CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Randomized, Open-label Study to Evaluate the Safety and Efficacy of Broadly Neutralizing Antibodies (bNAbs) GS-5423 and GS-2872 in Combination With the Capsid Inhibitor Lenacapavir as Long-Acting Treatment Dosed Every 6 Months in Virologically Suppressed Adults With HIV-1 Infection
Plain Language Short Title:	A Phase 2 Study of GS-5423 and GS-2872 in Combination With Capsid Inhibitor Lenacapavir in Virologically Suppressed Adults With HIV-1 Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number: **EU CT Number:** **ClinicalTrials.gov Identifier:**	163095 Not Applicable Not Available
Diagnosis or Condition:	Virologically Suppressed Adults With HIV-1 Infection
Protocol ID:	GS-US-536-5939
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Amendment 3: 13 May 2024
Amendment History:	Original: 02 November 2022 Amendment 1: 18 January 2023 Amendment 2: 26 June 2023 A high-level summary of the changes in each amendment is provided in Appendix 11.7.
Country-Specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 11.6.

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the investigational new drug application and are not considered to be investigational new drug application sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	antidrug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{0-t}	partial area under the concentration versus time curve from time "0" to time "t"
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
BCRP	breast cancer resistance protein
bNAb	broadly neutralizing antibody
CD4	clusters of differentiation 4
CD8	clusters of differentiation 8
CI	confidence interval
C_{max}	maximum observed concentration of drug
CRF	case report form
CSR	clinical study report
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
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESDD	early study drug discontinuation
EU	European Union
Fab	antigen-binding fragment
FAS	Full Analysis Set
Fc	crystallizable fragment
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Gilead	Gilead Sciences
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIVDQoL	HIV-dependent quality of life
HIVTPQ	HIV Treatment Preference Questionnaire
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HIVTSQc	HIV Treatment Satisfaction Questionnaire change version
HLT	high-level term
HTE	heavily treatment-experienced
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)
IND	investigational new drug
IQ	inhibitory quotient
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
IV	intravenous
LEN	lenacapavir
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
PBMC	peripheral blood mononuclear cell
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
POC	proof of concept
PRO	patient-reported outcome
PSD	post study drug
PT	preferred term
PWH	people with HIV-1
RNA	ribonucleic acid
SAC	Safety Assessment Committee
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SOC	system organ class

SSR	special situation report
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{max}	time (observed time point) of C_{max}
TN	treatment naive
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US, USA	United States, United States of America
VF	virologic failure
VR	virologic rebound

PROTOCOL SYNOPSIS

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

Study Title: A Phase 2 Randomized, Open-label, Study to Evaluate the Safety and Efficacy of Broadly Neutralizing Antibodies (bNAbs) GS-5423 and GS-2872 in Combination With the Capsid Inhibitor Lenacapavir as Long-Acting Treatment Dosed Every 6 Months in Virologically Suppressed Adults With HIV-1 Infection

Short Title: A Phase 2 Study of GS-5423 and GS-2872 in Combination With Capsid Inhibitor Lenacapavir in Virologically Suppressed Adults With HIV-1 Infection

IND Number: 163095
EU CT Number: Not Applicable
ClinicalTrials.gov Identifier: Not Available

Study Centers Planned:

Approximately 55 centers globally

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the efficacy of switching to a regimen of lenacapavir (LEN, Sunlenca®), GS-5423, and GS-2872 versus continuing on baseline oral antiretroviral (ARV) therapy (ART) as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26	• Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm
Secondary Objectives	**Secondary Endpoints**
• To evaluate the efficacy of switching to a regimen of LEN, GS-5423, and GS-2872 versus continuing on baseline oral ART as determined by the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 • To evaluate the efficacy of switching to a regimen of LEN, GS-5423, and GS-2872 versus continuing on baseline oral ART as determined by the proportion of participants maintaining virologic suppression (HIV-1 RNA < 50 copies/mL) at Weeks 26 and 52	• Proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 as determined by the US FDA-defined snapshot algorithm • Proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 and 52 as determined by the US FDA-defined snapshot algorithm • Changes from baseline in CD4+ T-cell counts at Weeks 26 and 52 • Proportion of participants experiencing treatment-emergent adverse events (TEAEs)

Secondary Objectives	Secondary Endpoints
• To evaluate CD4+ T-cell counts at Weeks 26 and 52 • To evaluate the safety and tolerability of the 2 treatment groups • To evaluate the pharmacokinetics (PK) of GS-5423, GS-2872, and LEN • To evaluate the immunogenicity of GS-5423 and GS-2872	• Trough concentrations at Weeks 26 and 52 and PK parameters (AUC_{0-t}, AUC_{last}, $t_{1/2}$, C_{max}, and T_{max}) for GS-5423, GS-2872, and LEN as appropriate • Incidence of anti–GS-5423 and anti–GS-2872 antibodies

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

Randomized Phase

Treatment Group 1

- Participants in Treatment Group 1 will receive the long-acting regimen consisting of LEN, GS-5423, and GS-2872.
- Participants will discontinue their baseline oral ART following administration of the complete study drugs on Day 1 (oral LEN, subcutaneous [SC] injectable LEN, and intravenous [IV] infusions of GS-5423 and GS-2872) and will self-administer oral LEN on Day 2. Participants will also receive study drug (SC LEN and IV infusions of GS-5423 and GS-2872) at Week 26.

Treatment Group 3

- Participants in Treatment Group 3 will continue their baseline oral ART as prescribed during the randomized phase.

Extension Phase

Treatment Group 1

- At Week 52, participants in Treatment Group 1 who receive the study drugs of LEN, GS-5423, and GS-2872, and complete the study through Week 52 with HIV-1 RNA < 50 copies/mL at the preceding Week 50 visit, will be given the option to participate in the study extension phase. In the study extension phase, participants will continue to receive their randomized study drugs every 26 weeks.
- Participants who elect not to participate or are not eligible to participate in the extension phase will resume their baseline oral ART (or appropriate regimen selected by the investigator).

Treatment Group 3

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

Number of Participants Planned: Approximately 75 total participants.

Target Population: Adults with HIV-1 on ART with demonstrated virologic suppression (HIV-1 RNA < 50 copies/mL) for at least 12 months prior to screening who meet protocol criteria for sensitivity to the bNAbs.

Duration of Intervention: Fifty-two weeks during the randomized phase. Participants who are eligible to participate in the extension phase have the option to continue to receive study drug until the product becomes accessible to participants through an access program, is commercially available, or Gilead Sciences, Inc. (Gilead) elects to discontinue the study, whichever occurs first.

Diagnosis and Main Eligibility Criteria:

- Between 18 and 65 years of age, inclusive, at screening.
- Body weight ≥ 40 kg at Screening Visit 2.
- On stable oral ART consisting of no more than 2 drug classes (with the exception of pharmacologic boosters cobicistat or ritonavir) for ≥ 1 year prior to Screening Visit 2. A change in ART regimen ≥ 28 days prior to Screening Visit 2 for reasons other than virologic failure (VF) (eg, tolerability, simplification, drug-drug interaction profile) is allowed.
- No clinically significant documented historical resistance to the current ART regimen with the exception of isolated nucleoside reverse transcriptase inhibitor mutations including M184V or ≤ 2 thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y, and/or K219Q).
- Plasma HIV-1 RNA < 50 copies/mL at Screening Visit 2.
- Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 12 months preceding Screening Visit 2 (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL). Virologic elevations of ≥ 50 copies/mL (transient detectable viremia or "blips") prior to screening are acceptable.
    - If HIV-1 sensitivity testing results are from > 12 months prior to screening (Inclusion Criterion 8), then documented plasma HIV-1 RNA < 50 copies/mL encompassing the time from sensitivity testing will be required.

- HIV-1 sensitivity results from screening or from the Study GS-US-536-5816 within 36 months prior to Screening Visit 2 meeting specific criteria:
    - Proviral phenotypic sensitivity to both GS-5423 and GS-2872 by the PhenoSense Assay (Monogram Biosciences). GS-5423 phenotypic sensitivity is defined as 90% inhibitory concentration (IC_{90}) ≤ 2 µg/mL; GS-2872 phenotypic sensitivity is defined as IC_{90} ≤ 2 µg/mL.
- CD4+ T-cell count ≥ 200 cells/µL at Screening Visit 2.
- Availability of a fully active alternative ART regimen, in the opinion of the investigator, in the event of discontinuation of the current ART regimen with development of resistance.

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

- Any prior receipt of LEN or a bNAb for HIV-1 treatment.
- Receipt of long-acting injectable ARV within 6 months of the Screening Visit 2.
- Hepatitis C virus (HCV) antibody positive and HCV RNA detectable.
- 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, negative HBV surface antibody regardless of HBV surface antigen status, at Screening Visit 2.

Study Procedures/Frequency: See Table 1 and Table 2.

Test Product, Dose, and Mode of Administration: Oral LEN, SC LEN injections, GS-5423 and GS-2872 IV infusions.

Treatment Group 1:

On Day 1, oral LEN 600 mg, SC LEN 927 mg, IV GS-5423 2550 mg and IV GS-2872 2550 mg will be administered. On Day 2, oral LEN 600 mg will be self-administered at home. At Weeks 26 and 52 and every 26 weeks during the extension phase SC LEN 927 mg, IV GS-5423 2550 mg, and IV GS-2872 2550 mg will be administered.

Treatment Group 3:

Participants in Treatment Group 3 will stay on their baseline oral ART regimen through Week 52. At Week 52, eligible participants will be administered oral LEN 600 mg, SC LEN 927 mg, IV GS-5423 2550 mg, and IV GS-2872 2550 mg. At Week 52 + 1 day, oral LEN 600 mg will be self-administered at home. During the extension phase, SC LEN 927 mg, IV GS-5423 2550 mg, and IV GS-2872 2550 mg will be administered every 26 weeks.

Reference Therapy, Dose, and Mode of Administration: Participants in Treatment Group 3 will continue on their baseline oral ART.

Statistical Methods:

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

The 2-sided 95% CI of the difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 between Treatment Group 1 and Treatment Group 3 will be constructed based on an unconditional exact method using 2 inverted 1-sided tests {Chan 1999}.

The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 and the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 and 52 as determined by the US FDA-defined snapshot algorithm will be analyzed using the same methods as for the primary efficacy endpoint.

The changes from baseline in CD4+ T-cell count at Week 26 and Week 52 will be summarized by treatment group using descriptive statistics. The differences in changes from baseline in CD4+ T-cell count between the treatment groups (Treatment Group 1 versus Treatment Group 3) and the associated 95% CIs will be constructed using analysis of covariance models, including baseline CD4+ T-cell count as a covariate and treatment (Treatment Group 1 versus Treatment Group 3) as a fixed effect in the models.

The number and proportion of participants experiencing TEAEs, serious adverse events (SAEs), and AEs leading to permanent study drug discontinuation, and treatment-emergent laboratory abnormalities will be summarized by treatment.

The incidence of anti-GS-5423 and anti-GS-2872 antibodies will be summarized by treatment group.

For the PK analyses, the serum or plasma concentrations of each analyte (GS-5423, GS-2872, and LEN [and metabolites, if applicable]) over time, including trough concentrations at Weeks 26 and 52, will be listed and summarized by nominal time and treatment group using descriptive statistics. PK parameters ($AUC_{0\text{-}t}$, AUC_{last}, $t_{1/2}$, C_{max}, T_{max}, as appropriate) will be listed and summarized by treatment group using descriptive statistics. Additional population PK analysis may be performed, as appropriate.

Independent Data Monitoring Committee

An independent data monitoring committee (DMC) will convene to review safety and efficacy data after approximately the first 50% of participants enrolled have completed their Week 12 visit or prematurely discontinued from the study drug.

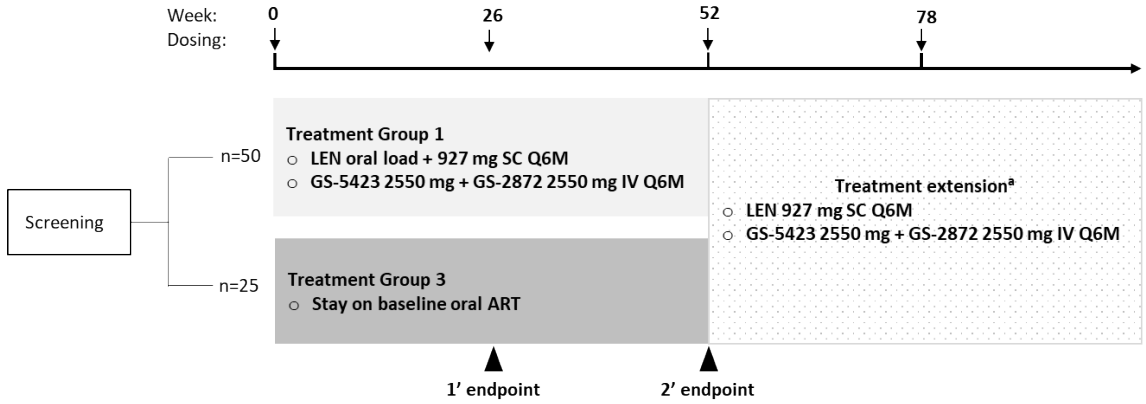
A futility assessment will be conducted based on the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 12 by the FDA-defined snapshot algorithm. If the lower bound of 95% CI of treatment difference [Treatment Group 1–Treatment Group 3] is > 0, the DMC may recommend discontinuation of Treatment Group 1 for futility. The final decision to discontinue a treatment group will be made by the sponsor based on the totality of efficacy, safety, PK, and other data.

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

Further details will be provided in the DMC charter.

STUDY SCHEMA

Figure 1. Study Schema*



*Treatment Group 2 was removed in Amendment 2
DMC = data monitoring committee; IV = intravenous; LEN = lenacapavir; Q6M = every 6 months; SC = subcutaneous

a In the treatment extension, participants randomized to Treatment Group 1 will continue to receive the study drugs every 26 weeks as in their randomized treatment phase. Participants from Treatment Group 3 who enter the extension phase will switch to receive LEN, GS-5423, and GS-2872. Participants from Treatment Group 3 will also receive a LEN 600 mg oral loading dose at the Week 52 visit. Both participants from Treatment Groups 1 and 3 will receive LEN 927 mg SC, GS-5423 2550 mg IV and GS-2872 2550 mg IV every 26 weeks.

STUDY PROCEDURES TABLE

Table 1. Study Procedures Table (Treatment Group 1)

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

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

Study Procedure	Screening		Randomized Phase											Extension Phase[u]			ESDD[c]	Post Study Drug Follow-up[c]	
	Visit 1	Visit 2[a]	Day 1	Day 2[b]	Day 8[b]	Day 15[b]	Wk 4	Wk 12	Wk 24	Wk 26	Wk 38	Wk 50	Wk 52	Wk 64, 90, 116, 142	Wk 76, 102, 128, 154	Wk 78, 104, 130, 156		PSD Day 30, 90, 180	PSD Day 270, 365
Visit Window (Days)			Within 28 Days of Screening Visit 2		± 3 Days			± 6 Days						± 6 Days				± 6 Days	
CCI																			
eGFR		X	X				X	X		X	X		X	X		X	X	X	
ECG[j]		X	X							X			X			X			
Plasma storage samples for virology testing			X				X	X	X	X	X	X	X	X	X	X	X		
Immunogenicity (ADA) serum sample[l]			X				X	X		X	X		X	X		X	X	X	X
Serum PK samples (GS-5423 & GS-2872)[m, n]			X				X	X	X	X	X	X	X	X		X	X	X	X
Plasma PK sample for LEN[m, o]			X				X	X	X	X	X	X	X	X		X	X	X	X
CCI																			

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

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

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

[redacted]

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

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

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

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

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

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

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

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

[redacted]

l On dosing days, ADA samples must be collected predose.

[redacted]

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

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

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

- Day 1: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of the second antibody infusion (GS-2872).
- Week 26 and subsequent dosing days: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN).
- A single any time sample at other scheduled visits.

[redacted]

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

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

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

CCI [redacted]

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

Table 2. Study Procedures Table (Treatment Group 3)

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

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

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

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

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

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

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

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

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

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

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

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

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

CCI [redacted]

k On dosing days, ADA samples must be collected predose.

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

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

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

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

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

CCI [redacted]

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

CCI [redacted]

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

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 with HIV-1 (PWH) infection, and globally there are over 39 million {UNAIDS Joint United Nations Programme on HIV/AIDS 2023}. 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 PWH. Identifying multiple ARVs with comparable dosing windows which can be combined in a regimen continues to pose a challenge in developing long-acting HIV treatment options.

Lenacapavir (LEN, Sunlenca®), which is administered subcutaneously once every 6 months, has the potential to address this unmet need, with suitable long-acting partner agents. Lenacapavir is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function targeted for the treatment of HIV-1 infection. Lenacapavir has potent antiviral activity with no overlapping resistance with any approved products. It has a low human clearance and is being developed as a long-acting ARV for treatment and for the prevention of HIV-1.

Monoclonal antibodies (mAbs) with broad, neutralizing activity against HIV-1 envelope glycoproteins {Burton 2015} also have the potential to be dosed less frequently and paired with other long-acting treatments, thus potentially mitigating the challenges of 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 potential clearance of latently infected cells {Gaebler 2022}, which is not achieved by ARV drugs. As biologics, broadly neutralizing antibodies (bNAbs) may spare PWH from adverse effects associated with chronic ART.

HIV-1, however, is a diverse virus whose variants have varying levels of sensitivity for any bNAb. Therefore, any bNAbs identified to date have incomplete breadth when measured for their ability to neutralize a diversity of HIV-1 isolates {Nishimura 2017}. 3BNC117 and 10-1074 are 2 of the most potent bNAbs that have been identified and clinically tested. Their combination is predicted to neutralize over 95% of HIV-1 variants {Kong 2015, Mouquet 2012,

Scheid 2011}. The parenteral administration of 3BNC117 and 10-1074 produces significant, transient reductions in plasma viremia in untreated PWH and maintains virologic suppression in virologically suppressed PWH who have received bNAbs at the time ART was interrupted {Caskey 2015, Caskey 2017, Gaebler 2022, Mendoza 2018, Sneller 2022}. When participants suppressed on ART with virus sensitive to 3BNC117 and 10-1074 discontinued ART and were dosed every 3 weeks with 3BNC117 and 10-1074, 9 of 11 (81%) participants maintained virologic suppression for a median of 21 weeks while plasma bNAbs concentrations remained high. Virologic rebound (VR) occurred when the concentration of one or both antibodies waned. Participants with early VR were found to harbor viruses resistant to 1 or both bNAbs at baseline when alternative methods were used for sensitivity testing {Mendoza 2018}. In a follow-up study, 3BNC117 and 10-1074 were administered together for over 20 weeks in PWH without prescreening for bNAb sensitivity and 13 of 17 (76%) maintained virologic suppression for at least 20 weeks when off other ART {Bar-On 2018}. In a posthoc analysis, the investigators did not find a correlation between outcomes and bNAb sensitivity at baseline. A third study demonstrated that 3BNC117 and 10-1074 maintained virologic suppression in 6 of 6 participants sensitive to both bNAbs, and observed early VR in a participant with resistance to both bNAbs at baseline {Sneller 2022}. The results of these studies provide early evidence for utilizing 3BNC117 and 10-1074 as components for treatment of HIV-1, though they are inconclusive as to the optimal testing method and clinical value of screening for bNAb sensitivity.

3BNC117 and 10-1074 have undergone modifications to increase their half-lives, resulting in GS-5423 (3BNC117-LS) and GS-2872 (10-1074-LS), and allow for the maintenance of high bNAb concentrations over long durations without changing viral neutralization potency. Coadministration of 2 bNAbs has maintained viral suppression in a substantial proportion of virologically suppressed PWH (up to 60%-85% across studies) and a combination of LEN, GS-5423 and GS-2872 maintained virologic suppression in 90% of participants in the proof of concept (POC) Phase 1b Study GS-US-536-5816. Pairing the long-acting bNAbs GS-5423 and GS-2872 with the long-acting ARV drug LEN may overcome the limitations of earlier studies with bNAbs alone and enable a safe, effective, and robust long-acting treatment option for PWH.

1.2. Background on Study Interventions

For the purpose of this protocol, study drug will be defined as LEN, GS-5423, GS-2872, and baseline oral ART.

1.2.1. Lenacapavir

1.2.1.1. General Information

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

For further information on LEN, refer to the investigator's brochure (IB), including information on the following:

- Nonclinical pharmacokinetics (PK) and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.2. GS-5423

1.2.2.1. General Information

GS-5423 is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that targets the CD4 binding site of HIV-1 glycoprotein 120 and shows neutralization activity against > 80% of viral strains. GS-5423 (also known as teropavimab or 3BNC117-LS) is derived from 3BNC117, differing only by 2 amino acid substitutions in the crystallizable fragment (Fc) portion of the antibody, which enhances the antibody binding affinity to the neonatal Fc receptor (FcRn), thus prolonging its half-life in vivo. Affinity binding to other Fc receptors remains unchanged. These modifications do not alter the antigen-binding fragment (Fab) of the antibody and therefore do not alter its interaction with antigen or safety profile. GS-5423 is a bNAb with potent antiviral activity and extended half-life that make it well suited for use as a long-acting parenteral ARV. GS-5423 has been characterized in nonclinical and clinical studies.

For further information on GS-5423, refer to the IB, including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.3. GS-2872

1.2.3.1. General Information

GS-2872 is a recombinant, fully human mAb of the IgG1λ isotype that specifically binds to the base of the V3 loop within the HIV-1 external membrane glycoprotein, gp120 and shows neutralization activity against 61% of viral strains. GS-2872 (also known as zinlirvimab or 10-1074-LS) and the original antibody from which it is derived, 10-1074, differ only by 2 amino acid substitutions in the Fc portion of the antibody, which enhances the antibody binding affinity to the FcRn, thus prolonging its half-life in vivo. Affinity binding to other Fc receptors remains unchanged. These modifications do not alter the Fab region of the antibody and therefore do not alter its interaction with antigen or safety profile. GS-2872 is a bNAb with potent antiviral activity and extended half-life that make it well suited for use as a long-acting parenteral ARV. GS-2872 has been characterized in nonclinical and clinical studies.

For further information on GS-2872, refer to the IB, including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.4. Clinical Studies of Lenacapavir With GS-5423 and GS-2872

GS-US-536-5816 is a randomized, blinded, proof of concept Phase 1b 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 ART.

The primary cohort included eligible adults with HIV-1, no history of virologic failure (VF) or ARV drug resistance, a CD4+ T-cells nadir ≥ 350 cells/μL, screening CD4+ T-cells count > 500 and on first-line ART for at least 2 years with demonstrated virologic suppression (HIV-1 RNA < 50 copies/mL) for at least 18 months who had sensitivity to both GS-5423 and GS-2872, as measured by the PhenoSense monoclonal antibody assay (Monogram Biosciences), were randomized in a 1:1 ratio to 2 treatment groups.

All participants received GS-5423 (30 mg/kg intravenous [IV]) and oral LEN 600 mg Day 1 and Day 2 and LEN for subcutaneous (SC) injection 927 mg on Day 1. The 2 randomization arms differed only in the dose of GS-2872 that they received (10 mg/kg or 30 mg/kg administered IV).

Participants discontinued their background oral ARV regimen 1 day prior to receiving study drugs on Day 1. At Week 26, all participants who remained virologically suppressed, resumed 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.

Twenty-one participants were enrolled into the primary cohort and randomized, 20 received the complete study drugs (10 in each treatment group), one participant received oral LEN and withdrew consent prior to completing dosing procedures. The median age of participants was 44 years (range: 25 to 61 years), 18 (86%) were male sex at birth; and at baseline, all had HIV-1 RNA < 50 copies/mL and CD4 count ≥ 500 cells/μL.

The primary endpoint was the incidence of treatment-emergent serious adverse events (TESAEs) through Week 26. There were no TESAEs, no treatment-emergent adverse events (TEAEs) leading to discontinuation of study drug or study and no deaths. The most common TEAEs were injection site reactions (ISRs) related to administration of SC LEN injection. There was 1 reported infusion-related reaction that was mild in severity and consisted of pyrexia and flushing after GS-2872 infusion which resolved without treatment. There were no clinically meaningful treatment-emergent laboratory abnormalities that were Grade 3 or higher. There was no observed difference in safety events between the 2 treatment groups.

Efficacy was assessed at Week 26 according to the US Food and Drug Administration (FDA) snapshot algorithm. At Week 26, 1 of 10 participants (10%) in the GS-2872 10 mg/kg treatment group and 0 of 10 participants in the GS-2872 30 mg/kg treatment group had HIV-1 RNA ≥ 50 copies/mL. Nine of 10 participants (90%) in each group maintained viral suppression with HIV-1 RNA < 50 copies/mL at Week 26; 1 participant in the GS-2872 30 mg/kg group had no virologic data in the Week 26 window, their last on-study HIV-1 RNA was < 50 copies/mL.

The mean (SD) CD4 cell counts at baseline were as follows: GS-2872 10 mg/kg group 903 (303.7) cells/µL; GS-2872 30 mg/kg group 1086 (333.6) cells/µL. The CD4+ T-cell count was maintained at Week 26 for both treatment groups.

For complete study details for the primary cohort, please refer to the IBs for GS-5423 and GS-2872.

Study GS-US-536-5816 also included a pilot cohort of participants who met sensitivity criteria for either GS-5423 or GS-2872 but not both; the other inclusion and exclusion criteria were identical to the primary cohort. Pilot cohort participants were randomized in a 1:1 ratio to the same 2 dosing groups as the primary cohort; randomization was stratified by the sensitivity to GS-5423 or GS-2872.

Eleven participants were enrolled into the pilot cohort and received the complete study drugs (5 in the GS-2872 10 mg/kg group and 6 in the GS-2872 30 mg/kg group). One participant restarted ART on Day 30 due to a protocol violation (chronic hepatis B infection) and continued on study; they are included in the safety analyses but excluded from the efficacy analyses. The median age of participants was 49 years (range: 28 to 63); 8 participants (73%) were assigned male at birth; and all had HIV-1 RNA < 50 copies/mL; and at baseline, all except 1 participant had CD4 cell count ≥ 500 cells/µL.

The primary endpoint was the incidence of TESAEs through Week 26. There was 1 TESAE and no Grade 2 or higher AEs related to study drug. There were no TEAEs leading to discontinuation of study drug or study and no deaths. There was 1 TESAE of soft-tissue infection, which was not related to study drug or procedures. The most common TEAEs were ISRs related to administration of SC LEN injections. There were no infusion-related reactions and no treatment-emergent laboratory abnormalities that were Grade 3 or 4. There was no observed difference in safety events between the 2 treatment groups.

Efficacy was assessed at Week 26 according to the US FDA snapshot algorithm. At Week 26, 2 of 4 participants (50%) in the GS-2872 10 mg/kg treatment group and 0 of 6 participants in the GS-2872 30 mg/kg treatment group had HIV-1 RNA ≥ 50 copies/mL. The 2 participants had VRwith HIV-1 RNA of 72 and 55 copies/mL respectively at Week 26; neither met the criteria for confirmed virologic failure (HIV-1 RNA ≥ 200 copies/mL on consecutive tests).

The mean (SD) CD4 cell counts at baseline were as follows: GS-2872 10 mg/kg group 1017 (628.7) cells/µL; GS-2872 30 mg/kg group 957 (189.1) cells/µL. The CD4+ T-cell count was maintained at Week 26 for both treatment groups.

1.3. Rationale for This Study

A combination of 2 potent bNAbs can control viral replication or maintain viral suppression in the absence of ART in PWH {Gaebler 2022, Mendoza 2018, Sneller 2022} though uncertainty remains on how to best identify people with sensitive viruses clinically. Some participants of clinical trials who received 2 bNAbs alone did not respond and had early VR, others rebounded when the serum antibody concentrations waned. In Study GS-US-536-5816, the bNAbs GS-5423 and GS-2872 were combined with LEN to improve the breadth and increase the barrier to resistance and durability of the study drugs. As detailed above, virologically suppressed PWH who had sensitivity to both bNAbs were enrolled, and 19 of 20 participants who received the complete study regimen maintained virologic suppression while on study drug through Week 26 or their last study visit. The combination regimen was safe and well tolerated.

The proposed Study GS-US-536-5939 builds directly on the findings of Study GS-US-536-5816. The study is open label to facilitate comparison of the study drugs, dosed parenterally every 6 months, to the standard of care regimen given as an oral pill(s) daily. The primary efficacy endpoint (HIV-1 RNA ≥ 50 copies/mL) at Week 26 is set forth in guidance from the US FDA for Phase 2 studies in a virologically suppressed population. Participants will be treated in their randomized groups until secondary outcomes for safety and efficacy at Week 52 to gather data through multiple dosing intervals of the study drugs.

Prior data suggests that engagement of the host immune system by bNAbs may contribute to enhanced HIV specific immune responses, control of HIV-1 replication even after neutralizing antibody concentrations decline and facilitate the clearance of latently infected cells, thus reducing an individual's HIV latent reservoir {Lu 2016}. Because GS-5423 and GS-2872 are human antibodies targeting viral antigens, chronic use may not be associated with a risk for toxicities that accompanies the use of most small molecule ARVs.

Developing safe and effective therapeutic options that maintain virologic suppression and facilitate adherence over a lifetime of therapy for PWH 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 PWH, the ideal goal of therapy remains complete and durable viral suppression. This Phase 2 study will build on the preliminary data demonstrating the efficacy and safety of a regimen consisting of LEN, GS-5423, and GS-2872 for the treatment of virologically suppressed PWH.

1.4. Rationale for Dose Selection

1.4.1. GS-5423 and GS-2872

In this study, the participants will receive 2550 mg of both GS-5423 and GS-2872 administered IV in combination with LEN every 26 weeks. The dose selection for GS-5423 and GS-2872 in this study is supported by data from the ongoing Phase 1b POC Study GS-US-536-5816, the first-in-human (FIH) studies of GS-5423 and GS-2872, YCO-0946 (NCT03254277) and YCO-0971 (NCT03554408) respectively, and the previously completed Phase 1 studies of the

non-LS forms of each antibody, 3BNC117 and 10-1074 {Bar-On 2018, Caskey 2015, Caskey 2017, Gaebler 2022, Mendoza 2018}.

The ongoing Phase 1b study (GS-US-536-5816) tested GS-5423 at 30 mg/kg and GS-2872 at 10 or 30 mg/kg, administered IV as a single dose in combination with LEN. In the primary cohort of the study, participants who are sensitive to both bNAbs were enrolled, whereas in the pilot cohort, participants who are sensitive to only one of the bNAbs were enrolled. In both cohorts, GS-5423 at 30 mg/kg and GS-2872 at both 10 and 30 mg/kg were well tolerated with no significant safety findings.

For the primary cohort: at Week 26, 0 of 10 participants in the GS-2872 30 mg/kg group and 1 of 10 participants (10.0%) in the GS-2872 10 mg/kg treatment group had HIV-1 RNA $\geq$ 50 copies/mL.

For the pilot cohort: at Week 26, 0 of 6 participants in the GS-2872 30 mg/kg group and 2 of 4 participants (50.0%) in the GS-2872 10 mg/kg treatment group had HIV-1 RNA $\geq$ 50 copies/mL.

Pooled efficacy results from both cohorts of the Phase 1b study showed no VRin 16 participants receiving GS-5423 30 mg/kg and GS-2872 30 mg/kg in combination with LEN; of 14 participants receiving GS-5423 30 mg/kg and GS-2872 10 mg/kg in combination with LEN, 3 participants had VR(21.4%), 1 from the primary cohort and 2 from the pilot cohort. No participant met the criteria for confirmed virologic failure.

Single doses of GS-5423 and GS-2872 alone and in combination were also shown to be safe and well tolerated up to 30 mg/kg in the FIH Studies YCO-0946 and YCO-0971 in healthy volunteers and virologically suppressed PWH.

The antiviral activities of the non-LS forms of each antibody, 3BNC117 and 10-1074, have been studied in multiple Phase 1 studies. In studies in PWH undergoing analytical treatment interruption (MCA-0906 {Mendoza 2018} and MCA-0965 {Gaebler 2022}), it was observed that the virological suppression was generally maintained when serum concentrations of both antibodies were above 10 µg/mL, although the data were limited, as only a single dose level was studied for both bNAbs. It is anticipated that GS-5423 and GS-2872 will demonstrate similar antiviral activity to the unmodified forms (3BNC117 and 10-1074), at the same concentrations based on the location of the amino acid substitutions in the Fc region.

Based on the PK simulations, a single IV dose of 2550 mg GS-5423 or 2550 mg GS-2872 is anticipated to maintain concentrations above 10 µg/mL in nearly 100% of participants at 6 months after dosing. 3BNC117 and 10-1074 have also been studied in viremic PWH as monotherapy and in combination {Bar-On 2018, Caskey 2015, Caskey 2017}. Correlations between serum antibody concentration and viral load reduction at the nadir from these studies suggest the antiviral response is saturated at the concentration range corresponding to the predicted C_{trough} levels maintained with doses of 2550 mg of GS-5423 and 2550 mg of GS-2872 at Week 26, although the data are limited.

The safety and efficacy results from studies with GS-5423 and GS-2872 taken together with PK modeling suggest that 2550 mg flat doses of GS-5423 and GS-2872 are expected to be safe and efficacious in combination with LEN to be evaluated in this Phase 2 study in virologically suppressed adults with HIV-1 infection.

1.4.2. Lenacapavir

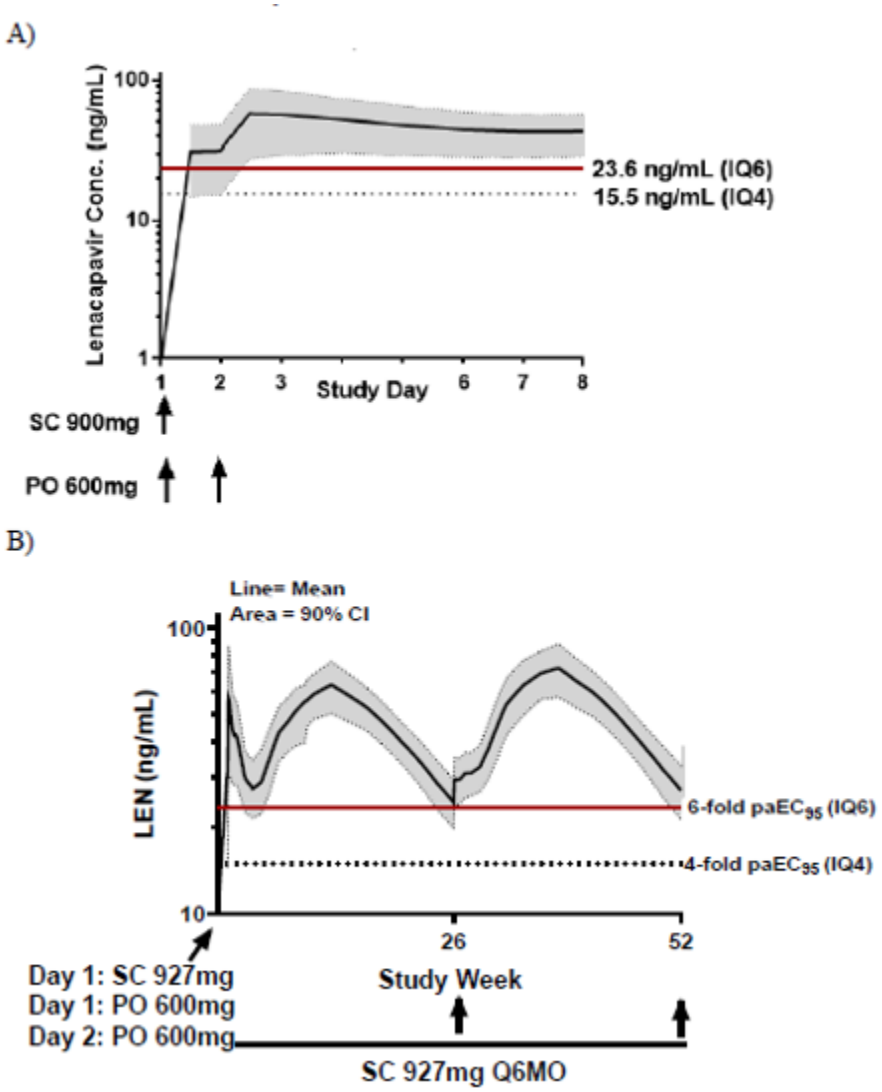
The LEN doses and formulations to be evaluated in this study are informed by antiviral activity, PK, and/or safety data from Phase 1b POC study (GS-US-200-4072), Phase 1 Studies GS-US-200-4071, GS-US-200-4538, and GS-US-200-5709, as well as available safety data from the ongoing Phase 2/3 clinical studies in heavily treatment-experienced (HTE) and treatment naive (TN) PWH (GS-US-200-4625 and GS-US-200-4334, respectively).

In the Phase 1b POC study (GS-US-200-4072), potent antiviral activity of LEN was demonstrated in TN and treatment-experienced but capsid inhibitor-naive PWH; 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 LEN concentrations on Day 10 were 1.1- to 20.5-fold higher than the $paEC_{95}$ for wild type HIV-1 (ie, inhibitory quotient [IQ] = 1.1 to 20.5; $paEC_{95}$ = 3.87 ng/mL in MT-4 cells). Study GS-US-200-4072 demonstrated that near maximal (94%) antiviral activity was observed at ≥ 15.5 ng/mL (4-fold higher than the $paEC_{95}$ from MT-4 cells [ie, IQ4]), indicating that substantial increases in antiviral activity with an increase in LEN exposure beyond this concentration target are not expected. 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 ≥ IQ4 (15.5 ng/mL) starting within a few days of dosing initiation, and maintained through Week 26.

Considering this target, a SC LEN regimen (927 mg or 2 × 1.5 mL at 309 mg/mL, administered every 26 weeks) preceded by a 14-day oral lead-in is being evaluated in ongoing clinical Phase 2/3 studies in HTE and TN PWH (GS-US-200-4625 and GS-US-200-4334). This regimen was predicted to achieve target concentrations within a few days of initiation of dosing and maintain it throughout the 6-month dosing interval. As clinical data of LEN to date do not raise concern for acute safety issues, where an oral lead-in would be beneficial, a simplified LEN regimen is being proposed for this study: SC 927 mg LEN injection, 309 mg/mL (2 × 1.5 mL) administered on Day 1 along with oral tablet doses of LEN 600 mg (2 × 300 mg) administered on Day 1 and Day 2. This will be followed by SC doses of LEN 927 mg administered every

26 weeks. The proposed simplified regimen is predicted to achieve target concentrations within a few days of dosing initiation with exposures maintained throughout the duration of the 6-month dosing interval (Figure 2). This is supported by preliminary PK data available through Day 197 postdose from Study GS-US-200-5709 (Cohort 2) where the proposed simplified regimen demonstrates good agreement between the observed and predicted/simulated data. This simplified regimen is being evaluated in ongoing clinical studies for prevention of HIV-1 (GS-US-528-9023 and GS-US-412-5624).

Figure 2. Simulated Plasma Profile of LEN Following the Proposed SC LEN Regimen Administered Every 26 Weeks With an Oral PK Load on Days 1 and 2



CI = confidence interval; IQ4 = inhibitory quotient of 4; IQ6 = inhibitory quotient of 6; LEN = lenacapavir; $paEC_{95}$ = protein-adjusted 95% effective concentration from MT-4 cells (3.87 ng/mL); PK = pharmacokinetic(s); PO = orally; Q6MO = every 6 months; SC = subcutaneous

1.5. Risk/Benefit Assessment for the Study

Potential risks associated with the study include adverse events (AEs), including ISRs with SC administration of LEN, infusion-related reactions, and antidrug antibody (ADA)-mediated reactions from GS-5423 and GS-2872. 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.

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 drugs or unrecognized preexisting resistance to GS-5423, GS-2872, and/or LEN is the possible development of resistance to 1 or more study drugs. Data are limited to inform whether the protocol's application of resistance testing for bNAbs can minimize this risk. A low rate of viral rebound was observed in Study GS-US-536-5816, which utilized the same sensitivity criteria as will be used in this study, suggesting that the study drugs will provide appropriately high efficacy in the study population. Strategies to further mitigate the risk for resistance 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 and data monitoring committee (DMC) futility assessments to identify and potentially discontinue treatment arms, thereby limiting the number of participants exposed to a treatment group that poses a risk to safety or efficacy. Each component of the study drugs 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 drugs 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 bNAb containing regimen due to enhanced engagement of the immune system, reduction of the latent viral reservoir and/or improved immunologic control of HIV-1, but the magnitude and clinical importance of these potential effects have not been determined. Potential benefits to participants also 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.

An unanticipated event such as a disaster or public health emergency may pose additional potential risks to participants such as adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.2 for further details on the risks and risk mitigation strategy.

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

1.6. Compliance

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

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

3. STUDY DESIGN

3.1. Study Design Overview

This is a Phase 2, randomized, open-label, active-controlled, multicenter study to evaluate the safety and efficacy of the long-acting regimen of LEN, GS-5423, and GS-2872. The study will include approximately 75 participants with sensitivity to GS-5423 and GS-2872 by protocol-defined criteria, who meet all eligibility criteria, and who will be randomized without stratification in a 2:1 ratio to Treatment Groups 1 and 3. Eligible participants have the option of participating in a study extension phase after completing study follow-up through Week 52.

3.1.1. Randomized Phase

Treatment Group 1

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

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

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

Treatment Group 3

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

3.1.2. Extension Phase

Treatment Group 1

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

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

Treatment Group 3

Participants in Treatment Group 3 who complete the study through Week 52 with HIV-1 RNA < 50 copies/mL at the preceding Week 50 visit and in the absence of confirmed VR (as defined in Section 6.3.9.2.2) throughout the randomized phase of the study will be given the option to participate in the extension phase and receive the study drugs of LEN, GS-5423, and GS-2872 every 26 weeks at the dose specified for Treatment Group 1. Treatment with LEN, GS-5423, and GS-2872 will start at Week 52 and at that time the baseline oral ART will be discontinued.

3.2. Duration of Intervention

Participants who are eligible to participate may receive up to 52 weeks of treatment during the randomized phase. Participants who are eligible to participate in the extension phase have the option to continue to receive study drug until the product becomes accessible to participants through an access program, is commercially available, or Gilead elects to discontinue the study, whichever occurs first.

3.3. Protocol-Specific Discontinuation Criteria

3.3.1. Criteria for Early Discontinuation for the Individual Participants

3.3.1.1. Criteria for Early Discontinuation for the Individual Participant From Study Intervention

Study interventions will be discontinued in the following instances:

- An AE that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
    - Following resolution of the AE, the participant may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity, such as a Grade 3 or higher infusion-related reaction to GS-5423 or GS-2872, per Common Terminology Criteria for Adverse Events (CTCAE) grading scale as defined in Section 7.6, 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.
- Lack of efficacy: Confirmed VF with emergent resistance to study drugs (refer to Section 6.3.9.2).
- Participant request to discontinue for any reason.
- Participant noncompliance.
- Pregnancy during the study; refer to Appendix 11.3.

- Loss to follow-up.
- Discontinuation of the study by sponsor.

3.3.1.2. Criteria for Early Discontinuation for the Individual Participant From the Study

The participant will be discontinued from the study early in the following instances:

- Withdrawal of consent
- Death
- Investigator decision to remove participant from the study
- Loss to follow-up (see Section 3.3.3)
- Discontinuation of study at the request of Gilead

3.3.2. Criteria for Early Discontinuation of the Study

The study will be discontinued in the following instance:

- Discontinuation of the study at the request of Gilead, regulatory agency, or an institutional review board (IRB).

3.3.3. Loss to Follow-up

Should the participant fail to return to the investigational site for a scheduled protocol-specific visit, sites will need to make at least 2 attempts by a combination of phone and certified mail to contact the participant. Sites must document both attempts to contact the participant. If a participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit scheduled. If a participant does not respond within 4 weeks after the second contact, the participant will be considered lost to follow-up and no additional contact will be required.

3.4. Definitions for Time of Primary Endpoint and End of Study

3.4.1. Primary Endpoint

The date for the last participant visit for the primary endpoint is the date of the last visit to perform assessments for the primary analysis.

3.4.2. End of Study

The end of this study will be the last participant's last observation (or visit).

3.5. 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.

3.6. Source Data

The source data for this study will be obtained from participants clinical/hospital records, central laboratory, specialty laboratory (eg, for PK/ADA and/or pharmacodynamic data), eCOA, and interactive response technology (IRT) data.

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 75 participants who are sensitive to both GS-5423 and GS-2872 by protocol-defined criteria and who meet the eligibility criteria will be randomized without stratification in a 2:1 ratio to Treatment Groups 1 and 3.

4.1.1. Participant Replacement

Participants who discontinue before the end of the 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) Body weight ≥ 40 kg at Screening Visit 2.

4) On stable oral ART consisting of no more than 2 drug classes (with the exception of pharmacologic boosters cobicistat or ritonavir) for ≥ 1 year prior to Screening Visit 2. A change in ART regimen ≥ 28 days prior to Screening Visit 2 for reasons other than VF (eg, tolerability, simplification, drug-drug interaction profile) is allowed.

5) No clinically significant documented historical resistance to the current ART regimen with the exception of isolated nucleoside reverse transcriptase inhibitor mutations including M184V or ≤ 2 thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y, and/or K219Q).

6) Plasma HIV-1 RNA < 50 copies/mL at Screening Visit 2.

7) Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 12 months preceding Screening Visit 2 (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL). Virologic elevations of ≥ 50 copies/mL (transient detectable viremia or “blips”) prior to screening are acceptable.

    A) If HIV-1 sensitivity testing results are from > 12 months prior to screening (Inclusion Criterion 8), then documented plasma HIV-1 RNA < 50 copies/mL encompassing the time from sensitivity testing will be required.

8) HIV-1 sensitivity results from screening or from the Study GS-US-536-5816 within 36 months prior to Screening Visit 2 meeting specific criteria:

   A) Proviral phenotypic sensitivity to both GS-5423 and GS-2872 by the PhenoSense Assay (Monogram Biosciences). GS-5423 phenotypic sensitivity is defined as 90% inhibitory concentration (IC_{90}) ≤ 2 µg/mL; GS-2872 phenotypic sensitivity is defined as IC_{90} ≤ 2 µg/mL.

9) CD4+ T-cell count ≥ 200 cells/µL at Screening Visit 2.

10) 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.

11) Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min according to the Modification of Diet in Renal Disease formula {Lacombe 2008, Levey 2006}.

12) All of the following laboratory results at Screening Visit 2:

   A) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 × upper limit of normal (ULN).

   B) Total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin.

   C) Absolute neutrophil count ≥ 750/mm^3; (chronic neutropenia with no clinical significance can enroll at investigator discretion).

   D) Platelets ≥ 50,000/mm^3; and hemoglobin ≥ 8.5 g/dL.

13) Participants assigned female at birth of childbearing potential (as defined in Appendix 11.3) must have a negative serum pregnancy test at Screening Visit 2 and negative urine pregnancy test at Day 1 prior to study drug administration.

14) Participants assigned female at birth of childbearing potential who engage in heterosexual intercourse must agree to utilize protocol-specified method(s) of contraception as described in Appendix 11.3.

4.3. Exclusion Criteria

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

1) Any prior receipt of LEN or a bNAb for HIV-1 treatment.

2) Receipt of long-acting injectable ARV within 6 months of Screening Visit 2.

3) Have been treated with immunosuppressant therapies or chemotherapeutic agents (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies) within 4 weeks of Screening Visit 2 (with the exception of a single short course of corticosteroids lasting ≤ 7 days) or have a comorbid condition with an anticipated need ongoing immunosuppressive treatment during the study.

4) Pregnant participants assigned female at birth or plans to become pregnant during the course of the study.

5) Lactating participants assigned female at birth.

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

7) Clinically significant abnormal electrocardiogram (ECG) at the Screening Visit 2.

8) Hepatitis C virus (HCV) antibody positive and HCV RNA detectable.

9) 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, negative HBV surface antibody regardless of HBV surface antigen status, at Screening Visit 2.

10) Active, serious infections (other than HIV-1 infection) requiring systemic antibiotic or antifungal therapy within 30 days prior to Screening Visit 2.

11) Have poor venous access that would limit phlebotomy or IV infusion of study drugs.

12) Have a history of any of the following:

    A) Opportunistic infection or illness indicative of Stage 3 HIV disease.

    B) Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

C) Malignancy within the past 5 years (prior to screening) or ongoing malignancy, other than basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma.

D) 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. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Randomization

5.1.1. Randomization

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

Randomization and Day 1 visits must not occur until participant eligibility has been confirmed. 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 participants. The participant number assignment and randomization may be performed up to 3 days prior to Day 1 visit provided all screening procedures have been completed and participant eligibility criteria has been confirmed.

Participants who meet eligibility criteria will be randomized in a 2:1 ratio to Treatment Groups 1 and 3.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

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, 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-5423 in histidine, acetate, trehalose, methionine, and polysorbate 20.

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.

5.2.2. Packaging and Labeling

5.2.2.1. Lenacapavir

Lenacapavir tablets, 300 mg, are packaged in white, high-density polyethylene 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, or 2 mL/vial drug product is supplied as 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 supplied as 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, or 2 mL/vial drug product, should be stored at 2 °C to 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 °C to 8 °C and protected from light. Storage conditions are specified on the study drug label.

5.3. Dosage and Administration

Treatment Group 1

Dose and administration of LEN, GS-5423, and GS-2872 for Treatment Group 1 are described below and in Table 3.

Day 1:

Participants will receive the following study drugs. All study drugs should be administered on the same day (ie, no visit window is permitted for Day 1 study drug administration).

- Oral LEN 600 mg will be administered orally with approximately 240 mL water, without regard to food.
- SC LEN 927 mg will be administered within 30 minutes after oral LEN, as 2 SC injections at separate injection sites in the abdomen, within 15 minutes.
- GS-5423 2550 mg IV infusion will be administered immediately following (up to 1 hour after) the last SC LEN injection. Infusions of GS-5423 will be administered over CCI
- GS-2872 2550 mg IV infusion will be administered at least 15 minutes following (up to 1 hour after) the completion of GS-5423 IV infusion. Infusions of GS-2872 will be administered over CCI

Participants will discontinue their baseline oral ART following administration of the complete study drugs on Day 1.

Day 2:

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

Week 26:

Virologic suppression (HIV-1 RNA < 50 copies/mL) from the preceding visit must be confirmed prior to proceeding with dosing visits.

Infusions of GS-5423 and GS-2872 will be sequentially administered following SC LEN injection:

- LEN 927 mg, as 2 SC injections at separate injection sites in the abdomen, within 15 minutes
- GS-5423 IV infusion of 2550 mg
- GS-2872 IV infusion of 2550 mg

Week 52 and Every 26 Weeks During the Extension Phase:

Virologic suppression (HIV-1 RNA < 50 copies/mL) from the preceding visit must be confirmed prior to proceeding with dosing visits.

At each dosing visit, the following study drugs will be administered:

- LEN 927 mg, as 2 SC injections at separate injection sites in the abdomen, within 15 minutes
- Infusions of GS-5423 and GS-2872 can either be coadministered (preferred option) or administered sequentially (investigator discretion) following SC LEN injection:
  - Coadministration
    - GS-5423 2550 mg and GS-2872 2550 mg IV infusion will be administered as a single infusion immediately following (up to 1 hour after) the last SC LEN injection. CCI [redacted]
  - Sequential administration
    - GS-5423 2550 mg IV infusion will be administered immediately following (up to 1 hour after) the last SC LEN injection. Infusions of GS-5423 will be administered over CCI [redacted]

- GS-2872 2550 mg IV infusion will be administered at least 15 minutes following (up to 1 hour after) the completion of GS-5423 IV infusion. Infusions of GS-2872 will be administered over CCI

Table 3. Treatment Group 1 Treatment Table

Study Day	Treatment Group 1
Day 1	LEN 600 mg (two 300-mg tablets, PO) LEN 927 mg (two 1.5-mL injections, SC) GS-5423 2550 mg (IV infusion) GS-2872 2550 mg (IV infusion)
Day 2	LEN 600 mg (two 300-mg tablets, PO)
Weeks 26, 52, and every 26 weeks during extension phase[a]	LEN 927 mg (two 1.5-mL injections, SC) GS-5423 2550 mg (IV infusion) GS-2872 2550 mg (IV infusion)

ART = antiretroviral therapy; DMC = data monitoring committee; IV = intravenous; LEN = lenacapavir; PO = orally; SC = subcutaneous

a Participants in Treatment Group 1 who reach Week 52 and meet criteria to enter the extension phase will receive the study regimen every 26 weeks during the extension phase.

Treatment Group 3

Day 1 Through Week 52:

Participants in Treatment Group 3 will stay on their baseline oral ART through Week 52.

Week 52:

Participants in Treatment Group 3 who are eligible and elect to participate in the extension phase will receive the study drugs of LEN, GS-5423, and GS-2872 as described below and in Table 4.

Participants will receive the following study drugs. All study drugs should be administered on the same day (ie, no visit window is permitted for Week 52 study drug administration):

- Oral LEN 600 mg will be administered orally with approximately 240 mL water, without regard to food.
- SC LEN 927 mg 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.
- Infusions of GS-5423 and GS-2872 will either be coadministered (preferred option) or administered sequentially (at investigator discretion) following SC LEN injection:
  - Coadministration
    - GS-5423 2550 mg and GS-2872 2550 mg IV infusion will be administered as a single infusion immediately following (up to 1 hour after) the last SC LEN injection. Infusions of GS-5423 and GS-2872 will be administered over CCI minutes. CCI

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— Sequential administration

- GS-5423 2550 mg IV infusion will be administered immediately following (up to 1 hour after) the last SC LEN injection. Infusions of GS-5423 will be administered over CCI minutes.
- GS-2872 2550 mg IV infusion will be administered at least 15 minutes following (up to 1 hour after) the completion of GS-5423 IV infusion. Infusions of GS-2872 will be administered over CCI minutes.

Participants will discontinue their baseline oral ART following administration of the complete study drugs on Week 52.

Week 52 + 1 Day:

Participants will self-administer oral LEN 600 mg at home with approximately 240 mL water, without regard to food, at approximately the same time as the oral LEN dose on Week 52.

Every 26 Weeks During the Extension Phase:

Virologic suppression (HIV-1 RNA < 50 copies/mL) from the preceding visit must be confirmed prior to proceeding with dosing visits.

At each dosing visit, the following study drugs will be administered:

- LEN 927 mg, as 2 SC injections at separate injection sites in the abdomen, within 15 minutes
- Infusions of GS-5423 and GS-2872 will either be coadministered (preferred option) or sequentially administered (investigator discretion)

Table 4. Treatment Group 3 Treatment Table

Study Day	Treatment Group 3
Day 1 through Week 52	Continue background regimen
Week 52	LEN 600 mg (two 300-mg tablets, PO) LEN 927 mg (two 1.5-mL injections, SC) GS-5423 2550 mg (IV infusion) GS-2872 2550 mg (IV infusion)
Week 52 + 1 Day (at home)	LEN 600 mg (two 300-mg tablets, PO)
Every 26 weeks during extension phase	LEN 927 mg (two 1.5-mL injections, SC) GS-5423 2550 mg (IV infusion) GS-2872 2550 mg (IV infusion)

ART = antiretroviral therapy; DMC = data monitoring committee; IV = intravenous; LEN = lenacapavir; PO = orally; SC = subcutaneous

5.3.1. Additional IV Infusion Instructions

GS-5423 and GS-2872, will be coadministered or administered as sequential separate IV infusions. If coadministered, the infusion of GS-5423 and GS-2872 will begin immediately following (up to 1 hour after) the last SC LEN injection. If sequentially administered, infusion of GS-5423 will begin immediately following (up to 1 hour after) the last SC LEN injection. Infusion of GS-2872 will begin at least 15 minutes following (up to 1 hour after) the completion of GS-5423 IV infusion.

Initial infusions of GS-5423 and GS-2872 will be administered over CCI minutes if coadministered as a single infusion. At subsequent coadministration dosing visits, infusions of GS-5423 and GS-2872 may be administered over CCI minutes and CCI minutes, at investigator discretion. If sequentially administered, separate infusions of GS-5423 and GS-2872 will each be administered over CCI minutes.

Participants will remain in a monitored clinical setting for at least 30 minutes after completion of the GS-5423 and GS-2872 infusion, if coadministered, or GS-2872 infusion, if sequentially administered. Vital signs (blood pressure, pulse, and temperature) will be recorded 30 minutes (± 10 minutes) after completion of the GS-5423 and GS-2872 infusion, if coadministered, or GS-2872 infusion, if sequentially administered. If symptoms occur, the symptoms and timing of occurrence will be recorded on the electronic case report form (eCRF).

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. For mild-moderate infusion-related reactions, after symptoms have resolved, drug infusion may be resumed at half the initial rate. 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.

Premedications will not be routinely administered prior to study drug administration. Participants who experience mild-moderate infusion-related reactions may be premedicated for subsequent infusions if determined necessary by the investigator. Premedication may consist of one or more of the following medications: diphenhydramine 25 mg (oral), ibuprofen 400 to 600 mg (oral), acetaminophen 500 to 650 mg (oral), prednisone 20 to 40 mg (oral) or equivalent alternative steroid.

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

5.3.2. Missed or Delayed Study Drug Doses

If more than 28 weeks have elapsed since the participant's last dose, the investigator must contact the medical monitor, and the participant should be instructed to resume their baseline oral ART (or alternative ART selected by the investigator). If it is determined to be clinically appropriate for the participant to continue the study regimen, the participant will discontinue their oral ART and restart the study regimen as described in Section 5.3, which will include oral LEN, SC LEN, and IV infusions of GS-5423 and GS-2872 (as described on Day 1 and Day 2 for Treatment Group 1; and Week 52 and Week 52 + 1 day as described for Treatment Group 3). Subsequent doses will be administered every 26 weeks thereafter.

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 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 the medical monitor 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.

Table 5. 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	—

Medication Class	Prohibited Medications	Use Discouraged and To Be Used With Caution
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	—	Concomitant use may increase corticosteroid exposure. Limit use to 7 days or less

ARV = antiretroviral; LEN = lenacapavir

There are no substantial safety or efficacy data regarding the concomitant administration of the COVID-19 vaccines or the monkeypox vaccines (JYNNEOS and ACAM2000) and LEN, GS-5423, and GS-2872. Participants for whom it is clinically indicated- should receive the COVID-19 and/or monkeypox vaccines, and study visits should continue as planned if vaccination occurs while the participant is on the study. Every attempt should be made to receive vaccinations > 2 weeks prior to or > 2 weeks after dosing of the study drugs. Investigators should follow local guidelines for concomitant administration of the COVID-19 and monkeypox vaccines with the study drug(s).

Tecovirimat is a drug with activity against orthopoxviruses. It is currently FDA approved for treatment of smallpox and available under IND for treatment of monkeypox for select patient groups. Clinically significant drug-drug interactions with LEN are not anticipated, contact the medical monitor for approval if tecovirimat is indicated for a study participant.

5.5. Accountability for Study Drug(s)

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 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. Study Drug Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure 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 procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If the study drug is destroyed at the 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 drugs. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be provided to Gilead.

If the site does not have an appropriate standard operating procedure for study drug destruction, used and unused study drugs 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.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant screened or enrolled in the study are presented in tabular form in Table 1 and Table 2 and described in the sections below.

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

6.1. Informed Consent

Written informed consent must be obtained from each participant before initiation of any study-related procedures. Refer to Section 9.1.4 for further information regarding informed consent.

6.2. Screening, Participant Enrollment, and Treatment Assignment

Due to the extended laboratory processing time of the GS-5423 and GS-2872 proviral DNA phenotype testing (up to approximately 10 weeks), the screening visit will be performed in 2 parts (Table 1 and Table 2). Participants meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 28 days after the Screening Visit 2 for the Day 1 visit.

If the screening window is exceeded in an otherwise eligible participant, the participant is allowed to rescreen (Screening Visit 2) 1 time after approval from the sponsor. Once a participant has started the rescreening process, a new screening window (28 days) will begin, during which time screening procedures will be repeated.

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.

Participants must continue to take their baseline oral ART until completion of study drug administration at the Day 1 visit (Treatment Group 1) or Week 52 visit (Treatment Group 3). 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 drugs as described in Section 5.3.

6.3. Instructions for Study Procedures

Study procedure and assessments are outlined in Table 1 and Table 2. The extension phase will continue beyond Week 156 with study visits at every 12 and 24 weeks between dosing visits (every 26 weeks).

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drug, record all serious adverse events (SAEs), as well as any AEs related to protocol-required procedures, on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After study drug administration, report all AEs and SAEs. See Section 7 for additional details.

6.3.2. Concomitant Medications

Review of concomitant medications will occur at the time points shown in Table 1 and Table 2. See Section 5.3.1 for more information about concomitant medications.

6.3.3. Electrocardiograms

Electrocardiograms will be assessed at the time points shown in Table 1 and Table 2.

6.3.4. Medical History and Demography

Medical history and demographic information are to be collected for each participant at screening as follows:

- Review medical history including HIV-1 disease-related events, available historical genotype/phenotype reports, available HIV-1 treatment history, substance (ie, illicit drug) use, and medications taken within 30 days of the screening visit.
- Obtain demographic information, including sex at birth, sexual orientation, and gender identity.

6.3.5. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined in Table 1 and Table 2. Laboratory assessments are listed in Table 6.

Table 6. Laboratory Analytes

Safety Laboratory Measurements			
Chemistry (Serum or Plasma)	**Hematology**	**Urinalysis**	**Other Laboratory Measurements**
ALT AST Alkaline phosphatase Gamma-glutamyltransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Albumin Lactate dehydrogenase Creatinine phosphokinase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Phosphorus Magnesium Potassium Sodium Uric acid Amylase Lipase Thyroid-stimulating hormone	CBC	Color & clarity Specific gravity pH Glucose Ketones Urobilinogen Blood Nitrate Leukocyte esterase Protein Uric acid Pregnancy test	Serum pregnancy test Serum FSH CD4+ and CD8+ T-cell count, and CD4/CD8 ratio Proviral DNA phenotype and genotype Plasma HIV-1 RNA HIV-1 Genotype/Phenotype HBcAb, HBsAg, HBsAb, HCVAb, HCV RNA HIV reservoir assay Immunogenicity (ADA) serum sample Plasma storage samples Pharmacokinetics

ADA = antidrug antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CD4 = clusters of differentiation 4; CD8 = clusters of differentiation 8; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCVAb = hepatitis C virus antibody; RNA = ribonucleic acid
Refer to Table 1 and Table 2 for collection time points.

6.3.6. Pharmacokinetics

Blood sample for the determination of plasma LEN and serum GS-5423 and GS-2872 concentrations will be collected in all participants at scheduled time points. The exact date and time of collection of PK samples must be carefully recorded. PK samples should be drawn from a separate catheter in the opposite arm from the one used for GS-5423 and GS-2872 IV infusions to avoid contamination.

Concentrations of LEN in plasma samples and GS-5423 and GS-2872 in serum samples will be determined using validated bioanalytical methods.

6.3.6.1. Pharmacokinetic Assessments for Treatment Group 1

The following serum PK and plasma PK samples will be collected for all participants in Treatment Group 1:

Serum PK for GS-5423 and GS-2872:

- Day 1: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of the second antibody infusion (GS-2872).
- Week 26: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN injection) and within 5 minutes after the end of the second antibody infusion (GS-2872).
- Week 52, and subsequent dosing days: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN) and within 5 minutes after the end of both antibody infusions (GS-5423 and GS-2872), if coadministered or after the end of the second antibody infusion (GS-2872), if sequentially administered.
- A single any time sample at scheduled visits as outlined in Table 1.

Plasma PK for LEN:

- Day 1: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of the second antibody infusion (GS-2872).
- Week 26 and subsequent dosing days: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN).
- A single any time sample at other scheduled visits as outlined in Table 1.

6.3.6.2. Pharmacokinetic Assessments for Treatment Group 3

The following serum PK and plasma PK samples will be collected for all participants in Treatment Group 3:

Serum PK for GS-5423 and GS-2872:

- Week 52: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of both antibody infusions (GS-5423 and GS-2872), if coadministered or the second antibody infusion (GS-2872), if sequentially administered.
- Week 78 and subsequent dosing visits: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN).
- A single any time sample at other scheduled visits as outlined in Table 2.

Plasma PK for LEN:

- Week 52: 0 hours (predose, ≤ 30 minutes prior to dosing of oral LEN) and within 5 minutes after the end of both antibody infusions (GS-5423 and GS-2872), if coadministered or the second antibody infusion (GS-2872), if sequentially administered.
- Week 78 and subsequent dosing days: 0 hours (predose, ≤ 30 minutes prior to dosing of SC LEN).
- A single any time sample at other scheduled visits as outlined in Table 2.

6.3.7. Immunogenicity Assessments

Blood samples will be collected to assess for the presence of serum ADA against GS-5423 and GS-2872 at scheduled time points according to Table 1 for Treatment Group 1 and Table 2 for Treatment Group 3.

Anti-GS-5423 and anti-GS-2872 antibodies will be determined in serum samples using validated bioanalytical methods.

6.3.9. Clinical Virology

6.3.9.1. Virology Testing

6.3.9.1.1. Virology Samples to Address the Study Objectives

Plasma samples will be collected from all participants who have provided consent for this study to assess HIV-1 RNA viral load at the time points specified in Table 1 and Table 2, including potential HIV-1 viral load retesting. Stored plasma samples may be used to assess HIV-1 genotype and phenotype at baseline or in confirmed cases of VF, as defined in Section 6.3.9.2. PBMC samples will be collected at screening for proviral DNA phenotype testing. PBMC samples for genotyping will be collected at screening but results are not required to determine eligibility. PBMC samples will be collected at the additional time points specified in Table 1 and Table 2 and may be used to characterize the HIV-1 reservoir.

6.3.9.2. Virologic Failure

Participants experiencing VR, as defined below, will be considered to be in a situation of VF and may be subject to resistance analysis.

6.3.9.2.1. Management of Virologic Rebound Participants who meet the following criteria will be considered to have VR:

a. At any visit after Day 1, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit, or

b. HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation

At any visit after Day 1, if the HIV-1 RNA is ≥ 50 copies/mL and < 200 copies/mL, a reflex HIV-1 RNA repeat test will be conducted on stored plasma samples, if available. If the repeat result is < 50 copies/mL, no further action is required. If the repeat result is ≥ 50 copies/mL, participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the original test with HIV-1 RNA ≥ 50 copies/mL) for confirmation of VR. If VR is confirmed and HIV-1 RNA is ≥ 50 copies/mL and < 200 copies/mL, the participant will be asked to return to the clinic for a scheduled or unscheduled blood draw (2 to 3 weeks after the date of the confirmatory draw) and the participant should be discussed with the medical monitor. If VR is confirmed and HIV-1 RNA is ≥ 200 copies/mL, the plasma sample from either the first instance or the confirmation visit will be used for HIV-1 capsid and envelope genotypic and phenotypic testing. A plasma sample from the confirmation visit will be the primary sample used for HIV-1 PR, RT, and IN genotypic and phenotypic testing. After a participant's first postbaseline resistance test, additional testing will be conducted on a case-by-case basis. Any participant may be discontinued at investigator's discretion or per local treatment guidelines.

If no resistance is detected from the genotype or phenotype, the participant may remain on study drugs, and the HIV-1 RNA test should be repeated (2 to 3 weeks after the date of confirmed test with HIV-1 RNA ≥ 50 copies/mL). If HIV-1 RNA levels remain ≥ 50 copies/mL, the participant's discontinuation should be discussed with the medical monitor. If resistance to study drug is detected, participants receiving a long-acting study drug regimen will be restarted on their baseline oral ART regimen (or compatible regimen selected by the investigator) and continue on-study follow-up but will not receive additional doses of the study drugs. Investigators who opt to discontinue study drugs for an individual participant must discuss with the medical monitor prior to study drug discontinuation.

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

6.3.9.2.2. Resistance Analysis at Participant's Last Visit

Participants with HIV-1 RNA ≥ 200 copies/mL at the last visit (ie, not confirmable) and on study drugs will be evaluated for resistance.

6.3.10. Patient-Reported Outcomes

Patient-reported outcome questionnaires (if available) will be completed by participants in both treatment groups at the visits specified in Table 1 and Table 2, and include HIV-dependent quality of life (HIVDQoL), the HIV Treatment Satisfaction Questionnaire status version (HIVTSQs), HIV Treatment Satisfaction Questionnaire change version (HIVTSQc), and the HIV Treatment Preference Questionnaire (HIVTPQ).

6.3.11. Assessments for Early Study Drug Discontinuation

6.3.11.1. Early Study Drug Discontinuation During the Randomized Phase

Treatment Group 1:

Participants who discontinue study drug prior to Week 52 should return to the clinic for an early study drug discontinuation (ESDD) visit to be performed within 72 hours of decision to discontinue study drug.

The participant will be asked to continue to attend scheduled study visits for at least 52 weeks past the last dosing visit.

- If the participant discontinues study drug but continues to attend the scheduled study visits for 52 weeks from their last dosing visit, they will complete all assessments except dosing and complete the study. No further follow-up visits are required.
- If the participant discontinues study drug and does not continue to attend study visits for 52 weeks from their last dosing visit, the participant is required to attend follow-up visits at 30, 90, and 180 days post-ESDD, as well as every 90 days thereafter until at least 365 days from the last study drug dosing visit. Refer to Table 1 for assessments.

At the 30-, 90-, 180-, and subsequent (referred to as 270- and 365-day) follow-up visits, as applicable, any assessment with abnormal results that the investigator determines to have a possible or probable causal relationship with the study drugs will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

If a participant discontinues study drug dosing (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (see Section 3.3). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

Treatment Group 3:

Participants who discontinue from the study prior to Week 52 should return to the clinic for an ESDD visit to be performed within 72 hours of decision to discontinue; only a 30-day follow-up visit is required.

6.3.11.2. Early Study Drug Discontinuation During the Extension Phase

For participants who decide to discontinue study drug during the extension phase but prior to study completion, an ESDD visit should be performed within 72 hours of decision to discontinue study drug.

The participant will be asked to continue to attend scheduled study visits for at least 52 weeks past the last dosing visit.

- If the participant discontinues study drug but continues to attend the scheduled study visits for 52 weeks from their last dosing visit, they will complete all assessments except dosing and complete the study. No further follow-up visits are required.

- If the participant discontinues study drug and does not continue to attend the scheduled study visits for 52 weeks from their last dosing visit, the participant is required to attend follow-up visits at 30, 90, and 180 days post-ESDD, as well as every 90 days thereafter until at least 365 days from the last study drug dosing visit. Refer to Table 1 and Table 2 for assessments.

At the 30-, 90-, 180-, and subsequent (referred to as 270- and 365-day) follow-up visits, as applicable, any assessment with abnormal results that the investigator determines to have a possible or probable causal relationship with the study drugs, will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

If a participant discontinues study drug dosing (eg, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (see Section 3.3). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.4. Poststudy Care

After the participant has completed/terminated their participation in the study, long-term care of the participant will return to the responsibility of their primary treating physicians.

6.5. Sample Storage

The stored biological samples may be used by the sponsor or its research partner for additional testing to provide supplemental data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by the sponsor for a period up to 15 years or per country requirements. CCI [redacted]

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 that does not necessarily have a causal relationship with the treatment. 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, or 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 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is 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 Medications Special Situations Reports

Special situations reports 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, participant, 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 that 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/alcohol 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 is defined as 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 subinvestigator 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 subinvestigator is responsible for assessing the relationship for each 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 or 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) Toxicity Grading Scale, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 11.4).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Before Study Drug Initiation

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

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until the end of the study duration and report the AEs on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities should be followed 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 occur 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 to Gilead Patient Safety as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the 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 Patient Safety.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug special situation reports (SSRs) that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead Patient Safety (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance with the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Medications Reports

7.3.5.1. Gilead Concomitant Medications Special Situations Report

Special situations reports involving a Gilead concomitant medication (not considered study drug), that occur after the participant first consents to participate in the study (ie, signing of the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead Patient Safety utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Medications Report

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

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 eCRF. 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 Situations 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 Patient Safety within 24 hours of the investigator's knowledge of the initial event and of any updates from the time of the ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

If for any reason 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 to:

Gilead Patient Safety
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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 Gilead Patient Safety.

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 within 24 hours of the investigator's knowledge to Gilead Patient Safety 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 and transmit the SSR information electronically, record the SSR on the paper special situations reporting form and transmit within 24 hours to:

Gilead Patient Safety
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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 Gilead Patient Safety.

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 Patient Safety utilizing the paper SSR form and transmitted to:

Gilead Patient Safety
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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 because of a non-Gilead concomitant medication, must be reported on the AE eCRF.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period per Appendix 11.3. Pregnancies should be reported to Gilead Patient Safety within 24 hours of becoming aware of the pregnancy using the pregnancy report form. Contact details for transmitting the pregnancy report form are as follows:

Gilead Patient Safety
Email: Safety_FC@gilead.com
or
Fax: 1-650-522-5477

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 because of 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 after the study must be reported to the Gilead Patient Safety.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead Patient Safety using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Patient Safety.
Gilead Patient Safety contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

Refer to Appendix 11.3 for Pregnancy Precautions, Definition for 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, or suspected unexpected serious adverse reactions.
In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant independent ethics committee in concerned Member States of applicable suspected unexpected serious adverse reactions as outlined in current regulations.

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

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

To minimize the possibility of exposing participants to unusual risk, the safety information from this study will also be reviewed by an independent DMC. The DMC will make recommendations regarding the study according to the DMC charter.

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

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, 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 dated July 2017 (Appendix 11.4). 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 (see Table 7).

Table 7. The Common Terminology Criteria for Adverse Events Version 5 Grading Scale

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

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs

7.7. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 11.5, 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 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 medical monitor.

All clinical sequelae in relation to 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.

For management of infusion-related reactions, please see Section 5.3.1.

7.7.1. Management of ISRs of Grade 3 or Higher or Persisting for More Than 26 Weeks

In clinical studies of SC LEN, Grade 3 or higher AEs of 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 injection 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 discuss the appropriate next steps for further assessment and management of ISR. ISRs that last longer than 26 weeks will be followed clinically until resolution or study completion, and the time of resolution will be documented. Photographic documentation of ISRs that meet above criteria is recommended but not mandatory. If obtained, documentation may be shared with the sponsor and study team.

7.7.2. Management of Ophthalmologic Toxicities/Symptoms of Ocular Disease

As described in the GS-5423 IB, in normal human tissue and rat tissue cross-reactivity studies, plasma membrane staining with a related fluoresceinated antibody, 3BNC117-FITC, was observed in conjunctival recesses in the human eye (1/3 donors) and the rat eye (1/2 donors). These findings were not observed in a normal human tissue cross-reactivity study of 3BNC117 and GS-5423. Additionally, in more than 150 participants in 5 clinical studies of 3BNC117, eye-related symptoms were carefully monitored, and ophthalmology exams, including slit-lamp examinations, were performed. These ophthalmology exams did not reveal any changes from baseline or pathology consistent with an effect related to a therapeutic antibody. However, if symptoms of ocular disease (eg, pruritus, conjunctival erythema, dryness, increased lacrimation, diplopia) develop after study infusions and persist for > 48 hours, or more urgent management is clinically indicated, participants should be promptly referred to an ophthalmologist for diagnosis and management.

7.7.3. Management of Other Toxicities

Unless otherwise specified in Section 7.7, toxicities will be managed according to the guidelines below and as described in Appendix 11.5.

- 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 study drug 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 DAIDS Toxicity Grading Scale, Version 2.1 dated July 2017 (refer to Appendix 11.4).

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

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

Continue investigational medicinal product at the discretion of the investigator.

7.7.3.2. Grade 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 or lower.
- If a laboratory abnormality recurs to Grade 3 or 4 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.

7.7.3.3. 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, creatine kinase 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. Internal Safety Team

Per Gilead's signal management process, an internal safety team consisting of members not directly involved in conduct of the study may review clinical study data for safety reasons. The internal safety team provides recommendations to relevant safety committees within Gilead's signal management process on further actions to protect participants involved in the LEN, GS-5423, and GS-2872 development program.

8. STATISTICAL CONSIDERATIONS

Details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

Before the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program and to support regulatory filings. Also, interim analyses may be used for publication and presentation at scientific meetings.

8.2.1.1. Planned Interim Analyses

In addition to the primary analysis, there will be 1 planned interim analysis:

- Week 52 analysis after all participants have completed their Week 52 visit or prematurely discontinued study drug

8.2.1.2. Data Monitoring Committee Analysis

There will be 1 planned DMC analysis after approximately the first 50% of participants enrolled have completed their Week 12 visit or prematurely discontinued from the study drug. Safety data will be reviewed by the DMC without formal stopping rules. A futility assessment will be conducted based on the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 12 as defined by the FDA-defined snapshot algorithm. If the lower bound of 95% CI of treatment difference (Treatment Group 1–Treatment Group 3) is > 0, the DMC may recommend discontinuation of Treatment Group 1 for futility. The final decision to discontinue a treatment group will be made by the sponsor based on the totality of efficacy, safety, PK, and other data.

In addition, if 4 or more participants in Treatment Group 1 experience confirmed VR (as defined in Section 6.3.9.2.2) before all participants reach Week 26, an ad hoc DMC meeting may be convened to assess the data.

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

Lastly, no alpha penalty due to the DMC analyses will be applied for the primary analysis of the primary efficacy endpoint given that the study is not adequately powered for a formal efficacy evaluation.

8.2.2. Primary Analysis

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

8.2.3. Final Analysis

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

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. 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 1 dose of either the complete long-acting study drug regimen (ie, SC LEN + GS-5423 + GS-2872) or baseline oral ART regimen on or after Day 1. Participants will be grouped according to the treatment to which they were randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of study drug. Participants will be grouped according to the treatment which they actually received.

8.3.1.3. Pharmacokinetics

8.3.1.3.1. Pharmacokinetic Analysis Set

The primary analysis set for general PK analyses is defined as the PK Analysis Set, which will include all randomized participants who have received at least 1 dose of GS-5423, GS-2872, or LEN, and have at least 1 nonmissing PK concentration value reported by the PK laboratory for the corresponding analytes (eg, GS-5423, GS-2872, LEN, and metabolites, if applicable).

8.3.1.4. Immunogenicity

The Immunogenicity Analysis Set will include all randomized participants who received at least 1 dose of GS-5423 or GS-2872 and had at least 1 nonmissing value for each immunogenicity evaluation (ie, anti–GS-5423 antibody or anti–GS-2872 antibody).

8.3.2. Data Handling Conventions

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

Laboratory data (other than HIV-1 RNA) that are continuous in nature but are above the upper limit of quantitation or less than the lower limit of quantitation (LLOQ) will be imputed to the value of the upper or lower limit plus or minus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 5.4, a value of 5.3 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 including sample size, mean, SD, median, first quartile, third quartile, minimum, and maximum for continuous variables and frequency and percentages for categorical variables.

Demographic summaries will include sex at birth, sexual orientation, gender identity, race, ethnicity, and age.

Baseline data will include a summary of body weight, height, body mass index, and HIV-1 infection (eg, CD4+ T-cell count).

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 as determined by the US FDA–defined snapshot algorithm {U. S. Department of Health and Human Services 2015}. The primary analysis of the efficacy will be based on the Full Analysis Set (FAS).

The 2-sided 95% CI of the difference in the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 26 between Treatment Group 1 and Treatment Group 3 will be constructed based on an unconditional exact method using 2 inverted 1-sided tests {Chan 1999}.

8.5.2. Secondary Analyses

The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 52 and the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 26 and 52 as determined by the US FDA-defined snapshot algorithm will be analyzed using the same methods as for the primary efficacy endpoint based on the FAS.

The changes from baseline in CD4+ T-cell count at Week 26 and Week 52 will be summarized by treatment group using descriptive statistics. The differences in changes from baseline in CD4+ T-cell count between the treatment groups (Treatment Group 1 versus Treatment Group 3) and the associated 95% confidence intervals will be constructed using analysis of covariance models, including baseline CD4+ T-cell count as a covariate and treatment (Treatment Group 1 versus Treatment Group 3) as a fixed effect in the models.

8.6. Safety Analysis

Safety data will be summarized by treatment group using the Safety Analysis Set. For Treatment Group 1, all safety data collected on or after the first dose date of study drug will be included. For Treatment Group 3, all safety data collected on or after the first dose date of study drug and up to 30 days after the last dose date will be included. All data will be summarized by treatment according to the study drug received. All collected data will be included in data listings for all enrolled participants.

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug will be generated from the study drug administration data in the case report form (CRF). Exposure data will be summarized by treatment group.

Dosing information for individual participants will be listed.

8.6.2. Adverse Events

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

Events will be summarized on the basis of the date of onset for the event. For Treatment Group 1, a TEAE will be defined as any AE that begins on or after the date of first dose of study drug. For Treatment Group 3, a TEAE will be defined as any AE that begins on or after the date of first dose of study drug and up to 30 days after the last dose date; or any AE leading to study drug discontinuation.

Summaries (number and proportion of participants) of treatment-emergent AEs and SAEs (by SOC, HLT [if applicable], and PT) 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 (using conventional units) will be summarized using only observed data. Absolute values and change from baseline at all scheduled visits 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, dated July 2017 (Appendix 11.4).

The number and proportion of participants experiencing treatment-emergent laboratory abnormalities will be summarized by treatment group. For Treatment Group 1, treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline. For Treatment Group 3, treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last dose of study drug plus 30 days. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

All laboratory abnormalities will be included in a data listing.

8.6.4. Other Safety Evaluations

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

8.7. Adjustments for Multiplicity

No adjustments will be made for multiplicity. Nominal 95% CIs and tests performed at the nominal 0.05 alpha level will be provided.

8.8. Pharmacokinetic Analysis

The serum or plasma concentrations of each analyte (GS-5423, GS-2872, and LEN [and metabolites, if applicable]) over time, including trough concentrations at Weeks 26 and 52, will be listed and summarized by nominal time and treatment group using descriptive statistics. PK parameters (AUC_{0-t}, AUC_{last}, $t_{1/2}$, C_{max}, T_{max}, as appropriate) will be listed and summarized by treatment group using descriptive statistics.

Additional population PK analysis and analysis of the relationship between PK and efficacy or safety endpoints may be performed, as appropriate.

8.9. Immunogenicity Analysis

Immunogenicity to GS-5423 and GS-2872 will be assessed using a 3-tier (screen, confirmatory, and titer) approach on study samples using a validated immunoassay. The incidence of anti-GS-5423 and anti-GS-2872 antibodies will be summarized by treatment group for the Immunogenicity Analysis Set. Titer summaries may also be generated, if relevant.

8.10. Patient-reported Outcomes Analysis

The patient-reported outcomes pertaining to quality of life (HIVDQoL), treatment satisfaction (HIVTSQs/HIVTSQc), and treatment preference (HIVTPQ) may be summarized by treatment group and visit using descriptive statistics.

8.11. Sample Size

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

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

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

8.12. Data Monitoring Committee

A multidisciplinary DMC consisting of non-Gilead personnel will review the progress of the study, perform interim reviews of safety and efficacy data, and provide recommendation to Gilead whether the nature, frequency, and severity of AEs associated with study drug warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study or treatment group termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with 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 the sponsor or proprietary interests in the study drug. This documentation must be provided before 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. The investigator will not begin any study participant activities until approval from the IRB 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 for any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB 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-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, the person conducting the consent discussion, and an impartial witness (if required by IRB or local requirements).

The ICF will inform participants about genomic testing and/or planned sample retention.

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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, IRB, 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. 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, eCRFs, study drug information, and any other study information, remains 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 investigational 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, eCRFs, IRB, 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; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (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, the 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 investigational 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 electronic data capture (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 CRF 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 IRB, 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 IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.2.2. Study Reports 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 3.4.2).

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 personnel 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 and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and the accuracy of the data recorded in the eCRF. The study monitor is responsible for routine review of the 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 investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or 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 study 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

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at his or her site. Should this be necessary, both parties will arrange discontinuation procedures and notify the participant, appropriate regulatory authority(ies), and IRB. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

9.3.5. Data Protection

Enterprise level technical and organizational controls have been developed at Gilead for the purpose of data protection. This includes user authentication and identification, fine grained access controls, end-to-end data encryption, security monitoring, network segregation, and physical security controls. Users of Gilead systems are provided training for security awareness and privacy.

To prepare for the possibility of a data security breach, Gilead maintains a business continuity and disaster recovery plan and conducts regular disaster recovery testing to ensure that Gilead systems are recoverable if a cyber or data security incident is experienced. Gilead's detailed incident response plan for any cyber or data security incident is based on the following 5 steps: detection, analysis, containment, eradication, and recovery. Gilead's standard clinical trial agreement with study sites also includes data privacy language and arrangements in case of data security breaches as follows:

Gilead and institutions will both act in accordance with the applicable data protection law. Furthermore, the study site and Gilead will cooperate with each other to take the necessary measures in order to comply with the applicable data protection law. Both Gilead and the study site shall implement appropriate technical and organizational measures to meet the requirements of the EU General Data Protection Regulation. If either party becomes aware of a personal data breach related to data processed under this agreement, that party shall promptly notify the other party. In such a case, parties will fully cooperate with each other to remedy the personal data breach and promptly fulfill the (statutory) notification obligations. A personal data breach refers to a personal data breach as described in Article 4, Article 33, and Article 34 of the EU General Data Protection Regulation and applicable national data protection laws.

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11. APPENDICES

11.1. Investigator Signature Page

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

A Phase 2 Randomized, Open-label Study to Evaluate the Safety and Efficacy of Broadly Neutralizing Antibodies (bNAbs) GS-5423 and GS-2872 in Combination With the Capsid Inhibitor Lenacapavir as Long-Acting Treatment Dosed Every 6 Months in Virologically Suppressed Adults With HIV-1 Infection

Amendment 3: 13 May 2024

CLINICAL STUDY PROTOCOL ACKNOWLEDGMENT

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

11.2. Disaster and Public Health Emergency Risk Assessment and Mitigation Plan

During an ongoing disaster or public health emergency (hereafter referred to as an "event"), 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 participants and sites:

    a) Participants may be unable to return to the site to get the study drug, or the site may be unable to accept any participant visits. Without study drugs, the participant would not be able to continue receiving the study drug as planned per protocol.

        Mitigation plan: study drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue study drug as determined by the principal investigator. A remote study visit, via phone or video conferencing, must be performed before remote study drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of study procedures. A qualified courier may be used to ship the study drug from sites to study participants if permitted by the local ethics committee/institutional review board/regulatory authority as applicable and with sponsor's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug, the participant would not be able to continue receiving the study drug as planned per protocol.

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

2) Participant safety monitoring and follow-up:

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

        Mitigation plan: For participants who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the participant within the target visit window date whenever possible. During the remote 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 AEs/SAEs.

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

iii) If applicable, confirm electronic diary questionnaires and participant-reported outcomes have been completed and transmitted.

iv) If applicable, confirm the participant's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in (1).

v) If applicable, remind the participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Participants 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 or other vendors may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow up per protocol. Any changes in the party conducting laboratory assessments for the study because of the event will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

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

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

3) Protocol and monitoring compliance:

a) Protocol deviations may occur in case scheduled visits cannot be conducted 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 because of the event must be reported in the electronic case report form and described in the clinical study report (CSR). Any remote study visits that

are conducted in lieu of clinic visits because of the event will be documented as a protocol deviation related to the event.

b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

   Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site 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.

4) Missing data and data integrity:

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

   Mitigation plan: Implications of a event on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the CSR will describe the impact of the event 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 the study drug(s) in study participants remains unchanged.

11.3. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth 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.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone 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 participant assigned female at birth of any age.

b. Definition of Fertility in a Participant Assigned Male at Birth

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

2) Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential

1) Study Drug Effects on Pregnancy and Hormonal Contraception

Lenacapavir (LEN) data on pregnant participants are limited or not available. Data from nonclinical toxicity studies of LEN have demonstrated no adverse effect on fertility or embryo-fetal development. Based on in vitro and in vivo drug-drug interaction liability assessment, a clinically significant drug-drug interaction with LEN and hormonal contraceptives is not expected; an oral contraception drug-drug interaction study was not done. Please refer to the latest version of the investigator's brochure (IB) for additional information.

GS-5423 and GS-2872 data on pregnant participants are limited or not available. As per International Council for Harmonisation guidance, monoclonal antibodies directed at viral targets, such as GS-5423 and GS-2872, do not require reproductive toxicity studies. As protein biologics, GS-5423 and GS-2872 are unlikely to have human genotoxicity/teratogenicity/fetotoxicity. A reduction in the clinical efficacy of hormonal contraception is not expected as GS-5423 and GS-2872 are not cytokine modulators and not anticipated to affect the expression of cytochrome P450 enzymes. Please refer to the latest version of the IB for additional information.

2) Contraception Requirements for Participants Assigned Female at Birth and of Childbearing Potential

The inclusion of participants assigned female at birth and of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at screening and a negative pregnancy test on the Day 1 visit prior to the dose of study drugs. 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 applicable also for participants assigned female at birth and of childbearing potential with infrequent or irregular periods. Pregnancy tests will be performed per the study procedures tables (Table 1 and Table 2).

Duration of required contraception for participants assigned female at birth and of childbearing potential enrolled in this clinical study should start from the screening visit until 6 months following last dose of study drug.

Participants assigned female at birth and of childbearing potential must agree to 1 of the following contraceptive methods:

- 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:

- Hormonal and nonhormonal intrauterine device
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success)

Or

Participants assigned female at birth and of childbearing potential who initiate use of a hormonal contraceptive greater than 5 days after onset of menses as their method of birth control should use additional backup contraception (eg, condoms) for 7 days or avoid sexual intercourse for 7 days. Hormonally based contraceptives or barrier methods permitted for use in this protocol are as follows:

- Hormonal methods
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone

- Subdermal contraceptive implant
- Transdermal contraceptive patch
- Contraceptive vaginal ring

- Barrier methods
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

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.

Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Participants Assigned Male at Birth

No contraception measures are needed.

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

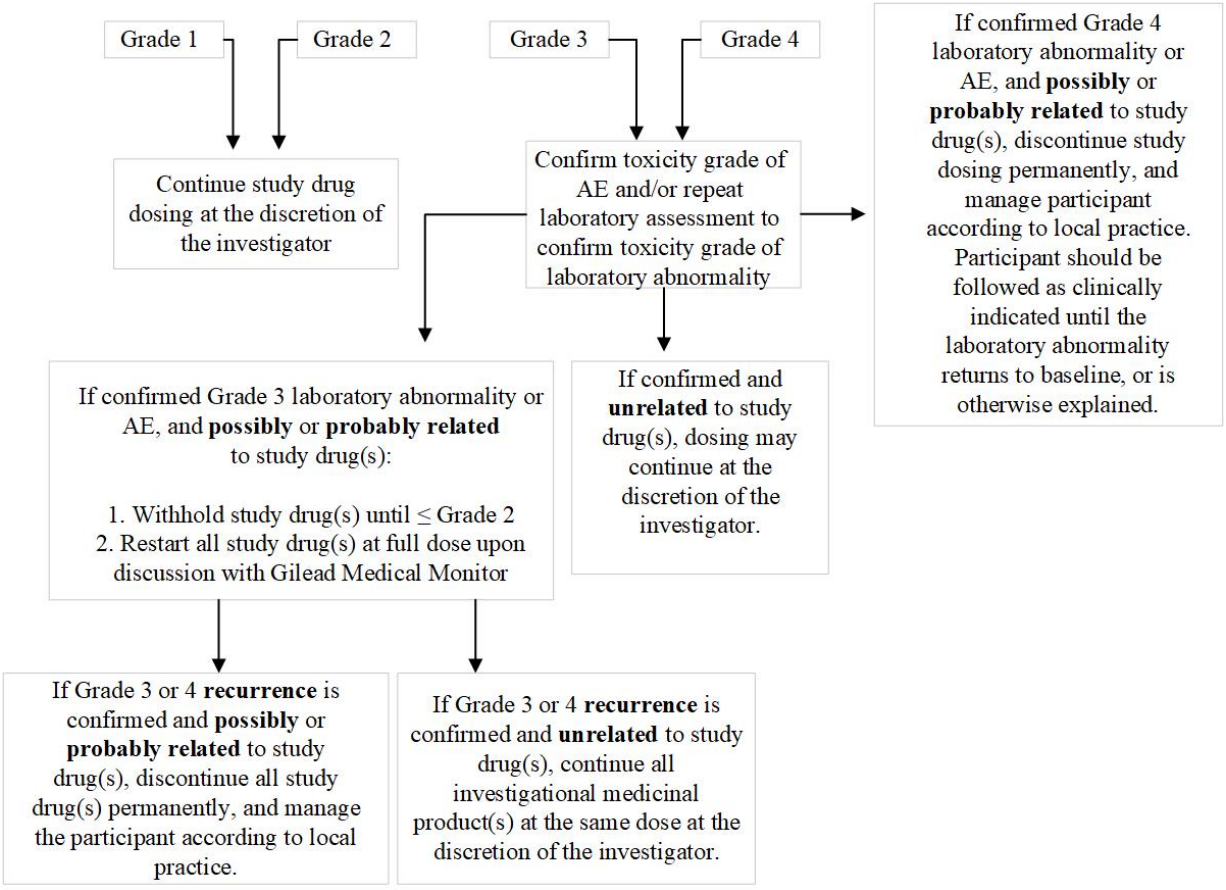
Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study until at least 700 days following the last dose of study drug. Study drug must be discontinued immediately.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

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

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

11.5. Management of Clinical and Laboratory Adverse Events



AE = adverse event

11.6. Country-Specific Requirements

Not applicable.

11.7. Amendment History

A high-level summary of amendment history is provided in tabular form below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing the previous version of the protocol to this amendment will be made available upon the publication of this protocol.

11.7.1. Amendment 3 (13 May 2024)

Rationale for Key Changes Included in Amendment 3	Affected Sections
Updated the dosage and administration guidance to reflect coadministration option starting at Week 52 (in conjunction with sequential administration).	Study Procedures Table (Tables 1 and 2), Sections 5.3 and 6.3.6
Updated HIV reservoir assay to include peripheral blood mononuclear cells (PBMCs).	Study Procedures Table (Tables 1 and 2)
Sample collection guidance split into 2 footnotes for better clarity (HIV reservoir sample and electrocardiogram data in 1 footnote and biomarker samples [PBMC and plasma] in a separate footnote).	Study Procedures Table (Tables 1 and 2)
CCI	
Updated wording in the risk assessment and risk mitigation plan to align with the current protocol template.	Section 1.5, Appendix 11.2
Added details regarding management of virologic rebound.	Section 6.3.9.2
Removed details regarding Fisher exact test per decision of Biostatistics group.	Section 8.4
Added section on data protection requirements to align with the standard text in the current Gilead protocol template.	Section 9.3.5
Minor editorial and formatting changes.	Throughout, as needed

11.7.2. Amendment 2 (26 June 2023)

Rationale for Key Changes Included in Amendment 2	Affected Sections
Emerging data from Study GS-US-536-5816 suggest a higher rate of virologic rebound in participants assigned to the GS-2872 10 mg/kg group; therefore, Treatment Group 2 was removed, leading to changes in dosage information and the statistical analysis plan including sample size.	Synopsis, Study Schema, Study Procedures Table, Sections 1, 2, 3, 4, 5, 6, 8
The number of study centers increased from 50 to 55.	Synopsis
Updated the window period of the PK sampling for study drugs to ≤ 30 minutes prior to dosing of oral LEN for consistency.	Study procedures Table 1 (footnote ‘o’) and Section 6.3.6.1
Clarified that HIV-1 sensitivity results from screening or from the Study GS-US-536-5816 within 36 months prior to Screening Visit 2 meeting specific criteria will be considered for the inclusion in the study.	Section 4.2
Aligned the screening visit (Screening Visit 2) as per the study procedure tables for the study assessments for eligibility.	Synopsis, Sections 4.2 and 4.3
Updated the background information for GS-5423 and GS-2872 to include their synonyms ‘zinlirvimab’and ‘teropavimab’ respectively.	Sections 1.2.2.1 and 1.2.3.1
Updated the language to clarify that the data from the DMC analysis and/or primary analysis will not be considered for the extension phase dose selection.	Synopsis, Study Schema (footnote a), Table 3 and 4 (footnote a), Sections 3.1.2, 5.3
Updated background information with respect to clinical studies of lenacapavir with GS-5423 and GS-2872.	Section 1.2.4
Clarified that the participants in Treatment Group 1 who reach Week 52 and meet criteria to enter the extension phase will receive the study regimen every 26 weeks during the extension phase.	Section 5.3, Table 3 footnote
Updated to clarify that a plasma sample from the confirmation visit will be the primary sample used for HIV-1 PR, RT, and IN genotypic and phenotypic testing.	Section 6.3.9
Minor changes to correct typographic errors, language, and to provide clarifications.	Throughout, as needed

11.7.3. Amendment 1 (18 January 2023)

Rationale for Key Changes Included in Amendment 1	Affected Sections
Instructions for management of ISRs persisting for more than 26 weeks were revised to clarify that ISRs lasting longer than 26 weeks will be followed clinically until resolution or study completion, and the time of resolution will be documented.	Section 7.7.1
Instructions for the management of ophthalmologic symptoms were added.	Section 7.7.2
Dosing and administration instructions for the handling of missed or delayed dosing were added for the cases that more than 28 weeks have passed since the last study drug dose.	Section 5.3.2
A footnote was added to clarify that participants eligible for the extension phase may opt to continue study visits beyond the last week listed under the Extension Phase column in the Study Procedures Table (Week 156), consistent with Section 3.2.	Study Procedures Table
Minor changes to correct typographic errors and clarifications.	Throughout, as needed

11.8. Sponsor Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

A Phase 2 Randomized, Open-label Study to Evaluate the Safety and Efficacy of Broadly Neutralizing Antibodies (bNAbs) GS-5423 and GS-2872 in Combination With the Capsid Inhibitor Lenacapavir as Long-Acting Treatment Dosed Every 6 Months in Virologically Suppressed Adults With HIV-1 Infection

Protocol Amendment 3: 13 May 2024

APPROVAL OF CLINICAL STUDY PROTOCOL

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

PPD	*[See appended electronic signature]*
Senior Associate Clinical Development Director, Virology	Signature
[See appended electronic signature]	
Date	

Protocol GS-US-536-5939 Amd 3.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	09-May-2024 16:41:26