-8. **Study GS-US-200-4071: Preliminary Mean (SD) LEN Plasma Concentration-Time Profiles Following Single-Dose Oral Administration of LEN 300-mg Tablets, Fasted or with a High-Fat or Low-Fat Meal (n = 8 Per Cohort)**



LEN = lenacapavir, GS-6207

Table 1-11. **Study GS-US-200-4071: Preliminary LEN Plasma Pharmacokinetic Parameters Following Single-Dose Oral Administration of LEN Tablets, Fasted or Following a High- or Low-Fat Meal (n = 8 Per Cohort)**

Parameter	50 mg (n = 8)	300 mg (n = 8)	900 mg (n = 8)	1800 mg (n = 8)	300 mg + High-Fat Meal (n = 8)	300 mg + Low-Fat Meal (n = 8)
AUC_{inf} (hr•ng/mL)	NC	7990 (56.1)	9900 (44.9)	NC	NC	NC
$AUC_{0\text{-}D8}$ (hr•ng/mL)[a]	694 (56.0)	2790 (81.5)	3900 (67.2)	5080 (56.3)	2540 (33.6)	2060 (55.7)
C_{max} (ng/mL)	8.24 (48.3)	33.7 (96.3)	43.9 (73.3)	53.8 (48.0)	35.0 (33.0)	28.1 (60.6)
T_{max} (hr)	4.00 (4.00, 5.50)	4.00 (4.00, 6.00)	4.00 (2.50, 20.0)	8.00 (5.00, 8.00)	5.00 (4.00, 6.00)	6.00 (4.00, 8.00)
$t_{1/2}$ (h) [days]	NC	265 (223, 349) [11.0]	322 (237, 333) [13.4]	NC	NC	NC

%CV = percentage coefficient of variation; LEN = lenacapavir; NC = not calculated due to insufficient PK sampling; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
PK parameters are presented as mean (%CV) except T_{max} and $t_{1/2}$ which are presented as median (Q1, Q3) and shown to 3 significant digits
a $AUC_{0\text{-}D8}$ calculated through Day 8 postdose

Safety Results

LEN tablets were generally safe and well tolerated across all treatment groups. A total of 9 of 56 participants (16.1%) had at least 1 AE reported. The most commonly reported AEs were headache (n = 3; 5.4%) and back pain (n = 2; 3.6%). No other AEs were reported by more than 1 participant. No Grade 3 or 4 AEs, deaths, SAEs, pregnancy, or AEs leading to permanent discontinuation of study drug were reported in any treatment group.

In a preliminary blinded review of safety data as of 03 September 2019, when all participants who had received LEN solution in capsules or placebo-to-match had completed or discontinued the study, the safety profile was similar to that observed with the tablets. The only AE reported for > 1 participant was headache (6.7%; 2 participants).

Dosing with LEN was generally safe and well tolerated in this study, with no notable differences in the overall safety profile of LEN administered as capsules or tablets. Overall, headache was the most common AE in participants who received LEN tablets; however, headache occurred at similar frequency in participants who received placebo tablets.

1.3. Rationale for This Study

Advances in ART have led to significant improvements in morbidity and mortality among PLWH by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. While combination ART for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality associated with HIV disease, there remains a significant medical need for new well-tolerated therapies that take into consideration the limitations of daily oral pills and provide new options for long-acting treatment.

A combination of 2 potent bNAbs, 3BNC117 and 10-1074, which target nonoverlapping epitopes on HIV envelope, can control viral replication in people with virus sensitivity to both bNAbs {Mendoza 2018} with subsequent virologic rebound (VR) a median of 21 weeks after stopping ART, after antibody concentrations declined. Two of 15 participants did not have detectable plasma HIV-1 viremia at 30 weeks, compared with historical data suggesting a median time to rebound of 2.3 weeks in participants undergoing analytical treatment interruption (ATI). This suggests that engagement of the host immune system by bNAbs may contribute to enhanced control of HIV-1 replication after antibody plasma concentrations decline and the bNAbs no longer exert a direct neutralizing effect on the virus. Fc engineering has extended the half-life of the antibodies 3BNC117 and 10-1074 without alteration to the Fab domain, which enables GS-5423 (formerly 3BNC117-LS) and GS-2872 (formerly 10-1074-LS) to maintain plasma concentrations in a predicted therapeutic range for 6 months.

Due to the diversity of the HIV-1 virus Env, an estimated 50% of clade B viruses are sensitive to both antibodies, and more than 90% of tested isolates are sensitive to either 3BNC117 or 10-1074. Combining the bNAbs GS-5423 and GS-2872 with LEN, a potent selective inhibitor of HIV-1 capsid with predicted breadth encompassing 100% of HIV viruses, is hypothesized to augment the breadth of the regimen, increase the barrier to resistance and durability of the study regimen which also provides the potential benefits of antibody mediated engagement of the host

immune system in controlling HIV-1. The PK of each study regimen component also enables dosing once in 6 months.

Pilot Cohort

The patient population that could benefit from a regimen of GS-5423, GS-2872, and LEN has not been defined. Utilizing bNAb phenotypic sensitivity testing may aid in identifying PLWH who will benefit, but the optimal criteria (eg, an IC_{90} threshold) for determining sensitivity to GS-5423 and GS-2872 remain undefined. In addition, prior studies have reported similar suppression rates whether bNAb sensitivity was a requisite for inclusion or no screening was performed. Therefore the applicability of these assays to clinical treatment with bNAbs has not been firmly established. The PhenoSense mAb assay (Monogram Biosciences), used to determine study eligibility, uses pseudoviruses derived from proviral DNA in PBMCs and may not fully characterize an individual's HIV-1 reservoir. Even with viruses that have lower susceptibility in the phenotypic assay (IC_{90} > 2 µg/mL), it is expected that the bNAbs will contribute to the overall regimen efficacy because systemic bNAb concentrations are maintained well above 10 ug/mL at 6 months. Using a combination of 2 bNAbs that target non-overlapping epitopes also has an additive effect, and may have a synergistic effect on potency, thus neutralizing viruses that have low susceptibility to individual bNAbs {Kong 2015, Wagh 2018}. For these reasons, the Pilot Cohort with sensitivity to only one bNAb (GS-5423 or GS-2872) by protocol criteria, will explore safety and efficacy of the full study regimen in the presence of lower sensitivity to one bNAb. Screened participants with decreased susceptibility to both bNAbs will be excluded to limit the risk of LEN monotherapy. Results from the Pilot Cohort will inform which potential patient populations could be safely and effectively treated by the study regimen LEN plus GS-5423 and GS-2872.

Enrollment into the optional Pilot Cohort will be gated by the Gilead Data Review Committee (GDRC) assessment of safety and efficacy data from the Primary Cohort after 20 participants have completed follow-up through Week 12. The Pilot Cohort will have the same treatments and assessments as the Primary Cohort.

Developing safe and effective therapeutic options that maintain virologic suppression and facilitate adherence over a lifetime of therapy for PLWH remains a priority. For many individuals, including some who struggle with daily oral pills, newer study drugs are needed to control viral replication, preserve immune function, and prevent clinical progression. In all PLWH, the ideal goal of therapy remains complete and durable viral suppression.

1.4. Rationale for Dose Selection of GS-5423 and GS-2872

Dose selection for GS-5423 (3BNC117-LS) and GS-2872 (10-1074-LS) in this study is supported by antiviral activity, PK, and safety data from the non-LS forms of each antibody, 3BNC117 and 10-1074, in a Phase 1b proof-of-concept (POC) study in HIV+ participants {Mendoza 2018}, as well the PK and safety data in healthy volunteers and participants with HIV of the LS forms of each antibody from the ongoing studies, YCO-0946 and YCO-0971.

In the Phase 1b POC study {Mendoza 2018}, MCA-906, the activity of the combination of 3BNC117 and 10-1074 in the setting of ATI was evaluated. In this study, participants who were sensitive to both antibodies (n = 9) maintained viral suppression for a median of 21 weeks after the last dose of the antibodies. An exploratory PK/pharmacodynamic (PD) analysis of these data suggest that in sensitive participants, virologic suppression was maintained when 3BNC117 and 10-1074 concentrations were > 10 µg/mL and > 100 µg/mL, respectively. Virologic breakthrough occurred when the concentrations of the less potent antibody, 3BNC117, fell below 10 µg/mL.

Based on the location of the amino acid substitutions to generate the LS forms of each antibody, as well as delays in time to infection observed in a nonhuman primate disease challenge model (refer to the 3BNC117-LS IB and 10-1074-LS IB), it is anticipated that the 10-1074-LS and 3BNC117-LS antibodies will demonstrate similar antiviral activity to the unmodified forms, at the same target concentrations.

Single doses of GS-5423 and GS-2872 were shown to be safe and well tolerated up to 30 mg/kg in Studies YCO-0946 and YCO-0971. Preliminary PK data from Study YCO-0946 suggest GS-5423 (3BNC117-LS) has a $t_{1/2}$ of approximately 54 days, and IV administration of GS-5423 30 mg/kg is anticipated to maintain concentrations > 10 µg/mL for 26 weeks. Preliminary PK data from Study YCO-0971 suggest GS-2872 (10-1074-LS) has a $t_{1/2}$ of approximately 80 days, and IV administration of GS-2872 10 mg/kg and 30 mg/kg are anticipated to maintain concentrations > 10 µg/mL and > 100 µg/mL, respectively, for 26 weeks.

Based on these data and analyses, GS-5423 will be administered at 30 mg/kg in both treatment groups of this study, targeting a concentration of > 10 µg/mL throughout the 6 months, and GS-2872 will be administered at 10 mg/kg in Treatment Group 1, and 30 mg/kg in Treatment Group 2, targeting > 10 µg/mL and > 100 µg/mL, respectively, throughout the 6 months. The proposed dose range for GS-2872 allows for sufficient dose separation to evaluate the antiviral activity of GS-2872 at 10 mg/kg and 30 mg/kg in combination with GS-5423 30 mg/kg and LEN 927 mg SC.

1.5. Rationale for Dose Selection of LEN

The dose and formulation selection for LEN in this study is supported by antiviral activity, PK, and safety data from the ongoing Phase 1b POC study (GS-US-200-4072) in treatment-naive (TN) and treatment-experienced (TE) but capsid inhibitor-naive PLWH, as well as PK and safety data from the two Phase 1 studies in healthy volunteers (GS-US-200-4538 and GS-US-200-4071).

In the Phase 1b POC study (GS-US-200-4072), potent antiviral activity of LEN was demonstrated; the mean maximum HIV-1 RNA decline over 10-day monotherapy after single SC doses of 50 to 750 mg was 1.8 to 2.3 $\log_{10}$ copies/mL. All participants achieved at least 1 $\log_{10}$ copies/mL decline in their HIV-1 RNA at Day 10. Day 10 antiviral activity was comparable across a dose range of single doses of 50 to 750 mg. At these doses, mean (%CV) LEN concentrations on Day 10 were 1.1- to 20.5-fold higher (ie, IQ = 1.1-20.5) than the paEC95 for wild type HIV-1 (paEC95 = 3.87 ng/mL in MT-4 cells).

Based on these data and the safety data available to date, the proposed LEN regimen for both treatment groups targets an exposure whereby the lower bound of the 90% CI of the C_{trough} is at least 4-fold higher than the paEC95 (ie, IQ4 based on paEC95 from MT-4 cells; 15.5 ng/mL) starting within a few days of dosing initiation, and maintained through Week 26.

1.6. Risk/Benefit Assessment for the Study

Potential risks associated with the study include unknown AEs, including injection site reaction with SC administration of LEN, and infusion reactions including ADA-mediated reactions from GS-5423 and GS-2872. Passive administration of anti–HIV-1 bNAbs, including GS-5423 and GS-2872, as well as the original bNAbs on which they are based (3BNC117 and 10-1074), have been previously evaluated in humans. As observed with other mAbs, anti–HIV-1 bNAbs were generally considered safe and well tolerated, and infusion reactions were more common for mAbs that contained murine elements, compared with fully human mAbs like GS-5423 and GS-2872. Clinical monitoring for possible immunologic symptoms will be conducted during and immediately following bNAb infusion, and study sites are required to: have appropriate supportive medications available, including, but not limited to, diphenhydramine, acetaminophen, and glucocorticoids during IV infusions; and to follow a protocol-specified management plan for infusion-related reactions. A limited number of participants will be enrolled (N = approximately 20) and an early safety review will assess the safety and tolerability of the investigational regimen. An additional optional Pilot Cohort (N = up to 20) of previously screened participants whose results have been reviewed centrally for genotypic sensitivity may be added after Gilead Data Review Committee (GDRC) review.

In general, risks include those associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of multiple phlebotomies. Strategies to mitigate any potential risks include close monitoring of laboratory values as well as AEs. Parameters for monitoring of AEs will be well defined and closely followed.

A potential risk of virologic breakthrough with exposure to suboptimal therapeutic concentrations of the study regimen or unrecognized preexisting resistance to both bNAbs and/or LEN could lead to HIV-1 developing resistance to one or more study drugs. Data are limited to inform whether resistance testing to bNAbs will minimize the risk of enrolling participants with preexisting resistance to both bNAbs. Strategies to mitigate the risk include frequent assessments of HIV-1 RNA to ensure that virologic breakthrough is rapidly identified, thus limiting the time during which drug resistance mutations could emerge. Participants must be taking standard first-line ART at baseline and not have any significant resistance to approved ART classes. Each component of the study regimen is from a novel class without any known or predicted cross-resistance with currently approved ART, thus the development of resistance to any component of the study regimen would have limited impact on a participant's future treatment options.

The potential direct benefits of the study include a long-acting regimen that is administered once in 6 months rather than daily, thus freeing participants from the requirement of daily adherence to ensure efficacy. Participants may benefit from the novel regimen due to enhanced engagement of the immune system from bNAb therapy, which may result in reduction of the latent viral

reservoir and/or improved immunologic control of HIV-1. Potential benefits to participants include the use of bNAbs, which may result in reduced risk of end-organ toxicities associated with some ART, and the participant's contribution to understanding the safety and tolerability of a novel long-acting treatment strategy including the PK of the regimen and contributions to helping develop new classes of ART with potential application for HIV-1 treatment, prevention, and cure.

Considering the above, the benefit-risk balance for this study is considered positive.

During a pandemic, additional potential risks to participants may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 7 for further details on the risks and risk mitigation strategy.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is as follows:

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

The secondary objectives of this study are as follows:

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

The exploratory objectives are as follows:

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

3. STUDY DESIGN

3.1. Endpoints

Study endpoints will be assessed in the Primary Cohort excluding the optional Pilot Cohort. Exploratory analysis may be conducted for the optional Pilot Cohort as applicable.

The primary endpoint of this study is as follows:

- Incidence of treatment-emergent SAEs through Week 26

The secondary endpoints of this study are as follows:

- Proportion of participants with HIV-1 RNA < 50 copies/mL at Week 26 as defined by the Food and Drug Administration (FDA)-defined snapshot algorithm
- Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as defined by the FDA-defined snapshot algorithm
- Proportion of participants with positive anti–GS-5423 or anti–GS-2872 antibodies at Week 26
- Change from baseline in CD4+ cell counts at Week 26
- Treatment-emergent resistance to study drugs through Week 26
- Incidence of treatment-emergent SAEs through Week 26, and treatment-emergent AEs through Week 26
- PK parameters for GS-5423, GS-2872, and LEN (and metabolites, if applicable) as appropriate: $AUC_{0\text{-}t}$, AUC_{last}, $t_{1/2}$, C_{max}, T_{max}, T_{last}, C_t through Week 52

The other endpoints of interest are as follows:

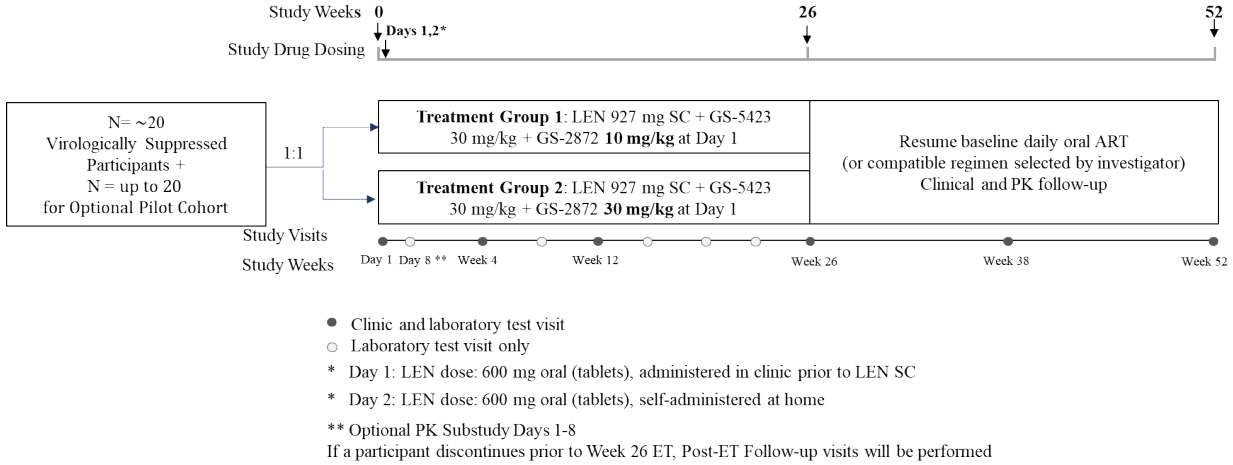
- Changes from baseline in HIV-1 reservoir in peripheral blood mononuclear cell (PBMC) at postbaseline visits
- Changes from baseline in HIV-1 specific T-cell response, immune cell phenotyping and proliferation, gene expression, antibody profiling, and soluble proteins levels (eg, cytokines, chemokines, inflammatory markers, etc).

3.2. Study Design

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

An overview of the study design is described below and shown in Figure 3-1.

Figure 3-1. Study Schema



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

3.3. Study Treatments

This study will enroll approximately 20 participants (Primary Cohort). After GDRC review (Section 5.1.3), an optional Pilot Cohort of up to 20 additional participants may be added.

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

Treatment Group 1:

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

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

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

Treatment Group 2:

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

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

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

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 ARV regimen 1 day prior to receiving study drugs on Day 1.

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

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

3.4. Duration of Treatment

Duration of study drug treatment is approximately 26 weeks.

3.5. End of Study

The end of study will be when the last participant has completed their final visit in the study.

3.6. Poststudy Care

Once a participant has completed their study participation, the long-term care of the participant will return to the responsibility of their primary treating physicians.

3.7. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, specialty laboratory (eg, for PK/ADA and/or PD data), and interactive response technology (IRT) data.

3.8. Biomarker Testing

3.8.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected from all participants who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dosage selection, and to better understand the biological pathways, biology of HIV-1 infection or related diseases, and/or the validation of a companion diagnostic for HIV cure. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include but may not be limited to the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state-of-the-art knowledge.

- Samples will be collected to measure biomarkers that may include but will not be limited to HIV-1 specific T-cell response, immune cell phenotyping, gene expression, antibody profiling, and soluble proteins levels (eg, cytokines, chemokines, inflammatory markers, etc.) at the following time points: baseline (Day 1 predose), and Weeks 4, 26, 38, and 52. Fc-gamma receptor (FcgR) single nucleotide polymorphisms (SNPs) will be evaluated using samples collected at the Day 1 visit.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.

3.8.2. Biomarker Samples for Optional Future Research

In addition to the study-specific informed consent to be signed by each study participant, participants will be required to document consent if they agree to allow the use of the remainder of their already collected biomarker and PK specimens for optional future research, in accordance with applicable regulations.

The specimens consented for optional future research may be used to advance development of the drug and/or increase our knowledge and understanding of the biology of the disease under investigation and related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The analysis of optional future research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The specimens used for optional future research will be destroyed no later than 15 years after the end of study or per country requirements.

3.8.3. Biomarker Samples for Optional Genomic Research

In addition to the study-specific informed consent to be signed by each study participant, participants will be required to document consent if they agree to provide additional samples for optional genomic research. Additional samples will be obtained from participants who agree to participate and provide their additional specific consent. These samples should be collected at the Day 1 visit, before administration of the first dose of study drug, but may be collected at any time during the study or at a separate poststudy visit, if necessary.

The specimens collected for optional future genomic research may be used to advance the development of the drug and/or increase our knowledge and understanding of the biology of the disease under investigation, or related diseases. These specimens may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, these specimens may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The samples collected for optional genomic research will be destroyed no later than 15 years after the end of the study or per country requirements.

3.9. Optional Pharmacokinetic Substudy

In addition to the study-specific informed consent to be signed by each study participant, participants will be required to document consent if they agree to provide samples for the Optional PK Substudy.

Plasma PK samples for LEN will be collected in a subset of participants (approximately n = 14 evaluable; approximately n = 7 from each treatment group).

Optional PK assessments will occur on the assigned days as outlined in Section 6.7.1 and Appendix 2.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 20 participants who meet all the eligibility criteria will be enrolled in the Primary Cohort. After GDRC review (Section 5.1.3), an optional Pilot Cohort of up to 20 additional participants may be added.

4.1.1. Participant Replacement

Participants who discontinue before the end of study will not be replaced.

4.2. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1) The ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures;

2) Between 18 and 65 years of age, inclusive, at screening;

3) Plasma HIV-1 RNA < 50 copies/mL at screening;

4) 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;

5) 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;

6) Proviral phenotypic sensitivity to both GS-5423 and GS-2872 at screening by the PhenoSense 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, within 18 months 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 µg/mL; GS-2872 sensitivity is defined as IC_{90} ≤ 2 µg/mL;

7) CD4+ count nadir ≥ 350 cells/µL;

8) Screening CD4+ count ≥ 500 cells/µL;

9) 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;

10) Normal ECG (if abnormal, determined by the investigator to be not clinically significant);

11) Adequate renal function:

Estimated glomerular filtration rate (eGFR) ≥ 70 mL/min according to the Cockcroft-Gault formula {Cockcroft 1976}:

Male: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}$ (mL/min)

Female: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = CL_{cr}$ (mL/min)

where, CL_{cr} = creatinine clearance;

12) Alanine aminotransferase (ALT) and AST ≤ 5 × upper limit of normal (ULN);

13) Alkaline phosphatase within normal limits;

14) Total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin;

15) Adequate hematologic function (absolute neutrophil count ≥ 750/mm^3; platelets ≥ 50,000/mm^3; and hemoglobin ≥ 8.5 g/dL). Those with chronic neutropenia with no clinical significance can enroll at investigator discretion;

16) Females of childbearing potential (as defined in Appendix 5) must have a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1 prior to study drug administration;

17) Male and female participants of childbearing potential who engage in heterosexual intercourse must agree to utilize protocol-specified method(s) of contraception as described in Appendix 5;

18) Female participants must refrain from egg donation and in vitro fertilization during study participation and until at least 700 days following the last dose of study drugs;

19) Male participants must refrain from sperm donation during treatment and until the end of the protocol-defined follow-up period.

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

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

2) 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;

3) Breastfeeding female;

4) Documented historical resistance to any component of the participant's current ART regimen;

5) Participation in any other clinical study, including observational studies, without prior approval from the sponsor;

6) Hepatitis C virus (HCV) antibody positive and HCV RNA detectable;

7) Chronic hepatitis B virus (HBV) infection, as determined by either:

   - Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status, at the screening visit, or
   - Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit;

8) Active, serious infections (other than HIV-1 infection) requiring systemic antibiotic or antifungal therapy within 42 days prior to Day 1;

9) Have poor venous access that would limit phlebotomy or IV infusion of study treatments;

10) Have a history of any of the following:

   - Opportunistic infection or illness indicative of Stage 3 HIV disease (refer to Appendix 6);
   - Known hypersensitivity to the study drug, the metabolites, or formulation excipient;
   - Have an implanted defibrillator or pacemaker;
   - Malignancy within the past 5 years (prior to screening) or ongoing malignancy, other than basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma;
   - Substance abuse or a psychiatric or medical condition that could, in the opinion of the investigator, compromise the participant's ability to participate in the study.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes Access

5.1.1. Randomization

Participants will be assigned a screening number in the IRT system at the time of consent.

Once eligibility has been confirmed, the investigator or designee will randomize the participant using the IRT system. Once a participant number has been assigned to a participant, it will not be reassigned to any other participant. The participant number assignment and randomization must be performed in clinic at the Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed.

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.

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-2972) to which the participant is sensitive.

The IRT will assign a study drug bottle or vials at the Day 1 visit for each participant.

5.1.2. Blinding

This study is designed as a randomized and blinded study, where Gilead personnel and site pharmacist will be unblinded while the investigational site(s) and participants participating in the study will remain blinded during the randomized phase. To mitigate the risks of inadvertently releasing the treatment information, Gilead staff will only be provided with the unblinded information when there is a need to access such information for data analysis to support safety and efficacy monitoring. Should Gilead staff receive unblinding information, they will maintain the confidentiality of the unblinded information, and will not communicate the information to blinded sites, or participants as specified in Gilead standard operating procedures (SOPs).

5.1.3. Planned Interim Unblinding

Additionally, to assess the safety and efficacy of the bNAbs GS-5423 and GS-2872 in combination with the HIV capsid inhibitor LEN for planning and development of the study regimen, an internal GDRC will be assembled. The GDRC will review participant-level data.

The GDRC will review the Week 12 data and other ad hoc analysis, if needed (see Section 0).

The membership, conduct, and meeting schedule of the internal unblinded team will be documented in the GDRC Charter and as specified in Gilead SOPs. After the GDRC review of Week 12 data of primary cohort, the optional Pilot Cohort may be enrolled on the recommendation of the GDRC.

5.1.4. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain treatment assignment directly from the IRT system for that participant. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study and therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study treatment discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

All participants will receive the same 3 active study drugs, with the only difference being the dose of GS-2872. Unblinding for medical care is not expected.

5.2. Description and Handling of Lenacapavir, GS-5423, and GS-2872

5.2.1. Formulation

5.2.1.1. Lenacapavir

Lenacapavir tablets, 300 mg, are capsule-shaped, film-coated beige tablets, debossed with "GSI" on one side of the tablet and "62L" on the other side of the tablet. Each tablet core contains the equivalent of 300 mg LEN free acid in the form of LEN sodium salt. In addition to the active ingredient, LEN tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, mannitol, poloxamer 407, copovidone, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, iron oxide red, iron oxide black, and iron oxide yellow.

Lenacapavir injection, 309 mg/mL, is a clear, yellow to brown solution for SC injection. In addition to the active ingredient (LEN sodium), LEN injection, 309 mg/mL, contains the following inactive ingredients: polyethylene glycol 300 and water for injection.

5.2.1.2. GS-5423

GS-5423 solution for infusion, 150 mg/mL, 1 mL/vial drug product will be supplied as a sterile, preservative-free, colorless to brownish yellow solution for IV administration. The drug product is composed of 150 mg/mL GS-5423 in histidine, acetate, trehalose, methionine, and polysorbate 20 at pH 5.2.

5.2.1.3. GS-2872

GS-2872 solution for infusion, 150 mg/mL, 1 mL/vial, or 2 mL/vial drug product will be supplied as a sterile, preservative-free, colorless to brownish yellow solution for IV administration. The drug product is composed of 150 mg/mL GS-2872 in histidine, acetate, trehalose, methionine, and polysorbate 20 at pH 5.5.

5.2.2. Packaging and Labeling

5.2.2.1. Lenacapavir

Lenacapavir tablets, 300 mg, are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains either 4 or 5 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, and aluminum-faced liner.

Lenacapavir injection, 309 mg/mL, is supplied as a sterile solution packaged in a single-use clear vial fitted with a rubber stopper and an aluminum flip-off seal.

5.2.2.2. GS-5423

GS-5423 solution for infusion, 150 mg/mL, 1 mL/vial drug product is filled in single-use 2R, Type I clear glass vials, with coated elastomeric stoppers, capped with polypropylene flip-off caps with aluminum overseals.

5.2.2.3. GS-2872

GS-2872 solution for infusion, 150 mg/mL, 1 mL/vial, or 2 mL/vial drug product is filled in single-use 2R, Type I clear glass vials, with coated elastomeric stoppers, capped with polypropylene flip-off caps with aluminum overseals.

Study drugs to be distributed to centers in the US shall be labeled to meet applicable requirements of the US FDA and/or other local regulations.

5.2.3. Storage and Handling

Until administration and dispensation to the participants, all study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.2.3.1. Lenacapavir

Lenacapavir tablets, 300 mg, should be stored below 30°C (86°F). Storage conditions are specified on the study drug label.

Lenacapavir injection, 309 mg/mL should be stored below 30°C (86°F) and protected from light. Storage conditions are specified on the study drug label.

5.2.3.2. GS-5423

GS-5423 solution for infusion, 150 mg/mL, 1 mL/vial drug product, should be stored at 2-8°C and protected from light. Storage conditions are specified on the study drug label.

5.2.3.3. GS-2872

GS-2872 solution for infusion, 150 mg/mL, 1 mL/vial, or 2 mL/vial drug product, should be stored at 2-8°C and protected from light. Storage conditions are specified on the study drug label.

5.3. Dosage and Administration of GS-5423, GS-2872, and Lenacapavir

On Day 1, all participants will receive the following study regimen:

- Oral LEN 600 mg will be administered orally (PO) with approximately 240 mL water, without regard to food.
- LEN 927 mg SC will be administered within 30 minutes after oral LEN for loading, as 2 SC injections at separate injection sites in the abdomen, within 15 minutes.
- GS-5423 30 mg/kg IV infusion will be administered immediately following (up to 1 hour after) the last SC LEN injection.
- GS-2872 10 mg/kg or 30 mg/kg (depending upon treatment group assignment) IV infusion will be administered at least 15 minutes following, and up to 1 hour after, the completion of GS-5423 IV infusion per Table 5-1.

On Day 1, all study drugs should be administered on the same day (ie, no visit window is permitted for Day 1 study drug administration).

On Day 2, all participants will self-administer oral LEN for loading 600 mg with approximately 240 mL water, without regard to food, at approximately the same time as the oral LEN dose for loading on Day 1.

Dose and administration of LEN, GS-5423, and GS-2872 for Treatment Groups 1 and 2 are described below.

Table 5-1. Treatment Table

Study Day	Treatment Group 1	Treatment Group 2
Day 1	LEN 600 mg (two 300 mg tablets, PO) LEN 927 mg (two 1.5 mL injections, SC) GS-5423 30 mg/kg (IV infusion) GS-2872 10 mg/kg (IV infusion)	LEN 600 mg (two 300 mg tablets, PO) LEN 927 mg (two 1.5 mL injections, SC) GS-5423 30 mg/kg (IV infusion) GS-2872 30 mg/kg (IV infusion)
Day 2	LEN 600 mg (two 300 mg tablets, PO)	LEN 600 mg (two 300 mg tablets, PO)

IV = intravenous; LEN = lenacapavir; PO = per oral; SC = subcutaneous

Supportive medications, including but not limited to diphenhydramine, acetaminophen, and steroids, will be available in the clinic settings during the IV infusions.

Study drug infusion will be temporarily stopped if an infusion-related adverse reaction occurs. Symptom severity will be evaluated, and supportive medications provided as clinically indicated. Study drug infusion may be slowed and resumed after symptoms have resolved if approved by the investigator. If the symptoms, in the judgment of the investigator, compromise the ability to continue study-specific procedures and are considered to not be in the participant's best interests, or recurrent symptoms prevent completion of infusion, the infusion will be permanently discontinued.

The exact time of study drug administrations must be recorded in the source document. For additional information, refer to the study Pharmacy Manual.

5.4. Prior and Concomitant Medications

Clinical data indicate LEN is a substrate of P-glycoprotein (P-gp) transporters, and an inhibitor of cytochrome P450 enzyme (CYP) 3A enzymes (moderate), breast cancer resistance protein (BCRP), and P-gp transporters. In vitro data suggest LEN is also a substrate of CYP3A and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) enzymes. Concomitant use of LEN with some medications or herbal/natural supplements that are inhibitors or inducers of CYP3A, UGT1A1, or P-gp may result in increased or decreased LEN exposure, respectively. Concomitant use of LEN with some medications or herbal/natural supplements that are substrates of CYP3A, P-gp, or BCRP may result in increased exposure of these medications.

Representative medications listed in Table 5-2 and herbal/natural supplements are currently excluded or should be used with caution while participating in this study; this table is not exhaustive. Any medication that is not on the list should be reviewed by Gilead prior to screening and throughout the study. Vitamins, acetaminophen, ibuprofen, and hormonal medications are allowed during the study period. Participants should discontinue disallowed concomitant medications 30 days prior to initiation of study drug, unless otherwise specified.

Vaccinations should not be administered within 14 days prior to infusion of GS-5423 and GS-2872 at Day 1.

Table 5-2. List of Representative Medications that are Prohibited or To Be Used with Caution due to the Potential for Drug-Drug Interaction with LEN

Medication Class	Prohibited Medications	Use Discouraged and To Be Used With Caution
Anticoagulants	—	Dabigatran etexilate: monitoring and/or dose reduction may be needed for certain populations per prescribing information
Anticonvulsants	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	—
Antimycobacterials	Rifampin, rifabutin, rifapentine	—
Antiretroviral agents	Any ARV not part of the study treatment regimen	—
Digoxin	—	Digoxin: concomitant use may result in increased levels of digoxin; use with caution and with appropriate monitoring of serum digoxin levels
Ergot derivatives	Ergotamine, ergonovine, dihydroergotamine, methylergonovine, ergometrine	—
Herbal/natural supplements	St. John's wort, echinacea, milk thistle (ie, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	—
3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors	—	Concentrations of some statins may increase with LEN. Start with the lowest dose and titrate to clinical response. For each of the following statins, the maximum allowed dose is: Simvastatin: 10 mg Lovastatin: 20 mg Atorvastatin: 40 mg Careful monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.
Phosphodiesterase-5 inhibitors	—	Sildenafil, vardenafil, tadalafil: It is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered.
Sedatives/hypnotics	—	Midazolam, triazolam
Systemic corticosteroids	All agents, including dexamethasone*	—

ARV = antiretroviral; LEN = lenacapavir
* Single dose hydrocortisone for treatment of infusion reaction is permitted

Medications to treat disease conditions excluded from the protocol are not listed under this concomitant medication section and are disallowed in the study. Medications for malignancy are not included in the table.

Should participants have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication. In instances where disallowed medication is initiated prior to discussion with Gilead, the investigator must notify Gilead as soon as they are aware of the use of the medication.

5.5. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug, (vials and bottles). This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug vials and bottles dispensed to participants must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug (vials and bottles)
- The date, participant number, and the study drug kit number dispensed
- The date, quantity of used and unused study drug (bottles) returned, along with the initials of the person recording the information

5.5.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained by Gilead for the electronic trial master file (eTMF). If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the unblinded study monitor must first perform drug accountability during a monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify the Gilead or the contract research organization (CRO).

6.1. Participant Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

Once the ICF has been obtained, all screening and eligibility tests and assessments have been assessed, and study eligibility has been confirmed, participants will be randomized to receive study drug on Day 1.

Participants will receive the study treatments as described in Section 5.3.

6.2. Pretreatment Assessments

6.2.1. Screening

Due to the extended laboratory processing time of the bNAb sensitivity testing (up to approximately 10 weeks), the screening visit for the Primary Cohort will be performed in 2 parts. 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).

The following will be performed and documented at screening:

Part 1:

- Obtain written informed consent
- Obtain medical history
- Review of AEs and concomitant study drugs
- Obtain laboratory sample for bNAb sensitivity testing

Part 2: To be performed once results of bNAb sensitivity testing are reviewed and participant is deemed eligible to proceed.

- Assess any changes in medical history, AEs, and concomitant medications
- Complete physical examination
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Weight
- Height
- ECG
- Obtain laboratory samples as described in Section 6.7

  (Note: results obtained > 28 days before Day 1 will require a retest and confirmation)

Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 days after the Screening Part 2 visit for the Day 1 visit. Participants must continue to take their prior treatment regimen up to 1 day prior to the Day 1 visit.

From the time of obtaining informed consent through the first administration of study drug, all SAEs, as well as any AEs related to protocol-mandated procedures, must be recorded on the AEs electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Randomization

Once eligibility has been confirmed prior to or during the Day 1 visit, the investigator or designee will randomize the participant using IRT. The participant number assignment and randomization must be performed in clinic at the Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed.

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.

6.4. Treatment Assessments

6.4.1. Day 1

The following procedures are to be completed at the Day 1 visit prior to study drug dosing:

- Review of inclusion/exclusion criteria to confirm eligibility
- Review of AEs and changes in concomitant medications
- Complete physical examination
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Weight
- ECG
- Obtain laboratory samples as described in Section 6.7

After Day 1 assessments:

- 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
  - Vital signs (blood pressure, pulse, respiration rate, and temperature) will be recorded 30 minutes (± 10 minutes) after completion of GS-2872 infusion
- Participant will be dispensed oral LEN tablets

6.4.2. Day 2

- Participant will self-administer 2 tablets of LEN (2 × 300 mg) orally at home at approximately the same time as Day 1. The site will confirm dosing with participants and document in the source document.
- Participants in the Optional PK Substudy will dose in the clinic and samples will be obtained as described in Section 6.7.1.
- Review of AEs and changes in concomitant medications

6.4.3. Day 8

- Participants in the Optional PK Substudy will visit the clinic for substudy sample collection
- Review of AEs and changes in concomitant medications

6.4.4. Weeks 4, 12, 26, 38, and 52

- Review of AEs and changes in concomitant medications
- Focused physical examination
- ECG at Weeks 26 and 52
- Weight
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Obtain laboratory samples as described in Section 6.7
- At Week 26, all participants will resume their baseline background oral ARV regimen (or compatible regimen selected by the investigator).

6.4.5. Weeks 8, 16, 20, and 24

- Review of AEs and changes in concomitant medications
- Obtain laboratory samples as described in Section 6.7

6.5. Early Termination

If a participant discontinues their participation prior to Week 26, an Early Termination (ET) visit will be performed.

The following will be performed at the ET visit:

- Review of AEs and changes in concomitant medications
- Complete physical examination
- Weight
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Obtain laboratory samples as described in Section 6.7
- 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

However, if there are any abnormal laboratory results indicating there is a possible or probable causal relationship with the study drug, every attempt should be made to keep the participant in the study and repeat those laboratory tests weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

The participant will be asked to continue attending the scheduled study visits through the Week 52 visit.

- If the participant decides to discontinue the study regimen but continues to attend study visits through Week 52, no other follow-up visits are required.

- If the participant decides to discontinue the study regimen and does not continue to attend study visits through Week 52, the post-ET 30-, 90-, and 180-Day follow-up visits are required. Refer to Section 6.5.1. The post-ET 180-Day follow-up visit may be conducted via a phone call per the investigator's discretion.

Any post-ET 90-Day follow-up visit occurring after the date the Week 52 visit would have occurred may be conducted via a phone call per the investigator's discretion.

If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.5.1. Post-Early Termination 30-Day, 90-Day, and 180-Day Follow-up Visits

The assessments below will be completed for participants who are required to complete the post-ET 30-, 90-, and 180-Day follow-up visits as noted in Section 6.7.

Follow-up visits will be scheduled based on the date of the ET visit. For scheduling the follow-up visits, a ±6-day window may be used.

The following evaluations are to be completed during a phone call and in-clinic for follow-up visits:

- Review of AEs and changes in concomitant medications

The following evaluations are to be completed at the in-clinic follow-up visits:

- Review of AEs and changes in concomitant medications
- Focused physical examination
- Weight
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Obtain laboratory samples as described in Section 6.7

- At the post-ET 30-, 90-, and 180-Day follow-up visits, as applicable, if there are any abnormal laboratory results indicating that there is a possible or probable causal relationship with the study drug(s), every attempt should be made to repeat those laboratory tests weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained. If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.
- If there are any AEs, every attempt should be made to keep the participant in the study and should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

6.6. Criteria for Discontinuation of Study Treatment

Study drug may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree and would not allow for subsequent study regimen administration
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the participant's best interest
- VF; refer to Section 6.8
- Participant request to discontinue for any reason
- Participant noncompliance with any of the study drugs
- Pregnancy during the study; refer to Appendix 5
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)

6.7. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined below, within Section 6, and in Appendix 2.

6.7.1. Blood Samples

Blood sample collection for the following laboratory analyses will be performed as specified:

- Proviral DNA phenotype by the PhenoSense mAb Assay DNA at Monogram Biosciences **at screening (Part 1)**
- Bulk viral outgrowth phenotype **at screening** for subsequent testing
- Proviral DNA genotype **at screening** for subsequent testing

- Hematology profile: complete blood count (CBC) with differential and platelet count at **screening, Day 1, Weeks 4, 12, 26, 38, 52, ET, and post-ET follow-up visits**

- Chemistry profile: alkaline phosphatase, AST, ALT, gamma-glutamyltransferase (GGT), total bilirubin, direct and indirect bilirubin, total protein, albumin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in participants with total amylase > 1.5 × ULN) **at screening, Day 1, Weeks 4, 12, 26, 38, 52, ET, and post-ET follow-up visits**

- Coagulation (prothrombin time, partial thromboplastin time, international normalized ratio) **at screening**

- Thyroid function: TSH, T3, and free T4 **at screening, Day 1, Weeks 4, 12, 26, 38, and 52**

- CD4+ cell count, CD8+ cell count, and CD4/CD8 ratio **at screening, Day 1, Weeks 4, 12, 26, 38, 52, ET, and post-ET follow-up visits**

- eGFR according to the Cockcroft-Gault formula for CL_{cr} **at screening, Day 1, Weeks 4, 12, 26, 38, 52, ET, and post-ET follow-up visits**

  Male: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}\ (\text{mL/min})$

  Female: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = CL_{cr}\ (\text{mL/min})$

- Serum follicle-stimulating hormone (FSH) test (required for female participants < 54 years of age who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure; see Appendix 5) **at screening**

- Serum pregnancy test (females of childbearing potential only) **at screening, Weeks 4, 12, 38, 52, ET, and post-ET follow-up visits)**. If the test is positive at screening, the participant will not be randomized.

- HBV and HCV serology: HBV surface antigen, HBV core antibody, and HBV surface antibody; HCV serology, with reflex to HCV RNA if positive **at screening**

- HIV-1 RNA **at all visits (except Days 2-8)**

- HIV reservoir assay on **Day 1 (predose) and at Week 52**

- Plasma storage samples for virology testing **at all visits (except screening, Days 2-8)**

- Immune biomarker collection on **Day 1 (predose), and at Weeks 4, 26, 38, and 52**

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

  Note: PK samples obtained on Day 1 should be drawn from a separate catheter in the opposite arm from the one used for GS-5423 and GS-2872 IV infusion to avoid contamination.

  The exact time of study drug administration and the exact time points (date and time) of collection of plasma samples must be carefully recorded. Serum PK samples for GS-5423 and GS-2872 will be collected at the following time points for all participants:

  — Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872)

  — A single anytime sample at Weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52

In case of ET prior to Week 52, applicable study drug single PK samples will be collected.

- **PK plasma samples for LEN will be collected in all participants as follows:**

  PK samples should be drawn from a separate catheter in the opposite arm from the one used for GS-5423 and GS-2872 IV infusion to avoid contamination.

  — Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872)

  — A single anytime sample at Weeks 4, 8, 12, 16, 20, 24, 26, 38, and 52

  — In case of ET prior to Week 52, applicable study drug single PK samples will be collected.

- **Optional PK Substudy:**

  If participants provide specific separate consent, plasma samples for LEN will be collected at the following times in a subset of participants who will dose in clinic on Day 2 (approximately n = 14 evaluable and n = 7 from each treatment group):

  — Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872), 4 hours after oral LEN dose for loading, and 8 hours after oral LEN dose for loading

    ■ The time points for Day 1 collection are the same for both plasma PK for LEN and the Optional PK Substudy; make sure to only collect once on Day 1 (predose), within 5 minutes after the end of the first antibody infusion (GS-5423), and within 5 minutes after the end of the second antibody infusion (GS-2872)

— Day 2: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), and single anytime sample between 1 and 6 hours after oral LEN dose for loading

— Day 8: single anytime sample

- **Immunogenicity Assessment:**

— Serum samples will be drawn on Day 1 (predose), Weeks 4, 12, 26, 38, and 52

- **Pharmacodynamic Biomarkers:**

— PBMC, whole blood, serum, and plasma samples will be collected on Day 1 (predose), Weeks 4, 26, 38, and 52 for exploratory analysis, which may include HIV-1 specific T-cell response, immune cell phenotyping, gene expression, antibody profiling, and soluble proteins (eg, cytokines, chemokines, inflammatory markers, etc.). FcgR SNP will be evaluated using samples collected at the Day 1 visit.

— If consent for pharmacogenomic testing is obtained, then a sample is to be collected for optional pharmacogenomic testing. This sample should 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.

6.7.2. Urine Samples

Urine samples will be collected for the following laboratory analyses at every study visit, unless otherwise specified:

- Urinalysis: including color and clarity, specific gravity, pH, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase and microscopic (if microscopic elements are seen), urine protein, albumin, creatinine, phosphate, calcium, magnesium, and uric acid **at screening, Day 1, Weeks 4, 12, 26, 38, 52, ET, and post-ET follow-up visits**

- Urine pregnancy test predose (females of childbearing potential only) **on Day 1**.

— If the test is positive, confirmatory serum test should be performed and study drug dosing should be delayed until results obtained

6.7.3. Blood and Urine Storage Samples

Any residual blood and urine samples collected at all visits (except the screening and ET visits) will be frozen and stored. These stored blood and urine samples may be used by Gilead or its research partners for HIV-1 genotyping/phenotyping assays or their development, for retesting the amount of HIV-1 in the blood, for measurement of antiviral drug levels in the blood, or for future testing to learn more about how the study drug has worked against HIV-1 or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without expressed consent of study participants. At the conclusion of this study, these samples may be retained in storage by Gilead for a period up to 15 years.

6.8. Management of Virologic Rebound and Virologic Failure

Virologic failure is defined as having a rebound of HIV-1 RNA ≥ 200 copies/mL at 2 consecutive visits on or before Week 26, at Week 26, or at study drug discontinuation. Participants who meet criteria for VF will have samples sent for genotypic and phenotypic testing, will restart their baseline ARV regimen (or compatible regimen selected by the investigator), and will continue study follow-up but will not receive additional doses of the study regimen.

6.8.1. Virologic Rebound

Participants who meet the criteria listed below will be considered to have VR (see Figure 6-1):

- At any post-Day 1 visit, a rebound in HIV-1 RNA ≥ 50 copies/mL that is subsequently confirmed at the following scheduled or unscheduled visit; OR
- Any participant with HIV RNA ≥ 50 copies/mL at study discontinuation or Week 26

At any post-Day 1 visit, if the HIV-1 RNA is ≥ 50 and < 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma samples by the study central laboratory, if available. If the repeat result is < 50 copies/mL, participants will resume scheduled study visits. If the repeat result is ≥ 50 copies/mL, participants will be asked to return to the clinic for a scheduled or unscheduled HIV-1 RNA retest (approximately 2 to 3 weeks after the date of the last test that resulted in HIV-1 RNA ≥ 50 copies/mL) for confirmation.

- HIV-1 RNA < 50 copies/mL at the confirmation visit: participants will resume scheduled study visits
- HIV-1 RNA ≥ 200 copies/mL at one visit except at study discontinuation or Week 26: participants will be asked to return to the clinic for a scheduled or unscheduled HIV-1 RNA (within 2 to 3 weeks after the date of last HIV-1 RNA) and resume scheduled study visits until confirmation results are available
- Participants with HIV-1 RNA ≥ 200 copies/mL at two consecutive visits or at study discontinuation or Week 26 meet criteria for VF, refer to Section 6.8.2.
- Participants with HIV-1 RNA between ≥ 50 and < 200 copies/mL at both the confirmation visit and the previous test, must be discussed with medical monitor.

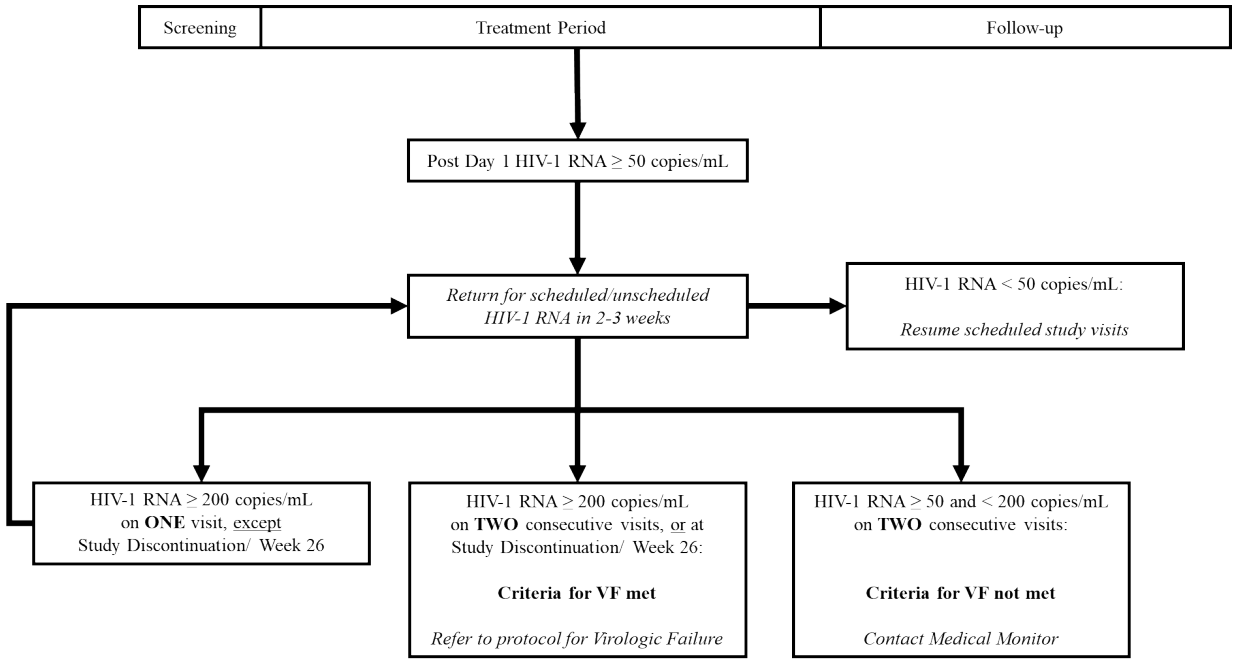
6.8.2. Virologic Failure

Participants who meet the criteria listed below will be considered to have VF:

- Participants with HIV-1 RNA ≥ 200 copies/mL on 2 consecutive visits will be considered to have VF. The blood sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing of capsid and env for study drugs (LEN, GS-5423, and GS-2872) and genotypic testing of RT, PI, and/or IN genes for the baseline ART regimen. Samples collected at baseline will be used for comparison of genotypic and phenotypic testing of study drugs at VF. The participant will be restarted on their baseline ART regimen (or compatible regimen selected by the investigator) and continue on study follow-up but will not receive additional doses of the study regimen. Participants will return for an unscheduled visit, 4 weeks after restarting their baseline ART regimen (or compatible regimen selected by the investigator) to confirm virologic suppression.
- Participants with HIV-1 RNA ≥ 200 copies/mL at study discontinuation or Week 26 will be considered to have VF. The blood sample from the last visit or Week 26 with HIV-1 RNA ≥ 200 (ie, not confirmable) will be the primary sample used for HIV-1 genotypic and phenotypic testing. The participant will be restarted on their baseline ART regimen (or compatible regimen selected by the investigator) and continue on study follow-up but will not receive additional doses of the study regimen. Participants will return for a unscheduled visit 4 weeks after restarting their baseline ART regimen (or compatible regimen selected by the investigator) to confirm virologic suppression.
- Participants with ongoing HIV-1 RNA ≥ 50 copies/mL but who do not meet criteria for VF must be discussed with the medical monitor.

For participants who are off study drug but remain on study, it will be the investigator's discretion to manage VR.

Figure 6-1. Virologic Rebound Schema



VF = virologic failure

6.9. End of Study

The end of this study will be when the last participant has completed their final visit.

6.10. Poststudy Care

Once a participant has completed their study participation, the long-term care of the participant will return to the responsibility of their primary treating physicians.

6.11. Sample Storage

The stored biological samples may be used by Gilead or its research partner for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years or per country requirements. If participants provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of the study or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one’s professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub investigator is responsible for assessing the relationship to study drug) using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug).

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture, biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017 (Appendix 4). For each episode, the highest grade attained should be reported as defined in the toxicity grading scale.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5 grading scale will be used to grade AEs determined to be infusion reactions.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until the end of the protocol-defined posttreatment follow-up period and report them on the eCRFs as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and Global Patient Safety (GLPS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after ICF is signed.

Any SAEs and deaths that occur throughout the duration of the study, including the protocol-required posttreatment follow-up period, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead GLPS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to GLPS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.4).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.4.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications does not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

Gilead GLPS
Email: PPD
or
Fax: PPD

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to GLPS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

- Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information to Gilead GLPS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If for any reason it is not possible to record the SSR information electronically, record the SSR on the paper special situation reporting form and transmit to:

Gilead GLPS
Email: PPD
or
Fax: PPD

- If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to GLPS.

- See Section 7.4.2.2 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

Gilead GLPS
Email: PPD
or
Fax: PPD

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

- Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

- The investigator should report pregnancies in female study participants and/or female partners of male participants that are identified after initiation of study drug and throughout the study, including the poststudy drug follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead GLPS
Email: PPD
or
Fax: PPD

- The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

- All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Gilead GLPS.

- The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS. Gilead GLPS contact information is as follows: email: PPD and fax: PPD
- Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Union (EU) Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line-listings, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned member states of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the DAIDS toxicity grading scale, Version 2.1 (Appendix 4). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

The CTCAE Version 5 grading scale will be used to grade AEs determined to be infusion-related reactions or cytokine release syndrome (see Table 7-1).

Table 7-1. The Common Terminology Criteria for Adverse Events (CTCAE) Version 5 Grading Scale

General Disorders and Administration Site Conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O_2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. **Navigational Note:** Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache.					

IV = intravenous; NSAIDs = nonsteroidal antiinflammatory drugs

7.7. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3, and as outlined below:

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as possible, and preferably within 3 calendar days after receipt of the original test results.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment-related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.7.1. Management of Adverse Events of Injection Site Reactions of Grade 3 or Higher or Persisting for More than 26 Weeks

In clinical studies of SC LEN, Grade 3 or higher AEs of injections site reactions (ISRs) were uncommon. Some participants experienced AEs of injection site nodule and induration, which decreased in size over 6 months or longer. For AEs of ISRs related to SC LEN administered from a borosilicate vial that are Grade 3 or higher or persisting for more than 26 weeks, particularly nodule and/or induration, the investigator must contact the Medical Monitor and obtain consultation with an independent dermatologist to evaluate the ISRs.

If clinically indicated as determined by the independent dermatologist, a biopsy of the SC injection site may be performed. The histopathology should be reviewed by an independent dermatopathologist; if a dermatopathologist is not locally available, the histopathology may be reviewed by an otherwise medically qualified person.

Photographic documentation of the ISRs that meet the criteria above is recommended, if possible, but is not mandatory. If obtained, the documentation may be shared by the investigator with the independent dermatologist or dermatopathologist and may be requested by the sponsor.

7.7.2. Management of Other Toxicities

Unless otherwise specified in Section 7.7, toxicities will be managed according to the guidelines below.

- All clinically significant Grade 3 and 4 laboratory abnormalities should be repeated within 3 calendar days to confirm toxicity grade. Confirmation of toxicity grade is required prior to the next dose of investigational medicinal product for any Grade 3 and 4 laboratory abnormality that in the opinion of the investigator is clinically significant and may pose a risk to the participant's safety.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (refer to Appendix 4).

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

7.7.2.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event Management of Clinical and Laboratory Adverse Events

- Grade 1 or 2 laboratory abnormality or clinical event

Continue investigational medicinal product at the discretion of the investigator.

7.7.2.2. Grades 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued, and the participant managed according to local practice including switching to an effective alternative ARV regimen with consideration of the long duration of exposure of investigational medicinal products and the risk of resistance if viremic. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.7.2.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued, and the participant managed according to local practice including switching to an effective alternative ARV regimen with consideration of the long duration of exposure of investigational medicinal products and the risk of resistance if viremic. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational medicinal product may be continued without dose interruption for a clinically nonsignificant Grade 3-4 laboratory abnormality (eg, CK elevation after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a Grade 3-4 clinical event considered unrelated to investigational medicinal product.

7.8. Safety Assessment Committee

Per Gilead's signal management and unblinding process, an internal Safety Assessment Committee can be requested to review unblinded clinical study for safety reasons. Members of the Safety Assessment Committee are not directly involved in conduct of the study. The Safety Assessment Committee provides recommendations to relevant safety committees (per Gilead's signal management process) whether further actions are necessary to protect participants involved in the LEN development program.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

Study endpoints will be assessed in the Primary Cohort excluding the optional Pilot Cohort. Exploratory analysis may be conducted for the optional Pilot Cohort as applicable.

The primary objective of this study is as follows:

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

The secondary objectives of this study are as follows:

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

The exploratory objectives are as follows:

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

8.1.2. Primary Endpoint

The primary endpoint of this study is as follows:

- Incidence of treatment-emergent SAEs through Week 26

8.1.3. Secondary Endpoints

The secondary endpoints of this study are as follows:

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

- Proportion of participants with positive anti–GS-5423 or anti–GS-2872 antibodies at Week 26
- Change from baseline in CD4+ cell counts at Week 26
- Treatment-emergent resistance to study drugs through Week 26
- Incidence of treatment-emergent SAEs through Week 26, and treatment-emergent AEs through Week 26
- PK parameters for GS-5423, GS-2872, and LEN (and metabolites, if applicable) as appropriate: $AUC_{0\text{-}t}$, AUC_{last}, $t_{1/2}$, C_{max}, T_{max}, T_{last}, C_t through Week 52

8.1.4. Other Endpoints of Interest

Other endpoints of interest are as follows:

- Changes from baseline in HIV-1 reservoir in PBMC at postbaseline visits
- Changes from baseline in HIV-1 specific T-cell response, immune cell phenotyping and proliferation, gene expression, antibody profiling, and plasma soluble proteins levels (eg, cytokines, chemokines, etc).

8.2. Planned Analyses

8.2.1. Interim Analysis

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

8.2.1.1 Gilead Data Review Committee Analysis

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

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

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

8.2.2. Primary Analysis

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

8.2.3. Final Analysis

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

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Randomized

The primary analysis set for by-participant listings is defined as the All Randomized Analysis Set, which will include all participants who are randomized into the study.

8.3.1.2. Efficacy

The primary analysis set for efficacy analysis is defined as the Full Analysis Set, which will include 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).

8.3.1.3. Safety

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all randomized participants who have received at least one dose of study drug.

All data collected during study will be included in the safety summaries.

8.3.1.4. Pharmacokinetics

8.3.1.4.1. Pharmacokinetic (PK) Substudy Analysis Set

The PK Substudy Analysis Set, which will include all randomized participants who are enrolled into the Optional PK Substudy, have received at least 1 dose of study drug, and have at least 1 nonmissing concentration value reported by the PK laboratory for corresponding analytes (eg, LEN or metabolites, if applicable).

8.3.1.4.2. Pharmacokinetic (PK) Analysis Set

The PK Analysis Set, which will include all randomized participants who have received at least 1 dose of study drug, and have at least 1 nonmissing concentration value reported by the PK

laboratory for the corresponding analytes (eg, GS-5423, GS-2872, LEN and metabolites, if applicable).

8.3.1.5. Immunogenicity

The 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 each immunogenicity evaluation (eg, anti–GS-5423 or anti–GS-2872).

8.3.2. Data Handling Conventions

Natural logarithm transformation for key PK parameters, such as AUC and C_{max} will be applied for PK analysis, as appropriate.

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at predose and one-half the lower limit of quantitation (LLOQ) for postdose time points.

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation (ULQ) will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Missing data can have an impact upon the interpretation of the study data. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group.

Demographic summaries will include sex, race/ethnicity, and age. Baseline data will include a summary of body weight, height, body mass index, and HIV-1 infection.

8.5. Efficacy Analysis

The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 as defined by the FDA-defined snapshot algorithm will be summarized by treatment group and overall using the Full Analysis Set. The 95% CIs will be constructed on the exact method. These efficacy endpoints will be compared between treatment groups by Fisher exact test.

The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 26 as defined by the FDA-defined snapshot algorithm will also be summarized by treatment group and overall in a similar manner.

The change from baseline in CD4+ cell count at Weeks 26 will be summarized by treatment group using descriptive statistics. Treatment-emergent resistance to study drugs will be summarized by treatment group.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the end of the protocol-defined follow-up period will be summarized by treatment group using Safety Analysis Set. Data for the pretreatment will be included in data listings. For participants who discontinue from only the oral LEN, only data collected up to 60 days after the last dose of the oral tablet will be included in the data summary.

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term, and lower-level term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. Any treatment-emergent AEs will be defined as any AE that begins on or after the date of first dose of study drug up to the end of the protocol-defined follow-up period. For participants who discontinue from only the oral LEN, only AEs collected up to 60 days after the last dose date will be considered treatment-emergent.

Summaries (number and percentage of participants) of treatment-emergent AEs (by SOC and preferred term) by treatment group will be provided. Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study drug, and effect on study drug dosing.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized by treatment group.

Graded laboratory abnormalities will be defined using the grading scheme in the DAIDS toxicity grading scale, Version 2.1 (Appendix 4).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time postbaseline through the duration of the study, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs and ECG data will be summarized by treatment group.

8.7. Adjustments for Multiplicity

No adjustments are planned.

8.8. Pharmacokinetic Analysis

Serum or plasma concentrations of each analyte (eg, GS-5423, GS-2872, and LEN [and metabolites, if applicable]) will be summarized by nominal sampling time and treatment using descriptive statistics for PK Substudy Analysis Set or PK Analysis Set as appropriate. Pharmacokinetic parameters ($AUC_{0\text{-}t}$, AUC_{last}, $t_{1/2}$, C_{max}, T_{max}, T_{last}, C_t, as appropriate) will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation %, SD, median, Q1, Q3, minimum, and maximum) by treatment group or overall, as appropriate. Serum or plasma concentrations of each analyte over time will be plotted in semi-logarithmic and linear formats as mean ± SD, and median (Q1, Q3), respectively.

8.9. Immunogenicity Analysis

Immunogenicity to GS-5423 and GS-2872 will be evaluated based upon the incidence of anti-GS-5423 antibody and anti–GS-2872 antibody formation, respectively. The number and percentage of participants positive or negative for anti–GS-5423 antibody and anti–GS-2872 antibody at each specified time point will be summarized, and supporting data including treatment, nominal visits, actual date and time of sampling, and anti–GS-5423 antibody and anti-GS-2872 antibody results will be included in a listing.

8.10. Sample Size

Although the sample size in this study is determined based on practical considerations and past experience with similar types of studies, assuming the 2 treatment groups have a similar virologic suppression rate, a total of 20 participants in the Primary Cohort will provide at least 35% power to show the lower bound of 95% CI for Week 26 virologic response rate (HIV-1 RNA < 50 copies/mL as defined by the FDA-defined snapshot algorithm) 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 8-1. 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 8-1. 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: SAS® Version 9.4. (SAS Institute Inc., Cary, NC, USA)

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

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative, and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

The ICF will inform participants about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each participant participating in the study, participants will be required to document agreement to provide additional samples or to allow the use of the remainder of their already collected specimens for optional future research, in accordance with applicable regulations. In addition to the study-specific ICF to be signed by each participant participating in the study, participants will be required to document agreement to provide additional samples for optional genomic research. The results of the tests done on the samples will not be given to the participant or the investigator.

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, case report forms (CRFs)/eCRFs, the study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, paper or electronic completed participant CRFs, and governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification
- Documentation that participant meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the eCRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.5).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority, and IRB In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

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

AMENDMENT 2: 30 March 2022

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD (Printed)	*[See appended electronic signature]* Signature
[See appended electronic signature] Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Study Procedures Table

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

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

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	X											
Randomization		X													
LEN Oral Administration[h]		X	X												
LEN SC Administration[i]		X													
GS-5423 IV Infusion Administration[i]		X													
GS-2872 IV Infusion Administration[i]		X													
Optional Pharmacogenomic Sample[j]															

a. For the Primary Cohort, screening procedures will be conducted in 2 parts: Part 2 will be performed once results of bNAb sensitivity testing from Part 1 are reviewed and participant is deemed eligible to proceed. For the optional Pilot Cohort, participants will be selected by the sponsor from the previously screened/failed participants in the Primary Cohort and will directly proceed to Screening Part 2 (no need to repeat Screening Part 1).

b. Refer to Section 6.5.1 for Post-ET 30-, 90-, and 180-Day follow-up visits.
- Counsel participant regarding the importance of continuing a complete ARV therapy in accordance to standard of care, and refer patient to an appropriate HIV treatment facility.

c. Vital signs: blood pressure, pulse, respiration rate, and temperature. On Day 1, vital signs should be recorded prior to start of study drug administration and 30 minutes (± 10 minutes) after completion of the GS-2872 infusion.

d. Serum FSH test (required for female participants < 54 years of age who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure; see Appendix 5)

e. HIV-1 genotype and phenotype testing for participants with virologic failure. Refer to Section 6.8.2.

f. PK serum samples will be collected in all participants for GS-5423 and GS-2872 as follows:
- The exact time of study drug administration and the exact time points (date and time) of collection of plasma samples must be carefully recorded.
- Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN for loading), within 5 minutes after the end of the first antibody infusion (GS-5423) and within 5 minutes after the end of the second antibody infusion (GS-2872)
- For ET visit, only single PK sample collection is required

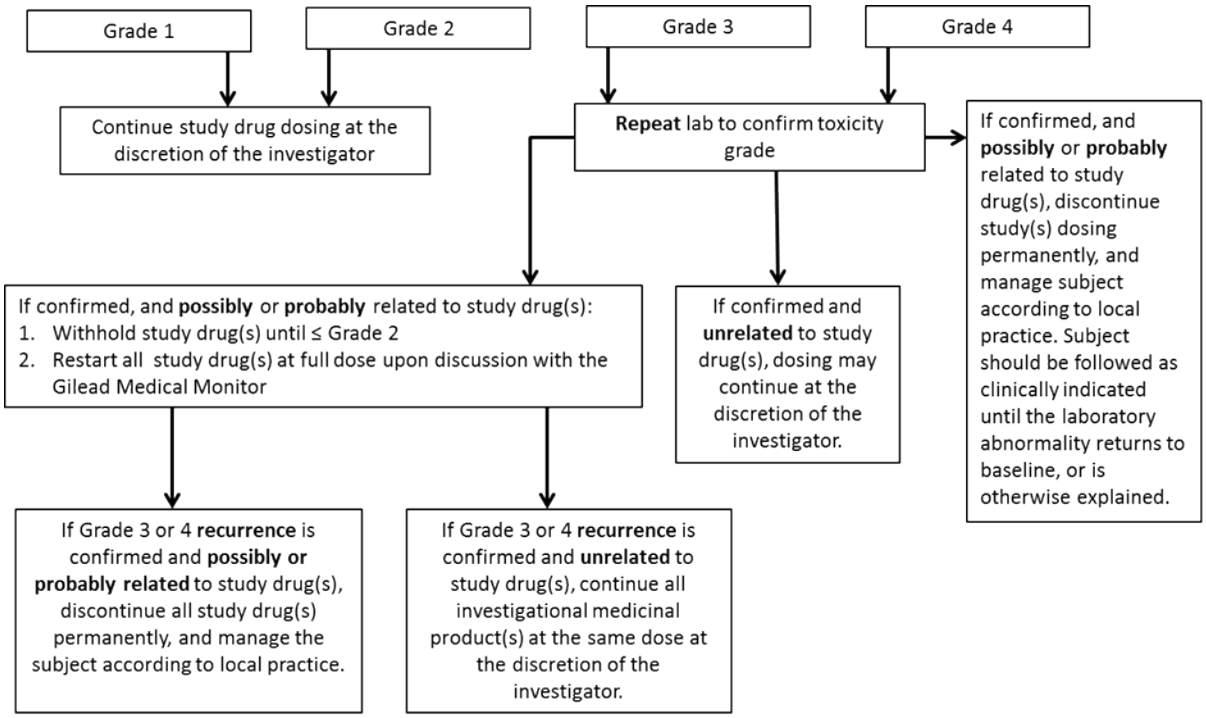
g. PK plasma samples for LEN will be collected in all participants as follows:
   - PK samples should be drawn from a separate catheter in the opposite arm from the one used for GS-5423 and GS-2872 IV infusion to avoid contamination.
   - Day 1: 0 hour (predose, ≤ 30 minutes prior to dosing of oral LEN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

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

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

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

Appendix 3. Management of Clinical and Laboratory Adverse Events



Grade 3 or 4 laboratory abnormalities include drop in platelets to < 50,000/mm^3.

Appendix 4. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

The Division of AIDS (DAIDS) scale is available at the following location:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born participant is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless the participant is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born participant is considered of fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Participants

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Nonclinical toxicity studies of lenacapavir (LEN, GS-6207) have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of LEN in pregnant women. Based on the available in vitro induction data, a drug-drug interaction with LEN and hormonal contraceptives that are not taken orally is not expected. Therefore, a barrier method with contraceptive steroids that are not taken orally is permitted in this study. However, LEN has insufficient data to exclude the possibility of a clinically relevant interaction with oral hormonal contraception that results in reduced contraception efficacy. Therefore, oral contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen.

GS-2872 and GS-5423 are contraindicated in pregnancy as their teratogenicity/fetotoxicity profile is unknown. A reduction in the clinical efficacy of hormonal contraception is not expected as GS-2872 and GS-5423 are not cytokine modulators. As protein biologics, GS-2872 and GS-5423 are not expected to be genotoxic but genotoxicity has not been evaluated in these compounds and so conservative contraceptive requirements are used in this study. Refer to the latest version of the investigator's brochure (IB) for additional information.

b) Contraception Requirements for Female Born Participants of Childbearing Potential

The inclusion of female born participants of childbearing potential requires using at least an acceptable effective contraceptive. They must have a negative serum pregnancy test at screening and a negative pregnancy test at the Day 1 visit prior to the dose of study drug. Pregnancy tests will be performed as defined by the study procedures in Appendix 2. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for female born participants of childbearing potential with infrequent or irregular periods. Female born participants of childbearing potential must agree to 1 of the following from screening until 700 days following the last dose of study drug:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Intrauterine device (IUD) with a failure rate of < 1% per year
- Tubal sterilization
- Essure® microinsert system (provided confirmation of success 3 months after procedure)
- Vasectomy in the male born partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
- Barrier methods (one female barrier and one male barrier must be used in combination):
  - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
  - Male barriers: Male condom (with or without spermicide)
- Hormonal Methods that <u>are not taken orally</u> (each method must be used with a barrier method, preferably male condom):
  - Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female born participants must also refrain from egg donation and in vitro fertilization during treatment and until at least 700 days following the last dose of study drug.

3) Contraception Requirements for Male Participants

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male participant's seminal fluid. Therefore, male participants with female partners of childbearing potential must use condoms during the study and until the end of the protocol-defined follow-up period. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male participants must also refrain from sperm donation during the study and until the end of the study protocol-defined follow-up period.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female participants will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study drug and throughout the study including the poststudy drug follow-up period. Study drug must be discontinued immediately, or interruption of study drug should be considered upon discussion with the medical monitor.

Male participants whose partner has become pregnant or suspects she is pregnant from the start of study drug and throughout the study including the poststudy drug follow-up period needs to report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 6. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)

Candidiasis of bronchi, trachea, or lungs

Candidiasis of esophagus

Cervical cancer, invasive

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (> 1 month duration)

Cytomegalovirus disease (other than liver, spleen or nodes)

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy, HIV-related

Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis or esophagitis

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (> 1 month duration)

Kaposi's sarcoma

Lymphoma, Burkitt's (or equivalent term)

Lymphoma, immunoblastic (or equivalent term)

Lymphoma, primary, of brain

Mycobacterium avium complex or *Myobacterium kansasii*, disseminated or extrapulmonary

Mycobacterium tuberculosis, of any site, pulmonary, disseminated or extrapulmonary

Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

Pneumocystis jirovecii (previously known as "*Pneumocystis carinii*) pneumonia

Pneumonia, recurrent

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent

Toxoplasmosis of brain

Wasting syndrome attributed to HIV infection

CDC Stage-3-Defining Opportunistic Illnesses in HIV Infection - 2014 {Schneider 2008}

Appendix 7. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to sites:

   Shipments of study drug could be delayed because of transportation issues. Without study drug participant would not be able to stay on the study drug as planned per protocol.

   Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify Gilead or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. Gilead will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

Participant safety monitoring and follow-up:

a) Participant may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

   Mitigation plan: For participants who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

   i) Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

   ii) Review current list of concomitant medications and document any new concomitant medications.

   iii) Review study restrictions with the participant.

   iv) Counsel the participant on the importance of obtaining the final safety laboratory assessments at their local lab.

b) Participant may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular scheduled and follow-up visits per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

Home health service provider may be utilized to perform protocol scheduled study visits at participant's home as home healthcare visit to collect protocol-specified clinical laboratory samples and assessments, except for Screening, Day 1, Weeks 26, 52, and ET visits, if approved by site in compliance with local EC/IRB and national laws and regulations and participant's consent.

c) Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

Protocol and monitoring compliance:

d) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

e) Monitors may be unable to carry out source data review (SDR) or source data verification (SDV), or study drug accountability or assess protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

Missing data and data integrity:

f) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

   Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of study drug(s) in study participants remains unchanged.

protocol GS-US-536-5816 amendment 2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	PPD eSigned	30-Mar-2022 18:30:31