SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.1—SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

LENACAPAVIR

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ART	ARV therapy
ARV	antiretroviral
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
BA	bioavailability
BCS	Biopharmaceutics Classification System
BIC	Bictegravir
CI	confidence interval
C_{max}	maximum observed concentration of drug
CSR	clinical study report
EC_{95}	95% effective concentration
F	relative bioavailability
FA	free acid
HIV, HIV-1	human immunodeficiency virus (type 1)
HTE	highly treatment-experienced
IQ4	inhibitory quotient of 4
IV	intravenous
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LEN	lenacapavir
LEN SDD	LEN spray-dried dispersion
LEN suspension	LEN free acid suspension
NaS	sodium salt
NaSP	sodium salt with poloxamer
PBMC	peripheral blood mononuclear cell
PEG	polyethylene glycol
PK	pharmacokinetic(s)
POC	proof-of-concept
PopPK	population pharmacokinetic
PWH	people with HIV
Q6M	every 6 months
RE	relative error
SAD	single ascending dose
SC	subcutaneous
TAF	Tenofovir Alafenamide
TFV	Tenofovir
TFV-DP	Tenofovir Diphosphate
T_{max}	to maximal exposure
USP	United States Pharmacopeia

1. BACKGROUND AND OVERVIEW

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38 million people with HIV (PWH) worldwide and approximately 26 million on antiretroviral (ARV) treatment {UNAIDS 2020}. Advances in combination ARV therapy (ART) for HIV have led to significant improvements in quality of life among PWH by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. Most currently approved ARV drugs target 1 of the following 4 steps of the HIV lifecycle: the inhibition of viral entry, reverse transcription, viral DNA integration, or the proteolysis of viral polyproteins essential for virion maturation. While combination ART for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality previously associated with HIV disease, there remains a significant medical need for new, well-tolerated therapies that take into consideration HIV genetic variability, ARV resistance, new options for regimen simplification, as well as the desires of PWH for alternative, longer-acting options.

Some treatment-experienced PWH eventually lose the virologic, immunologic, or clinical benefit from their current regimens. People with HIV who have multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {British HIV Association 2016, European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019, Saag 2020, U. S. Department of Health and Human Services 2015}. These challenges are also relevant for adolescents, particularly those with perinatal HIV-1 transmission. Developing safe and effective therapies for heavily treatment-experienced (HTE) PWH with multidrug-resistant HIV remains a priority. For these individuals, newer treatments are needed to control viral replication, preserve immune function, and prevent clinical progression.

Lenacapavir (LEN; GS-6207) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function, which is being developed for the treatment and prevention of HIV-1 infection. Lenacapavir inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

This document provides a summary of the associated analytical methods that support Studies GS-US-200-4070, GS-US-200-4071, GS-US-200-4072, GS-US-200-4329, GS-US-200-4330, GS-US-200-4331, GS-US-200-4332, GS-US-200-4333, GS-US-200-4334, GS-US-200-4538, GS-US-200-4625, and GS-US-200-5709. Bioanalytical and method validation reports that support these studies are provided in Appendix 5.3 and cross-validation results are provided in Appendix 5.4.

1.1. Formulation Development

Two commercial formulations of lenacapavir (LEN; GS-6207) were developed: LEN tablets, 300 mg and LEN injection, 309 mg/mL. Lenacapavir tablets, 300 mg, were developed for oral administration, and are administered as a PK loading combined with the initial subcutaneous (SC) administration of LEN injection, 309 mg/mL.

The designated commercial oral drug product is an immediate-release tablet containing 300 mg LEN, equivalent to 306.8 mg LEN sodium. Lenacapavir sodium is spray-dried with [redacted] and [redacted] to form LEN spray-dried dispersion (LEN SDD) as a drug product intermediate. Lenacapavir SDD is dry granulated with [redacted], [redacted], [redacted], and [redacted]. The resulting granules are lubricated with magnesium stearate and compressed into LEN tablets, 300 mg, which are then film-coated with Opadry II Green [redacted].

Early development of the LEN oral product used a solution in capsule (LEN capsule), which was formulated using [redacted] LEN free acid (FA), the initial drug substance form that was isolated. Subsequently, LEN was isolated as a [redacted] sodium salt (LEN sodium) that was formulated as LEN SDD and incorporated in an immediate-release tablet (LEN tablet).

Lenacapavir capsules and LEN tablets were evaluated in the GS-US-200-4071 study conducted in healthy participants. Lenacapavir tablets achieved higher exposure than LEN capsules and were selected as the oral formulation. The LEN tablet, 300 mg, is the oral formulation used in ongoing clinical studies, including the Phase 2/3 studies, and primary stability studies. Lenacapavir tablet, 300 mg, is the intended commercial formulation.

The designated commercial SC LEN injection product is a sterile, preservative-free solution containing LEN 309 mg/mL, incorporated into the drug product as 315 mg/mL LEN sodium. Lenacapavir sodium is dissolved in a mixture of polyethylene glycol (PEG) 300 and water for injection, and the resulting solution is filtered, filled into vials, and terminally sterilized.

To develop the SC LEN product, a LEN FA suspension (LEN suspension) formulation was first evaluated in the GS-US-200-4070 study conducted in healthy participants. This SC suspension formulation was also used in the GS-US-200-4072 Phase 1b proof-of-concept (POC) study conducted in people with HIV (PWH); however, this formulation was not used in further clinical development due to [redacted] to achieve an every-6-month (Q6M) dosing interval with a 100-mg/mL suspension. Solution formulations with [redacted]. Solution formulations of LEN in PEG 300 and water for injection were evaluated in the GS-US-200-4538 study conducted in healthy participants. These included a solution formulation of LEN FA (LEN FA solution), a solution formulation of a [redacted] ratio of LEN FA: sodium hydroxide to form an in situ sodium salt (LEN sodium solution), and solution formulations of LEN sodium containing poloxamer 188 (LEN NaSP solution). The observed duration of release from a 927-mg dose of the LEN sodium solution, 309 mg/mL, indicated this formulation provided the highest confidence of achieving the desired Q6M dosing interval. Because the proposed commercial form of LEN drug substance is the sodium salt, a solution formulation of LEN sodium in PEG 300 and water for injection (LEN injection) was selected for use in the Phase 2 and Phase 2/3 studies (GS-US-200-4334 and GS-US-200-4625). To support a SC dosing interval of Q6M, a 927-mg dose of LEN was administered as LEN injection, 309 mg/mL, in these studies. Lenacapavir injection, 309 mg/mL, used in the Phase 2/3 study and in primary stability studies is the intended commercial formulation.

Detailed information on the formulation development of LEN, including the qualitative and quantitative composition, is provided in Section 3.2.P.2.2. of Module 3.

Table 1. LEN Formulation Used in Phase 2/3 Registrational Study

Formulation	Drug Form and Strength	Phase 2/3 Study
LEN Tablet	Tablet (300 mg)	GS-US-200-4625
LEN Injection	Injection (309 mg/mL)	GS-US-200-4625

LEN = lenacapavir

Table 2. Formulation Summary for Key Studies With LEN

Study	Product	Drug Substance Form	Formulation	Summary of Results Location
GS-US-200-4070 FIH	LEN suspension	LEN free acid	LEN 100-mg/mL suspension	m2.7.1, Section 2.1.1
GS-US-200-4071 FIH oral capsules and FE	LEN capsule LEN tablet	LEN free acid (capsules) LEN sodium (tablets)	LEN 50-mg/mL, 100-mg/mL capsules LEN 50-mg, 300-mg tablets	m2.7.1, Section 2.2.1
GS-US-200-4072 POC	LEN suspension	LEN free acid	LEN 100-mg/mL suspension	m2.7.2, Section 2.3.1
GS-US-200-4329 ADME	LEN solution	LEN free acid [^{14}C]-LEN free acid	LEN 3-mg/mL solution[a]	m2.7.2, Section 2.2.1
GS-US-200-4330 RI	LEN tablet	LEN sodium	LEN 300-mg tablet	m2.7.2, Section 2.4.1
GS-US-200-4331 HI	LEN tablet	LEN sodium	LEN 300-mg tablet	m2.7.2, Section 2.4.2
GS-US-200-4332 TQT	LEN tablet	LEN sodium	LEN 300-mg tablet	m2.7.2, Section 2.2.2
GS-US-200-4333 DDI	LEN capsule LEN tablet	LEN free acid (capsules) LEN sodium (tablets)	LEN 50-mg/mL capsule and 300-mg tablet	m2.7.2, Section 2.5.1
GS-US-200-4334 Ph2	LEN tablet LEN injection, 309 mg/mL	LEN sodium (tablets) LEN sodium (injection)	LEN 50-mg, 300-mg tablet LEN 309-mg/mL injection	m2.7.3, Section 2.2
GS-US-200-4538 FIH solution	LEN solution	LEN free acid (free acid and sodium solutions) LEN sodium (NaSP solutions)	LEN 300-mg/mL FA, LEN 309-mg/mL NaS, LEN 155-mg/mL NaS, LEN 300-mg/mL NaSP, LEN 50-mg/mL NaSP, LEN 75-mg/mL NaSP	m2.7.1, Section 2.1.2
GS-US-200-4625 Ph 2/3	LEN tablet LEN injection, 309 mg/mL	LEN sodium	LEN 300-mg tablet LEN 309-mg/mL injection	m2.7.3, Section 2.1
GS-US-200-5709 regimen PK	LEN tablet LEN injection, 309 mg/mL	LEN sodium	LEN 300-mg tablet LEN 309-mg/mL injection	m2.7.2, Section 2.2.3

ADME = absorption, distribution, metabolism, and excretion; DDI = drug-drug interaction; FA = free acid; FIH = first in human; HI = hepatic impairment; LEN = lenacapavir; NaS = sodium salt; NaSP = sodium salt with poloxamer; Ph2 = Phase 2; PK = pharmacokinetics; POC = proof-of-concept; RI = renal impairment; TQT = thorough QT

a Participants received a single dose of LEN 20 mg containing a mixture of both unlabeled LEN and [^{14}C] LEN (equivalent to ~200 µCi).

1.2. Dissolution Profile

According to the Biopharmaceutics Classification System (BCS), LEN is a Class 4 compound with low aqueous solubility and low apparent permeability with respect to dose. Dissolution of the designated commercial product was performed using a United States Pharmacopeia (USP)/European Pharmacopeia (Ph. Eur.) Type 2 (Paddle) apparatus operated at 75 rpm. The dissolution medium was 900 mL of 30 mM potassium phosphate, pH 6.0 with 2.0% Cremophor EL at 37 °C.

Dissolution profiles for the drug product lots [redacted], [redacted], and [redacted] are summarized in Table 4, Table 5, and Table 6, respectively. Lot [redacted] was used in Phase 1 PK Study GS-US-200-4071. Provided for comparison are lots [redacted] and [redacted], which are representative of the designated commercial tablet manufacturing process at the proposed commercial manufacturing site for LEN tablets, 300 mg, [redacted] ([redacted], Germany). Dissolution data are comparable between the tablet lots and consistent with the dissolution profile expected for an immediate-release formulation with not less than 80% of LEN dissolved by 30 minutes. Detailed information on the dissolution profiles of LEN tablets, 300 mg, is provided in Section 3.2.P.5.4 of Module 3.

Table 3. Biopharmaceutics Classification of LEN

Drug	LEN
BCS	4

BCS = Biopharmaceutics Classification System; LEN = Lenacapavir

Table 4. In Vitro Dissolution Profile for LEN Tablets, 300 mg, Lot [redacted]

Time (minutes)	Mean LEN Dissolved (%, N = 12)
[redacted]	

LEN = Lenacapavir; N = number of participants in a population; USP = United States Pharmacopeia
Dissolution conditions: USP apparatus 2 with sinker, 900 mL of 30 mM potassium phosphate buffer, pH 6.0 with 2.0% Cremophor EL maintained at 37 °C, 75 rpm
Source: Section 3.2.P.5.4 of Module 3

Table 5. In Vitro Dissolution Profile for LEN Tablets, 300 mg, Lot [redacted]

Time (minutes)	Mean LEN Dissolved (%, N = 12)
[redacted]	

LEN = Lenacapavir; N = number of participants in a population
Source: Section 3.2.P.5.4 of Module 3

Table 6. In Vitro Dissolution Profile for LEN Tablets, 300 mg, Lot [redacted]

Time (minutes)	Mean LEN Dissolved (%, N = 12)
[redacted]	

LEN = Lenacapavir; N = number of participants in a population
Source: Section 3.2.P.5.4 of Module 3

1.3. Bioanalytical Methods

Descriptions of validated methods for LEN, its metabolites, and any coadministered drugs are provided in this section. Methods used for each study in this submission are presented in a tabular summary in Appendix 5.2, where the most current versions of methods are listed and are cumulative for all previous versions. Validation reports and sample analysis reports cited in the corresponding clinical study reports (CSRs) were those in effect at the time of final approval of the CSR.

1.3.1. Determination of LEN and its Metabolites in Human Plasma and Urine

Two bioanalytical methods for the determination of LEN in human plasma with K_2-EDTA as an anticoagulant were validated at [redacted] ([redacted] USA).

1.3.1.1. Determination of LEN in Human Plasma (GS07HPP)

The initial plasma bioanalytical method GS07HPP was validated at the calibrated range of 0.5 to 500 ng/mL at [redacted] ([redacted] USA) under [redacted] Validation Report 8359841. The method involved supported-liquid extraction of LEN and its deuterated internal standard ([redacted]) from human plasma, followed by LC-MS/MS.

Bioanalytical method GS07HPP was used for Studies GS-US-200-4070, GS-US-200-4071, GS-US-200-4072, GS-US-200-4330, GS-US-200-4332, GS-US-200-4334, GS-US-200-4538, GS-US-200-4625, and GS-US-200-5709. All the study samples were analyzed in the timeframe supported by frozen stability storage data.

Specific details on the bioanalytical method GS07HPP used for individual studies are provided in Appendix 5.3. The bioanalytical method validation parameters are provided in Appendix 5.3.1 and are summarized in the CSR.

1.3.1.2. Determination of LEN in Human Plasma (GS7LHPP)

A second plasma bioanalytical method GS7LHPP was validated at the lower calibrated range of 0.1 to 100 ng/mL at [redacted] ([redacted] USA) under [redacted] Validation Report 8402886. The method involved supported-liquid extraction of LEN and its deuterated internal standard ([redacted]) from human plasma, followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Bioanalytical method GS7LHPP was used for Studies GS-US-200-4071, GS-US-200-4329, GS-US-200-4331, and GS-US-200-4333. All the study samples were analyzed in the timeframe supported by frozen stability storage data.

Specific details on the bioanalytical method GS7LHPP used for individual studies are provided in Appendix 5.3. The bioanalytical method validation parameters are provided in Appendix 5.3.2 and are summarized in the CSRs.

1.3.1.3. Determination of LEN in Human Urine

The urine bioanalytical method GS07HUP was validated at the calibrated range of 5 to 5000 ng/mL at [redacted] ([redacted] USA) under [redacted] Validation Report 8359842. The method involved liquid-liquid extraction of LEN and its deuterated internal standard ([redacted]) from human urine treated with Tween 80, followed by LC-MS/MS.

Bioanalytical method GS07HUP was used for Studies GS-US-200-4071, GS-US-200-4329 and GS-US-200-4330. All the study samples were analyzed in the timeframe supported by frozen stability storage data.

Specific details on the bioanalytical method GS07HUP used for individual studies are provided in Appendix 5.3. The bioanalytical method validation parameters are provided in Appendix 5.3.3 and are summarized in the CSRs.

1.3.2. Cross-Validation of Bioanalytical Methods

Qualification of methods with different assay ranges was cross-validated as applicable. Cross-validations with spiked matrix standards and pooled participant samples were conducted at each bioanalytical laboratory to establish interlaboratory comparability. All of the methods met the precision and accuracy (P&A) run acceptance criteria stated in method cross-validation plans.

1.3.2.1. Cross-Validation of Two Bioanalytical Methods for Determination of LEN in Human Plasma

A cross-validation study between the two validated methods GS07HPP (higher calibration curve range method) and GS7LHPP (lower calibration curve range method) for the determination of LEN in human plasma by LC-MS/MS was completed by [redacted] ([redacted] USA). The cross-validation results were reported in [redacted] Study Number 8406716, met the cross-validation acceptance criteria, and indicated that the two validated methods were equivalent.

Specific details on cross-validations of the bioanalytical methods used for individual studies are provided in Appendix 5.4.

1.3.3. Determination of Coadministered Drugs in Human Plasma and Urine

This section describes the bioanalytical methods used to determine coadministered drugs in human plasma and the corresponding validation data that support LEN clinical studies. The validation reports for the LEN studies in this section were current as of this report. Additional analytes which are not relevant to the current submission may have been coadministered in the studies, however, are not included in the sections below.

Specific details on the bioanalytical methods used to determine coadministered drugs are provided here.

1.3.3.1. Determination of Tenofovir Alafenamide (TAF) in Human Plasma

The bioanalytical method for determination of tenofovir alafenamide (TAF) in human plasma was developed and validated under Validation Report [redacted] 60-1578 at [redacted] ([redacted] USA). This method involved protein precipitation extraction of TAF and its internal standard (TAF-d7) from human plasma followed by LC-MS/MS. Bioanalytical method validation parameters are summarized in Table 7.

Table 7. Bioanalytical Method Validation Parameters for Determination of TAF in Human Plasma

	TAF
Calibrated Range (ng/mL)	1 to 1000
Interassay Precision Range (%CV)	3.8 to 6.3
Interassay Accuracy Range (%RE)	−7.3 to −5.6
Studies Supported	GS-US-200-4072, GS-US-200-4333, and GS-US-200-4334

CV = coefficient of variation; RE = relative error; TAF = tenofovir alafenamide
Source: [redacted]60-1578 Amendment 1

1.3.3.2. Determination of Tenofovir (TFV) in Human Plasma

The bioanalytical method for determination of tenofovir (TFV) in human plasma was developed and validated under Validation Report [redacted]60-1368 at [redacted]([redacted]USA). This method involved solid phase extraction of TFV and its internal standard (TFV-d6) from human plasma followed by LC-MS/MS. Bioanalytical method validation parameters are summarized in Table 8.

Table 8. Bioanalytical Method Validation Parameters for Determination of TFV in Human Plasma

	TFV
Calibrated Range (ng/mL)	0.3 to 300
Interassay Precision Range (%CV)	1.8 to 4.8
Interassay Accuracy Range (%RE)	−2.7 to 2.7
Studies Supported	GS-US-200-4072, GS-US-200-4333, and GS-US-200-4334

CV = coefficient of variation; RE = relative error; TFV = tenofovir
Source: [redacted]60-1368 Amendment 3

1.3.3.3. Determination of Bictegravir (BIC) in Human Plasma

The bioanalytical method for determination of bictegravir (BIC, GS-9883) in human plasma was developed and validated under Validation Report [redacted]60-1511 at [redacted]([redacted]USA). This method involved protein precipitation extraction of BIC and its internal standard [redacted] from human plasma followed by LC-MS/MS. Bioanalytical method validation parameters are summarized in Table 9.

Table 9. Bioanalytical Method Validation Parameters for Determination of BIC in Human Plasma

	BIC
Calibrated Range (ng/mL)	20 to 20,000
Interassay Precision Range (%CV)	3.9 to 5.7
Interassay Accuracy Range (%RE)	2.4 to 5.8
Studies Supported	GS-US-200-4334

BIC = bictegravir; CV = coefficient of variation; RE = relative error
Source: [redacted] 60-1511 Amendment 5

1.3.3.4. Determination of Tenofovir Diphosphate (TFV-DP) in Human Peripheral Blood Mononuclear Cells

The bioanalytical method for determination of tenofovir diphosphate (TFV-DP) in human peripheral blood mononuclear cells (PBMCs) was developed and validated under Validation Report [redacted] 60-1574 at [redacted] ([redacted] USA). This method involved cell lysis extraction of TFV-DP and its internal standard ($^{13}C_5$-TFV-DP) from human PBMCs followed by LC-MS/MS. Bioanalytical method validation parameters are summarized in Table 10.

Table 10. Bioanalytical Method Validation Parameters for Determination of TFV-DP in PBMC

	TFV-DP
Calibrated Range (ng/mL)	1.8 to 900
Interassay Precision Range (%CV)	1.8 to 7.1
Interassay Accuracy Range (%RE)	0.2 to 2.4
Studies Supported	GS-US-200-4072 and GS-US-200-4334

CV = coefficient of variation; PBMC = peripheral blood mononuclear cells; RE = relative error; TFV-DP = tenofovir diphosphate
Source: [redacted] 60-1574 Amendment 6

1.3.3.5. Determination of Pitavastatin in Human Plasma

A commercial bioanalytical method for determination of pitavastatin in human plasma was developed and validated under Validation Report [redacted] 42-2001 at [redacted] ([redacted] USA). This method involved liquid-liquid extraction of pitavastatin and its internal standard (pitavastatin-d_5) from human plasma followed by LC-MS/MS. Bioanalytical method validation parameters are summarized in Table 11.

Table 11. Bioanalytical Method Validation Parameters for Determination of Pitavastatin in Human Plasma

	Pitavastatin
Calibrated Range (ng/mL)	0.2 to 200
Interassay Precision Range (%CV)	1.8 to 4.2
Interassay Accuracy Range (%RE)	−6.9 to 5.0
Studies Supported	GS-US-200-4333

CV = coefficient of variation; RE = relative error
Source: [redacted] 42-2001

1.3.3.6. Determination of Rosuvastatin in Human Plasma

A commercial bioanalytical method for determination of rosuvastatin in human plasma was developed and validated under Validation Report [redacted] 42-1043 at [redacted] ([redacted] USA). This method involved liquid-liquid extraction of rosuvastatin and its internal standard (rosuvastatin-d_6) from human plasma followed by LC-MS/MS. Bioanalytical method validation parameters are summarized in Table 12.

Table 12. Bioanalytical Method Validation Parameters for Determination of Rosuvastatin in Human Plasma

	Rosuvastatin
Calibrated Range (ng/mL)	0.05 to 50
Interassay Precision Range (%CV)	1.9 to 5.7
Interassay Accuracy Range (%RE)	1.2 to 6.0
Studies Supported	GS-US-200-4333

CV = coefficient of variation; RE = relative error
Source: [redacted] 42-1043 Amendment 5

1.3.3.7. Determination of Midazolam and 1'-Hydroxymidazolam (1'-OH Midazolam) in Human Plasma

A commercial bioanalytical method for determination of midazolam and 1'-OH midazolam in human plasma was developed and validated under Validation Report [redacted] 42-1703 at [redacted] ([redacted] USA). This method involved liquid-liquid extraction of midazolam, 1'-OH midazolam and internal standards (midazolam-d_4 and 1'-OH midazolam-d_4) from human plasma followed by LC-MS/MS. Bioanalytical method validation parameters are summarized in Table 13.

Table 13. Bioanalytical Method Validation Parameters for Determination of Midazolam and 1'-OH Midazolam in Human Plasma

	Midazolam	1'-OH Midazolam
Calibrated Range (ng/mL)	0.1 to 100	0.1 to 100
Interassay Precision Range (%CV)	1.8 to 6.9	2.0 to 6.7
Interassay Accuracy Range (%RE)	−0.5 to 7.3	2.3 to 9.5
Studies Supported	GS-US-200-4333	

CV = coefficient of variation; RE = relative error
Source: [redacted]42-1703

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

The studies that inform the key biopharmaceutical properties of the LEN oral and SC formulations are as follows:

Study GS-US-200-4070 was a Phase 1 randomized, blinded, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and PK of SC LEN in healthy participants. A study narrative is provided in Section 2.1.1 of this document.

Study GS-US-200-4538 was a Phase 1 randomized, blinded, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and PK of SC solutions of LEN in healthy participants. A study narrative is provided in Section 2.1.2 of this document.

Study GS-US-200-4071 was a Phase 1 study in healthy participants to evaluate the safety, tolerability and PK of oral LEN, and the effect of food on LEN PK. A study narrative is provided in Section 2.2.1 of this document.

Additional summaries of clinical studies included in this marketing application may be found in m2.7.2 for clinical pharmacology studies, m2.7.3 for clinical efficacy studies, and m2.7.4 for clinical safety studies.

2.1. Subcutaneous Formulation Evaluation

2.1.1. Study GS-US-200-4070

<table>
<tr><td>Location:</td><td>GS-US-200-4070</td></tr>
<tr><td>Title:</td><td>A Phase 1 Randomized, Blinded, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Subcutaneous GS-6207 in Healthy Subjects</td></tr>
<tr><td>Primary Objective(s):</td><td>• To assess the safety and tolerability of escalating single SC doses of LEN compared with placebo in healthy participants
• To assess the PK of LEN in healthy participants</td></tr>
<tr><td>Study Design and Participant Population:</td><td>This was a Phase 1, randomized, blinded, placebo-controlled, multicenter, single-dose study with dose escalation.
Eligible participants were randomized in a 4:1 ratio per cohort (8 active and 2 placebo) to receive either LEN or placebo as described in the table below. A single dose of LEN or placebo was administered SC in the abdomen on Day 1.
Cohort 5 was not initiated as the doses evaluated in Cohorts 1 through 4 allowed for characterization of the PK of LEN across a sufficiently wide dose range.
<table>
<tr><th>Cohort</th><th>Number of Participants (active:placebo)</th><th>Dose of LEN or Placebo</th></tr>
<tr><td>1</td><td>8:2</td><td>30 mg</td></tr>
<tr><td>2</td><td>8:2</td><td>Up to 100 mg</td></tr>
<tr><td>3</td><td>8:2</td><td>Up to 300 mg</td></tr>
<tr><td>4</td><td>8:2</td><td>Up to 450 mg</td></tr>
<tr><td>5[a]</td><td>8:2</td><td>Up to 600 mg</td></tr>
</table>
a Cohort 5 was not dosed</td></tr>
</table>

Of the 90 participants screened for this study, 40 were randomized and received a single dose of LEN or placebo (8 participants received LEN and 2 participants received placebo in each cohort).
All 40 randomized participants received study drug across cohorts (10 participants per cohort, in which 8 participants received LEN), of whom 38 participants (95.0%) completed the study.
Two participants prematurely discontinued the study due to being lost to follow-up at Days 36 and 169.

Summary of Results and Conclusions:

Pharmacokinetic Results:
Following single-dose administration of LEN at doses of 30, 100, 300, or 450 mg, LEN PK profiles were consistent with sustained delivery. The PK of LEN was characterized by prolonged exposure, with measurable concentrations in the majority of participants for up to 16, 24, 28, and 32 weeks following doses of 30, 100, 300, and 450 mg, respectively. The median $t_{1/2}$ across doses ranged between approximately 32 and 45 days. Lenacapavir mean C_{max} and AUC_{inf} increased in a dose proportion manner. At doses of 100 mg or greater, mean LEN plasma concentrations exceeded the protein-adjusted 95% effective concentration (EC_{95}) for wild type human immunodeficiency virus type 1 (HIV-1) (3.87 ng/mL) for at least 12 weeks.

PK Parameter Geometric Mean (95% CI)	LEN			
	30 mg (N = 8)	100 mg (N = 8)	300 mg (N = 8)	450 mg (N = 8)
AUC_{inf} (h*ng/mL)	8479.9 (6280.8, 11448.9)	25737.0 (17647.4, 37534.9)	84734.0 (70822.3, 101378.3)	105704.6 (84237.7, 132642.0)
AUC_{last} (h*ng/mL)	4913.5 (3121.1, 7735.3)	22040.6 (16169.6, 30043.3)	66200.2 (41483.6, 105643.2)	93383.8 (70842.9, 123096.9)
AUC_{exp} (%)	15.03 (7.24, 31.23)	5.58 (2.64, 11.77)	3.04 (1.05, 8.79)	2.40 (0.98, 5.86)
C_{max} (ng/mL)	3.0 (2.0, 4.4)	12.7 (7.8, 20.7)	46.3 (36.8, 58.3)	54.2 (37.5, 78.2)
T_{max} (day)[a]	35.00 (16.50, 38.50)	21.00 (9.50, 39.02)	31.50 (14.00, 35.00)	14.00 (6.00, 31.50)
C_{last} (ng/mL)	0.86 (0.67, 1.11)	1.53 (1.04, 2.24)	2.47 (0.99, 6.15)	2.07 (1.02, 4.21)
T_{last} (day)[a]	112.05 (81.51, 140.02)	168.01 (150.06, 168.02)	195.95 (168.00, 223.99)	223.97 (214.94, 224.00)
λ_z (1/day)	0.015 (0.006, 0.034)	0.022 (0.013, 0.037)	0.017 (0.011, 0.026)	0.018 (0.013, 0.024)
CL/F (L/h)	3.5 (2.6, 4.8)	3.9 (2.7, 5.7)	3.5 (3.0, 4.2)	4.3 (3.4, 5.3)
$t_{1/2}$ (day)[a]	37.01 (32.79, 46.15)	31.88 (21.25, 48.18)	45.41 (26.56, 62.53)	39.71 (29.66, 48.65)
Vz/F (L)	5825.8 (3134.3, 10828.7)	4321.6 (2034.7, 9178.6)	4939.0 (3324.8, 7336.8)	5808.8 (4777.3, 7063.0)

95% CI = 95% confidence interval; LEN = Lenacapavir; N = number of participants in a population; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
Means presented were geometric means.
a median (Q1, Q3)

Conclusions:

- Subcutaneously administered LEN was generally safe and well tolerated. The safety profile of LEN was similar at doses of 30 mg to 450 mg LEN.
- Dose-proportional increases in plasma exposure (as measured by AUC_{inf} and C_{max}) were observed following single dose administration of LEN at doses between 30 and 450 mg.
- The PK was characterized by sustained exposure at all evaluated doses, with measurable concentrations for up to 32 weeks. The median $t_{1/2}$ was approximately 32 to 45 days.
- At doses of 100 mg or greater, mean LEN plasma concentrations exceeded the protein-adjusted EC_{95} for wild type HIV-1 (3.87 ng/mL) for at least 12 weeks.

2.1.2. Study GS-US-200-4538

Location:	GS-US-200-4538
Title:	A Phase 1 Randomized, Blinded, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Subcutaneous Solutions of GS-6207 in Healthy Subjects
Primary Objective(s):	• To assess the safety and tolerability of escalating single doses of SC LEN injectable solutions compared with placebo in healthy participants • To assess the PK of SC injectable solutions of LEN in healthy participants
Study Design and Participant Population:	This was a randomized, blinded, placebo-controlled, single center, single-dose Phase 1 study with staggered dose escalations. The study had 8 parts (Parts A to H). Parts A to G were to characterize the PK of single ascending doses (SAD) of different LEN formulations. Part H was to characterize the impact of injection number and/or volume on PK of a formulation(s) selected for further clinical development. Eligible participants were randomized in a 4:1 ratio per cohort to receive either LEN or placebo. Doses were administered SC in the abdomen, in the morning, and could be administered as multiple injections at different abdominal sites, as appropriate. For any given cohort, the sponsor could hold dosing, select an intermediate dose, or stop enrollment at any time based on the review of the cumulative safety and PK data. Cohorts 2 to 4 (Part A), 8 (Part B), 11 to 12 (Part C), 14 to 16 (Part D), 17 to 20 (Part E), 23 to 24 (Part F), 26 to 28 (Part G), and 29 to 32 (Part H) were not initiated as the safety, tolerability, and PK of escalating single doses of the LEN SC dose formulations were adequately assessed in the cohorts studied.

Part A (SAD Formulation 1, 300 mg/mL, free acid [FA]):

Cohort	Participants	Dose Level
1	8 Active, 2 Placebo	300 mg LEN or placebo (1 × 1 mL injection)
2[a]	8 Active, 2 Placebo	Up to 900 mg LEN or placebo
3[a]	8 Active, 2 Placebo	Up to 1200 mg LEN or placebo
4[a]	8 Active, 2 Placebo	Up to 1200 mg LEN or placebo

FA = free acid; LEN = lenacapavir; SAD = single ascending dose.
a Cohorts 2 to 4 were not dosed.

Part B (SAD Formulation 2, 309 mg/mL, sodium salt [NaS]):

Cohort	Participants	Dose Level
5	8 Active, 2 Placebo	309 mg LEN or placebo (1 × 1 mL injection)
6	8 Active, 2 Placebo	927 mg LEN or placebo (3 × 1 mL injections)
7	8 Active, 2 Placebo	927 mg LEN or placebo (2 × 1.5 mL injections)
8[a]	8 Active, 2 Placebo	Up to 2472 mg LEN or placebo

LEN = lenacapavir; NaS = sodium salt; SAD = single ascending dose.
a Cohort 8 was not dosed.

Part C (SAD Formulation 3, 155 mg/mL, NaS):

Cohort	Participants	Dose Level
9	8 Active, 2 Placebo	309 mg LEN or placebo (1 × 2 mL injection)
10	8 Active, 2 Placebo	927 mg LEN or placebo (3 × 2 mL injections)
11[a]	8 Active, 2 Placebo	Up to 1236 mg LEN or placebo
12[a]	8 Active, 2 Placebo	Up to 1236 mg LEN or placebo

LEN = lenacapavir; NaS = sodium salt; SAD = single ascending dose.
a Cohorts 11 to 12 were not dosed

Part D (SAD Formulation 4, 300 mg/mL, sodium salt with poloxamer [NaSP]):

Cohort	Participants	Dose Level
13	8 Active, 2 Placebo	900 mg LEN or placebo (3 × 1 mL injections)
14[a]	8 Active, 2 Placebo	Up to 2400 mg LEN or placebo
15[a]	8 Active, 2 Placebo	Up to 2400 mg LEN or placebo
16[a]	8 Active, 2 Placebo	Up to 2400 mg LEN or placebo

LEN = lenacapavir; NaSP = sodium salt with poloxamer; SAD = single ascending dose.
a Cohorts 14 to 16 were not dosed.

Part E (SAD Formulation 5, 150 mg/mL, NaSP):

Cohort	Participants	Dose Level
17[a]	8 Active, 2 Placebo	900 mg LEN or placebo
18[a]	8 Active, 2 Placebo	Up to 1200 mg LEN or placebo
19[a]	8 Active, 2 Placebo	Up to 1200 mg LEN or placebo
20[a]	8 Active, 2 Placebo	Up to 1200 mg LEN or placebo

LEN = lenacapavir; NaSP = sodium salt with poloxamer; SAD = single ascending dose.
a Part E was not initiated. Cohorts 17 to 20 were not dosed.

Part F (SAD Formulation 6, 75 mg/mL, NaSP):

Cohort	Participants	Dose Level
21	8 Active, 2 Placebo	75 mg LEN or placebo (1 × 1 mL injection)
22	8 Active, 2 Placebo	225 mg LEN or placebo (2 × 1.5 mL injections)
23[a]	8 Active, 2 Placebo	Up to 600 mg LEN or placebo
24[a]	8 Active, 2 Placebo	Up to 600 mg LEN or placebo

LEN = lenacapavir; NaSP = sodium salt with poloxamer; SAD = single ascending dose.
a Cohorts 23 to 24 were not dosed.

Part G (SAD Formulation 7, 50 mg/mL, NaSP):

Cohort	Participants	Dose Level
25	8 Active, 2 Placebo	50 mg LEN or placebo (1 × 1 mL injection)
26[a]	8 Active, 2 Placebo	Up to 150 mg LEN or placebo
27[a]	8 Active, 2 Placebo	Up to 400 mg LEN or placebo
28[a]	8 Active, 2 Placebo	Up to 400 mg LEN or placebo

LEN = lenacapavir; NaSP = sodium salt with poloxamer; SAD = single ascending dose.
a Cohorts 26 to 28 were not dosed.

Part H: Evaluation of Number of Injections and Injection Volume on PK (Single Doses; Formulation Was to be Selected Upon Review of Data From Parts A to G):

Cohort	Participants	Dose Level
29[a]	8 Active, 2 Placebo	Up to 1200 mg (Formulations 1, 3, 5) LEN or placebo, or Up to 2400 mg (Formulations 2 and 4) LEN or placebo, or Up to 600 mg (Formulation 6) LEN or placebo, or Up to 400 mg (Formulation 7) LEN or placebo
30[a]	8 Active, 2 Placebo	Up to 1200 mg (Formulations 1, 3, 5) LEN or placebo, or Up to 2400 mg (Formulations 2 and 4) LEN or placebo, or Up to 600 mg (Formulation 6) LEN or placebo, or Up to 400 mg (Formulation 7) LEN or placebo
31[a]	8 Active, 2 Placebo	Up to 1200 mg (Formulations 1, 3, 5) LEN or placebo, or Up to 2400 mg (Formulations 2 and 4) LEN or placebo, or Up to 600 mg (Formulation 6) LEN or placebo, or Up to 400 mg (Formulation 7) LEN or placebo
32[a]	8 Active, 2 Placebo	Up to 1200 mg (Formulations 1, 3, 5) LEN or placebo, or Up to 2400 mg (Formulations 2 and 4) LEN or placebo, or Up to 600 mg (Formulation 6) LEN or placebo, or Up to 400 mg (Formulation 7) LEN or placebo

LEN = lenacapavir
a Part H was not initiated. Cohorts 29 to 32 were not dosed.

A total of 100 participants were randomized into the study. Ten cohorts were studied; in each cohort, 8 participants received LEN and 2 participants received placebo.

All 100 participants completed study drug dosing. Seventy-eight participants (78.0%) completed the study. Twenty-two participants prematurely discontinued the study: 15 out of 80 participants (18.8%) who received LEN and 1 out of 20 participants (5.0%) who received placebo were lost to follow-up, and 6 out of 80 participants (7.5%) who received LEN withdrew consent.

Summary of Results and Conclusions:

Pharmacokinetic Results:

Following single-dose administration of LEN SC FA, NaS and NaSP formulations (50 to 309 mg/mL), LEN PK profiles exhibited sustained delivery, with apparent $t_{1/2}$ ranging from 17 days to 118 days across the formulations evaluated. Lenacapavir PK was generally dose proportional for formulations for which a range of doses was administered. Administration of 927 mg of 309-mg/mL NaS formulation maintains the lower bound of the 90% CI for LEN concentration above or near the inhibitory quotient of 4 (IQ4) for at least 28 weeks postdose.

Within this study, the effect of salt form (NaS versus FA), addition of poloxamer, LEN concentration (50, 75, 150, and approximately 300 mg/mL), and injection volume on the PK of LEN SC formulations were evaluated. The use of a NaS form of LEN resulted in a faster release than the FA (Cohort 5 versus Cohort 1). A decrease in LEN concentration (Cohort 10 versus Cohorts 6/7, and Cohorts 21 to 25 versus Cohort 13) or addition of poloxamer (NaSP) (Cohort 13 versus Cohorts 6/7) results in faster initial release and apparent elimination. A volume of 1.0 mL versus 1.5 mL per injection did not affect LEN PK (Cohort 6 versus Cohort 7).

Cohort / dose Formulation	**Volume**	**AUC_{inf} (h*ng/mL)**	**C_{max} (ng/mL)**	**T_{max} (h)**	**$t_{1/2}$ (h)**
Cohort 1 / 300 mg LEN 300 mg/mL FA	1 × 1 mL	62561.8 (43801.4, 89357.5)	11.2 (8.3, 15.1)	2016.78 (1848.24, 2388.20)	2831.30 (1682.79, 4591.81)
Cohort 5 / 309 mg LEN 309 mg/mL NaS	1 × 1 mL	63679.2 (49196.1, 82426.2)	16.0 (10.9, 23.5)	2352.22 (1405.14, 3336.09)	1859.94 (1665.30, 2386.67)
Cohort 6 / 927 mg LEN 309 mg/mL NaS	3 × 1 mL	216741.4 (153341.5, 306354.4)	57.8 (34.8, 95.9)	1848.00 (1680.00, 2016.00)	1277.39 (1184.33, 1334.53)
Cohort 7 / 927 mg LEN 309 mg/mL NaS	2 × 1.5 mL	224133.5 (171071.8, 293653.4)	54.9 (35.1, 85.9)	2016.94 (1680.00, 2629.08)	1939.25 (1486.68, 2354.08)
Cohort 9 / 309 mg LEN 155 mg/mL NaS	1 × 2 mL	86815.8 (66454.3, 113416.0)	32.1 (18.2, 56.6)	1344.30 (1344.00, 1680.00)	1147.57 (1072.73, 1437.94)
Cohort 10 / 927 mg LEN 155 mg/mL NaS	3 × 2 mL	235941.0 (198329.8, 280684.9)	98.7 (78.8, 123.8)	1176.71 (924.51, 1344.01)	1203.61 (1112.25, 1714.23)
Cohort 13 / 900 mg LEN 300 mg/mL NaSP	3 × 1 mL	200810.8 (153611.2, 262513.2)	86.9 (57.7, 130.7)	1848.00 (1093.45, 2016.00)	1122.83 (826.42, 1560.76)
Cohort 21 / 75 mg LEN 75 mg/mL NaS	1 × 1 mL	19567.5 (15516.0, 24676.7)	25.2 (19.6, 32.4)	120.00 (48.00, 144.00)	477.53 (452.59, 536.77)
Cohort 22 / 225 mg LEN 75 mg/mL NaSP	2 × 1.5 mL	56363.7 (48420.6, 65609.8)	98.2 (69.8, 138.1)	120.00 (72.00, 120.00)	413.32 (367.69, 430.86)
Cohort 25 / 50 mg LEN 50 mg/mL NaSP	1 × 1 mL	11984.6 (10111.3, 14204.9)	15.9 (11.7, 21.5)	72.00 (48.00, 168.00)	444.44 (365.10, 532.04)

95% CI = 95% confidence interval; LEN = lenacapavir; NaS = sodium salt; NaSP = sodium salt with poloxamer; Q1 = first quartile; Q3 = third quartile
AUC_{inf} and C_{max} are reported as geometric mean (95% CI); T_{max} and $t_{1/2}$ are reported as median (Q1-Q3).

	Conclusions: • Subcutaneously administered LEN was generally safe and well tolerated. • Lenacapavir SC formulations exhibit sustained release, with apparent $t_{1/2}$ ranging from 17 to 118 days across formulations evaluated. • Lenacapavir SC PK can be affected by salt form, LEN concentration, and addition of poloxamer. Lenacapavir formulations with higher initial rates of release of LEN have a corresponding increase in apparent $t_{1/2}$. • Lenacapavir PK is dose proportional for the formulations that were evaluated in this study. • Administration of 927 mg of 309-mg/mL NaS formulation maintains the lower bound of the 90% CI for LEN concentration above or near the IQ4 for at least 28 weeks postdose.

2.2. Oral Formulation Evaluation

2.2.1. Study GS-US-200-4071

Location:	GS-US-200-4071
Title:	A Phase 1 Study in Healthy Volunteers to Evaluate the Safety, Tolerability and Pharmacokinetics of Oral GS-6207, and the Effect of Food on GS-6207 Pharmacokinetics
Primary Objective(s):	• To evaluate the safety and tolerability of escalating single and multiple oral doses of LEN • To characterize the single- and multiple-dose PK of oral LEN • To evaluate the effect of concomitant food intake on oral LEN PK
Study Design and Participant Population:	This was a Phase 1 study in healthy participants (hereafter referred to as participants) evaluating the safety, tolerability, and PK of various LEN oral formulations (see table below) and the effect of food on the PK of the LEN oral tablets.

Formulation	Description
Formulation 1	LEN solution in capsule, FA (50 mg/mL)
Formulation 2	LEN solution in capsule, FA (100 mg/mL)
Formulation 3	LEN tablets (50 or 300 mg unit strength)

LEN = lenacapavir

This study proceeded in 4 parts, as follows:

Study Part A (Cohorts 1 and 2): Randomized, blinded, placebo-controlled, single- and multiple-dose (once daily) study with staggered dose escalations, oral solution in capsule (FA, 50 mg/mL)

Study Part B (Cohorts 3 to 6): Randomized, blinded, placebo-controlled, single-dose study with staggered dose escalations, oral solution in capsule (FA, 50 or 100 mg/mL)

Study Part C (Cohorts 7 to 11): Randomized, blinded, placebo-controlled, single-dose study with staggered dose escalations, oral tablets (50 mg or 300 mg)

Study Part D (Cohorts 12 to 17): Open-label, parallel-group, single-dose food effect study, oral tablets (300 mg)

For any given cohort, the sponsor could have elected to hold dosing, selected an intermediate dose, or stopped study enrollment at any time based on the review of the preliminary safety and PK data.

Cohorts 6 (Study Part B), 11 (Study Part C), and 14 to 17 (Study Part D) were not initiated as the safety, tolerability, and PK of escalating single doses of LEN oral capsules and tablets were adequately assessed in Cohorts 1 to 5 (oral capsule), 7 to 10 (oral tablet), and 12 and 13 (food effect).

Study Part A (single ascending dose (SAD)/multiple ascending dose (MAD), Oral Solution in Capsule, Free Acid; Formulation 1)

Eligible participants were randomized in a 4:1 ratio per cohort (8 active and 2 placebo) to receive either LEN or placebo under fasted conditions.

Cohort	Period 1 (Single-Dose) Day 1	Washout Days 2-10	Period 2 (Multiple Doses) Days 11-20
1	30 mg (50 mg/mL) LEN or placebo, (1 × solution-filled capsule)	—	30 mg (50 mg/mL) LEN or placebo, QD, (1 × solution-filled capsule)
2	100 mg (50 mg/mL) LEN or placebo, (3 × solution-filled capsules)	—	100 mg (50 mg/mL) LEN or placebo, QD, (3 × solution-filled capsules)

LEN = lenacapavir; QD = once daily

Study Part B (SAD, Oral Solution in Capsule, Free Acid; Formulations 1 and 2)

Eligible participants were randomized in a 4:1 ratio per cohort (8 active and 2 placebo) to receive a single dose of either LEN or placebo under fasted conditions.

Cohort	Single Ascending Doses Day 1
3	300 mg (100 mg/mL) LEN or placebo, (4 × solution-filled capsules)
4	75 mg (100 mg/mL) LEN or placebo, (1 × solution-filled capsule)
5	300 mg (50 mg/mL) LEN or placebo, (8 × solution-filled capsules)
6[a]	Up to 900 mg (100 mg/mL) LEN or placebo

LEN = lenacapavir
a Cohort 6 was not dosed.

Study Part C (SAD, Oral Tablet; Formulation 3)

Eligible participants were randomized in a 4:1 ratio per cohort (8 active and 2 placebo) to receive a single dose of either LEN or placebo under fasted conditions.

Cohort	Single Ascending Doses Day 1
7	300 mg LEN or placebo, (1 × 300-mg tablet)
8	900 mg LEN or placebo, (3 × 300-mg tablets)
9	1800 mg LEN or placebo, (6 × 300-mg tablet)
10	50 mg LEN or placebo, (1 × 50-mg tablet)
11[a]	Up to 1800 mg LEN or placebo

LEN = lenacapavir
a Cohort 11 was not dosed.

Study Part D (Food Effect, Oral Tablet; Formulation 3)

The effect of a meal type (high-fat, moderate-fat, or light) on the PK of LEN oral tablet was to be evaluated. Within each cohort (n = 8), participants received a single dose of open-label LEN tablets under fed conditions.

Cohort	Treatment Day 1
12	300 mg LEN (1 × 300-mg tablet) with high-fat, high-calorie meal
13	300 mg LEN (1 × 300-mg tablet) with light meal
14[a]	Up to 1800 mg LEN (tablet) with moderate-fat meal
15[a]	Up to 1800 mg LEN (tablet) with high-fat, high-calorie meal
16[a]	Up to 1800 mg LEN (tablet) with light meal
17[a]	Up to 1800 mg LEN (tablet) with moderate-fat meal

LEN = lenacapavir

a Cohorts 14 to 17 were not dosed.

A total of 106 participants were randomized or enrolled into the study. Of the 106 participants, 40 participants received LEN capsules (50-mg/mL capsules or 100-mg/mL capsules), 10 participants received placebo capsules, 48 participants received LEN tablets (50 mg or 300 mg), and 8 participants received placebo tablets.

All participants completed study drug dosing and all but 4 participants (1 participant who received LEN capsule and 3 participants who received LEN tablet), who were lost to follow-up, completed the study.

Summary of Results and Conclusions:

Pharmacokinetic Results:

The PK of LEN following single-dose administration of LEN oral solution-filled capsules at doses of 30, 100, 300 mg (50 mg/mL LEN), or 75 and 300 mg (100 mg/mL LEN), was characterized by median maximum plasma concentrations of LEN (C_{max}) occurring between 6 and 38 hours postdose, and the median $t_{1/2}$ of oral LEN ranging from 12 to 15 days. Within each formulation, over the doses administered, the increase in AUC and C_{max} was less than dose proportional, suggesting LEN exhibits solubility limited absorption. Additionally, LEN exposure (as assessed by AUC_{inf} and C_{max}) following administration of 300 mg LEN 100 mg/mL was approximately 2-fold lower than that following administration of 300 mg LEN 50 mg/mL, suggesting the concentration of the solution affects PK.

Lenacapavir oral capsules were administered once daily, for 10 days (30 mg and 100 mg, 50 mg/mL). Steady state exposure of LEN was not achieved by Day 10; however, consistent with its $t_{1/2}$, the mean LEN C_{max} and $AUC_{0\text{-}24hr}$ were at least 10-fold higher than those after a single dose.

PK Parameter Geometric Mean (95% CI)	LEN 30 mg (50 mg/mL) (N = 8)	LEN 100 mg (50 mg/mL) (N = 8)	LEN 300 mg (50 mg/mL) (N = 8)
AUC_{inf} (h*ng/mL)	ND	ND	2057.5 (1357.1, 3119.5)
$AUC_{0\text{-}24}$ (h*ng/mL)	16.2 (12.5, 20.9)	30.8 (19.9, 47.7)	ND
AUC_{last} (h*ng/mL)	140.0 (109.9, 178.2)	287.7 (190.3, 434.9)	1979.7 (1287.2, 3044.8)
$\%AUC_{exp}$	ND	ND	3.30 (2.12, 5.14)
C_{max} (ng/mL)	1.1 (0.9, 1.4)	2.3 (1.4, 3.8)	4.3 (2.8, 6.4)
T_{max} (h)[a]	29.00 (4.00, 108.00)	26.00 (4.00, 96.00)	6.99 (4.00, 28.00)
T_{last} (h)[a]	168.00 (168.00, 168.00)	168.00 (168.00, 168.00)	1535.78 (1344.00, 1847.99)
$t_{1/2}$ (h)[a] [days][b]	ND	ND	318.21 (292.62, 346.16) [13.3]

95% CI = 95% confidence interval; LEN = lenacapavir; N = number of participants in a population; ND = not determined; PK = pharmacokinetic

Means presented were geometric means.

a median (Q1, Q3)

b median $t_{1/2}$ presented in days to 3 significant digits

PK Parameter Geometric Mean (95% CI)	LEN 300 mg (100 mg/mL) (N = 8)	LEN 75 mg (100 mg/mL) (N = 8)
AUC_{inf} (h*ng/mL)	1160.1 (896.0, 1502.0)	495.5 (375.9, 653.1)
AUC_{last} (h*ng/mL)	1010.8 (714.8, 1429.3)	435.4 (321.4, 589.9)
$\%AUC_{exp}$	8.25 (4.07, 16.75)	11.40 (8.47, 15.34)
C_{max} (ng/mL)	2.2 (1.7, 2.9)	1.2 (0.9, 1.7)
T_{max} (h)[a]	6.00 (4.00, 27.00)	38.00 (4.00, 72.00)
T_{last} (h)[a]	1344.23 (1068.42, 1512.94)	1008.00 (840.00, 1019.32)
$t_{1/2}$ (h)[a] [days][b]	363.18 (303.61, 378.65) [15.1]	294.03 (266.85, 315.54) [12.3]

95% CI = 95% confidence interval; LEN = lenacapavir; N = number of participants in a population; PK = pharmacokinetic
Means presented were geometric means.
a median (Q1, Q3)
b median $t_{1/2}$ presented in days to 3 significant figures

The PK of LEN following single-dose administration of LEN oral tablets at doses of 50, 300, 900 and 1800 mg was characterized by median maximum plasma concentrations of LEN (C_{max}) occurring between 4 and 8 hours postdose, and the median $t_{1/2}$ of oral LEN ranging from 10 to 13 days. Over the dose range evaluated, the increase in AUC and C_{max} was less than dose proportional. In comparison to the oral solution in capsule, LEN 300-mg tablet AUC_{inf} was approximately 3.4-fold and 6.3-fold higher than observed following a 300-mg dose of 50-mg/mL or 100-mg/mL solution in capsule, respectively.

PK Parameter Geometric Mean (95% CI)	LEN 50 mg (1 × 50-mg tablet) (N = 8)	LEN 300 mg (1 × 300-mg tablet) (N = 8)	LEN 900 mg (3 × 300-mg tablets) (N = 8)	LEN 1800 mg (6 × 300-mg tablets) (N = 8)
AUC_{inf} (h*ng/mL)	2296.4 (1431.6, 3683.7)	6513.7 (3825.6, 11090.8)	8882.3 (5936.3, 13290.4)	13331.6 (9845.4, 18052.1)
C_{max} (ng/mL)	7.4 (5.0, 11.2)	22.8 (10.5, 49.8)	33.7 (17.3, 65.6)	46.4 (26.9, 80.0)
T_{max} (h)[a]	4.00 (4.00, 5.00)	4.00 (4.00, 6.00)	4.00 (3.00, 16.00)	8.00 (6.00, 8.00)
$t_{1/2}$ (h)[a] [days][b]	298.62 (270.20, 415.10) [12.4]	242.64 (204.37, 281.36) [10.1]	288.52 (255.47, 326.89) [12.0]	311.24 (261.50, 361.61) [13.0]

95% CI = 95% confidence interval; LEN = lenacapavir; N = number of participants in a population; PK = pharmacokinetic
Means presented were geometric means.
a median (Q1, Q3)
b median $t_{1/2}$ presented in days to 3 significant figures

Lenacapavir exposure (as assessed by AUC_{inf} and C_{max}) and time to maximal exposure (T_{max}) were comparable following administration of LEN 300-mg tablets under fasted conditions or with a high- or low-fat meal, supporting administration of LEN tablets with or without food in future clinical studies.

PK Parameter Geometric Mean (95% CI)	LEN 300 mg Fasted (N = 8)	LEN 300 mg + High-Fat Meal (N = 8)	LEN 300 mg + Light Meal (N = 8)	%GLSM Ratio (90%CI)	
				High-Fat/ Fasted	Light-Meal/ Fasted
AUC_{inf} (h*ng/mL)	6513.7 (3825.6, 11090.8)	7505.4 (5338.7, 10551.4)	6424.2 (4022.8, 10259.0)	115.22 (71.97, 184.48)	98.63 (58.17, 167.21)
C_{max} (ng/mL)	22.8 (10.5, 49.8)	33.2 (24.5, 44.9)	26.5 (14.4, 48.8)	145.16 (77.90, 270.48)	115.82 (55.40, 242.14)
T_{max} (h)[a]	4.00 (4.00, 6.00)	5.00 (4.00, 6.00)	6.00 (4.00, 8.00)	NC	NC
$t_{1/2}$ (h)[a] [days][b]	242.64 (204.37, 281.36) [10.1]	267.11 (243.70, 357.17) [11.1]	287.46 (255.37, 321.85) [12.0]	NC	NC

95% CI = 95% confidence interval; GLSM = geometric least-square mean; LEN = lenacapavir; N = number of participants in a population; NC = not calculated; PK = pharmacokinetic
Means presented were geometric means.
a median (Q1, Q3)
b median $t_{1/2}$ presented in days to 3 significant figures

Conclusions:

- Lenacapavir administered as solution-filled capsules or tablets was generally safe and well tolerated.
- Oral LEN tablets exhibit less than dose proportional increases in exposure (AUC_{inf} and C_{max}) over the dose range of 50 to 1800 mg.
- Exposure (AUC_{inf}) following single dose administration of LEN 300-mg tablets is 3.4- to 6.3-fold higher than LEN 300-mg oral solution in capsules.
- Oral LEN has a $t_{1/2}$ of approximately 12 days, supportive of daily, or less frequent dosing.
- Lenacapavir oral tablets can be administered without regard to food.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Phase 2/3 LEN SC and Oral Formulation Selection

The PK and safety of LEN oral and SC formulations have been comprehensively characterized in Phase 1 studies in healthy participants. Selection of the LEN oral + SC regimen was informed by PK from Studies GS-US-200-4070, GS-US-200-4538, and GS-US-200-4071. Lenacapavir doses for the ongoing Phase 2 and Phase 2/3 studies (GS-US-200-4334 and GS-US-200-4625) were selected such that the lower bound of the 90% confidence interval (90% CI) of LEN C_{trough} concentrations were at least 4-fold greater than the in vitro protein-adjusted EC_{95} (3.87 ng/mL; MT-4 cells), corresponding to an IQ4 (15.5 ng/mL). This target is supported by the results of the dose ranging proof of concept study (GS-US-200-4072), where near maximal antiviral activity was observed at IQ4, indicating that substantial increases in antiviral activity with an increase in LEN exposure beyond IQ4 were not expected. The use of this concentration target ensures that the majority of participants will be at or above IQ4 for the duration of treatment.

The selected dosing regimen for the ongoing Phase 2 and Phase 2/3 studies (GS-US-200-4334 and GS-US-200-4625) includes administration of oral LEN 600 mg on Days 1 and 2, and 300 mg on Day 8, followed by 927 mg SC LEN injection, 309 mg/mL every 6 months (26 weeks), starting on Day 15. This regimen is predicted to achieve target concentrations within a few days of initiation of dosing and maintain it throughout the 6-month (26-week) dosing interval.

Study GS-US-200-4070 evaluated the safety, tolerability and PK of a SC suspension formulation of LEN across a dose range of 30 to 450 mg. The PK of LEN was characterized by prolonged exposure, with a median $t_{1/2}$ across doses ranged between approximately 32 and 45 days. Lenacapavir mean C_{max} and AUC_{inf} increased in a dose-proportional manner. This SC suspension formulation was used in the GS-US-200-4072 Phase 1b POC study, but will not be used in future clinical development due to the high dose volume required to achieve an every-6-month (Q6M) dosing interval with a 100-mg/mL suspension.

Study GS-US-200-4538 evaluated the safety, tolerability, and PK of SC solutions of LEN in healthy participants, including a FA formulation, a sodium salt formulation, and a sodium salt formulation with poloxamer at various concentrations. Modification of LEN salt form (FA versus NaS), LEN concentration, and addition of poloxamer each can impact the PK of LEN SC formulations. Use of a NaS, a lower concentration of LEN, and the addition of poloxamer can each increase the rate of initial release of LEN, with corresponding decrease in apparent $t_{1/2}$.

The 927-mg dose of the 309-mg/mL NaS formulation, administered as 2 × 1.5 mL SC injections (Formulation 2, Cohort 7), provides LEN concentrations at which the lower bound of the 90% CI exceeds IQ4 for at least 24 weeks, with levels minimally decreasing by Week 28 postdose (lower bound of 90% CI = IQ3.7 at Week 28 postdose). Similar PK profiles were observed following administration of LEN 309 mg/mL NaS as 3 × 1 mL injections (927 mg; Cohort 6) and as 2 × 1.5 mL injections (927 mg; Cohort 7), suggesting that an injection volume of 1 mL versus 1.5 mL does not impact the PK profile of LEN. As a result, a regimen composed of 2 × 1.5 mL was selected to deliver a total dose of 927 mg with fewer injections.

In conjunction with an oral lead in regimen, 927 mg SC LEN (309 mg/mL, sodium salt), was selected for use in a Phase 2/3 study in highly treatment-experienced (HTE) PWH (GS-US-200-4625) and a Phase 2 study in treatment-naive PWH (GS-US-200-4334), with a dosing interval of Q6M.

Study GS-US-200-4071 evaluated the PK of LEN following single-dose administration of oral tablets at doses of 50, 300, 900, and 1800 mg. Lenacapavir PK was characterized by median maximum plasma concentrations of LEN (C_{max}) occurring between 4 and 8 hours postdose, and the median $t_{1/2}$ of oral LEN ranging from 10 to 13 days. Over the dose range evaluated, the increase in AUC and C_{max} was less than dose proportional. In comparison to the oral solution in capsule, LEN 300-mg tablet AUC_{∞} was approximately 3.5-fold and 6.6-fold higher than observed following a 300-mg dose of 50-mg/mL or 100-mg/mL solution in capsule, respectively. To reduce pill burden, the 300-mg LEN tablet formulation was selected for use in the Phase 2 and Phase 2/3 studies.

3.2. Bioavailability of LEN

Oral Administration

The absolute bioavailability of LEN following oral administration was estimated based on the observed exposure of LEN following administration of intravenous (IV) LEN 10 or 20 mg and oral LEN 300 mg to healthy participants (Studies GS-US-200-4329, m2.7.2, Section 2.2.1 and GS-US-200-4071, Section 2.2.1). Comparison of LEN AUC between IV and oral administration, and when correcting for dose, indicates that absolute bioavailability (%F) following administration of LEN 300 mg is low (%F of approximately 10%). Based on population analysis of PK data across studies, the estimated %F for LEN 600 mg is approximately 6.5% (CTRA-2021-1054 LEN PopPK).

These data are consistent with nonclinical findings of low bioavailability following oral administration to rats and dogs (m2.6.4, Section 3.3.3). Lenacapavir displays low aqueous solubility; the maximum equilibrium solubility in simulated intestinal fluid under fasted state at 3.9 µg/mL and under fed state at 4.1 µg/mL (m3, Section 3.2.S.1.3) and both nonclinical and clinical data indicate that LEN is a substrate of P-gp (m2.6.4, Section 7.4 and Study GS-US-200-4333, m2.7.2, Section 2.5.1). Low bioavailability following oral administration is likely due to low solubility and active efflux in the intestine.

Subcutaneous Administration

The absolute bioavailability of LEN following SC administration was estimated based on the observed exposure of LEN following IV and abdominal SC administration in healthy participants (Studies GS-US-200-4329, m2.7.2, Section 2.2.1, and GS-US-200-4538, Section 2.1.2, respectively). Comparison of LEN AUC following administration of IV LEN 10 or 20 mg and SC LEN 927 mg, and when correcting for dose, indicates that LEN is completely absorbed following SC administration of the 927-mg dose.

Due to slow redissolution from the site of administration {Zheng 2018}, the absorption profile of SC LEN is complex, involving a combination of delayed and first-order absorption kinetics leading to a T_{max} of 77 to 84 days postdose (Study GS-US-200-4538, Section 2.1.2, and CTRA-2021-1054 LEN PopPK).

3.3. Effect of Food

The effect of food on oral LEN was evaluated with a high- or low-fat meal relative to fasted conditions using the 300-mg tablet formulation (intended commercial formulation, Study GS-US-200-4071, Section 2.2.1).

For the SC LEN formulation, the effect of food was not evaluated.

Administration of LEN tablets with either a high-fat, high-calorie meal (approximately 1000 kcal and 50% fat) or a light meal (approximately 400 kcal and 25% fat) resulted in comparable AUC or C_{max}, relative to fasted conditions. Based on these results, food is not expected to have a clinically relevant effect on the PK of LEN oral tablets. Lenacapavir is administered without regard to food in the ongoing Phase 2 and Phase 2/3 studies (GS-US-200-4334 and GS-US-200-4625). These data support dosing of LEN tablets with without regard to food. Based on popPK analysis, food status was not identified as a statistically significant covariate on LEN PK (CTRA-2021-1054 LEN PopPK).

Further details on the effect of food including the results of population PK analysis are presented in m2.7.2, Section 3.1.7.1.

3.4. Discussion and Conclusions

- Various SC formulation were evaluated, including a FA formulation, a sodium salt formulation, and a sodium salt formulation with poloxamer at various concentrations. Use of LEN salt form, a lower concentration of LEN, and the addition of poloxamer can each increase the rate of initial release of LEN, with corresponding decrease in apparent $t_{1/2}$.
- To support a SC LEN dosing interval of every 6 months (26 weeks), 927 mg of the LEN injection, 309 mg/mL was the SC formulation selected for use in the HTE population; the FA suspension formulation was not used in further clinical development due to the high dose volume required to achieve Q6M dosing interval with a 100-mg/mL suspension.
- Comparison of LEN AUC following IV LEN 10 or 20 mg and SC LEN 927 mg administration, and when correcting for dose, indicates that LEN is completely absorbed following SC administration of the 927-mg dose.
- In comparison to the oral solution in capsule, LEN 300-mg tablet AUC_{∞} was approximately 3.5 fold and 6.6 fold higher than observed following a 300-mg dose of 50-mg/mL or 100-mg/mL solution in capsule, respectively. To reduce pill burden, the 300-mg LEN tablet formulation was selected for use in the Phase 2 and Phase 2/3 studies.
- Comparison of LEN AUC following IV and oral administration, and when correcting for dose, indicates that absolute bioavailability following LEN 600-mg tablet administration is low (% F of approximately 10%). Based on population PK modeling, the estimated % F for LEN 600 mg is approximately 6.5%.
- Administration of LEN tablet with food does not change LEN exposure for LEN tablets and LEN tablet was administered without regard to food in Phase 2 and Phase 2/3 clinical studies. Therefore, the dosing recommendation for the LEN tablet formulation is without regard to food.

4. REFERENCES

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5. APPENDICES

5.1. Tabular Summary of Biopharmaceutic Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-200-4070	• To assess the safety and tolerability of escalating single SC doses of LEN compared with placebo in healthy volunteers • To assess the PK of LEN in healthy volunteers	Phase 1, randomized, blinded, placebo-controlled, SAD study	Participants were randomized to receive LEN or placebo (4:1 ratio per cohort). • Cohort 1: 30 mg • Cohort 2: 100 mg • Cohort 3: 300 mg • Cohort 4: 450 mg • Cohort 5 (not enrolled): up to 600 mg	1 day	Randomized: 40 participants; Completed: 38 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-200-4071	• To evaluate the safety and tolerability of escalating single and multiple oral doses of LEN • To characterize the single- and multiple-dose PK of oral LEN • To evaluate the effect of concomitant food intake on oral LEN PK	Phase 1, randomized, blinded, placebo-controlled, single and multiple ascending dose study in volunteers	For Study Parts A to C, participants were randomized to receive LEN or placebo (4:1 ratio per cohort).Study Part D involved open-label, parallel-group, single-dose cohorts. Study Part A (SAD/MAD; Formulation 1: LEN 50-mg/mL solution in capsule, free acid): • Cohort 1: 30 mg (50 mg/mL) • Cohort 2: 100 mg (50 mg/mL) Study Part B (SAD; Formulations 1 and 2: LEN 50- or 100-mg/mL solution in capsule, free acid): • Cohort 3: 300 mg (100 mg/mL)	Less than or equal to 11 days	Randomized: 106 participants; Completed: 102 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				• Cohort 4: 75 mg (100 mg/mL) • Cohort 5: 300 mg (50 mg/mL) • Cohort 6 (not enrolled): up to 900 mg (100 mg/mL) Study Part C (SAD; Formulation 3: LEN 50- or 300-mg tablet): • Cohort 7: 300 mg (1 × 300-mg tablet) • Cohort 8: 900 mg (3 × 300-mg tablet) • Cohort 9: 1800 mg (6 × 300-mg tablet) • Cohort 10: 50 mg (1 × 50-mg tablet) • Cohort 11 (not enrolled): up to 1800 mg Study Part D (Food Effect; Formulation 3: LEN 50- or 300-mg tablet): • Cohort 12: 300 mg (1 × 300-mg tablet) with high-fat/high-calorie meal • Cohort 13: 300 mg (1 × 300-mg tablet) with light meal • Cohorts 14 to 17 (not enrolled): up to 1800 mg with high-fat/high-calorie (Cohort 15), moderate-fat (Cohorts 14 and 17), or light (Cohort 16) meal				

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-200-4538	• To assess the safety and tolerability of escalating single doses of SC LEN injectable solutions compared with placebo in healthy volunteers • To assess the PK of SC injectable solutions of LEN in healthy volunteers	Phase 1, randomized, blinded, placebo-controlled, SAD study	Participants were randomized to receive LEN or placebo (4:1 ratio per cohort). Part A (SAD; Formulation 1: LEN 300 mg/mL, free acid): • Cohort 1: 300 mg • Cohort 2 (not enrolled): up to 900 mg • Cohorts 3 and 4 (not enrolled): up to 1200 mg Part B (SAD; Formulation 2: LEN 309 mg/mL, sodium salt): • Cohort 5: 309 mg • Cohorts 6 and 7: 927 mg • Cohort 8 (not enrolled): up to 2472 mg Part C (SAD; Formulation 3: LEN 155 mg/mL, sodium salt): • Cohort 9: 309 mg • Cohort 10: 927 mg • Cohorts 11 and 12 (not enrolled): up to 1236 mg Part D (SAD; Formulation 4: LEN 300 mg/mL, sodium salt with poloxamer): • Cohort 13: 900 mg • Cohorts 14 to 16 (not enrolled): up to 2400 mg Part E (SAD; Formulation 5: LEN 150 mg/mL, sodium salt with poloxamer): • Cohort 17 (not enrolled): 900 mg	1 day	Randomized: 100 participants; Completed: 78 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				• Cohorts 18 to 20 (not enrolled): up to 1200 mg Part F (SAD; Formulation 6: LEN 75 mg/mL, sodium salt with poloxamer): • Cohort 21: 75 mg • Cohort 22: 225 mg • Cohorts 23 and 24 (not enrolled): up to 600 mg Part G (SAD; Formulation 7: LEN 50 mg/mL, sodium salt with poloxamer): • Cohort 25: 50 mg • Cohort 26 (not enrolled): up to 150 mg • Cohorts 27 and 28 (not enrolled): up to 400 mg Part H: Cohorts 29 to 32 (not enrolled): up to 1200 mg (Formulations 1, 3, and 5); up to 2400 mg (Formulations 2 and 4); up to 600 mg (Formulation 6); or up to 400 mg (Formulation 7)				

LEN = lenacapavir; PK = pharmacokinetic(s); SAD = single ascending dose.

5.2. Overall Summary of Bioanalytical Methods and Performance of Methods for Individual Studies

An overall summary of bioanalytical methods, method validation reports, and sample analysis reports for individual studies is provided below for studies conducted to support the LEN clinical development program. The most current versions of the validation reports and sample analysis reports are listed and are cumulative for all previous versions. Validation reports and sample analysis reports cited in the corresponding CSRs were those in effect at the time of CSR approval.

Table 14. Summary of Bioanalytical Methods for Individual Studies

Study No.	Matrix	Analyte	Current Validation Report[a]	Calibrated Range	Sample Analysis Report
GS-US-200-4070	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8383612 Amendment 1
GS-US-200-4071	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8388965 Amendment 1
			[redacted] 8402886 Amendment 1	0.1 to 100 ng/mL	
	Urine		[redacted] 8359842 Amendment 2	5 to 5000 ng/mL	
GS-US-200-4072	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8398724
		TAF	[redacted] 60-1578 Amendment 1	1 to 1000 ng/mL	[redacted] 60-1945A
		TFV	[redacted] 60-1368 Amendment 3	0.3 to 300 ng/mL	[redacted] 60-1945B
	PBMC	TFV-DP	[redacted] 60-1574 Amendment 6	1.8 to 900 ng/mL	[redacted] 60-1945C/D
GS-US-200-4329	Plasma	LEN	[redacted] 8402886 Amendment 1	0.1 to 100 ng/mL	[redacted] 8405056 Amendment 1
	Urine		[redacted] 8359842 Amendment 2	5 to 5000 ng/mL	
GS-US-200-4330	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8423539
	Urine		[redacted] 8359842 Amendment 2	5 to 5000 ng/mL	
GS-US-200-4331	Plasma	LEN	[redacted] 8402886 Amendment 1	0.1 to 100 ng/mL	[redacted] 8415462
GS-US-200-4332	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8446838

Study No.	Matrix	Analyte	Current Validation Report[a]	Calibrated Range	Sample Analysis Report
GS-US-200-4333	Plasma	LEN	[redacted] 8402886 Amendment 1	0.1 to 100 ng/mL	[redacted] 8410223
		PIT	[redacted] 42-2001	0.2 to 200 ng/mL	[redacted] 60-2003A
		ROS	[redacted] 42-1043 Amendment 5	0.05 to 50 ng/mL	[redacted] 60-2003B
		TAF	[redacted] 60-1578 Amendment 1	1 to 1000 ng/mL	[redacted] 60-2003C
		TFV	[redacted] 60-1435 Amendment 4	0.3 to 300 ng/mL	[redacted] 60-2003D
		MDZ	[redacted] 42-1703	0.1 to 100 ng/mL	[redacted] 60-2003E
		1-OH-MDZ		0.1 to 100 ng/mL	
GS-US-200-4334	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8418722 Amendment 1
		BIC	[redacted] 60-1511 Amendment 5	20 to 20,000 ng/mL	[redacted] 60-1981C
		TAF	[redacted] 60-1578 Amendment 1	1 to 1000 ng/mL	[redacted] 60-1981A
		TFV	[redacted] 60-1435 Amendment 4	0.3 to 300 ng/mL	[redacted] 60-1981B
	PBMC	TFV-DP	[redacted] 60-1574 Amendment 6	1.8 to 900 ng/mL	[redacted] 60-1981D/E
GS-US-200-4538	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8400584
GS-US-200-4625	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8418685
GS-US-200-5709	Plasma	LEN	[redacted] 8359841 Amendment 2	0.5 to 500 ng/mL	[redacted] 8425047

1-OH-MDZ = 1'-hydroxymidazolam; BIC = bictegravir; LEN = lenacapavir; MDZ = midazolam; PIT = pitavastatin; [redacted].; ROS = rosuvastatin; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir diphosphate

a The most current versions of the validation reports and sample analysis reports are listed and are cumulative for all previous versions. Validation reports and sample analysis reports cited in the corresponding CSRs were those in effect at the time of CSR approval.

Table 15. Bioanalytical Method Life-cycle Information

	Plasma Method Validation #1	Plasma Method Cross-validation	GS-US-200-4070	GS-US-200-4071	GS-US-200-4072	GS-US-200-4330	GS-US-200-4332	GS-US-200-4334	GS-US-200-4538	GS-US-200-4625	GS-US-200-5709
Analyte	LEN										
Validation type	Full validation	Cross-validation	N/A								
eCTD reference number	N/A	N/A	m2.7.1, Section 2.1.1	m2.7.1, Section 2.2.1	m2.7.2, Section 2.3.1	m2.7.2, Section 2.4.1	m2.7.2, Section 2.2.2	m2.7.3, Section 2.2	m2.7.1, Section 2.1.2	m2.7.3, Section 2.1	m2.7.2, Section 2.2.3
Method ID	GS07HPP	GS07HPP, GS7LHPP	GS07HPP								
Duration of time method in usea	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bioanalytical site	[redacted] (USA)										
Matrix	Plasma										
Platform	liquid chromatography/tandem mass spectrometry (LC-MS/MS)										
Format	N/A										
Stock reference, lot number, expiration date	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calibration range from LLOQ to ULOQ	0.500 to 500 ng/mL	0.5 to 500 ng/mL, 0.100 to 100 ng/mL	0.500 to 500 ng/mL								
Matrix study population	Normal	Normal	Normal	Normal	Diseased	Normal	Normal	Diseased	Normal	Diseased	Normal
Link to reports and applicable amendmentsb	[redacted] 8359841 Amendment 2 Report issued [redacted] Amd 1 issued [redacted] Amd 2 issued [redacted]	[redacted] Cross-Validation Report 8406716 Report issued [redacted]	[redacted] 8383612 Amendment 1	[redacted] 8388965 Amendment 1	[redacted] 8398724	[redacted] 8423539	[redacted] 8446838	[redacted] 8418722 Amendment 1	[redacted] 8400584	[redacted] 8418685	[redacted] 8425047
Synopsis of amendment history	Extend, long-term storage stability	N/A	N/A								

LC-MS/MS = liquid chromatography tandem mass spectrometry; LEN = lenacapavir; LLOQ = lower limit of quantitation; N/A = not applicable; ULOQ = upper limit of quantitation
a Sample analysis dates (first and last) are used for duration of time method in use for each study.
b Current amendments are inclusive of all prior amendments.

Table 16. Bioanalytical Method Life-cycle Information

	Plasma Method Validation #2	Plasma Method Cross-validation	GS-US-200-4071	GS-US-200-4329	GS-US-200-4331	GS-US-200-4333
Analyte	LEN					
Validation type	Full validation	Cross-validation	N/A			
eCTD reference number	N/A	N/A	m2.7.1, Section 2.2.1	m2.7.2, Section 2.2.1	m2.7.2, Section 2.4.2	m2.7.2, Section 2.5.1
Method ID	GS7LHPP	GS07HPP, GS7LHPP	GS7LHPP			
Duration of time method in use[a]	[redacted]/20[redacted] – [redacted]/20[redacted]	N/A	[redacted]20[redacted] – [redacted]20[redacted]	[redacted]20[redacted] – [redacted]20[redacted]	[redacted]20[redacted] – [redacted]20[redacted]	[redacted]20[redacted] – [redacted]20[redacted]
Bioanalytical site	[redacted] ([redacted] USA)					
Matrix	Plasma					
Platform	liquid chromatography/tandem mass spectrometry (LC-MS/MS)					
Format	N/A					
Stock reference, lot number, expiration date	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]
Calibration range LLOQ to ULOQ	0.100–100 ng/mL	0.5 to 500 ng/mL, 0.100 to 100 ng/mL	0.100–100 ng/mL			
Matrix study population	Normal	Normal	Normal	Normal	Normal	Normal
Link to reports and applicable amendments[b]	[redacted]8402886 Amendment 1 Report issued [redacted]20[redacted] Amd 1 issued [redacted]20[redacted]	[redacted] Cross-Validation Report 8406716 Report issued [redacted]20[redacted]	[redacted]8388965 Amendment 1	[redacted]8405056 Amendment 1	[redacted]8415462	[redacted]8410223
Synopsis of amendment history	Extend, long-term storage stability	N/A	N/A			

LC-MS/MS = liquid chromatography tandem mass spectrometry; LEN = lenacapavir; LLOQ = lower limit of quantitation; N/A = not applicable; ULOQ = upper limit of quantitation
a Sample analysis dates (first and last) are used for duration of time method in use for each study.
b Current amendments are inclusive of all prior amendments.

Table 17. Bioanalytical Method Life-cycle Information

	Urine Method Validation	GS-US-200-4071	GS-US-200-4329	GS-US-200-4330
Analyte	LEN			
Validation type	Full validation	N/A		
eCTD reference number	N/A	m2.7.1, Section 2.2.1	m2.7.2, Section 2.2.1	m2.7.2, Section 2.4.1
Method ID	GS07HUP			
Duration of time method in use[a]	[redacted]/20[redacted] – [redacted]/20[redacted]	[redacted]20[redacted] – [redacted]20[redacted]	[redacted]20[redacted] – [redacted]20[redacted]	[redacted]20[redacted] – [redacted]20[redacted]
Bioanalytical site	[redacted] ([redacted] USA)			
Matrix	Urine			
Platform	liquid chromatography/tandem mass spectrometry (LC-MS/MS)			
Format	N/A			
Stock reference, lot number, expiration date	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]	[redacted] retest date: [redacted]20[redacted] [redacted] retest date: [redacted]20[redacted]
Calibration range LLOQ to ULOQ	5.00–5000 ng/mL			
Matrix study population	Normal	Normal	Normal	Normal
Link to reports and applicable amendments[b]	[redacted]8359842 Amendment 2 Report issued [redacted]20[redacted] Amd 1 issued [redacted]20[redacted] Amd 2 issued [redacted]20[redacted]	[redacted]8388965 Amendment 1	[redacted]8405056 Amendment 1	[redacted]8423539
Synopsis of amendment history	Extend, long-term storage stability	N/A		

LC-MS/MS = liquid chromatography tandem mass spectrometry; LEN = lenacapavir; LLOQ = lower limit of quantitation; N/A = not applicable; ULOQ = upper limit of quantitation
a Sample analysis dates (first and last) are used for duration of time method in use for each study.
b Current amendments are inclusive of all prior amendments.

5.3. Summary of Bioanalytical Methods and Performance Methods for Individual Studies

5.3.1. Summary Method Performance of Bioanalytical Method GS07HPP for Quantitative Determination of LEN in Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	[redacted] 8359841 Amendment 2 Validation of a Method for the Determination of GS-6207 in Human Plasma by HPLC With MS/MS Detection		
Method description	The initial plasma bioanalytical method GS07HPP was validated at the calibrated range of 0.5 to 500 ng/mL at [redacted] ([redacted] USA) under [redacted] Validation Report 8359841. The method involved supported-liquid extraction of LEN and its deuterated internal standard ([redacted]) from human plasma, followed by LC-MS/MS.		
Materials used for standard calibration curve and concentration	Reference Standard: LEN	Lot number: [redacted]	
	Internal Standard: [redacted]	Lot number: [redacted]	
	Calibration curve concentrations for LEN	1.50, 20.0, 250, 375 ng/mL	
Validated assay range	0.500 to 500 ng/mL		
Material used for quality controls (QCs) and concentration	LEN Reference Standard:	Lot number: [redacted]	
	Internal Standard: [redacted]	Lot number: [redacted]	
	QC concentrations for LEN:	0.500, 1.50, 20.0, 250, 375, 2500 ng/mL	
Minimum required dilutions	Not applicable		
Source and lot of reagents	Not applicable		
Regression model and weighting	Linear regression $1/x^2$ weighting, where x is nominal concentration		

Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrator concentrations from LLOQ to ULOQ	8	[redacted] 8359841 Amendment 2 Table 7.2
	Number of replicate wells to produce a reportable value:	1	
	Cumulative accuracy (%RE) from LLOQ to ULOQ: LEN	−6.2 to 3.3%	[redacted] 8359841 Amendment 2 Table 7.2
	Cumulative precision (%CV) from LLOQ to ULOQ LEN	≤ 8.3%	[redacted] 8359841 Amendment 2 Table 7.2
QC performance during accuracy and precision runs	**Cumulative accuracy (%RE) in 3 QCs** LEN	−8.5 to 14.2%	[redacted] 8359841 Amendment 2 Table 7.4
	Interbatch %CV (QCs) LEN	≤ 8.7%	[redacted] 8359841 Amendment 2 Table 7.4
Selectivity and matrix effect	**Selectivity**		[redacted] 8359841 Amendment 2 Figure 8.8-8.13
	Assessment: Evaluated by extracting and analyzing individual lots of blank human plasma for interference peak at analyte retention time in absence of LEN and [redacted].		
	Number of total lots tested:	6	
	Range of observed bias	All lots: no interfering peak was ≥ 20% of the mean analyte peak area of the lowest calibration curve standard.	
	Overall result	PASS	

	Matrix Effect:	[redacted]8359841 Amendment 2 Table 7.6
	Assessment: Blank matrix from 6 individuals was used. Each individual blank matrix samples were spiked at the nominal LLOQ concentration and was analyzed without internal standard. All 6 individual matrices tested should demonstrate lack of significant interference (≤ 20.0% of the mean [acceptable] LLOQ calibration standard response and ≤ 5.0% of IS response in the control zero sample) in the chromatographic regions of the analyte and IS. Blank matrix from 6 different individuals, each spiked at the LLOQ QC concentration and analyzed with internal standard. At least 5 individual matrices must generate individual concentration values within ± 20.0% bias (%RE) of the nominal concentration. The mean concentration for the 6 matrices must generate overall mean bias and precision values of ± 20.0% from nominal and RSD% ≤ 20.0%, respectively.	
	Number of total lots tested: 6	
	Range of observed bias: LEN: %RSD (%CV) ≤ 5.5% for IS normalized responses	
	Overall result: PASS	
Interference and specificity	Evaluation: Interference tests to evaluate the potential interference of coadministered drugs (TAF, TFV, FTC and GS-9883) on the bioanalysis of LEN were conducted within the sample analysis reports of the clinical studies with the relevant coadministered drugs. All coadministered drugs showed no interference on the quantitation of LEN.	see BA report [redacted]8398724 and [redacted]8359841 Amendment 2
Hemolysis effect	Evaluation: Low QC and high QC samples prepared in blank plasma containing 2% (run 6) or 5% (run 10) lysed whole blood.	[redacted]8359841 Amendment 2 Table 7.9
	Replicates: 6	
	LEN, run 6	
	Low QC concentration: 1.50 ng/mL Mean %RE: 1.63% %CV: 7.7%	
	High QC concentration: 375 ng/mL Mean %RE: 377% %CV: 5.8%	
	LEN result: PASS, no effect of hemolysis on LEN	
	LEN, run 10	
	Low QC concentration: 1.50 ng/mL Mean %RE: 1.53% %CV: 2.8%	
	High QC concentration: 375 ng/mL Mean %RE: 371% %CV: 2.6%	
	LEN result: PASS, no effect of hemolysis on LEN	
	Overall result: PASS, no effect of hemolysis on LEN	
	The following method deviation occurred during this study and is documented in the data: Hemolysis testing was performed in run 6 using 2% hemolyzed plasma instead of 5%, which was directed in the method and the validation analytical plan. Hemolysis was repeated in run 10 using 5% hemolyzed plasma and the data met acceptance criteria. The deviation does not adversely affect the results of this portion of the study.	

Lipemic effect

Evaluation: Analytes spiked at low and high QC concentrations into 1 lot of blank lipemic plasma.

Replicates:	6
Run 6	
Low QC concentration: Mean %RE: %CV:	1.50 ng/mL 1.52% 5.0%
High QC concentration: Mean %RE: %CV:	375 ng/mL 365% 5.8%
LEN result:	PASS, no effect of lipemia on LEN
Run 9	
Low QC concentration: Mean %RE: %CV:	1.50 ng/mL 1.51% 3.6%
High QC concentration: Mean %RE: %CV:	375 ng/mL 357% 3.0%
LEN result:	PASS, no effect of lipemia on LEN
Overall result:	PASS, no effect of lipemia

Hyperlipidemia tests were performed in run 6 where the high QC concentrations had acceptable results, but it was noted that there were lower internal standard responses found in some of the replicates, therefore the test was repeated in run 9. In run 9 hyperlipidemia had results that met acceptance criteria and the internal standard response was as expected.

[redacted]8359841 Amendment 2 Table 7.10

Dilution linearity and hook effect

Dilutions

Analyte	Concentration (ng/mL)	Dilution Factor	Replicates	%RE	%CV
N/A	N/A	N/A	N/A	N/A	N/A

N/A

Hook Effect

Not applicable

N/A

Bench-top stability

LEN, 2 to 8°C (run 6)

Hours	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV
24 h	1.50 (Low QC)	6	1.49	−0.7%	9.9%
	375 (High QC)	6	354	−5.6%	5.5%

LEN, 2 to 8°C (run 9)

Hours	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV
24 h	1.50 (Low QC)	6	1.50	0.0%	3.6%
	375 (High QC)	6	360	−4.0%	1.2%

Matrix bench-top stability test was performed in run 6 where the high QC concentrations had acceptable results, but it was noted that there were lower internal standard responses found in some of the replicates, therefore the test was repeated in run 9. In run 9 matrix bench-top stability had results that met acceptance criteria and the internal standard response was as expected.

[redacted]8359841 Amendment 2 Table 7.13

Processed sample stability

LEN, 2 to 8°C

Hours	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV
96 h	1.50 (Low QC)	6	1.44	−4.0%	5.1%
	375 (High QC)	6	358	−4.5%	2.1%

[redacted] 8359841 Amendment 2 Table 7.16

Freeze-thaw stability

LEN, −10 to −30°C

Freeze/ Thaw Cycles	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV
5	1.50 (Low QC)	6	1.56	4.0%	9.6%
	375 (High QC)	6	372	−0.8%	8.2%

LEN, −60 to −80°C

Freeze/ Thaw Cycles	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV
5	1.50 (Low QC)	6	1.23* 1.48**	−18.0%* −1.3%**	51.0%* 9.2%**
	375 (High QC)	6	353	−5.9%	6.0%

* Statistics including Outlier value, ** Statistics excluding Outlier value
Outlier value based on Grubb's Outlier test

[redacted] 8359841 Amendment 2 Table 7.14

Long-term storage stability

LEN, −10 to −30°C

Days	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	Mean % Change From Nominal	%CV
748	1.50 (Low QC)	6	1.54	2.7%	2.2%
	375 (High QC)	6	368	−1.9%	1.2%

LEN, −60 to −80°C

748	1.50 (Low QC)	6	1.54	2.7%	7.9%
	375 (High QC)	6	363	−3.2%	2.0%

SUMMARY: Established Long-Term Storage Stability

Analyte	Temperature	Maximum Established Stability
LEN	−10 to −30°C	748 Days
LEN	−60 to −80°C	748 Days

[redacted] 8359841 Amendment 2 Table 7.15

Parallelism

Not Applicable

N/A

Carry-over

Assessment: Two blank matrix samples were analyzed immediately following the highest calibration standard. Minimally this must be towards the end of the run immediately following the highest calibration standard. Minimally this must be towards the end of the run.
Carry-over = Mean observed response signal of injected blanks/mean response signal of LLOQ in same run, expressed as a percentage.

Replicates:	2
LEN carry-over:	Passes acceptance criteria

[redacted] 8359841 Amendment 2 Figure 8.7

Method Performance in Study GS-US-200-4070 [redacted]8383612 Amendment 1 Determination of GS-6207 in Human Plasma Samples From GS-US-200-4070					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted]8383612 Amendment 1 Table 8.1
	LEN	31	27	87.1%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted]8383612 Amendment 1 Table 8.3
	LEN	−3.0 to 2.5%	≤ 5.9%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted]8383612 Amendment 1 Table 8.5
	LEN	−1.1 to 3.5%	≤ 7.0%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 11.2% of study samples, and 96.4% of samples (81 of 84) met the prespecified criteria.				[redacted]8383612 Amendment 1 Table 8.6
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted]8359841 Amendment 2 Sample Analysis [redacted]8383612 Amendment 1
	−60°C to −80°C	LEN	748 days	112 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.				
Method Performance in Study GS-US-200-4071 [redacted]8388965 Amendment 1 Determination of GS-6207 in Human Plasma and Urine Samples From GS-US-200-4071					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted]8388965 Amendment 1 Table 10.1
	LEN	67	58	86.6%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted]8388965 Amendment 1 Table 10.3
	LEN	−2.8 to 1.8%	≤ 6.1%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted]8388965 Amendment 1 Table 10.5
	LEN	−1.9 to 2.5%	≤ 5.9%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 8.3% of study samples, 98.3% of reanalyzed samples (175 of 178) had results that were able to be calculated for this statistic, and 95.4% of samples (167 of 175) met the prespecified criteria.				[redacted]8388965 Amendment 1 Table 10.6
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted]8359841 Amendment 2 Sample Analysis [redacted]8388965 Amendment 1
	−60°C to −80°C	LEN	748 days	42 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.				

<table>
<tr><td colspan="5">Method Performance in Study GS-US-200-4072
[redacted]8398724
Determination of GS-6207 in Human Plasma Samples From GS-US-200-4072</td></tr>
<tr><td>Assay passing rate</td><td>Analyte</td><td>Total Runs</td><td>Passing Runs</td><td>Passing rate</td><td>[redacted]8398724
Table 8.1</td></tr>
<tr><td></td><td>LEN</td><td>25</td><td>21</td><td>84.0%</td><td></td></tr>
<tr><td>Standard curve performance</td><td>Analyte</td><td colspan="2">Cumulative Bias Range (%RE)</td><td>Cumulative Precision (%CV)</td><td>[redacted]8398724
Table 8.3</td></tr>
<tr><td></td><td>LEN</td><td colspan="2">−4.6 to 3.5%</td><td>≤ 4.7%</td><td></td></tr>
<tr><td>QC performance</td><td>Analyte</td><td>Cumulative Bias Range (%RE)</td><td colspan="2">Cumulative Precision (%CV)</td><td>[redacted]8398724
Table 8.5</td></tr>
<tr><td></td><td>LEN</td><td>−2.7 to 3.0%</td><td colspan="2">≤ 4.1%</td><td></td></tr>
<tr><td>Method reproducibility</td><td colspan="4">Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 10.8% of study samples, and 100.0% of samples (71 of 71) met the prespecified criteria.</td><td>[redacted]8398724
Table 8.6</td></tr>
<tr><td>Study sample analysis/stability</td><td>Storage Temperature</td><td>Analyte</td><td>Established Stability</td><td>Maximum Storage for a Sample From This Study</td><td>Validation [redacted]8359841 Amendment 2
Sample Analysis [redacted]8398724</td></tr>
<tr><td></td><td>−60°C to −80°C</td><td>LEN</td><td>748 days</td><td>207 days</td><td></td></tr>
<tr><td>Standard calibration curve performance during accuracy and precision runs</td><td colspan="4">Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.</td><td></td></tr>
<tr><td colspan="5">Method Performance in Study GS-US-200-4330
[redacted]8423539
Sample Analysis for the Determination of GS-6207 in Human Plasma and Urine Samples in Support of GS-US-200-4330</td></tr>
<tr><td>Assay passing rate</td><td>Analyte</td><td>Total Runs</td><td>Passing Runs</td><td>Passing rate</td><td>[redacted]8423539
Table 9.1</td></tr>
<tr><td></td><td>LEN</td><td>9</td><td>9</td><td>100.0%</td><td></td></tr>
<tr><td>Standard curve performance</td><td>Analyte</td><td colspan="2">Cumulative Bias Range (%RE)</td><td>Cumulative Precision (%CV)</td><td>[redacted]8423539
Table 9.3</td></tr>
<tr><td></td><td>LEN</td><td colspan="2">−2.2 to 2.5%</td><td>≤ 6.0%</td><td></td></tr>
<tr><td>QC performance</td><td>Analyte</td><td>Cumulative Bias Range (%RE)</td><td colspan="2">Cumulative Precision (%CV)</td><td>[redacted]8423539
Table 9.5</td></tr>
<tr><td></td><td>LEN</td><td>−1.9 to 3.0%</td><td colspan="2">≤ 3.4%</td><td></td></tr>
<tr><td>Method reproducibility</td><td colspan="4">Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 11.6% of study samples, and 100.0% of samples (44 of 44) met the prespecified criteria.</td><td>[redacted]8423539
Table 9.7</td></tr>
<tr><td>Study sample analysis/stability</td><td>Storage Temperature</td><td>Analyte</td><td>Established Stability</td><td>Maximum Storage for a Sample From This Study</td><td>Validation [redacted]8359841 Amendment 2
Sample Analysis [redacted]8423539</td></tr>
<tr><td></td><td>−60°C to −80°C</td><td>LEN</td><td>748 days</td><td>174 days</td><td></td></tr>
<tr><td>Standard calibration curve performance during accuracy and precision runs</td><td colspan="4">Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.</td><td></td></tr>
</table>

Method Performance in Study GS-US-200-4332 [redacted] 8446838 Determination of GS-6207 in Human Plasma Samples in Support of GS-US-200-4332					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8446838 Table 8.1
	LEN	23	25	92.0%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8446838 Table 8.3
	LEN	−2.8 to 1.3%	≤ 3.8%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8446838 Table 8.5
	LEN	−4.4 to 2.7%	≤ 4.0%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 10.0% of study samples, and 98.9% of samples (93 of 94) met the prespecified criteria.				[redacted] 8446838 Table 8.7
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample from This Study**	Validation [redacted] 8359841 Amendment 2 Sample Analysis [redacted] 8446838
	−60°C to −80°C	LEN	748 days	44 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.				
Method Performance in Study GS-US-200-4334 [redacted] 8418722 Amendment 1 Determination of GS-6207 in Human Plasma Samples From GS-US-200-4334					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8418722 Amendment 1 Table 8.1
	LEN	36	36	100.0%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8418722 Amendment 1 Table 8.3
	LEN	−3.0 to 1.8%	≤ 4.1%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8418722 Amendment 1 Table 8.5
	LEN	−7.2 to 1.5%	≤ 4.5%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 8.7% of study samples, and 100.0% of samples (158 of 158) met the prespecified criteria.				[redacted] 8418722 Amendment 1 Table 8.7
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8359841 Amendment 2 Sample Analysis [redacted] 8418722 Amendment 1
	−60°C to −80°C	LEN	748 days	163 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.				

Method Performance in Study GS-US-200-4538 [redacted] 8400584 Determination of GS-6207 in Human Plasma Samples From GS-US-200-4538					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8400584 Table 8.1
	LEN	67	59	88.1%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8400584 Table 8.3
	LEN	−2.6 to 1.7	≤ 5.8%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8400584 Table 8.5
	LEN	−1.9 to 2.7	≤ 5.0%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 8.1% of study samples, and 99.4% of samples (170 of 171) met the prespecified criteria.				[redacted] 8400584 Table 8.6
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8359841 Amendment 2 Sample Analysis [redacted] 8400584
	−60°C to −80°C	LEN	748 days	182 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.				
Method Performance in Study GS-US-200-4625 [redacted] 8418685 Determination of GS-6207 in Human Plasma Samples from GS-US-200-4625					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8418685 Table 8.1
	LEN	29	29	100.0%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8418685 Table 8.3
	LEN	−3.2 to 1.7%	≤ 4.3%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8418685 Table 8.5
	LEN	−7.6 to 1.5%	≤ 3.2%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 10.0% of study samples, and 100% of samples (114 of 114) met the prespecified criteria.				[redacted] 8418685 Table 8.7
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8359841 Amendment 2 Sample Analysis [redacted] 8418685
	−60°C to −80°C	LEN	748 days	582 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.				

Method Performance in Study GS-US-200-5709 [redacted]8425047 Determination of GS-6207 in Human Plasma Samples From GS-US-200-5709					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted]8425047 Table 8.1
	LEN	73	68	93.2%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted]8425047 Table 8.3
	LEN	−2.6 to 1.7%	≤ 4.5%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted]8425047 Table 8.5
	LEN	−3.6 to 1.5%	≤ 4.6%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 7.6% of study samples, and 99.0% of samples (201 of 203) met the prespecified criteria.				[redacted]8425047 Table 8.7
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted]8359841 Amendment 2 Sample Analysis [redacted]8425047
	−60°C to −80°C	LEN	748 days	144 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.500, 1.00, 4.00, 12.0, 40.0, 200, 400, and 500 ng/mL; each analyzed in 2 replicates.				

CV = coefficient of variation; HPLC = high-performance liquid chromatography; IS = internal standard; ISR = incurred sample reproducibility; LC-MS/MS = liquid chromatography tandem mass spectrometry; LEN = lenacapavir; LLOQ = lower limit of quantitation; N/A = not applicable; QC = quality controls; RE = relative error; RSD = relative standard deviation; ULOQ = upper limit of quantitation

5.3.2. Summary Method Performance of Bioanalytical Method GS7LHPP for Quantitative Determination of LEN in Plasma

Bioanalytical method validation report name, amendments, and hyperlinks	[redacted]8402886 Amendment 1 Validation of a Lower LLOQ (0.100 ng/mL) Method for the Determination of GS-6207 in Human Plasma by HPLC With MS/MS Detection			
Method description	A second plasma bioanalytical method GS7LHPP was validated at the lower calibrated range of 0.1 to 100 ng/mL at [redacted] ([redacted] USA) under [redacted] Validation Report 8402886. The method involved supported-liquid extraction of LEN and its deuterated internal standard ([redacted]) from human plasma, followed by LC-MS/MS.			
Materials used for standard calibration curve and concentration	Reference Standard: LEN	Lot number: [redacted]		
	Internal Standard: [redacted]	Lot number: [redacted]		
	Calibration curve concentrations for LEN	0.100, 0.200, 0.800, 2.40, 8.00, 40.0, 80.0, 100 ng/mL		
Validated assay range	0.100–100 ng/mL			
Material used for quality controls (QCs) and concentration	Reference Standard: LEN	Lot number: [redacted]		
	Internal Standard: [redacted]	Lot number: [redacted]		
	QC concentrations for LEN	0.100, 0.300, 4.00, 50.0, 75.0, 750 ng/mL		
Minimum required dilutions	Not applicable			
Source and lot of reagents	Not applicable			
Regression model and weighting	Linear regression $1/x^2$ weighting, where x is nominal concentration			
Validation parameters	**Method validation summary**			**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrator concentrations From LLOQ to ULOQ		8	[redacted] 8402886 Amendment 1 Table 7.2
	Number of replicate wells to produce a reportable value:		1	
	Cumulative accuracy (%RE) from LLOQ to ULOQ:	LEN	−5.0 to 2.0%	[redacted] 8402886 Amendment 1 Table 7.2
	Cumulative precision (%CV) from LLOQ to ULOQ	LEN	≤ 6.9%	[redacted] 8402886 Amendment 1 Table 7.2
QC performance during accuracy and precision runs	**Cumulative accuracy (%RE) in 3 QCs**	LEN	−6.5 to −4.6%	[redacted] 8402886 Amendment 1 Table 7.4
	Interbatch %CV (QCs)	LEN	≤ 8.5%	[redacted] 8402886 Amendment 1 Table 7.4

Selectivity and matrix effect	**Selectivity**		[redacted] 8402886 Amendment 1 Figure 8.8-8.13
	Assessment: Evaluated by extracting and analyzing individual lots of blank human plasma for interference peak at analyte retention time in absence of LEN and [redacted]		
	Number of total lots tested:	6	
	Range of observed bias	All lots: no interfering peak was ≥ 20% of the mean analyte peak area of the lowest calibration curve standard.	
	Overall result	PASS	
	Matrix Effect:		[redacted] 8402886 Amendment 1 Table 7.6
	Assessment: Blank matrix from 6 individuals was used. Each individual blank matrix samples were spiked at the nominal LLOQ concentration and was analyzed without internal standard. All 6 individual matrices tested should demonstrate lack of significant interference (≤ 20.0% of the mean [acceptable] LLOQ calibration standard response and ≤ 5.0% of IS response in the control zero sample) in the chromatographic regions of the analyte and IS. Blank matrix from 6 different individuals, each spiked at the LLOQ QC concentration and analyzed with internal standard. At least 5 individual matrices must generate individual concentration values within ± 20.0% bias (%RE) of the nominal concentration. The mean concentration for the 6 matrices must generate overall mean bias and precision values of ± 20.0% from nominal and RSD% ≤ 20.0%, respectively.		
	Number of total lots tested:	6	
	Range of observed bias: LEN:	%RSD (%CV) ≤ 12.7 for IS normalized responses	
	Overall result	PASS	
Interference and specificity	Evaluation: Interference tests to evaluate the potential interference of coadministered drugs (PIT, ROS, TAF, TFV, MDZ and 1'-OH-MDZ) on the bioanalysis of LEN were conducted within the sample analysis report of the clinical study with the relevant coadministered drugs. All coadministered drugs showed no interference on the quantitation of LEN.		see BA report [redacted] 8410223
Hemolysis effect	Evaluation: Low QC and high QC samples prepared in blank plasma containing 5% lysed whole blood.		[redacted] 8402886 Amendment 1 Table 7.9
	Replicates:	6	
	LEN		
	Low QC concentration: Mean %RE: %CV:	0.300 ng/mL 4.3% 7.1%	
	High QC concentration: Mean %RE: %CV:	75.0 ng/mL 0.8% 2.8%	
	LEN result:	PASS, no effect of hemolysis on LEN	
Lipemic effect	Evaluation: Analytes spiked at low and high QC concentrations into 6 lot of blank lipemic plasma.		[redacted] 8402886 Amendment 1 Table 7.10
	Replicates:	6	
	LEN		
	Low QC concentration: Mean %RE: %CV:	0.300 ng/mL −4.3% 3.3%	
	High QC concentration: Mean %RE: %CV:	75.0 ng/mL 0.0% 3.8%	
	LEN result:	PASS, no effect of lipemia on LEN	

Dilution linearity and hook effect	**Dilutions**						N/A
	Analyte	Concentration (ng/mL)	Dilution Factor	Replicates	%RE	%CV	
	N/A	N/A	N/A	N/A	N/A	N/A	
	Hook Effect						N/A
	Not applicable						
Bench-top stability	LEN, 2 to 8□C						[redacted] 8402886 Amendment 1 Table 7.13
	Hours	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	24 h	0.300 (Low QC)	6	0.282	−6.0%	6.7%	
		75.0 (High QC)	6	70.0	−6.7%	2.5%	
Processed sample stability	LEN, 2 to 8□C						[redacted] 8402886 Amendment 1 Table 7.16
	Hours	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	98 h	0.300 (Low QC)	6	0.297	−1.0%	4.6%	
		75.0 (High QC)	6	72.1	−3.9%	3.1%	
Freeze-thaw stability	LEN, −10 to −30°C						[redacted] 8402886 Amendment 1 Table 7.14
	Freeze/ Thaw Cycles	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	5	0.300 (Low QC)	6	0.288	−4.0%	2.8%	
		75.0 (High QC)	6	70.0	−6.7%	2.2%	
	LEN, −60 to −80°C						
	Freeze/ Thaw Cycles	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	5	0.300 (Low QC)	6	0.276	−8.0%	2.9%	
		75.0 (High QC)	6	58.2	−9.1%	3.7%	
Long-term storage stability	LEN, −10 to −30°C						[redacted] 8402886 Amendment 1 Table 7.15
	Days	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	Mean % Change From Nominal	%CV	
	401	0.300 (Low QC)	6	0.277	−7.7%	7.6%	
		75.0 (High QC)	6	69.1	−7.9%	3.8%	
	LEN, −60 to −80°C						
	401	0.300 (Low QC)	6	0.280	−6.7%	7.1%	
		75.0 (High QC)	6	68.2	−9.1%	4.2%	
	SUMMARY: Established Long-Term Storage Stability						
	Analyte		Temperature	Maximum Established Stability			
	LEN		−10 to −30°C	401 Days			
	LEN		−60 to −80°C	401 Days			
Parallelism	Not Applicable						N/A

Carry-over	Assessment: Two blank matrix samples were analyzed immediately following the highest calibration standard. Minimally this must be towards the end of the run immediately following the highest calibration standard. Minimally this must be towards the end of the run. Carry-over = Mean observed response signal of injected blanks/mean response signal of LLOQ in same run, expressed as a percentage. Replicates: 2 LEN carry-over: Passes acceptance criteria	[redacted] 8402886 Amendment 1 Figure 8.7

Method Performance in Study GS-US-200-4071
[redacted] 8388965 Amendment 1
Determination of GS-6207 in Human Plasma and Urine Samples From GS-US-200-4071

Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8388965 Amendment 1 Table 10.7
	LEN	11	11	100.0%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8388965 Amendment 1 Table 10.9
	LEN	−3.0 to 2.1%	≤ 7.0%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8388965 Amendment 1 Table 10.11
	LEN	−1.3 to 4.8%	≤ 5.6%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was not performed for Method GS7LHPP.				N/A
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8402886 Amendment 1 Sample Analysis [redacted] 8388965 Amendment 1
	−60°C to −80°C	LEN	401 days	335 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.100, 0.200, 0.800, 2.40, 8.00, 40.0, 80, and 100 ng/mL; each analyzed in 2 replicates.				

Method Performance in Study GS-US-200-4329
[redacted] 8405056 Amendment 1
Determination of GS-6207 in Human Plasma and Urine Samples From GS-US-200-4329

Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8405056 Amendment 1 Table 9.1
	LEN	21	18	85.7%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8405056 Amendment 1 Table 9.3
	LEN	−1.0 to 1.0%	≤ 4.3%		

QC performance	Analyte	Cumulative Bias Range (%RE)	Cumulative Precision (%CV)	Total Error	[redacted] 8405056 Amendment 1 Table 9.5
	LEN	−3.5 to 2.0%	≤ 4.2%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 10.6% of study samples, 95.6% of reanalyzed samples (43 of 45) had results that were able to be calculated for this statistic, and 100% of samples (43 of 43) met the prespecified criteria.				[redacted] 8405056 Amendment 1 Table 9.7
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8402886 Amendment 1 Sample Analysis [redacted] 8405056 Amendment 1
	−60°C to −80°C	LEN	401 days	160 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.100, 0.200, 0.800, 2.40, 8.00, 40.0, 80, and 100 ng/mL; each analyzed in 2 replicates.				

Method Performance in Study GS-US-200-4331
[redacted] 8415462
Determination of GS-6207 in Human Plasma in Support of GS-US-200-4331

Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8415462 Table 8.1
	LEN	13	12	92.3%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8415462 Table 8.3
	LEN	−0.9 to 0.5%	≤ 4.8%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8415462 Table 8.5
	LEN	−1.7 to 0.5%	≤ 4.1%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 10.3% of study samples, and 100.0% of samples (44 of 44) met the prespecified criteria.				[redacted] 8415462 Table 8.7
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8402886 Amendment 1 Sample Analysis [redacted] 8415462 Table 8.7
	−60°C to −80°C	LEN	401 days	209 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.100, 0.200, 0.800, 2.40, 8.00, 40.0, 80, and 100 ng/mL; each analyzed in 2 replicates.				

Method Performance in Study GS-US-200-4333 [redacted] 8410223 Determination of GS-6207 in Human Plasma Samples From GS-US-200-4333					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8410223 Table 8.1
	LEN	151	149	98.7%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**		[redacted] 8410223 Table 8.3
	LEN	−0.6 to 0.5	≤ 5.5%		
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8410223 Table 8.5
	LEN	−5.1 to 1.0%	≤ 7.0%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 6.6% of study samples, and 98.8% of samples (395 of 400) met the prespecified criteria.				[redacted] 8410223 Table 8.7
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8402886 Amendment 1 Sample Analysis [redacted] 8410223
	−60°C to −80°C	LEN	401 days	205 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 0.100, 0.200, 0.800, 2.40, 8.00, 40.0, 80, and 100 ng/mL; each analyzed in 2 replicates.				

1-OH-MDZ = 1'-hydroxymidazolam; CV = coefficient of variation; HPLC = high-performance liquid chromatography; IS = internal standard; ISR = incurred sample reproducibility; LC-MS/MS = liquid chromatography tandem mass spectrometry; LEN = lenacapavir; LLOQ = lower limit of quantitation; MDZ = midazolam; MS/MS = tandem mass spectrometry; N/A = not applicable; PIT = pitavastatin; QC = quality controls; RE = relative error; ROS = rosuvastatin; RSD = relative standard deviation; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir diphosphate; ULOQ = upper limit of quantitation

5.3.3. Summary Method Performance of Bioanalytical Method GS07HUP for Quantitative Determination of LEN in Urine

Bioanalytical method validation report name, amendments, and hyperlinks	[redacted] 8359842 Amendment 2 Validation of a Method for the Determination of GS-6207 in Tween Treated Human Urine by HPLC With MS/MS Detection			
Method description	The urine bioanalytical method GS07HUP was validated at the calibrated range of 5 to 5000 ng/mL at [redacted] ([redacted] USA) under [redacted] Validation Report 8359842. The method involved liquid-liquid extraction of LEN and its deuterated internal standard ([redacted]) from human urine treated with Tween 80, followed by LC-MS/MS.			
Materials used for standard calibration curve and concentration	Reference Standard: LEN	Lot number: [redacted], [redacted], [redacted]		
	Internal Standard: [redacted]	Lot number: [redacted], [redacted]		
	Calibration curve concentrations for LEN	5.00, 10.0, 25.0, 150, 500, 2000, 4000, 5000 ng/mL		
Validated assay range	5.00–5000 ng/mL			
Material used for quality controls (QCs) and concentration	Reference Standard: LEN	Lot number: [redacted], [redacted], [redacted]		
	Internal Standard: [redacted]	Lot number: [redacted], [redacted]		
	QC concentrations for LEN:	5.00, 15.0, 150, 2000, 3750, 37500 ng/mL		
Minimum required dilutions	Not Applicable			
Source and lot of reagents	Not Applicable			
Regression model and weighting	Linear regression $1/x^2$ weighting, where x is nominal concentration			
Validation parameters	**Method validation summary**			**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrator concentrations from LLOQ to ULOQ	8		[redacted] 8359842 Amendment 2 Table 7.2
	Number of replicate wells to produce a reportable value:	1		
	Cumulative accuracy (%RE) from LLOQ to ULOQ:	LEN	−3.4 to 2.8%	[redacted] 8359842 Amendment 2 Table 7.2
	Cumulative precision (%CV) from LLOQ to ULOQ	LEN	≤4.6%	
QC performance during accuracy and precision runs	**Cumulative accuracy (%RE) in 3 tested QCs**	LEN	−1.3 to 4.0%	[redacted] 8359842 Amendment 2 Table 7.4
	Interbatch %CV (QCs)	LEN	≤7.1%	
Selectivity and matrix effect	**Selectivity**			8359842 Amendment 2 Figure 8.8-8.13
	Assessment: Evaluated by extracting and analyzing individual lots of blank human urine for interference peak at analyte retention time in absence of LEN and [redacted]			
	Number of total lots tested:	6		
	Range of observed bias	All lots: no interfering peak was ≥ 20% of the mean analyte peak area of the lowest calibration curve standard.		
	Overall result	PASS		

	Matrix Effect:						[redacted]8359842 Amendment 2 Table 7.6
	Assessment: Blank matrix from 6 individuals was used. Each individual blank matrix samples were spiked at the nominal LLOQ concentration and was analyzed without internal standard. All 6 individual matrices tested should demonstrate lack of significant interference (≤ 20.0% of the mean [acceptable] LLOQ calibration standard response and ≤ 5.0% of IS response in the control zero sample) in the chromatographic regions of the analyte and IS. Blank matrix from 6 different individuals, each spiked at the LLOQ QC concentration and analyzed with internal standard. At least 5 individual matrices must generate individual concentration values within ± 20.0% bias (%RE) of the nominal concentration. The mean concentration for the 6 matrices must generate overall mean bias and precision values of ± 20.0% from nominal and RSD% ≤ 20.0%, respectively.						
	Number of total lots tested:	6					
	Range of observed bias: LEN:	%RSD (%CV) ≤ 8.2 for IS normalized responses					
	Overall result	PASS					
Interference and specificity	Not applicable						N/A
Hemolysis effect	Evaluation:	N/A					N/A
	Replicates:	N/A					
Lipemic effect	Evaluation:	N/A					N/A
	Replicates:	N/A					
Dilution linearity and hook effect	**Dilutions**						N/A
	Analyte	Concentration (ng/mL)	Dilution Factor	Replicates	%RE	%CV	
	N/A	N/A	N/A	N/A	N/A	N/A	
	Hook Effect						N/A
	Not applicable						
Bench-top stability	LEN, 2 to 8°C						[redacted]8359842 Amendment 2 Table 7.12
	Hours	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	25 h	15.0 (Low QC)	6	16.2	8.0%	3.8%	
		3750 (High QC)	6	3740	−0.3%	2.0%	
Processed sample stability	LEN, 2 to 8°C						[redacted]8359842 Amendment 2 Table 7.16
	Hours	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	239 h	15.0 (Low QC)	6	15.9	6.0%	4.3%	
		3750 (High QC)	6	3750	1.9%	0.8%	
Freeze-thaw stability	LEN, −10 to −30°C						[redacted]8359842 Amendment 2 Table 7.14
	Freeze/ Thaw Cycles	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	5	15.0 (Low QC)	6	15.9	6.0%	2.2%	
	5	3750 (High QC)	6	3750	0%	2.4%	
	LEN, −60 to −80°C						
	Freeze/ Thaw Cycles	Nominal Concentration (ng/mL)	Replicates	Mean (ng/mL)	%Change From Nominal	%CV	
	5	15.0 (Low QC)	6	15.8	5.3%	3.7%	
	5	3750 (High QC)	6	3720	−0.8%	2.1%	

<table>
<tr><td>Long-term storage stability</td><td>
<table>
<tr><td colspan="6">LEN, −10 to −30°C</td></tr>
<tr><td>Days</td><td>Nominal Concentration (ng/mL)</td><td>Replicates</td><td>Mean (ng/mL)</td><td>Mean % Change From Nominal</td><td>%CV</td></tr>
<tr><td>438</td><td>15.0 (Low QC)</td><td>6</td><td>15.7</td><td>4.7%</td><td>4.1%</td></tr>
<tr><td>438</td><td>3750 (High QC)</td><td>6</td><td>3770</td><td>0.5%</td><td>1.2%</td></tr>
<tr><td colspan="6">LEN, −60 to −80°C</td></tr>
<tr><td>438</td><td>15.0 (Low QC)</td><td>6</td><td>15.9</td><td>6.0%</td><td>4.9%</td></tr>
<tr><td>438</td><td>3750 (High QC)</td><td>6</td><td>3690</td><td>−1.6%</td><td>2.4%</td></tr>
<tr><td colspan="6">SUMMARY: Established Long-Term Storage Stability</td></tr>
<tr><td colspan="2">Analyte</td><td colspan="2">Temperature</td><td colspan="2">Maximum Established Stability</td></tr>
<tr><td colspan="2">LEN</td><td colspan="2">−10 to −30°C</td><td colspan="2">807 Days</td></tr>
<tr><td colspan="2">LEN</td><td colspan="2">−60 to −80°C</td><td colspan="2">807 Days</td></tr>
</table>
</td><td>[redacted]8359842 Amendment 2 Table 7.15</td></tr>
<tr><td>Parallelism</td><td>Not Applicable</td><td>N/A</td></tr>
<tr><td>Carry-over</td><td>Assessment: Two blank matrix samples were analyzed immediately following the highest calibration standard. Minimally this must be towards the end of the run immediately following the highest calibration standard. Minimally this must be towards the end of the run.
Carry-over = Mean observed response signal of injected blanks/mean response signal of LLOQ in same run, expressed as a percentage.
<table>
<tr><td>Replicates:</td><td>2</td></tr>
<tr><td>LEN carry-over:</td><td>Passes acceptance criteria</td></tr>
</table>
</td><td>[redacted]8359842 Amendment 2 Figure 8.7</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td colspan="3">Method Performance in Study GS-US-200-4071
[redacted]8388965 Amendment 1
Determination of GS-6207 in Human Plasma and Urine Samples From GS-US-200-4071</td></tr>
<tr><td>Assay passing rate</td><td>
<table>
<tr><td>Analyte</td><td>Total Runs</td><td>Passing Runs</td><td>Passing rate</td></tr>
<tr><td>LEN</td><td>6</td><td>6</td><td>100%</td></tr>
</table>
</td><td>[redacted]8388965 Amendment 1 Table 10.13</td></tr>
<tr><td>Standard curve performance</td><td>
<table>
<tr><td>Analyte</td><td>Cumulative Bias Range (%RE)</td><td>Cumulative Precision (%CV)</td></tr>
<tr><td>LEN</td><td>−4.2 to 4.0%</td><td>≤4.0%</td></tr>
</table>
</td><td>[redacted]8388965 Amendment 1 Table 10.15</td></tr>
<tr><td>QC performance</td><td>
<table>
<tr><td>Analyte</td><td>Cumulative Bias Range (%RE)</td><td>Cumulative Precision (%CV)</td><td>Total Error</td></tr>
<tr><td>LEN</td><td>−2.7 to 2.0%</td><td>≤4.3%</td><td>N/A</td></tr>
</table>
</td><td>[redacted]8388965 Amendment 1 Table 10.17</td></tr>
<tr><td>Method reproducibility</td><td>Incurred sample reproducibility (ISR) assessment was not performed for method GS07HUP. ISR analysis of human urine samples was removed from the SAP as there were insufficient urine samples with results above the low QC to conduct ISR per the laboratory standard operating procedure (SOP).</td><td>N/A</td></tr>
<tr><td>Study sample analysis/stability</td><td>
<table>
<tr><td>Storage Temperature</td><td>Analyte</td><td>Established Stability</td><td>Maximum Storage for a Sample From This Study</td></tr>
<tr><td>−60°C to −80°C</td><td>LEN</td><td>807 days</td><td>82 days</td></tr>
</table>
</td><td>Validation [redacted]8359842 Amendment 2 Sample Analysis [redacted]8388965 Amendment 1</td></tr>
<tr><td>Standard calibration curve performance during accuracy and precision runs</td><td>Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 5.00, 10.0, 25.0, 150, 2000, 4000, and 5000 ng/mL; each analyzed in 2 replicates.</td><td></td></tr>
</table>

Method Performance in Study GS-US-200-4329 [redacted] 8405056 Amendment 1 Determination of GS-6207 in Human Plasma and Urine Samples From GS-US-200-4329					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8405056 Amendment 1 Table 9.8
	LEN	5	5	100%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**		**Cumulative Precision (%CV)**	[redacted] 8405056 Amendment 1 Table 9.10
	LEN	−3.0 to 3.4%		≤3.7%	
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8405056 Amendment 1 Table 9.12
	LEN	−1.9 to 2.7%	≤3.5%	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was not performed for method GS07HUP. ISR analysis of human urine samples was removed from the SAP as there were insufficient urine samples with results above the low QC to conduct ISR per the laboratory SOP.				N/A
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8359842 Amendment 2 Sample Analysis [redacted] 8388965 Amendment 1
	−60°C to −80°C	LEN	807 days	82 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 5.00, 10.0, 25.0, 150, 2000, 4000, and 5000 ng/mL; each analyzed in 2 replicates.				
Method Performance in Study GS-US-200-4330 [redacted] 8423539 Sample Analysis for the Determination of GS-6207 in Human Plasma and Urine Samples in Support of GS-US-200-4330					
Assay passing rate	**Analyte**	**Total Runs**	**Passing Runs**	**Passing rate**	[redacted] 8423539 Table 9.1
	LEN	14	14	100%	
Standard curve performance	**Analyte**	**Cumulative Bias Range (%RE)**		**Cumulative Precision (%CV)**	[redacted] 8423539 Table 9.3
	LEN	−2.2 to 2.5%		≤6.0%	
QC performance	**Analyte**	**Cumulative Bias Range (%RE)**	**Cumulative Precision (%CV)**	**Total Error**	[redacted] 8423539 Table 9.5
	LEN	−1.9 to 3.0	≤3.4	N/A	
Method reproducibility	Incurred sample reproducibility (ISR) assessment was performed by reanalysis of 11.1% of study samples, and 100.0% of samples (20 of 20) met the prespecified criteria.				[redacted] 8423539 Table 9.13
Study sample analysis/stability	**Storage Temperature**	**Analyte**	**Established Stability**	**Maximum Storage for a Sample From This Study**	Validation [redacted] 8359842 Amendment 2 Sample Analysis [redacted] 8423539
	−60 to −80°C	LEN	807 days	206 days	
Standard calibration curve performance during accuracy and precision runs	Each run used 8 calibration standard concentrations from the LLOQ to the ULOQ of nominal concentrations of 5.00, 10.0, 25.0, 150, 2000, 4000, and 5000 ng/mL; each analyzed in 2 replicates.				

CV = coefficient of variation; HPLC = high-performance liquid chromatography; IS = internal standard; ISR = incurred sample reproducibility; LC-MS/MS = liquid chromatography tandem mass spectrometry; LEN = lenacapavir; LLOQ = lower limit of quantitation; MS/MS = tandem mass spectrometry; N/A = not applicable; QC = quality controls; RE = relative error; RSD = relative standard deviation; SOP = standard operating procedure; ULOQ = upper limit of quantitation

5.4. Summary of Bioanalytical Method Cross-Validations

5.4.1. Summary of LEN Method GS07HPP Modifications and Cross-Validation Results With LEN Method GS7LHPP

<table>
<tr><td>Bioanalytical method validation report name and hyperlink</td><td colspan="5">[redacted] Cross-Validation Report 8406716
Cross-Validation Between Two Validated Methods With Different Curve Ranges for the Determination of GS-6207 in Human Plasma by LC-MS/MS</td></tr>
<tr><td>Changes in method</td><td colspan="5">Assay range</td></tr>
<tr><td>New validated assay range, if any</td><td>Analyte</td><td colspan="2">Method GS07HPP range</td><td colspan="2">Method GS7LHPP range:</td></tr>
<tr><td></td><td>LEN</td><td colspan="2">0.5 to 500 ng/mL</td><td colspan="2">0.100 to 100 ng/mL</td></tr>
<tr><td>Validation parameters</td><td colspan="4">Cross-validation performance</td><td>Source location</td></tr>
<tr><td>Standard calibration curve performance during accuracy and precision runs</td><td>Analyte</td><td colspan="2">Cumulative Accuracy From LLOQ to ULOQ (%RE)</td><td colspan="2">Cumulative Precision From LLOQ to ULOQ (%CV)</td><td>[redacted] Cross-Validation Report 8406716 Table 8.2 and Table 8.3</td></tr>
<tr><td></td><td>Method GS07HPP</td><td>Method GS7LHPP</td><td colspan="2">Method GS07HPP</td><td>Method GS7LHPP</td></tr>
<tr><td></td><td>LEN</td><td>−4.8 to 4.5%</td><td>−2.9 to 4.2%</td><td colspan="2">N/A</td><td>N/A</td></tr>
<tr><td>QC performance during accuracy and precision runs</td><td>Analyte</td><td colspan="2">Cumulative Accuracy in 4 QCs (%RE)</td><td colspan="2">Interbatch Precision in 4 QCs (%CV)</td><td>[redacted] Cross-Validation Report 8406716 Table 8.6 and Table 8.7</td></tr>
<tr><td></td><td>Method GS07HPP</td><td>Method GS7LHPP</td><td colspan="2">Method GS07HPP</td><td>Method GS7LHPP</td></tr>
<tr><td></td><td>LEN</td><td>−5.3 to 9.3%</td><td>−2.3 to 2.0%</td><td colspan="2">N/A</td><td>N/A</td></tr>
<tr><td></td><td>Analyte</td><td colspan="2">% Total Error in 4 QCs</td><td colspan="2"></td><td></td></tr>
<tr><td></td><td></td><td colspan="2">Method GS07HPP</td><td colspan="2">Method GS7LHPP</td><td></td></tr>
<tr><td></td><td>LEN</td><td colspan="2">N/A</td><td colspan="2">N/A</td><td></td></tr>
<tr><td>Cross-validation</td><td colspan="4">Evaluation Specifics (QCs)</td><td></td></tr>
<tr><td></td><td colspan="2">Sample Type:</td><td colspan="2" rowspan="4">See Below</td><td></td></tr>
<tr><td></td><td colspan="2">Number of Samples Analyzed:</td><td></td></tr>
<tr><td></td><td colspan="2">Individual Sample Acceptance Criteria:</td><td></td></tr>
<tr><td></td><td colspan="2">Overall Acceptance Criteria:</td><td></td></tr>
<tr><td></td><td colspan="4">Results (QCs):</td><td></td></tr>
<tr><td></td><td colspan="2">LEN:</td><td colspan="2" rowspan="2">See Below</td><td></td></tr>
<tr><td></td><td colspan="2">Overall Conclusion:</td><td></td></tr>
<tr><td></td><td colspan="4">Cross-validation QC samples of LEN were prepared by [redacted] at 1.50, 10.0, 40 and 75 ng/mL QC concentrations, with 6 QC samples prepared at each concentration level. These cross-validation QC plasma samples were analyzed individually at [redacted] using both plasma methods (Method GS07HPP and Method S7LHPP).
Acceptance criteria: %RSD must be ≤ 15.0% and mean bias values must be within ± 15.0% of the nominal concentration for each QC level.
Results: Mean concentrations of these prepared QCs determined at [redacted] using both plasma methods were within the acceptance criteria of ± 15.0% of the nominal value.
Twenty-one incurred pooled plasma samples with LEN concentrations between 1.50 ng/mL and 75.0 ng/mL were prepared by [redacted] from GS-US-200-4071. These incurred pooled plasma samples were analyzed individually at [redacted] using both plasma methods (Method GS07HPP and Method S7LHPP).</td><td>[redacted] Cross-Validation Report 8406716 Table 8.8 through Table 8.11 and Table 8.12</td></tr>
</table>

	Acceptance criteria: The percent difference between the 2 values obtained from the 2 methods for the same sample must be within ± 15.0% to be considered acceptable. More than two-thirds of the test samples must meet the acceptance criteria. Results: The % difference between the 2 values obtained from the 2 methods for the same sample were within the acceptance criteria of ± 15.0%. Overall Conclusion: Cross-validation QC comparison sample data met acceptance criteria as stated above and are presented in Table 8.8 through Table 8.11 in [redacted] Cross-Validation Report 8406716. Cross-validation comparison of concentrations of LEN in pooled human plasma samples data met acceptance criteria as stated above and are presented in Table 8.12 in [redacted] Cross-Validation Report 8406716. Based on the above cross-validation study data, the two methods (GS07HPP and GS7LHPP) are comparable.		
List other parameters	Not applicable	N/A	N/A
Partial validation	Not applicable	N/A	N/A

CV = coefficient of variation; LC-MS/MS = liquid chromatography tandem mass spectrometry; LEN = lenacapavir; LLOQ = lower limit of quantitation; N/A = not applicable; QC = quality controls; RSD = relative standard deviation; ULOQ = upper limit of quantitation

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.2—SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

LENACAPAVIR

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine
%CV	percentage coefficient of variation
%F	absolute bioavailability
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ARAs	acid-reducing agents
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AUC	area under the concentration versus time curve
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
$AUC_{x\text{-}xx}$	partial area under the concentration versus time curve from time "x" to time "xx"
BCRP	breast cancer resistance protein
BID	twice daily
BLQ	below limit of quantitation
BMI	body mass index
BSEP	bile salt export pump
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
C_0	concentration at time 0 hours
CA	capsid
CAI	capsid inhibitor
CC_{50}	half-maximal cytotoxic concentration
CD4	clusters of differentiation 4
CI	confidence interval
CL	clearance
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{max}	maximum observed concentration of drug
COBI	cobicistat
CPT	Child-Pugh-Turcotte
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval
C_{trough}	concentration at the end of the dosing interval

c-QT	concentration-QT
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRV	darunavir
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
EC_{50}	half-maximal effective concentration
EC_{90}	90% effective concentration
EC_{95}	95% effective concentration
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{MDRD}$	estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation
E_{max}	maximum (pharmacodynamic) effect
EMA	European Medicines Agency
F, FTC	emtricitabine (Emtriva®)
FAM	famotidine
FC	fold change
FDA	Food and Drug Administration
FR	failing regimen
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GLP	good laboratory practice
GLSM	geometric least-squares mean
GSS	genotypic susceptibility score
H2RA	histamine 2 receptor agonist
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HTE	heavily treatment experienced
IC_{50}	half-maximal inhibitory concentration
IN	integrase
INR	international normalized ratio
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
IQR	interquartile range
IRB	institutional review board
IV	intravenous
k_a	first-order absorption
k_{dir}	SC first-order direct absorption rate constant

k_{tr}	SC first-order transit absorption rate constant
LEN	lenacapavir, GS-6207
LLOQ	lower limit of quantitation
MATE	multidrug and toxin extrusion
MDZ	midazolam
MOXI	moxifloxacin
N, n	number of participants in a population (N) or subset (n)
NaS	sodium salt
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOEL	no observed effect level
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OBR	optimized background regimen
OCT	organic cation transporter
OSS	overall susceptibility score
$paEC_{95}$	protein-adjusted 95% effective concentration
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamic
P-gp	P-glycoprotein
PI	protease inhibitor
PIT	pitavastatin
PK	pharmacokinetic(s)
PopPK	population PK
PR	protease
PSS	phenotypic susceptibility score
PWH	people with HIV
Q	intercompartmental clearance
Q1	first quartile
Q3	third quartile
Q4	fourth quartile
QD	once daily
QT (interval)	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
ΔΔQTcF	time-matched, baseline-adjusted, placebo-corrected QTcF
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
QTcI	QT interval corrected for heart rate using participant-specific correction factor
-R	resistant

RAP	Resistance Analysis Population
RIF	rifampin
RNA	ribonucleic acid
ROS	rosuvastatin
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTV	ritonavir
SC	subcutaneous
SD	standard deviation
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TAF	tenofovir alafenamide
TFV	tenofovir
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
TN	treatment-naive
TQT	thorough QT
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
US, USA	United States
V_c	central volume of distribution
V_p	peripheral volume of distribution
VF	virologic failure
VORI	voriconazole
V_z	volume of distribution of the drug after intravenous administration
V_z/F	apparent volume of distribution of the drug
WT	wild-type

1. BACKGROUND AND OVERVIEW

1.1. Background

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38 million people with HIV (PWH) worldwide and approximately 26 million on antiretroviral (ARV) treatment {UNAIDS 2020}{UNAIDS 2020}. Advances in combination ARV therapy (ART) for HIV have led to significant improvements in quality of life among PWH by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. Most currently approved ARV drugs target 1 of the following 4 steps of the HIV lifecycle: the inhibition of viral entry, reverse transcription, viral DNA integration, or the proteolysis of viral polyproteins essential for virion maturation. While combination ART for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality previously associated with HIV disease, there remains a significant medical need for new, well-tolerated therapies that take into consideration HIV genetic variability, ARV resistance, new options for regimen simplification, as well as the desires of PWH for alternative, longer-acting options.

Some treatment-experienced PWH eventually lose the virologic, immunologic, or clinical benefit from their current regimens. People with HIV who have multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {British HIV Association 2016, European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019, Saag 2020, U. S. Department of Health and Human Services 2015}. These challenges are also relevant for adolescents, particularly those with perinatal HIV-1 transmission. Developing safe and effective therapies for heavily treatment-experienced (HTE) PWH with multidrug-resistant HIV remains a priority. For these individuals, newer treatments are needed to control viral replication, preserve immune function, and prevent clinical progression.

Lenacapavir (LEN; GS-6207) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function, which is being developed for the treatment and prevention of HIV-1 infection. Lenacapavir inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

1.2. Overview

Clinical studies contributing to the characterization of the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of LEN are discussed in this summary of clinical pharmacology. These studies are further described in Section 1.3.

This document is organized as follows:

- Section 1: provides an overview of the clinical pharmacology program.

- Section 2: provides summaries of individual clinical studies and population PK (PopPK) analyses.
- Section 3: presents an integrated summary of the clinical pharmacology of LEN.
  - Sections 3.1 to 3.1.3: presents the absorption, metabolism, distribution, and elimination (ADME) characteristics as determined through in vitro, nonclinical, and clinical studies.
  - Section 3.1.4: presents single- and multiple-dose PK of LEN
  - Section 3.1.5: describes the PopPK
  - Sections 3.1.6 and 3.1.7 present PK across various populations and the effects of intrinsic and extrinsic factors, including the following:
    - Section 3.1.6.3.1: describes the effect of renal impairment on the PK of LEN
    - Section 3.1.6.3.2: describes the effect of hepatic impairment on the PK of LEN
    - Section 3.1.7.1: describes the effect of food on the PK of LEN
    - Section 3.1.7.2: describes known and potential drug-drug interactions (DDIs) for LEN
  - Section 3.2: describes the PK-PD relationships, with efficacy and safety parameters discussed in Sections 3.2.2 and 3.2.3, respectively
- Sections 4.1 and 4.2: present the nonclinical and clinical virology of LEN, respectively.

Pharmacokinetic studies related to biopharmaceutics are referenced in this summary and are discussed in detail in the Summary of Biopharmaceutic Studies (m2.7.1).

1.3. Clinical Pharmacology Program

1.3.1. Human Biomaterials Studies

Nonclinical studies using human biomaterials are discussed in detail, and in the context of PK data in other species, in the Nonclinical Pharmacokinetics Written Summary (m2.6.4). Results of studies using human biomaterials pertinent to clinical PK (eg, ADME, DDI liability) are included in this summary.

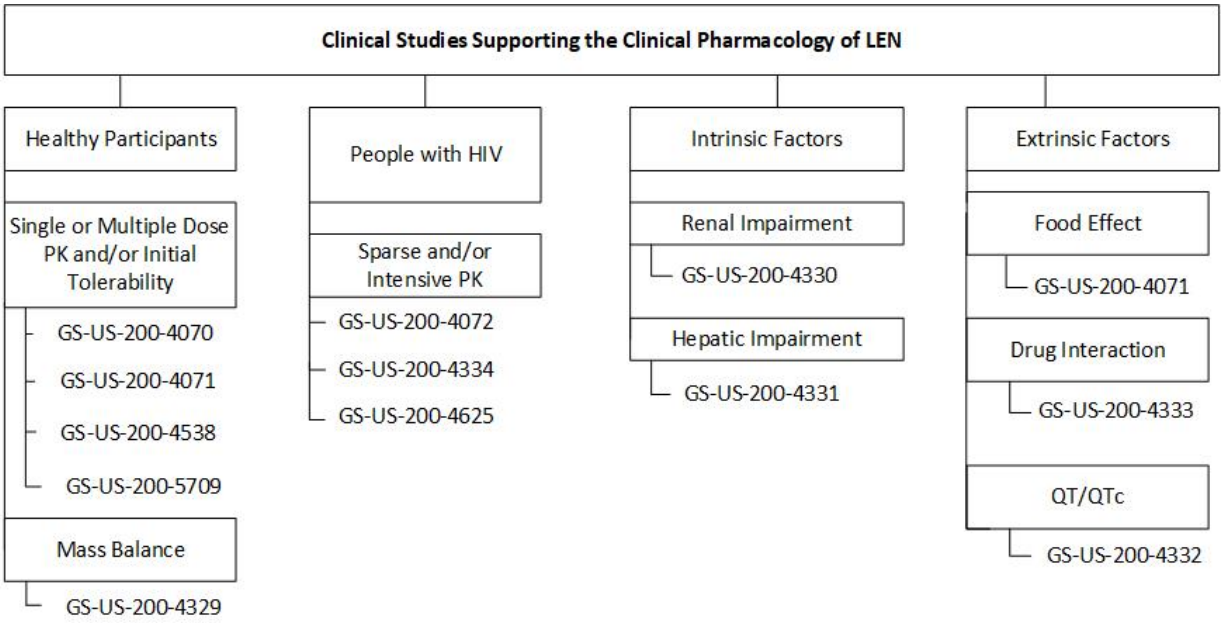
1.3.2. Bioanalytical Methods

The bioanalytical methods used for the determination of plasma or urine concentrations of LEN from clinical studies are described in m2.7.1, Section 1.3. An overview of the validated bioanalytical methods used for the determination of plasma or urine concentrations of LEN in the individual clinical studies is provided in m2.7.1, Appendix 5.2.

1.3.3. Clinical Pharmacology Studies of LEN

Figure 1 and Table 1 summarize the 12 clinical studies that characterize the clinical pharmacology of LEN both with respect to participant population and specific type of clinical pharmacology assessment. Summaries of each of these studies are available in Section 2 and in the tabular summary of clinical pharmacology studies in Appendix 6.1. Information regarding LEN formulations used throughout clinical development is provided in m2.7.1.

Figure 1. Clinical Studies Supporting the Clinical Pharmacology of LEN by Study Type and Study Population



LEN = lenacapavir; PK = pharmacokinetics

Table 1. Overview of Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of LEN

Study Number/ Location	Study Description	Test Treatment(s)				Reference Treatment(s) Dose and Formulation
		Dosage Form	Batch Number	Dose	n[a]	
GS-US-200-4070 (m2.7.1, Section 2.1.1)	Phase 1 placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and PK of SC LEN in healthy participants	LEN 100-mg/mL suspension	[redacted]	30 mg 100 mg 300 mg 450 mg	32	Placebo suspension
GS-US-200-4071 (m2.7.1, Section 2.2.1)	Phase 1 single- and multiple-dose study evaluating the safety, tolerability, and PK of various LEN oral formulations and the effect of food on the PK of LEN oral tablets in healthy participants	LEN 50-mg/mL capsules	[redacted]	30 mg 100 mg 300 mg	88	Placebo capsule
		LEN 100-mg/mL capsules	[redacted]	75 mg 300 mg		Placebo capsule
		LEN 50-mg tablet	[redacted]	50 mg		Placebo tablet
		LEN 300-mg tablet	[redacted]	300 mg 900 mg 1800 mg		Placebo tablet
GS-US-200-4072 (Section 2.3.1)	Phase 1b randomized, double-blind, placebo-controlled monotherapy study in PWH (Part A)	LEN 100-mg/mL injectable suspension	[redacted]	20 mg 50 mg 150 mg 450 mg 750 mg	29	Placebo injectable suspension
GS-US-200-4329 (Section 2.2.1)	Phase 1 mass-balance study to evaluate the PK, metabolism, and excretion of a single intravenous dose of radiolabeled [^{14}C]-LEN in healthy participants	LEN 3-mg/mL solution	[redacted]	10 mg	18	Placebo solution
		[^{14}C]LEN 3-mg/mL[c] solution (~30 µCi/mL)	[redacted]	20 mg		Not applicable
GS-US-200-4330 (Section 2.4.1)	Phase 1 study to evaluate the PK of single-dose LEN in participants with normal and severe renal impairment	LEN 300-mg tablet	[redacted]	300 mg	20	Not applicable
GS-US-200-4331 (Section 2.4.2)	Phase 1 study to evaluate the PK of single-dose LEN in participants with normal or impaired hepatic function	LEN 300-mg tablet	[redacted]	300 mg	20	Not applicable
GS-US-200-4332 (Section 2.2.2)	Phase 1 study to evaluate the effect of LEN on QT/QTc interval in healthy participants	LEN 300-mg tablet Moxifloxacin 400-mg tablet	[redacted]	600 mg	97	Placebo tablet Moxifloxacin 400-mg tablet Placebo moxifloxacin tablet

Study Number/ Location	Study Description	Test Treatment(s)				Reference Treatment(s) Dose and Formulation
		Dosage Form	Batch Number	Dose	n[a]	
GS-US-200-4333 (Section 2.5.1)	Phase 1 study to evaluate the effect of transporters and cytochrome P450 enzyme inhibitors on the PK and safety of LEN in healthy participants	LEN 300-mg tablet LEN 50-mg capsule	[redacted]	300 mg	291	LEN 50-mg capsule LEN 300-mg tablet PIT 2-mg tablet ROS 5-mg tablet TAF 25-mg tablet MDZ 2-mg/mL oral syrup
		COBI 150-mg tablet	[redacted]	150 mg		
		DRV/COBI 800/150-mg tablet	[redacted]	800/150 mg		
		VORI 200-mg tablet	[redacted]	200 mg 400 mg		
		ATV/COBI 300/150-mg tablet	[redacted]	300/150 mg		
		RIF 300-mg tablet	[redacted]	600 mg		
		EFV 600-mg tablet	[redacted]	600 mg		
		FAM 40-mg tablet	[redacted]	40 mg		
		PIT 2-mg tablet	[redacted]	2 mg		
		ROS 5-mg tablet	[redacted]	5 mg		
		TAF 25-mg tablet	[redacted]	25 mg		
		MDZ 2-mg/mL oral syrup	[redacted]	2.5 mg		
GS-US-200-4538 (m2.7.1, Section 2.1.2)	Phase 1 placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and PK of SC solutions of LEN in healthy participants	LEN SC Formulation 1 (300 mg/mL, FA)	[redacted]	300 mg	100	Placebo SC Formulation
		LEN SC Formulation 2 (309 mg/mL, NaS)	[redacted]	309 mg 927 mg		Placebo SC Formulation
		LEN SC Formulation 3 (155 mg/mL, NaS)	[redacted]	309 mg 927 mg		Placebo SC Formulation
		LEN SC Formulation 4 (300 mg/mL, NaSP)	[redacted]	900 mg		Placebo SC Formulation
		LEN SC Formulation 6 (75 mg/mL, NaSP)	[redacted]	75 mg 225 mg		Placebo SC Formulation
		LEN SC Formulation 7 (50 mg/mL, NaSP)	[redacted]	50 mg		Placebo SC Formulation

Study Number/ Location	Study Description	Test Treatment(s)				Reference Treatment(s) Dose and Formulation
		Dosage Form	Batch Number	Dose	n[a]	
GS-US-200-5709 (Section 2.2.3)	Phase 1 study to evaluate the safety, tolerability, and PK of multiple-dose oral and/or SC LEN in healthy participants	LEN 300-mg tablet	[redacted]	300 mg 600 mg	60	Not applicable
		LEN SC (309 mg/mL, NaS)	[redacted]	927 mg		
GS-US-200-4334 (m2.7.3, Section 2.2)	Phase 2 randomized, open-label, active-controlled study evaluating the safety and efficacy of LEN in combination with other antiretroviral agents in PWH	LEN 300-mg tablet	[redacted]	50 mg 300 mg 900 mg	182	BVY 50/200/25-mg tablet[e]
		LEN 50-mg tablet	[redacted]			
		LEN SC (309 mg/mL, NaS)	[redacted]	927 mg		
		DVY 200/25-mg tablet	[redacted]	200/25 mg		
		TAF 25-mg tablet	[redacted]	25 mg		
		BIC 75-mg tablet	[redacted]	75 mg		
GS-US-200-4625 (m2.7.3, Section 2.1)	Phase 2/3 randomized, placebo-controlled study to evaluate the safety and efficacy of LEN in combination with an optimized background regimen in heavily treatment-experienced PWH with multidrug resistance	LEN 300-mg tablet	[redacted]	300 mg 600 mg	72	Placebo tablet
		LEN SC (309 mg/mL, NaS)	[redacted]	927 mg		

ATV = atazanavir; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); COBI = cobicistat; DRV = darunavir; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); EFV = efavirenz; FA = free acid; FAM = famotidine; LEN = lenacapavir; MDZ = midazolam; NaS = sodium salt; NaSP = sodium salt with poloxamer; PK = pharmacokinetics; PIT = pitavastatin; PWH = people with HIV; RIF = rifampin; ROS = rosuvastatin; SC = subcutaneous; TAF = tenofovir alafenamide; VORI = voriconazole

a Number of participants who were administered any test treatment.
b LEN free acid batch used for clinical compounding. Drug substance lot number 6207-A-1R was used to compound the NaSP formulations (Formulations 4, 6, and 7).
c Participants received a single dose of LEN 20 mg containing a mixture of both unlabeled LEN and [^{14}C]LEN (equivalent to approximately 200 µCi).
d Formulation 3 was compounded from Formulation 2.
e Administered to Treatment Group 4

1.4. Virology Introduction

A comprehensive program of nonclinical experiments and clinical studies characterized the antiviral activity of LEN.

1.4.1. Nonclinical Virology

Nonclinical virology studies characterized the antiviral activity of LEN against laboratory strains and clinical isolates (wild-type [WT] and drug-resistant strains) of HIV-1 and other viruses in target cell lines and primary cell cultures (eg, peripheral blood mononuclear cells [PBMCs]). These studies characterized the following specific PD characteristics:

- Primary PD: mechanism of action, antiviral activity against HIV (WT and drug-resistant strains), including drug-resistance selections (Section 4.1.1)
- Secondary PD: cytotoxicity and effect against non-HIV viruses (Section 4.1.2)
- PD drug interactions (Section 4.1.3)

The detailed characterization of nonclinical virology is presented in Nonclinical Pharmacology Written Summary (m2.6.2) and Nonclinical Pharmacology Tabulated Summary (m2.6.3).

1.4.2. Clinical Virology

Clinical virology analyses were performed for PWH with data from 1 Phase 2/3 study (GS-US-200-4625), 1 Phase 2 study (GS-US-200-4334), and 1 Phase 1 study (GS-US-200-4072). Resistance analyses were performed on plasma HIV-1 isolates from all participants who met prespecified criteria. Results from these analyses are provided in Section 4.2.1.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Studies pertinent to the PK of LEN using human biomaterials are discussed in detail and in the context of PK data in other species in m2.6.4. References to using human biomaterials pertinent to clinical PK are also included in this summary as appropriate (Section 3).

2.2. Studies in Healthy Participants

2.2.1. Study GS-US-200-4329

Location:	GS-US-200-4329 Final
Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Metabolism and Excretion of IV GS-6207 in Healthy Subjects
Primary Objective(s):	• To evaluate the PK of lenacapavir (LEN, GS-6207) (and metabolites, if applicable) following single ascending intravenous (IV) doses of LEN or a single IV dose of radiolabeled [^{14}C]LEN • To determine the mass balance of LEN following administration of a single IV dose of radiolabeled [^{14}C]LEN
Study Design and Participant Population:	This Phase 1 study in healthy participants was performed in 2 parts, as follows: Study Part A was a randomized, blinded (sponsor unblinded), placebo-controlled, single ascending dose study, and Study Part B was an open-label, mass-balance study. In Study Part A, the safety, tolerability, and PK of LEN following administration of a single IV dose of LEN were evaluated, and in Study Part B, the mass balance, metabolite profile, route of elimination, and PK of LEN in humans following administration of a single IV dose of radiolabeled [^{14}C]LEN were evaluated. In Part A, eligible participants were randomized in an 8:3 ratio to receive LEN or placebo. A single dose of LEN or placebo was administered as a 1-hour IV infusion on the morning of Day 1. The study treatments within each cohort were as follows:

	Participants	Single Ascending Doses
Cohort	**Active:Placebo**	**Day 1**
1	8:3	10 mg LEN or placebo
2[a]	8:3	Up to 30 mg LEN or placebo

LEN = lenacapavir
a Based on review of PK data from Cohort 1, LEN concentrations were reasonably close to the desired dose in Study Part B. The dose selected for Study Part B (20 mg) was less than 3-fold higher than the dose evaluated in Cohort 1, and therefore, initiation of Cohort 2 was not required.

In Part B, eligible participants received a single IV dose of LEN 20 mg, containing a mixture of both unlabeled LEN and [^{14}C]LEN (equivalent to approximately 200 µCi).

Eligible participants were healthy, nonsmoking (≥ 90 days), male and nonpregnant, nonlactating female participants aged 18 to 55 years, inclusive (Study Part A only), or male participants aged 18 to 45 years, inclusive (Study Part B), with body mass index (BMI) of ≥ 19 and ≤ 30 kg/m^2, normal 12-lead electrocardiogram (ECG) or an ECG with abnormalities deemed clinically insignificant by the investigator, normal renal function (estimated creatinine clearance [CL_{cr}] calculated using the Cockcroft-Gault equation [≥ 90 mL/min]), and no significant medical history. Participants were also in good general health as determined by the investigator at the screening evaluation performed no more than 28 days prior to the scheduled first dose of study drug.

Summary of Results and Conclusions:	**Pharmacokinetic Results:** Following a single dose of [^{14}C]LEN (20 mg; approximately 200 μCi), the median T_{max} of drug-derived radioactivity in both whole blood and plasma was 1.00 hour postdose; mean values for C_{max} were 149 and 248 ng eq/g, respectively. Mean whole blood-to-plasma concentration ratios of [^{14}C]-radioactivity ranged from 0.500 to 0.695 through 336 hours postdose, indicating low association of radioactivity with red blood cells. A mean 75.9% of the dose was recovered in feces and 0.237% was recovered in urine through the last collection interval, indicating that fecal elimination is the primary elimination route of LEN and its metabolites. Most of the administered radioactive dose was recovered in the first 1608 hours postdose (74.7% in feces and urine combined). Plasma PK parameters of LEN were as expected, dose proportional for the AUC_{inf} across the single dose of LEN 10 mg and 20 mg (2338.6 and 4373.3 h*ng/mL, respectively), and similar to historical data. Lenacapavir was metabolized via oxidation, N-dealkylation, hydrogenation, amid hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation. In the AUC-pooled plasma sample ($AUC_{0\text{-}1176h}$), a large percentage of the circulating radioactivity (68.8%) was associated with unchanged LEN. No single metabolite contributed > 10% of total radioactivity exposure through 1176 hours postdose. The profile of radioactivity in the AUC-pooled plasma sample showed 2 minor radioactive peaks (P9 and P11) that were identified as likely LEN photolysis and/or radiolysis degradant products [redacted], [redacted] and [redacted], which co-eluted together, respectively, each of which contributed to < 10% of the total exposure. The remaining unidentified minor components each contributed to < 2% of the total radioactivity exposure (approximately 12% in total). The total radioactivity exposure from the sum of all identified components in the plasma was approximately 88%. Adjusting for the 75.9% mean cumulative fecal recovery of the administered radioactive dose, LEN and the LEN-hexose conjugate metabolite (M42, M35) were the 2 most abundant components recovered in the feces and accounted for a mean abundance of 43.4% (32.9% of dose) and 8.7% (6.6% of dose) of the administered [^{14}C]-dose, respectively. Other metabolites were identified in feces, each of which accounted for < 2% of the dose.
	Conclusions: The conclusions from Study GS-US-200-4329 are as follows: • Lenacapavir exhibited dose proportional increases in plasma exposure between the 10-mg and 20-mg dose. • Lenacapavir was primarily eliminated in the feces (75.9%), renal excretion being a minor pathway (0.237%). • The predominant species circulating in plasma was unchanged LEN (68.8%); no single circulating metabolite accounted for > 10% of plasma drug-related exposure. • Intravenously administered LEN was generally safe and well tolerated.

2.2.2. Study GS-US-200-4332

Location:	GS-US-200-4332 Final
Title:	A Phase 1, Double-Blinded, Randomized, Placebo- and Positive-Controlled, Parallel Study With Nested Crossover Design to Evaluate the Effect of Lenacapavir (LEN) on the QT/QTc Interval in Healthy Participants
Primary Objective(s):	• To evaluate the effect of LEN on time-matched, baseline-adjusted, placebo-corrected QTcF
Study Design and Participant Population:	This Phase 1, double-blinded, randomized, placebo- and positive-controlled, 3-sequence, parallel (with nested crossover), multiple-dose study evaluated the effect of LEN on the QT/QTc interval in healthy participants. Eligible participants in each group were randomized in a 2:1:1 manner to treatment sequences 1, 2, and 3, respectively. Participants and study staff responsible for the study administration were blinded to all treatments for the entire duration of the study. The study treatments were as follows: • Treatment A (Positive Control): Single oral dose of moxifloxacin 400 mg (MOXI; 1 × 400-mg tablet), under fed conditions, in the morning. • Treatment B (Placebo Control-1): Single oral dose of placebo-to-match (PTM) MOXI (1 tablet), under fed conditions, in the morning. • Treatment C (Therapeutic and Supratherapeutic Exposure to LEN): Administration of LEN 600 mg (2 × 300-mg tablet) twice daily for 8 days, under fed conditions. The PM dose was administered 12 hours after the AM dose. The last dose of LEN was administered in the AM on the eighth day of treatment (Day 12). • Treatment D (Placebo Control-2): Administration of PTM LEN (2 tablets) twice daily for 8 days, under fed conditions. The PM dose was administered 12 hours after the AM dose. The last dose of PTM LEN was administered in the AM on the eighth day of treatment (Day 12). The study enrolled an approximately even distribution of healthy male and nonpregnant, nonlactating female participants, with a BMI of ≥ 19.0 and ≤ 30.0 kg/m^2, normal 12-lead ECG (or one with clinically insignificant abnormalities, other than those specified in the exclusion criteria, as determined by the investigator), normal renal function (CL_{cr} ≥ 90 mL/min using the Cockcroft-Gault equation), and no significant medical history. A total of 97 participants were randomized into this study, and 95 participants received study drug and completed the study.
Summary of Results and Conclusions:	**Pharmacokinetic/Pharmacodynamic Results:** Twice-daily administration of oral LEN 600 mg for up to 8 days resulted in C_{max} values that were approximately 2.2- and 8.8-fold higher on Study Days 6 and 12, respectively, in comparison with the therapeutic C_{max} derived from PopPK estimates from the Phase 2/3 registrational study in HTE PWH. Likewise, LEN AUC_{tau} on Study Days 6 and 12 of this study was approximately 3.5- and 15.0-fold higher, respectively, relative to the Phase 2/3 therapeutic exposure estimate. Overall, the exposure to LEN achieved in this study was deemed more than adequate to cover the supratherapeutic exposures in the case of an overdose, unexpected/additional DDI(s), or in the setting of organ dysfunction. The PD analysis demonstrated the expected effect of the single dose of MOXI (positive control) on QTcF interval, indicating that the study had the sensitivity to detect small changes in the corrected QT interval. Assay sensitivity was established by the MOXI response in which the lower bound of the 2-sided 96.67% CI (or equivalently, lower bound of the 1-sided 98.33% CI) for the mean difference of change from the time-matched, baseline-adjusted QTcF between MOXI and PTM MOXI was above 5 msec at 2 out of the 3 prespecified time points.

The primary analysis evaluated the effect of LEN on time-matched, baseline-adjusted, and placebo-corrected QTcF. The upper limit of the 2-sided 90% CIs (or equivalently, upper limit of the 1-sided 95% CI) for the time-matched, baseline-adjusted mean differences in QTcF between LEN and PTM LEN was slightly above 10 msec at ≤ 3 postdose time points on Study Days 6 and 12. Exploratory noninferiority evaluation using the individual-specific QTcI correction showed the upper bounds of the 2-sided 90% CIs (or equivalently, upper bounds of the 1-sided 95% CIs) were below 10 msec at all time points on Study Day 6, and marginally above 10 msec at 2 out of the 9 postdose time points on Study Day 12, thereby not meeting noninferiority at those time points. On Study Day 12 at the supratherapeutic exposure (9-fold higher than the therapeutic exposure to LEN), the maximum mean (upper bound of the 2-sided 90% CIs) increase in baseline-adjusted, placebo-corrected QTcF interval was 7.9 (11.9) msec. Accordingly, the lack of QTc prolongation effect of LEN was not ruled out based on the prespecified model.

However, this prespecified model did not appropriately adjust for baseline imbalance in QTc, which was large and unexpected. As such, time-matched baseline QTc as the covariate in the prespecified model was replaced with the averaged baseline QTc in the post hoc model, which led to less bias and improved precision. In the post hoc models, estimated QTc effects were less than or equal to 5 msec with upper bounds of QTc effects below 10 msec for all time points on Study Days 6 and 12. On Study Day 12 at the supratherapeutic dose, the maximum mean (upper bound of the 2-sided 90% CIs) increase in QTcF using participant level average-baseline adjustment was 5.0 (8.0) msec.

Furthermore, the concentration-QT (c-QT) analyses showed a lack of association between plasma concentrations of LEN and time-matched, baseline-adjusted, placebo-corrected QTcF over a wide range of concentrations (nearly 0.2- to 18-fold of the mean therapeutic C_{max} derived from the PopPK modeling estimates from the Phase 2/3 study in HTE PWH in the prespecified and the more robust post hoc model [$P = 0.092$ and $P = 0.3592$, respectively]). With increasing LEN concentrations, there was no evidence of QTc prolongation. Moreover, in the prespecified model at the maximum observed LEN C_{max} in this study (which is about 3.5-fold higher than the maximum LEN concentration expected with the Phase 2/3 dosing regimen derived from PopPK estimates), mean ΔΔQTcF was predicted to be approximately 3.70 msec, and the upper bound of the 2-sided 90% CI of ΔΔQTcF was notably below 10 msec (5.81 msec). These data are consistent with the projections from a more robust c-QT model, wherein the upper bound of the 2-sided 90% CIs of ΔΔQTcF remained below 10 msec at the therapeutic and supratherapeutic concentrations of LEN. Specifically, at supratherapeutic exposures (9-fold higher than the therapeutic exposures), mean ΔΔQTcF was predicted to be 2.63 msec, and the upper bound of the 2-sided 90% CI of ΔΔQTcF was 4.81 msec. Additionally, LEN administration was not associated with clinically significant ECG changes in this study.

In summary, the totality of data indicates that LEN does not have a clinically relevant effect on QTc.

Conclusions:

The conclusions from Study GS-US-200-4332 are as follows:

- Twice-daily administration of oral LEN 600 mg for 8 days (Study Days 5 to 12) was generally well tolerated in healthy participants.
- Lenacapavir systemic exposures achieved in this study were deemed as more than adequate to cover the supratherapeutic exposures in the event of a LEN overdose, any additional/unexpected DDI(s), or in the setting of organ dysfunction.
- The expected increase in QTc upon administration of MOXI demonstrated assay sensitivity.
- In the prespecified model, noninferiority of QTcF on LEN versus placebo was not met at a few postdose time points. However, in the post hoc model with a more robust adjustment, noninferiority of QTcF on LEN versus placebo was met at all postdose time points.

	• In the prespecified or post hoc model, the concentration-QTc analyses did not demonstrate any positive association between plasma concentrations of LEN and change in QTcF over a wide range of concentrations ($P = 0.092$ and $P = 0.3592$, respectively). • In the post hoc model of concentration QT analyses, at supratherapeutic exposures to LEN (9-fold higher than the therapeutic exposures), mean ΔΔQTcF was predicted to be 2.63 msec, and the upper bound of the 2-sided 90% CI of ΔΔQTcF was 4.81 msec. • The totality of data indicates that LEN does not have a clinically relevant effect on QTcF.

2.2.3. Study GS-US-200-5709

Location:	GS-US-200-5709 Interim
Title:	A Phase 1 Study in Healthy Participants to Evaluate the Safety, Tolerability and Pharmacokinetics of Lenacapavir (LEN)
Primary Objective(s):	• To characterize the PK of multiple-dose oral and SC LEN • To evaluate the safety and tolerability of multiple-dose oral and SC LEN
Study Design and Participant Population:	This is an ongoing, Phase 1, open-label, multicohort, multidose oral and/or SC LEN study to evaluate the safety and tolerability of multiple-dose oral and SC LEN and to characterize the PK of multiple-dose oral and SC LEN in healthy participants. Participants were enrolled in 1 of 3 cohorts: • Cohort 1: Participants received oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2, 300 mg (1 × 300-mg tablet) on Day 8, and SC LEN 927 mg (2 × 1.5 mL 309 mg/mL sodium salt [NaS]) on Day 15, followed by a washout period (Days 16 to 463 [± 5 days]). • Cohort 2: Participants received SC LEN 927 mg (2 × 1.5 mL 309 mg/mL NaS) and oral LEN 600 mg (2 ×300-mg tablets) on Days 1 and 2, followed by a washout period (Days 3 to 743 [± 5 days]). • Cohort 3: Participants received oral LEN 600 mg (2 × 300-mg tablets) twice daily on Days 1 to 10 and oral LEN 600 mg (2 × 300-mg tablets) once on Day 11. Eligible participants were healthy male and nonpregnant, nonlactating female, between 18 to 45 years, with BMI of ≥ 19.0 and ≤ 30.0 kg/m^2, normal 12-lead ECG or an ECG with abnormalities deemed clinically insignificant by the investigator, normal renal function (CL_{cr} ≥ 90 mL/min estimated using the Cockcroft-Gault equation), liver biometric tests such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin below the upper limit of normal at screening, and no significant medical history. Participants were also in good general health as determined by the investigator at the screening evaluation performed no more than 28 days prior to the scheduled first dose of study drug. The interim clinical study report (CSR) summarizes the interim analysis conducted on ongoing data from Cohort 1 (Treatment A; through [redacted]20[redacted]), ongoing data from Cohort 2 (Treatment B; through [redacted]20[redacted]), and final data from Cohort 3 (Treatment C). The number of participants enrolled and treated by cohort were: • Cohort 1: As of [redacted]20[redacted], a total of 31 participants were enrolled into Cohort 1. All 31 participants received treatment, and 30 participants completed study drug (1 participant prematurely discontinued study drug due to an adverse event [AE]). • Cohort 2: As of [redacted]20[redacted], a total of 14 participants were enrolled into Cohort 2 and all participants received treatment and completed study drug. • Cohort 3: A total of 15 participants were enrolled into Cohort 3 and all participants received treatment and completed the study.

Summary of Results and Conclusions:	**Pharmacokinetic Results:** **Cohort 1** For Cohort 1, the dosing regimen comprised oral LEN 600 mg daily dosing (Days 1 and 2), an oral LEN 300-mg dose (Day 8), and SC LEN 927 mg (Day 15). Mean LEN predose concentration and the lower bound 90% CI exceeded inhibitory quotient of 1 (IQ1), the protein-adjusted 95% effective concentration ($paEC_{95}$) on Day 2 and inhibitory quotient of 4 (IQ4) (4-fold higher than $paEC_{95}$) on Days 8 and 15. Mean LEN concentrations and their lower bound 90% CIs achieved IQ4 postdose on Day 2, and this was maintained through Week 18. Following SC administration on Day 15, preliminary PK data indicate C_{max} was achieved approximately 70 days (median T_{max}) postdose. During the 14-day oral lead-in period, mean $AUC_{0\text{-}14d}$ (%CV) was 7949.3 h*ng/mL (42.0%). **Cohort 2** For Cohort 2, the dosing regimen comprised SC LEN 927 mg and oral LEN 600 mg on Day 1, followed by oral LEN 600 mg on Day 2. Mean LEN plasma concentrations and their lower bound 90% CIs achieved IQ4 within 2 hours postdose on Day 2, and this was maintained through Day 15. From Days 0 to 14, mean $AUC_{0\text{-}14d}$ (%CV) was 8635.0 h*ng/mL (28.7%), was comparable with Cohort 1 (7949.3 h*ng/mL [42.0%]), and was in-line with the simulated profile from noncompartmental analysis based simulations. **Cohort 3** For Cohort 3, the dosing regimen comprised oral LEN 600 mg twice daily dosing (Days 1 through 10), followed by an oral LEN 600-mg dose in the morning on Day 11. Mean LEN plasma concentrations achieved therapeutic exposure by Day 3 and supratherapeutic exposures by Day 8. Consistent with its long half-life, LEN exhibited significant accumulation over the course of 10 days with twice daily dosing; C_{max} and $AUC_{0\text{-}12h}$ were 53-fold and 72-fold higher, respectively, on Day 11 than on Day 1.
	Conclusions: The conclusions from this interim analysis of Study GS-US-200-5709 are as follows: • Lenacapavir administered as a SC injection or as tablets was generally safe and well tolerated. • In Cohort 1, exposures with the lower bound 90% CIs of mean concentrations 4-fold higher than the $paEC_{95}$ were achieved within a few days of dosing initiation and were maintained through Week 18. • In Cohort 2, mean LEN plasma concentrations and their lower bound 90% CIs achieved IQ4 within 2 hours postdose on Day 2, and this was maintained through Day 15. • Pharmacokinetics was comparable between Cohort 2 (a simplified regimen) and Cohort 1 (the Phase 2/3 regimen for the HTE indication). • In Cohort 3, LEN exhibited significant accumulation over the course of 10 days twice daily oral dosing; C_{max} and $AUC_{0\text{-}12h}$ were 53-fold and 72-fold higher, respectively, on Day 11 than on Day 1.

2.3. Studies in People With HIV

2.3.1. Study GS-US-200-4072

Location:	GS-US-200-4072 Final
Title:	A Phase 1b Randomized, Double-Blinded, Placebo Controlled, Multi-Cohort Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-6207 Administered Subcutaneously in HIV-1 Infected Subjects
Primary Objective(s):	**Part A (Cohorts 1-5)** • To evaluate the short-term antiviral activity of LEN compared with placebo, with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in adult PWH who were ARV treatment naive or were experienced but capsid inhibitor (CAI) naive **Part B (Cohorts 6-8)** (Part B results are not included in this document) • To evaluate the short-term antiviral activity of tenofovir alafenamide (TAF) with respect to the maximum reduction of plasma HIV-1 RNA (log_{10} copies/mL) from Day 1 through Day 10 in adult PWH who were ARV treatment naive or were experienced but without resistance to TAF
Study Design and Participant Population:	This was a randomized, double-blinded, placebo-controlled, multicenter, multicohort study of LEN (Part A). In Part A (Cohorts 1-5), participants in each cohort (n = 8) were randomized in a 3:1 ratio to receive active LEN (n = 6) or placebo (n = 2). A single SC dose of LEN or placebo was administered in the abdomen on Day 1. The LEN doses evaluated in Cohorts 2 through 5 were determined based on cumulative safety data (through at least Day 14) and available PK and antiviral activity data from previous cohorts, as well as available safety data (through at least Day 14) and PK data from Study GS-US-200-4070. Doses of LEN 150, 50, 450, 20, and 750 mg were administered in Cohorts 1, 2, 3, 4, and 5, respectively. Duration of dosing was 1 day. All study participants underwent study visits through Day 225. All participants initiated once-daily bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF, Biktarvy® [BVY]) on Day 10 after completion of all assessments and continued dosing through Day 225, as a standard-of-care oral combination ART to mitigate the potential risks of developing resistance to LEN. Eligible participants had plasma HIV-1 RNA ≥ 5000 copies/mL but ≤ 400,000 copies/mL and CD4 cell count > 200 cells/mm^3; were ARV treatment naive or experienced but integrase strand-transfer inhibitor (INSTI) naive, and had not received any anti-HIV treatment within 12 weeks prior to screening; had a screening genotype report that showed sensitivity to BVY and at least 1 agent in the nonnucleoside reverse transcriptase inhibitor or protease inhibitor classes such that a viable standard-of-care ARV treatment could be given in the future; had adequate renal function (estimated glomerular filtration rate [eGFR] ≥ 70 mL/min); had no clinically significant abnormalities in ECG at screening; were not pregnant or lactating; and were willing to initiate BVY on Day 10 after completion of all assessments.
Summary of Results and Conclusions:	**Efficacy Results:** A summary of the efficacy end points following administration of LEN 20, 50, 150, 450, and 750 mg subcutaneously is presented in the Table below. Overall, antiviral activity was comparable across the dose range of 50 to 750 mg. All but 1 participant who received LEN had a maximum reduction of ≥ 1 log_{10} copies/mL in their HIV-1 RNA through Day 10; the participant who did not have a maximum reduction of ≥ 1 log_{10} copies/mL received LEN 20 mg. The maximum reduction of HIV-1 RNA from Days 1 through 10 was significantly greater for each of the LEN treatment groups versus placebo. The mean (SD) maximum reductions from baseline through Day 10 were as follows: LEN 20 mg −1.35 (0.318) log_{10} copies/mL; LEN 50 mg −1.79 (0.476) log_{10} copies/mL; LEN 150 mg −1.76 (0.203) log_{10} copies/mL; LEN 450 mg −2.20 (0. 468) log_{10} copies/mL; LEN 750 mg −2.26 (0.662) log_{10} copies/mL; placebo −0.17 (0.128) log_{10} copies/mL.

A total of 3 participants achieved HIV-1 RNA < 50 copies/mL by Day 10 (1 participant in each of the LEN 50 mg, 450 mg, and 750 mg groups). No participant in the other LEN or placebo groups achieved HIV-1 RNA < 50 copies/mL by Day 10.

Efficacy End Points	**LEN 20 mg (N = 6)**	**LEN 50 mg (N = 6)**	**LEN 150 mg (N = 6)**	**LEN 450 mg (N = 6)**	**LEN 750 mg (N = 5)**	**Placebo (N = 10)**
Maximum Reduction From Baseline HIV-1 RNA (log_{10} copies/mL)						
Mean (SD)	−1.35 (0.318)	−1.79 (0.476)	−1.76 (0.203)	−2.20 (0.468)	−2.26 (0.662)	−0.17 (0.128)
Participants Achieving HIV-1 RNA < 50 copies/mL by Day 10						
< 50 copies/mL	0	1 (16.7%)	0	1 (16.7%)	1 (20.0%)	0
≥ 50 copies/mL	6 (100.0%)	5 (83.3%)	6 (100.0%)	5 (83.3%)	4 (80.0%)	10 (100.0%)
Change From Baseline in HIV-1 RNA (log_{10} copies/mL) at Day 10						
Mean (SD)	−1.29 (0.349)	−1.79 (0.476)	−1.76 (0.203)	−2.14 (0.476)	−2.26 (0.662)	−0.08 (0.180)

LEN = lenacapavir

Pharmacokinetic Results:

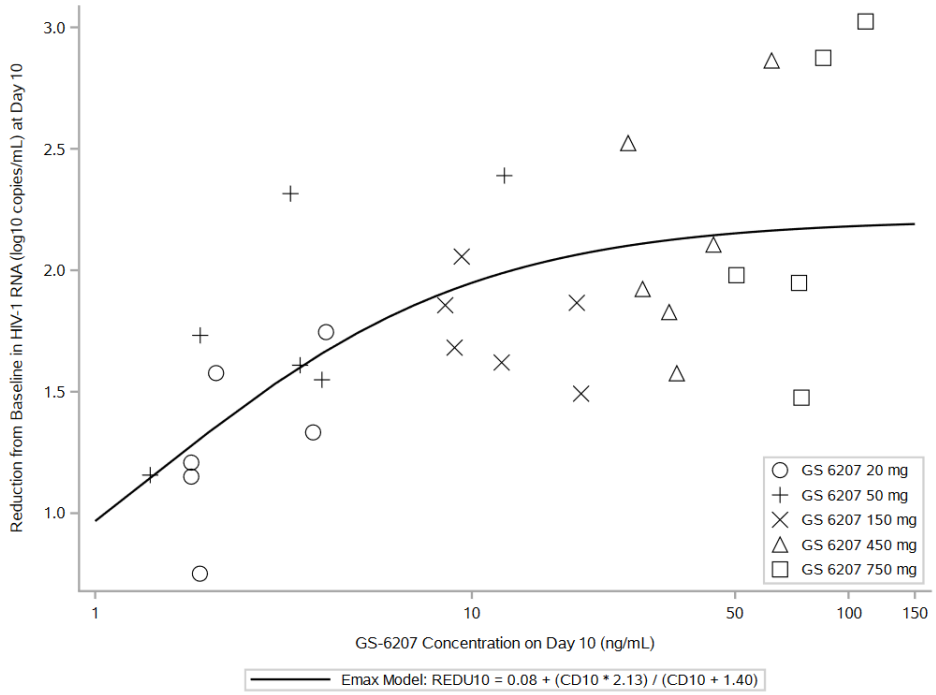
Following single-dose administration of LEN at doses of 20, 50, 150, 450, and 750 mg, LEN PK profiles were consistent with sustained delivery. The PK of LEN was characterized by prolonged exposure, with measurable plasma concentrations for at least 32 weeks following doses of 150, 450, and 750 mg. The mean LEN plasma concentrations on Day 10 were 2.6, 4.4, 12.9, 38.2, and 79.2 ng/mL, respectively. These values correspond to approximately 0.7-, 1.1-, 3.3-, 9.9-, and 20.5-fold higher, respectively, than the $paEC_{95}$ for WT HIV-1 (3.87 ng/mL) in MT-4 cells. The median $t_{1/2}$ across doses ranged between approximately 36 and 45 days. Lenacapavir C_{max} and AUC_{inf} increased in a dose proportional manner across the range of doses evaluated.

PK Parameter	LEN 20 mg (N = 6)	LEN 50 mg (N = 6)	LEN 150 mg (N = 6)	LEN 450 mg (N = 6)	LEN 750 mg (N = 5)
AUC_{inf} (h*ng/mL)	6564.3 (39.0)	9124.1 (48.7)	31,537.0 (21.6)	106,041.1 (18.8)	181,861.0 (40.2)
AUC_{last} (h*ng/mL)	5084.3 (42.1)	7524.4 (55.0)	28,866.4 (28.6)	102,919.0 (19.4)	171,173.9 (47.0)
C_{D10} (ng/mL)	2.6 (41.4)	4.4 (90.3)	12.9 (39.3)	38.2 (35.1)	79.2 (27.7)
C_{max} (ng/mL)	3.0 (33.2)	5.4 (74.5)	17.1 (43.0)	60.1 (28.2)	116.6 (34.6)
T_{max} (h) [days]	445.23 (48.97, 678.60) [18.6]	192.38 (23.97, 310.83) [8.0]	145.33 (143.83, 194.12) [6.1]	495.94 (174.07, 1033.60) [20.7]	192.70 (169.92, 673.83) [8.0]
C_{last} (ng/mL)	0.8 (38.3)	0.8 (19.6)	1.2 (60.7)	2.2 (54.6)	4.4 (62.2)
T_{last} (h) [days]	2702.77 (2063.18, 3360.22) [112.6]	3035.51 (2670.95, 3413.23) [126.5]	5032.92 (4059.35, 5376.67) [209.7]	5077.32 (4730.07, 5402.73) [211.6]	5379.47 (5378.75, 5384.12) [224.1]
$t_{1/2}$ (h) [days]	920.97 (729.18, 965.22) [38.4]	867.83 (591.64, 1261.06) [36.2]	1070.87 (534.77, 1928.10) [44.6]	900.03 (522.17, 1211.86) [37.5]	1033.67 (801.42, 1951.48) [43.1]
CL/F (L/h)	3.5 (40.9)	9.7 (119.1)	4.9 (19.7)	4.4 (20.1)	4.7 (38.7)
V_z/F (L)	5252.0 (45.6)	13,673.8 (83.2)	9225.4 (69.2)	5572.0 (45.3)	10,470.1 (85.7)

%CV = percentage coefficient of variation; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3) hours [median days].

Pharmacokinetic/Pharmacodynamic Results:

Based on an E_{max} model for LEN, the E_{max} was predicted to be a 2.13-log_{10} copies/mL decline in HIV-1 RNA at Day 10, with a 90% effective concentration (EC_{90}) value of 12.6 ng/mL, suggesting that mean LEN concentrations ≥ 12.6 ng/mL are predicted to provide near maximal (94%) antiviral activity.



C_{D10} = LEN concentration on Day 10 (ng/mL); E_{max} = maximum (pharmacodynamics) effect; LEN = lenacapavir, GS-6207; PD = pharmacodynamic(s); PK = pharmacokinetic(s)
Reduction from baseline in HIV-1 RNA (log_{10} copies/mL) at Day 10 is defined as the difference between baseline and Day 10 HIV-1 RNA values (REDU10).
CD10 = LEN concentration on Day 10 (ng/mL).

Conclusions:

The conclusions from Part A of Study GS-US-200-4072 are as follows:

- All but 1 participant who received LEN had a maximum reduction of ≥ 1 log_{10} copies/mL in their HIV-1 RNA through Day 10.
- Single-dose PK of LEN in PWH was consistent with that observed in healthy participants.
- Based on the exposure-response relationship for LEN, the E_{max} was predicted to be a 2.13-log_{10} copies/mL decline in HIV-1 RNA at Day 10, with an in vivo EC_{90} of 12.6 ng/mL.
- Subcutaneously administered LEN was generally safe and well tolerated.

2.4. Intrinsic Factor Studies

2.4.1. Study GS-US-200-4330

Location:	GS-US-200-4330 Final
Title:	A Phase 1 Open-Label, Parallel-Design, Single-Dose Study to Evaluate the Pharmacokinetics of GS-6207 in Participants with Normal Renal Function and Severe Renal Impairment
Primary Objective(s):	• To evaluate the single-dose PK of LEN in participants with severe renal impairment or matched healthy controls with normal renal function
Study Design and Participant Population:	This Phase 1, open-label, single-dose, parallel-group study evaluated the PK and safety of a single oral dose of LEN in participants with impaired renal function and matched healthy controls. Participants with severe renal impairment were categorized by the classification of renal function based on CL_{cr} using the Cockcroft-Gault equation for renal function as recommended by the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Each participant in the healthy control group was matched for sex at birth, age (± 10 years), and BMI (± 20%, 18 ≤ BMI ≤ 40 kg/m^2) with a participant in the severe renal impairment group. Participants received a single oral dose of LEN 300 mg on Day 1. Duration of dosing was 1 day. The study duration (not including screening) was approximately 60 days (± 1 day) including follow-up. Eligible participants were male and nonpregnant/nonlactating female participants, ages 18 through 79 years with severe renal impairment or normal renal function (CL_{cr} ≥ 90 mL/min). Participants with renal impairment must have had a severe renal impairment classification (15 ≤ CL_{cr} ≤ 29 mL/min) at screening and unchanged during the 3 months prior to study drug dosing. A total of 10 participants with severe renal impairment and 10 matched healthy controls with normal renal function were enrolled in the study. All 20 participants completed the study.

Summary of Results and Conclusions:

Pharmacokinetic Results:

The plasma concentration-time profile and plasma PK parameters of LEN (by renal group) are presented below.

PK Parameter	Geometric Mean (95%CI)		Severe Renal Impairment/Matched Healthy Control %GLSM Ratio (90% CI)
	Severe Renal Impairment (N = 10)	Matched Healthy Control (N = 10)	
C_{max} (ng/mL)	51.5 (18.9, 140.5)	19.7 (13.2, 29.3)	262 (112, 614)
AUC_{last} (h*ng/mL)	11,456.2 (5210.4, 25,188.9)	6048.1 (4087.7, 8948.8)	189 (95.2, 377)
AUC_{inf} (h*ng/mL)	12,100.1 (5579.1, 26,243.1)	6591.2 (4518.3, 9615.1)	184 (93.6, 360)
CL/F (mL/h)	24,793.1 (11,431.6, 53,771.8)	45,515.3 (31,201.0, 66,396.7)	—
T_{max} (h)[a]	8.00 (6.00, 24.0)	6.00 (6.00, 8.00)	—
$t_{1/2}$ (h)[a]	234 (178, 354)	318 (270, 357)	—

GLSM = geometric least squared mean; LEN = lenacapavir; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
GLSM Ratio = (Severe Renal Impairment/Matched Healthy Control) × 100
a The $t_{1/2}$ and T_{max} are presented as median (Q1, Q3)
Source: GS-US-200-4330 CSR, Tables 15.10.1.1.2.1, 15.10.1.1.4

The PK of LEN was evaluated in participants with severe renal impairment and matched healthy controls with normal renal function following administration of a single dose of LEN 300 mg under fed conditions. Lenacapavir C_{max} and AUC_{inf} increased by 162% and 84%, respectively, in participants with severe renal impairment compared with their matched healthy controls. Unbound fractions of LEN were similar in the severe renal impairment group relative to their matched healthy controls.

Conclusions:

The conclusions from Study GS-US-200-4330 are as follows:

- Lenacapavir C_{max} and AUC_{inf} increased 162% and 84%, respectively, in participants with severe renal impairment compared with their matched healthy controls. These observed increases in LEN exposure with severe renal impairment (< 2-fold) are not deemed clinically meaningful and do not indicate the necessity for dose adjustment in patients with renal impairment.
- In participants with severe renal impairment (determined by estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation [$eGFR_{MDRD}$]), the single oral dose of LEN 300 mg was generally safe and well tolerated.

2.4.2. Study GS-US-200-4331

Location:	GS-US-200-4331 Final
Title:	A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of GS-6207 in Subjects with Normal and Impaired Hepatic Function
Primary Objective(s):	• To evaluate the single-dose PK of LEN in participants with normal or moderately impaired hepatic function
Study Design and Participant Population:	This Phase 1, open-label, parallel-group study evaluated the PK of a single oral dose of LEN in participants with normal or impaired hepatic function. This study was designed to evaluate the PK and safety of LEN in participants with moderate (Child-Pugh-Turcotte [CPT] Class B) impairment of hepatic function compared with matched participants with normal hepatic function. Each participant in the control group was matched for sex at birth, age (± 10 years), race, and BMI (± 15%) with a participant in the moderate hepatic impairment group. Participants received a single oral dose of LEN 300 mg under fed conditions (600 calories, 27% fat) on Day 1. Duration of dosing was 1 day. Study duration was up to 121 days (not including screening window). Eligible participants were male or nonpregnant, nonlactating female participants, aged 18 to 75 years of age (inclusive), with a BMI between 18.0 to 38.0 kg/m² (inclusive), with moderately impaired or normal hepatic function. Participants with moderate hepatic impairment had a score of 7 to 9 on the CPT classification at screening without evidence of worsening clinical and/or laboratory signs of hepatic impairment within 2 months prior or within the screening period. A total of 10 participants with moderate hepatic impairment and 10 matched healthy control participants with normal hepatic function were enrolled in the study. Of the 20 participants enrolled in the study, 19 participants completed the study (10 with moderate hepatic impairment; 9 with normal hepatic function). One participant with normal hepatic function prematurely discontinued the study (lost to follow-up).
Summary of Results and Conclusions:	**Pharmacokinetic Results:** The plasma PK parameters for LEN and statistical comparisons are presented below.

PK Parameter	Geometric Mean (95% CI)		Moderate Hepatic Impairment/ Normal Hepatic Function %GLSM Ratio (90% CI)
	Moderate Hepatic Impairment (N = 10)	Normal Hepatic Function (N = 10)	
AUC_{inf} (h*ng/mL)	11,997.2 (7785.7, 18486.8)	8184.2 (5652.0, 11,850.9)	146.59 (94.70, 226.91)
AUC_{last} (h*ng/mL)	11,877.9 (7705.6, 18309.3)	7586.3 (5223.3, 11,018.4)	156.57 (100.98, 242.76)
C_{max} (ng/mL)	61.1 (33.9, 110.3)	23.4 (15.8, 34.7)	261.23 (151.03, 451.85)

GLSM = geometric least-squares mean; PK = pharmacokinetics
N represents the number of participants in the PK Analysis Set.
GLSM ratio = (Moderate Hepatic Impairment/Normal Hepatic Impairment) × 100
Source: GS-US-200-4331 CSR, Tables 15.10.1.1.2.1, 15.10.1.1.4

Lenacapavir AUC_{inf} and C_{max} were approximately 47% and 161% higher, respectively, in participants with moderate hepatic impairment relative to their matched healthy controls with normal hepatic function. A sensitivity analysis was performed excluding the AUC from 2 participants who had their last PK collection at Day 29. This analysis resulted in a similar fold change (FC) in AUC for participants with moderate hepatic impairment compared with their matched healthy controls with normal hepatic function. Lenacapavir plasma protein binding were similar in both groups. Exploratory analyses indicated no significant relationships between LEN exposure (AUC and C_{max}) and CPT score or individual elements of CPT classification (albumin, total bilirubin, prothrombin time, and international normalized ratio [INR]).

	Conclusions: The conclusions from Study GS-US-200-4331 are as follows: • Lenacapavir AUC and C_{max} were 1.5- and 2.6-fold higher, respectively, in moderate hepatically impaired participants as compared with their matched healthy controls with normal hepatic function. • Based on cumulative safety data in the LEN SC and oral clinical program, no dose adjustment of LEN is recommended in people with mild to moderate hepatic impairment. • The single oral dose of LEN 300 mg was generally safe and well tolerated.

2.5. Extrinsic Factor Studies

2.5.1. Study GS-US-200-4333

Location:	GS-US-200-4333 Final
Title:	A Phase 1 Study to Evaluate Transporter and Cytochrome (CYP) 450-Mediated Drug-Drug Interactions Between GS-6207 and Probe Drugs
Primary Objective(s):	• To evaluate the effect of a cytochrome P450 enzyme (CYP)3A inhibitor, a mixed CYP3A/P-glycoprotein (CYP3A/P-gp) inhibitor, and a mixed CYP3A/P-gp/uridine diphosphate glucuronosyltransferase (UGT)1A1 inhibitor on the PK of LEN • To evaluate the effect of an inducer of CYP3A/P-gp/UGT and an inducer of CYP3A/P-gp on the PK of LEN • To evaluate the effect of a histamine 2 receptor agonist (H2RA) on the PK of LEN • To evaluate the effect of LEN on the PK of an organic anion transporting polypeptide (OATP) substrate • To evaluate the effect of LEN on the PK of a breast cancer resistance protein (BCRP) substrate • To evaluate the effect of LEN on the PK of a P-gp substrate • To evaluate the effect of LEN on the PK of a CYP3A substrate
Study Design and Participant Population:	This was a Phase 1, single-center, parallel-design, open-label, single- and multiple-dose, multiple-cohort study to evaluate transporter and CYP-mediated DDIs between LEN and probe drugs in healthy participants. An approximately even distribution of healthy male and healthy nonpregnant, nonlactating female participants aged 18 through 45 years, inclusive, were enrolled into the study. Participants may not have participated in more than 1 part/cohort of the study. Cohorts 1 through 11 were initiated in parallel or in a staggered fashion and occurred in any order. Following completion of screening and Day −1 procedures, eligible participants received study treatments as shown below. **Cohort 1:** LEN (reference treatment for Cohorts 2 and 3) Treatment A: Single dose of oral LEN 300 mg (6 × 50-mg capsules) administered in the morning under fed conditions

Cohort	Day 1
1	A: LEN 300 mg

LEN = lenacapavir

Cohort 2: Cobicistat (COBI; Tybost®) (mixed CYP3A/P-gp inhibitor) and LEN

Treatment B: COBI 150 mg administered orally once daily in the morning under fed conditions on Days 1 through 90

Based on review of preliminary LEN PK through at least Day 24, dosing of Treatment B in Period 3 could have been discontinued prior to Day 90.

	Period 1	Period 2	Period 3
Cohort	Days 1 through 10	Day 11	Day 12 up to Day 90
2	B: COBI 150 mg (QD)	B: COBI 150 mg (QD) + A: LEN 300 mg	B: COBI 150 mg (QD)

COBI = cobicistat; QD = once daily; LEN = lenacapavir

Cohort 3: Darunavir (DRV)/COBI (mixed CYP3A/P-gp inhibitor and inducer) and LEN

Treatment C: DRV/COBI (800/150 mg) administered orally once daily in the morning under fed conditions on Days 1 through 90

Based on review of preliminary LEN PK through at least Day 24, dosing of Treatment C in Period 3 could have been discontinued prior to Day 90.

Cohort	Period 1	Period 2	Period 3
	Days 1 through 10	Day 11	Day 12 up to Day 90
3	C: DRV/COBI 800/150 mg (QD)	C: DRV/COBI 800/150 mg (QD) + A: LEN 300 mg	C: DRV/COBI 800/150 mg (QD)

COBI = cobicistat; DRV = darunavir; QD = once daily; LEN = lenacapavir

Cohort 4: LEN (reference treatment for Cohorts 5, 8, 9, and 10)

Treatment D: Single dose of oral LEN 300 mg (1 × 300-mg tablet) administered in the morning under fasted conditions

Cohort	Day 1
4	D: LEN 300 mg (tablet; fasted)

LEN = lenacapavir

Cohort 5: Voriconazole (VORI; CYP3A inhibitor) and LEN

Treatment E: VORI 400 mg twice daily on Day 1, followed by 200 mg twice daily on Days 2 through 24, administered under fasted conditions in the morning and on an empty stomach in the evening. On the day of discharge (Day 25), VORI 200 mg was administered in the morning under fasted condition.

Cohort	Period 1	Period 2	Period 3	Period 4
	Day 1	Day 2	Days 3 through 24	Day 25 (Discharge)
5	E: VORI: 400 mg BID	E: VORI: 200 mg BID + D: LEN 300 mg	E: VORI: 200 mg BID	E: VORI: 200 mg AM

BID = twice daily; LEN = lenacapavir; VORI = voriconazole

Cohort 6: LEN (reference for Cohort 7)

Treatment F: Single dose of oral LEN 300 mg (1 × 300-mg tablet) administered in the morning under fed conditions

Cohort	Day 1
6	F: LEN 300 mg (tablet; fed)

LEN = lenacapavir

Cohort 7: Atazanavir/Cobicistat (ATV/COBI; mixed P-gp/CYP3A/UGT1A1 inhibitor) and LEN

Treatment G: ATV/COBI (300/150 mg) once daily in the morning under fed conditions on Days 1 through 60

Cohort	Period 1	Period 2	Period 3
	Days 1 through 9	Day 10	Days 11 through 60
7	G: ATV/COBI 300/150 mg QD	G: ATV/COBI 300/150 mg QD + F: LEN 300 mg	G: ATV/COBI 300/150 mg QD

ATV = atazanavir; COBI = cobicistat; LEN = lenacapavir; QD = once daily

Cohort 8: Rifampin (RIF; strong CYP3A and P-gp/UGT inducer) and LEN

Treatment H: RIF (600 mg) administered once daily in the evening under fasted conditions on Days 1 through 25. On the day of discharge (Day 26), no dose was administered.

	Period 1	Period 2	Period 3
Cohort	**Days 1 through 13**	**Day 14**	**Days 15 through 25**
8	H: RIF (600 mg) QD; PM dosing	D: LEN 300 mg (AM dosing) + H: RIF (600 mg) QD; PM dosing	H: RIF (600 mg) QD; PM dosing

LEN = lenacapavir; QD = once daily; RIF = rifampin

Cohort 9: Efavirenz (EFV; moderate CYP3A and P-gp inducer) and LEN

Treatment I: EFV (600 mg) administered once daily in the evening under fasted conditions on Days 1 through 25. On the day of discharge (Day 26), no dose was administered.

	Period 1	Period 2	Period 3
Cohort	**Days 1 through 13**	**Day 14**	**Days 15 through 25**
9	I: EFV (600 mg) QD; PM dosing	D: LEN 300 mg (AM dosing) + I: EFV (600 mg) QD; PM dosing	I: EFV (600 mg) QD; PM dosing

EFV = efavirenz; LEN = lenacapavir; QD = once daily

Cohort 10: Famotidine (FAM; H2RA) and LEN

Treatment J: FAM (40 mg) administered in the morning under fasted conditions on Day 1

	Period 1
Cohort	**Day 1**
10	J: FAM 40 mg, then D: LEN 300 mg (2 hours after FAM dose)

FAM = famotidine; LEN = lenacapavir

Cohort 11: Pitavastatin (PIT; OATP substrate), rosuvastatin (ROS; BCRP substrate), tenofovir alafenamide (TAF; P-gp substrate), midazolam (MDZ; CYP3A substrate), and LEN

Treatment K: PIT 2 mg administered in the morning on Days 1, 15, and 27 under fed conditions

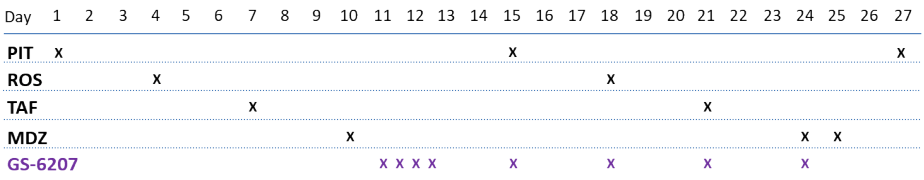
Treatment L: ROS 5 mg administered in the morning on Days 4 and 18 under fed conditions

Treatment M: TAF 25 mg administered in the morning on Days 7 and 21 under fed conditions

Treatment N: MDZ 2.5 mg administered in the morning on Days 10, 24, and 25 under fed conditions

Treatment O: LEN (600 mg; 2 × 300-mg tablets) administered twice daily on Days 11 and 12, then 600 mg once in the morning on Days 15, 18, 21, and 24, under fed conditions

Treatment Schema Summary



Cohort	Period 1 Day 1	Period 2 Day 4	Period 3 Day 7	Period 4 Day 10
11	K: PIT (2 mg)	L: ROS (5 mg)	M: TAF (25 mg)	N: MDZ (2.5 mg)

Cohort	Period 5 Days 11-12	Period 6 Day 15	Period 7 Day 18	Period 8 Day 21
11	O: LEN (600 mg) BID	O: LEN (600 mg) + K: PIT (2 mg)	O: LEN (600 mg) + L: ROS (5 mg)	O: LEN (600 mg) + M: TAF (25 mg)

Cohort	Period 9 Day 24	Period 10 Day 25	Period 11 Day 27
11	O: LEN (600 mg) + N: MDZ (2.5 mg)	N: MDZ (2.5 mg)	K: PIT (2 mg)

BID = twice daily; LEN = lenacapavir; MDZ = midazolam; PIT = pitavastatin; ROS = rosuvastatin; TAF = tenofovir alafenamide

A total of 291 participants were enrolled in the study: 30 in each of Cohorts 1, 2, and 3; 27 into Cohort 4; 25 in each of Cohorts 5, 6, 7, 8, and 10; 18 in Cohort 9, and 31 in Cohort 11.

Reasons for discontinuation of study drug in 17 participants were: AEs in 8 participants (4 participants in Cohort 7, 2 participants in Cohort 3, and 1 participant each in Cohorts 5 and 11); participant decision for 5 participants, investigator's discretion for 3 participants; and discontinuation at the request of Gilead, a regulatory agency, or institutional review board (IRB) for 1 participant in Cohort 11 (due to Grade 3 AE of transaminases increased after treatment with ROS+LEN).

Reasons for discontinuation from the study in 19 participants were: withdrawal of consent in 7 participants; discontinuation at the request of Gilead, a regulatory agency, or IRB for 4 participants (3 participants in Cohort 7 and 1 participant in Cohort 11); AEs for 3 participants (2 participants in Cohort 3 and 1 participant in Cohort 7); investigator's discretion for 3 participants; and protocol violation for 2 participants.

Summary of Results and Conclusions:

Pharmacokinetic Results:

LEN as a Perpetrator of Drug Interactions (Cohort 11)

- Coadministration of single-dose PIT (an OATP substrate) both simultaneously with LEN and staggered from LEN did not result in changes in PIT AUC and C_{max}.
- Coadministration of single-dose ROS (a BCRP substrate) simultaneously with LEN resulted in a 31% increase in AUC_{inf} and a 57% increase in C_{max} for ROS.
- Coadministration of single-dose TAF (a P-gp substrate) simultaneously with LEN resulted in a 32% increase in AUC_{last} with a smaller effect on C_{max} (approximately 24% increase) for TAF.
- Coadministration of single-dose TAF (a P-gp substrate) simultaneously with LEN resulted in a 47% increase in AUC_{inf} with a smaller increase in C_{max} (approximately 23% increase) for tenofovir (TFV).
- Coadministration of single-dose MDZ simultaneous with LEN resulted in 259% and 94% increases in AUC_{inf} and C_{max} of MDZ, respectively. Coadministration of single-dose MDZ staggered from LEN resulted in 308% and 116% increases in AUC_{inf} and C_{max} of MDZ, respectively. For 1-OH-MDZ, AUC_{inf} and C_{max} values were reduced by 16% to 24% and 48%, respectively.

LEN as a Victim of Drug Interactions (Cohorts 1 to 10)

Inhibition:

- Coadministration of single-dose LEN with a strong CYP3A4/P-gp inhibitor (COBI) and a mixed CYP3A4/P-gp inhibitor and inducer (DRV/COBI) under fed conditions resulted in 128% and 94% increases in AUC_{inf}, respectively, and 110% and 130% increases in C_{max}, respectively.
- Coadministration of a single-dose LEN with the potent CYP3A4 inhibitor (VORI) under fasting conditions resulted in a 41% increase in AUC_{inf}, with no change in C_{max}.
- Coadministration of single-dose LEN with ATV/COBI resulted in a 321% increase in AUC_{inf} and a 560% increase in C_{max}.

Induction:

- Coadministration of single-dose LEN with strong inducer (RIF) under fasting conditions resulted in an 84% decrease in AUC_{inf} and a 55% decrease in C_{max}.
- Coadministration of single-dose LEN with a moderate inducer (EFV) under fasting conditions resulted in a 56% decrease in AUC_{inf} and a 36% decrease in $C_{max.}$

Acid-Reducing Agent:

- Administration of single-dose LEN 2 hours after a gastric acid reducer (FAM) under fasting conditions resulted in a 28% increase in AUC_{inf}, whereas C_{max} was unchanged.

Conclusions:

The conclusions from Study GS-US-200-4333 are as follows:

- For LEN as a perpetrator, LEN appeared to inhibit P-gp transporter (as observed with coadministration of LEN with TAF resulting in a 32% increase in AUC_{inf}) and BCRP transporter (as observed with coadministration of LEN with ROS resulting in a 31% increase in AUC_{inf}); however, these interactions are unlikely to be clinically meaningful. LEN does not inhibit OATP transporters (as observed with coadministration of LEN with PIT). Therefore, substrates of P-gp, BCRP, and OATP can be coadministered with LEN. LEN is a moderate inhibitor of CYP3A (as observed with coadministration of LEN with MDZ resulting in a 259% increase in AUC_{inf}). Caution is advised if LEN is coadministered with sensitive CYP3A substrates that have a narrow therapeutic index.
- For LEN as a victim of inhibition, strong CYP3A4/P-gp/UGT1A1 inhibitors (ATV/COBI) increased LEN concentrations to a larger degree (321% increase in LEN AUC_{inf}) than coadministration with only a strong CYP3A4 inhibitor (VORI increased LEN AUC_{inf} by 41%) or CYP3A4/P-gp inhibitors (COBI and DRV/COBI increased LEN AUC_{inf} by 128% and 94%, respectively).
- For LEN as a victim of induction, strong and moderate inducers of CYP3A4/P-gp decreased LEN exposures by 84% and 56% (RIF and EFV, respectively) and may result in loss of virologic response; therefore, concomitant use of strong and moderate inducers of CYP3A4/P-gp with LEN should be avoided.
- For LEN as a victim of an acid-reducing agent (ARA), administration of a single dose of LEN 2 hours after FAM did not result in clinically significant changes in LEN PK (28% increase in LEN AUC_{inf}). Accordingly, there are no restrictions for use of LEN with ARAs.
- Lenacapavir administered as a tablet or capsule formulation at a dose of 300 mg or 600 mg, alone or in combination with COBI, DRV/COBI, ATV/COBI, PIT, ROS, TAF, MDZ, VORI, RIF, EFV, or FAM was safe and generally well tolerated in healthy participants.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

The clinical pharmacology of LEN across all supporting studies is described in the following sections. Unless otherwise specified, oral LEN 300-mg tablets and abdominal SC LEN injection, 309 mg/mL NaS, are being submitted for review and are the formulations discussed in the subsections below. All clinical studies supporting the clinical pharmacology for this marketing application are described in Section 1.3.3. In addition, the highlights of clinical pharmacology and cardiac safety are provided in Appendix 6.2.

Selection of the LEN oral + SC regimen was informed by its PK from Studies GS-US-200-4070, GS-US-200-4538, and GS-US-200-4071 in healthy participants and in a proof-of-concept Phase 1b study (Study GS-US-200-4072; suspension formulation) in PWH. Based on the data from the proof-of-concept study, a concentration of 15.5 ng/mL (corresponding to an IQ of 4 based on $paEC_{95}$ from MT-4 cells; 3.87 ng/mL = IQ1) is anticipated to provide antiviral activity in the HTE population. The Phase 2/3 regimen was selected to target an exposure whereby the lower bound of the 90% CI of the C_{trough} is above IQ4 within a few days of dosing initiation and maintained through the end of the dosing interval (every 26 weeks). The safety and PK of combined oral and SC LEN were also evaluated in healthy participants with the same regimen used in the ongoing Phase 2 and Phase 2/3 studies and a simplified regimen (SC on Day 1 along with oral loading on Day 1 and 2) (Study GS-US-200-5709, Section 2.2.3).

Lenacapavir doses for the Phase 2 and 2/3 studies (Study GS-US-200-4334, Summary of Clinical Efficacy [m2.7.3], Section 2.2 and Study GS-US-200-4625, m2.7.3, Section 2.1) were selected such that the lower bound of the 90% CI of LEN C_{trough} concentrations were at least 4-fold greater than the in vitro $paEC_{95}$ (3.87 ng/mL = IQ1; MT-4 cells), corresponding to an IQ4 (15.5 ng/mL). This target is supported by the results of the dose-ranging proof-of-concept study (Study GS-US-200-4072, Section 2.3.1), in which near maximal antiviral activity was observed at IQ4, indicating that substantial increases in antiviral activity with an increase in LEN exposure were not expected.

3.1. Pharmacokinetics

The following sections summarize the results of clinical and pertinent nonclinical studies investigating the absorption, distribution, metabolism, elimination, and single- and multiple-dose PK of LEN following oral and SC administration. The results of nonclinical studies are discussed in detail in m2.6.4.

3.1.1. Absorption

3.1.1.1. Oral Administration

The absolute bioavailability of LEN following oral administration was estimated based on the observed exposure to LEN following administration of IV LEN 10 or 20 mg and oral LEN 300 mg to healthy participants (Study GS-US-200-4329, Section 2.2.1 and GS-US-200-4071, m2.7.1, Section 2.2.1). Comparison of LEN AUC between IV and oral administration, and when correcting for dose, indicates that absolute bioavailability (%F) following administration of LEN 300 mg is low (%F of approximately 10%) in healthy participants. Based on population analysis of PK data across studies, the estimated %F for LEN 600 mg is approximately 6.24% in PWH (CTRA-2021-1054 LEN PopPK).

These data are consistent with nonclinical findings of low bioavailability following oral administration to rats and dogs (m2.6.4, Section 3.3.3). Lenacapavir displays low aqueous solubility; the maximum equilibrium solubility in simulated intestinal fluid under fasted state at 3.9 µg/mL and under fed state at 4.1 µg/mL (m3, Section 3.2.S.1.3) and both nonclinical and clinical data indicate that LEN is a substrate of P-gp (m2.6.4, Section 7.4 and Study GS-US-200-4333, Section 2.5.1). Low bioavailability following oral administration is likely due to low solubility and active efflux in the intestine. Median LEN T_{max} occurred at approximately 4 hours postdose under fasting conditions (Study GS-US-200-4071, m2.7.1, Section 2.2.1).

The absorption of LEN is neither affected by the presence of food nor ARAs. In healthy participants, LEN (300 mg) AUC_{inf}, C_{max}, and T_{max} were comparable following administration of a low- or high-fat meal. The geometric least squared mean (GLSM) (90% CI) ratio for AUC_{inf} values were 115 (72 to 184) and 99 (58 to 167) for high-fat and light meals relative to fasting, respectively, whereas corresponding C_{max} GLSM ratios were 145 (78 to 270) and 116 (55 to 242), respectively, with similar range of T_{max} values compared to fasting (Study GS-US-200-4071, m2.7.1, Section 2.2.1). Similarly, LEN PK (AUC and C_{max}) following a single oral dose of famotidine 40 mg administered 2 hours prior to LEN did not result in clinically meaningful changes (Study GS-US-200-4333, Section 2.5.1).

3.1.1.2. Subcutaneous Administration

The absolute bioavailability of LEN following SC administration was estimated based on the observed exposure to LEN following IV and abdominal SC administration in healthy participants (Study GS-US-200-4329, Section 2.2.1 and GS-US-200-4538, m2.7.1, Section 2.1.2, respectively). Comparison of LEN AUC following administration of IV LEN 10 or 20 mg and SC LEN 927 mg, and when correcting for dose, indicates that LEN is completely absorbed over six months following SC administration of the 927-mg dose.

Due to slow release from the site of administration {Zheng 2018}, the absorption profile of SC LEN is complex, involving a combination of delayed and first-order absorption kinetics leading to a T_{max} of 77 to 84 days postdose (Study GS-US-200-4538, m2.7.1, Section 2.1.2, and CTRA-2021-1054 LEN PopPK).

3.1.2. Distribution

In vitro, LEN is highly bound to plasma proteins (> 98.5%) in all species tested, including human (m2.6.4, Section 4.1). Consistent with in vitro data, LEN protein binding was high (> 99%) in ex vivo healthy participants plasma and the extent of LEN plasma protein binding was unchanged by severe renal impairment or moderate hepatic impairment (Study GS-US-200-4330, Section 2.4.1 and Study GS-US-200-4331, Section 2.4.2).

Following IV administration of LEN 10 mg and 20 mg to healthy participants, LEN V_z values are approximately 1793 L and 1990 L, respectively, values that are much greater than total body water, indicating extensive tissue distribution (Study GS-US-200-4329, Section 2.2.1). Corresponding CL values were approximately 4.4 L/h and 4.9 L/h, respectively. These findings are in agreement with nonclinical data; in rats, tissue distribution of [^{14}C]LEN and its metabolites following a single dose (LEN 3 mg/kg) was rapid and extensive (m2.6.4, Section 2.1.3).

Following single-dose oral administration of LEN 300-mg tablet at doses of 300, 900, and 1800 mg to healthy participants, the mean (%CV) values for V_z/F were 19,240 L (65%), 51,077 (65%), and 68,712 (60%), respectively (Study GS-US-200-4071, m2.7.1, Section 2.2.1).

Following single-dose abdominal SC administration of LEN 927 mg administered as LEN injection, 309 mg/mL (NaS), to healthy participants, mean V_z/F values ranged between 9500 to 11,700 L (Study GS-US-200-4538, m2.7.1, Section 2.1.2).

Following a single IV dose of [^{14}C]LEN 20 mg to healthy male participants, the blood-to-plasma ratio of [^{14}C]-radioactivity was approximately 0.50 to 0.70 through 336 hours postdose, indicating that LEN was predominantly distributed to plasma rather than the cellular components of blood (Study GS-US-200-4329, Section 2.2.1).

3.1.3. Metabolism and Elimination

The metabolism of LEN, including metabolic routes leading to elimination, was characterized in vitro, in hepatic microsomes and hepatocytes (m2.6.4, Section 5.1); in vivo, in rats and dogs (m2.6.4, Section 5.2); and in a human mass-balance PK study (Study GS-US-200-4329, Section 2.2.1).

Following a single IV dose of [^{14}C]LEN 20 mg to healthy male participants, the systemic clearance of LEN was substantially lower than hepatic blood flow (hepatic extraction ratio (ER) = 0.03) (Study GS-US-200-4329, Section 2.2.1). This finding indicates that presystemic clearance following oral absorption is minimal and therefore LEN metabolism and elimination are expected to be similar when administered as an oral tablet or SC solution.

Following a single IV dose of [^{14}C]LEN 20 mg in healthy male participants, a mean 75.9% of the dose was recovered in feces and 0.237% was recovered in urine through the last collection interval, indicating that fecal elimination is the primary elimination route of LEN and its metabolites. Most of the administered radioactive dose was recovered in the first 1608 hours postdose (74.7% in feces and urine combined).

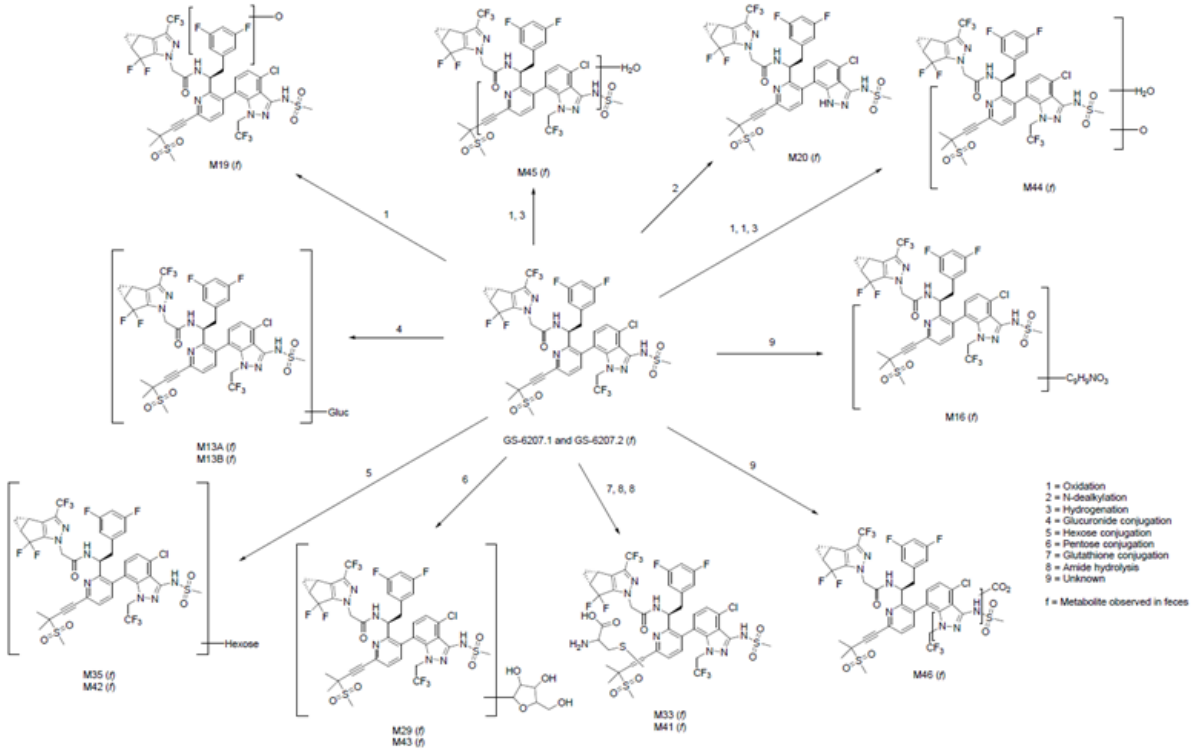
Lenacapavir was metabolized via oxidation, N-dealkylation, hydrogenation, amid hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation. In the AUC-pooled plasma sample ($AUC_{0\text{-}1176h}$), a large percentage of the circulating radioactivity (68.8%) was associated with unchanged LEN. No single metabolite contributed > 10% of total radioactivity exposure through 1176 hours postdose. The total radioactivity exposure from the sum of all identified components in the plasma was approximately 88%. Adjusting for the 75.9% mean cumulative fecal recovery of the administered radioactive dose, LEN and the LEN-hexose conjugate metabolite (M42, M35) were the 2 most abundant components recovered in the feces and accounted for a mean abundance of 43.4% (32.9% of dose) and 8.7% (6.6% of dose) of the administered [^{14}C]-dose, respectively. Other metabolites were identified in feces, each of which accounted for < 2% of the dose.

The disposition of LEN in human was consistent with nonclinical species. The major route of elimination of LEN in rats and dogs was excretion in bile and direct intestinal secretion (and fecal elimination) as intact LEN (m2.6.4). Both nonclinical data and human mass-balance results suggest that UGT1A1 is a minor pathway for LEN metabolism. Intestinal secretion of intact LEN appeared to be mediated by P-gp. Consistent with disposition of LEN in human, metabolism played a lesser role in rat and dog. The LEN metabolites that were identified were formed via oxidation or direct conjugation. Intact LEN was the only major circulating plasma component in rat and dog. Less than 1% of the [^{14}C]LEN was eliminated in urine.

Figure 2 presents a proposed major biotransformation pathway for [^{14}C]LEN. There were no unique human metabolites; all human metabolites were also found in nonclinical species. Overall, clinical and nonclinical data indicate that excretion of unchanged parent drug into the feces is the primary clearance pathway for LEN.

Based on observed data, median $t_{1/2}$ ranged from approximately 10 to 12 days for the 300 to 900 mg dose range, with mean CL/F of 55 L/h (C_{max} and AUC were not proportional to dose for oral tablets) after single doses of LEN 300 mg tablet (Study GS-US-200-4071, m2.7.1, Section 2.2.1). For LEN SC, median $t_{1/2}$ ranged from 8 to 12 weeks, with mean CL/F was approximately 4.2 L/h after single doses (Study GS-US-200-4538, m2.7.1, Section 2.1.2).

Figure 2. Proposed Major Biotransformation and Excretion Pathway for LEN in Humans



Source: GS-US-200-4329 CSR, Figure 8

3.1.4. Single- and Multiple-Dose Pharmacokinetics

Pharmacokinetics of LEN oral (tablet) and SC formulations (suspension and solution) has been comprehensively characterized in Phase 1 studies in healthy participants. The LEN oral tablet and SC solution formulations (intended commercial formulations) were evaluated in the ongoing Phase 2 and 2/3 studies (Studies GS-US-200-4334, m2.7.3, Section 2.2 and GS-US-200-4625, m2.7.3, Section 2.1). For SC formulations, the site of injection was the abdomen for all studies in which LEN was administered SC.

3.1.4.1. Single-Dose Pharmacokinetics of Oral Tablet Formulation of LEN in Healthy Participants

Table 2 presents the LEN plasma PK parameters following single-dose oral administration of LEN tablets at doses of 50, 300, 900, and 1800 mg to healthy participants. The PK of LEN was characterized by median LEN C_{max} occurring between 4 and 8 hours postdose, and the median $t_{1/2}$ of oral LEN ranging from 10 to 13 days. Over the studied dose range, the increase in AUC_{inf} and C_{max} was less than dose proportional.

Table 2. GS-US-200-4071: LEN Plasma PK Parameters Following Single-Dose Oral Administration of LEN Tablets Under Fasted Conditions in Healthy Participants (LEN PK Analysis Set)

PK Parameter Geometric Mean (95% CI)	LEN			
	50 mg (1 × 50-mg tablet) (N = 8)	**300 mg (1 × 300-mg tablet) (N = 8)**	**900 mg (3 × 300-mg tablets) (N = 8)**	**1800 mg (6 × 300-mg tablets) (N = 8)**
AUC_{inf} (h*ng/mL)	2296.4 (1431.6, 3683.7)	6513.7 (3825.6, 11090.8)	8882.3 (5936.3, 13290.4))	13331.6 (9845.4, 18052.1)
C_{max} (ng/mL)	7.4 (5.0,11.2)	22.8 (10.5, 49.8)	33.7 (17.3, 65.6)	46.4 (26.9, 80.0)
T_{max} (h)[a]	4.00 (4.00, 5.00)	4.00 (4.00, 6.00)	4.00 (3.00, 16.00)	8.00 (6.00, 8.00)
$t_{1/2}$ (h)[a] [days][b]	298.62 (270.20, 415.10) [12.4]	242.64 (204.37, 281.36) [10.1]	288.52 (255.47, 326.89) [12.0]	311.24 (261.50, 361.61) [13.0]

LEN = lenacapavir; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
a median (Q1, Q3)
b median $t_{1/2}$ presented in days to 3 significant figures
Source: GS-US-200-4071 CSR, Tables 15.10.1.1.2.3 and 15.10.1.1.5.3

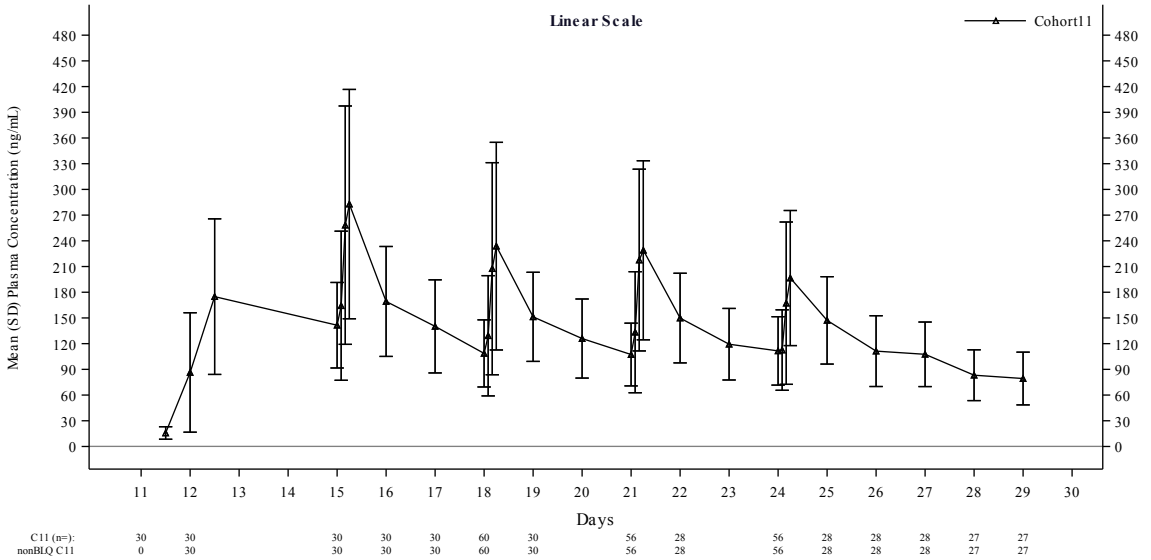
3.1.4.2. Multiple-Dose Pharmacokinetics of Oral Tablet Formulation of LEN in Healthy Participants

Pharmacokinetics of LEN following multiple-dose administration of the oral tablet formulation of LEN was evaluated in Studies GS-US-200-4333, GS-US-200-5709, and GS-US-200-4332. In Study GS-US-200-4333 (Cohort 11), LEN was administered 600 mg twice daily for 2 days, then 600 mg every 3 days as a 300 mg tablet formulation under fed conditions to evaluate the effect of LEN on drug transporters and metabolizing enzymes. In the GS-US-200-5709 (Cohort 3) and GS-US-200-4332 studies, LEN was administered 600 mg twice daily for 8 days as a supratherapeutic regimen.

3.1.4.2.1. Study GS-US-200-4333

Following the loading regimen of 600 mg twice daily for 2 days, single doses of LEN 600 mg were given with each probe substrate in Cohort 11. Mean concentrations of LEN were at or above clinically relevant C_{max} concentrations (ie, > 100 ng/mL) throughout the drug interaction evaluation (Figure 3).

Figure 3. GS-US-200-4333: Mean (SD) LEN Plasma Concentration Versus Time During Evaluation of LEN as a Perpetrator in Cohort 11 (LEN PK Analysis Set, Linear Scale)



BLQ = below limit of quantitation; GS-6207 = LEN; LLOQ = lower limit of quantitation; PK = pharmacokinetic
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ was defined as 0.1 ng/mL for LEN.
Postdose concentration values ≤ LLOQ are not presented in the figure.
Figures on the linear scale in which lower bars were negative were truncated to 0 on the Y-axis.
Source: GS-US-200-4333 CSR, Figure 11

3.1.4.2.2. Study GS-US-200-4332

Table 3 presents LEN plasma PK parameters on Study Days 6 and 12 following twice-daily oral administration of 600 mg of LEN for up to 8 days. On the intensive sampling days, LEN plasma concentrations gradually increased and attained maximum levels (T_{max}) at 5 hours postdose following 2 days of LEN twice-daily dosing, and at 4 hours postdose following 8 days of LEN twice-daily dosing. Mean plasma C_{max} and AUC were approximately 4.0- and 4.3fold higher, respectively, on Study Day 12 relative to Study Day 6 exposures. Additionally, C_{max} values were approximately 2.2- and 8.8-fold higher on Study Days 6 and 12, respectively, in comparison with the therapeutic C_{max} derived from PopPK estimates from the Phase 2/3 registrational study in HTE PWH (mean C_{max} values were 292 and 1070 ng/mL on Days 6 and 12, respectively, versus 136 ng/mL). Likewise, LEN AUC_{tau} on Study Days 6 and 12 of this study was approximately 3.5- and 15.0-fold higher, respectively, relative to the Phase 2/3 therapeutic exposure estimate.

Table 3. GS-US-200-4332: Summary of LEN PK Parameters on Study Days 6 and 12 (LEN PK Analysis Set)

PK Parameter Mean (%CV)	LEN Day 6 (N = 47)	LEN Day 12 (N = 47)	%GLSM Ratio (90% CI) LEN Day 6 vs Day 12
AUC_{last} (h*ng/mL)	2734.1 (64.2)	10640.6 (39.4)	430.25 (392.19, 472.01)
C_{max} (ng/mL)	292.1 (64.4)	1070.4 (37.9)	403.80 (367.69, 443.45)
T_{max} (h)[a]	5.00 (5.00, 11.97)	4.00 (0.00, 5.00)	
C_{last} (ng/mL)	258.6 (56.4)	771.7 (37.7)	

%CV = percentage coefficient of variation; GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile
a Data presented as median (Q1, Q3).
N represents the number of participants in the PK Analysis Set.
Mean values are presented as unadjusted arithmetic means.
Participant [redacted] terminated early due to an adverse event on Day 5 and is excluded from analysis.
Source: Study GS-US-200-4332 CSR, Table 14

3.1.4.3. Single-Dose Pharmacokinetics of Subcutaneous Solution Formulation of LEN Injection in Healthy Participants

Table 4 presents the LEN plasma PK parameters following single-dose SC administration of LEN 309 mg administered as a 1-mL LEN injection, 309 mg/mL (NaS), or a single dose of LEN 927 mg administered as either 3 × 1-mL injections or 2 × 1.5-mL injections of LEN injection, 309 mg/mL (NaS).

Pharmacokinetic data following administration of single doses of SC LEN injection, 309 mg/mL (NaS) indicate that LEN exposures were generally dose proportional following administration of 309 mg to 927 mg LEN injection, 309 mg/mL (NaS). A slow initial release of LEN is observed, as demonstrated by a median T_{max} of 77 to 84 days (Table 4); however, concentrations exceeding the target IQ of 4 (4-fold higher than the $paEC_{95}$ from MT-4 cells; 3.87 ng/mL) were observed for at least 26 weeks (169 days) following a single dose of LEN 927 mg, with an apparent terminal $t_{1/2}$ of 53 to 81 days (7 to 11 weeks), supporting dosing at every 6 month interval (Study GS-US-200-4538, m2.7.1, Section 2.1.2 and Section 3.2.1). The PK of LEN 927 mg was similar following SC administration as either 3 × 1.0-mL or 2 × 1.5-mL injections of LEN injection, 309 mg/mL (NaS) (Table 4).

Table 4. GS-US-200-4538: Plasma PK Parameters Following Single-Dose SC Administration of LEN Injection, 309 mg/mL (NaS) Formulation in Healthy Participants (LEN PK Analysis Set)

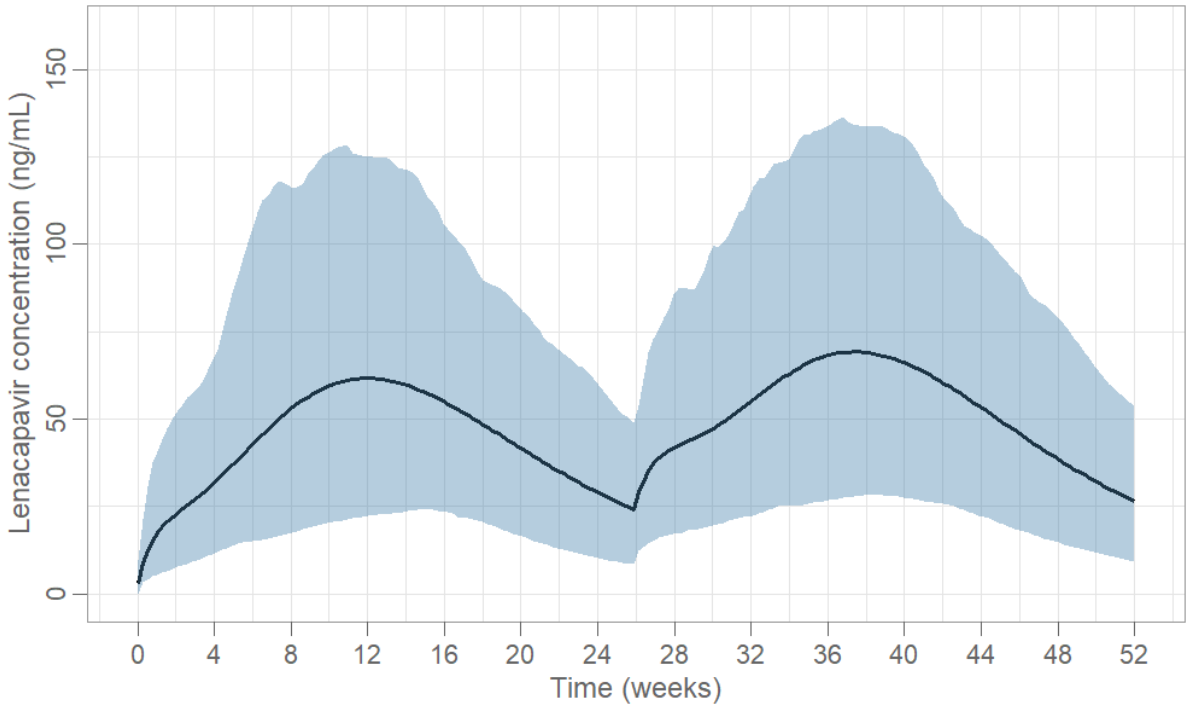
PK Parameter Geometric Mean (95% CI)	LEN		
	309 mg (1 × 1-mL 309 mg/mL [NaS]) (N = 8)	**927 mg (3 × 1-mL injections, 309 mg/mL [NaS]) (N = 8)**	**927 mg (2 × 1.5-mL injections, 309 mg/mL [NaS]) (N = 8)**
AUC_{6month} (h*ng/mL)	41,932.9 (31,534.0, 55,760.9)	171,099.1 (109,027.1, 268,510.5)[b]	159,934.5 (121,838.6, 209,942.0)[c]
AUC_{last} (h*ng/mL)	60,868.9 (46,646.9, 79,427.2)	140,235.8 (57,678.5, 340,960.7)	145947.8 (56,710.4, 375,606.1)
AUC_{inf} (h*ng/mL)	63,679.2 (49,196.1, 82,426.2)	216,741.4 (153,341.5, 306,354.4)[b]	224,133.5 (171,071.8, 293,653.4)[c]
AUC_{exp} (%)	4.1 (2.9, 5.8)	1.4 (0.6, 3.4)[b]	3.6 (2.2, 6.0)[c]
C_{max} (ng/mL)	16.0 (10.9, 23.5)	57.8 (34.8, 95.9)	54.9 (35.1, 85.9)
T_{max} (h) [days][a]	2352.22 (1405.14, 3336.09) [98.0]	1848.00 (1680.00, 2016.00) [77.0]	2016.94 (1680.00, 2629.08) [84.0]
T_{last} (h) [days][a]	10716.63 (10202.20, 10910.43) [446.5]	9407.78 (6431.48, 9432.14) [392.0]	10756.65 (9183.46, 10756.97) [448.1]
$t_{1/2}$ (h) [days][a]	1859.94 (1665.30, 2386.67) [77.5]	1277.39 (1184.33, 1334.53) [53.2][b]	1939.25 (1486.68, 2354.08) [80.8][c]

LEN = lenacapavir; NaS = sodium salt; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
a median (Q1, Q3) hours [median days]
b N = 6
c N = 7
Source: GS-US-200-4538 CSR, Table 15.10.1.1.2.2

3.1.4.4. Multiple-Dose Pharmacokinetics of Subcutaneous Solution Formulation of LEN in PWH

Using the developed PopPK model, multiple-dose SC administration was simulated. Bayesian post hoc model parameters were used to calculate the accumulation ratio after 2 SC doses at Day 1 and at Week 26. The accumulation ratio was derived using the $AUC_{tau\ Day\ 1\ to\ Week\ 26}$ and the $AUC_{tau\ Weeks\ 26\ to\ 52}$. The median ($5^{th}$ and 95^{th} percentiles) of the resulting accumulation ratio is 1.17 (1.09 to 1.51), showing minimal accumulation following multiple SC doses (Figure 4).

Figure 4. Simulated LEN Concentration-Time Profile in PWH Who Received SC Doses on Day 1 and Week 26



LEN = lenacapavir; PI = prediction interval; PopPK = population pharmacokinetic; SC = subcutaneous
The solid black line and blue shaded area represent the simulated mean and 90% PI lenacapavir concentrations in adult participants with HIV receiving 2 SC doses on Day 1 and Week 26.
Source: CTRA-2021-1054 LEN PopPK

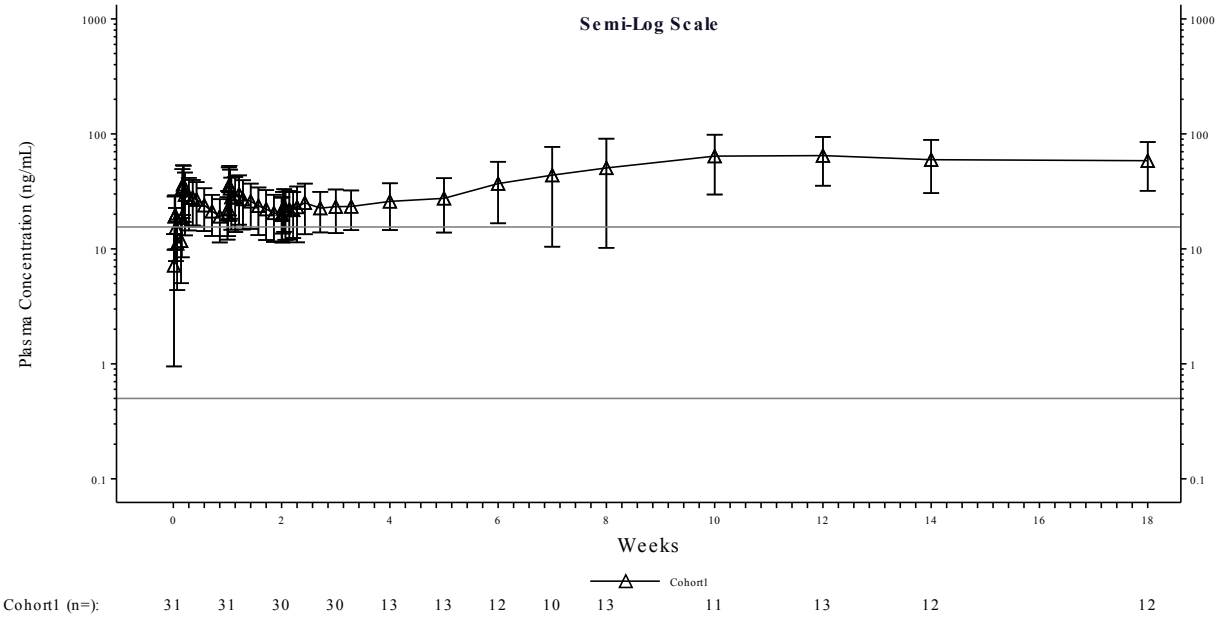
3.1.4.5. Pharmacokinetics of Oral and Subcutaneous Dosing Regimen Used in Phase 2 and Phase 2/3 Studies

Study GS-US-200-5709 is an ongoing Phase 1 study in healthy participants evaluating the safety and PK of LEN oral + SC regimens (Cohorts 1 and 2). The oral + SC regimen in Cohort 1 is the same regimen used in the ongoing Phase 2 and 2/3 studies (Studies GS-US-200-4334 and GS-US-200-4625): oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2, oral LEN 300 mg (1 × 300-mg tablet) on Day 8, and SC LEN 927 mg (2 × 1.5-mL, LEN injection, 309 mg/mL [NaS]) on Day 15. Cohort 2 of Study GS-US-200-5709 evaluated a simplified regimen composed of single SC doses LEN 927 mg (2 × 1.5-mL LEN injection, 309 mg/mL [NaS]) and oral 600 mg (2 × 300-mg tablets) on Day 1, followed by oral 600 mg (2 × 300-mg tablets) on Day 2.

For Cohort 1, mean ± SD LEN plasma concentration-time profile through data cutoff (Day 127 for Cohort 1A and Day 24 for Cohort 1B) are presented in Figure 5. Lenacapavir PK parameters for Days 1, 2, 8, and 15 are summarized in Table 5.

Within a few hours postdose on Day 2, the mean plasma concentrations of LEN and their lower bound 90% CIs exceeded IQ4 (15.5 ng/mL), and the values remained above IQ4 through Week 18 (Study GS-US-200-5709, Section 2.2.3). During the 14-day oral lead-in period, mean $AUC_{0\text{-}14d}$ (%CV) was 7949.3 ng*h/mL (42.0%).

Figure 5. GS-US-200-5709: Mean (SD) Plasma LEN Concentration Versus Time (Cohort 1: Over All Days) (LEN PK Analysis Set)



BLQ = below the limit of quantitation; IQ4 = inhibitory quotient of 4; LEN = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetics
Cohort 1 dosing was 600 mg oral LEN on Days 1 and 2, 300 mg oral LEN on Day 8, and 927 mg SC LEN on Day 15.
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ is defined as 0.5 ng/mL for LEN.
Postdose concentration values ≤ LLOQ are not presented on the figure.
Figures on the semilogarithmic scale were set to include all lower bar and mean/median values > 0 on the Y-axis.
Reference lines indicate IQ4 (15.5 ng/mL) and LLOQ (0.5 ng/mL).
Source: GS-US-200-5709 Interim CSR, Figure 8

Table 5. GS-US-200-5709: Summary Statistics of Plasma Pharmacokinetic Parameters (Cohort 1) (LEN PK Analysis Set)

	LEN			
PK Parameter Mean (% CV)	**Day 1 600 mg oral LEN (2 × 300 mg tablets) (N = 31)**	**Day 2 600 mg oral LEN (2 × 300 mg tablets) (N = 31)**	**Day 8 300 mg oral LEN (1 × 300 mg tablet) (N = 31)**	**Day 15 927 mg SC LEN (2 × 1.5 mL 309 mg/mL NaS) (N = 14)**
C_{max} (ng/mL)[a]	19.8 (16.7, 23.6)	36.7 (31.0, 43.5)	35.7 (30.3, 42.1)	68.2 (47.4, 98.2)
T_{max} (h)[b] [days]	4.00 (4.00, 6.00) [0.17]	6.00 (4.00, 8.00) [0.25]	6.00 (4.00, 8.00) [0.25]	1683.88 (1682.45, 2688.22)[c] [70.1]
C_{last} (ng/mL)	11.2 (60.8)	19.2 (40.8)	20.6 (43.1)	37.3 (72.0)
T_{last} (h)[b] [days]	12.00 (12.00, 12.00) [0.5]	120.00 (120.00, 120.00) [5.0]	144.00 (144.00, 144.00) [6.0]	214.00 (214.00, 2688.22) [8.9]
C_0 (ng/mL)	BLQ (NA)	11.8 (57.3)	20.1 (40.0)	19.7 (41.2)
Lower 90% CI of C_0 (ng/mL)	NA	9.70	17.6	17.2[b]

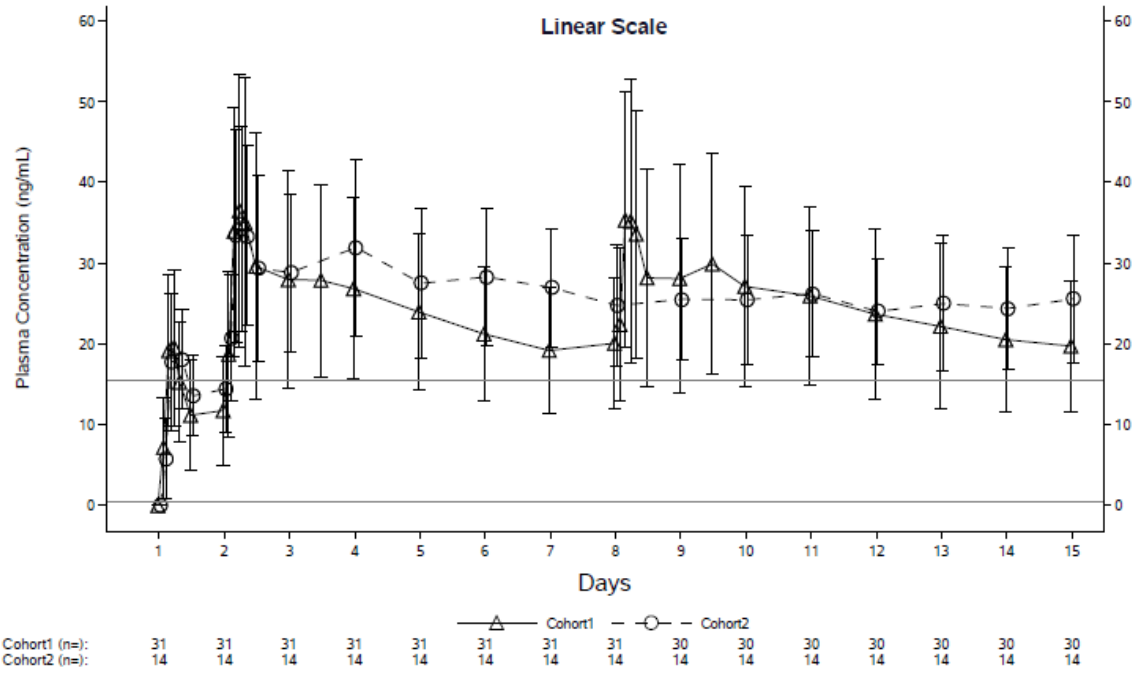
BLQ = below the limit of quantitation; %CV = percentage coefficient of variation; LEN = lenacapavir; LLOQ = lower limit of quantitation; NA = not applicable; NaS = sodium salt; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
a geometric mean (95%CI)
b median (Q1, Q3)
c N = 14 for C_{max} and T_{max}
C_0 represents concentration at time 0 hours.
Values BLQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ is defined as 0.5 ng/mL for LEN.
Source: GS-US-200-5709 Interim CSR, Table 15.10.1.1.2.1

For Cohort 2, mean (SD) LEN plasma concentration-time profiles following SC LEN 927 mg and oral LEN 600 mg on Day 1, followed by oral LEN 600 mg on Day 2 are presented in Figure 6 overlaid with Cohort 1 data up to Day 15. LEN PK parameters for Days 1 and 2 are summarized in Table 6.

Within a few hours postdose (approximately 4h) on Day 2, the mean plasma concentrations and their lower bound 90% CIs exceeded IQ4 (15.5 ng/mL), and the values remained above IQ4 through Day 15 (Study GS-US-200-5709, Section 2.2.3).

Lenacapavir exposure, the time course for achieving plasma concentrations, and the desired target of lower bound 90% CIs exceeding IQ4 (15.5 ng/mL) through Day 15 were comparable between Cohort 2 (a simplified regimen) and Cohort 1 (the Phase 2/3 regimen) in this study.

Figure 6. **GS-US-200-5709: Mean (SD) LEN Plasma Concentration Versus Time (Cohort 1: Up to Day 15 Predose) Versus (Cohort 2, Simplified Regimen: Up to Day 15) (LEN PK Analysis Set)**



BLQ = below the limit of quantitation; IQ4 = inhibitory quotient of 4; LEN = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetics
Cohort 1 dosing was 600 mg oral LEN on Days 1 and 2, 300 mg oral LEN on Day 8, and 927 mg SC LEN on Day 15.
Cohort 2 dosing was 927 mg SC LEN and 600 mg oral LEN on Day 1, and 600 mg oral LEN on Day 2.
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
Reference lines indicate IQ4 (15.5 ng/mL) and LLOQ (0.5 ng/mL).
Postdose concentration values ≤ LLOQ are not presented on the figure.
Figures on the linear scale in which lower bars were negative were truncated to 0 on the Y-axis.
Source: Figure req13091.1

Table 6. GS-US-200-5709: Summary Statistics of Plasma Pharmacokinetic Parameters (Cohort 2) (LEN PK Analysis Set)

PK Parameter Mean (%CV)	LEN	
	Day 1 927 mg SC LEN 600 mg oral LEN (2 × 300 mg tablets) (N = 14)	**Day 2 600 mg oral LEN (2 × 300 mg tablets) (N = 14)**
C_{max} (ng/mL)	19.9 (35.5)	38.6 (33.5)
T_{max} (h)[a] [days]	6.00 (4.00, 8.00) [0.25]	8.00 (6.00, 48.00) [0.33]
C_{last} (ng/mL)	13.6 (36.5)	25.6 (31.2)
T_{last} (h)[a] [days]	12.00 (12.00, 12.00) [0.50]	312.00 (312.00, 312.00) [13.00]

BLQ = below the limit of quantitation; %CV = percentage coefficient of variation; LEN = lenacapavir; LLOQ = lower limit of quantitation; NA = not applicable; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
a median (Q1, Q3)
Values BLQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.
LLOQ is defined as 0.5 ng/mL for LEN.
Source: GS-US-200-5709 Interim CSR, Table 16

3.1.5. Population Pharmacokinetics

Population PK modeling was conducted using NONMEM and the model was established to describe the plasma PK of LEN in healthy participants and PWH receiving LEN, including identification of covariates influencing PK.

For population PK analysis of LEN, plasma concentration data from 5 Phase 1 studies in healthy participants, 1 Phase 2 in treatment naive PWH, and 1 Phase 2/3 study in HTE PWH were utilized. Following administration of LEN, PK data collected through [redacted] 20[redacted] were utilized for the population PK models (CTRA-2021-1054 LEN PopPK). Table 7 presents the number of observations and participants included in the LEN PopPK Model Development and Demographic PK Analysis dataset.

Table 7. Number of Observations and Participants in the Population PK Model Development and Evaluation Datasets for LEN

	Number of Measurable PK Observations	Number of Participants[c]
PopPK Model Development Dataset[a]	7053	384
Demographic PK Analysis Dataset[b]	6855	384

LEN = lenacapavir; PK = pharmacokinetic(s); PopPK = population pharmacokinetic(s); PWH = people with HIV

a PopPK Model Development Dataset included healthy participants and PWH who received LEN and had evaluable PK parameters in Studies GS-US-200-4329, GS-US-200-4071, GS-US-200-4333, GS-US-200-4334, GS-US-200-4538, GS-US-200-4625, or GS-US-200-5709.

b Demographic Population PK Analysis Dataset included healthy participants and PWH who received LEN and had evaluable PK parameters in Studies GS-US-200-4329, GS-US-200-4071, GS-US-200-4333, GS-US-200-4334, GS-US-200-4538, GS-US-200-4625, or GS-US-200-5709.

c Number of healthy participants N = 173 (Studies GS-US-200-4329, GS-US-200-4071, GS-US-200-4333, GS-US-200-4538, and GS-US-200-5709), and PWH N = 211 (Studies GS-US-200-4334 and GS-US-200-4625)

Source: CTRA-2021-1054 LEN PopPK

The final PopPK model that best described LEN plasma concentration data was a 2-compartment PK model with first-order absorption (k_a) for oral, and 2 different absorptions for SC, a direct first-order absorption and an absorption with transit time with 4 transit compartments, and first-order elimination from the central compartment, with interindividual variability terms on k_a, SC first-order transit absorption rate constant (k_{tr}), CL/F, and V_p/F. Covariate analysis indicated effects of weight on CL, central volume of distribution (V_c), peripheral volume of distribution (V_p), and intercompartmental clearance (Q); age on CL and V_p; HIV-infection status on CL and V_p; sex on CL; and dose on CL, boosters or pharmacoenhancers (cobicistat or ritonavir [COBI or RTV]) were found to affect oral bioavailability resulting in 58.7% increase. No other covariates tested (race, ethnicity, BMI, body surface area, eGFR, formulation, and fasting versus fed administration status) were identified as significant for the PopPK of LEN. Details on the LEN PopPK model and the effect of these collective covariates are described in the LEN PopPK Report (CTRA-2021-1054 LEN PopPK) and in Sections 3.1.6 and 3.1.7.

Values of LEN CL/F, V_c/F, Vp/F, Q, k_a, SC first-order direct absorption rate constant (k_{dir}), and k_{tr} for the "typical" 70-kg PWH (median body weight in the Demographic PK Analysis Dataset) were generated using the PopPK model. Following oral administration, the typical values for CL, Q, V_c, and V_p were 4.05 L/h, 41.2 L/h, 68 L, and 908 L, respectively, with an absolute oral bioavailability of 6.24%. The k_a was 0.0287 h^{-1}. Similarly, following SC administration, the typical values for CL, Q, V_c, and V_p were 4.21 L/h, 41.2 L/h, 68 L, and 908 L, respectively, with an absolute SC bioavailability of 103%. The k_{tr} and k_{dir} were 0.00201 h^{-1} and 0.000376 h^{-1}, respectively.

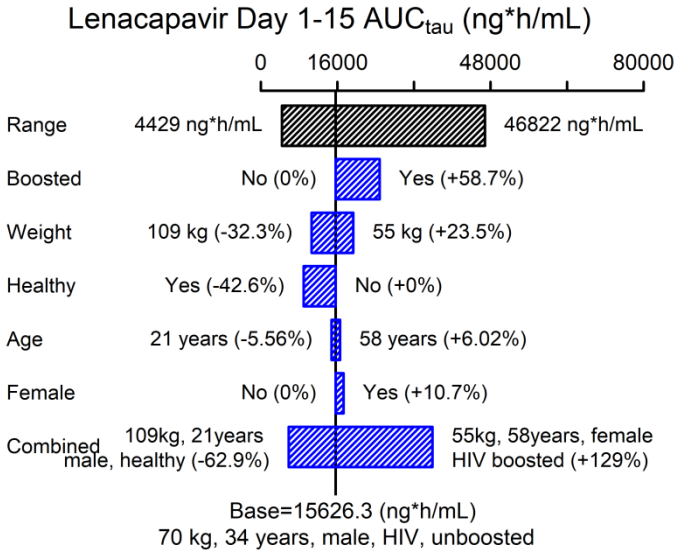
3.1.6. Effect of Intrinsic Factors

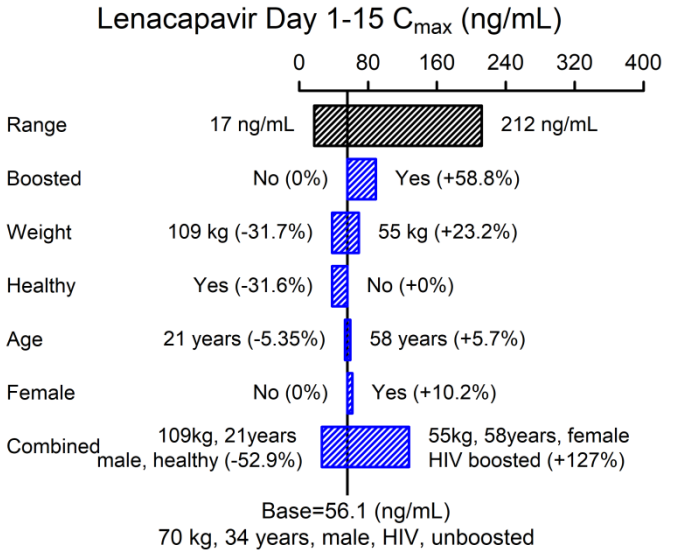
Results of dedicated Phase 1 studies in healthy participants that specifically evaluated intrinsic factors are included in the following sections, if available. Population PK analyses of LEN evaluated the broader potential impact of demographic, treatment, and disease-related factors on PK as covariates in healthy participants and PWH (Section 3.1.5). Sensitivity analysis and statistical comparisons were used to further assess the magnitude of difference in exposure between healthy participants and PWH as well as the impact of model-identified statistically significant covariates on exposure within PWH receiving LEN.

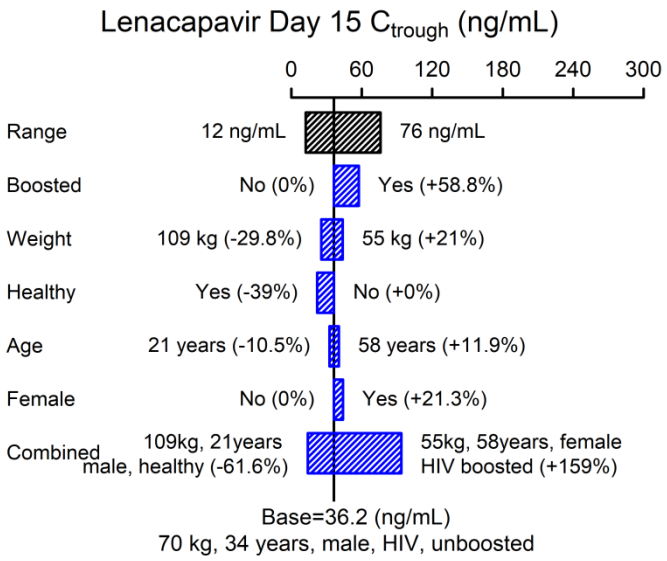
3.1.6.1. Pharmacokinetic Sensitivity Analyses of Participant Covariates

Population PK analysis identified HIV-infection status, age, weight, sex and booster (ie, pharmacoenhancer, such as COBI or RTV) as statistically significant covariates on LEN exposure (Section 3.1.5). Figure 7 and Figure 8 present the sensitivity analysis of statistically significant covariates on LEN exposures. The sensitivity analysis demonstrates that, for the oral lead-in period, the booster effects were the most influential covariates, with an increase in LEN exposures of +58.8%. These were followed by weight effects, with a percentage change in LEN exposures ranging from approximately −32.3% to +23.5% for participants with extreme covariate values (ie, 5th and 95th weight percentiles), respectively. For exposure associated with the SC administration on Day 15, age, weight, and HIV-infection status were the most influential covariates, with overall changes in LEN exposures of approximately 50% for all 3 covariates. The effect of sex was a minimally influential covariate, with a percentage change < 22% for all exposure outcomes considered. Differences in LEN exposure between healthy participants and PWH are further assessed as described in Section 3.1.4.3. Lenacapavir exposures in the Phase 2 and 2/3 population by weight quartiles status are presented in Sections 3.1.6.4 and 3.1.7 as part of demographic or extrinsic factors, as applicable.

Figure 7. **Impact of Statistically Significant Covariates on LEN AUC_{tau}, C_{max}, and C_{trough} on Days 1-15 (Oral Lead-in Period) (LEN PopPK Analysis)**

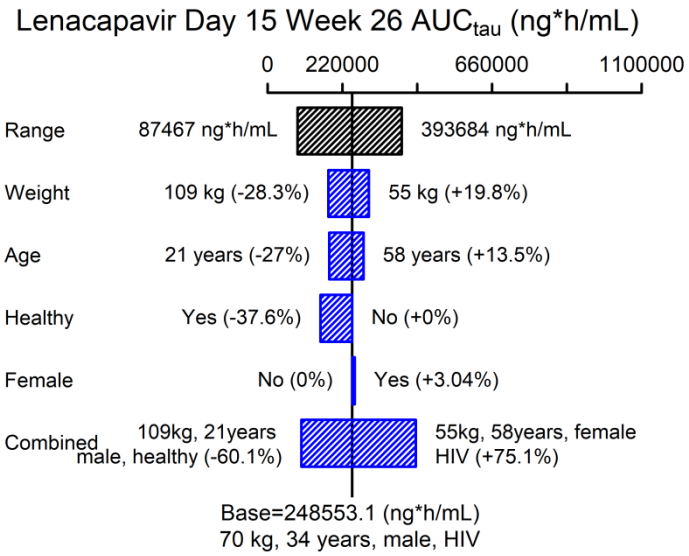


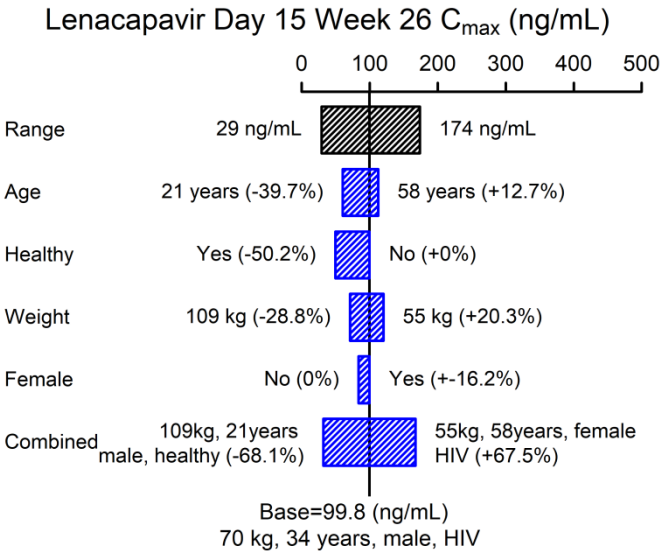


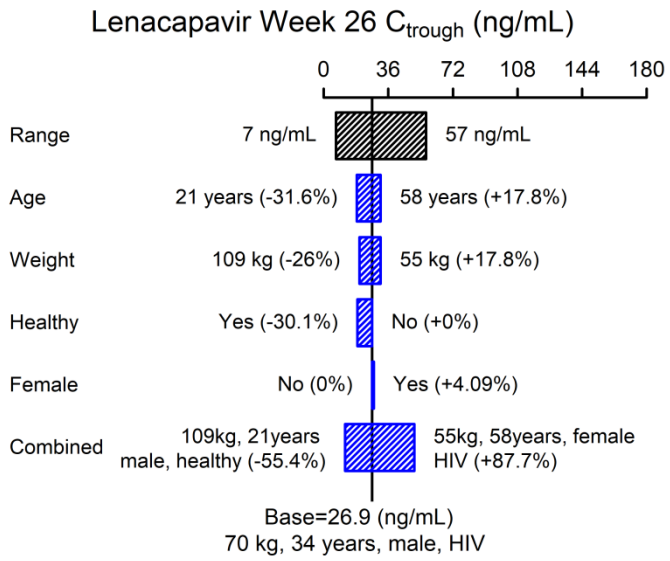


LEN = lenacapavir; PopPK = population pharmacokinetic(s)
Base, as represented by the black vertical line and values, refers to the median post hoc AUC_{tau}, C_{max}, and C_{trough} on Days 1 to 15 of LEN. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the entire analyzed population. Each blue shaded bar represents the influence of single or combined covariates on the steady-state exposure. The label at the left end of the bar represents the covariate(s) being evaluated. The upper and lower values for each covariate capture 90% of the plausible range in the population. The length of each bar describes the potential impact of that covariate(s) on LEN exposure, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The covariates are listed in descending order of influence. The plot for AUC_{tau} is shown in the upper panel, the plot for C_{max} is shown in the middle panel, and C_{trough} is shown in the lower panel.
Source: CTRA-2021-1054 LEN PopPK

Figure 8. **Impact of Statistically Significant Covariates on LEN AUC_{tau}, C_{max}, and C_{trough} on Day 15 to Week 26 (SC Administration) (LEN PopPK Analysis)**







LEN = lenacapavir; PopPK = population pharmacokinetic(s); SC = subcutaneous
Base, as represented by the black vertical line and values, refers to the median post hoc AUC_{tau}, C_{max}, and C_{trough} on Day 15 Week 26 of LEN. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the entire analyzed population. Each blue shaded bar represents the influence of single or combined covariates on the steady-state exposure. The label at the left end of the bar represents the covariate(s) being evaluated. The upper and lower values for each covariate capture 90% of the plausible range in the population. The length of each bar describes the potential impact of that covariate(s) on LEN exposure, with the percentage value in the parentheses at each end representing the percent change of exposure from the base. The covariates are listed in descending order of influence. The plot for AUC_{tau} is shown in the upper panel, the plot for C_{max} is shown in the middle panel, and C_{trough} is shown in the lower panel. Week 26 indicates the number of weeks after SC administration.
Source: CTRA-2021-1054 LEN PopPK

3.1.6.2. Comparison of Pharmacokinetics in People With HIV Relative to Healthy Participants

Population PK and sensitivity analyses demonstrated that HIV-infection status had impact on LEN PK exposure (Section 3.1.6.1).

Lenacapavir exposures (AUC_{tau}, C_{max} and C_{trough}) were 30% to 50% lower in healthy participants as compared to HTE PWH (CTRA-2021-1054 LEN PopPK). In other words, the exposure in HTE PWH were 43% to 100% higher as compared with healthy participants. Importantly, the mean (%CV) C_{trough} of LEN following administration of LEN to PWH (N = 62) in the Phase 2/3 study at Day 15 and at Week 26 was 48.6 (52.1) ng/mL and 35.1 (59.2) ng/mL, respectively, resulting in an IQ of 12.6-fold and 9.1-fold above the $paEC_{95}$ (3.87 ng/mL) against WT HIV-1 virus. A total of 59 PWH participants had LEN concentrations above 15.5 ng/mL corresponding to IQ4 at Day 15 and 56 PWH participants had concentrations above IQ4 at Week 26 (CTRA-2021-1054 LEN PopPK).

3.1.6.3. Effect of Organ Dysfunction

3.1.6.3.1. Effect of Renal Impairment on LEN PK

The effect of renal impairment on the PK of LEN was evaluated in a dedicated Phase 1 study in participants with severe renal impairment ($15 \leq CL_{cr} \leq 29$ mL/min at screening that was unchanged over 3 months) and healthy matched control participants with normal renal function (matched for age [± 10 years]), sex, and BMI (± 20%, $18 \leq BMI \leq 40$ kg/m^2) (Study GS-US-200-4330, Section 2.4.1). Participants received a single dose of oral LEN 300 mg under fed conditions (600 calories, 27% fat).

Lenacapavir exposures (AUC_{inf} and C_{max}) increased 84% and 162%, respectively, in participants with severe renal impairment compared with healthy matched participants (Table 8). Lenacapavir plasma protein binding were similar in both groups. Exploratory analyses showed lack of a correlation between LEN exposure (AUC and C_{max}) and baseline renal function estimated by eGFR calculated by the Modification of Diet in Renal Disease Study equation for participants with severe renal impairment (Spearman correlation coefficient = −0.030 and −0.091 for LEN AUC_{inf} and $C_{max,}$ respectively) (Study GS-US-200-4330, Section 2.4.1).

These observed increases in LEN exposure with severe renal impairment (< 2-fold) are not deemed clinically meaningful and do not indicate the necessity for dose adjustment in patients with renal impairment because of the following reasons:

- Based on nonclinical data and preliminary data from the LEN mass-balance study (Study GS-US-200-4329, Section 2.2.1), renal route plays a minor role (< 1% of dose recovered) in LEN elimination.

- Population PK analysis that included mild and moderate renal impaired participants (N = 40, CL_{cr} range 46.8 to 86.9 mL/min) did not identify renal function as a statistically significant covariate on LEN exposure (CTRA-2021-1054 LEN PopPK).

- Cumulative safety data from clinical studies suggest that LEN is well tolerated and adverse reactions were generally mild (Summary of Clinical Safety [m2.7.4]).

- In Study GS-US-200-4071 up to 1800 mg of single dose oral LEN was tolerated in the healthy participants. In Study GS-US-200-4332, twice-daily administration of oral LEN 600 mg for up to 8 days resulted in C_{max} values that were approximately 2.2- and 8.8-fold higher on Study Days 6 and 12, respectively, in comparison with the therapeutic C_{max} derived from PopPK estimates from the Phase 2/3 registrational study in HTE PWH. Likewise, LEN AUC_{tau} on Study Days 6 and 12 of this study was approximately 3.5- and 15.0-fold higher, respectively, relative to the Phase 2/3 therapeutic exposure estimate. A similar occurrence of any AEs was reported for both Day 6 LEN (27.1%,13 participants) and Day 12 LEN (27.7%, 13 participants).

Lenacapavir has not been studied in people with end-stage renal disease not on dialysis. As LEN is greater than 98.5% protein bound, dialysis is not expected to alter exposures to LEN.

Table 8. GS-US-200-4330: LEN PK Parameters Following a Single Dose of Oral LEN 300 mg in Participants With Severe Renal Impairment and Matched Healthy Participants (LEN PK Analysis Set)

PK Parameter	Geometric Mean (95% CI)		Renal Impairment/Healthy Match %GLSM Ratio (90% CI)
	Severe Renal Impairment (N = 10)	Healthy Match Control (N = 10)	
AUC_{inf} (h*ng/mL)	12,100.1 (5579.1, 26,243.1)	6591.2 (4518.3, 9615.1)	183.58 (93.55, 360.24)
AUC_{last} (h*ng/mL)	11,456.2 (5210.4, 25,188.9)	6048.1 (4087.7, 8948.8)	189.42 (95.19, 376.91)
C_{max} (ng/mL)	51.5 (18.9, 140.5)	19.7 (13.2, 29.3)	261.95 (111.77, 613.91)
CL/F (mL/h)	24,793.1 (11,431.6, 53,771.8)	45,515.3 (31,201.0, 66,396.7)	—
T_{max} (h)[a]	8.00 (6.00, 24.0)	6.00 (6.00, 8.00)	—
$t_{1/2}$ (h)[a]	234 (178, 354)	319 (270, 357)	—

GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
GLSM Ratio = (Severe Renal Impairment/Healthy Match Control) × 100
a $t_{1/2}$ and T_{max} are presented as median (Q1, Q3)
Source: GS-US-200-4330 CSR, Table 15.10.1.1.2.1

3.1.6.3.2. Hepatic Impairment

The effect of hepatic impairment on the PK of LEN was evaluated in a dedicated Phase 1 study in participants with moderate hepatic impairment (CPT Class B) and healthy matched control participants with normal hepatic function (matched for sex at birth, age [± 10 years], race, and BMI [± 15% 18 ≤ BMI ≤ 38 kg/m^2]); Study GS-US-200-4331, Section 2.4.2). Participants received a single, oral dose of LEN 300 mg under fed conditions (600 calories, 27% fat). Lenacapavir AUC_{inf} and C_{max} were approximately 47% and 161% higher, respectively, in participants with moderate hepatic impairment relative to their matched healthy controls with normal hepatic function (Table 9). Lenacapavir plasma protein binding were similar in both groups. Exploratory analyses indicated no significant relationships between LEN exposure (AUC and C_{max}) and CPT score or individual elements of CPT classification (albumin, total bilirubin, prothrombin time, and INR).

These findings are generally consistent with nonclinical data and the human ADME study, which indicated that LEN is cleared by metabolism, excretion into bile, and intestinal secretion by P-gp, with 75.9% of the dose recovered in feces (Section 3.1.3). However, unchanged LEN accounted for 68.8% of plasma and 32.9% of feces. In addition, based on cumulative safety data from clinical studies across a range of oral and SC doses, LEN is well tolerated (m2.7.4) as detailed above in Section 3.1.6.3.1. Considering the overall clinical safety as well as limited metabolism of LEN, no dose adjustment is recommended in participants with mild to moderate hepatic impairment. Lenacapavir has not been evaluated in participants with severe hepatic impairment.

Table 9. GS-US-200-4331: Effect of Moderate Hepatic Impairment on the Pharmacokinetics of LEN Following Single-Dosing of LEN 300 mg (LEN PK Analysis Set)

PK Parameter	Geometric Mean (95% CI)		Hepatic Impairment/Normal Hepatic Function GLSM Ratio (%) 90% CI
	Moderate Hepatic Impairment (N = 10)	Normal Hepatic Function (N = 10)	
AUC_{inf} (h*ng/mL)	11,997.2 7785.7, 18,486.8)	8184.2 (5652.0, 11,850.9)	146.59 (94.70, 226.91)
AUC_{last} (h*ng/mL)	11,877.9 (7705.6, 18,309.3)	7586.3 (5223.3, 11,018.4)	156.57 (100.98, 242.76)
C_{max} (ng/mL)	61.1 (33.9, 110.3)	23.4 (15.8, 34.7)	261.23 (151.03, 451.85)

GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile
GLSM Ratio = (Hepatic Impairment/Normal Hepatic Function) × 100
Source: GS-US-200-4331 CSR, Table 15.10.1.1.2.1

3.1.6.4. Demographic Factors

Demographic factors are discussed in the following sections. Only demographic factors identified by PopPK modeling as statistically significant covariates influencing the PK of LEN are discussed in detail, including statistical comparisons to illustrate the magnitude of any difference in the PK parameters. Additionally, a recommendation is provided for using LEN in each of the demographic categories.

3.1.6.4.1. Age

Age was identified as a statistically significant covariate on the PK of LEN (CTRA-2021-1054 LEN PopPK). The change in exposure (−39.7 to +19.9%) observed in participants ≥ 50 years old, was not considered clinically meaningful based on the exposure-efficacy/safety relationship for LEN. Thus, no dose adjustment of LEN is warranted based on age (CTRA-2021-1054 LEN PopPK).

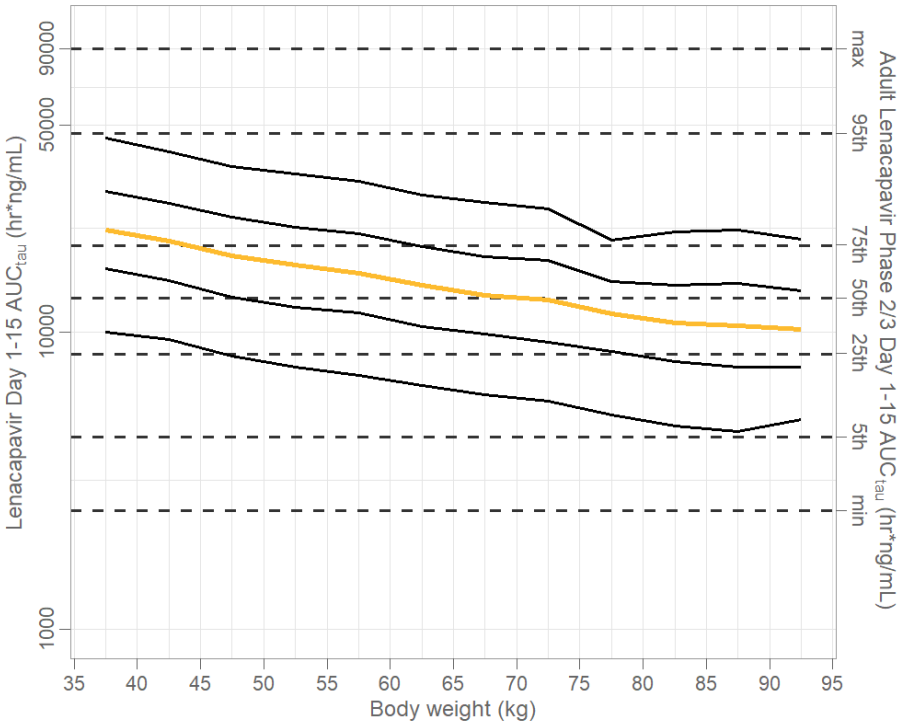
3.1.6.4.1.1. Geriatrics

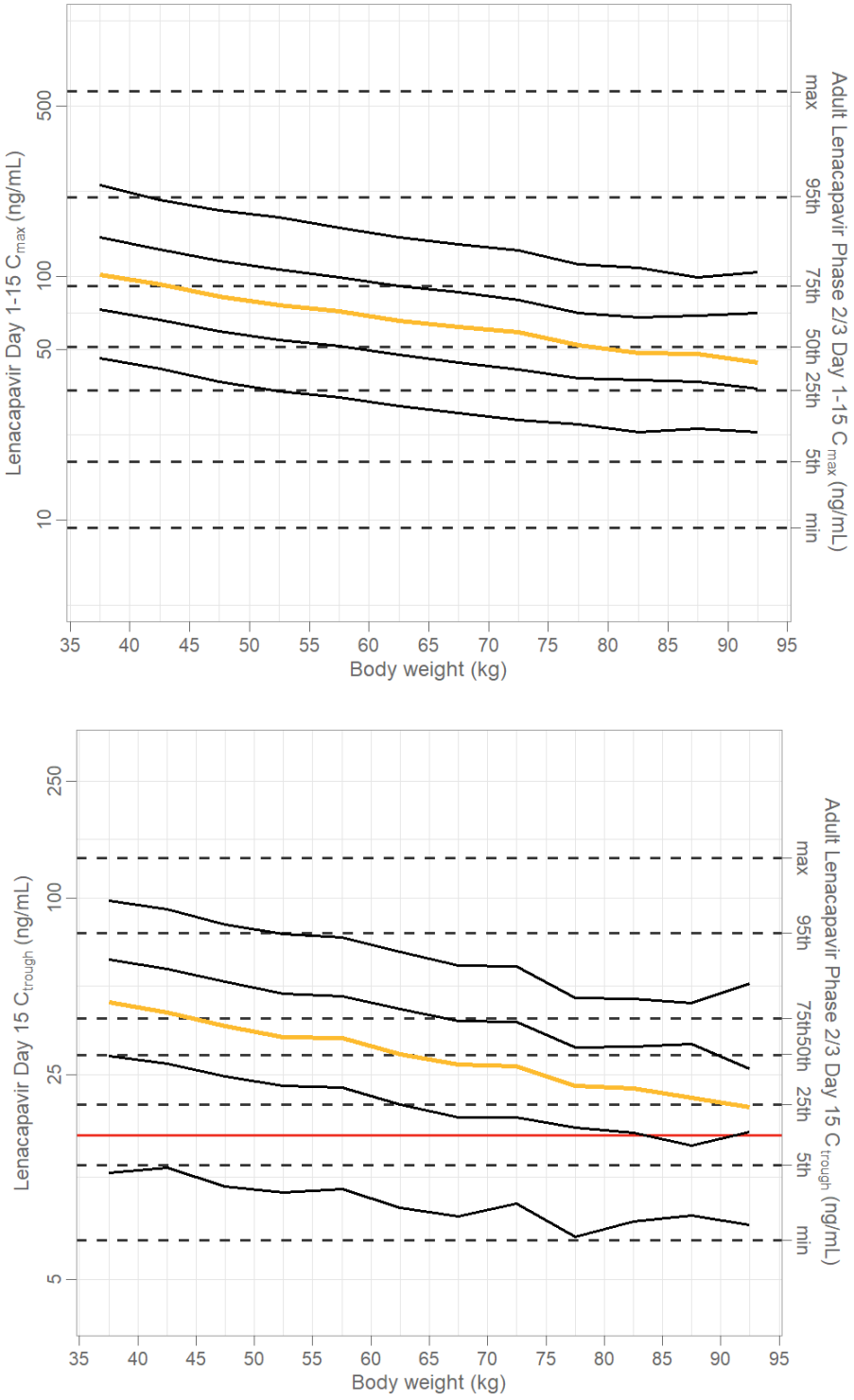
No clinically meaningful difference in exposure was observed in participants ≥ 65 to 78 years old (N = 5) compared with participants < 65 years old (N = 155) (Table Req12982.1).

3.1.6.4.1.2. Pediatrics

Use of LEN in pediatric participants has not been evaluated in clinical studies at this time. Furthermore, while the protocol allowed it, no adolescents have been enrolled in the LEN clinical development program. In the absence of observed LEN PK data, model-based simulations were performed in pediatric participants 12 < 18 years of age and weighing ≥ 35 kg following the Phase 2/3 dosing regimen. Lenacapavir-simulated exposures (Figure 9, Figure 10, and Figure 11) were largely contained within the range observed in the adult Phase 2/3 population. The median simulated exposures were found to be within the 25th and 75th percentiles of adult's exposure across all weight groups. Based on these simulations, LEN may be administered to adolescent HTE PWH 12 to < 18 years of age and weighting ≥ 35 kg without any dose modification (CTRA-2021-1054 LEN PopPK).

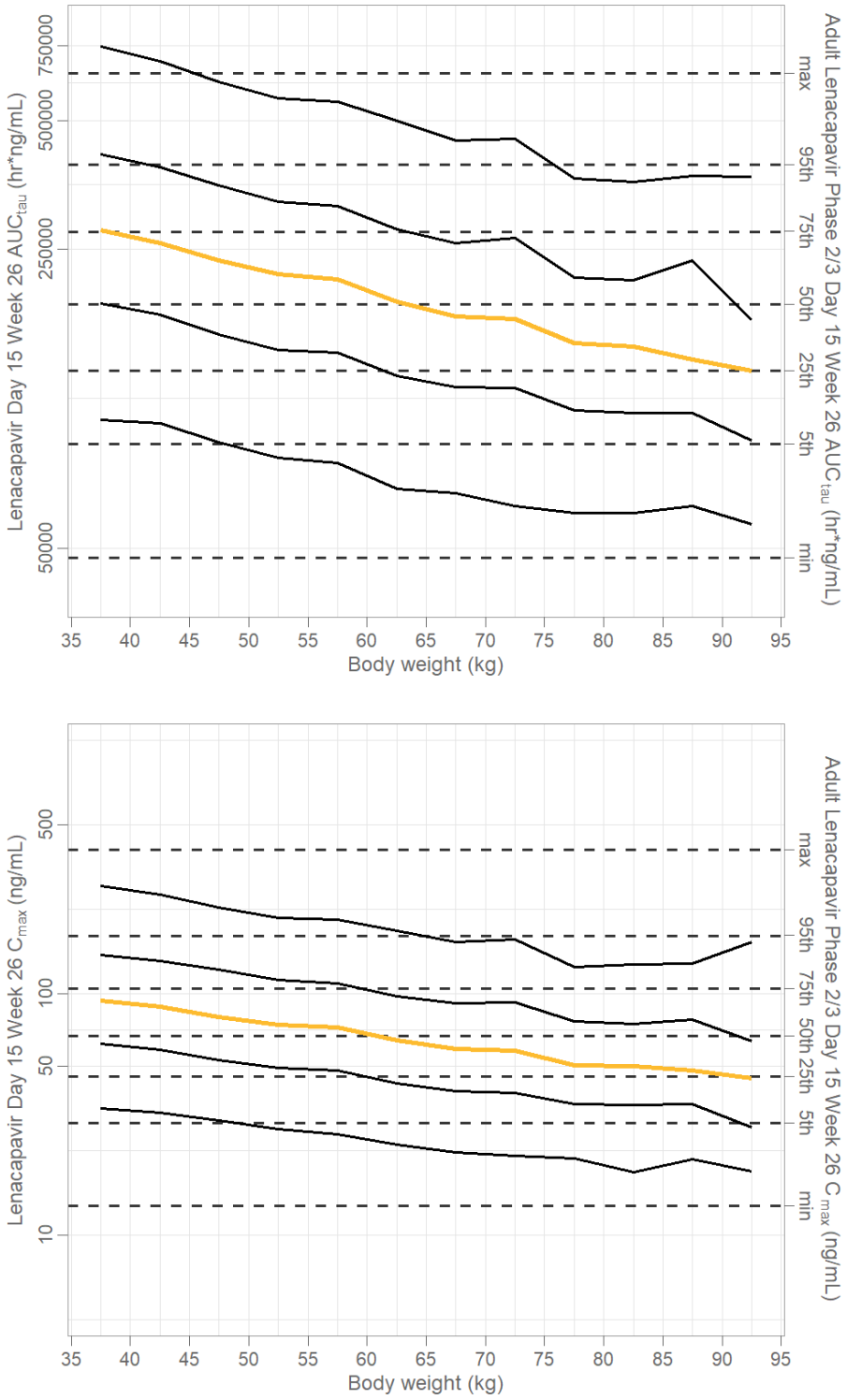
Figure 9. PopPK Model-Based, Simulated LEN AUC_{tau}, C_{max}, and C_{trough} Days 1 to 15 (Oral Lead-In Period) in Pediatric Participants ≥ 35 kg With HIV Who Received the Phase 2/3 Regimen

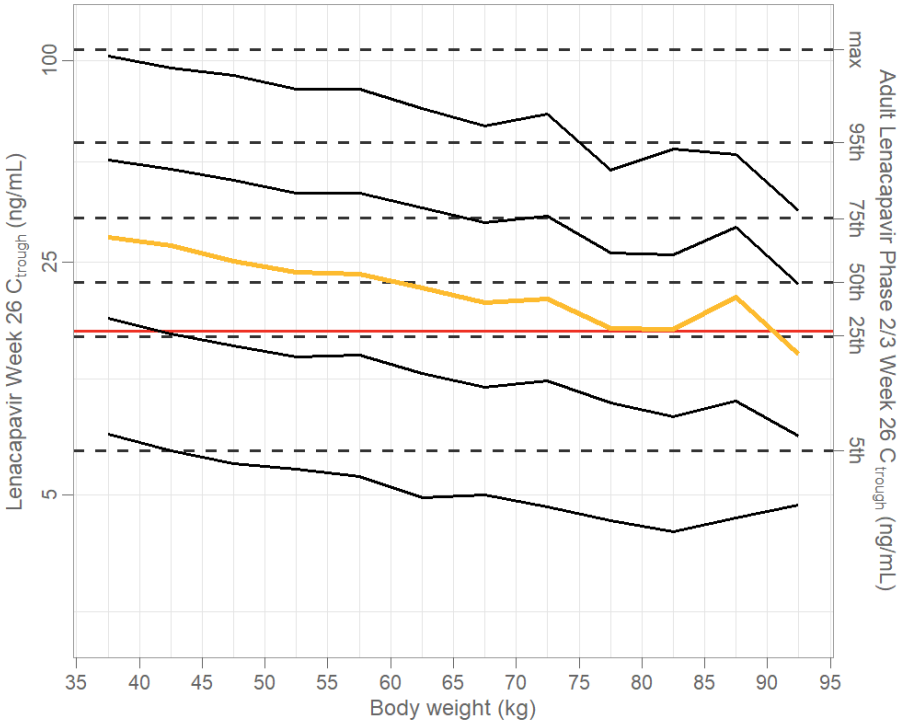




LEN = lenacapavir; PopPK = population pharmacokinetic
Solid lines represent the 5th, 25th, 50th (yellow), 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; horizontal red solid line represents the IQ4 threshold at 15.5 ng/mL. Adult exposures are the PopPK-predicted exposures from the current analysis. Min; 5th, 25th, 50th, 75th, and 95th percentiles; and max are shown. Top, mid, and bottom panels show, respectively, AUC_{tau}, C_{max}, and C_{trough}.
Source: CTRA-2021-1054 LEN PopPK

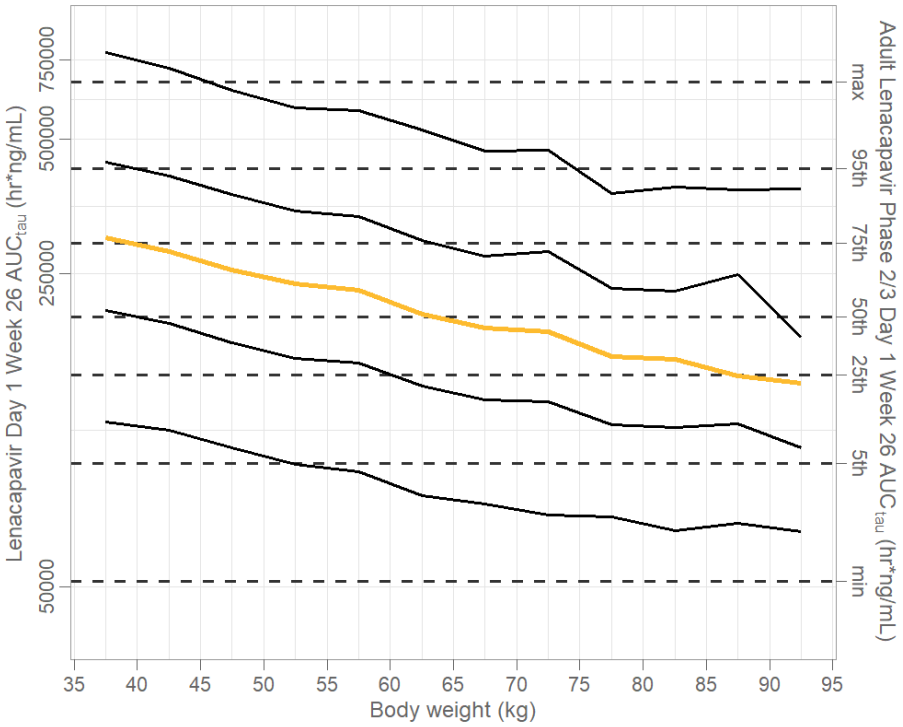
Figure 10. **PopPK Model-Based, Simulated LEN AUC_{tau}, C_{max}, and C_{trough} Day 15 to Week 26 (SC Administration) in Pediatric Participants ≥ 35 kg With HIV Who Received the Phase 2/3 Regimen**

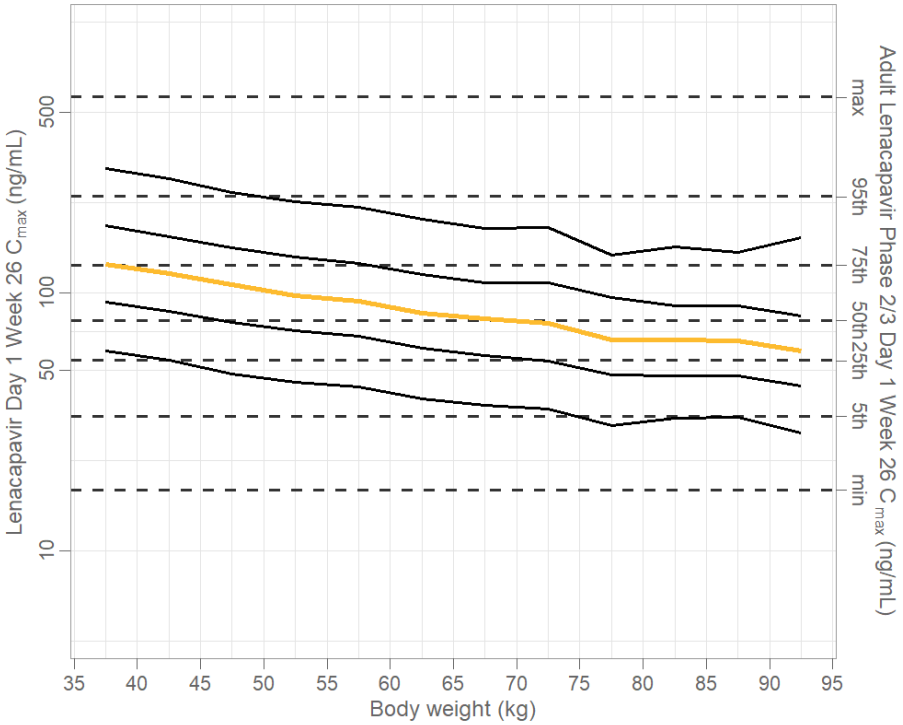




LEN = lenacapavir; PopPK = population pharmacokinetic; SC = subcutaneous
Solid lines represent the 5th, 25th, 50th (yellow), 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures; horizontal red solid line represents the IQ4 threshold at 15.5 ng/mL. Adult exposures are the PopPK-predicted exposures from the current analysis. Min; 5th, 25th, 50th, 75th, and 95th percentiles; and max are shown. Top, mid, and bottom panels show, respectively, AUC_{tau}, C_{max}, and C_{trough}. Week 26 indicates the number of weeks after SC administration. In the bottom panel, the minimum C_{trough} value observed in adults is not shown (0.2 ng/mL).
Source: CTRA-2021-1054 LEN PopPK

Figure 11. **PopPK Model-Based, Simulated LEN AUC_{tau} and C_{max} Day 1 to Week 26 (Entire Treatment Duration) in Pediatric Participants ≥ 35 kg With HIV Who Received the Phase 2/3 Regimen**





LEN = lenacapavir; PopPK = population pharmacokinetic; SC = subcutaneous
Solid lines represent the 5th, 25th, 50th, 75th, and 95th percentiles of simulated pediatric exposures; horizontal dashed lines represent distribution of adult exposures. Adult exposures are the PopPK-predicted exposures from the current analysis. Min; 5th, 25th, 50th, 75th, and 95th percentiles; and max are shown. Top and bottom panels show, respectively, AUC_{tau}, and C_{max}. Week 26 indicates the number of weeks after SC administration.
Source: CTRA-2021-1054 LEN PopPK

3.1.6.4.2. Weight

Body weight was identified as a statistically significant covariate for LEN PK based on population PK analyses (CTRA-2021-1054 LEN PopPK).

Consistent with the identified covariate effect, LEN exposures were found to increase with decreasing weight. These differences were small (20% to 23%) compared to a > 40 kg difference in median weight of first quartile (Q1) versus fourth quartile (Q4) and not considered clinically meaningful based on the exposure-efficacy/safety relationship for LEN. The exposure data across body weight quartiles showed that there were no clinically relevant differences in the overall range and distribution of AUC and C_{max} for the dosing regimen. While C_{trough} was lower (39%) in quartile 4, it was well above the IQ4, suggesting no dose adjustment is warranted based on body weight.

3.1.6.4.3. Race/Ethnicity

No impact of race or ethnicity was identified on the PK of LEN (CTRA-2021-1054 LEN PopPK). Therefore, no dose adjustment of LEN is warranted based on race or ethnicity.

3.1.6.4.4. Sex

Sex was identified as a statistically significant covariate for LEN PK based on PopPK analyses (CTRA-2021-1054 LEN PopPK). Overall, LEN exposures were higher in female participants than those observed in male participants. However, the effect of sex was a minimally influential covariate, with a percent change less than 22% for all PK parameters. Furthermore, dose adjustment is therefore not required as the exposure difference is not clinically meaningful.

3.1.7. Effect of Extrinsic Factors

An integrated summary of the results of dedicated Phase 1 studies and PopPK modeling is presented in the following sections to convey the clinical relevance, or lack thereof, regarding specific extrinsic factors and to provide dosing recommendation for use of LEN, where applicable.

3.1.7.1. Food Effect

The effect of food on LEN PK was evaluated with a high- or low-fat meal relative to fasted conditions using the 300-mg tablet formulation (intended commercial formulation, Study GS-US-200-4071, m2.7.1, Section 2.2.1).

For the SC LEN formulation, the effect of food was not evaluated as food is not expected to have any influence on exposure following SC administration.

Administration of LEN tablets with either a high-fat, high-calorie meal (approximately 1000 kcal and 50% fat) or a light meal (approximately 400 kcal and 25% fat) resulted in comparable AUC or C_{max}, relative to fasted conditions. The 90% CIs of GLSM ratio for the AUC and C_{max} for both high-fat versus fasted and low-fat versus fasted included 100% (Study GS-US-200-4071, m2.7.1, Section 2.2.1). Based on these results, food is not expected to have a clinically relevant effect on the PK of LEN oral tablets. Lenacapavir is administered without regard to food in the ongoing Phase 2 and 2/3 studies (Studies GS-US-200-4334 and GS-US-200-4625). These data support dosing of LEN tablets (for oral loading) without regard to food. Based on PopPK analysis, food status was not identified as a statistically significant covariate on LEN PK (CTRA-2021-1054 LEN PopPK).

Table 10. GS-US-200-4071: Effect of Food on the PK of LEN Following Single-Dose Oral Administration of LEN 300-mg Tablets (LEN PK Analysis Set)

PK Parameter Geometric Mean (95% CI)	300 mg Fasted (N = 8)	300 mg + High-Fat Meal (N = 8)	300 mg + Light Meal (N = 8)	%GLSM Ratio (90%CI)	
				High Fat/ Fasted	Light Meal/ Fasted
AUC_{inf} (h*ng/mL)	6513.7 (3825.6, 11090.8)	7505.4 (5338.7, 10551.4)	6424.2 (4022.8, 10259.0)	115.22 (71.97, 184.48)	98.63 (58.17, 167.21)
C_{max} (ng/mL)	22.8 (10.5, 49.8)	33.2 (24.5, 44.9)	26.5 (14.4, 48.8)	145.16 (77.90, 270.48)	115.82 (55.40, 242.14)
T_{max} (h)[a]	4.00 (4.00, 6.00)	5.00 (4.00, 6.00)	6.00 (4.00, 8.00)	NC	NC
$t_{1/2}$ (h)[a] [days][b]	242.64 (204.37, 281.36) [10.1]	267.11 (243.70, 357.17) [11.1]	287.46 (255.37, 321.85) [12.0]	NC	NC

GLSM = geometric least-square mean; LEN = lenacapavir; NC = not calculated; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
a median (Q1, Q3)
b median $t_{1/2}$ presented in days to 3 significant figures
Source: GS-US-200-4071 CSR, Table 15.10.1.1.2.3

3.1.7.2. Drug-Drug Interaction Potential

3.1.7.2.1. Potential for LEN to Affect Other Drugs

In vitro studies conducted to assess the potential for LEN to perpetrate DDIs suggest LEN may be an inhibitor of OATP and CYP3A (m2.6.4). In addition, nonclinical data indicate pH may affect the solubility of oral LEN. Inhibition of intestinal efflux transporters (P-gp and BCRP) following oral dosing of LEN cannot be ruled out from in vitro data as concentrations above 1 µM were not evaluated (m2.6.4).

At concentrations up to 25 µM, LEN had little or no inhibitory effect on the reversible activities of human hepatic microsomal CYPs 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 (half-maximal inhibitory concentration [IC_{50}] > 25 µM). Clinically relevant interactions with substrates of these enzymes are unlikely (m2.6.4).

Lenacapavir inhibited human UGT1A1 with an IC_{50} of 3.2 µM. The human plasma concentration of LEN is low (0.112 µM); SC or oral administration of LEN is unlikely to cause marked drug interactions through inhibition of this enzyme based on the regulatory guideline assessment.

Lenacapavir did not inhibit organic anion transporter (OAT)1-, OAT3-, organic cation transporter (OCT)1-, OCT2-, and multidrug and toxin extrusion (MATE)2-K-mediated transport when tested up to 10 µM. Lenacapavir showed concentration-dependent inhibition of MATE1 and bile salt export pump (BSEP) mediated transport with IC_{50} values of 2.39 and 1.21 µM, respectively. These data suggest a low potential for LEN to cause clinically relevant DDI mediated by MATE1 and BSEP inhibition. Lenacapavir showed dose-dependent inhibition of OATP1B1 and OATP1B3 mediated uptake with IC_{50} values of 0.021 and 0.049 µM, respectively (m2.6.4).

Based on the nonclinical DDI characterization of LEN, the effects of LEN on the PK of coadministered drugs (eg, commonly used medications and/or mechanistic probes) were evaluated in healthy participants in a Phase 1 study (Study GS-US-200-4333, Section 2.5.1). Table 11 summarizes the effect of oral LEN on the PK coadministered drugs in healthy participants.

Table 11. GS-US-200-4333: Effect of Oral LEN 600 mg Administered Twice Daily at Clinically Relevant Plasma Concentrations[a] on the PK of Coadministered Drugs in Healthy Participants (PK Analysis Set)

Probe	Abbreviation	Pathway	Test/Reference %GLSM Ratio (90% CI)	
			C_{max}	AUC_{inf}
LEN as perpetrator				
Pitavastatin (simultaneous administration)	PIT	OATP substrate	99.88 (83.57, 119.38)	111.44 (99.63, 124.65)
Pitavastatin (staggered administration 3 days after LEN)			85.13 (68.72, 105.47)	96.40 (87.06, 106.74)
Rosuvastatin	ROS	BCRP substrate	157.48 (138.08, 179.62)	130.72 (119.20, 143.35)
Midazolam (simultaneous administration)	MDZ	CYP3A substrate	193.64 (180.63, 207.59)	358.99 (329.52, 391.10)
	1-OH MDZ		54.07 (49.67, 58.86)	75.71 (71.63, 80.02)
Midazolam (staggered administration 24h after LEN)	MDZ		215.69 (201.84, 230.49)	407.58 (377.09, 440.54)
	1-OH MDZ		52.01 (47.59, 56.83)	83.65 (79.78, 87.71)
Tenofovir alafenamide	TAF	P-gp substrate	124.46 (98.34, 157.53)	131.83 (109.22, 159.13)[b]
	TFV		123.08 (105.25, 143.93)	147.39Ca (126.95, 171.11)

BRCP = breast cancer resistance protein; CYP = cytochrome P450 enzyme; GLSM = geometric least-squares mean; LEN = lenacapavir; MDZ = midazolam; OATP = organic anion transporting polypeptide; P-gp = P-glycoprotein; PIT = pitavastatin; PK = pharmacokinetics; ROS = rosuvastatin; TAF = tenofovir alafenamide; TFV = tenofovir

a Following the loading regimen of LEN 600 mg twice daily for 2 days, single doses of LEN 600 mg were administered with each probe substrate.

b value is AUC_{last}

Source: Study GS-US-200-4333 CSR, Tables 24, 26, 28, 30, and 32

Coadministration of PIT, a probe substrate for OATP given either simultaneously with LEN or staggered from LEN, resulted in no change in the PK of PIT. Based on these results, LEN is not considered a clinically relevant inhibitor or inducer of OATP.

Coadministration of ROS, a probe substrate for BCRP, with LEN resulted in a 31% increase in ROS AUC_{inf}. Based on these results, LEN is a weak inhibitor of BCRP transporters.

Coadministration of MDZ, a probe substrate for CYP3A, with LEN resulted in a 259% increase in MDZ AUC_{inf}. Based on these results, LEN moderately inhibits CYP3A (refer to Table 13 for the proposed recommendations for this interaction). Staggered administration of MDZ was evaluated to characterize the DDI liability of SC LEN on the CYP3A pathway. Coadministration of single dose MDZ staggered from LEN resulted in 308% and 116% increases in AUC_{inf} and C_{max} of MDZ, respectively.

Coadministration of tenofovir alafenamide (TAF), a probe substrate for P-gp, with LEN resulted in a 32% increase in TAF AUC_{last}. Based on these results, LEN is a weak inhibitor of P-gp transporters.

3.1.7.2.2. Potential for Other Drugs to Affect LEN Pharmacokinetics (LEN as a Victim)

In vitro studies conducted to assess the potential for drug transporters and metabolizing enzymes to influence the disposition of LEN have identified LEN as a potential substrate for P-gp, CYP3A, and UGT1A1. Lenacapavir is a Biopharmaceutics Classification System Class IV molecule with low solubility in biorelevant fluids and exhibits low permeability across monolayers of human colorectal carcinoma cells (Caco-2) with measurable efflux. Lenacapavir is a weak base with pH-dependent solubility (higher solubility at pH ≥ 6) indicating a potential for interaction with gastric ARAs. As such, a Phase 1 study evaluated the effect of strong CYP/P-gp inhibitors, strong UGT1A1/CYP3A/P-gp inhibitors, strong and moderate inducers and gastric ARAs on the PK of LEN (Study GS-US-200-4333, Section 2.5.1). Table 12 summarizes the effect of coadministered drugs on the PK of LEN following administration of oral LEN in healthy participants.

Table 12. GS-US-200-4333: Effect of Coadministered Drugs on the PK of LEN following Administration of Oral LEN 300 mg in Healthy Participants (PK Analysis Set)

Probe	Abbreviation	Pathway	Test / Reference %GLSM Ratio (90% CI)	
			C_{max}	AUC_{inf}
Cobicistat	COBI	Strong CYP and P-gp inhibitor	209.74 (161.98, 271.60)	227.62 (174.98, 296.09)
Darunavir/cobicistat	DRV/COBI	Strong CYP3A and an inhibitor and inducer of P-gp	229.65 (178.75, 295.05)	194.16 (149.59, 252.01)
Atazanavir/cobicistat	ATV/COBI	Strong CYP3A, P-gp and UGT1A1inhibitor	659.99 (498.87, 873.14)	421.44 (319.01, 556.75)
Voriconazole	VORI	Strong CYP3A inhibitor	109.49 (81.30, 147.45)	141.19 (109.89, 181.40)
Rifampin	RIF	Strong CYP3A, P-gp andUGT1A1 inducer	44.72 (33.56, 59.58)	15.50 (12.16, 19.75)
Efavirenz	EFV	Moderate CYP3A and P-gp inducer	64.14 (44.52, 92.41)	43.63 (32.12, 59.27)
Famotidine[a]	FAM	H2RA, acid-reducing agent	100.57 (75.22, 134.45)	127.74 (100.17, 162.89)

CYP = cytochrome P450 enzyme; FAM = famotidine; GLSM = geometric least-squares mean; H2RA = histamine 2 receptor antagonist; LEN = lenacapavir; P-gp = P-glycoprotein; PK = pharmacokinetics; UGT = uridine diphosphate glucuronosyltransferase
a Famotidine was administered 2 hours before LEN
Source: Study GS-US-200-4333 CSR, Tables 24, 26, 28, 30, and 32

Coadministration of LEN with multiple doses of strong CYP3A inhibitor, VORI, resulted in moderate increases (41%) in LEN AUC (Study GS-US-200-4333, Section 2.5.1). These data confirm that LEN is a substrate of CYP3A. Coadministration of oral LEN with multiple doses of strong CYP3A and P-gp inhibitors, COBI and darunavir/cobicistat (DRV/COBI), resulted in increases (128% for COBI and 94% for DRV/COBI) in LEN AUC_{inf} (Study GS-US-200-4333). These data confirm that LEN is a substrate of both CYP3A and P-gp. Coadministration of LEN with multiple doses of strong CYP3A, P-gp and UGT1A1 inhibitor, atazanavir/cobicistat (ATV/COBI), resulted in an increase (321%) in LEN AUC_{inf} (Study GS-US-200-4333).

Coadministration of RIF, a CYP3A, P-gp and UGT1A1 inducer, with LEN resulted in an 84% decrease in LEN AUC (GLSM Ratio of 16%, Study GS-US-200-4333). Coadministration of EFV, a moderate CYP3A and P-gp inducer, resulted in a 56% decrease in LEN AUC_{inf} (GLSM ratio of 44%, Study GS-US-200-4333). These data confirm that LEN is susceptible to induction effects.

Administration of LEN 2 hours after administration of FAM (40 mg twice daily), when maximal gastric acid suppression activity is expected, resulted in a 28% increase in LEN AUC_{inf} compared with administration of LEN alone (Study GS-US-200-4333). These data demonstrate that LEN exposure is not affected by gastric ARAs to a clinically relevant extent.

3.1.7.2.3. Summary of Potential Drug-Drug Interaction Following Administration of LEN

LEN as a Perpetrator

- Based on the evaluation of various probe substrates coadministered with LEN, LEN appears to inhibit P-gp transporters (as observed with coadministration of LEN with TAF resulting in a 32% increase in AUC_{last}) and BCRP transporters (as observed with coadministration of LEN with ROS resulting in a 31% increase in AUC_{inf}). Lenacapavir does not inhibit OATP transporters (as observed with coadministration of LEN with PIT).

- Based on the magnitude of effect on CYP3A probe substrate (259% increase in MDZ AUC_{inf}), LEN can be considered a moderate inhibitor of CYP3A following oral administration. The similar magnitude of effect of LEN on MDZ when MDZ administered was staggered 24 hours after LEN administration suggests that similar effects would be expected following SC administration of LEN.

LEN as a Victim

Inhibition

- Coadministration of a single dose of LEN with a strong CYP3A4 inhibitor (VORI) resulted in increases of 41% in AUC_{inf}.

- Coadministration of a single dose of LEN with a strong CYP3A4 and P-gp inhibitor (COBI) and a strong inhibitor of CYP3A, and an inhibitor and inducer of P-gp (DRV/COBI) resulted in 128% and 94% increases in AUC_{inf}, respectively, confirming that LEN is a substrate of both CYP3A and P-gp.

- Coadministration of a single dose of LEN with a strong CYP3A4, P-gp and UGT1A1 inhibitor together (ATV+COBI) resulted in 321% increase in AUC_{inf}. The larger effect observed with ATV/COBI relative to COBI alone suggests that UGT1A1 is an elimination pathway for LEN when CYP3A and P-gp are also inhibited.

Induction

- Coadministration of a single dose of LEN with a strong CYP3A4, P-gp, and UGT1A1 inducer (RIF) resulted in decreases of 84% in AUC_{inf} and 55% in C_{max}. In comparison, coadministration of single doses of LEN with a moderate CYP3A4 and P-gp inducer (EFV) led to decreases of 56% in AUC_{tau} and 36% in C_{max}.

Acid-Reducing Agents

- Coadministration of a single dose of LEN 2 hours after administration of FAM did not result in clinically significant changes in LEN PK.

3.1.7.2.4. Recommendations for Managing Potentially Clinically Relevant Drug-Drug Interactions

Table 13. Potentially Significant Drug Interactions

Concomitant Drug Class	Clinical Recommendation
Sensitive CYP3A4 substrates with narrow therapeutic index	Caution advised with coadministration
Strong inhibitors of CYP3A4, P-gp and UGT1A1	Coadministration not recommended
Strong inducers of CYP3A4, P-gp and UGT1A1	Contraindicated
Moderate inducers of CYP3A4 and P-gp inducer	Coadministration not recommended

CYP = cytochrome P450 enzyme; P-gp = P-glycoprotein; UGT = uridine diphosphate glucuronosyltransferase

As a perpetrator, LEN inhibits P-gp and BCRP transporters; however, these interactions are unlikely to be clinically meaningful. Lenacapavir does not inhibit OATP transporters. Therefore, substrates of P-gp, BCRP, and OATP can be coadministered with LEN. Lenacapavir is a moderate inhibitor of CYP3A. Therefore, caution is advised if LEN is coadministered with sensitive CYP3A substrates that have a narrow therapeutic index.

As a victim, administration of oral LEN with gastric ARAs such as histamine 2 receptor agonists does not affect the PK of LEN to a clinically relevant extent. Therefore, LEN may be administered with gastric ARAs. Based on cumulative safety data from clinical studies across a range of oral and SC doses, LEN is well tolerated and adverse reactions were generally mild in both healthy participants and PWH (m2.7.4). Single oral doses of LEN up to 1800 mg and multiple doses of oral LEN given 600 mg twice daily for up to 8 days were tolerated in healthy participants. In Study GS-US-200-4332 on Day 12, C_{max} values were up to 8.8-fold higher and AUC_{tau} values were up to 15.0-fold higher, in comparison corresponding therapeutic values derived from PopPK estimates from the pivotal Phase 2/3 study in HTE PWH. These higher exposures were not associated with higher incidents of AEs in Study GS-US-200-4332. As such, drug interactions of LEN with strong CYP3A4 inhibitors (eg, VORI) and strong CYP3A4 and P-gp inhibitors (eg, COBI, DRV/COBI) are not considered to be clinically significant. However, when all 3 pathways (ie, CYP3A4, P-gp and UGT1A1) are inhibited, a larger increase in exposure is observed (321% increase in LEN AUC_{inf} and 560% increase in C_{max} with ATV/COBI). Therefore, strong inhibitors of CYP3A, P-gp and UGT1A1 together (ie, all 3 pathways) are not recommended with LEN.

Drugs that are strong inducers of CYP3A, P-gp and UGT1A1 (eg, RIF), or that are moderate inducers of CYP3A and P-gp (eg, EFV), may significantly decrease plasma concentrations of LEN (84% decrease in AUC_{inf} by RIF and 56% decrease in AUC_{inf} by EFV), which may result in loss of therapeutic effect and development of resistance. Therefore, strong inducers of CYP3A, P-gp, and UGT1A1, such as RIF, are contraindicated with LEN. Additionally, moderate inducers of CYP3A and P-gp, such as EFV, are not recommended with LEN. Residual concentrations of LEN may remain in the systemic circulation of patients for prolonged periods (up to 13 months after SC administration). If LEN is discontinued following SC administration, the mean plasma concentrations are estimated to be below the threshold for DDI liability as a perpetrator (m2.6.4) around 36-weeks (approximately 9 months) after the SC dose (data not shown, LEN PopPK Report). Thus, these residual concentrations are not expected to affect the exposures to other

drugs (ie, sensitive CYP3A substrates) that are initiated 9 months after the last SC dose of LEN. These concentrations are not expected to affect the exposures to other ARV agents that are initiated after discontinuation of LEN.

In the population PK analyses, concomitant use of optimized background regimen (OBR) medications including pharmacoenhancers RTV and COBI boosted regimens was evaluated as a potential covariate influencing LEN PK due to their frequent use in HTE PWH. The concomitant use of either RTV or COBI boosted regimens was not identified as a significant covariate for LEN PK, confirming that LEN may be coadministered with either RTV or COBI (CTRA-2021-1054 LEN PopPK).

3.2. Pharmacokinetics/Pharmacodynamics

A list of all tables, figures, and listings related to PK-PD analysis are presented in Appendix 6.3.

3.2.1. Rationale for Dose Selection in People With HIV

All data for LEN in the Phase 2 and 2/3 clinical studies in PWH (Studies GS-US-200-4334, m2.7.3, Section 2.2 and GS-US-200-4625, m2.7.3, Section 2.1) were generated with the intended commercial formulations of oral LEN 300-mg tablets and SC LEN injection, 309 mg/mL (NaS).

3.2.1.1. Rationale for the Selected Phase 2 and 2/3 Dosing Regimen (Oral LEN 600 mg on Days 1 and 2, Oral LEN 300 mg on Day 8, Then SC LEN Injection 927 mg on Day 15 and Every 6 Months Thereafter)

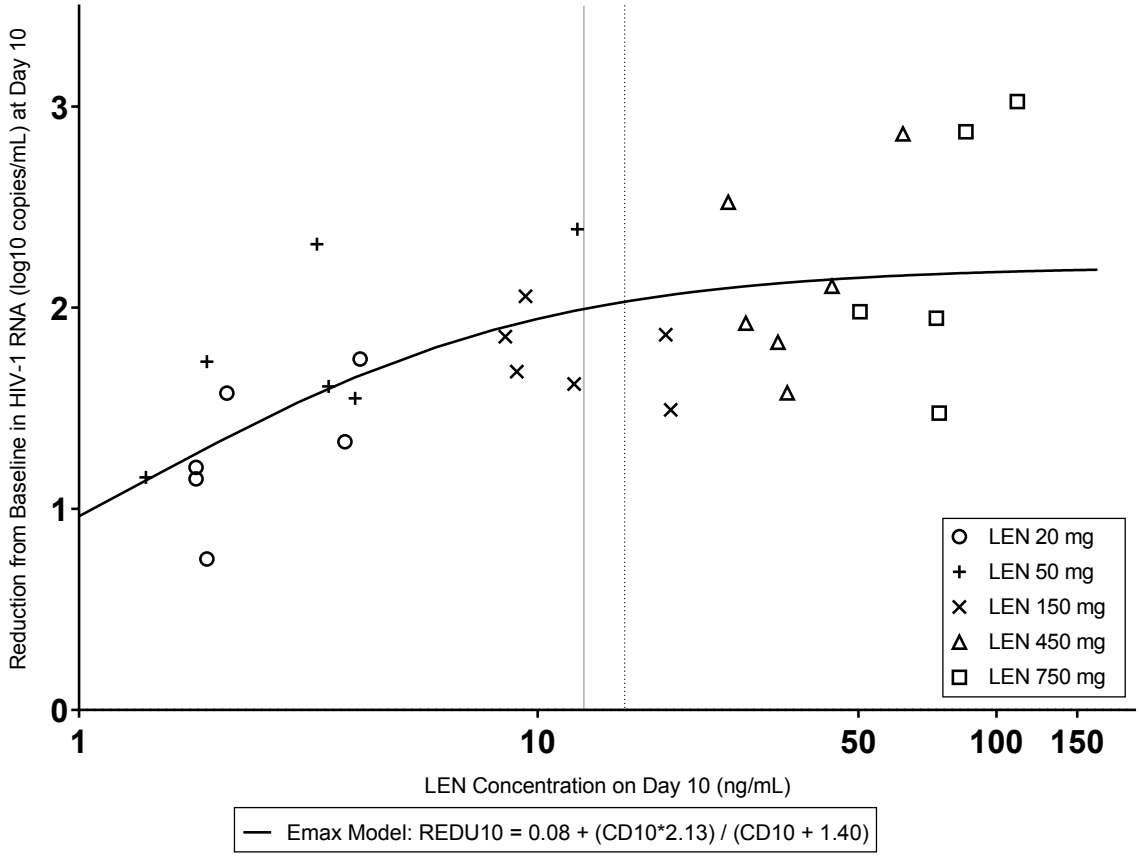
The efficacy, safety, and PK of the LEN oral and SC formulations have been comprehensively characterized in Phase 1 studies in healthy participants (Studies GS-US-200-4070, m2.7.1, Section 2.1.1; GS-US-200-4538, m2.7.1, Section 2.1.2; and GS-US-200-4071, m2.7.1, Section 2.2.1) and the dose ranging proof-of-concept study (Study GS-US-200-4072, Section 2.3.1) in PWH. Using modeling and simulation based on the observed Phase 1 data, the Phase 2 and Phase 2/3 regimen was selected to target an exposure whereby the lower bound of the 90% CI of the C_{trough} is at least 4-fold higher than the in vitro $paEC_{95}$ (3.87 ng/mL = IQ1; MT-4 cells), corresponding to an IQ4 (15.5 ng/mL) within a few days of dosing initiation, and through the end of the dosing interval (every 26 weeks).

The target of IQ4 is supported by the results of the dose ranging proof-of-concept study (Study GS-US-200-4072, Section 2.3.1). In this study, treatment-naive (TN) or treatment-experienced but CAI–naive PWH were administered single ascending doses of an early LEN SC suspension formulation and the decline in HIV-1 RNA was evaluated (Study GS-US-200-4072). Based on fitting of Day 10 LEN plasma concentrations to an E_{max} model of concentration-response relationship to the reduction from baseline in HIV-1 RNA, the E_{max} at Day 10 was estimated to be a 2.13-log_{10} copies/mL decline in HIV-1 RNA (Figure 12). Study GS-US-200-4072 demonstrated that near maximal (94%) antiviral activity was observed at $\geq$ 15.5 ng/mL, indicating that substantial increases in antiviral activity with an increase in LEN exposure beyond this concentration target are not expected. Likewise, dosing in a manner that maintains LEN concentrations at or above IQ4 (15.5 ng/mL) in the majority of participants for the duration of treatment should ensure maintenance of maximum virologic effect.

Additional considerations supporting the 14-day oral lead-in period of the Phase 2/3 regimen included rapid achievement of target LEN concentrations within a few days, which was critical given the short duration of the 14-day Functional Monotherapy Period that defined the primary end point of the GS-US-200-4625 study (Study GS-US-200-4625, m2.7.3, Section 2.1). In addition, the 14-day oral lead-in period provided an opportunity to confirm LEN tolerability prior to the administration of the long-acting SC formulation, for which there was relatively limited safety data at the time the Phase 2 and Phase 2/3 studies were initiated. Taken together, the selected lead-in regimen enabled rapid attainment of target concentrations (Days 1 and 2) and maintenance of target concentrations (Day 8) during a 14-day period selected to confirm tolerability of LEN prior to administration of the long-acting SC formulation.

Therefore, the LEN dosing regimen selected for Phase 2 and 2/3 studies consisted of oral LEN 600 mg on Days 1 and 2, oral LEN 300 mg on Day 8, then SC LEN injection 927 mg on Day 15 and every 6 months (26 weeks) thereafter. This regimen was predicted to achieve target concentrations within a few days of initiation of dosing and maintaining it throughout the 6-month dosing interval. Based on simulated data, at the end of 26 weeks after SC dose, LEN was predicted to maintain a mean concentration (90% CI) of 29.2 (24.6, 32.5) ng/mL corresponding to IQ (90% CI) of 7.5 (6.3, 8.4) in PWH (CTRA-2021-1054 LEN PopPK).

Figure 12. GS-US-200-4072: Relationship Between LEN Concentration on Day 10 and Reduction From Baseline in Plasma HIV-1 RNA at Day 10 With E_{max} Model – Part A (PK/PD Analysis Set)



E_{max} = maximum (pharmacodynamics) effect; IQ = inhibitory quotient; LEN = lenacapavir
Vertical lines: Solid line represents LEN concentration required to achieve 90% Emax (12.6 ng/mL) and dotted line represents LEN concentration at IQ4 (15.5 ng/mL).
Reduction from baseline in HIV-1 RNA (log10 copies/mL) at Day 10 is defined as the difference between baseline and Day 10 HIV-1 RNA values (REDU10).
C_{D10} = LEN concentration on Day 10 (ng/mL).
Source: Study GS-US-200-4072 CSR, Figure 10

3.2.1.2. Rationale for a 4-Week Dosing Window With the 6 Month Dosing Interval For LEN SC Maintenance Dosing

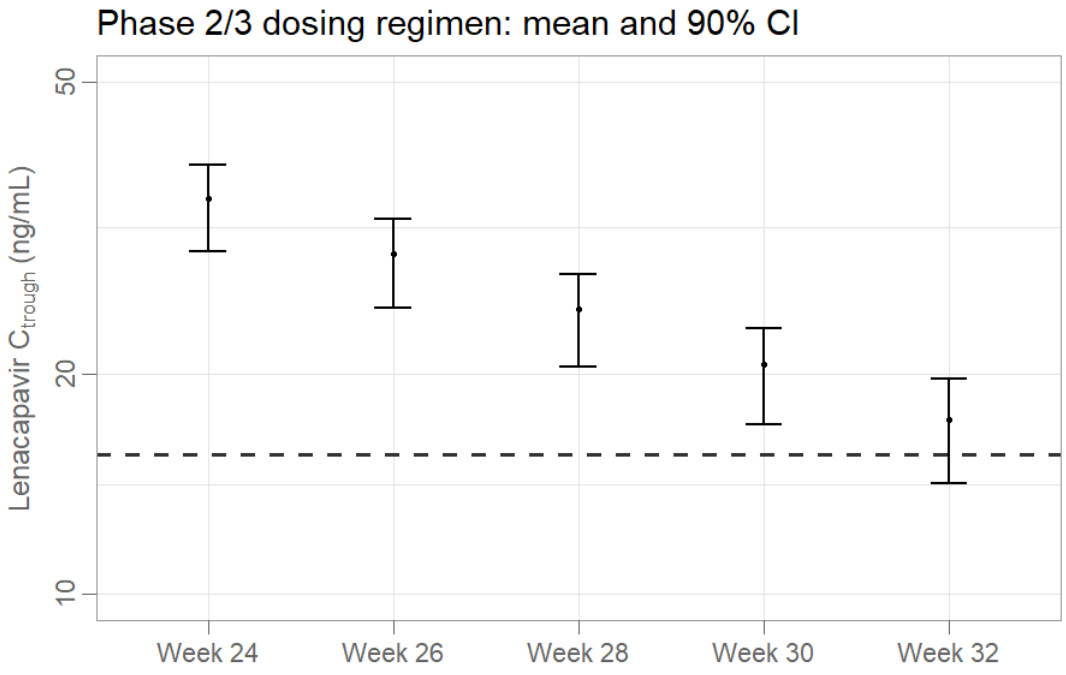
The LEN commercial SC solution formulation requires administration by a healthcare professional, therefore a specified dosing window around every 6 months in which the SC injection can be scheduled in-line with regular healthcare professional visits without compromising efficacy would help in maintaining adherence. Modeling and simulation results of the Phase 2/3 dose regimen indicate that a 4-week window around Week 26 (ie, Weeks 24 to 28) after SC administration will maintain safe and efficacious LEN exposures (Figure 13). The mean (90% CI) concentrations of LEN at Weeks 24, 26, 28, 30 and Week 32 are as follows: 34.6 (29.4, 38.5), 29.2 (24.6, 32.5), 24.5 (20.4, 27.3), 20.6 (17.0, 23.1) and 17.3 (14.2, 19.7) ng/mL

respectively (CTRA-2021-1054 LEN PopPK). Specifically, if the maintenance SC dose is delayed by 2 weeks (ie, Week 28), mean (90% CI) LEN concentrations are predicted to be 24.5 (20.4, 27.3) ng/mL, corresponding to a mean IQ (90% CI) of 6.3 (5.2, 7.1) (Figure 13). If the maintenance SC dose is administered 2 weeks earlier (ie, Week 24) than the planned 26-week (6 month) dosing interval, LEN concentrations are predicted to remain within a range that can be supported with existing safety data. Furthermore, the 4-week window can be applied for subsequent SC doses after Week 26.

For the Phase 2 and Phase 2/3 studies, SC LEN doses are being administered within 24 to 28 weeks from the previous SC LEN dose as per protocol. For participants who were not dosed within the 28 week window and continued in the studies, the oral LEN lead-in regimen was restarted prior to subsequent SC LEN administration (oral LEN 600 mg daily for 2 days followed by oral LEN 300 mg 6 days later, with SC LEN injection 927 mg restarting 1 week later).

In conclusion, a 4-week dosing window around the 6 month dosing interval maintains safe and efficacious LEN exposures. As such, patients can receive SC LEN within 24 to 26 weeks after the previous SC injection and up to 28 weeks after the previous SC injection. If more than 28 weeks have elapsed since the last injection and if clinically appropriate to continue treatment with LEN, the oral initiation regimen can be restarted.

Figure 13. Simulated LEN C_{trough} on Weeks 24 to 32 in Adult PWH Who Received the Phase 2/3 Dosing Regimen



IQ4 = inhibitory quotient 4; LEN = lenacapavir; PWH = people with HIV; SC = subcutaneous
The points and error bars represent mean and 90% CI simulated LEN C_{trough} exposures. The horizontal dashed line represents the IQ4 threshold at 15.5 ng/mL. Weeks 24 to 32 indicate the number of weeks after SC administration.
Source: CTRA-2021-1054 LEN PopPK

3.2.1.3. Rationale for Simplified LEN Oral and SC Regimen

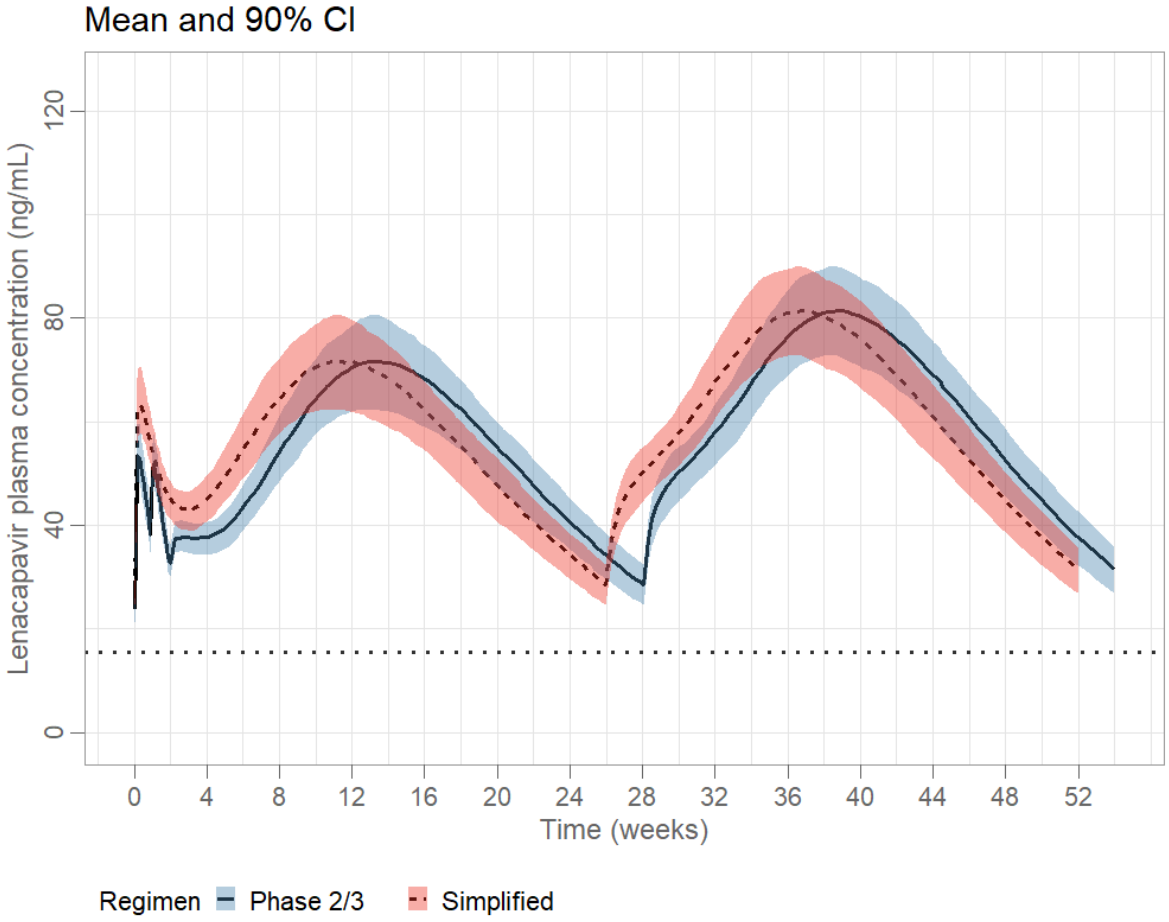
The LEN oral + SC dose regimen evaluated in the Phase 2/3 study (Section 3.2.1.1) allowed for a 14-day oral lead-in period, where participants are receiving oral LEN on the defined schedule but have not yet received SC LEN. This oral lead-in period enabled an assessment of safety and tolerability of LEN prior to SC LEN administration. However, this specific oral lead-in period can be modified/simplified to improve adherence without compromising efficacy and safety.

Given the established safety profile (m2.7.4) and lack of exposure-safety relationship from the Phase 2 and 2/3 studies (Section 3.2.3), the following "simplified" regimen is proposed: oral LEN 600 mg (2 × LEN 300-mg tablets) and SC LEN injection 927 mg (2 × 1.5-mL LEN injection, 309 mg/mL [NaS]) on Day 1, oral LEN 600 mg (2 × LEN 300-mg tablets) on Day 2 followed by SC LEN injection 927 mg (2 × 1.5-mL LEN injection, 309 mg/mL [NaS]) every 6 months (26 weeks) thereafter.

Pharmacokinetic modeling and simulation indicates that this simplified regimen will yield a comparable LEN PK profile to that of the Phase 2/3 study dose regimen (Figure 14, Table 14). The observed LEN concentration profiles of the simplified regimen and the Phase 2/3 regimen from Study GS-US-200-5709 in healthy participants supported the conclusions from the PK modeling and simulation (Figure 6). Of note, the exposures in healthy participants were 30% to 50% lower as compared with PWH. In PWH, the target IQ4 (15.5 ng/mL) was rapidly achieved compared to healthy participants and maintained similarly using simplified regimen and Phase 2/3 dosing regimen.

In conclusion, LEN exposure and the time course for achieving the desired target of lower bound 90% CIs exceeding IQ4 (15.5 ng/mL) were comparable between simplified regimen and the Phase 2/3 regimen for the HTE indication.

Figure 14. Simulated LEN Concentration-Time Profile for the Entire Treatment Duration in Adult PWH Who Received the Phase 2/3 or the Simplified Dosing Regimen



IQ4 = inhibitory quotient 4; LEN = lenacapavir; PWH = people with HIV
The solid black line and blue shaded area represent the simulated mean and 90% CI LEN concentrations in adult PWH receiving the Phase 2/3 dosing regimen. The dashed black line and red shaded area represent the simulated mean and 90% CI LEN concentrations in adult PWH receiving the simplified dosing regimen. The horizontal dotted line represents the IQ4 threshold at 15.5 ng/mL.
Source: CTRA-2021-1054 LEN PopPK

Table 14. Comparison of PK Parameters Following Phase 2/3 Regimen Versus Simplified Regimen in Adult PWH

PK Parameter	Mean (%CV)	
	Phase 2/3 Regimen (N = 62)[a]	Simplified Regimen[b] (Simulated)
$AUC_{Day\ 1\text{-}15}$ (h*ng/mL)	25,962.9 (67.8)	17701.8 (52.9)
$C_{max\ Day\ 1\text{-}15}$ (ng/mL)	124.4 (85.1)	76.6 (55.01)
$C_{trough\ Day\ 15}$ (ng/mL)	48.6 (52.1)	45.2 (57.0)
$AUC_{Day\ 15\text{-}Week\ 26}$[c] (h*ng/mL)	251,907.2 (48.2)	216,554.8 (68.4)
$C_{max\ Day\ 15\text{-}Week\ 26}$ (ng/mL)	87.3 (49.4)	79.5 (73.4)
$C_{trough\ Week\ 26}$ (ng/mL)	35.1 (59.2)	29.2 (90.8)
$AUC_{Day\ 1\text{-}Week\ 26}$ (h*ng/mL)	277,902.9 (46.7)	234,294.8 (65.1)
$C_{max\ Day\ 1\text{-}Week\ 26}$ (ng/mL)	136.2 (75.2)	97.1 (61.6)

%CV = percentage coefficient of variation; PK = pharmacokinetic; PopPK = population pharmacokinetic
a Post hoc exposures from Study GS-US-200-4625 in HTE population
b Simulated exposures utilizing PopPK model
c For Phase 2/3 regimen, Week 26 = 28 weeks from first oral LEN
Source: CTRA-2021-1054 LEN PopPK

3.2.2. Pharmacokinetic-Pharmacodynamic Relationship for the Treatment of HIV-1 Infection

Exposure-efficacy relationships for LEN were evaluated in HTE PWH with multidrug resistance who received LEN in the Phase 2/3 study (Study GS-US-200-4625, m2.7.3, Section 2.1) using LEN exposure estimates derived from PopPK modeling (CTRA-2021-1054 LEN PopPK). For PK-PD analyses, the primary efficacy end point is the proportion of participants with HIV-1 RNA $\geq 0.5\ log_{10}$ reduction at Day 15. The secondary efficacy end point 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}. Further details are described in m2.7.3, Section 3.2.

Table 15 presents the number of PWH with evaluable LEN PopPK parameters for functional monotherapy ($AUC_{Day\ 1\text{-}15}$, $C_{max\ Day\ 1\text{-}15}$, and $C_{trough\ Day\ 15}$) and virologic data at Day 15 included in the exposure-response analyses (N = 24).

Table 15. Number of Participants in the Population PK Dataset With Evaluable PopPK Exposure Parameters Used for Exposure-Response Analyses (LEN PK/PD Analysis Sets) for Functional Monotherapy

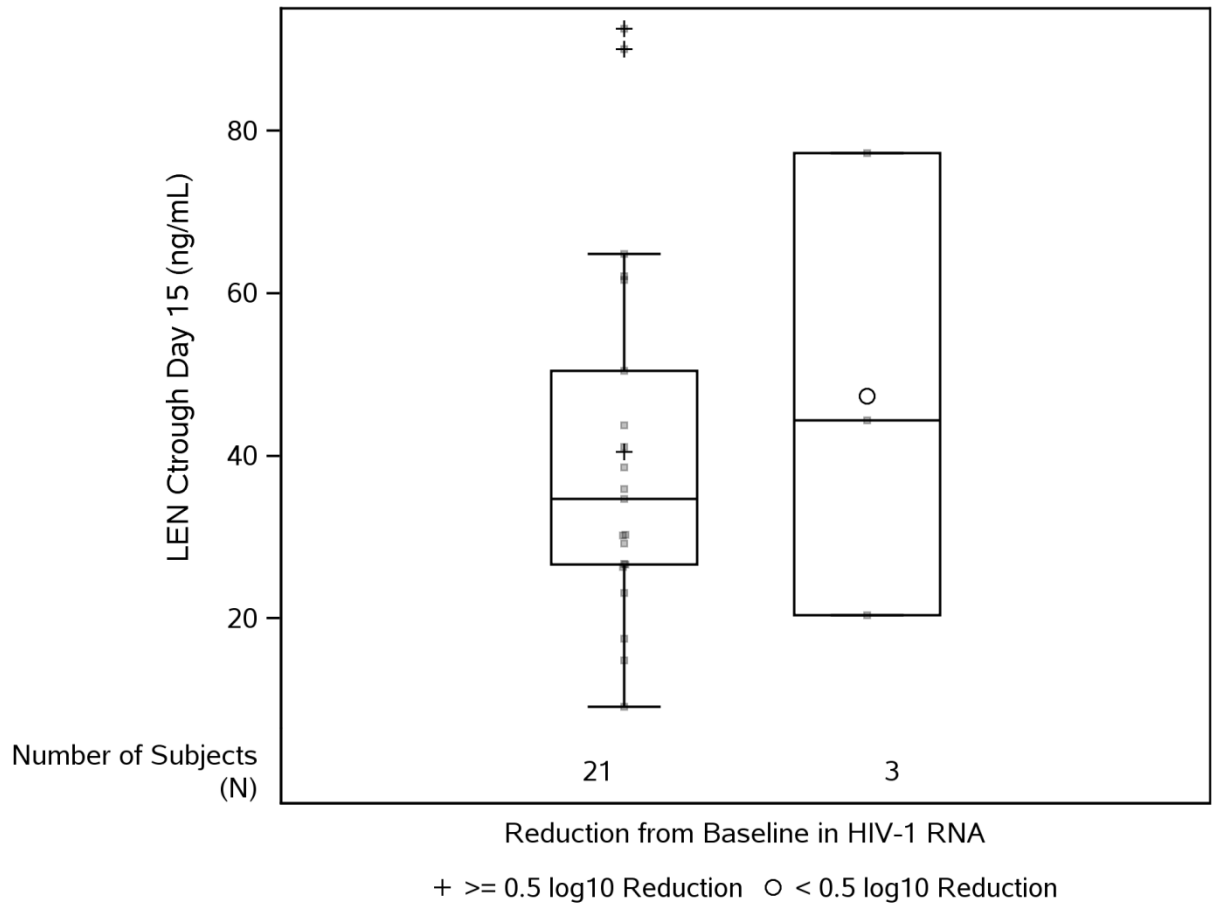
Analysis Set	Analyte	PWH With Evaluable Exposure Estimates (N)	
		All Participants (Safety)	Participants With Virologic Data at Day 15 (Efficacy)
Safety/Efficacy PK/PD[a]	LEN	24	24

LEN = lenacapavir; PD = pharmacodynamics; PK = pharmacokinetics; PopPK = population pharmacokinetic(s); PWH = people with HIV
Source: LEN Integrated PK/PD, Table 1

3.2.2.1. Functional Monotherapy

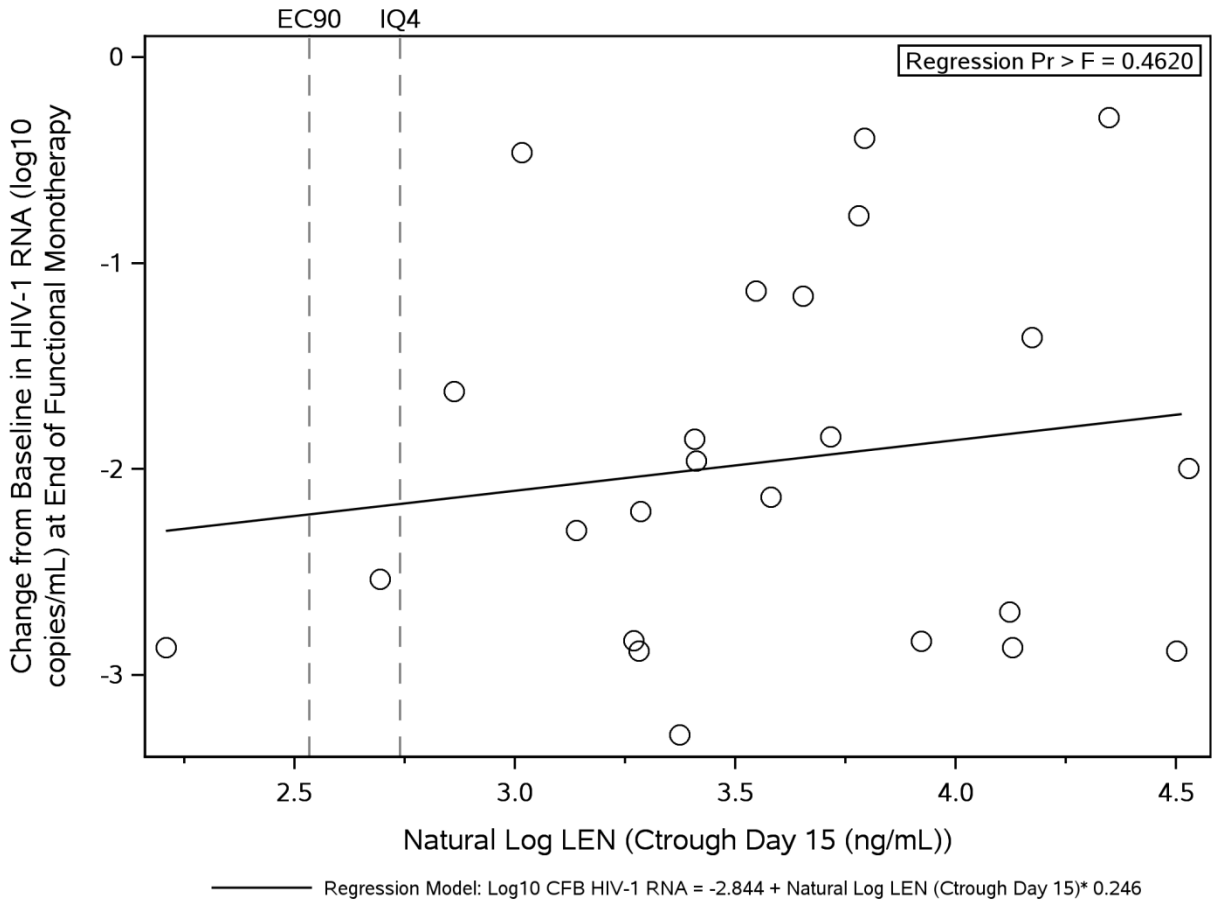
The efficacy of LEN, administered in the oral lead-in period and SC maintenance dose, in the treatment of HIV infection was evaluated by determining the proportion of participants who achieved the primary efficacy end point as a function of the exposure parameters $AUC_{Day\ 1\text{-}15}$, $C_{max\ Day\ 1\text{-}15}$, and $C_{trough\ Day\ 15}$ (LEN Integrated PK/PD, Tables 4.1, 4.2, 4.3, and Figure 2.1). Values for $C_{trough\ Day\ 15}$ showed no apparent relation between LEN exposure and achieving the primary end point of a 0.5 log reduction of HIV-1 RNA copies (Figure 15). The same observation can be made from Table 16, which presents the proportion of population quartiles of LEN exposures in PWH and the percentage of participants who achieved the primary efficacy end point. Virologic response rates were high across all exposure ranges for LEN. Taking into account the $paEC_{95}$ for WT HIV-1 virus (3.87 ng/mL) (Section 3.1.6.2), the lowest exposure quartile for LEN trough concentrations (C_{trough} range of 9.1 to 26.3 ng/mL, which corresponds to an IQ range of 2.3 to 6.8) showed similar virologic response rates as the highest exposure quartile for LEN trough concentrations (C_{trough} range of 61.7 to 92.6 ng/mL, which corresponds to an IQ range of 15.9 to 23.9). As such, a flat exposure-response relationship is observed in Figure 16 for $C_{trough\ Day15}$. Similar results were observed for $C_{max\ Day1\text{-}15}$ and $AUC_{Day1\text{-}15}$ (LEN Integrated PK/PD, Table 1 and Figure 3). Note that only 1 dosing regimen was evaluated in Study GS-US-200-4625 which may limit the assessment of exposure-response relationship because the target concentrations were at or above IQ4 for majority of the participants. As noted in Section 3.2.1.1, when several doses of SC LEN (20 mg to 750 mg) were evaluated in Study GS-US-200-4072, a correlation between exposure and response was observed with near maximal antiviral activity around IQ4.

Figure 15. **GS-US-200-4625: Functional Monotherapy Period Analysis (Cohort 1A): Number of Participants Achieving ≥ 0.5 log_{10} Reduction From Baseline in HIV-1 RNA (LEN Population PK/PD Analysis Set)**



LEN = lenacapavir; IQR = interquartile range; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
Box plots denote median and IQR (Q3 - Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
to receive oral LEN during the Functional Monotherapy Period (Cohort 1A).
Grey values in the background represent the actual data.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
LEN PK parameters of the Functional Monotherapy Period refers to the LEN PK parameters of the oral LEN lead-in period limited to participants randomized.
Source: LEN Integrated PK/PD, Figure 2.1 and Table 4.1

Figure 16. **GS-US-200-4625: Functional Monotherapy Period Analysis (Cohort 1A): Linear Regression of Change From Baseline in HIV-1 RNA (log_{10} copies/mL) Versus LEN PK Parameters (LEN Population PK/PD Analysis Set)**



EC_{90} = 90% effective concentration; IQ4 = inhibitory quotient 4; LEN = lenacapavir; PK = pharmacokinetic(s)
Vertical lines indicate the EC_{90} (12.6 ng/mL) and IQ4 (15.5 ng/mL).
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
LEN PK parameters of the Functional Monotherapy Period refers to the LEN PK parameters of the oral LEN lead-in period limited to participants randomized to receive oral LEN during the Functional Monotherapy Period (Cohort 1A).
Source: LEN Integrated PK/PD, Figure 3

Table 16. GS-US-200-4625: Functional Monotherapy Period Analysis (Cohort 1A): Percentage of Participants Achieving ≥ 0.5 log_{10} Reduction From Baseline in HIV-1 RNA by LEN PK Exposure Quartile (LEN Population PK/PD Analysis Set)

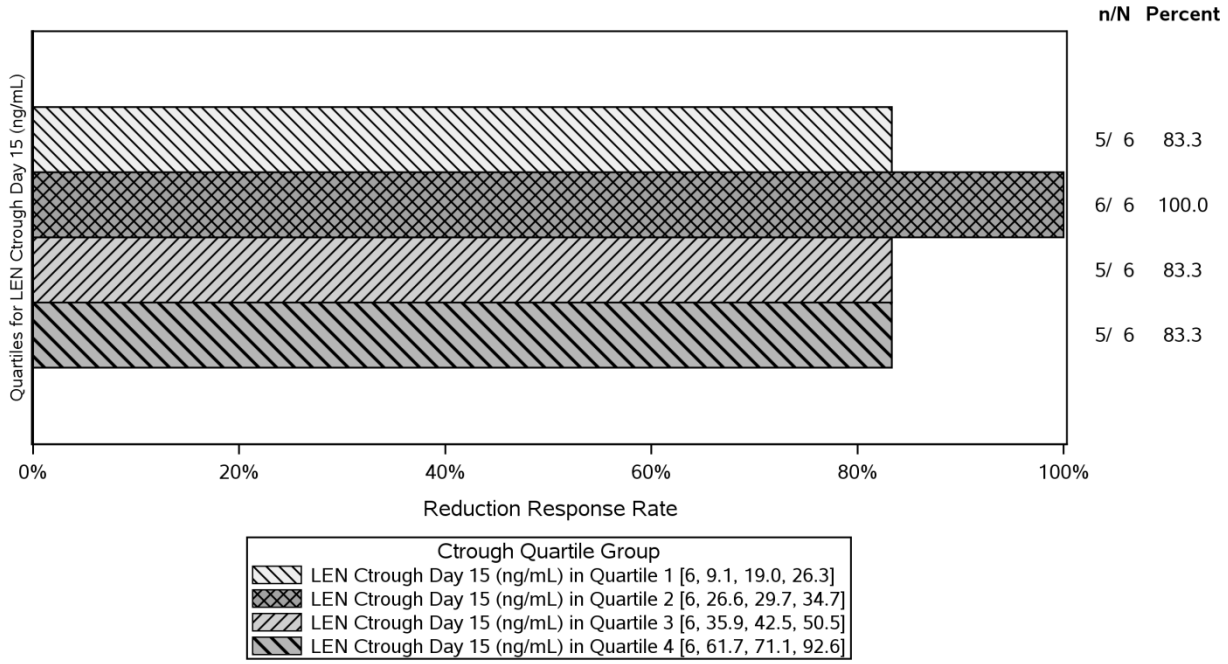
	LEN (N = 24)
$AUC_{Day\ 1\text{-}15}$ (h*ng/mL) Quartile Subgroups [minimum, median, and maximum]	
$AUC_{Day\ 1\text{-}15}$ (h*ng/mL) in Quartile 1 [3715.1, 8618.3, 10811.8]	5/6 (83.3%)
$AUC_{Day\ 1\text{-}15}$ (h*ng/mL) in Quartile 2 [11363.0, 12922.2, 16197.1]	6/6 (100.0%)
$AUC_{Day\ 1\text{-}15}$ (h*ng/mL) in Quartile 3 [16386.7, 21945.5, 31914.9]	5/6 (83.3%)
$AUC_{Day\ 1\text{-}15}$ (h*ng/mL) in Quartile 4 [34682.0, 47510.4, 59996.1]	5/6 (83.3%)
$C_{max\ Day\ 1\text{-}15}$ (ng/mL) Quartile Subgroups [minimum, median, and maximum]	
$C_{max\ Day\ 1\text{-}15}$ (ng/mL) in Quartile 1 [15.3, 35.2, 48.2]	5/6 (83.3%)
$C_{max\ Day\ 1\text{-}15}$ (ng/mL) in Quartile 2 [56.5, 65.6, 72.4]	5/6 (83.3%)
$C_{max\ Day\ 1\text{-}15}$ (ng/mL) in Quartile 3 [72.7, 91.2, 140.2]	6/6 (100.0%)
$C_{max\ Day\ 1\text{-}15}$ (ng/mL) in Quartile 4 [152.2, 203.8, 497.0]	5/6 (83.3%)
$C_{trough\ Day\ 15}$ (ng/mL) Quartile Subgroups [minimum, median, and maximum]	
$C_{trough\ Day\ 15}$ (ng/mL) in Quartile 1 [9.1, 19.0, 26.3]	5/6 (83.3%)
$C_{trough\ Day\ 15}$ (ng/mL) in Quartile 2 [26.6, 29.7, 34.7]	6/6 (100.0%)
$C_{trough\ Day\ 15}$ (ng/mL) in Quartile 3 [35.9, 42.5, 50.5]	5/6 (83.3%)
$C_{trough\ Day\ 15}$ (ng/mL) in Quartile 4 [61.7, 71.1, 92.6]	5/6 (83.3%)

LEN = lenacapavir; PD = pharmacodynamics; PK = pharmacokinetic(s)
Numbers presented in the square bracket were the minimum, median, and maximum for participants included in that subgroup. Quartiles were determined for all participants, so imbalances may be present when excluding participants with no virologic data in the Day 15 window.
The LEN PK/PD Analysis Set includes all participants who were randomized and had oral dose of LEN in Study GS-US-200-4625 Cohort 1A and who had at least 1 nonmissing LEN PK parameter (AUC, C_{max}, or C_{trough}) estimated from the population PK analysis.
Source: LEN Integrated PK/PD, Table 2.1.1, Table 2.1.2, Table 2.1.3, and Table 3.1

The efficacy of LEN, administered in the oral lead-in period, for the treatment of HIV infection was further evaluated by determining the proportion of PWH who achieved the primary efficacy end point as a function of Phase 2/3 population quartiles of LEN exposure ($C_{trough\ Day\ 15}$, $C_{max\ Day\ 1\text{-}15}$).

Figure 17 presents the proportion of PWH who achieved HIV-1 RNA ≥ 0.5 log_{10} reduction from baseline HIV-1 RNA, stratified by population quartiles (above/below quartile) of LEN $C_{trough\ Day\ 15}$. Those proportions were high across all LEN C_{trough} strata combinations and the median E_{max} of greater than 96% was observed in all quartiles (LEN Integrated PK/PD, Table 6). Similarly, high proportions were observed across all LEN $C_{max\ Day1\text{-}15}$ strata combinations (LEN Integrated PK/PD, Figure 1.1.1 and Figure 1.1.2).

Figure 17. GS-US-200-4625: Functional Monotherapy Period Analysis (Cohort 1A): Percentage of Participants Achieving ≥ 0.5 log_{10} Reduction From Baseline in HIV-1 RNA by LEN C_{trough} Day 15 Quartile (LEN Population PK/PD Analysis Set)



LEN = lenacapavir; PD = pharmacodynamics; PK = pharmacokinetics
The LEN PK/PD Analysis Set includes all participants who were randomized and had oral dose of LEN in Study GS-US-200-4625 Cohort 1A and who had at least 1 nonmissing LEN PK parameter (AUC, C_{max}, or C_{trough}) estimated from the population PK analysis.
Source: LEN Integrated PK/PD, Figure 1.1.3, Listing 1.1

3.2.2.2. Overall Regimen

Table 17 presents the number of PWH with evaluable LEN PopPK parameters for the overall regimen ($AUC_{Day\ 1\text{-}Week\ 26}$, $C_{max\ Day\ 1\text{-}Week\ 26}$, and $C_{trough\ Week\ 26}$) and virologic data at Week 26 (snapshot algorithm previously described) included in the exposure-response analyses. Based on the PopPK data cut, a total of 62 participants had evaluable PK parameters that were included in safety PK/PD analysis and 41 participants with virologic data were included in efficacy analysis (Figure 18) (CTRA-2021-1054 LEN PopPK).

Table 17. GS-US-200-4625: Number of Participants in the Population PK Dataset With Evaluable PopPK Exposure Parameters Used for Exposure-Response Analyses (LEN PK/PD Analysis Sets)

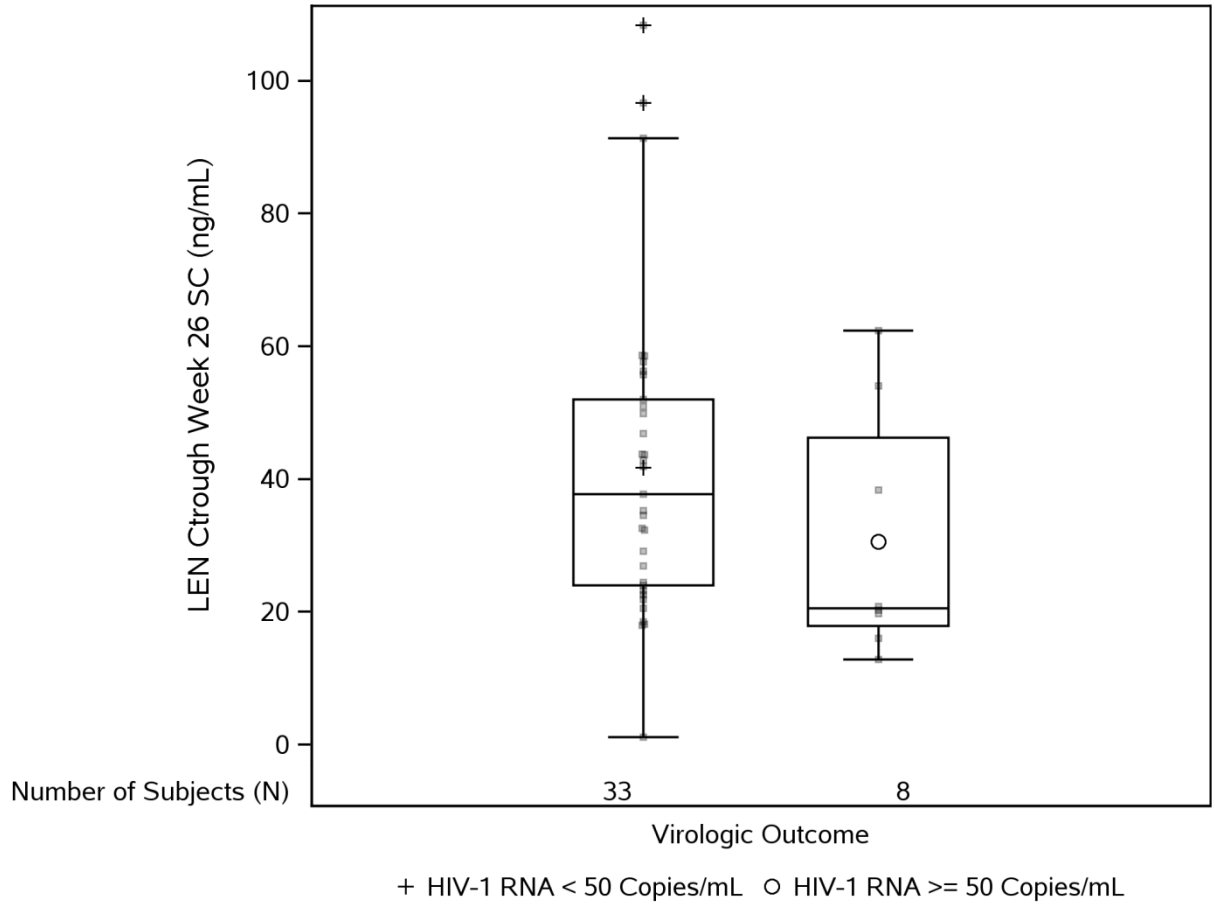
Analysis Set	Analyte	PWH With Evaluable Exposure Estimates (N)	
		All Participants (Safety)	Participants With Virological Data Day 1-Week 26 (Efficacy)
Safety/Efficacy PK/PD[a]	LEN	62	41

LEN = lenacapavir; PD = pharmacodynamics; PK = pharmacokinetics; PopPK = population pharmacokinetic(s); PWH = people with HIV
Source: LEN Integrated PK/PD, Table 2.2.1, Table 2.2.2, Table 2.2.3, Table 2.3.1, and Table 2.3.2

The efficacy of LEN for the overall regimen administered in the oral lead-in period and SC maintenance dose in the treatment of HIV infection was evaluated by determining the proportion of participants who achieved the secondary efficacy end point of HIV-1 RNA < 50 copies/mL at Week 26 (snapshot algorithm previously described) against $C_{trough\ Week\ 26}$ presented in Figure 19. A total of 33 of 41 participants had HIV-1 RNA < 50 copies/mL; $AUC_{Day\ 1\text{-}Week\ 26}$ and $C_{max\ Day\ 1\text{-}Week\ 26}$ showed similar results (Figure 18, LEN Integrated PK/PD, Figure 2.3). However, following the end of the Functional Monotherapy Period, in addition to LEN, an OBR was part of the treatment. The efficacy observed during the SC portion of LEN (Day 15-Week 26) is in combination with an OBR.

The percentage of participants who achieved the secondary efficacy end point as a function of the Phase 2/3 population quartiles of LEN exposure ($AUC_{Day\ 1\text{-}Week\ 26}$, $C_{max\ Day\ 1\text{-}Week\ 26}$, and $C_{trough\ Week\ 26}$) is shown in Table 18, which presents the proportion of population quartiles of LEN exposures in PWH. Virologic response rates were high across all exposure ranges for LEN.

Figure 18. **GS-US-200-4625: Box Plot of LEN PK Parameters by Virologic Outcome (HIV-1 RNA < 50 copies/mL Snapshot Algorithm) at Week 26 SC (LEN Population PK/PD Analysis Set, Excluding Subjects with No Virologic Data in Week 26 SC Window)**



LEN = lenacapavir; IQR = interquartile range; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
LEN Population PK/PD analysis set includes all participants who were randomized and had at least 1 dose of LEN and who had at least 1 nonmissing LEN PK parameter estimated from the population PK analysis.
Grey values in the background represent the actual data.
Box plots denote median and IQR (Q3 - Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
Source Integrated PK/PD, Figure 2.2

Table 18. GS-US-200-4625: Percentage of Participants With HIV-1 RNA < 50 copies/mL (Snapshot Algorithm) at Week 26 SC by LEN PK Exposure Quartile (LEN Population PK/PD Analysis Set)

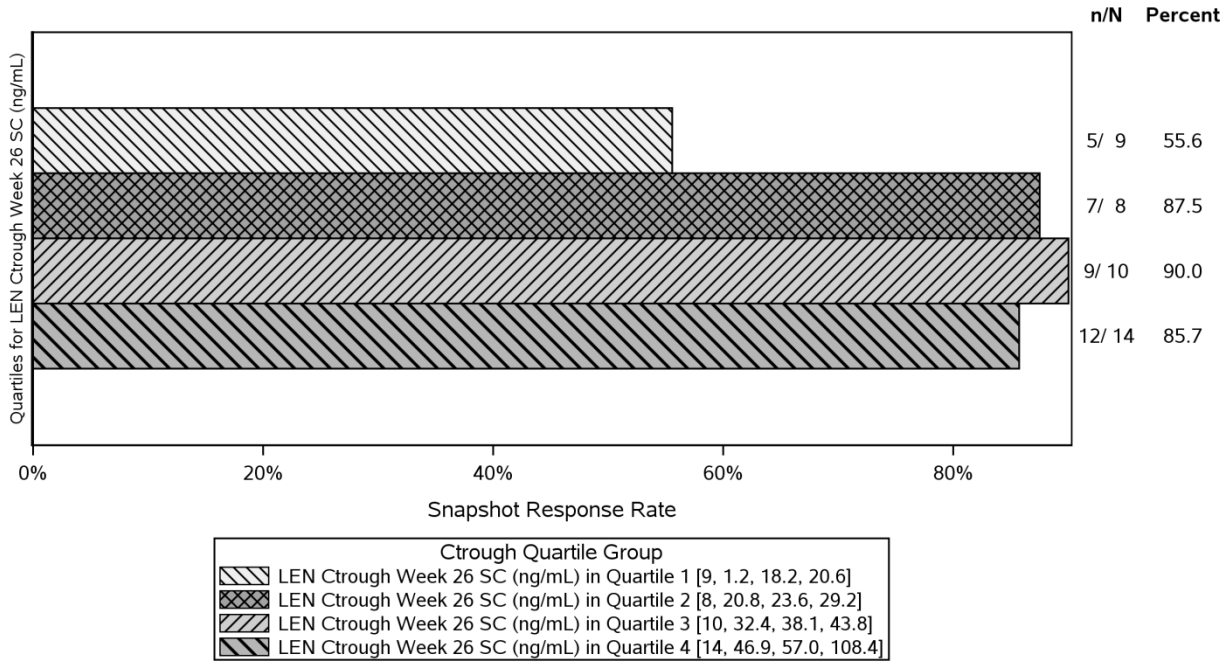
	LEN (N = 41)
$AUC_{Day\ 1\text{-}Week\ 26}$ (h*ng/mL) Quartile Subgroups [minimum, median, and maximum]	
$AUC_{Day\ 1\text{-}Week\ 26\ SC}$ (h*ng/mL) in Quartile 1 [92527.7, 152925.6, 169043.9]	7/11 (63.6%)
$AUC_{Day\ 1\text{-}Week\ 26\ SC}$ (h*ng/mL) in Quartile 2 [174556.4, 208521.1, 226874.1]	10/12 (83.3%)
$AUC_{Day\ 1\text{-}Week\ 26\ SC}$ (h*ng/mL) in Quartile 3 [277351.7, 309517.5, 355389.1]	7/8 (87.5%)
$AUC_{Day\ 1\text{-}Week\ 26\ SC}$ (h*ng/mL) in Quartile 4 [367457.9, 404826.7, 670952.3]	9/10 (90.0%)
$C_{max\ Day\ 1\text{-}Week\ 26}$ (ng/mL) Quartile Subgroups [minimum, median, and maximum]	
$C_{max\ Day\ 1\text{-}Week\ 26}$ (ng/mL) in Quartile 1 [27.4, 56.3, 66.5]	8/13 (61.5%)
$C_{max\ Day\ 1\text{-}Week\ 26}$ (ng/mL) in Quartile 2 [66.8, 75.3, 96.5]	7/8 (87.5%)
$C_{max\ Day\ 1\text{-}Week\ 26}$ (ng/mL) in Quartile 3 [107.1, 134.4, 171.1]	11/12 (91.7%)
$C_{max\ Day\ 1\text{-}Week\ 26}$ (ng/mL) in Quartile 4 [193.7, 209.8, 497.0]	7/8 (87.5%)
$C_{trough\ Week\ 26}$ (ng/mL) Quartile Subgroups [minimum, median, and maximum]	
$C_{trough\ Week\ 26}$ (ng/mL) in Quartile 1 [1.2, 18.2, 20.6]	5/9 (55.6%)
$C_{trough\ Week\ 26}$ (ng/mL) in Quartile 2 [20.8, 23.6, 29.2]	7/8 (87.5%)
$C_{trough\ Week\ 26}$ (ng/mL) in Quartile 3 [32.4, 38.1, 43.8]	9/10 (90.0%)
$C_{trough\ Week\ 26}$ (ng/mL) in Quartile 4 [46.9, 57.0, 108.4]	12/14 (85.7%)

LEN = lenacapavir; PD = pharmacodynamics; PK = pharmacokinetic(s)
Numbers presented in the square bracket were the minimum, median, and maximum for participants included in that subgroup, excluding participants with no virologic data.
Quartiles were determined for all participants, so imbalances may be present when excluding participants with no virologic data in the Week 26 window.
The LEN PK/PD Analysis Set includes all participants who were randomized and had oral dose of LEN in Study GS-US-200-4625 and who had at least 1 nonmissing LEN PK parameter (AUC, C_{max}, or C_{trough}) estimated from the population PK analysis.
Source: LEN Integrated PK/PD, Table 3.3, Table 2.3.1, Table 2.2.2, Table 2.2.3

The secondary efficacy of LEN, administered in the Phase 2/3 regimen (Overall regimen), for the treatment of HIV infection was further evaluated by determining the proportion of PWH who achieved < 50 copies/mL at Week 26 (snapshot algorithm) as a function of Phase 2/3 population quartiles of LEN exposure ($C_{trough\ Week\ 26}$). Figure 19 presents the proportions of PWH who had HIV-1 RNA < 50 copies/mL at Week 26, stratified by population quartiles of LEN $C_{trough\ Week\ 26}$. Those proportions were high for the top 3 LEN C_{trough} strata combinations with median concentrations ranging from 23.6 to 57.0 ng/mL. While the median concentrations for quartile 1 were 18.2 ng/mL, the minimum concentration of LEN was 1.2 ng/mL in 1 participant, which was below IQ1 (3.87 ng/mL); however, C_{max} of 110.5 ng/mL was observed for this participant, and HIV-1 RNA < 50 copies/mL was observed at Week 26 for this participant. Similarly, high proportions were observed across all LEN $AUC_{Day1\text{-}Week\ 26}$ and $C_{max\ Day1\text{-}Week\ 26}$ strata combinations (LEN Integrated PK/PD, Figure 1.3.1 and Figure 1.3.2). Furthermore, analysis

with SC portion with PK parameters $AUC_{Day15\text{-}Week\ 26}$ and $C_{max\ Day15\text{-}Week\ 26}$ showed similar results (LEN Integrated PK/PD, Figure 1.2.1, Figure 1.2.2, and Table 3.2).

Figure 19. GS-US-200-4625: Percentage of Participants with HIV-1 RNA < 50 copies/mL (Snapshot Algorithm) at Week 26 SC by LEN $C_{trough\ Week\ 26}$ SC Quartile (LEN Population PK/PD Analysis Set, Excluding Subjects with No Virologic Data in Week 26 SC Window)



LEN = lenacapavir; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous
LEN Population PK/PD Analysis Set includes all participants who were randomized and had at least 1 dose of LEN and who had at least 1 nonmissing LEN PK parameter estimated from the population PK analysis.
Quartiles were determined for all participants, so imbalances may be present when excluding participants with no virologic data in the Week 26 SC window.
Numbers presented in the square bracket were the sample size, minimum, median, and maximum for participants included in that subgroup, excluding participants with no virologic data.
Source: LEN Integrated PK/PD, Figure 1.2.3 and Listing 1.2

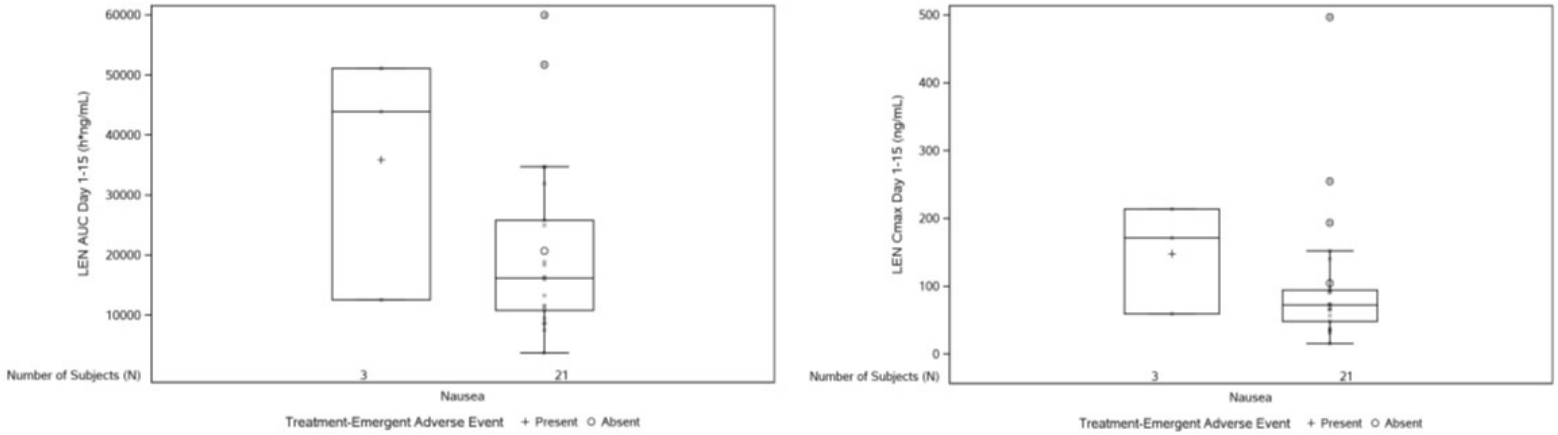
3.2.3. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

The PK/PD relationship between LEN plasma concentrations and the change in QTcF following twice-daily oral administration of LEN 600 mg for 8 days (from Study Days 5 to 12) was examined. In addition, exposure-safety relationships (LEN PK/PD Analysis Set) were evaluated in HTE and TN HIV-infected participants in Phase 2 and Phase 2/3 studies (Studies GS-US-200-4334 and GS-US-200-4625) who received LEN, using LEN exposure estimates (AUC_{tau} and C_{max}) derived from population PK modeling (CTRA-2021-1054 LEN PopPK). The safety parameters evaluated were incidences of the most common AEs observed in Phase 2/3 study in HTE PWH (GS-US-200-4625) and TN participants (GS-US-200-4334).

3.2.3.1. Safety Profile of LEN in HTE PWH (GS-US-200-4625)

The PK/PD relationships between LEN exposure parameters and AEs were evaluated in HTE PWH in Study GS-US-200-4625. Figure 20 presents box plots of LEN AUC_{tau} and C_{max} for functional monotherapy by presence or absence of common AEs in participants receiving LEN. For functional monotherapy, only 3 incidences of nausea were identified as treatment emergent AEs (LEN Integrated PK/PD, Table 7.1), 1 was in the 2nd quartile and 2 were in the highest quartile (LEN Integrated PK/PD, Figure 5.1.1 and Figure 5.1.2). Lenacapavir AUC_{tau} and C_{max} for these 3 participants were within the range of exposures from the other participants who did not have nausea (LEN Integrated PK/PD, Table 8.1). However, this evaluation was limited by the small number of events.

Figure 20. Box Plots of LEN $AUC_{Day\ 1\text{-}15}$ and $C_{max\ Day\ 1\text{-}15}$ by Presence or Absence of Selected Treatment-Emergent Adverse Events GS-US-200-4625 Functional Monotherapy Period Analysis (Cohort 1A) (LEN Population PK/PD Analysis Set)

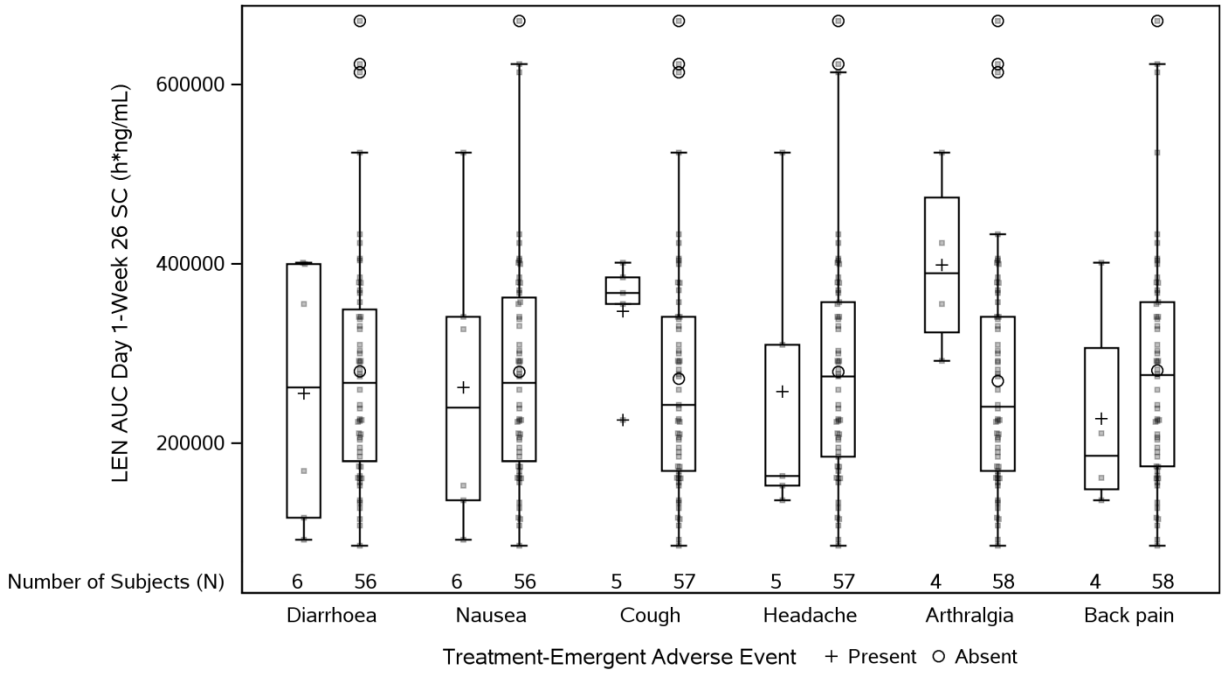


AEs = adverse events; LEN = lenacapavir; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Box plots denote median and IQR (Q3 - Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
Grey values in the background represent the actual data.
AEs were coded using MedDRA 23.1. Treatment-emergent AE is defined as an AE that began on or after first dose date of oral LEN and prior to the first dose date of the open-label SC LEN in the Functional Monotherapy Period.
AEs that occurred in ≥ 2 participants were included, excluding system organ class term of 'infections and infestations.'
Source: LEN Integrated PK/PD, Figure 4.1, Listing 2.1

The PK-PD relationships between LEN exposure parameters and AEs for the overall regimen (Day 1 to Week 26) were evaluated separately. The relationship between LEN exposure and incidence of AEs (present/absent) are shown in Figure 21 for $AUC_{Day1- Week 26}$ and Figure 22 for $C_{max\ Day1-Week\ 26}$.

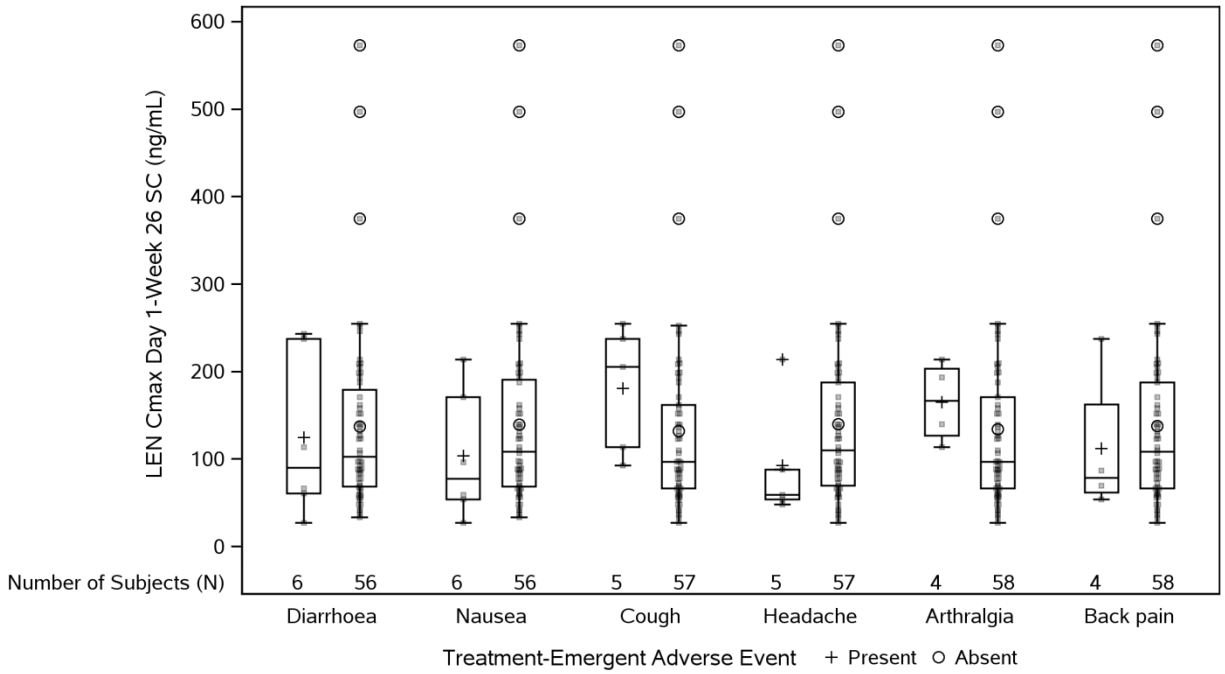
The most common AEs detected for the overall regimen were diarrhea and nausea (6 participants each), cough and headache (5 participants each), and arthralgia, back pain, constipation and pyrexia (4 participants each) (LEN Integrated PK/PD, Figure 4.2, Table 7.2, Listing 2.2 and 2.3). Constipation and pyrexia are only presented in LEN Integrated PK/PD, Figure 4.2. Lenacapavir exposures ($AUC_{Day1-Week\ 26}$ and $C_{max\ Day1-Week\ 26}$) were similar regardless of the presence or absence of the evaluated AE, indicating a lack of association between LEN exposure and common AEs (LEN Integrated PK/PD, Table 8.2, Figure 5.2.1, and Figure 5.2.2).

Figure 21. GS-US-200-4625: Box Plot of LEN $AUC_{Day\ 1-Week\ 26}$ by Presence or Absence of Selected Treatment-Emergent Adverse Events (LEN Population PK/PD Analysis Set)



AEs = adverse events; LEN = lenacapavir; IQR = interquartile range; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Box plots denote median and IQR (Q3 - Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
Grey values in the background represent the actual data.
Adverse events (AEs) were coded using MedDRA 23.1. Treatment-emergent AE is defined as an AE that began on or after first dose date of LEN.
Top 5 AE categories (or more if a tie on the 5th; excluding system organ class term of 'infections and infestations' and high-level term of 'injection site reactions') with the highest incidence rates included.
Preferred terms were presented by descending order of frequency and alphabetically within a tie (constipation, pyrexia shown in Figure 4.2 LEN Integrated PK/PD).
Source LEN Integrated PK/PD, Figure 4.2, Listing 2.2

Figure 22. GS-US-200-4625: Box Plot of LEN C_{max} Day 1-Week 26 by Presence or Absence of Selected Treatment-Emergent Adverse Events (LEN Population PK/PD Analysis Set)

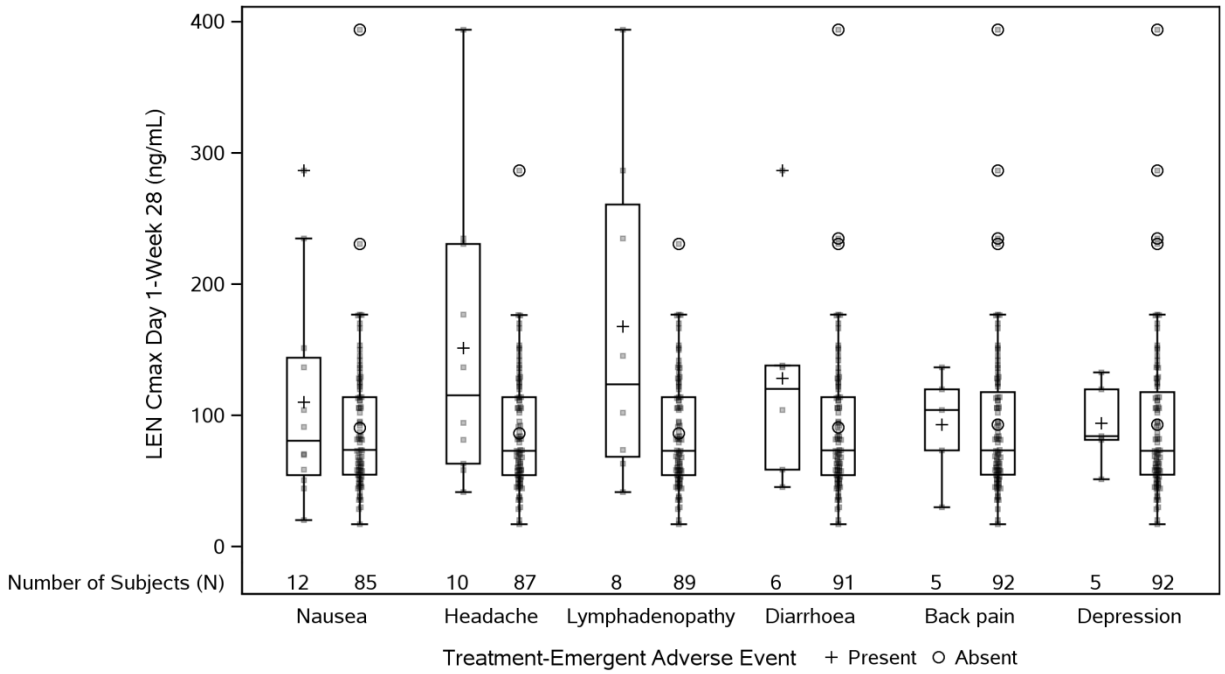


AEs = adverse events; LEN = lenacapavir; IQR = interquartile range; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Box plots denote median and IQR (Q3 - Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
Grey jittered values in the background represent the actual data.
AEs were coded using MedDRA 23.1. Treatment-emergent AE is defined as an AE that began on or after first dose date of LEN.
Top 5 AE categories (or more if a tie on the 5th; excluding system organ class term of 'infections and infestations' and high-level term of 'injection site reactions') with the highest incidence rates included.
Preferred terms were presented by descending order of frequency and alphabetically within a tie (constipation, pyrexia shown in Figure 4.2 LEN Integrated PK/PD).
Source LEN Integrated PK/PD, Figure 4.2 and Listing 2.2

3.2.3.2. Safety Profile of LEN in Treatment-Naive PWH (GS-US-200-4334)

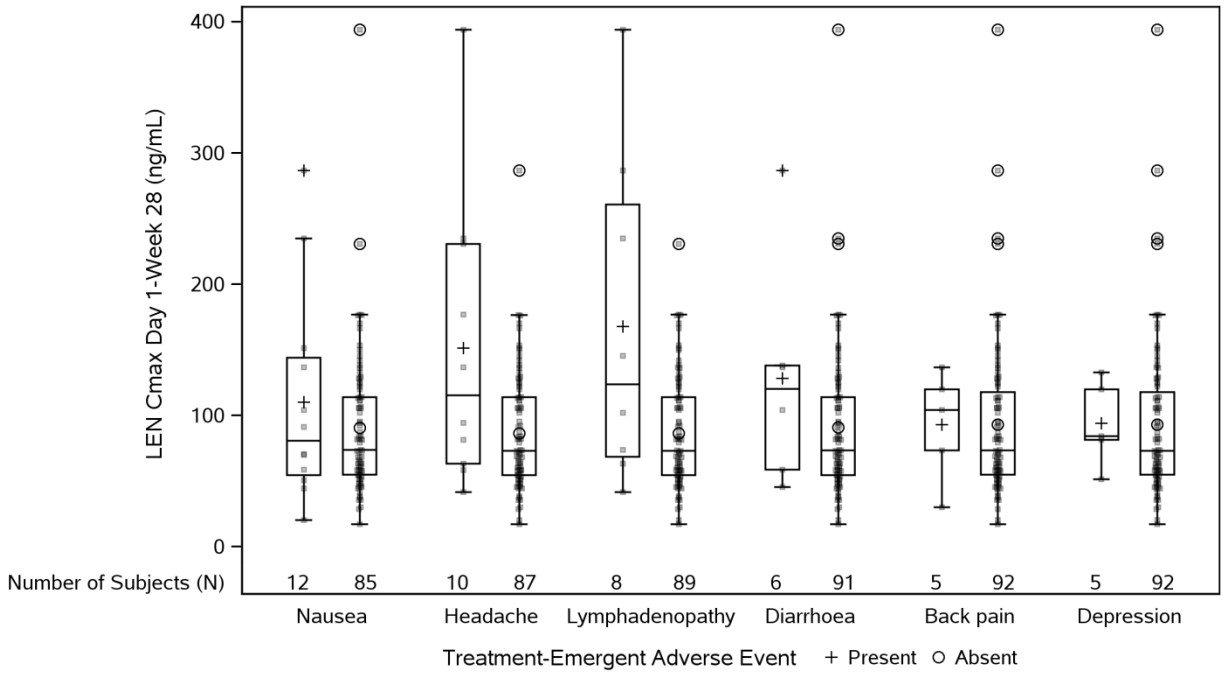
The PK-PD relationships between LEN exposure parameters and AEs were further evaluated in a Phase 2 study in TN PWH. The PK/PD Analysis Set included 97 participants from Group 1 and Group 2 in Study GS-US-200-4334 who received oral and SC LEN. Figure 23 and Figure 24 present box plots of LEN AUC_{tau} and C_{max}, respectively, by presence or absence of common AEs in participants receiving LEN. LEN exposures (AUC_{tau} and C_{max}) were similar regardless of the presence or absence of the evaluated adverse effect (LEN Integrated PK/PD, Table 8.3), indicating a lack of association between LEN exposure and common AEs of nausea, headache, lymphadenopathy, diarrhea, back pain, depression, hypertension and pyrexia (LEN Integrated PK/PD, Figure 5.3.1, Figure 5.3.2, and Table 7.3). Hypertension and pyrexia are only presented in LEN Integrated PK/PD, Figure 5.3.1 and Figure 5.3.2.

Figure 23. **Box Plot of LEN AUC $_{\text{Day 1-Week 26}}$ by Presence or Absence of Selected Treatment-Emergent Adverse Events GS-US-200-4334 Groups 1 and 2 (LEN Population PK/PD Analysis Set)**



AEs = adverse events; LEN = lenacapavir; IQR = interquartile range; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
Box plots denote median and IQR (Q3 - Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
Grey jittered values in the background represent the actual data.
AEs were coded using MedDRA 23.1. Treatment-emergent AE is defined as an AE that began on or after first dose date of LEN.
Top 5 AE categories (or more if a tie on the 5th; excluding system organ class term of 'infections and infestations' and high-level term of 'injection site reactions') with the highest incidence rates included. Preferred terms were presented by descending order of frequency and alphabetically within a tie (hypertension, pyrexia shown in Figure 4.3 LEN Integrated PK/PD).
Source LEN Integrated PK/PD, Figure 4.3, Table 2.4.1, Table 2.4.2, Table 2.4.3, and Listing 2.3

Figure 24. **Box Plot of LEN C_{max} Day 1-Week 26 by Presence or Absence of Selected Treatment-Emergent Adverse Events GS-US-200-4334 Groups 1 and 2 (LEN Population PK/PD Analysis Set)**



AEs = adverse events; LEN = lenacapavir; IQR = interquartile range; PD = pharmacodynamic(s); PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile
Box plots denote median and IQR (Q3 - Q1) while whiskers denote maximum and minimum values within 1.5 × IQR.
Symbols within the box plot denote the mean while symbols beyond the whiskers denote outliers > 1.5 × IQR.
Grey jittered values in the background represent the actual data.
AEs were coded using MedDRA 23.1. Treatment-emergent AE is defined as an AE that began on or after first dose date of LEN.
Top 5 AE categories (or more if a tie on the 5th; excluding system organ class term of 'infections and infestations' and high-level term of 'injection site reactions') with the highest incidence rates included. Preferred terms were presented by descending order of frequency and alphabetically within a tie (hypertension, pyrexia shown in Figure 4.3 LEN Integrated PK/PD.
Source LEN Integrated PK/PD, Figure 4.3, Table 2.4.1, Table 2.4.2, Table 2.4.3, and Listing 2.3

3.2.3.3. Evaluation of QT Interval Prolongation

The QT/QTc risk for LEN has been evaluated in multiple studies, including the in vitro human ether-a-go-go-related gene (hERG) assay, in vivo cardiovascular studies, a dedicated TQT study (Study GS-US-200-4332) and clinical studies. A non-Good Laboratory Practice hERG assay using 1, 3, and 10 µM concentrations of LEN demonstrated no inhibition of the hERG potassium current (PC-200-2013); however, based on the limit of solubility of LEN and the apparent precipitation observed at higher concentration, no IC_{50} on the hERG current was estimated. In a study conducted in male and female beagle dogs, LEN had no effect on cardiovascular parameters after a single SC dose of 100 mg/kg nor after repeated SC doses of 10 and 30 mg/kg administered every other week for 4 injections (TX-200-2006). The no observed effect level (NOEL) for ECG and blood pressure changes is 100 mg/kg for a single SC administration and 30 mg/kg for repeat SC administration. Based on the LEN C_{max} in male and female dogs after the first 100 mg/kg SC dose (4700 ng/mL), exposure at the NOEL is approximately 35-fold above the predicted therapeutic exposure (approximately 136.2 ng/mL).

Study GS-US-200-4332 was a Phase 1, double-blinded, randomized, placebo- and positive-controlled, 3-sequence, parallel (with nested crossover), multiple-dose study to evaluate the effect of LEN on the QT/QTc interval in healthy participants. A parallel design instead of a crossover design was chosen for this study due to the long half-life of oral LEN (approximately 12 days). Additionally, LEN is primarily eliminated unchanged (Section 3.1.3), with no single circulating metabolite accounting for > 10% of plasma drug-related exposure, and no accumulation of metabolite is expected following multiple dosing.

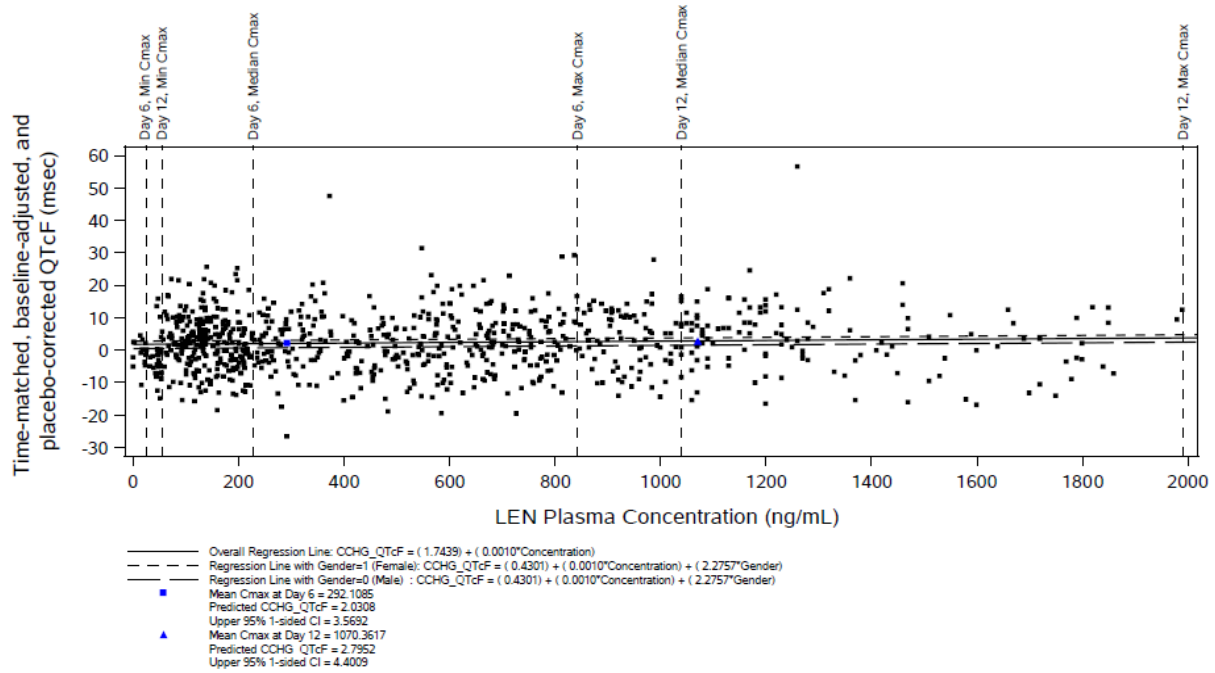
Following twice-daily oral administration of LEN 600 mg for 8 days (from Study Days 5 to 12), LEN C_{max} attained in this study was approximately 2.2- and 8.8-fold higher on Study Days 6 and 12, respectively, while LEN AUC_{tau} was approximately 3.5- and 15.0-fold higher on Study Days 6 and 12, respectively, in comparison with the expected therapeutic exposure estimates from the Phase 2/3 pivotal study of LEN in HTE PWH (Study GS-US-200-4625). Lenacapavir systemic exposures achieved in this study were above the exposures expected in the event of any DDI(s) or organ dysfunction. Additionally, the assay sensitivity was established with moxifloxacin.

The GS-US-200-4332 study data showed a large and unexpected imbalance in baseline QTcF between LEN and placebo treatment arms. To appropriately adjust for this imbalance, additional post hoc analyses were conducted along with the prespecified analysis.

The primary analysis evaluated the effect of LEN on time-matched, baseline-adjusted, and placebo-corrected QTcF (GS-US-200-4332 CSR, Tables 17 and 18). The upper limit of the 2-sided 90% CIs (or equivalently, upper limit of the 1-sided 95% CIs) for the time-matched, baseline-adjusted mean differences in QTcF between LEN and placebo was slightly at or above 10 msec at 3 postdose time points on Study Day 6 (slightly above therapeutic exposure) and 4 postdose time points on Day 12 (supratherapeutic exposure). The maximum increase at Day 12 was seen at 5 hours postdose, with a maximum mean (upper bound of the 2-sided 90% CIs) increase in baseline-adjusted, placebo-corrected QTcF interval of 7.9 (11.9) msec.

In contrast, prespecified c-QT analyses showed a lack of association between plasma concentrations of LEN and QTcF (time-matched, baseline-adjusted, placebo-corrected) over a wide range of concentrations (nearly 0.2- to 18-fold of the mean therapeutic C_{max} derived from the PopPK modeling estimates from the Phase 2/3 study in HTE PWH) that exceeded the exposures from DDI and organ impairment studies (Figure 25). Thus, with increasing LEN concentrations, there was no evidence of QTc prolongation ($P \leq 0.096$ for slope of concentration, GS-US-200-4332 CSR, Table 27).

Figure 25 **GS-US-200-4332: Scatter Plot of Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF Versus LEN Plasma Concentrations (Reference Therapeutic Exposure Derived From Phase 2/3 Study GS-US-200-4625) (PK/PD Analysis Set) – Prespecified Model Without Baseline QTcF Adjustment**



CCHG_QTcF = time-matched, baseline-adjusted, and placebo-corrected QTcF; LEN = lenacapavir; PD = pharmacodynamic(s); PK = pharmacokinetic(s)
Overall PK/PD regression included concentration as a continuous covariate and participant as a random effect.
PK/PD regression with gender included gender as a fixed effect, concentration as a covariate and participant as a random effect.
Upper 95% 1-sided CI was calculated based on overall PK/PD regression model.
Vertical dashed lines indicate minimum, median, and maximum C_{max} on Day 6 and Day 12.
Participant [redacted] early terminated due to an adverse event on Day 5 and is excluded from analysis.
Participant [redacted] Day 6 (4 hour postdose), Participant [redacted] Day 1 (4 hour postdose), and Participant [redacted] Day 1 (5 hour postdose) had electrocardiogram Holter monitoring collected after pharmacokinetic sample collection and are excluded from analysis at these time points.
Source: GS-US-200-4332 CSR, Figure 9

However, these prespecified models did not appropriately adjust for baseline imbalance in QTcF. Therefore, three additional post hoc analyses were conducted. The first post hoc analysis was conducted for the noninferiority evaluation by replacing the covariate of time-matched baseline QTcF with the participant-level averaged baseline (referred to as "averaged baseline") QTcF in the prespecified mixed-effect model. The second post hoc analysis was conducted similarly as the first post hoc analysis using averaged baseline QTcF in the model for the assay sensitivity analysis. The third post hoc analysis was the c-QT analysis using a linear mixed-effects model, as specified in the recommendations of "Scientific white paper on concentration-QTc modeling" {Garnett 2018} to robustly model the exposure-response relationship between LEN concentrations and QTc interval. For this model, the dependent variable is the time-matched, baseline-adjusted QTcF (ΔQTcF).

In the noninferiority test of the primary analysis using the prespecified model, the estimated treatment effects (ΔΔQTcF) were larger than the observed and the corresponding 90% CIs were wider than expected, suggesting that the large and unexpected imbalance in baseline QTcF between treatment groups had not been appropriately adjusted in the model; the mean difference in the averaged baseline QTcF (LEN – placebo) was 6.5 msec. Therefore, a post hoc analysis was conducted replacing the covariate of time-matched baseline QTcF with the averaged baseline QTcF, which provides less bias compared to time-matched baseline and greater statistical power when baseline imbalance exists {Huang 2021, Lu 2013, Meng 2010}. Using this method, the estimated treatment effects (ΔΔQTcF) were closer to the observed ones and the width of the 90% CIs was narrower, suggesting an improved accuracy and precision of the noninferiority evaluation. The estimated treatment effects were less than or equal to 5 msec and the upper bounds of ΔΔQTcF were below 10 msec for all time points (GS-US-200-4332 CSR, Table 19, Table 20, and Figure 6). Assay sensitivity was established in the post hoc analysis using averaged baseline QTcF as the covariate in the model.

For post hoc c-QT analysis, a linear mixed-effects model describing ΔQTcF as a function of LEN plasma concentration with treatment, visit, time, averaged baseline QTcF, and gender as fixed effects, and intercept and slope of concentration as random effects was selected based on the smallest Akaike information criterion. The results of this analysis corroborated a lack of association between LEN plasma concentrations and change in QTcF ($P = 0.3592$ for slope of concentration). Based on the analysis, the mean ΔΔQTcF and its corresponding upper limit of the 2-sided 90% CIs were predicted at the mean C_{max} of LEN on Study Days 6 and 12, and the expected therapeutic concentrations of LEN (derived from the exposure estimates from the Phase 2/3 study in HTE PWH [Study GS-US-200-4625]). The results of this analysis are summarized in Table 19. At the mean LEN C_{max} of approximately 1070 ng/mL following twice-daily oral administration of LEN 600 mg for 8 days (Study Day 12), mean ΔΔQTcF is predicted to be approximately 2.63 msec, and the upper bound of the 2-sided 90% CI of ΔΔQTcF is below 10 msec (4.81 msec). Likewise, at the estimated therapeutic mean LEN C_{max} ranging from 111.8 to 151.6 ng/mL (dosed with or without boosters), ΔΔQTcF is predicted to be ≤ 1.57 msec, and the upper bound of the 2-sided 90% CI of ΔΔQTcF is below 10 msec (≤ 3.84 msec). These model-estimated parameters are in agreement with the projections from the bootstrap analysis. In addition, treatment-emergent absolute QTcF intervals > 450 msec, > 480, or > 500 msec were not observed in Study GS-US-200-4332 (Study GS-US-200-4332 CSR, Table 21) for any participant following any treatment.

Table 19. GS-US-200-4332: Summary of Predicted Time-Matched, Baseline-Adjusted and Placebo-Corrected QTcF (msec) at the Mean Peak Concentrations of LEN on Study Days 6 and 12 and the Expected Therapeutic Concentrations of LEN (PK/PD Analysis Set)

Label	LEN Concentration (ng/mL)	Model			Bootstrap[a]		
		Predicted Mean ΔΔQTcF (msec)	90% CI (msec)		Median (msec)[b]	90% CI (msec)	
			Lower	Upper		Lower	Upper
Mean C_{max} TQT Study Day 6	292.1	1.73	-0.42	3.89	1.68	-0.57	4.14
Mean C_{max} TQT Study Day 12	1070.4	2.63	0.44	4.81	2.61	0.57	4.72
Mean C_{max} Day 1−Week 28[c]	136.2	1.55	-0.74	3.84	1.50	-0.95	4.25
Mean C_{max} Day 1−Week 28 With Booster[d]	151.6	1.57	-0.71	3.84	1.52	-0.91	4.24
Mean C_{max} Day 1−Week 28 Without Booster[e]	111.8	1.52	-0.79	3.83	1.48	-1.00	4.29

HTE = heavily treatment experienced; LEN = lenacapavir; PD = pharmacodynamics; PK = pharmacokinetics; PopPK = population pharmacokinetics; PWH = people with HIV; TQT = thorough QT

a Bootstrap median and 90% CI values are taken from 3000 nonparametric bootstrap calculations.

b Bootstrap median is used as bootstrap estimate of mean value.

c Mean C_{max} from PopPK modeling from the Phase 2/3 registrational study (GS-US-200-4625) in HTE PWH taking LEN (with or without boosters) on the clinical dosing regimen of a 14-day oral lead-in (Days 1 to 15), followed by a subcutaneous maintenance dose of 927 mg (LEN injection, 309 mg/mL) to be administered once every 26 weeks.

d Mean C_{max} from PopPK modeling from the Phase 2/3 registrational study (GS-US-200-4625) in HTE PWH taking LEN with boosters.

e Mean C_{max} from PopPK modeling from the Phase 2/3 registrational study (GS-US-200-4625) in HTE PWH taking LEN without boosters.

Participant [redacted] terminated early due to an adverse event on Day 5 and is excluded from analysis.

Participant [redacted] Day 6 (4 hour postdose), Participant [redacted] Day 1 (4 hour postdose), and Participant [redacted] Day 1 (5 hour postdose) had electrocardiogram Holter monitoring collected after pharmacokinetic sample collection and are excluded from analysis at these time points.

Source: Study GS-US-200-4332 CSR, Table 30

In Studies GS-US-200-4625, GS-US-200-4334, and the pooled Studies GS-US-200-4538 and GS-US-200-5709, there were no clinically significant abnormal ECGs at screening or posttreatment.

In summary, the totality of the data indicates no clinically relevant effect of LEN on QTc interval.

3.3. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Conclusions

A comprehensive clinical pharmacology program was conducted using LEN in Phase 1, 2, or 2/3 studies to support the use of LEN for the treatment of HIV infection. Phase 1 clinical studies evaluated single-dose escalations for both the LEN tablets' and SC formulations' PK in healthy participants and PWH, ADME, a thorough QT (TQT) study, the potential for LEN to affect other drugs, and the potential of food, other drugs, organ impairment, or other demographic factors to affect LEN. The PK of LEN was also evaluated in PWH in Phase 2 and 2/3 clinical studies. Population PK analyses evaluated intrinsic and extrinsic factors affecting the PK of LEN in HIV-infected participants, and potential relationships were evaluated between LEN exposure and efficacy and safety outcomes. The PK and PK-PD conclusions based on these data are summarized in the following sections.

3.3.1. Absorption

Oral Administration

Lenacapavir is absorbed following oral administration with peak plasma concentrations occurring 4 hours after administration of LEN. Absolute bioavailability following oral LEN administration is low (approximately 6.2% to 10%). Lenacapavir is a substrate of P-gp.

Lenacapavir AUC, C_{max} and T_{max} were comparable following administration of a low fat (approximately 400 kcal, 25% fat) or high-fat (approximately 1000 kcal, 50% fat) meal relative to fasted conditions. Lenacapavir can be administered without regard to food.

Subcutaneous Administration

Lenacapavir is completely absorbed following SC administration. Due to slow release from the site of SC administration, the absorption profile of LEN is complex with peak plasma concentrations occurring 77 to 84 days postdose.

3.3.2. Distribution

The apparent volume of distribution was 19,240 L after oral administration and ranged from 9,500 to 11,700 L after SC administration.

Lenacapavir is highly bound to plasma proteins (> 98.5%).

3.3.3. Metabolism

Following a single IV dose of radiolabeled-LEN to healthy participants, 76% of the total radioactivity was recovered from feces and < 1% from urine. Unchanged LEN constituted 68.8% of circulating total radioactivity in plasma and 32.9% of feces.

Lenacapavir is cleared by metabolism, excretion into bile and intestinal secretion by P-gp. Metabolism plays a minor role in LEN elimination. Lenacapavir was metabolized via oxidation, N-dealkylation, hydrogenation, amid hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation; primarily via CYP3A4 and UGT1A1. No single metabolite contributed > 10% of total radioactive exposure.

3.3.4. Elimination

The median half-life after oral and SC administration ranged from 10 to 12 days, and 8 to 12 weeks, respectively. Mean apparent clearance was 55 L/h following oral administration and 4.2 L/h following SC administration.

3.3.5. Effect of Intrinsic Factors

Population analyses using data from adult trials did not identify any clinically relevant differences due to age, gender, race/ethnicity or weight on the PK of LEN. No dose adjustment of LEN is required for participants > 65 years of age. Health status (PWH versus healthy) was identified as a statistically significant covariate. Lenacapavir exposures were approximately 30% to 50% lower in healthy participants as compared with HTE PWH.

Lenacapavir-simulated exposures in pediatric participants 12 to < 18 years of age and weighing ≥ 35 kg were generally within the range observed in the adult population in the Phase 2/3 study (Study GS-US-200-4625); median simulated exposures were within the 25th and 75th percentiles of adult exposures.

Renal Impairment

Lenacapavir exposures were increased (84% and 162% for AUC and C_{max}, respectively) in participants with severe renal impairment (estimated CL_{cr} ≥ 15 and < 30 mL/minute) compared with participants with normal renal function; however, this increase was not considered clinically relevant. Lenacapavir has not been studied in patients with end-stage renal disease. As LEN is > 98.5% protein bound, dialysis is not expected to alter exposures to LEN. No dose adjustment of LEN is required in patients with mild, moderate, or severe renal impairment (CL_{cr} ≥ 15 mL/min).

Hepatic Impairment

Lenacapavir mean exposures were increased (47% and 161% for AUC_{inf} and C_{max}, respectively) in participants with moderate hepatic impairment (Child-Pugh B) compared with participants with normal hepatic function; however, the increase was not considered clinically meaningful.

No dose adjustment of LEN is required in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). The PK of LEN have not been studied in patients with severe hepatic impairment (Child-Pugh C).

3.3.6. Effect of Extrinsic Factors

The impact of extrinsic factors on the PK of LEN was evaluated in Phase 1 studies and DDI studies, and as part of PopPK analyses.

Lenacapavir AUC, C_{max} and T_{max} were comparable following administration of a low-fat (approximately 400 kcal, 25% fat) or high-fat (approximately 1000 kcal, 50% fat) meal relative to fasted conditions. Lenacapavir can be administered without regard to food.

Administration of oral LEN with gastric ARAs such as histamine 2 receptor agonists does not affect the PK of LEN to a clinically relevant extent. Therefore, LEN may be administered with gastric ARAs.

Lenacapavir is a substrate of CYP3A (minor contribution), P-gp and UGT1A1 (minor contribution). Drugs that are strong inducers of CYP3A, P-gp and UGT1A1 (eg, RIF), or that are moderate inducers of CYP3A and P gp (eg, EFV), may significantly decrease plasma concentrations of LEN, which may result in loss of therapeutic effect and development of resistance. Concomitant administration with strong inducers such as RIF is contraindicated and moderate inducers such as efavirenz is not recommended with LEN. Strong CY3A4 inhibitors alone (eg, VORI) or strong inhibitors of CYP3A4 and P-gp together (eg, COBI) do not result in a clinically relevant increase in LEN exposures. Strong inhibitors of CYP3A, P-gp, and UGT1A1 together (ie, all 3 pathways), such as ATV/COBI, may significantly increase plasma concentrations of LEN. Concomitant administration with strong inhibitors of CYP3A, P-gp and UGT1A1 together such as ATV/COBI is not recommended.

Lenacapavir appears to weakly inhibit BCRP (eg, ROS) and P-gp (eg, TFV), and moderately inhibits CYP3A (eg, MDZ). Therefore, caution is advised if LEN is coadministered with sensitive CYP3A substrates with narrow therapeutic index, but not P-gp, BCRP, or OATP substrates.

3.3.7. Clinical Pharmacokinetics/Pharmacodynamics

A Phase 2/3 regimen consisting of oral LEN 600 mg on Day 1, Day 2, oral LEN 300 mg on Day 8 followed by SC LEN injection 927 mg on Day 15 was selected based on the totality of PK, safety, and efficacy data from Phase 1 and 2 studies in conjunction with the knowledge that trough concentration maintained above $paEC_{95}$ is desired for HTE. This Phase 2/3 regimen provided near maximal virologic response and an IQ of 12.6-fold above the $paEC_{95}$ against WT HIV-1 virus during Functional monotherapy and 9.1-fold 26 weeks after SC administration.

In the Phase 2/3 studies, exposure-efficacy relationships of LEN exposures (AUC_{tau}, $C_{max,}$ and C_{trough}) across quartiles versus the primary efficacy end point (HIV-1 RNA $\geq$ 0.5 $\log_{10}$ reduction from baseline HIV-1 RNA, at the end of Functional monotherapy) and secondary efficacy end point (HIV-1 RNA < 50 copies/mL at Week 26 using the US FDA-defined snapshot algorithm), were examined. All analyses consistently revealed high virologic response rates across all groups (including participants with the lowest quartile exposure to LEN) with no trends in exposure-response relationships because the majority (56/62) of the patients achieved concentrations above IQ4 in the Phase 2/3 studies.

Relationships between LEN exposure parameters and safety parameters from Phase 2 and Phase 2/3 studies were evaluated. Lenacapavir exposures (AUC_{tau} and C_{max}) were similar regardless of the presence or absence of the most common AEs, indicating a lack of association between LEN and findings of diarrhea, nausea, cough, headache, arthralgia, back pain, constipation and pyrexia diarrhea in the Phase 2/3 study.

With respect to cardiac safety (QTc interval), the pre-specified noninferiority of QTcF on LEN versus placebo in the TQT study (Study GS-US-200-4332) was not met at a few postdose time points. However, an imbalance in baseline QTc between LEN and placebo treatment arms was observed. Post hoc analysis accounting for this imbalance in baseline resulted in upper bounds of ΔΔQTcF below 10 msec for all time points. Additionally, the prespecified concentration-QTc analyses did not demonstrate any association between plasma concentrations of LEN and QTcF intervals over a wide range of concentrations that exceeded the exposures from DDI and organ impairment studies. Using the post hoc concentration-QT analysis, at supratherapeutic exposures (9-fold higher than the therapeutic exposures) to LEN, the predicted mean (upper 90% CI) increase in baseline-adjusted, placebo-corrected QTcF interval was 2.6 (4.8) msec., and there was no association ($P = 0.36$) between observed LEN plasma concentrations and change in QTcF. In addition, no cardiac safety concerns were noted from in vivo cardiovascular studies in dog and clinical studies. The totality of data indicates that LEN does not have a clinically relevant effect on QTcF.

4. VIROLOGY SUMMARY

Nonclinical and clinical virology studies are discussed in the following sections.

4.1. Nonclinical Virology

A summary of nonclinical virology is provided in the following sections, and a full description of nonclinical virology is provided in m2.6.2. A tabular listing of nonclinical virology studies is provided in Appendix 6.4.

4.1.1. Primary Pharmacodynamics

Lenacapavir is a multistage inhibitor of HIV-1 capsid (CA) with high potency and selectivity in antiviral assays. Protein X-ray crystallography and biochemical assays indicate that LEN binds at the intermolecular interface between 2 adjacent CA monomers within a CA hexamer. Lenacapavir binding increased the rate and extent of in vitro CA assembly, resulting in malformed CA polymers (PC-200-2022, PC-200-2023).

In HIV-1 antiviral assays using the MT-4 T-lymphoblastoid cell line, primary human CD4+ T lymphocytes, and monocyte-derived macrophages, the half-maximal effective concentration (EC_{50}) of LEN ranged from 0.030 to 0.190 nM and the selectivity indices ranged from 140,000 to > 1,670,000 (PC-200-2018, PC-200-2019). In acutely infected cells, LEN binding to CA results in potent suppression of both early- and late-stage processes essential for HIV-1 replication, with EC_{50} values of 0.023 nM and 0.439 nM, respectively (PC-200-2021). Lenacapavir interferes with late-stage virus production and CA core formation events. Lenacapavir also interferes with an early-stage process occurring after reverse transcription but before the integration of viral DNA (PC-200-2024). When tested against clinical isolates of all HIV-1 groups (M, N, O), including subtypes A, A1, AE, AG, B, BF, C, D, E, F, G, and H, LEN displayed similar antiviral activity against all isolates, with mean EC_{50} values of 0.05 nM (ranging from 0.02 to 0.16 nM) and 0.24 nM (ranging from 0.15 to 0.36 nM) in PBMCs and the HEK293T cell line, respectively (PC-200-2020, PC-200-2041). Consistent with these findings, the CA protein sequence is highly conserved across 8 major HIV-1 subtypes, including the majority of residues within the LEN binding site (PC-200-2032). Most CA polymorphisms near the LEN binding site displayed WT susceptibility to LEN (PC-200-2038). Lenacapavir showed potent antiviral activity against 2 HIV-2 isolates but was 15- to 25-fold less active relative to HIV-1 (PC-200-2020).

Lenacapavir maintains potent antiviral activity against HIV-1 mutants and HIV-1 clinical isolates resistant to currently approved ARVs from the nucleoside reverse transcriptase inhibitor (NRTI), nonnucleoside reverse transcriptase inhibitor (NNRTI), INSTI and protease inhibitor (PI) classes (PC-200-2027, PC-200-2044). In addition, the antiviral activity of LEN in clinical isolates was unaffected by the presence of naturally occurring Gag polymorphisms or Gag cleavage site mutations associated with PI treatment and known to be associated with resistance to maturation inhibitors (PC-200-2036, PC-200-2037).

HIV-1 isolates with reduced susceptibility to LEN have been selected in cell culture (PC-200-2025). Lenacapavir selected for single and double CA amino acid substitutions, including L56I, M66I, Q67H, K70N, N74D/S and T107N. HIV-1 variants encoding these individual mutations conferred resistance to LEN (3.8- to > 3226-fold), with the majority of the mutants, including those conferring moderate to high-level LEN resistance, displaying substantially reduced replication capacity relative to the WT virus in CD4+ T lymphocytes and macrophages (PC-200-2026, PC-200-2045, PC-200-2046). Capsid population-level and deep sequence analyses of >10,000 publicly available sequences and clinical isolates suggest that known LEN resistance associated mutations are present below 1% in the patient population (PC-200-2032). The LEN-resistant mutants remained susceptible to other classes of ARVs (NNRTIs, NRTIs, PIs, INSTIs, maturation inhibitors) (PC-200-2025, PC-200-2045, PC-200-2046).

The in vitro activity of LEN was reduced in the presence of human serum due to protein binding. The 95% effective concentration (EC_{95}) calculated from a high resolution antiviral dose response in MT-4 cells was used in conjunction with the human serum shift determined by equilibrium dialysis (Pharmacokinetics Tabulated Summary [m2.6.5], Section 4, AD-200-2020) to calculate a $paEC_{95}$ value of 4 nM (PC-200-2018).

4.1.2. Secondary Pharmacodynamics

4.1.2.1. Cytotoxicity

Lenacapavir showed low cytotoxicity in primary human hepatocytes (half-maximal cytotoxic concentration [CC_{50}] > 50 µM) and in several nontarget human cell lines of different tissue origin (CC_{50} values > 44 µM), including 2 cell lines that were adapted for growth in galactose-containing medium to increase their sensitivity to mitochondrial toxicity (PC-200-2028).

4.1.2.2. Off-Target Activity

Lenacapavir is a specific inhibitor of HIV-1, with no measurable antiviral activity against non-HIV viruses such as hepatitis C virus and human rhinovirus and weak antiviral activity against hepatitis B virus and respiratory syncytial virus (PC-200-2029).

Lenacapavir had no pharmacologically significant binding affinity to a diverse panel of 87 molecular targets, including ion channels, nuclear receptors, transporters, and enzymes (PC-200-2012).

4.1.3. Pharmacodynamic Drug Interactions

In vitro 2-drug combination studies have shown that LEN has synergistic anti-HIV-1 activity when combined with approved drugs representative of NRTI, NNRTI, INSTI, and PI classes. No antagonistic antiviral interaction was found between LEN and the tested clinically relevant classes of ARVs (PC-200-2030).

4.2. Clinical Virology

Analyses were performed for PWH with clinical virology data from Phase 1b Study GS-US-200-4072, Phase 2 Study GS-US-200-4334, and Phase 2/3 Study GS-US-200-4625. A summary of the main findings from these analyses are provided in Section 4.2.1.

For the purpose of screening, genotyping and phenotyping of CA were performed for all participants enrolled in Studies GS-US-200-4072, GS-US-200-4334, and GS-US-200-4625. Genotypic assays for HIV-1 protease (PR), reverse transcriptase (RT), and integrase (IN) were performed for participants enrolled in Studies GS-US-200-4072, GS-US-200-4334, and GS-US-200-4625; for some participants in Study GS-US-200-4625, historical genotyping data were obtained at screening. Phenotyping of PR/RT and IN were performed at screening for participants enrolled in Study GS-US-200-4625. A retrospective analysis of susceptibility to HIV-1 entry inhibitors was conducted on baseline samples from all randomized participants in Study GS-US-200-4625.

For participants in Study GS-US-200-4625, a genotypic susceptibility score (GSS), phenotypic susceptibility score (PSS), and overall susceptibility score (OSS) for drugs from the 4 main drug classes and entry inhibitors were determined based on the baseline resistance results. Possible scores for these categories are 1, 0.5, or 0, corresponding to sensitive, partially sensitive/resistant, or resistant, respectively. Susceptibility scores were used to assess the strength of incoming failing treatment regimens as well as the potential strength of OBRs.

Table 20 summarizes all of the previously identified drug-resistance mutations by ARV drug class.

Table 20. Resistance Substitutions by Antiretroviral Class

Resistance Associated Mutations[a]	
Drug Class	**Drugs and Codon Mutations**
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (N(t)RTIs)	*Abacavir, Emtricitabine, Lamivudine, Tenofovir, Zidovudine, Didanosine, Stavudine*
Primary NRTI-R substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219E/Q
Multi-NRTI (Thymidine Analogue Mutations [TAMs])	M41L, D67N, K70R, L210W, T215Y/F[b], K219Q/E/N/R
Multi-NRTI: T69 Insertion Complex[b]	T69 Insertion/Deletion: T69S-SS, -SA, -SG, or others
Multi-NRTI: 151 Complex	A62V, V75I, F77L, F116Y, Q151M
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	*Delavirdine, Doravirine, Efavirenz, Etravirine, Nevirapine, Rilpivirine*
Primary NNRTI-R substitutions	L100I, K101E/H/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C, M230L/I

Resistance Associated Mutations[a]	
Drug Class	**Drugs and Codon Mutations**
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106I/T, V179D/F/T, G190E, F227L/R, L234I
Protease Inhibitors (PIs)	*Atazanavir, Darunavir, Lopinavir, Tipranavir, Fosamprenavir, Indinavir, Nelfinavir, Saquinavir Ritonavir*
Primary PI-R substitutions	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L/V, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
Secondary PI-R substitutions	L10I/F/R/V/C, V11I, I13V, G16E, K20I/M/R/T/V, L24I, L33F/I/V, E34Q, E35G, M36I/L/V, K43T, F53L/Y, I54A/S/T, D60E, I62V, L63P, I64L/M/V, H69K/R, A71V/T/I/L, G73A/C/S/T, V77I, V82I, I85V, N88D, L89M/I/V, I93L/M
Entry Inhibitors	*Enfuvirtide, Maraviroc, Fostemsavir*
Resistance-associated substitutions (*env*)	G36D/S, I37V, V38A/E/M, Q39R, Q40H, N42T, N43D
Integrase Strand Transfer Inhibitors (INSTIs)	*Bictegravir, Cabotegravir, Dolutegravir, Elvitegravir, Raltegravir*
Primary INSTI-R substitutions	T66I/A/K, E92Q/G/V, G118R, F121C/Y, G140R, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R substitutions	M50I, L68V/I, L74M, T97A, S119P/R/T, E138K/A/T, G140A/C/S, P145S, Q146R/I/K/L/P, S153F/Y, E157K/Q
Capsid Inhibitors (CAIs)	*Lenacapavir*
Primary CAI-R substitutions[c]	L56I, M66I, Q67H, K70N, N74D/S, T107N

CAI = capsid inhibitor; FTC = emtricitabine; INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistant; RT = reverse transcriptase; TAF = tenofovir alafenamide; TAM = thymidine analogue mutation

a Adapted from the current International Antiviral Society-USA (IAS-USA) Guidelines lists, with some modifications {Wensing 2019}

b Reversion mutations at RT codon T215, including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either FTC or TAF

c Mutations observed during in vitro resistance selection experiments (PC-200-2025); all mutations observed at these positions will be reported, regardless of substitution

Resistance testing was performed for any participant meeting the criteria of the Resistance Analysis Population (RAP):

- The RAP included any participants who received at least 1 dose of study drug, maintained their study regimen, and had confirmed virologic failure through the end of study or at key study end points, or was viremic at the last study visit (completion or early discontinuation).
- The final RAP did not include participants who remained on study medication and later suppressed HIV-1 RNA to < 50 copies/mL in the absence of emerging resistance mutations.

- In the Phase 1 proof-of-concept study (Study GS-US-200-4072), resistance testing was also performed at Day 10, regardless of virologic status.

Resistance analyses consisted of genotypic and phenotypic assessment of the HIV-1 CA, PR, RT, and IN proteins. A summary of the results from these analyses are provided in Section 4.2.1.

A full description of the resistance analysis methodologies is provided in the virology analysis plan (PC-200-2035). Full details of the RAP, final RAP, and the clinical virology resistance analyses from the LEN Phase 2/3, 2, and 1b studies can be found in the virology study reports PC-200-2043 [Study GS-US-200-4625], PC-200-2042 [Study GS-US-200-4334], and PC-200-2039 [Study GS-US-200-4072]. A summary of the main findings is described below.

4.2.1. Virology Resistance Analyses at Baseline and in the Resistance Analysis Population From Phase 2/3, Phase 2, and Phase 1b Studies

4.2.1.1. Study GS-US-200-4625

4.2.1.1.1. Study Characteristics and Viral Response

Study GS-US-200-4625 is an ongoing Phase 2/3 study to evaluate the safety and efficacy of LEN in combination with an OBR in HTE PWH with multidrug resistant infection.
Study GS-US-200-4625 enrolled participants with multidrug resistance receiving a nonsuppressive treatment regimen and comprised 2 cohorts of participants: a randomized cohort (Cohort 1) that included a placebo-controlled 14-day LEN Functional Monotherapy Period (Cohort 1A: LEN; Cohort 1B: placebo), and a nonrandomized cohort (Cohort 2). Treatment assignment in Cohort 1 was unblinded for each participant at the end of the Functional Monotherapy Period when all Cohort 1 participants initiated their OBR, and participants initially assigned to placebo started LEN treatment with OBR.

A total of 72 participants were enrolled, divided equally into 2 cohorts of 36:

Cohort 1 (Randomized Cohort) (n = 36):

Participants were required to have an HIV-1 RNA decline of < 0.5 $\log_{10}$ copies/mL at the Cohort Selection visit compared with the screening visit and have HIV-1 RNA ≥ 400 copies/mL to enroll in Cohort 1. Participants were randomized in a 2:1 ratio for enrollment in Cohort 1:

- Induction: Oral LEN (Cohort 1A, n = 24) or placebo-to-match (Cohort 1B, n = 12):
  Cohort 1A: Oral LEN on Day 1 and Day 2 (600 mg) and Day 8 (300 mg) + failing regimen (FR), followed by SC LEN 927 mg + OBR on Day 15
  Cohort 1B: Oral placebo-to-match on Day 1 and Day 2 (600 mg) and Day 8 (300 mg) + FR, followed by oral LEN on Day 15 and Day 16 (600 mg) and Day 22 (300 mg) along with OBR starting on Day 15; SC LEN 927 mg on Day 29

- Maintenance: SC LEN 927 mg at Week 26 and every 26 weeks thereafter

Cohort 2 (Nonrandomized Cohort) (n = 36):

Participants were enrolled in Cohort 2 after Cohort 1 was fully enrolled, or if participants did not meet the criteria for randomization in Cohort 1 (ie, HIV-1 RNA decline ≥ 0.5 $\log_{10}$ copies/mL at the Cohort Selection visit compared with screening visit, and/or HIV-1 RNA < 400 copies/mL)

- Induction: Oral LEN (Day 1 and Day 2: 600 mg; Day 8: 300 mg), then SC LEN 927 mg (Day 15) + OBR on Day 1

- Maintenance: SC LEN 927 mg at Week 26 and every 26 weeks thereafter

All treatments were given without regard to food.

A significantly greater percentage of participants receiving LEN had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period than those receiving placebo (87.5% versus. 16.7, $P < 0.0001$). The percentages of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm were 80.6% (29 of 36 participants) and 88.9% (32 of 36 participants), respectively. The percentages of participants in Cohort 2 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm were 66.7% (4 of 6 participants) and 66.7% (4 of 6 participants), respectively (Study GS-US-200-4625, m2.7.3, Section 2.1).

4.2.1.1.2. Baseline Virology Data

Resistance reports (screening genotypic/phenotypic assays or historical reports) were obtained prior to enrollment as part of the enrollment criteria for all 72 participants who entered Study GS-US-200-4625. Overall Susceptibility Scores were obtained from the resistance reports for all ARVs from the 4 main drug classes (26 drugs).

The high burden of HIV-1 resistance at study entry required in the study was confirmed for 71/72 participants (Table 21). Consistent with study entry criteria, all 71 participants had resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV drugs (NRTI, NNRTI, PI, INSTI). One participant (Participant [redacted]) showed required resistance to the INSTI and NNRTI classes but only partial resistance to 1 NRTI (didanosine), as resistance to emtricitabine (FTC) and lamivudine (3TC) in the presence of M184V/I did not count towards the total number of resistant NRTIs.

Across HTE participants, the median number of ARV agents with resistance per class approached the total number of ARV agents per class (median of 4 out of a total of 4, median of 5 out of a total of 6, median of 5 out of a total of 7, and median of 7 out of a total of 9, for INSTIs, NNRTIs, NRTIs, and PIs, respectively; Table 21). Almost half of the participants had HIV-1 with 4-class resistance (45.8%, Table 22).

No participant harbored LEN-associated resistance mutations at study entry (Table 23). However, the presence of resistance mutations to the 4 main ARV drug classes was high, consistent with the high level of resistance observed in the OSS analysis.

Table 21. GS-US-200-4625: Number of Antiretroviral Drugs with Resistance and Number of Participants with ≥ 2 Drug Resistance By Drug Class at Baseline

Drug Classes		Number of ARV Drugs with Resistance[a]			
		Cohort 1[b]		Cohort 2	
		Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
INSTI (4 drugs)	*Median # of drugs*	4	4	4	4
	Range	(0 – 4)	(0 – 4)	(0 – 4)	(0 – 4)
	Participants with data	24	11	35	70
	Participants with ≥ 2[c]	20	7	23	50
NNRTI (6 drugs)	*Median # of drugs*	5.5	5	4	5
	Range	(0 – 6)	(2 – 6)	(2 – 6)	(0 – 6)
	Participants with data	24	12	36	72
	Participants with ≥ 2[c]	22	12	36	70
NRTI (7 drugs)	*Median # of drugs*	6.5	7	4.5	5
	Range	(2 – 7)	(4 – 7)	(2 – 7)	(2 – 7)
	Participants with data	24	12	36	72
	Participants with ≥ 2[c]	24	12	36	72
NRTI[d] (7 drugs)	*Median # of drugs*	5	5	3	4
	Range	(2 – 7)	(2 – 5)	(1 – 7)	(1 – 7)
	Participants with data	24	12	36	72
	Participants with ≥ 2[c]	24	12	33[e]	69[e]
PI (9 drugs)	*Median # of drugs*	8	7.5	6.5	7
	Range	(0 – 9)	(0 – 9)	(0 – 9)	(0 – 9)
	Participants with data	24	12	36	72
	Participants with ≥ 2[c]	20	8	30	58

3TC = lamivudine; ARV = antiretroviral; FR = failing regimen; FTC = emtricitabine; INSTI = integrase strand-transfer inhibitor (bictegravir, dolutegravir, elvitegravir, raltegravir); LEN = lenacapavir; NNRTI = non-nucleoside reverse transcriptase inhibitor (delavirdine [DLV], doravirine, efavirenz, etravirine, nevirapine, rilpivirine); NRTI = nucleoside reverse transcriptase inhibitor abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine); OBR = optimized background regimen; PI = protease inhibitor (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir)

a The primary resistance data for this table are the overall susceptibility scores for each drug.

b Participants continued their FR during the randomized functional monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15.

c Participants with ≥ 2 drugs with resistance.

d Count of NRTI drugs with resistance was adjusted to discount resistance to FTC and 3TC in the presence of M184V/I per protocol requirements.

e Three participants in Cohort 2 had resistance to only 1 NRTI after M184V/I adjustment. An important protocol deviation was issued for Participant [redacted] who was enrolled with resistance to only 2 drug classes instead of ≥ 3 according to the protocol requirements. For Participant [redacted], resistance to the discontinued NRTI zalcitabine (ddC) was included in the total per investigator's decision. Participant [redacted] had resistance to only 1 NRTI but had resistance to the 3 other classes of drugs (Study GS-US-200-4625, m2.7.3, Section 2.1).

Source: m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listings 2 and 3

Table 22. GS-US-200-4625: Overall Combinations of Class Resistance (≥ 2 Drug Resistance per Drug Class) at Baseline

	Number of Participants, n (%)			
	Cohort 1[a]		Cohort 2	
Drug Classes	Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
All Four Classes	14 (58.3)	3 (25)	16 (44.4)	33 (45.8)
NNRTI-NRTI-PI	4 (16.7)	5 (41.7)	13 (36.1)	22 (30.6)
INSTI-NRTI-PI	2 (8.3)	0	0	2 (2.8)
INSTI-NNRTI-PI	0	0	1 (2.8)	1 (1.4)
INSTI-NNRTI-NRTI	4 (16.7)	4 (33.3)	5 (13.9)	13 (18.1)
Totals	24	12	35[b]	71[b]

FR = failing regimen; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; PI = protease inhibitor

a Participants continued their FR during the randomized functional monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15.

b Participant [redacted] who was enrolled with resistance to only 2 drug classes instead of ≥ 3 (protocol requirement) is not included.

Source: m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listings 2 and 3

Table 23. GS-US-200-4625: Summary of Baseline HIV-1 Subtype and CA, PR, RT, and IN Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Participants, n (%)			
	Cohort 1[b]		Cohort 2	
	Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
Subtype B	22 (91.7)	11 (91.7)	23 (63.9)	56 (77.8)
Non-B Subtype	2 (8.3)	1 (8.3)	13 (36.1)	16 (22.2)
CAI-Associated	0	0	0	0
NRTI-Associated	23 (95.8)	12 (100)	35 (100)	70 (98.6)
INSTI-Associated (Primary)	18 (75)	6 (60)	22 (62.9)	46 (66.7)
INSTI-R (Secondary)	19 (79.2)	7 (70)	22 (62.9)	48 (69.6)
NNRTI-Associated	21 (87.5)	12 (100)	34 (97.1)	67 (94.4)
PI-Associated (Primary)	20 (83.3)	7 (63.6)	31 (86.1)	59 (83.1)
PI-Associated (Secondary)	24 (100)	11 (100)	34 (94.4)	69 (97.2)

CA = capsid; CAI = capsid inhibitor; FR = failing regimen; IN = integrase; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; PI = protease inhibitor; PR = protease; -R = resistant; RT = reverse transcriptase

a Drug resistance mutations are defined in Table 20

b Participants continued their FR during the randomized functional monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15

Source: m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listings 1, 2, and 3

To further characterize participants' resistance profiles, baseline susceptibility analysis of HIV-1 entry inhibitors was conducted after enrollment; these data were not used to determine eligibility (Table 24). Resistance to maraviroc was most frequently observed in the participants (67.2%), followed by resistance to fostemsavir and ibalizumab (31.5% and 29.3%, respectively). Resistance to enfuvirtide was the least frequently observed (8.6%).

Table 24. GS-US-200-4625: Summary of Baseline Resistance to HIV-1 Entry Inhibitors

Drug Name	Number of Participants With OSS = 0[a]/Number of Participants With Data (%)			
	Cohort 1[b]		Cohort 2	
	Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
Enfuvirtide	2/23 (8.7)	3/10 (30)	0/25 (0)	5/58 (8.6)
Fostemsavir	5/23 (21.7)	5/10 (50)	7/21 (33.3)	17/54 (31.5)
Ibalizumab	8/23 (34.8)	3/10 (30)	6/25 (24)	17/58 (29.3)
Maraviroc	19/24 (79.2)	8/11 (72.7)	14/26 (53.8)	41/61 (67.2)

FR = failing regimen; LEN = lenacapavir; OBR = optimized background regimen; OSS = overall susceptibility score
a Possible scores for OSS are 1, 0.5, or 0, corresponding to sensitive, partially sensitive/resistant, or resistant, respectively.
b Participants continued their FR during the randomized functional monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15.
Source: m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listing 7

As part of the baseline analysis, viral samples from all enrolled participant were also phenotypically evaluated against LEN (m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listing 1). Notably, viruses with resistance to entry inhibitors fostemsavir, maraviroc, enfuvirtide, and ibalizumab showed no cross resistance to LEN, with a mean FC from WT of 0.97, 0.97, 0.92, and 1.0, respectively (m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listings 1 and 7).

HIV-1 subtype was determined at screening for all participants (PhenoSense GT assay, Monogram Biosciences). Participants enrolled in this study mostly had HIV-1 subtype B (56 of 72, 77.8%; Table 23). A higher number of participants in Cohort 2 had a non-B HIV-1 subtype than Cohort 1 (13 of 36 compared with 3 of 36, respectively; Fisher's exact test *P* value < 0.01), reflecting the higher geographical diversity of participants in Cohort 2 than in Cohort 1 (Study GS-US-200-4625, m2.7.3, Section 2.1).

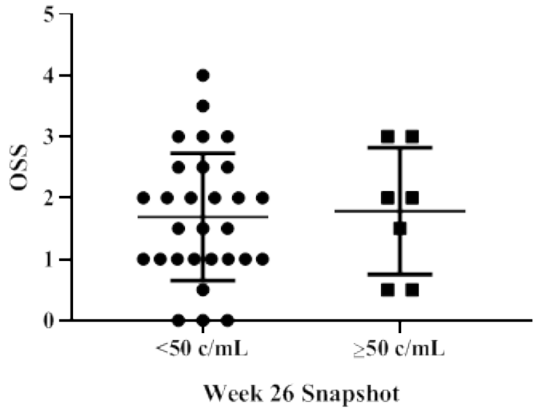
The Week 26 interim efficacy analysis comprises 42 participants with virologic data through Week 26, including all 36 participants from Cohort 1 and 6 of 36 participants from Cohort 2. An analysis of the treatment response at Week 26 (US FDA-defined snapshot algorithm) according to the OSS of OBR was conducted for the 36 participants from the randomized cohort (Cohort 1).

A direct correlation between OSS of OBR and treatment response was not observed in this interim dataset, as the mean OSS of OBR for participants with treatment success and treatment failure was very similar (mean OSS of 1.7 and 1.8, respectively; Figure 26; m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listing 8) and a wide range of OSS was observed for both response categories (OBR OSS ranging from 0 to 4 and 0.5 to 3 for participants with treatment success and participants with treatment failure, respectively).

In additional efficacy analyses by subgroups (GS-US-200-4625 CSR, Table 17), the OSS of the OBR, number of fully active agents in OBR, presence or absence of INSTI resistance, use of dolutegravir with or without darunavir in the OBR, and use of ibalizumab did not appear to have clinically meaningful impact on treatment response at Week 26.

Additional analyses once all participants from Cohort 2 have reached the study end points will explore further the relationship between response and OSS of the OBR.

Figure 26. Week 26 Treatment Response (US FDA-Defined Snapshot Algorithm) By OSS of OBR (Randomized Cohort, n = 36)



FDA = Food and Drug Administration; OBR = optimized background regimen; OSS = overall susceptibility score; US = United States
Horizontal lines indicate mean OSS ± SD for each group.

4.2.1.1.3. Virology Analyses in Participants Experiencing Virologic Failure in Study GS-US-200-4625

The Week 26 analysis includes all 72 participants enrolled in the study, 42 of them with data through Week 26, including all 36 participants from Cohort 1 and 6 of 36 participants from Cohort 2.

Of the 72 participants enrolled in Cohorts 1 and 2, 17 participants met the criteria for inclusion in the RAP. The RAP consisted of 6 participants in Cohort 1A: 6 of 24, 25%; 5 participants in Cohort 1B: 5 of 12, 41.7%; and 6 participants in Cohort 2: 6 of 36, 16.7%) (Table 25). Two participants from Cohort 1A and 1 participant from Cohort 2 achieved HIV-1 RNA resuppression to < 50 copies/mL in the absence of CA resistance and were not included in the final RAP.

The final RAP comprised 4 participants in Cohort 1A, 5 participants in Cohort 1B, and 5 participants in Cohort 2. Of the 14 participants in the final RAP, 6 did not have emergent resistance in CA, and 8 developed LEN-associated resistance mutations in CA (1 in Cohort 1A, 3 in Cohort 1B, and 4 in Cohort 2). The LEN-associated CA mutation M66I was observed in 6 participants, alone or with other LEN-associated substitutions (at CA residues 67, 70, 74, and 107), and was associated with a median LEN phenotypic FC of 234 in comparison to the WT

control. The Q67H + K70R resistance pattern was observed in 1 participant, with a LEN phenotypic FC of 14.8. One participant had emergence of a K70H mutation, which has not been previously observed in vitro, along with T107T/N, with a LEN FC of 265 (Table 26).

No additional other CA mutations emerged in multiple participants except for the R229R/K mutation that was observed in 2 participants who also developed M66I or M66M/I (Participants [redacted] and [redacted]; Table 26). The potential role of that substitution is unknown, but that residue is located outside of the LEN binding site, near the C-terminus of the CA protein.

Among the 8 participants who developed LEN-associated CA resistance mutations, 3 participants (Participants [redacted], [redacted], and [redacted]) were receiving an OBR with no fully active ARVs based on the baseline OSS (m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listing 7) and were therefore at a higher risk of developing resistance against the sole active agent in their treatment regimen, LEN; Participant [redacted] resuppressed in the presence of emergent LEN resistance, following an OBR change. Three participants (Participants [redacted], [redacted], [redacted]) had a rebound back to baseline level after development of LEN resistance although they were receiving active drugs in their regimen (number of fully active drugs = 1 to 3; m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listing 8), suggestive of potential treatment adherence issues. The remaining 2 participants (Participants [redacted] and [redacted]) had HIV-1 RNA resuppression after they experienced a viral load rebound at the time of LEN resistance emergence, suggestive of potential treatment adherence issues at the time of rebound.

Only 1 RAP participant had emerging resistance mutations outside of the CA protein, with no accompanying emergent CA mutations: Participant [redacted] developed the K103N/S and M184M/I/V RT mutations while receiving an OBR composed of the NNRTI doravirine along with BVY (Table 26). This participant met the criteria for resistance analysis due to suboptimal virologic response at Week 4; however, this participant's HIV level was resuppressed to < 50 copies/mL by Week 26 and was not included in the final RAP.

Table 25. GS-US-200-4625: Summary of HIV-1 Capsid Genotypic Resistance Observed Through Week 26

Categories	Number of Participants, n (%)			
	Cohort 1[a]		Cohort 2	
	Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
RAP	6 (25)	5 (41.7)	6 (16.7)	17 (23.6)
Participants With Data	6 (25)	5 (41.7)	6 (16.7)	17 (23.6)
Resuppressed HIV-1 RNA < 50 copies/mL	2 (8.3)	0	1 (2.8)	3 (4.2)
Final RAP[b]	4 (16.7)	5 (41.7)	5 (13.9)	14 (19.4)
Participants With Data	4 (16.7)	5 (41.7)	5 (13.9)	14 (19.4)
Developed Any CAI-R[c]	1 (4.2)	3 (25)	4 (11.1)	8 (11.1)
M66I	1 (4.2)	3 (25)	2 (5.6)	6 (8.3)
Q67H/N	0	1 (8.3)	2 (5.6)	3 (4.2)
K70R/S/H	1 (4.2)	0	2 (5.6)	3 (4.2)
N74D	0	1 (8.3)	0	1 (1.4)
A105S/T	0	2 (16.7)	1 (2.8)	3 (4.2)
T107N	0	0	2 (5.6)	2 (2.8)
No CAI-R Emergence	3 (12.5)	2 (16.7)	1 (2.8)	6 (8.3)

CA = capsid; CAI = capsid inhibitor; FR = failing regimen; LEN = lenacapavir; OBR = optimized background regimen; -R = resistance; RAP = resistance analyses population

a Participants continued their FR during the randomized Functional Monotherapy Period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15.

b Does not include participants who resuppressed HIV-1 RNA to < 50 copies/mL in the absence of CA resistance emergence while maintaining study drugs

c Three of 8 participants with emergent LEN resistance resuppressed HIV-1 RNA to < 50 copies/mL, with (1 participant) or without (2 participants) a change in OBR

Source: m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listing 4

Table 26. GS-US-200-4625: Details of Participants in the Week 26 Resistance Analysis Population

Participant ID	Treatment Group	VF Category[a]	OBR	HIV-1 Subtype	VF Visit	HIV-1 RNA[b]	Emergent Resistance Mutations[c]				LEN Susceptibility[d]
							CA	PR	RT	IN	
[redacted]	Placebo + FR	VR	DTG, RPV, DRV/co	B	Week 26	561	**M66I**	None	None	None	138
[redacted]	Placebo + FR	VR	DTG, DRV/c, T-20, MVC, 3TC	B	Week 10	2870	**M66I N74D**	None	None	None	>1428
					Week 10-R	5440	**M66I N74D**	None	None	None	>869
					Week 22	206	**M66I Q67Q/H N74D**	None	None	None	AF
[redacted]	LEN + FR	V at LV	DOR, BIC/F/TAF FTR	B	Week 4-R	293	AF	None	None	None	AF
					Week 26	342	None	AF	AF	None	AF
[redacted]	Placebo + FR	SVR	DRV/co/F/ TAF	B	Week 4	8380	None	ND	ND	ND	0.6
					Week 4-R	6380	None	None	None	AF	0.7
					Week 22	4950	None	ND	ND	ND	0.7
[redacted]	LEN + FR	SVR	BIC/F/TAF	B	Week 4	137	None	None	None	None	AF
					Week 4-R	111	None	None	None	None	AF
[redacted]	LEN + FR	VR	BIC/F/TAF	B	Week 26	157	None	ND	ND	ND	AF
[redacted]	Placebo + FR	V at LV	DTG, DRV/co, F/TAF, IMAB	B	Week 4	2150	**M66M/I**	None	None	None	AF
					Week 26	2420	**M66M/I**	None	None	ND	46
[redacted]	LEN + FR	V at LV	BIC/F/TAF, DRV/r, MVC	B	Week 4	186	None	None	None	None	AF

Participant ID	Treatment Group	VF Category[a]	OBR	HIV-1 Subtype	VF Visit	HIV-1 RNA[b]	Emergent Resistance Mutations[c]				LEN Susceptibility[d]
							CA	PR	RT	IN	
[redacted]	LEN + FR	SVR	DOR, DRV/co/F/TAF	B	Week 4	156	None	AF	AF	ND	AF
[redacted]	Placebo + FR	V at LV	MVC, DTG, DTG/3TC, IMAB, FTR	B	Week 4	260	None	None	None	None	AF
[redacted]	LEN + FR	SVR	DTG, DRV/r, TDF	AE	Week 4	39000	**M66M/I**	ND	ND	ND	AF
					Week 4-R	25200	**M66M/I K70K/N/R/S**	ND	ND	ND	AF
[redacted]	LEN + OBR	SVR	DTG, TDF, DRV/co	B	Week 4	702	None	None	None	None	AF
					Week 10	1280	None	None	None	None	AF
					Week 26	2350	None	None	None	None	AF
[redacted]	LEN + OBR	SVR	DOR, BIC/F/TAF	B	Week 4	424	None	None	**K103N/S M184M/I/V**	AF	1.5
[redacted]	LEN + OBR	SVR	DTG, FTC/TAF, FPV, IMAB	B	Week 4	101000	**M66M/I Q67Q/H/K/N**	AF	AF	AF	AF
					Week 10	68100	**M66M/I Q67Q/H/K/N K70K/R T107T/C**	None	None	AF	12.2
[redacted]	LEN + OBR	VR	DTG, DRV/co	BF	Week 10	10500	**K70H T107T/N**	None	None	None	265
[redacted]	LEN + OBR	VR	FTR, DOR, IMAB	B	Week 4	11000	**M66I T107A**	ND	ND	ND	239
					Week 10	6220	**M66I T107A**	None	None	None	234
					Week 10-R	9310	**M66I T107A**	None	None	None	AF
[redacted]	LEN + OBR	SVR	DTG, DRV/r, + BIC/F/TAF	B	Week 4	75500	**Q67H K70R**	ND	ND	ND	14.8

3TC = lamivudine; AF = assay failure; BIC = bictegravir; CA = capsid; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; FPV = fosamprenavir; FR = failing regimen; F, FTC = emtricitabine; FTR = fostemsavir; IMAB = ibalizumab; IN = integrase; LEN = lenacapavir; MVC = maraviroc; ND = not determined; OBR = optimized background regimen; PR = protease; -R = retest; RPV = rilpivirine; RT = reverse transcriptase; SVR = suboptimal virologic response; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; V at LV = viremic at last visit; VF = virologic failure; VR = virologic rebound; WT = wild-type; /co = cobicistat boosting; /r = ritonavir boosting

a SVR = HIV-1 RNA ≥ 50 copies/mL and < 1 $\log_{10}$ HIV-1 RNA reduction from the start of oral LEN (Day 1 for Cohort 1A and Cohort 2 participants, or Day 15 for Cohort 1B participants) at the Week 4 visit, confirmed at a scheduled or unscheduled visit at least 2 weeks following Week 4. VR = At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA to ≥ 50 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit, or at any visit, a > 1 $\log_{10}$ increase in HIV-1 RNA from the nadir, which was subsequently confirmed at the following scheduled or unscheduled visit. V at LV = Any study participant with HIV-1 RNA ≥ 50 copies/mL at the study end point or study discontinuation.

b HIV-1 RNA data are expressed in copies/mL.

c Compared with screening/baseline genotype. Drug resistance mutations are defined in Table 20**.**

d Phenotypic fold change compared with WT control. Median fold change for samples with M66I was 234-fold above WT.

e Participant resuppressed HIV-1 RNA to < 50 copies/mL in the absence of CA resistance emergence while maintaining study drugs and was not included in the final RAP.

Source: m5.3.5.4, PC-200-2043: GS-US-200-4625 Virology Listings 4, 5, and 6

4.2.1.1.4. Resistance Conclusions

Study GS-US-200-4625 enrolled 72 HTE PWH with limited treatment options due to multidrug resistance. The OSS analysis showed that the median number of ARV agents with resistance per class approached the total number of ARV agents per class. At baseline, HIV-1 with 4-class resistance was found in 45.8% of participants. Resistance mutations to the NRTI class were found in 98.6% of participants, to the NNRTI class in 94.4% of participants, to the PI class in 83.1% of participants, and to the INSTI class in 66.7% of participants. Additionally, phenotypic resistance to at least 1 of the entry inhibitor drugs was found in 67.2% of participants at baseline. All participants had HIV-1 that was phenotypically sensitive to LEN.

In Study GS-US-200-4625, the RAP included 17 participants: 6 participants in Cohort 1A (6 of 24 participants, 25%), 5 participants in Cohort 1B (5 of 12 participants, 41.7%), and 6 participants in Cohort 2 (6 of 36 participants, 16.7%). Three participants resuppressed HIV-1 RNA < 50 copies/mL by Week 26 in the absence of CA resistance emergence and were not included in the final RAP.

The final RAP included 14 participants: 4 participants in Cohort 1A, 5 participants in Cohort 1B, and 5 participants in Cohort 2. Eight of 14 participants (11.1%) had emergent LEN-associated mutations in CA. The M66I CA mutation was observed in 6 participants (8.3%), alone and in combination with other LEN-associated CA mutations, and exhibited a median FC in LEN susceptibility of 234-fold above WT. One participant had a K70H CA mutation emerging, associated with a 265-fold decrease in LEN susceptibility compared with WT. One participant had a Q67H + K70R CA resistance pattern that was associated with a 14.8-fold decrease in LEN susceptibility. The virologic profiles for these 8 participants with emergent CA resistance suggest that LEN may have been the sole ARV in these participants at the time of virologic failure. Three of 8 participants with emergent LEN resistance resuppressed, with (1 participant) or without (2 participants) a change in OBR. Six participants (8.3%) in the RAP did not have emergence of LEN-associated CA resistance mutations. There were no emergent resistance mutations to components of the OBR.

4.2.1.2. Study GS-US-200-4334

4.2.1.2.1. Study Characteristics and Viral Response

Study GS-US-200-4334 is an ongoing Phase 2, randomized, open-label, active-controlled, multicenter study to assess the safety and efficacy of LEN-containing regimens in TN PWH 18 years of age or older.

A total of 182 participants were enrolled in 1 of the following 4 treatment groups:

Treatment Group 1: SC LEN + (DVY → TAF) (n = 52)

- Induction: Oral LEN (Day 1 and Day 2: 600 mg; Day 8: 300 mg), then SC LEN 927 mg (Day 15) + oral daily emtricitabine/tenofovir alafenamide (F/TAF) (200/25 mg coformulated; Descovy® [DVY]) from Day 1 onwards for a total of 28 weeks.

- Maintenance: SC LEN 927 mg at Week 28 and every 26 weeks thereafter + oral daily TAF (25 mg) from Week 28 onwards.

Treatment Group 2: SC LEN + (DVY → BIC) (n = 53)

- Induction: Oral LEN (Day 1 and Day 2: 600 mg; Day 8: 300 mg), then SC LEN 927 mg (Day 15) + oral daily DVY from Day 1 onwards for a total of 28 weeks

- Maintenance: SC LEN 927 mg at Week 28 and every 26 weeks thereafter + oral daily BIC (75 mg) from Week 28 onwards

Treatment Group 3: Oral LEN + DVY (n = 52)

- Oral LEN (Day 1 and Day 2: 600 mg), then oral daily LEN 50 mg (Day 3 onwards) + oral daily DVY from Day 1 onwards

Treatment Group 4: Oral BVY (n = 25)

- Oral daily BVY (50/200/25 mg) from Day 1 onwards

All treatments were given without regard to food. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

Results from the Week 28 efficacy analysis using the US FDA-defined snapshot algorithm demonstrated comparable percentages of participants with HIV-1 RNA < 50 copies/mL in each treatment group, with no significant difference between each of the LEN-containing treatment groups and the BVY treatment group, as follows: SC LEN + (DVY → TAF) (94.2%), SC LEN + (DVY → BIC) (92.5%), Oral LEN + DVY (94.2%) or BVY (100%) (Study GS-US-200-4334, m2.7.3, Section 2.2).

4.2.1.2.2. Baseline Virology Data

Baseline genotypic data for HIV-1 PR/RT, IN, and CA were obtained at screening to assess for preexisting resistance for all participants in Study GS-US-200-4334. All enrolled participants demonstrated full genotypic sensitivity to LEN, BIC, FTC, and TFV at baseline, except for one participant (Participant [redacted]) with M41L + T215Y in RT. Preexisting resistance mutations to antiviral agents were present at low levels (0 to 15.9% across ARV classes) in the study population (Table 27).

The HIV-1 subtype was determined for each participant using the screening genotype. The predominant subtype across study participants was B (92.9% overall) (Table 27).

Consistent with the CA genotyping results, participants were sensitive to LEN based on phenotypic assessments (data available for 175/182 participants; mean phenotypic FC from WT virus = 1.01 [Range: 0.50–2.53]) (m5.3.5.4, PC-200-2042, GS-US-200-4334 Virology Listing 1).

Table 27. GS-US-200-4334: Summary of Pretreatment HIV-1 Subtype and CA, PR, RT, and IN Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Participants, n (%)				
	SC LEN + (DVY → TAF) (n = 52)	SC LEN + (DVY → BIC) (n = 53)	Oral LEN + DVY (n = 52)	Oral BVY (n = 25)	All (n = 182)
Subtype B	47 (90.4)	49 (92.5)	50 (96.2)	23 (92.0)	169 (92.9)
Non-B Subtype	5 (9.6)	4 (7.5)	2 (3.8)	2 (8.0)	13 (7.1)
CAI-Associated	0	0	0	0	0
NRTI-Associated	0 (0.0)	3 (5.7)	0 (0.0)	0 (0.0)	3 (1.6)
INSTI-Associated (Primary)	0	0	0	0	0
NNRTI-Associated	5 (9.6)	8 (15.1)	11 (21.2)	5 (20.0)	29 (15.9)
PI-Associated (Primary)	1 (1.9)	1 (1.9)	1 (1.9)	0 (0.0)	3 (1.6)

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CA = capsid; CAI = capsid inhibitor; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); IN = integrase; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistant; RT = reverse transcriptase; SC = subcutaneous; TAF = tenofovir alafenamide

a Drug resistance mutations are defined in Table 20

Source: m5.3.5.4, PC-200-2042: GS-US-200-4334 Virology Listings 1, 2, and 3

4.2.1.2.3. Virology Analyses in Participants in the Resistance Analysis Population

Of the 182 participants enrolled and treated in Study GS-US-200-4334, 3 (1.6%) met the virologic failure (VF) criteria, or demonstrated irregular viral response consistent with VF, through Week 28 and were included in the RAP.

The RAP consisted of 3 participants who received LEN (SC LEN + [DVY → TAF]: 1 of 52, 1.9%; SC LEN + [DVY → BIC]: 1 of 53, 1.9%; Oral LEN + DVY: 1 of 52, 1.9%) and no participant (0 of 25) in the BVY treatment group (Table 28).

The final RAP (which did not include participants who resuppressed HIV-1 RNA to < 50 copies/mL in the absence of emerging resistance mutation while maintaining study drugs) comprised 1 participant in the SC LEN + (DVY → BIC) group (1 of 52, 1.9%), and no participants in the other 3 groups (SC LEN + [DVY → TAF], Oral LEN + DVY, or BVY) (Table 28).

The 3 participants who received LEN were included in the initial RAP and evaluated for the development of resistance through Week 28. Participant [redacted] in the SC LEN + (DVY → TAF) group and Participant [redacted] in the Oral LEN + DVY group achieved HIV-1 RNA resuppression to < 50 copies/mL while continuing study drugs, did not have emergent resistance, and were therefore not included in the final RAP (Table 28, Table 29).

The final RAP included 1 participant from the SC LEN + (DVY → BIC) group. Participant [redacted] developed genotypic and phenotypic resistance to both LEN (Q67H + K70R; LEN fold change = 20) and FTC (M184M/I; FTC fold change > 58), suggestive of poor adherence; resistance to TFV was not observed (TFV fold change = 0.46) (Table 29). The participant resuppressed after starting a new regimen (dolutegravir + zidovudine/3TC + tenofovir disoproxil fumarate).

Table 28. GS-US-200-4334: Summary of HIV-1 Genotypic Resistance Observed Through Week 28

Resistance Category[a]	Number of Participants, n (%)				
	SC LEN + (DVY → TAF) (n = 52)	SC LEN + (DVY → BIC) (n = 53)	Oral LEN + DVY (n = 52)	BVY (n = 25)	All (n = 182)
RAP	1 (1.9)	1 (1.9)	1 (1.9)	0	3 (1.6)
Participants With Data	1 (1.9)	1 (1.9)	1 (1.9)	0	3 (1.6)
Resuppressed HIV-1 RNA < 50 copies/mL	1 (1.9)	0	1 (1.9)	0	2 (1.1)
Final RAP[b]	0	1 (1.9)	0	0	1 (0.5)
Participants With Data	0	1 (1.9)	0	0	1 (0.5)
Developed Resistance Mutations to Any Drugs in Regimen	0	1 (1.9)	0	0	1 (0.5)
Developed Any CAI-R	0	1 (1.9)	0	0	1 (0.5)
Q67H	0	1 (1.9)	0	0	1 (0.5)
K70R	0	1 (1.9)	0	0	1 (0.5)
Developed Any NRTI-R	0	1 (1.9)	0	0	1 (0.5)
M184M/I	0	1 (1.9)	0	0	1 (0.5)
Developed Any Primary INSTI-R	0	0	0	0	0

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CAI = capsid inhibitor; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NRTI = nucleoside reverse transcriptase inhibitor; -R = resistant; RAP = resistance analysis population; SC = subcutaneous

a Drug-resistance mutations are defined in Table 20

b Does not include participants who resuppressed HIV-1 RNA to < 50 copies/mL in the absence of resistance emergence while maintaining study drugs

Source: m5.3.5.4, PC-200-2042: GS-US-200-4334 Virology Listings 4, 5, and 6

Table 29. GS-US-200-4334: Details of Participants in the Week 28 Resistance Analysis Population

Participant ID	Treatment Group	BL HIV-1 RNA (copies/mL)	HIV-1 Subtype	Failure Time Point	HIV-1 RNA at Failure (copies/mL)	Emergent Resistance Mutations[a]			Drug Susceptibility (FC From WT)[b]			
						CA	RT	IN	LEN	FTC	TFV[c]	BIC
[redacted]	SC LEN + (DVY → TAF)	146,000	B	Week 22 Retest	357	None	None	None	0.78	0.87	0.83	ND
[redacted]	SC LEN + (DVY → BIC)	117,000	B	Week 10	96,700	**Q67H, K70R**	**M184M/I**	None	20	> 58	0.46	ND
[redacted]	Oral LEN + DVY	1,560	B	Week 16	72	None	ND	ND	1.05	ND	ND	ND
				Week 16 Retest	96	None	None	ND	AF	0.65	0.71	ND

AF = assay failure; BIC, B = bictegravir; BL = baseline; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CA = capsid; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); LEN = lenacapavir; FC = fold change; FTC = emtricitabine; IN = integrase; ND = not determined; RT = reverse transcriptase; SC = subcutaneous; TAF = tenofovir alafenamide; TFV = tenofovir; WT = wild-type

a Compared with screening/baseline genotype. Drug resistance mutations are defined in Table 20.

b Phenotypic FC compared with WT control.

c Monogram Biosciences PhenoSense GT assay was performed with TFV, the parent compound of TAF.

d Participant resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs

Source: m5.3.5.4, PC-200-2042: GS-US-200-4334 Virology Listings 4, 5, and 6

4.2.1.2.4. Resistance Conclusions

In Study GS-US-200-4334, the Week 28 RAP comprised 3 participants: 2 participants were from the SC LEN treatment groups (SC LEN + [DVY → TAF]: 1 of 52 participants, 1.9%; SC LEN + [DVY → BIC]: 1 of 53 participants, 1.9%) and 1 participant was from the Oral LEN + DVY group (1 of 52 participants, 1.9%). No participants from the BVY group met the criteria for inclusion in the RAP. One participant from the SC LEN + (DVY → TAF) group and 1 participant from the Oral LEN + DVY group resuppressed HIV-1 RNA to < 50 copies/mL in the absence of emergent resistance while continuing study drugs and were not included in the final RAP.

The final RAP included 1 participant from the SC LEN + (DVY → BIC) group who developed resistance mutations to study drugs (Q67H and K70R in CA; M184M/I in RT).

4.2.1.3. Study GS-US-200-4072

4.2.1.3.1. Study Characteristics and Viral Response

Study GS-US-200-4072 was a Phase 1b, randomized, double-blinded, placebo-controlled, multicenter, multicohort study of LEN (Part A) and TAF (Part B) monotherapy in PWH.

A total of 51 participants were enrolled into one of the following treatment groups:

In Part A, 39 participants were enrolled into 5 cohorts. Participants in each cohort were randomized in a 3:1 ratio to receive active LEN (n = 6) or placebo (n = 2) administered as a single SC dose on Day 1. Doses of LEN 150, 50, 450, 20, and 750 mg were administered in Cohorts 1, 2, 3, 4, and 5, respectively.

In Part B, 12 participants were enrolled to receive active TAF, administered as a single oral dose on Day 1. Part B clinical virology results are not discussed in this document.

On Day 10, all participants initiated once-daily BVY treatment and continued through Day 225 as a standard-of-care oral combination ART.

4.2.1.3.2. Baseline Virology Data

HIV-1 genotyping of the PR/RT, IN, and CA genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all participants who entered Study GS-US-200-4072. Consistent with enrollment criteria, all enrolled participants demonstrated genotypic sensitivity to LEN, BIC, FTC, and TFV at baseline. Preexisting resistance mutations to antiviral agents were present at low levels (0 to 23.1% across ARV classes) in the study population (Table 30).

The HIV-1 subtype was determined for each participant using the screening genotype. The predominant subtype across study participants was B (89.7%; Table 30).

Table 30. GS-US-200-4072: Summary of Pretreatment HIV-1 Subtype and CA, PR, RT, and IN Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Participants, n (%)
	Part A (n = 39)[b]
Subtype B	35 (89.7)
Non-B Subtype	4 (10.3)
CAI-Associated	0
NRTI-Associated	6 (15.4)
INSTI-Associated (Primary)	0
NNRTI-Associated	9 (23.1)
PI-Associated (Primary)	0

CA = capsid; CAI = capsid inhibitor; IN = integrase; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; RT = reverse transcriptase
a Drug-resistance mutations are defined in Table 20
b Part A includes 29 participants who received LEN (LEN 20 mg, 50 mg, 150 mg, 450 mg, or 750 mg) and 10 participants who received placebo
Source: m.5.3.5.4, PC-200-2039: GS-US-200-4072 Virology Listings 1, 2, and 3

4.2.1.3.3. Virology Analyses in Participants at Day 10

All 39 enrolled and treated participants in Part A were evaluated for the development of resistance at Day 10.

Two participants who received LEN during the monotherapy period developed the Q67H CA mutation at Day 10 (Table 31). Following dosing with LEN 20 mg, Participant [redacted] developed the Q67Q/H mixture with WT; phenotypic resistance was low (phenotypic fold change from WT virus = 1.55). Participant [redacted] (LEN 50 mg group) developed genotypic resistance to LEN (Q67H); phenotypic assessment of this sample was not successful (Table 31). Neither participant experienced viral rebound during the monotherapy period.

Table 31. GS-US-200-4072: Capsid Genotypic and Phenotypic Data of Participants With LEN Emerging Resistance at Day 10

Participant ID	Treatment Group	HIV-1 Subtype	Maximum HIV-1 RNA Response[a]	Day	Emergent CA Mutations[b]	LEN Susceptibility (FC From WT)[c]
[redacted]	LEN 20 mg	B	−1.74	10	**Q67Q/H**	1.55
				9	None	ND
				8	None	ND
				7	None	ND
				4	None	ND
				3	None	ND
				2	None	ND
				1	None	ND
[redacted]	LEN 50 mg	AE	−2.39	10	**Q67H**	AF
				8	None	ND
				7	None	ND
				4	None	ND
				3	None	ND
				2	None	ND
				1	None	ND

AF = assay failure; CA = capsid; FC = fold change; LEN = lenacapavir; ND = not determined; WT = wild-type
a Change in plasma HIV-1 RNA from Day 1 to Day 10 (log_{10} copies/mL) (Study GS-US-200-4072, Section 2.3.1)
b Compared with screening/baseline genotype. Mutations associated with LEN resistance in vitro are shown in **bold.**
c Lenacapavir phenotypic FC compared with WT control
Source: m5.3.5.4, PC-200-2039: GS-US-200-4072 Virology Listing 4

4.2.1.3.4. Virology Analyses in Participants Experiencing Virologic Failure After Monotherapy (Day 10 Through Day 225)

Of the 39 enrolled and treated participants in Part A of Study GS-US-200-4072, 2 (5.1%) met the criteria for inclusion in the post-monotherapy RAP (Table 32). The RAP comprised 1 participant who received LEN 150 mg during the monotherapy period and 1 participant who received placebo (Table 32).

Both participants were evaluated for the development of resistance from Day 10 through Day 225 (Table 32). Participant [redacted], who received placebo during the monotherapy period, had confirmed viral rebound at Day 113 and achieved HIV-1 RNA resuppression to < 50 copies/mL upon further treatment with BVY, with no resistance emerging in RT and IN assay failure, and was therefore not included in the final RAP.

The final RAP (which did not include participants who resuppressed HIV-1 RNA to < 50 copies/mL in the absence of emerging resistance mutation while maintaining study drugs) included 1 participant who received LEN 150 mg during the monotherapy period. Participant [redacted] was viremic at the final visit on Day 225 and had no genotypic or phenotypic resistance to LEN, FTC, TFV, or BIC (Table 33).

Table 32. GS-US-200-4072: Summary of HIV-1 Genotypic Resistance After Monotherapy (Day 10 through Day 225)

Resistance Category[a]	Number of participants, n (%)[b]					
	LEN 20 mg (n = 6)	LEN 50 mg (n = 6)	LEN 150 mg (n = 6)	LEN 450 mg (n = 6)	LEN 750 mg (n = 5)	Placebo (n = 10)
RAP	0	0	1 (16.7)	0	0	1 (10)
Participants With Data	0	0	1 (16.7)	0	0	1 (10)
Resuppressed HIV-1 RNA < 50 copies/mL	0	0	0	0	0	1 (10)
Final RAP[c]	0	0	1 (16.7)	0	0	0
Participants With Data	0	0	1 (16.7)	0	0	0
Developed Resistance Mutations to Any Drugs in Regimen	0	0	0	0	0	0

LEN = lenacapavir; RAP = resistance analysis population
a Drug-resistance mutations are defined in Table 20
b Treatment group designation from monotherapy phase (up to Day 10); after Day 10, all participants received Biktarvy
c Does not include participants who resuppressed HIV-1 RNA to < 50 copies/mL in the absence of resistance emergence while maintaining study drugs
Source: m5.3.5.4, PC-200-2039: GS-US-200-4072 Virology Listings 4, 5, and 6

Table 33. GS-US-200-4072: Details of Participants in the Post-monotherapy Resistance Analysis Population

Participant ID	Treatment Group[a]	Failure Time Point	HIV-1 Subtype	HIV-1 RNA (copies/mL)	Emergent Resistance Mutations[b]			Drug Susceptibility (FC from WT)[c]			
					CA	RT	IN	LEN	FTC	TFV[d]	BIC
[redacted]	Placebo	Day 113	B	243	None	None	AF	0.68	0.74	0.65	AF
[redacted]	LEN 150 mg	Day 141[f]	B	3,110	None	ND	ND	1.30	ND	ND	ND
		Day 225	ND	88,700	None	None	None	1.44	0.97	0.78	0.97

AF = assay failure; BIC = bictegravir; CA = capsid; FC = fold change; FTC = emtricitabine; IN = integrase; LEN = lenacapavir; ND = not determined; RT = reverse transcriptase; TFV = tenofovir; WT = wild-type

a Treatment group from monotherapy phase (up to Day 10); after Day 10, all participants received Biktarvy

b Compared with screening/baseline genotype. Drug resistance mutations are defined in Table 20.

c Phenotypic FC compared with WT control

d Monogram Biosciences PhenoSense GT assay was performed with TFV, the parent compound of tenofovir alafenamide

e Participant resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs

f Unconfirmed viral rebound

Source: m5.3.5.4, PC-200-2039: GS-US-200-4072 Virology Listings 4, 5, and 6

4.2.1.3.5. Resistance Conclusions

A virology analysis was conducted for the Phase 1b Study GS-US-200-4072 in PWH who received single-dose LEN monotherapy up to Day 10, followed by once-daily oral therapy with BVY for the duration of the study.

All 39 enrolled and treated participants were evaluated for the development of resistance at Day 10. Across the LEN groups, 2 participants (2 of 28 with resistance data, 7.1%) developed genotypic resistance to study drug at Day 10. One participant who received LEN 20 mg developed Q67Q/H, and 1 participant who received LEN 50 mg developed Q67H.

The post-monotherapy RAP included 1 participant who received placebo during the monotherapy period and 1 participant who received LEN 150 mg. The participant from the placebo group resuppressed HIV-1 RNA to < 50 copies/mL while taking BVY and was not included in the final RAP.

The final post-monotherapy RAP included 1 participant who received LEN 150 mg during the monotherapy period. This participant had no emergent resistance in CA, IN, or RT.

4.2.2. Clinical Virology Conclusions

Virology analyses were conducted for Phase 2/3 Study GS-US-200-4625, Phase 2 Study GS-US-200-4334, and Phase 1b Study GS-US-200-4072 in PWH who received LEN.

In the HTE population in Study GS-US-200-4625, resistance development to LEN was observed in 11.1% (8 of 72) of participants through Week 26, reflecting the limited treatment options available for this population. The virologic profiles for the 8 participants with emergent CA resistance suggest that LEN may have been the sole ARV in these participants at the time of virologic failure. The most prevalent mutation observed M66I, alone or combination with other known LEN-associated CA mutations, was associated with a mean decrease in LEN susceptibility of 234-fold, when compared to WT.

In the TN population in Study GS-US-200-4334, emergence of resistance mutations through Week 28 was rare (Q67H + K70R; 0.6% [1 of 157] of participants who received oral or SC LEN). In the predominantly TN population in Study GS-US-200-4072, emergence of resistance (Q67H) was noted in 2 participants receiving subtherapeutic doses of LEN.

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6. APPENDIX

6.1. Tabular Summary of Clinical Pharmacology Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-200-4329	• To evaluate the PK of LEN (and metabolites, if applicable) following single ascending IV doses of LEN or a single IV dose of radiolabeled [14C]LEN • To determine the mass balance of LEN following administration of a single IV dose of radiolabeled [14C]LEN	Part A: Phase 1, randomized, blinded, placebo-controlled, SAD study Part B: Phase 1, open-label, single-center, mass-balance study	Part A: • Cohort 1: single dose of LEN 10 mg or placebo • Cohort 2 (not enrolled): single dose of LEN up to 30 mg or placebo Part B: • Cohort 3: single IV dose of LEN 20 mg containing a mixture of unlabeled LEN and [^{14}C]LEN (equivalent to approximately 200 µCi)	1 day	Enrolled: 21 participants; Completed: 11 participants	Healthy nonsmoking (≥ 90 days) male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-200-5709	• To characterize the PK of multiple-dose oral and SC LEN • To evaluate the safety and tolerability of multiple-dose oral and SC LEN	Phase 1, open-label, multiple-cohort, multiple-dose study	Cohort 1: Treatment A: oral tablets of LEN on Day 1 (600 mg; 2 × 300 mg tablets), Day 2 (600 mg; 2 × 300 mg tablets), Day 8 (300 mg; 1 × 300 mg tablet), SC LEN on Day 15 (927 mg; 2 × 1.5 mL of LEN injection), all administered under fed conditions. Cohort 2: Treatment B: SC LEN (927 mg; 2 × 1.5 mL of LEN injection) and oral 600 mg (2 × 300 mg tablets) on Day 1 followed by oral 600 mg on Day 2 (2 × 300 mg tablets), all administered under fed conditions. Cohort 3: Treatment C: oral LEN twice daily on Days 1 to 10 (600 mg; 2 × 300 mg tablets), and last dose of LEN (600 mg; 2 × 300 mg tablets) in the morning on Day 11, all administered under fed conditions	Cohort 1: 4 days Cohort 2: 2 days Cohort 3: 11 days	Enrolled: 60 participants; Cohort 1: 31 participants Cohort 2: 14 participants Cohort 3: 15 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study ongoing; Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Patient PK and Initial Tolerability	GS-US-200-4072	Part A: • To evaluate the short-term antiviral activity of LEN compared with placebo with respect to the maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Days 1 through 10 in adult PWH who were ARV treatment naive or were experienced but CAI naive Part B: • To evaluate the short-term antiviral activity of TAF with respect to the maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Day 1 through Day 10 in adult PWH who were ARV treatment naive or were experienced but without resistance to TAF	Phase 1b, randomized, double-blind, placebo-controlled, multicohort study	Part A: • Cohort 1: LEN 150 mg or placebo • Cohort 2: LEN 50 mg or placebo • Cohort 3: LEN 450 mg or placebo • Cohort 4: LEN 20 mg or placebo • Cohort 5: LEN 750 mg or placebo Part B: • Cohort 6: TAF 200 mg • Cohort 7: TAF 600 mg • Cohort 8 (not enrolled): TAF up to 600 mg	1 day	Part A: Randomized: 41 participants; Completed: 38 participants Part B: Enrolled: 12 participants; Completed: 12 participants	Adult PWH who were ARV treatment naive or were experienced but CAI and INSTI naive (Part A only), had not received any ART within 12 weeks of screening, and had genotypic sensitivity to BVY	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Intrinsic Factor PK	GS-US-200-4330	To evaluate the single-dose PK of LEN in participants with severe renal impairment or matched healthy controls with normal renal function	Phase 1, open-label, single-dose, parallel-group study	Single dose of LEN 300 mg(1 × 300-mg tablet)	1 day	Enrolled: 20 participants (10 with severe renal impairment and 10 matched healthy volunteers with normal renal function); Completed: 20 participants	Participants with severe renal impairment classification ($15 \leq CL_{cr} \leq 29$ mL/min) at screening and matched healthy participants with normal renal function ($CL_{cr} \geq 90$ mL/min)	Study completed; Final CSR
Intrinsic Factor PK	GS-US-200-4331	To evaluate the single-dose PK of LEN in participants with normal or moderately impaired hepatic function	Phase 1, open-label, multicenter, single-dose, parallel-group study	Single dose of LEN 300 mg (1 × 300-mg tablet)	1 day	Enrolled: 20 participants (10 with moderate hepatic impairment and 10 matched healthy controls with normal hepatic function); Completed: 19 participants	Male and nonpregnant, nonlactating female participants with moderately impaired and normal hepatic function	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-200-4333	• To evaluate the effect of a CYP3A inhibitor, a mixed CYP3A/P-gp inhibitor, and a mixed CYP3A/P-gp/ UGT1A1 inhibitor on the PK of LEN • To evaluate the effect of an inducer of CYP3A/P-gp/UGT and an inducer of CYP3A/P-gp on the PK of LEN • To evaluate the effect of an H2RA on the PK of LEN • To evaluate the effect of LEN on the PK of an OATP substrate, a BCRP substrate, a P-gp substrate, and a CYP3A substrate	Phase 1, open-label, single-center, parallel-design, single- and multiple-dose, multicohort study	LEN 300 mg (6 × 50-mg capsules): • Cohort 1: LEN • Cohort 2: COBI 150 mg and LEN • Cohort 3: DRV/COBI 800/150 mg and LEN LEN 300 mg (1 × 300-mg tablet): • Cohort 4: LEN • Cohort 5: VORI 400 mg, VORI 200 mg, and LEN • Cohort 6: LEN (under fed conditions) • Cohort 7: ATV/COBI 300/150 mg and LEN • Cohort 8: RIF 600 mg and LEN • Cohort 9: EFV 600 mg and LEN • Cohort 10: FAM 40 mg and LEN LEN 600 mg (2 × 300-mg tablets): • Cohort 11: PIT 2 mg, ROS 5 mg, TAF 25 mg, MDZ 2.5 mg, and LEN	Cohorts 1, 4, 6, and 10: 1 day Cohorts 2 and 3: up to 90 days Cohort 5: 25 days Cohort 7: 60 days Cohorts 8 and 9: 25 days Cohort 11: 27 days	Enrolled: 291 participants; Completed: 272 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PD and PK/PD	GS-US-200-4332	To evaluate the effect of LEN on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, double-blinded, randomized, placebo- and positive-controlled, 3-sequence, parallel (with nested crossover), multiple-dose study	Treatment A (Positive Control): Single oral dose of 400 mg MOXI (1 × 400-mg tablet), under fed conditions, in the morning Treatment B (Placebo Control-1): Single oral dose of placebo-to-match MOXI (1 tablet), under fed conditions, in the morning Treatment C (Therapeutic and Supratherapeutic Exposure of LEN): Twice-daily 600 mg of LEN (2 × 300-mg tablet) for 8 days, under fed conditions Treatment D (Placebo Control-2): Twice-daily placebo for LEN (2 tablets) for 8 days, under fed conditions	10 days	Randomized: 97 participants; Completed: 95 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

ARV = antiretroviral; ART = antiretroviral therapy; ATV = atazanavir; BCRP = breast cancer resistance protein; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CAI = capsid inhibitor; CL_{cr} = creatinine clearance; COBI = cobicistat (Tybost®); CSR = clinical study report; CYP = cytochrome P450 enzyme; DRV = darunavir; EFV = efavirenz; FAM = famotidine; H2RA = histamine 2 receptor antagonist; INSTI = integrase strand-transfer inhibitor; IV = intravenous; LEN = lenacapavir; MAD = multiple ascending dose; MDZ = midazolam; MOXI = moxifloxacin; OATP = organic anion transporting polypeptide; PD = pharmacodynamic(s); P-gp = P-glycoprotein; PIT = pitavastatin; PK = pharmacokinetic(s); PWH = people with HIV; QTcF = QT interval corrected for heart rate using the Fridericia formula; RIF = rifampin; ROS = rosuvastatin; SAD = single ascending dose; SC = subcutaneous; TAF = tenofovir alafenamide (Vemlidy®); UGT = uridine diphosphate glucuronosyltransferase; VORI = voriconazole

6.2. Lenacapavir - Highlights of Clinical Pharmacology

Therapeutic dose and exposure

Proposed Clinical dosing regimen:

Initiation: Day 1: oral LEN 600 mg + subcutaneous (SC) lenacapavir (LEN) injection 927 mg
Day 2: oral LEN 600 mg
Maintenance: 927 mg SC injection every 6 months (26 ± 2 weeks)

The Phase 2/3 registrational study (Study GS-US-200-4625; CAPELLA) in heavily treatment-experienced people with HIV (PWH) utilized a different dosing regimen: 14-day loading regimen comprising single oral doses of LEN 600 mg, 600 mg, and 300 mg on Days 1, 2, and 8, respectively, followed by a SC maintenance dose of 927 mg administered once every 6 months (26 weeks), starting on Day 15. The proposed simplified clinical dosing regimen and Phase 2/3 dosing regimen provides similar exposure as shown in Table 1.

Table 1 Population PK Parameter Estimates of LEN Following Oral and Subcutaneous Administration in Heavily Treatment Experienced Patients with HIV

PK Parameter Mean (%CV)	Dosing Regimen in CAPELLA[a] Days 1 and 2: LEN 600 mg (oral); Day 8: LEN 300 mg (oral) Day 15 LEN 927 mg (SC) Day 1 to end of Month 6	Proposed Simplified Dosing Regimen[b] Day 1: LEN 600 mg (oral) + LEN 927 mg SC Day 2: LEN 600 mg (oral) Day 1 to end of Month 6
C_{max} (ng/mL)	136.2 (75.2)	97.1 (61.6)
AUC_{tau} (h*ng/mL)	277902.9 (46.7)	234294.8 (65.1)
C_{trough} (ng/mL)	35.1 (59.2)	29.2 (90.8)

CV = Coefficient of Variation; LEN = lenacapavir; PK = pharmacokinetic; SC = subcutaneous
a Post hoc exposures from CAPELLA (N = 62) using population PK analysis.
b Simulated exposures utilizing population PK analysis, based on predictive modeling

Maximum Dose or Exposure Tested

Single Dose	**Oral LEN**: 1800 mg (mean AUC_{inf} 14124.4 h*ng/mL and mean C_{max} 53.8 ng/mL) **SC LEN**: 927 mg (mean AUC_{inf} 226,534.1 h*ng/mL and mean C_{max} 67.0 ng/mL)
Multiple Dose	The highest LEN exposures were observed in the TQT study (GS-US-200-4332). Lenacapavir was administrated as: LEN 600 mg twice-daily orally for 7 days followed by once on Day 8, which resulted in a mean C_{max} of 1070.4 ng/mL and mean AUC_{0-12h} of 10640.6 ng*h/mL.

Range of linear PK

For oral tablet doses (50 to 1800 mg), LEN exposure increased in a less than dose proportional manner, suggesting that absorption of oral LEN may be solubility-limited.

For SC injection, LEN PK are dose proportional over the doses of 309 to 927 mg.

Health Status

Based on Population PK modeling, LEN exposures were lower (30% to 50%) in healthy participants as compared to adult PWH.

Accumulation

SC LEN: approximately 1.17-fold when administered once every 26 weeks.

Absorption	Bioavailability	**Oral LEN**: ~ 6.2% to 10% **SC LEN**: ~ 100%
	T_{max}	**Oral LEN**: ~ 4 hours **SC LEN:** ~ 77 to 84 days
	P-glycoprotein (P-gp)	LEN is a P-gp substrate
Distribution	V_d/F	**Oral LEN**: 19,240 L **SC LEN**: 9500 to 11700 L
	% bound Blood:plasma ratio	Plasma protein binding is > 98.5%; primarily bound to albumin Approximately 0.50 to 0.70
Metabolism	Overall, metabolism plays a minor role in LEN elimination. Lenacapavir is metabolized via multiple pathways: oxidation, N-dealkylation, hydrogenation, amide hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation; primarily via cytochrome P450 enzyme (CYP)3A4 and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Unchanged LEN was the predominant moiety in plasma (68.8%) and feces (32.9%). No single circulating metabolite accounted for > 10% of plasma drug-related exposure.	
Elimination	Following a single intravenous dose of [^{14}C]LEN 20 mg in healthy male participants, a mean 75.9% of the dose was recovered in feces and 0.237% was recovered in urine.	
	Median $t_{1/2}$	**Oral LEN:** ~10 to 12 days **SC LEN**: ~8 to 12 weeks
	CL/F	**Oral LEN:** ~55 L/h **SC LEN:** ~ 4.2 L/h
IntrinsicFactors (Age, Race/ Ethnicity, Sex, Body weight)	Age, gender, race/ethnicity, or body weight had no clinically meaningful impact on LEN PK.	
Intrinsic factors (Hepatic and Renal Impairment)	In Child-Pugh Turcotte Class B hepatic impaired participants, LEN AUC_{inf} and C_{max} were 47% and 161% higher than participants with normal hepatic function, respectively. However, the increase was not clinically relevant. Lenacapavir has not been evaluated in Child-Pugh Turcotte Class C participants. Lenacapavir exposures were higher (AUC_{inf} and C_{max} increased 84% and 162%, respectively) in participants with severe renal impairment (estimated creatinine clearance ≥ 15 and ≤ 29 mL/minute) compared with participants with normal renal function; however, the increase was not clinically relevant. Lenacapavir has not been studied in participants with end-stage renal disease.	
Extrinsic Factors (Drug interactions)	Lenacapavir is not a clinically relevant inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 and UGT1A1. Lenacapavir is not an inducer of CYP1A2 and 2B6. Lenacapavir is not a clinically relevant inhibitor of organic anion transporting polypeptide (OATP), OAT1-, OAT3-, organic cation transporter (OCT)1-, OCT2-, multidrug and toxin extrusion 1 (MATE1), bile salt export pump (BSEP) and MATE2-K-mediated transport.	
	<u>LEN as a Victim</u> • Inhibitors — Voriconazole (strong CYP3A4 inhibitor) increased LEN AUC_{inf} by 41% and C_{max} by	

	9%. — Cobicistat (strong CYP3A4/P-gp inhibitor) increased LEN AUC_{inf} by 128% and C_{max} by 110%. — Atazanavir/cobicistat (strong CYP3A4, P-gp and UGT1A1 inhibitor) increased LEN AUC_{inf} by 321% and C_{max} by 560%. — Darunavir/cobicistat (mixed CYP3A4/P-gp inhibitor and inducer) increased LEN AUC_{inf} by 94% and C_{max} by 130%. • ***Inducers*** — Rifampin (strong CYP3A4/UGT1A1/P-gp inducer) resulted in decreases of 84% in LEN AUC_{inf} and C_{max} by 55%. — Efavirenz (moderate CYP3A4/P-gp inducer) led to decreases of 56% in LEN AUC_{inf} and C_{max} by 36%. • ***Acid-Reducing Agents*** — Famotidine did not affect LEN PK.
	LEN as a perpetrator • ***Enzymes:*** — Lenacapavir is a moderate inhibitor of CYP3A. LEN increased midazolam AUC_{inf} by 259% and C_{max} by 93%. • ***Transporters*** — Weak inhibitor of P-gp: LEN increased tenofovir alafenamide AUC_{last} by 32% and C_{max} by 24%. — Weak inhibitor of BCRP: LEN increased rosuvastatin AUC_{inf} by 31% and C_{max} by 57%.
Extrinsic factors (Food Effect)	The PK of LEN was generally similar following administration of high-fat meal (AUC_{inf}~ 15% higher; C_{max}~ 45% higher) and low-fat meal (AUC_{inf} ~1% lower; C_{max} ~16% higher) relative to fasting conditions. Lenacapavir oral tablets can be taken with or without food.
PK/PD	The target inhibitory quotient of 4 (IQ4) (15.5 ng/mL) was rapidly (~1 hour) achieved and were similarly maintained using either the simplified regimen or the Phase 2/3 dosing regimen. Based on the simulated data, at the end of 26 weeks using the proposed simplified regimen, predicted mean (90% CI) LEN concentrations were 29.2 (24.6, 32.5) ng/mL corresponding to IQ (90% CI) of 7.5 (6.3, 8.4) in PWH.
Bridging to the proposed marketed formulation	The proposed marketed oral and SC formulations were used in the pivotal study (GS-US-200-4625).
TQT study	In a parallel-design thorough QT/QTc study, LEN had no clinically relevant effect on the QTcF interval. In a concentration-QT analysis, at supratherapeutic exposures (9-fold higher than the therapeutic exposures) to LEN, the predicted mean (upper 90% CI) increase in baseline-adjusted, placebo-corrected QTcF interval was 2.6 (4.8) msec., and there was no association (p = 0.36) between observed LEN plasma concentrations and change in QTcF.

6.3. Pharmacokinetic/Pharmacodynamic and Ad Hoc Analyses

Outputs presenting data from prespecified LEN PK-PD analyses are included in this submission. Additional outputs with numbering beginning with "Table Req" or "Figure Req" present data from analyses that were not prespecified in a Statistical Analysis Plan.

6.4. Tabular Summary of Applicable Nonclinical Studies

6.4.1. Tabular Summary of Nonclinical Virology Studies

Test Article: LEN

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Primary Pharmacodynamics					
Antiviral Activity and Cytotoxicity of GS-6207 in MT-4 Cells	No	Human lymphoblastoid T-cell line MT-4, HIV-1 IIIb virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2018
Antiviral Activity and Cytotoxicity of GS‑6207 in Primary CD4+ T Lymphocytes and Monocyte-Derived Macrophages	No	Primary human CD4+ T lymphocytes, primary human monocyte-derived macrophages, human PBMCs, HIV-1 BaL virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2019
Antiviral Activity of GS-6207 Against HIV Clinical Isolates	No	Human PBMCs, HIV-1 92UG031, HIV-1 92UG037, HIV-1 89BZ_167, HIV-1 90US_873, HIV-1 91US001, HIV-1 91US004, HIV-1 96th_NP1538, HIV-1 BaL, HIV-1 JR-CSF, HIV-1 YU-2, HIV-1 92BR025, HIV-1 98US_MSC5016, HIV-1 92UG001, HIV-1 98UG_57128, HIV-1 CMU02, HIV-1 CMU08, HIV-1 93BR020, HIV-1 JV1083, HIV-1 YBF30, HIV-1 BCF01, HIV-1 90TH_CM235, HIV-1 01CM008BBY, HIV-1 91DJ263, HIV-2 CBL‑20, and HIV-2 CDC310319 viruses	In Vitro	[redacted] USA	PC-200-2020

Test Article: LEN

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Inhibition of HIV-1 Early-Stage and Late‑Stage Replication Steps in MT-2 Cells by GS-6207	No	Human embryonic kidney cell line HEK293T transfected with DNA plasmids encoding VSVG-pseudotyped HIV-1 NL4-3-deltaEnv-FFLuc reporter virus with and without capsid mutations. Target cells: Human lymphoblastoid T-cell line MT-2. Virus: VSVG-pseudotyped recombinant HIV‑1 virus NL4-3-deltaEnv-FFLuc containing firefly luciferase reporter gene, with and without capsid mutations	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA.	PC-200-2021
Binding of GS-6207 to Recombinant HIV‑1 Capsid Protein and Effects on In Vitro Capsid Assembly	No	Purified recombinant cross-linked WT and mutant capsid hexamer protein, expressed and isolated from E coli. In vitro capsid assembly: Purified recombinant WT HIV-1 capsid protein, expressed and isolated from E coli	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA; [redacted] USA	PC-200-2022
Inhibition of Proper Capsid Core Formation and HIV-1 Assembly by GS‑6207	No	Human lymphoblastoid T-cell line chronically infected with HIV-1 IIIb virus (MT-2/IIIb), with infectivity analysis on human lymphoblastoid T-cell line CEM-NKR CCR5+Luc+. HIV-1 assembly defect: Human embryonic kidney cell line HEK293T transfected with DNA plasmids encoding VSVG-pseudotyped HIV-1 NL4-3-deltaEnv-FFLuc reporter virus with and without capsid mutations	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA; [redacted] USA	PC-200-2023

Test Article: LEN

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Effect of GS-6207 on the Early Stages of HIV-1 Replication Cycle in Target Cells	No	Human lymphoblastoid T-cell line CEM-NKR CCR5+Luc+, recombinant HIV-1 virus NL4-3-deltaEnv-FFLuc containing firefly luciferase reporter gene and pseudotyped with envelope proteins of distinct tropism. Human PBMCs, HIV-1 virus NL4-3-BlaM-Vpr containing copackaged β-lactamase reporter enzyme. Human lymphoblastoid T-cell line MT-2, VSVG-pseudotyped recombinant HIV-1 virus NL4-3-deltaEnv-FFLuc containing firefly luciferase reporter gene	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2024
In Vitro HIV-1 Resistance Selection Studies With GS-6207	No	Human lymphoblastoid T-cell line MT-2, clonal HIV-1 HXB2D virus. Human PBMCs, HIV-1 BaL, HIV-1 92US657, HIV-1 91US006, HIV-1 7576, HIV-1 7406, HIV-1 7476	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2025
Characterization of Site-Directed HIV-1 Capsid Mutants Resistant to GS-6207	No	Human lymphoblastoid T-cell line MT-2, VSVG-pseudotyped recombinant HIV-1 virus NL4-3-deltaEnv-FFLuc containing firefly luciferase reporter gene. Human lymphoblastoid T-cell line CEM-NKR CCR5+Luc+, recombinant HIV-1 virus NL4-3-JRFL-secNLuc encoding secreted NanoLuc luciferase reporter gene, with and without various site-directed capsid mutations. Primary human CD4+ T lymphocytes, primary human monocyte-derived macrophages, recombinant HIV-1 virus NL4-3-JRFL-secNLuc encoding secreted NanoLuc luciferase reporter gene, with and without various site-directed capsid mutations	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2026

Test Article: LEN

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Activity of GS-6207 Against Drug-Resistant HIV-1 Mutant Variants	No	Human lymphoblastoid T-cell line MT-2, HIV-1 HXB2D virus and HXB2D virus variants containing various site-directed mutations associated with NRTI, NNRTI, INSTI or PI resistance	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2027
Assessment of HIV-1 Capsid Protein Polymorphisms in the GS-6207 Binding Site	No	In silico analysis of viral DNA sequences from human patients at the population and deep sequence level	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA; [redacted] Germany	PC-200-2032
Antiviral Activity of GS-6207 Against a Panel of HIV-1 Patient Isolates	No	Human lymphoblastoid T-cell line MT-2, HIV-1 Patient Isolates	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2036
Antiviral Activity of GS-6207 Against HIV Gag Cleavage Site Mutations	No	Human lymphoblastoid T-cell line MT-2, HIV-1 Patient Isolates and Site-Directed Mutants	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2037
Impact of HIV-1 Capsid Protein Polymorphisms on GS-6207 Antiviral Activity	No	Human lymphoblastoid T-cell line MT-4, HIV-1 NL4.3 virus and Site-Directed Mutants	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2038
Antiviral Activity of Lenacapavir Against a Panel of HIV-1 Clinical Isolates With Diverse HIV Subtype	No	Human Embryonic Kidney (HEK293T) Cell Line, Patient-Derived Recombinant HIV-1 Isolates	In Vitro	[redacted] USA	PC-200-2041
Antiviral Activity of LEN in Isolates With Resistance to the Four Main Antiretroviral Classes	No	Human Embryonic Kidney (HEK293T) Cell Line, Patient-Derived Recombinant HIV-1 Isolates	In Vitro	[redacted] USA	PC-200-2044

Test Article: LEN

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Antiviral Activity of LEN in LEN-Resistant Site-Directed Mutants in the Replicative Multicycle Assay	No	Human lymphoblastoid T-cell line MT-2, HIV-1 Site-Directed Mutants	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2045
Antiviral Activity of LEN in LEN-Resistant Site-Directed Mutants in the Single-Cycle Assay	No	Human Embryonic Kidney (HEK293T) Cell Line, Site-Directed Mutant Recombinant HIV-1 Viruses	In Vitro	[redacted] USA	PC-200-2046
Secondary Pharmacodynamics					
Molecular Target Screen of GS-6207	No	Human, rat, hamster, rabbit, guinea pig, and pig receptors and transporters	In Vitro	[redacted] Taiwan,	PC-200-2012 ([redacted] AB35840)
Cytotoxicity of GS-6207 in Human Cell Lines and Primary Cells Nonpermissive to HIV-1 Infection	No	Human hepatoma cell line Huh7, galactose-adapted human hepatoma cell line Gal-HepG2, galactose-adapted human prostate carcinoma cell line Gal-PC-3, normal human embryonic lung fibroblast cell line (MRC-5), and primary human hepatocytes	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2028

Test Article: LEN

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No.
Antiviral Activity of GS-6207 Against Non-HIV Viruses	No	**HCV:** Human carcinoma cell line Huh7-derived HCV-1b (Con1/SG-hRLucNeo) and HCV-2a (JFH-1/hRLucNeo2a) replicons **HBV:** Human hepatoma cell line HepG2 stably expressing NTCP receptor (HepG2-NTCP), infected with HBV AD38 virus **HRV:** Human cervical adenocarcinoma cell line H1-HeLa, infected with HRV-16 virus **RSV:** Human epithelial type 2 cell line HEp-2, infected with RSV A2 virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2029
Pharmacodynamic Drug Interactions					
In Vitro Antiviral Activity of GS-6207 in Combination With Other Antiretroviral Agents	No	Human lymphoblastoid T-cell line MT-2, HIV-1 IIIb virus	In Vitro	Gilead Sciences, Inc., Foster City, CA, USA	PC-200-2030

CRO = contract research organization; GLP = good laboratory practice; HBV = hepatitis B virus; HCV = hepatitis C virus; HRV = human rhinovirus; INSTI = integrase strand-transfer inhibitor; LEN, GS-6207 = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTCP = sodium-taurocholate cotransporter protein; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PI = protease inhibitor; R.O.C. = Republic of China; RSV = respiratory syncytia virus; SC = subcutaneous; USA = United States of America; WT = wild type

a An entry of "Yes" indicates that the study includes a GLP compliance statement.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY

LENACAPAVIR

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BIC, B	bictegravir
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CD4	clusters of differentiation 4
CI	confidence interval
CSR	clinical study report
C_{trough}	concentration at the end of the dosing interval
DNA	deoxyribonucleic acid
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FTC, F	emtricitabine (Emtriva®)
Gilead	Gilead Sciences
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HTE	heavily treatment experienced
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
LEN	lenacapavir (GS-6207)
LSM	least-squares mean
M = E	missing = excluded
M = F	missing = failure
N or n	number of participants in a population (N) or subset (n)
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OBR	optimized background regimen
PI	protease inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PWH	people with HIV
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SC	subcutaneous

SD	standard deviation
TAF	tenofovir alafenamide (Vemlidy®)
US	United States

1. BACKGROUND AND OVERVIEW

1.1. Background

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38 million people with HIV (PWH) worldwide and approximately 26 million on antiretroviral (ARV) treatment {UNAIDS 2020}. Advances in combination ARV therapy (ART) for HIV have led to significant improvements in quality of life among PWH by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. Most currently approved ARV drugs target 1 of the following 4 steps of the HIV lifecycle: the inhibition of viral entry, reverse transcription, viral DNA integration, or the proteolysis of viral polyproteins essential for virion maturation. While combination ART for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality previously associated with HIV disease, there remains a significant medical need for new, well-tolerated therapies that take into consideration HIV genetic variability, ARV resistance, new options for regimen simplification, as well as the desires of PWH for alternative, longer-acting options.

Some treatment-experienced PWH eventually lose the virologic, immunologic, or clinical benefit from their current regimens. People with HIV who have multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {British HIV Association 2016, European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019, Saag 2020, U.S. Department of Health and Human Services 2015}. These challenges are also relevant for adolescents, particularly those with perinatal HIV-1 transmission. Developing safe and effective therapies for heavily treatment-experienced (HTE) PWH with multidrug-resistant HIV remains a priority. For these individuals, newer treatments are needed to control viral replication, preserve immune function, and prevent clinical progression.

Lenacapavir (LEN; GS-6207) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function, which is being developed for the treatment and prevention of HIV-1 infection. Lenacapavir inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

1.2. Overview of Clinical Efficacy

1.2.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

The proposed indication for LEN is primarily based on data from a Phase 2/3 study in HTE PWH with multidrug resistance (Study GS-US-200-4625). Information on the study design and population for this study is presented in Table 1.

Table 1. Overview of the Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented	Location of Study Narrative and CSR
GS-US-200-4625	Phase 2/3, randomized, placebo-controlled, multicenter study	HTE PWH	**Cohort 1 (N = 36):** ***Cohort 1A (N = 24):*** • Functional Monotherapy Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + failing regimen • Maintenance Period: SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR ***Cohort 1B (N = 12):*** • Functional Monotherapy Period: placebo on Days 1, 2, and 8 + failing regimen • Maintenance Period: oral LEN 600 mg on Days 15 and 16 and 300 mg on Day 22 + SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR **Cohort 2 (N = 36):** • Oral Lead-in Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + OBR • Maintenance Period: SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR	Efficacy, PK[d], and safety	Section 2.1 GS-US-200-4625 Interim Week 26

CSR = clinical study report; HTE = heavily treatment experienced; LEN = lenacapavir; OBR = optimized background regimen; PK = pharmacokinetic(s); PWH = people with HIV; SC = subcutaneous

a Participants who were enrolled and received at least 1 dose of study drug.

b Oral LEN 300 and 600 mg were administered as 1 × 300-mg tablet and 2 × 300-mg tablets, respectively, and SC LEN injection 927 mg (309 mg/mL) was administered as 2 × 1.5-mL injections.

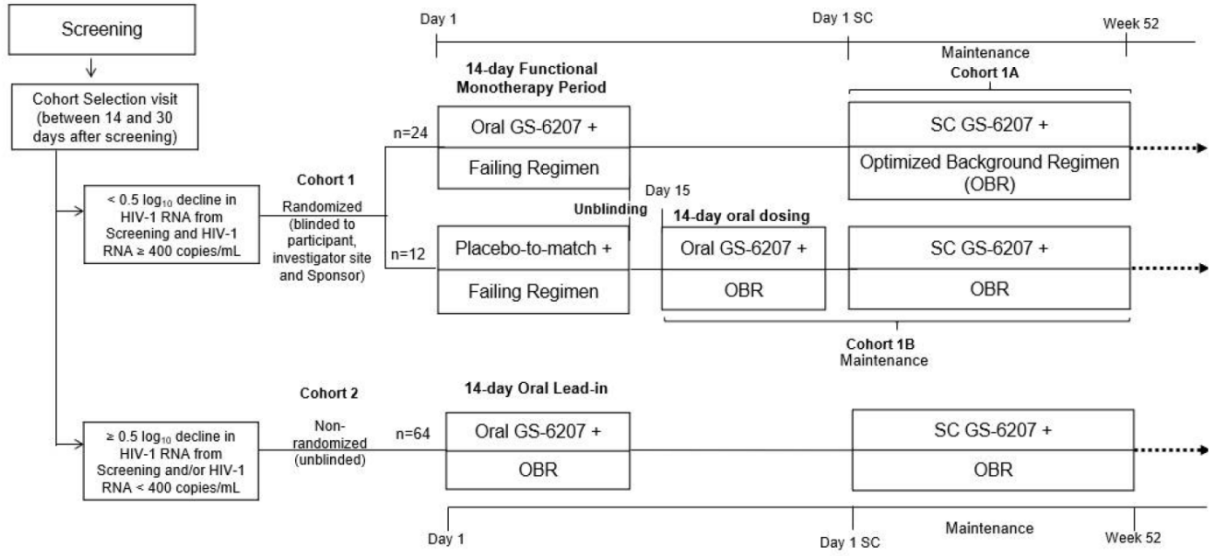
c The Day 1 SC visit occurred 14 days after the first dose of oral LEN.

d Results of the PK analyses are not discussed in the text of the CSR.

Study GS-US-200-4625 is an ongoing Phase 2/3, randomized, placebo-controlled, multicenter study of LEN in combination with an optimized background regimen (OBR) in HTE PWH with multidrug resistance. Eligible participants were HTE PWH aged ≥ 18 years (all sites) or aged ≥ 12 years and weighing ≥ 35 kg (sites in North America and Dominican Republic) who were receiving a stable failing regimen for > 8 weeks before screening and were willing to continue that regimen until Day 1 (or until Day 14 for participants in Cohort 1); had plasma HIV-1 RNA ≥ 400 copies/mL at screening; had resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications (nucleoside reverse transcriptase inhibitors [NRTIs], nonnucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], or integrase strand-transfer inhibitors [INSTIs]); and had ≤ 2 fully active ARV medications remaining from the 4 main classes that could be effectively combined to form a viable regimen in the opinion of the investigator based on resistance, tolerability, contraindication, safety, drug access, or acceptability to the participant.

HIV-1 RNA results from the cohort-selection visit (14 to 30 days after the screening visit) were used to determine whether eligible participants were randomized into Cohort 1 or enrolled into Cohort 2 (Figure 1).

Figure 1. GS-US-200-4625: Study Design Schema



GS-6207 = lenacapavir; OBR = optimized background regimen; SC = subcutaneous
Eligible participants were enrolled into Cohort 2 if Cohort 1 was fully enrolled.

The primary efficacy end point for Study GS-US-200-4625 is the proportion of participants in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period.

Secondary efficacy end points summarized in this document include the proportions of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the United States (US) Food and Drug Administration (FDA)–defined snapshot algorithm.

Other efficacy end points include the proportions of participants in Cohort 2 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 (US FDA-defined snapshot algorithm), changes from baseline in HIV-1 RNA and CD4 cell count by visit, and the proportion of participants with HIV-1 RNA < 50 copies/mL by visit using imputation methods (missing = failure [M = F] and missing = excluded [M = E]).

This summary document provides efficacy data from the interim analysis of Cohorts 1 and 2 in Study GS-US-200-4625, which was conducted after all participants in Cohort 1 had completed the Week 26 visit (ie, 26 weeks after the first dose of subcutaneous [SC] LEN injection) or had prematurely discontinued study drug. Statistical methods are described in the statistical analysis plan (GS-US-200-4625 Interim Week 26 clinical study report [CSR], Appendix 16.1.9).

1.2.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

Supportive efficacy data for LEN are provided from a Phase 2 study in treatment-naive PWH (Study GS-US-200-4334). Information on the study design and population for this study is presented in Table 2.

Table 2. Overview of Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented	Location of Study Narrative and CSR
GS-US-200-4334	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment-naive PWH	**Treatment Group 1 (SC LEN + [DVY → TAF]) (N = 52):** • Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[c] + SC LEN injection 927 mg on Day 15 • Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months (26 weeks) thereafter + oral daily TAF 25 mg[c] **Treatment Group 2 (SC LEN + [DVY → BIC]) (N = 53):** • Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[c] + SC LEN injection 927 mg on Day 15 • Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months (26 weeks) thereafter + oral daily BIC 75 mg[c] **Treatment Group 3 (Oral LEN + DVY) (N = 52):** oral LEN 600 mg on Days 1 and 2 and oral daily LEN 50 mg from Day 3 onwards + oral daily DVY (F/TAF 200/25 mg) **Treatment Group 4 (BVY) (N = 25):** oral daily BVY (B/F/TAF 50/200/25 mg)	Efficacy, PK, and safety	Section 2.2 GS-US-200-4334 Interim Week 28

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); CSR = clinical study report; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; PK = pharmacokinetic(s); PWH = people with HIV; SC = subcutaneous; TAF = tenofovir alafenamide

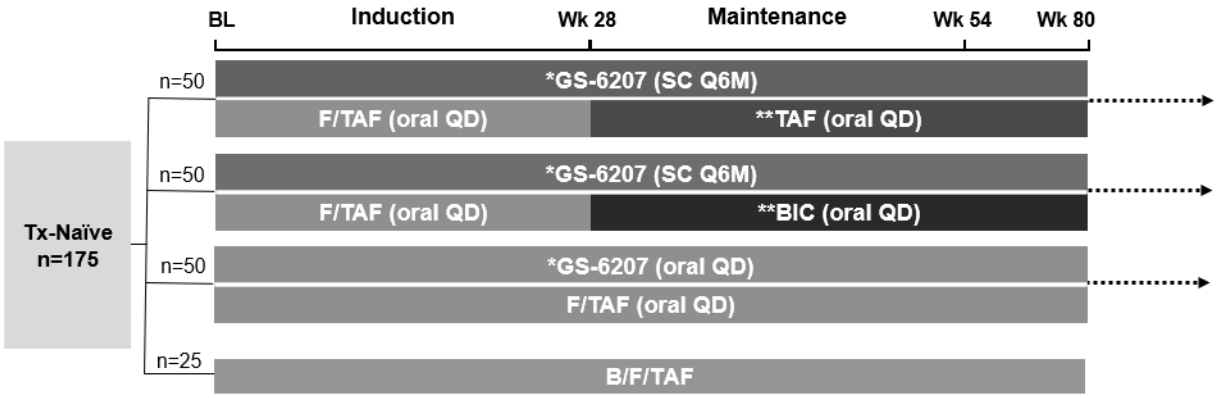
a Participants who were randomized and received at least 1 dose of study drug.

b Oral LEN 50, 300, and 600 mg were administered as 1 × 50-mg tablet, 1 × 300-mg tablet, and 2 × 300-mg tablets, respectively, and SC LEN injection 927 mg (309 mg/mL) was administered as 2 × 1.5-mL injections.

c Participants in Treatment Groups 1 or 2 with HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 discontinued DVY at Week 28 and initiated oral daily TAF or BIC, respectively; those with values ≥ 50 copies/mL discontinued study drug at or prior to Week 28.

Study GS-US-200-4334 is an ongoing Phase 2, randomized, open-label, active-controlled, multicenter study of LEN in combination with other ARV agents in treatment-naive PWH. Study GS-US-200-4334 uses bictegravir (BIC; B)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (Biktarvy®; BVY) as the active comparator, allowing for comparisons between the LEN-containing regimens with a guideline-recommended initial regimen for treatment-naive PWH {European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019}. Eligible participants were ARV-naive (no use of any ARV within 1 month of screening) PWH aged ≥ 18 years who had plasma HIV-1 RNA ≥ 200 copies/mL and CD4 cell count ≥ 200 cells/µL at screening. Participants who met all eligibility criteria were randomized in a 2:2:2:1 ratio to 1 of 4 treatment groups (Figure 2). Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

Figure 2. GS-US-200-4334: Study Design Schema



*Treatment Groups 1, 2 and 3 will have oral PK loading doses
**Participants in Treatment Groups 1 and 2 will need to have HIV-1 RNA results < 50 copies/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28; those with values ≥ 50 copies/mL will discontinue the study at Week 28.

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BL = baseline; F/TAF = emtricitabine/tenofovir alafenamide; GS-6207 = lenacapavir; PK = pharmacokinetic(s); Q6M = every 6 months; QD = once daily; SC = subcutaneous; TAF = tenofovir alafenamide; Tx = treatment; Wk x = Week x

The primary efficacy end point for Study GS-US-200-4334 (proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the US FDA-defined snapshot algorithm) was not analyzed for the Week 28 analysis because the majority of participants had not yet reached Week 54.

Secondary efficacy end points summarized in this document include the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 28 (US FDA-defined snapshot algorithm) and changes from baseline in HIV-1 RNA and CD4 cell count at Week 28. Additionally, the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 28 using imputation methods (M = F and M = E) is presented.

This summary document provides efficacy data from the interim analysis of Study GS-US-200-4334, which was conducted after all participants had completed the Week 28 visit or had prematurely discontinued study drug. Statistical methods are described in the statistical analysis plan (GS-US-200-4334 Interim Week 28 CSR, Appendix 16.1.9).

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Complete study descriptions and results for Studies GS-US-200-4625 and GS-US-200-4334 are available in the individual CSRs. Narratives of these studies are presented in the following sections.

2.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

Location:	GS-US-200-4625 Interim Week 26
Title:	A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination With an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance
Study Objectives:	The primary objective of this study is as follows: • To evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for PWH with multidrug resistance The secondary objective of this study is as follows: • To evaluate the safety and efficacy of LEN in combination with an OBR at Weeks 26 and 52
Study Design and Participant Population:	This is an ongoing Phase 2/3, randomized, placebo-controlled, multicenter study evaluating the safety and efficacy of LEN in combination with an OBR in HTE PWH with multidrug resistance. Participants who met all eligibility criteria returned to the clinic between 14 and 30 days after the screening visit for a cohort-selection visit. Eligible participants who had both a decline in HIV-1 RNA of < 0.5 $\log_{10}$ copies/mL compared with the screening visit and HIV-1 RNA ≥ 400 copies/mL at the cohort-selection visit were randomized in a blinded fashion and in a 2:1 ratio to receive either oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 (Cohort 1A) or placebo (Cohort 1B) during the Functional Monotherapy Period while they continued their failing regimen. After each participant completed the Functional Monotherapy Period, the participant's treatment assignment was unblinded. During the Maintenance Period, participants in Cohort 1A received SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) and initiated their OBR on Day 1 SC (ie, 14 days after the first dose of oral LEN). Participants in Cohort 1B received oral LEN 600 mg (2 × 300-mg tablets) on Days 15 and 16 and 300 mg (1 × 300-mg tablet) on Day 22 and initiated their OBR on Day 15; they received SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 1 SC (ie, 14 days after the first dose of oral LEN) while continuing their OBR. Eligible participants were enrolled into Cohort 2 if Cohort 1 was fully enrolled or if they did not meet the criteria for randomization into Cohort 1, possibly due to improved adherence after the screening visit. During the Oral Lead-in Period, all participants in Cohort 2 received oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 and initiated their OBR on Day 1. During the Maintenance Period, participants received SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 1 SC (ie, 14 days after the first dose of oral LEN) and continued their OBR. Participants in Cohorts 1 and 2 received their subsequent SC LEN injection at the Week 26 visit. At the Week 52 visit, participants in both cohorts are given the option to receive SC LEN injection and continue in the study to receive SC LEN injection every 6 months (26 weeks) while continuing their OBR, until the product becomes accessible to participants through an access program or until Gilead Sciences (Gilead) elects to discontinue the study in the country. Both the oral LEN tablets and SC LEN injections were administered without regard to food.

	Eligible participants were HTE PWH aged ≥ 18 years (all sites) or aged ≥ 12 years and weighing ≥ 35 kg (sites in North America and Dominican Republic) who were receiving a stable failing regimen for > 8 weeks before screening and were willing to continue that regimen until Day 1 (or until Day 14 for participants in Cohort 1); had plasma HIV-1 RNA ≥ 400 copies/mL at screening; had resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications (NRTIs, NNRTIs, PIs, or INSTIs); and had ≤ 2 fully active ARV medications remaining from the 4 main classes that could be effectively combined to form a viable regimen in the opinion of the investigator based on resistance, tolerability, contraindication, safety, drug access, or acceptability to the participant. The CSR describes the interim analysis of Cohorts 1 and 2, which was conducted after all participants in Cohort 1 had completed the Week 26 visit (ie, 26 weeks after the first dose of SC LEN injection) or had prematurely discontinued study drug. Of the 144 participants screened for the study, 72 participants were enrolled and received at least 1 dose of study drug (Cohort 1: LEN 24 participants, placebo 12 participants; Cohort 2: LEN + OBR 36 participants). All 72 participants completed the Functional Monotherapy or Oral Lead-in Period and received SC LEN injection on Day 1 SC. One participant in Cohort 2 prematurely discontinued study drug in the Maintenance Period due to death on Study Day 90.
Summary of Results and Conclusions:	• Lenacapavir met the primary end point of superiority to placebo. A significantly greater proportion of participants who received LEN (87.5%) had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline than those who received placebo (16.7%) ($P < 0.0001$). • Lenacapavir led to a rapid and clinically relevant decline in viral load when added to a failing regimen in HTE PWH. The mean (SD) change from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period was greater for participants who received LEN than those who received placebo, as follows: LEN −1.93 (0.893) $\log_{10}$ copies/mL; placebo −0.29 (0.614) $\log_{10}$ copies/mL (adjusted difference in least-squares mean [LSM] by baseline $\log_{10}$ HIV-1 RNA: −2.17 [95% CI: −2.74 to −1.59]; $P < 0.0001$). • Lenacapavir in combination with an OBR led to high rates of virologic suppression at Week 26. These results were consistent even in participants who had suboptimal OBR (eg, low overall susceptibility score, no or 1 fully active agent, INSTI resistance, no dolutegravir or darunavir), demonstrating a clinically meaningful contribution of LEN towards virologic suppression. For the All LEN Analysis, the percentages of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm were 80.6% (29 of 36 participants) and 88.9% (32 participants), respectively. The percentage of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 copies/mL at Week 26 was 78.6% (33 of 42 participants) based on the M = F analysis. • There were clinically meaningful increases in CD4 cell count from baseline to Week 26. For the All LEN Analysis, the mean (SD) change from baseline in CD4 cell count at Week 26 was 90 (102.1) cells/μL. • Lenacapavir administered orally or subcutaneously was generally safe and well tolerated. There were no discontinuations from study drug due to adverse events (AEs). For the All LEN Analysis, the majority of AEs were Grade 1 or 2 in severity.

2.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

Location: GS-US-200-4334 Interim Week 28

Title: A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination With Other Antiretroviral Agents in People Living With HIV

Study Objectives:

The primary objective of this study is as follows:

- To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54

The secondary objectives of this study are as follows:

- To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80
- To evaluate the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4 cell count at Weeks 28, 38, 54, and 80
- To evaluate the safety and tolerability of the LEN-containing regimens through 28, 38, 54, and 80 weeks of treatment
- To evaluate the pharmacokinetics (PK) of LEN, BIC, and TAF

Study Design and Participant Population:

This is an ongoing Phase 2, randomized, open-label, active-controlled, multicenter study evaluating the safety and efficacy of LEN in combination with other ARV agents in treatment-naive PWH. Participants who met all eligibility criteria were randomized in a 2:2:2:1 ratio to 1 of the 4 treatment groups below. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

Treatment Group	Time Period	Study Treatments
1	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 • Oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15
	Maintenance (Weeks 28 through 80)	• SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily TAF 25 mg[a]
2	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 • Oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15
	Maintenance (Weeks 28 through 80)	• SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily BIC 75 mg[a]
3	Day 1 through Week 80	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and oral daily LEN 50 mg (1 × 50-mg tablet) from Day 3 onwards • Oral daily DVY (F/TAF 200/25 mg)
4	Day 1 through Week 80	• Oral daily BVY (B/F/TAF 50/200/25 mg)

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir;
BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy);
DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide

a Participants in Treatment Groups 1 or 2 with HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 discontinued DVY at Week 28 and initiated oral daily TAF or BIC, respectively; those with values ≥ 50 copies/mL discontinued study drug at or prior to Week 28.

All study drugs were administered without regard to food.

	At Week 80, participants in Treatment Group 4 will complete the study. Participants willing to continue the study beyond Week 80 in Treatment Groups 1 to 3 will continue to receive SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) every 6 months (26 weeks) (Treatment Groups 1 and 2) or oral daily LEN 50 mg (Treatment Group 3) from Week 80 until the product becomes accessible to participants through an access program or until Gilead elects to discontinue the study in the country. Participants in Treatment Groups 1 to 3 will also receive TAF, BIC, or DVY, as applicable. Eligible participants were ARV-naive (no use of any ARV within 1 month of screening) PWH aged ≥ 18 years who had plasma HIV-1 RNA ≥ 200 copies/mL and CD4 cell count ≥ 200 cells/μL at screening. The CSR describes the interim analysis of the study, which was conducted after all participants had completed the Week 28 visit or had prematurely discontinued study drug. Of the 249 participants screened for the study, 183 participants were randomized, and 182 participants received at least 1 dose of study drug. A total of 17 participants (9.3%) prematurely discontinued study drug (14 of 105 participants [13.3%] in the SC LEN total group, 3 of 52 participants [5.8%] in the Oral LEN + DVY group, and 0 participants in the BVY group). The reasons for premature discontinuation of study drug in the SC LEN total group were participant decision (3.8%, 4 participants), lack of efficacy and lost to follow-up (each 2.9%, 3 participants), and AE and investigator's discretion (each 1.9%, 2 participants). The reasons for premature discontinuation of study drug in the Oral LEN + DVY group were lost to follow-up (3.8%, 2 participants) and participant decision (1.9%, 1 participant). None of these discontinuations affected the overall quality or interpretation of the study data.
Summary of Results and Conclusions:	• Overall, 147 of 157 participants (93.6%) who received SC or oral LEN and 25 of 25 participants (100.0%) who received BVY had HIV-1 RNA < 50 copies/mL at Week 28 using the US FDA-defined snapshot algorithm. Most of the remaining participants who received SC or oral LEN had no virologic data in the Week 28 window. • Subcutaneously and orally administered LEN was generally safe and well tolerated. Similar percentages of participants in the LEN total and BVY groups had any AE by Week 28 (LEN total 86.6%, 136 participants; BVY 84.0%, 21 participants); the majority of AEs were Grade 1 or 2 in severity. • For both SC LEN and oral LEN, mean LEN concentrations above inhibitory quotient (IQ) 4 (15.5 ng/mL) were achieved by Day 2 and were maintained throughout the duration of the PK follow-up for this interim analysis.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Study Populations

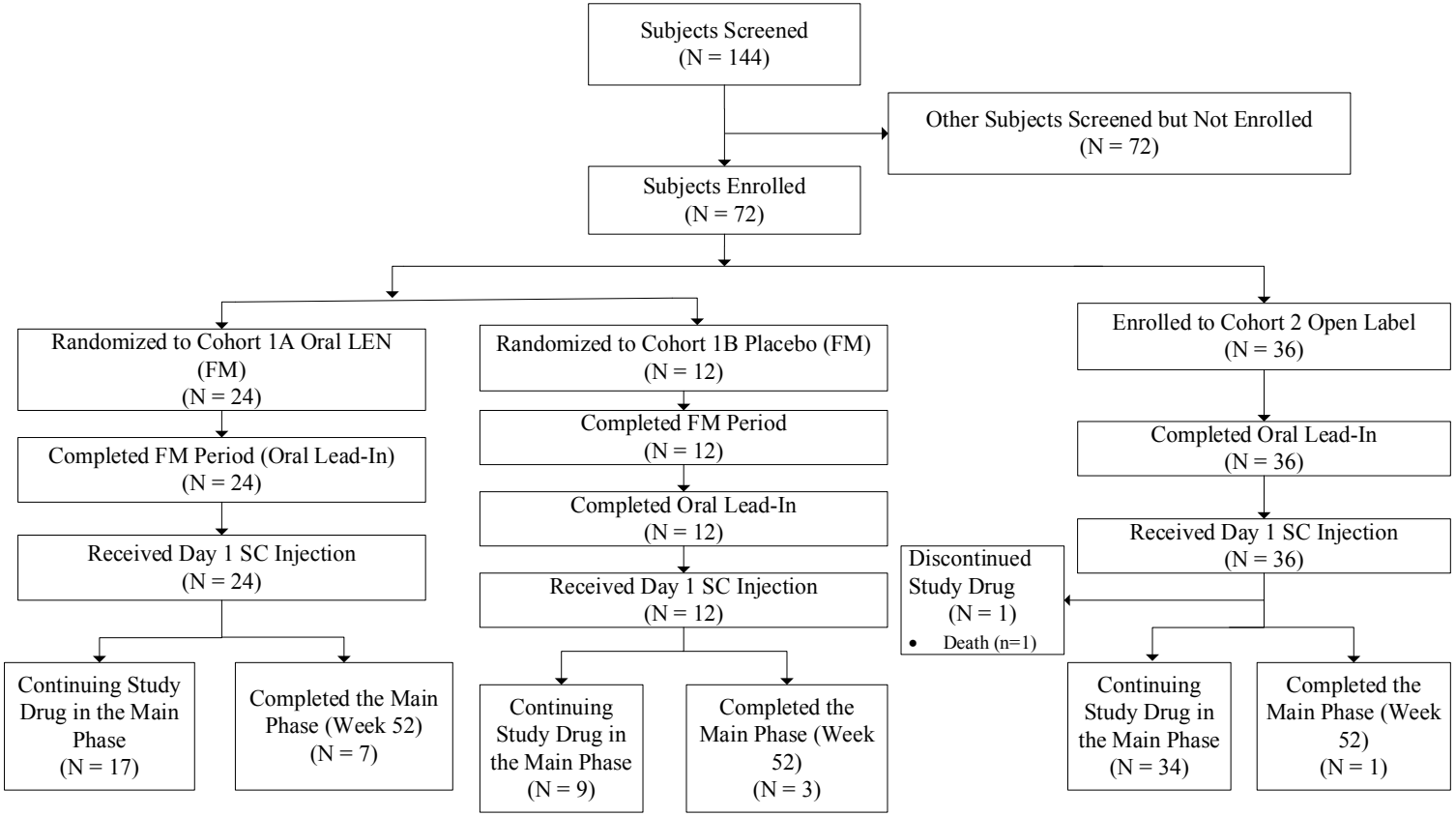
Participant disposition, demographic and other baseline characteristics, and analysis populations are presented by study for Studies GS-US-200-4625 and GS-US-200-4334. Detailed results are presented in the individual CSRs (GS-US-200-4625 Interim Week 26 CSR, Section 8; GS-US-200-4334 Interim Week 28 CSR, Section 8).

3.1.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

3.1.1.1. Participant Disposition

Of the 144 participants screened for the study, 72 participants were enrolled and received at least 1 dose of study drug (Cohort 1: LEN 24 participants, placebo 12 participants; Cohort 2: LEN + OBR 36 participants) (Figure 3 and Table 3). All 72 participants completed the Functional Monotherapy or Oral Lead-in Period and received SC LEN injection on Day 1 SC. One participant in Cohort 2 prematurely discontinued study drug in the Maintenance Period due to death on Study Day 90.

Figure 3. GS-US-200-4625: Disposition of Participants (Main Phase Only) (All Screened Participants)



FM = Functional Monotherapy; LEN = lenacapavir; SC = subcutaneous
Main Phase is defined as data collected through Week 52 (52 weeks from the first dose of SC LEN).
Includes case report form data collected up to [redacted] 20[redacted]
Source: GS-US-200-4625 Interim Week 26 CSR, Figure 15.8.1

Table 3. GS-US-200-4625: Disposition of Participants (All Screened Participants)

	Cohort 1			Cohort 2	Total
	LEN	Placebo	Total		
Screened	—	—	—	—	144
Met all eligibility criteria but not enrolled	—	—	—	—	0
All enrolled	24	12	36	36	72
Safety Analysis Set	24	12	36	36	72
Study drug disposition in main phase					
Oral lead-in before the first SC injection					
Completed study drug	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Continuing study drug	0	0	0	0	0
Prematurely discontinued study drug	0	0	0	0	0
After the first SC injection					
Received Day 1 SC injection	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Continuing study drug	17 (70.8%)	9 (75.0%)	26 (72.2%)	34 (94.4%)	60 (83.3%)
Completed study drug	7 (29.2%)	3 (25.0%)	10 (27.8%)	1 (2.8%)	11 (15.3%)
Prematurely discontinued study drug	0	0	0	1 (2.8%)	1 (1.4%)
Reason for prematurely discontinued study drug					
Death	0	0	0	1 (2.8%)	1 (1.4%)
Study drug disposition in the extension phase					
Treated in the extension phase	7	3	10	1	11
Continuing study drug	7 (100.0%)	3 (100.0%)	10 (100.0%)	1 (100.0%)	11 (100.0%)
Prematurely discontinued study drug	0	0	0	0	0
Study disposition throughout the study					
Continuing study	24 (100.0%)	12 (100.0%)	36 (100.0%)	35 (97.2%)	71 (98.6%)
Completed study	0	0	0	0	0
Prematurely discontinued study	0	0	0	1 (2.8%)	1 (1.4%)
Reason for premature discontinuation					
Death	0	0	0	1 (2.8%)	1 (1.4%)

LEN = lenacapavir; SC = subcutaneous
"Main Phase" is defined as data collected through Week 52 (52 weeks from the first dose of SC LEN).
Percentages for study drug disposition for the Main Phase and study disposition were calculated based on the number of participants in the Safety Analysis Set.
Percentages for disposition status for the extension phase were calculated based on the number of participants treated in the extension phase.
Included case report form data collected up to [redacted] 20[redacted].
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.8.1.3.1

3.1.1.2. Demographic and Other Baseline Characteristics

3.1.1.2.1. Demographic and Baseline Disease Characteristics

Cohort 1

For Cohort 1 in Study GS-US-200-4625, demographic and baseline characteristics were generally similar between the LEN and placebo groups (Table 4). The majority of participants were male (72.2%, 26 of 36 participants), White or Black (each 45.7%, 16 participants), and not Hispanic or Latino (71.4%, 25 participants). The median age was 54 years (range: 24 to 71).

Baseline disease characteristics were consistent with the profile of the HTE population, with a median number of prior ARV medications of 9 (range: 2 to 24) and 75.0% of participants (27 participants) with a CD4 cell count < 200 cells/μL (a hallmark of severe immune suppression and the criterion to diagnose AIDS) (Table 5). Baseline differences were observed between the LEN and placebo groups in HIV-1 RNA (log_{10} copies/mL), HIV-1 RNA categories, CD4 cell count, and CD4 percentage; these differences did not have an impact on the interpretation of the efficacy data.

The most common prior ARV medication drug classes were as follows: INSTIs (97.2%, 35 participants), NRTIs (94.4%, 34 participants), NNRTIs (88.9%, 32 participants), and PIs (83.3%, 30 participants). Known resistance to ≥ 2 drugs in a class was as follows: NRTIs (97.2%, 35 participants), NNRTIs (94.4%, 34 participants), PIs (77.8%, 28 participants), and INSTIs (75.0%, 27 participants).

Cohort 2

For Cohort 2 in Study GS-US-200-4625, the majority of participants were male (77.8%, 28 of 36 participants), White (36.1%, 13 participants) or Asian (33.3%, 12 participants), and not Hispanic or Latino (86.1%, 31 participants) (Table 4). The median age was 49 years (range: 23 to 78).

The baseline disease characteristics, prior ARVs, and resistance characteristics for Cohort 2 were consistent with the profile of the HTE population (Table 5).

Table 4. GS-US-200-4625: Demographic and Baseline Characteristics (Safety Analysis Set)

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
Age (years)						
N	24	12	36	36	72	0.2393
Mean (SD)	54 (11.3)	49 (10.9)	52 (11.2)	48 (13.7)	50 (12.6)	
Median	55	54	54	49	52	
Q1, Q3	50, 61	49, 55	49, 59	38, 60	45, 59	
Min, max	24, 71	27, 59	24, 71	23, 78	23, 78	
Sex at birth						
Male	17 (70.8%)	9 (75.0%)	26 (72.2%)	28 (77.8%)	54 (75.0%)	0.7953
Female	7 (29.2%)	3 (25.0%)	10 (27.8%)	8 (22.2%)	18 (25.0%)	
Race						
American Indian or Alaska Native	0	0	0	0	0	0.7525
Asian	2 (8.3%)	1 (9.1%)	3 (8.6%)	12 (33.3%)	15 (21.1%)	
Black	10 (41.7%)	6 (54.5%)	16 (45.7%)	11 (30.6%)	27 (38.0%)	
Native Hawaiian or Pacific Islander	0	0	0	0	0	
White	12 (50.0%)	4 (36.4%)	16 (45.7%)	13 (36.1%)	29 (40.8%)	
Other	0	0	0	0	0	
Not Permitted	0	1	1	0	1	
Ethnicity						
Hispanic or Latino	6 (25.0%)	4 (36.4%)	10 (28.6%)	5 (13.9%)	15 (21.1%)	0.4959
Not Hispanic or Latino	18 (75.0%)	7 (63.6%)	25 (71.4%)	31 (86.1%)	56 (78.9%)	
Not Permitted	0	1	1	0	1	
Body mass index (kg/m^2)						
N	24	12	36	36	72	0.5913
Mean (SD)	26.0 (5.38)	24.8 (4.58)	25.6 (5.09)	26.5 (5.76)	26.1 (5.42)	
Median	24.7	24.3	24.7	25.6	25.0	
Q1, Q3	21.4, 30.2	21.8, 27.8	21.7, 29.5	22.7, 29.4	22.1, 29.4	
Min, max	18.4, 37.1	18.7, 33.5	18.4, 37.1	14.9, 42.6	14.9, 42.6	

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Denominator for percentages was the Safety Analysis Set.
Age (in years) was calculated from the date of first study drug dosing (Day 1) if dosed or enrollment if not dosed.
Not Permitted = local regulators did not allow collection of race or ethnicity information.
Body mass index (kg/m^2) = [Weight (kg)/Height (cm)^2]*10,000.
P value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) for categorical data and the 2-sided Wilcoxon rank sum test for continuous data.
Participants who reported "Not Permitted" were excluded from the percentage and *P* value calculation.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.8.3.1

Table 5. GS-US-200-4625: Other Baseline Disease Characteristics: HIV and Antiretroviral Medication History (Safety Analysis Set)

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
HIV-1 RNA (log_{10} copies/mL)						
N	24	12	36	36	72	0.0041
Mean (SD)	3.97 (0.922)	4.87 (0.393)	4.27 (0.890)	4.06 (1.164)	4.17 (1.034)	
Median	4.19	4.93	4.50	4.49	4.49	
Q1, Q3	3.20, 4.57	4.46, 5.26	4.08, 4.89	3.28, 4.90	3.51, 4.90	
Min, max	2.33, 5.40	4.33, 5.33	2.33, 5.40	1.28, 5.70	1.28, 5.70	
HIV-1 RNA categories (copies/mL)						
≤ 100,000	23 (95.8%)	6 (50.0%)	29 (80.6%)	29 (80.6%)	58 (80.6%)	0.0012
> 100,000	1 (4.2%)	6 (50.0%)	7 (19.4%)	7 (19.4%)	14 (19.4%)	
CD4 cell count (cells/µL)						
N	24	12	36	36	72	0.0062
Mean (SD)	199 (166.1)	85 (62.9)	161 (149.5)	258 (273.4)	210 (224.2)	
Median	172	85	127	195	150	
Q1, Q3	99, 248	39, 109	79, 201	56, 392	76, 286	
Min, max	16, 827	6, 237	6, 827	3, 1296	3, 1296	
CD4 cell count categories (cells/µL)						
< 50	3 (12.5%)	4 (33.3%)	7 (19.4%)	9 (25.0%)	16 (22.2%)	0.4276
≥ 50 to < 200	13 (54.2%)	7 (58.3%)	20 (55.6%)	10 (27.8%)	30 (41.7%)	
≥ 200 to < 350	6 (25.0%)	1 (8.3%)	7 (19.4%)	8 (22.2%)	15 (20.8%)	
≥ 350 to < 500	1 (4.2%)	0	1 (2.8%)	4 (11.1%)	5 (6.9%)	
≥ 500	1 (4.2%)	0	1 (2.8%)	5 (13.9%)	6 (8.3%)	
CD4 percentage (%)						
N	24	12	36	36	72	0.0317
Mean (SD)	10.8 (7.77)	5.9 (4.12)	9.2 (7.11)	11.5 (8.62)	10.3 (7.93)	
Median	10.5	4.5	6.9	10.4	8.9	
Q1, Q3	5.6, 14.8	3.6, 7.7	4.5, 12.6	3.5, 17.5	4.2, 15.1	
Min, max	1.0, 32.0	1.2, 16.4	1.0, 32.0	0.4, 29.5	0.4, 32.0	
Number of prior ARV medications						
N	24	12	36	36	72	0.7876
Mean (SD)	11 (6.2)	10 (6.0)	11 (6.1)	13 (5.6)	12 (5.9)	
Median	9	9	9	13	11	
Q1, Q3	8, 16	5, 13	7, 14	10, 17	8, 16	
Min, max	2, 24	3, 22	2, 24	3, 25	2, 25	

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
Known resistance to ≥ 2 drugs in class						
NRTI	23 (95.8%)	12 (100.0%)	35 (97.2%)	36 (100.0%)	71 (98.6%)	—
NNRTI	22 (91.7%)	12 (100.0%)	34 (94.4%)	36 (100.0%)	70 (97.2%)	
PI	20 (83.3%)	8 (66.7%)	28 (77.8%)	30 (83.3%)	58 (80.6%)	
INSTI	20 (83.3%)	7 (58.3%)	27 (75.0%)	23 (63.9%)	50 (69.4%)	

ARV = antiretroviral; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; Q1 = first quartile; Q3 = third quartile
Prior ARV = nonstudy drug ARV with the start date prior to the first dose date of study drug.
When counting number of ARVs and summarizing by drug class, cobicistat and ritonavir used as a boosting agent were excluded.
P value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) for categorical data and the 2-sided Wilcoxon rank sum test for continuous data.
Source: GS-US-200-4625 Interim Week 26 CSR, Tables 15.8.3.2.1 and 15.8.3.2.2

3.1.1.2.2. Failing Regimens and Optimized Background Regimens

Cohort 1

For Cohort 1 in Study GS-US-200-4625, the median number of ARVs in the failing regimen was 3 (range: 1 to 7) (Table 6). The compositions of participants' failing regimens were characteristic of those of PWH with multidrug resistance, for example, PI (boosted darunavir twice daily), INSTI (dolutegravir twice daily), chemokine receptor 5 entry inhibitor (maraviroc), CD4-directed post-attachment inhibitor (ibalizumab), attachment inhibitor (fostemsavir, which was investigational at the time of enrollment), and fusion inhibitor (enfuvirtide).

The median number of ARVs in the OBR was 4 (range: 2 to 7). The compositions of participants' failing regimens and OBRs were similar, suggesting that they had few remaining treatment options prior to enrolling. Specifically, 16.7% of participants (6 of 36 participants) continued their failing regimen as their OBR, suggesting that there were no viable agents that could have further optimized the regimen.

The percentages of participants by number of fully active ARV agents in the OBR were as follows: 16.7%, 6 participants (no fully active ARV agents); 38.9%, 14 participants (1 fully active ARV agent); 25.0%, 9 participants (2 fully active ARV agents); and 19.4%, 7 participants (≥ 3 fully active ARV agents).

Cohort 2

The failing regimens and OBRs for Cohort 2 in Study GS-US-200-4625 were similar to those of Cohort 1 and were consistent with the profile of the HTE population (Table 6).

Table 6. GS-US-200-4625: Other Baseline Characteristics: Failing Regimens and Optimized Background Regimens (Safety Analysis Set)

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
Failing Regimens						
Number of ARVs in the failing regimen						
N	24	12	36	36	72	1.0000
Mean (SD)	4 (1.6)	4 (1.3)	4 (1.5)	4 (1.2)	4 (1.4)	
Median	3	3	3	4	3	
Q1, Q3	3, 5	3, 5	3, 5	3, 4	3, 5	
Min, max	1, 7	2, 6	1, 7	2, 7	1, 7	
Failing regimen drug class exposure						
NRTI	19 (79.2%)	11 (91.7%)	30 (83.3%)	29 (80.6%)	59 (81.9%)	—
NNRTI	6 (25.0%)	3 (25.0%)	9 (25.0%)	13 (36.1%)	22 (30.6%)	
PI	14 (58.3%)	6 (50.0%)	20 (55.6%)	25 (69.4%)	45 (62.5%)	
INSTI	17 (70.8%)	8 (66.7%)	25 (69.4%)	24 (66.7%)	49 (68.1%)	
Fusion inhibitor	1 (4.2%)	1 (8.3%)	2 (5.6%)	2 (5.6%)	4 (5.6%)	
CCR5 entry inhibitor	1 (4.2%)	3 (25.0%)	4 (11.1%)	6 (16.7%)	10 (13.9%)	
CD4-directed post-attachment inhibitor	9 (37.5%)	2 (16.7%)	11 (30.6%)	3 (8.3%)	14 (19.4%)	
Attachment inhibitor	2 (8.3%)	0	2 (5.6%)	2 (5.6%)	4 (5.6%)	
OSS based on failing regimen						
N	24	12	36	36	72	0.3855
Mean (SD)	0.9 (0.89)	0.6 (0.68)	0.8 (0.83)	1.3 (0.84)	1.1 (0.86)	
Median	1.0	0.5	0.8	1.5	1.0	
Q1, Q3	0.0, 1.3	0.0, 1.0	0.0, 1.0	0.8, 2.0	0.5, 1.5	
Min, max	0.0, 3.5	0.0, 2.0	0.0, 3.5	0.0, 3.0	0.0, 3.5	
Number of fully active ARV agents from failing regimen						
0	12 (50.0%)	7 (58.3%)	19 (52.8%)	11 (30.6%)	30 (41.7%)	—
1	7 (29.2%)	4 (33.3%)	11 (30.6%)	15 (41.7%)	26 (36.1%)	
2	4 (16.7%)	1 (8.3%)	5 (13.9%)	9 (25.0%)	14 (19.4%)	
3 or more	1 (4.2%)	0	1 (2.8%)	1 (2.8%)	2 (2.8%)	
Used as part of failing regimen						
DTG BID (no DRV BID)	0 (0.0%)	1 (8.3%)	1 (2.8%)	2 (5.6%)	3 (4.2%)	—
DRV BID (no DTG BID)	1 (4.2%)	1 (8.3%)	2 (5.6%)	5 (13.9%)	7 (9.7%)	
DTG BID + DRV BID	4 (16.7%)	1 (8.3%)	5 (13.9%)	10 (27.8%)	15 (20.8%)	
Optimized Background Regimens						
Number of ARVs in the baseline OBR						
N	24	12	36	36	72	0.8755
Mean (SD)	4 (1.1)	4 (1.4)	4 (1.2)	4 (1.0)	4 (1.1)	
Median	4	4	4	4	4	
Q1, Q3	3, 5	3, 5	3, 5	3, 4	3, 4	
Min, max	2, 6	2, 7	2, 7	2, 6	2, 7	

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
Baseline OBR drug class exposure						
NRTI	23 (95.8%)	9 (75.0%)	32 (88.9%)	29 (80.6%)	61 (84.7%)	—
NNRTI	6 (25.0%)	4 (33.3%)	10 (27.8%)	14 (38.9%)	24 (33.3%)	
PI	12 (50.0%)	9 (75.0%)	21 (58.3%)	24 (66.7%)	45 (62.5%)	
INSTI	16 (66.7%)	9 (75.0%)	25 (69.4%)	22 (61.1%)	47 (65.3%)	
Fusion inhibitor	1 (4.2%)	2 (16.7%)	3 (8.3%)	2 (5.6%)	5 (6.9%)	
CCR5 entry inhibitor	2 (8.3%)	4 (33.3%)	6 (16.7%)	4 (11.1%)	10 (13.9%)	
CD4-directed post-attachment inhibitor	9 (37.5%)	3 (25.0%)	12 (33.3%)	5 (13.9%)	17 (23.6%)	
Attachment inhibitor	3 (12.5%)	0	3 (8.3%)	5 (13.9%)	8 (11.1%)	
Number of fully active ARV agents from baseline OBR						
0	4 (16.7%)	2 (16.7%)	6 (16.7%)	6 (16.7%)	12 (16.7%)	—
1	7 (29.2%)	7 (58.3%)	14 (38.9%)	13 (36.1%)	27 (37.5%)	
2	9 (37.5%)	0	9 (25.0%)	10 (27.8%)	19 (26.4%)	
3 or more	4 (16.7%)	3 (25.0%)	7 (19.4%)	7 (19.4%)	14 (19.4%)	
OSS based on baseline OBR						
N	24	12	36	36	72	0.4750
Mean (SD)	1.8 (1.04)	1.5 (1.01)	1.7 (1.02)	1.8 (0.93)	1.8 (0.97)	
Median	2.0	1.3	1.8	2.0	2.0	
Q1, Q3	1.0, 2.5	1.0, 2.5	1.0, 2.5	1.0, 2.3	1.0, 2.5	
Min, max	0.0, 4.0	0.0, 3.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	
OSS category based on baseline OBR						
0	2 (8.3%)	1 (8.3%)	3 (8.3%)	2 (5.6%)	5 (6.9%)	0.6960
0.5	2 (8.3%)	1 (8.3%)	3 (8.3%)	3 (8.3%)	6 (8.3%)	
1	4 (16.7%)	4 (33.3%)	8 (22.2%)	5 (13.9%)	13 (18.1%)	
1.5	2 (8.3%)	2 (16.7%)	4 (11.1%)	6 (16.7%)	10 (13.9%)	
2	7 (29.2%)	1 (8.3%)	8 (22.2%)	11 (30.6%)	19 (26.4%)	
> 2	7 (29.2%)	3 (25.0%)	10 (27.8%)	9 (25.0%)	19 (26.4%)	

ARV = antiretroviral; BID = twice daily; CCR5 = chemokine receptor 5; DRV = darunavir; DTG = dolutegravir; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; OSS = overall susceptibility score; PI = protease inhibitor; Q1 = first quartile; Q3 = third quartile

Failing regimen = nonstudy drug ARV taken on the day before the first dose date of study drug (Day −1); fully active agent = OSS for that agent is 1.

When counting number of ARVs and summarizing by drug class, cobicistat and ritonavir used as a boosting agent were excluded.

OBR at baseline was defined as any nonstudy drug ARV medications that were started on or prior to Study Day 28 from the first dose date of open-label LEN and were used for a minimum duration of 28 days, regardless of temporary interruption, on or after the first dose of open-label LEN.

The OSS for the failing regimen was calculated by summing up the sensitivity/susceptibility scores from all drugs in the failing regimen.

The OSS for the baseline OBR was calculated by summing up the sensitivity/susceptibility scores from all drugs in the baseline OBR.

P value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) for categorical data and the 2-sided Wilcoxon rank sum test for continuous data.

P value was not provided for drug class exposure summary as a participant could have more than 1 drug class exposure.

Source: GS-US-200-4625 Interim Week 26 CSR, Tables 15.8.3.2.2, 15.8.3.2.3, and Req13088.1

3.1.1.3. Analysis Populations

For Cohort 1 in Study GS-US-200-4625, a total of 36 participants were randomized and included in the All Enrolled Analysis Set (Table 7). All 36 participants received at least 1 dose of study drug and were included in both the Full Analysis Set (FAS) and Safety Analysis Set for the Functional Monotherapy Period Analysis. One participant in the placebo group received a new ARV during the Functional Monotherapy Period and was excluded from the Per-Protocol (PP) Analysis Set.

For Cohorts 1 and 2 overall, all 72 enrolled participants received at least 1 dose of LEN (ie, blinded or open-label LEN) and were included in the FAS and Safety Analysis Set for the All LEN Analysis.

Table 7. GS-US-200-4625: Analysis Sets (All Enrolled Analysis Set)

	Cohort 1				
Analysis Set	**LEN (N = 24)**	**Placebo (N = 12)**	**Total (N = 36)**	**Cohort 2 (N = 36)**	**Total (N = 72)**
All Enrolled Analysis Set	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Full Analysis Set for the Functional Monotherapy Period Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	0	36 (50.0%)
Per-Protocol Analysis Set for the Functional Monotherapy Period Analysis	24 (100.0%)	11 (91.7%)	35 (97.2%)	0	35 (48.6%)
Added a new ARV during the Functional Monotherapy Period[a]	0	1 (8.3%)	1 (2.8%)	0	1 (1.4%)
Full Analysis Set for the All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Safety Analysis Set for the Functional Monotherapy Period Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	0	36 (50.0%)
Safety Analysis Set for the All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
PK Analysis Set	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)

ARV = antiretroviral; LEN = lenacapavir; PK = pharmacokinetic(s)
a Initiated optimized background regimen on Day 1 in error.
Denominator for percentages was the All Enrolled Analysis Set.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.8.5

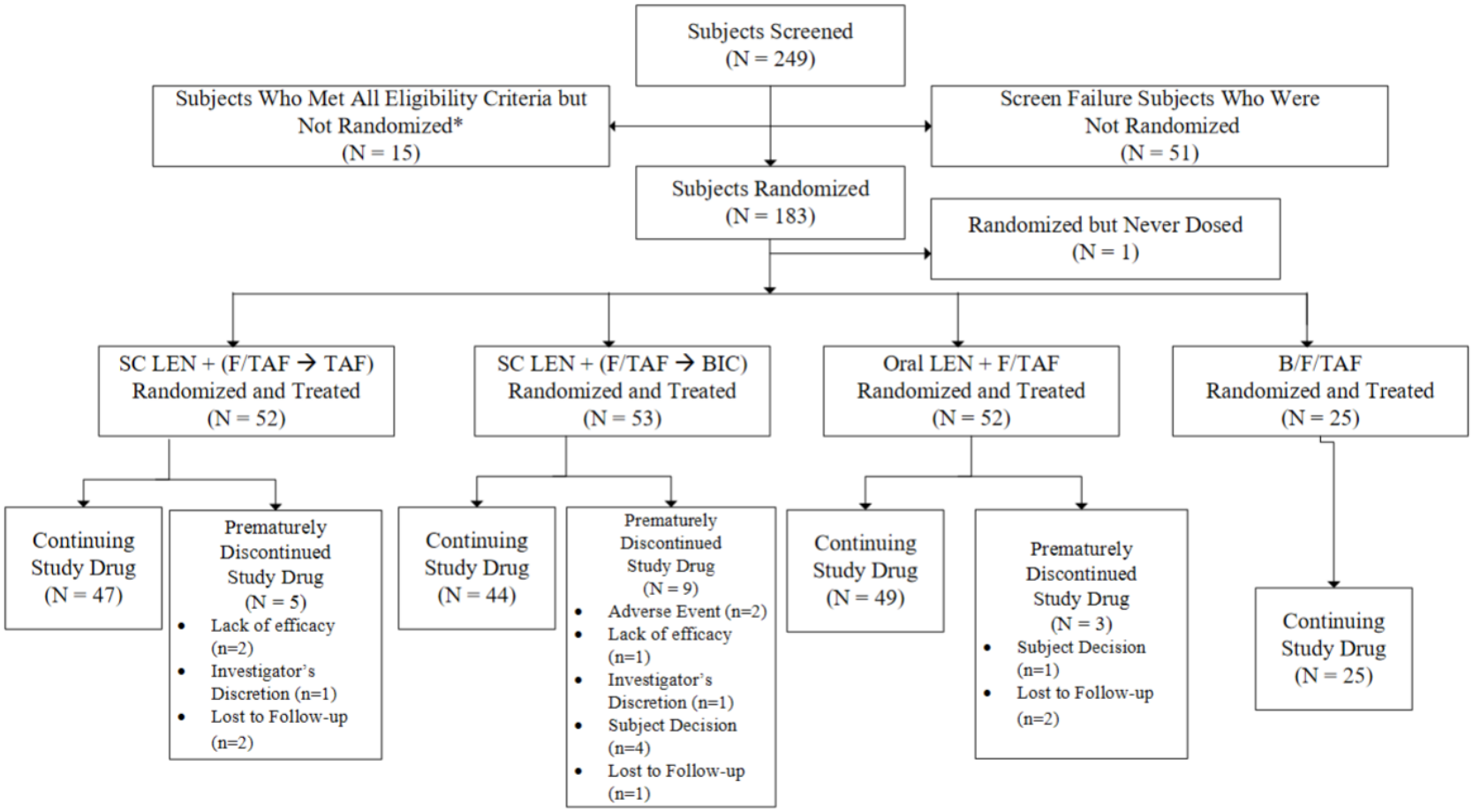
3.1.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

3.1.2.1. Participant Disposition

Of the 249 participants screened for the study, 183 participants were randomized, and 182 participants received at least 1 dose of study drug (Figure 4 and Table 8). A total of 17 participants (9.3%) prematurely discontinued study drug (14 of 105 participants [13.3%] in the SC LEN total group, 3 of 52 participants [5.8%] in the Oral LEN + DVY group, and 0 participants in the BVY group). The reasons for premature discontinuation of study drug in the SC LEN total group were participant decision (3.8%, 4 participants), lack of efficacy and lost to follow-up (each 2.9%, 3 participants), and AE and investigator's discretion (each 1.9%, 2 participants). The reasons for premature discontinuation of study drug in the Oral LEN + DVY group were lost to follow-up (3.8%, 2 participants) and participant decision (1.9%, 1 participant).

None of these discontinuations affected the overall quality or interpretation of the study data.

Figure 4. GS-US-200-4334: Disposition of Participants (All Screened Participants)



B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide

* Among 15 participants who met all eligibility criteria but not randomized, the reasons (n) were: investigator's discretion (1); withdrew consent (9); lost to follow-up (3); and outside of visit window (1). One participant is not a screen failure (missed 2 criteria but met all other criteria) and not enrolled due to lost to follow-up.

Included case report form data collected up to [redacted]20[redacted].

Screen failure participants are the participants who did not meet all eligibility criteria.

Source: GS-US-200-4334 Interim Week 28 CSR, Figure 15.8.1

Table 8. GS-US-200-4334: Disposition of Participants (All Screened Analysis Set)

	SC LEN + (DVY → TAF)	SC LEN + (DVY → BIC)	Oral LEN + DVY	BVY	SC LEN Total	LEN Total	Total
Participants screened	—	—	—	—	—	—	249
Participants met all eligibility criteria and not randomized	—	—	—	—	—	—	15
Adverse event	—	—	—	—	—	—	0
Investigator's discretion	—	—	—	—	—	—	1
Withdrew consent	—	—	—	—	—	—	9
Lost to follow-up	—	—	—	—	—	—	3
Outside of visit window	—	—	—	—	—	—	1
Study enrollment closed	—	—	—	—	—	—	0
Other	—	—	—	—	—	—	0
All Randomized Analysis Set	52	53	52	26	105	157	183
All randomized but never dosed	0	0	0	1	0	0	1
Safety Analysis Set	52	53	52	25	105	157	182
Study drug completion status							
Continuing study drug	47 (90.4%)	44 (83.0%)	49 (94.2%)	25 (100.0%)	91 (86.7%)	140 (89.2%)	165 (90.7%)
Completed study drug	0	0	0	0	0	0	0
Prematurely discontinued study drug	5 (9.6%)	9 (17.0%)	3 (5.8%)	0	14 (13.3%)	17 (10.8%)	17 (9.3%)
Reason for premature discontinuation of study drug							
Adverse event	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)	2 (1.1%)
Death	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Lack of efficacy	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)	3 (1.6%)
Investigator's discretion	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)	2 (1.1%)
Noncompliance with study drug	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Participant decision	0	4 (7.5%)	1 (1.9%)	0	4 (3.8%)	5 (3.2%)	5 (2.7%)
Lost to follow-up	2 (3.8%)	1 (1.9%)	2 (3.8%)	0	3 (2.9%)	5 (3.2%)	5 (2.7%)
Study terminated by sponsor	0	0	0	0	0	0	0

	SC LEN + (DVY → TAF)	SC LEN + (DVY → BIC)	Oral LEN + DVY	BVY	SC LEN Total	LEN Total	Total
Study completion status							
Continuing study	49 (94.2%)	46 (86.8%)	49 (94.2%)	25 (100.0%)	95 (90.5%)	144 (91.7%)	169 (92.9%)
Completed study	0	0	0	0	0	0	0
Prematurely discontinued study	3 (5.8%)	7 (13.2%)	3 (5.8%)	0	10 (9.5%)	13 (8.3%)	13 (7.1%)
Reason for premature discontinuation of study							
Adverse event	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Lack of efficacy	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)	1 (0.5%)
Investigator's discretion	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)	2 (1.1%)
Noncompliance with study drug	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Withdrew consent	0	4 (7.5%)	1 (1.9%)	0	4 (3.8%)	5 (3.2%)	5 (2.7%)
Lost to follow-up	2 (3.8%)	1 (1.9%)	2 (3.8%)	0	3 (2.9%)	5 (3.2%)	5 (2.7%)
Study terminated by sponsor	0	0	0	0	0	0	0

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide
The denominator for percentages is based on the number of participants in the Safety Analysis Set.
Included case report form data collected up to [redacted] 20[redacted] .
One participant is not a screen failure (missed 2 criteria but met all other criteria) and not enrolled due to lost to follow-up.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.8.1.3

3.1.2.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics were similar across the treatment groups in Study GS-US-200-4334 (Table 9). Most participants were male (93.4%, 170 of 182 participants). Race was balanced between Black versus non-Black (52.2% [95 participants] versus 47.8% [87 participants], respectively), as was ethnicity between Hispanic or Latino versus not Hispanic or Latino (45.1% [82 participants] versus 54.9% [100 participants], respectively). The median age was 29 years (range: 19 to 72).

Baseline disease characteristics were similar across the treatment groups (Table 10). Overall, the median (first quartile [Q1], third quartile [Q3]) baseline HIV-1 RNA value was 4.37 (3.86, 4.74) $\log_{10}$ copies/mL, and the median (Q1, Q3) baseline CD4 cell count was 437 (332, 599) cells/µL. The majority of participants had HIV-1 RNA ≤ 100,000 copies/mL (85.2%, 155 participants), and the majority had a CD4 cell count ≥ 350 to < 500 cells/µL (31.9%, 58 participants) or ≥ 500 cells/µL (37.4%, 68 participants).

Table 9. GS-US-200-4334: Demographic and Baseline Characteristics (Safety Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 182)	*P* Value
Age (years)								
N	52	53	52	25	105	157	182	0.3837
Mean (SD)	33 (9.5)	30 (8.8)	32 (12.3)	33 (11.1)	32 (9.3)	32 (10.3)	32 (10.4)	
Median	31	28	28	29	30	29	29	
Q1, Q3	26, 40	24, 33	24, 36	26, 33	25, 36	24, 36	24, 36	
Min, max	19, 61	19, 56	19, 72	21, 61	19, 61	19, 72	19, 72	
Sex at birth								
Male	47 (90.4%)	52 (98.1%)	46 (88.5%)	25 (100.0%)	99 (94.3%)	145 (92.4%)	170 (93.4%)	0.0908
Female	5 (9.6%)	1 (1.9%)	6 (11.5%)	0	6 (5.7%)	12 (7.6%)	12 (6.6%)	
Race								
American Indian or Alaska Native	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)	1 (0.5%)	0.6726
Asian	1 (1.9%)	0	1 (1.9%)	0	1 (1.0%)	2 (1.3%)	2 (1.1%)	
Black	24 (46.2%)	24 (45.3%)	31 (59.6%)	16 (64.0%)	48 (45.7%)	79 (50.3%)	95 (52.2%)	
Native Hawaiian or Pacific Islander	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)	2 (1.1%)	
White	23 (44.2%)	28 (52.8%)	19 (36.5%)	8 (32.0%)	51 (48.6%)	70 (44.6%)	78 (42.9%)	
Other	2 (3.8%)	0	1 (1.9%)	1 (4.0%)	2 (1.9%)	3 (1.9%)	4 (2.2%)	
Race group								
Black	24 (46.2%)	24 (45.3%)	31 (59.6%)	16 (64.0%)	48 (45.7%)	79 (50.3%)	95 (52.2%)	0.2313
Non-Black	28 (53.8%)	29 (54.7%)	21 (40.4%)	9 (36.0%)	57 (54.3%)	78 (49.7%)	87 (47.8%)	
Ethnicity								
Hispanic or Latino	25 (48.1%)	21 (39.6%)	24 (46.2%)	12 (48.0%)	46 (43.8%)	70 (44.6%)	82 (45.1%)	0.8178
Not Hispanic or Latino	27 (51.9%)	32 (60.4%)	28 (53.8%)	13 (52.0%)	59 (56.2%)	87 (55.4%)	100 (54.9%)	

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 182)	*P* Value
Body mass index (kg/m^2)								
N	52	53	52	25	105	157	182	0.7920
Mean (SD)	27.3 (7.82)	26.2 (5.90)	26.6 (5.67)	27.1 (6.05)	26.8 (6.91)	26.7 (6.51)	26.8 (6.43)	
Median	26.4	24.9	26.0	26.9	25.2	25.8	25.8	
Q1, Q3	21.1, 30.0	21.9, 28.7	22.4, 30.4	23.3, 31.0	21.6, 29.3	21.9, 29.5	22.2, 29.8	
Min, max	17.5, 51.1	18.7, 48.9	17.3, 44.3	17.0, 44.1	17.5, 51.1	17.3, 51.1	17.0, 51.1	

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Denominator for percentages was the Safety Analysis Set.
Age (in years) was collected on the first dose date of study drug (Day 1) if dosed, randomization if not dosed, or informed consent if not enrolled.
Body mass index (kg/m^2) = [Weight (kg)/Height (cm)^2]*10,000
For categorical data, *P* value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) to compare across treatment groups.
For continuous data, *P* value was from the 2-sided Kruskal-Wallis test to compare across treatment groups.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.8.3.1

Table 10. GS-US-200-4334: Baseline Disease Characteristics (Safety Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 182)	*P* Value
HIV-1 RNA (log_{10} copies/mL)								
N	52	53	52	25	105	157	182	0.5266
Mean (SD)	4.18 (0.672)	4.35 (0.670)	4.33 (0.722)	4.35 (0.780)	4.27 (0.673)	4.29 (0.688)	4.30 (0.700)	
Median	4.27	4.32	4.53	4.37	4.32	4.36	4.37	
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.88, 4.70	3.85, 4.73	3.86, 4.74	
Min, max	2.27, 5.63	2.46, 5.75	2.35, 5.54	2.10, 5.92	2.27, 5.75	2.27, 5.75	2.10, 5.92	
HIV-1 RNA categories (copies/mL)								
≤ 100,000	47 (90.4%)	44 (83.0%)	43 (82.7%)	21 (84.0%)	91 (86.7%)	134 (85.4%)	155 (85.2%)	0.6630
> 100,000	5 (9.6%)	9 (17.0%)	9 (17.3%)	4 (16.0%)	14 (13.3%)	23 (14.6%)	27 (14.8%)	
CD4 cell count (cells/μL)								
N	52	53	52	25	105	157	182	0.6194
Mean (SD)	506 (297.0)	490 (209.9)	470 (221.7)	534 (260.0)	498 (255.7)	489 (244.6)	495 (246.5)	
Median	404	450	409	482	434	417	437	
Q1, Q3	320, 599	332, 599	301, 600	393, 527	321, 599	320, 599	332, 599	
Min, max	213, 1846	187, 991	175, 1091	232, 1443	187, 1846	175, 1846	175, 1846	
CD4 cell count categories (cells/μL)								
< 50	0	0	0	0	0	0	0	0.4852
≥ 50 to < 200	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)	4 (2.2%)	
≥ 200 to < 350	17 (32.7%)	15 (28.3%)	16 (30.8%)	4 (16.0%)	32 (30.5%)	48 (30.6%)	52 (28.6%)	
≥ 350 to < 500	17 (32.7%)	15 (28.3%)	15 (28.8%)	11 (44.0%)	32 (30.5%)	47 (29.9%)	58 (31.9%)	
≥ 500	18 (34.6%)	22 (41.5%)	18 (34.6%)	10 (40.0%)	40 (38.1%)	58 (36.9%)	68 (37.4%)	
CD4 percentage (%)								
N	52	53	52	25	105	157	182	0.2088
Mean (SD)	24.2 (9.92)	24.1 (8.04)	22.7 (8.28)	26.2 (8.18)	24.2 (8.98)	23.7 (8.75)	24.0 (8.70)	
Median	22.4	24.6	20.9	26.1	23.3	22.5	23.1	
Q1, Q3	18.9, 27.3	17.7, 29.1	17.4, 25.5	20.5, 30.0	18.4, 28.5	18.1, 27.9	18.5, 28.2	
Min, max	8.0, 63.0	8.0, 40.4	8.9, 45.8	12.0, 43.5	8.0, 63.0	8.0, 63.0	8.0, 63.0	

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
For categorical data, *P* value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) to compare across treatment groups.
For continuous data, *P* value was from the 2-sided Kruskal-Wallis test to compare across treatment groups.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.8.3.2

3.1.2.3. Analysis Populations

Overall, a total of 183 participants were randomized into Study GS-US-200-4334 and were included in the All Randomized Analysis Set (Table 11). Of these, 182 participants received at least 1 dose of study drug and were included in both the FAS and Safety Analysis Set. The PK Analysis Set included 175 participants, the PK Substudy Analysis Set included 34 participants, and the Peripheral Blood Mononuclear Cell Substudy Analysis Set included 19 participants.

Table 11. GS-US-200-4334: Analysis Sets (All Randomized Analysis Set)

Analysis Set	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 26)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 183)
All Randomized Analysis Set	52	53	52	26	105	157	183
Full Analysis Set	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (96.2%)	105 (100.0%)	157 (100.0%)	182 (99.5%)
Safety Analysis Set	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (96.2%)	105 (100.0%)	157 (100.0%)	182 (99.5%)
PK Analysis Set	49 (94.2%)	49 (92.5%)	52 (100.0%)	25 (96.2%)	98 (93.3%)	150 (95.5%)	175 (95.6%)
PK Substudy Analysis Set	11 (21.2%)	14 (26.4%)	9 (17.3%)	0	25 (23.8%)	34 (21.7%)	34 (18.6%)
PBMC Substudy Analysis Set	7 (13.5%)	12 (22.6%)	0	0	19 (18.1%)	19 (12.1%)	19 (10.4%)

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); LEN = lenacapavir; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); SC = subcutaneous; TAF = tenofovir alafenamide
The denominator for percentage is the number of participants in the All Randomized Analysis Set.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.8.5

3.2. Comparison of Efficacy Results of All Studies

Given the difference in study populations, efficacy results are summarized by study for Studies GS-US-200-4625 and GS-US-200-4334. Detailed efficacy results are presented in the individual CSRs (GS-US-200-4625 Interim Week 26 CSR, Section 9; GS-US-200-4334 Interim Week 28 CSR, Section 9).

3.2.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

3.2.1.1. Primary Efficacy End Point: Reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL From Baseline

For the primary analysis of the primary efficacy end point in Study GS-US-200-4625, a significantly greater percentage of participants who received LEN had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period than those who received placebo (87.5% [21 of 24 participants] versus 16.7% [2 of 12 participants], respectively; $P < 0.0001$) (Table 12).

Table 12. GS-US-200-4625: Number and Proportion of Participants Achieving a Reduction in HIV-1 RNA of ≥ 0.5 log_{10} copies/mL From Baseline – Functional Monotherapy Period Analysis (Full Analysis Set)

	Cohort 1		LEN vs Placebo	
	LEN (N = 24)	Placebo (N = 12)	*P* Value	Proportional Difference (95% CI)
Number and proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 log_{10} copies/mL from baseline	21 (87.5%)	2 (16.7%)	< 0.0001	70.8% (34.9% to 90.0%)

LEN = lenacapavir
The 95% CI of the difference in percentages of response between treatment groups and the corresponding *P* value were calculated based on an unconditional exact method using 2 invert 1-sided tests (Chan and Zhang method).
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.9.1.1

To address the imbalance in baseline HIV-1 RNA between the LEN and placebo groups, a post hoc analysis of the primary efficacy end point with adjustment for baseline HIV-1 RNA using rank analysis of covariance was conducted. Results from this post hoc analysis confirmed that the difference between the groups remained statistically significant (*P* = 0.0003). To address the imbalance in baseline CD4 cell count between the LEN and placebo groups, post hoc analyses of the primary efficacy end point were conducted in participants with comparable or clinically relevant CD4 cell counts. These analyses showed that the difference between groups remained statistically significant for the comparison between participants in the LEN group with the lowest baseline CD4 cell counts (median: 98.5 cells/μL; n = 12) and participants in the placebo group (median: 84.5 cells/μL; n = 12) (*P* = 0.0008) and between participants in the LEN and placebo groups (n = 16 and 11, respectively) with a baseline CD4 cell count < 200 cells/μL (*P* < 0.0001).

One participant in the placebo group who initiated an OBR on Day 1 rather than Day 15 had a reduction in HIV-1 RNA of 1.929 log_{10} copies/mL from baseline at Day 15; this participant was excluded from the PP Analysis Set. The results based on the PP Analysis Set were consistent with those for the FAS and confirmed the primary efficacy end point (reduction in HIV-1 RNA of ≥ 0.5 log_{10} copies/mL from baseline: LEN 87.5%, 21 of 24 participants; placebo 9.1%, 1 of 11 participants; *P* < 0.0001).

3.2.1.2. Secondary Efficacy End Points: HIV-1 RNA < 50 and < 200 copies/mL at Week 26 in Cohort 1 (US FDA-Defined Snapshot Algorithm)

For the All LEN Analysis in Study GS-US-200-4625, the percentages of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm were 80.6% (29 of 36 participants) and 88.9% (32 participants), respectively (Table 13).

Table 13. GS-US-200-4625: Virologic Outcome at Week 26 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 and 200 copies/mL – All LEN Analysis (Full Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 6)	Total (N = 42)
Using HIV-1 RNA Cutoff at 50 copies/mL					
HIV-1 RNA < 50 copies/mL	21 (87.5%)	8 (66.7%)	29 (80.6%)	4 (66.7%)	33 (78.6%)
95% CI	67.6% to 97.3%	34.9% to 90.1%	64.0% to 91.8%	22.3% to 95.7%	63.2% to 89.7%
HIV-1 RNA ≥ 50 copies/mL	3 (12.5%)	4 (33.3%)	7 (19.4%)	1 (16.7%)	8 (19.0%)
HIV-1 RNA ≥ 50 copies/mL in Week 26 window	3 (12.5%)	4 (33.3%)	7 (19.4%)	1 (16.7%)	8 (19.0%)
Discontinued study drug due to lack of efficacy	0	0	0	0	0
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA ≥ 50 copies/mL	0	0	0	0	0
No virologic data in Week 26 window	0	0	0	1 (16.7%)	1 (2.4%)
Discontinued study drug due to AE/death	0	0	0	1 (16.7%)	1 (2.4%)
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA < 50 copies/mL	0	0	0	0	0
Missing data during window but on study drug	0	0	0	0	0
Using HIV-1 RNA Cutoff at 200 copies/mL					
HIV-1 RNA < 200 copies/mL	23 (95.8%)	9 (75.0%)	32 (88.9%)	4 (66.7%)	36 (85.7%)
95% CI	78.9% to 99.9%	42.8% to 94.5%	73.9% to 96.9%	22.3% to 95.7%	71.5% to 94.6%
HIV-1 RNA ≥ 200 copies/mL	1 (4.2%)	3 (25.0%)	4 (11.1%)	1 (16.7%)	5 (11.9%)
HIV-1 RNA ≥ 200 copies/mL in Week 26 window	1 (4.2%)	3 (25.0%)	4 (11.1%)	1 (16.7%)	5 (11.9%)
Discontinued study drug due to lack of efficacy	0	0	0	0	0
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA ≥ 200 copies/mL	0	0	0	0	0

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 6)	Total (N = 42)
No virologic data in Week 26 window	0	0	0	1 (16.7%)	1 (2.4%)
Discontinued study drug due to AE/death	0	0	0	1 (16.7%)	1 (2.4%)
Discontinued study drug due to other reasons[a] and last available HIV-1 RNA < 200 copies/mL	0	0	0	0	0
Missing data during window but on study drug	0	0	0	0	0

AE = adverse event; FDA = Food and Drug Administration; LEN = lenacapavir; US = United States
a Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
For Cohort 2, the participants who have not reached the Week 26 visit but are still ongoing are excluded from the snapshot analysis.
The Week 26 window is between Days 184 and 232 (inclusive).
Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the first subcutaneous LEN, was used in this analysis.
The 95% CIs of the percentages of participants with HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Week 26 were calculated based on the Exact method.
Source: GS-US-200-4625 Interim Week 26 CSR, Tables 15.9.2.1 and 15.9.2.2

3.2.1.3. Other Efficacy Analyses

3.2.1.3.1. HIV-1 RNA < 50 and < 200 copies/mL at Week 26 in Cohort 2 (US FDA-Defined Snapshot Algorithm)

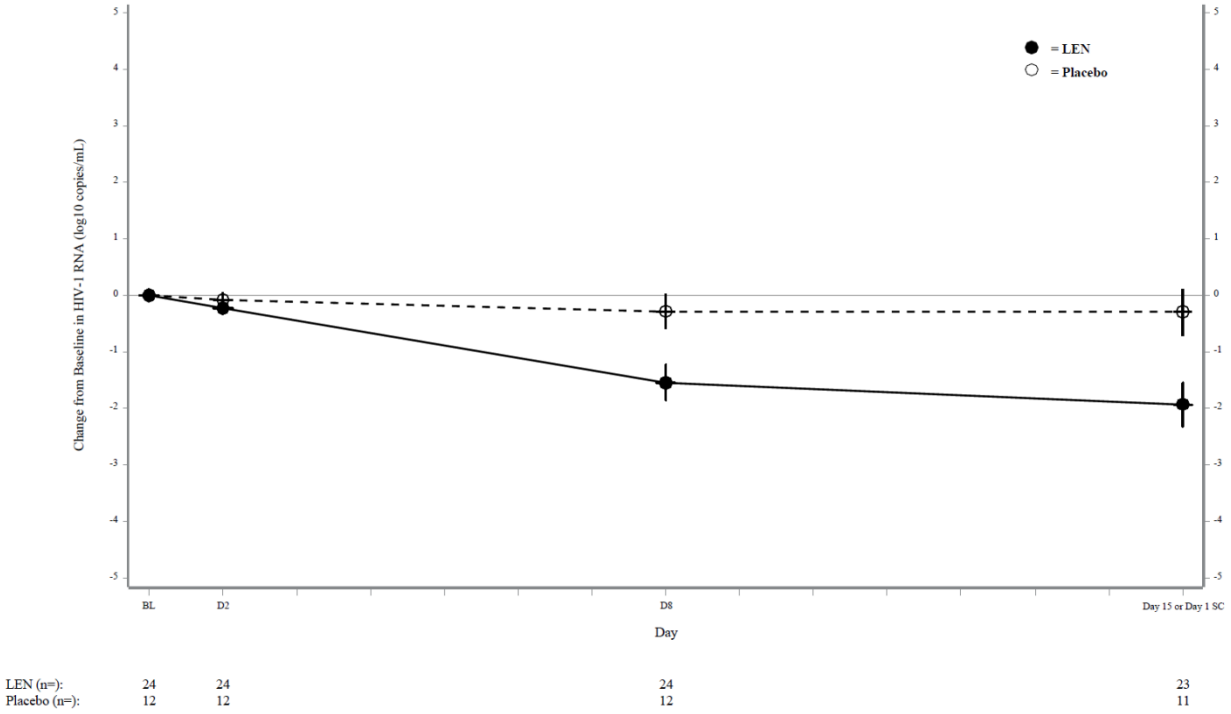
For the All LEN Analysis in Study GS-US-200-4625, the percentages of participants in Cohort 2 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm were each 66.7% (4 of 6 participants) (Table 13). Most participants in Cohort 2 had not yet reached Week 26.

3.2.1.3.2. Change From Baseline in HIV-1 RNA

Functional Monotherapy Period

For the Functional Monotherapy Period in Study GS-US-200-4625, the mean (SD) baseline HIV-1 RNA value was lower for participants who received LEN than those who received placebo, as follows: LEN 3.97 (0.922) $\log_{10}$ copies/mL; placebo 4.87 (0.393) $\log_{10}$ copies/mL (difference in LSM: −0.90 [95% CI: −1.47 to −0.33]; $P = 0.0028$). The mean (SD) change from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period was greater for participants who received LEN than those who received placebo, as follows: LEN −1.93 (0.893) $\log_{10}$ copies/mL; placebo −0.29 (0.614) $\log_{10}$ copies/mL (adjusted difference in LSM by baseline $\log_{10}$ HIV-1 RNA: −2.17 [95% CI: −2.74 to −1.59]; $P < 0.0001$) (Figure 5).

Figure 5. GS-US-200-4625: Mean (95% CI) Change From Baseline in HIV-1 RNA (log_{10} copies/mL) by Visit – Functional Monotherapy Period Analysis (Full Analysis Set)



BL = baseline; Dx = Day x; LEN = lenacapavir; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of blinded study drug.
Source: GS-US-200-4625 Interim Week 26 CSR, Figure 15.9.1.1

All LEN Analysis

For the All LEN Analysis in Study GS-US-200-4625, the mean (SD) baseline HIV-1 RNA value was 4.11 (1.031) log_{10} copies/mL, and the mean (SD) change from baseline in HIV-1 RNA at Week 26 was −2.45 (1.162) log_{10} copies/mL.

3.2.1.3.3. Change From Baseline in CD4 Cell Count

For the All LEN Analysis in Study GS-US-200-4625, the mean (SD) baseline CD4 cell count was 212 (226.2) cells/µL, and the mean (SD) change from baseline in CD4 cell count at Week 26 was 90 (102.1) cells/µL.

3.2.1.3.4. HIV-1 RNA < 50 copies/mL Using Imputation Methods (Missing = Failure and Missing = Excluded)

For the All LEN Analysis in Study GS-US-200-4625, the percentage of participants with HIV-1 RNA < 50 copies/mL at Week 26 was 78.6% (33 of 42 participants) based on the M = F analysis (Table 14). Similar results were observed for the M = E analysis.

Table 14. GS-US-200-4625: Number and Proportion of Participants With HIV-1 RNA < 50 copies/mL at Week 26 Using Imputation Methods (Missing = Failure and Missing = Excluded) − All LEN Analysis (Full Analysis Set)

Participants With HIV-1 RNA < 50 copies/mL	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Missing = failure					
Week 26	21/24 (87.5%)	8/12 (66.7%)	29/36 (80.6%)	4/6 (66.7%)	33/42 (78.6%)
Missing = excluded					
Week 26	21/24 (87.5%)	8/12 (66.7%)	29/36 (80.6%)	4/5 (80.0%)	33/41 (80.5%)

LEN = lenacapavir
For the missing = failure analysis, the denominator for percentages was based on the number of participants in the Full Analysis Set for the All LEN Analysis, excluding ongoing participants who had missing HIV-1 RNA at a visit and had not reached the upper limit of the analysis window for the corresponding visit.
For the missing = excluded analysis, the denominator for percentages was based on the number of participants in the Full Analysis Set for the All LEN Analysis with nonmissing HIV-1 RNA value at each visit.
Source: GS-US-200-4625 Interim Week 26 CSR, Tables 15.9.5.1 and 15.9.5.2

3.2.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

3.2.2.1. Secondary Efficacy End Points

3.2.2.1.1. HIV-1 RNA < 50 copies/mL at Week 28 (US FDA-Defined Snapshot Algorithm)

The percentages of participants with HIV-1 RNA < 50 copies/mL at Week 28 using the US FDA-defined snapshot algorithm were similar across treatment groups in Study GS-US-200-4334, with no significant differences between each of the LEN-containing groups and the BVY group, as follows (Table 15):

- LEN total: 93.6%, 147 of 157 participants
- SC LEN + (DVY → TAF): 94.2%, 49 of 52 participants
- SC LEN + (DVY → BIC): 92.5%, 49 of 53 participants
- Oral LEN + DVY: 94.2%, 49 of 52 participants
- BVY: 100.0%, 25 of 25 participants

A total of 2 participants had HIV-1 RNA ≥ 50 copies/mL at Week 28 using the US FDA-defined snapshot algorithm. Both participants were in the SC LEN + (DVY → BIC) group and had prematurely discontinued study drug before the Week 28 window, as follows:

- One participant did not meet the protocol-defined criterion of HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 to initiate the maintenance regimen at Week 28; the participant started dolutegravir, lamivudine/zidovudine, and tenofovir disoproxil fumarate and had HIV-1 RNA < 50 copies/mL at Week 28.
- One participant prematurely discontinued study drug due to participant decision on Day 2.

Table 15. GS-US-200-4334: Virologic Outcome at Week 28 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (Full Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
HIV-1 RNA < 50 copies/mL	49 (94.2%)	49 (92.5%)	49 (94.2%)	25 (100.0%)	98 (93.3%)	147 (93.6%)
HIV-1 RNA ≥ 50 copies/mL	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)
HIV-1 RNA ≥ 50 copies/mL in Week 28 window	0	0	0	0	0	0
Discontinued study drug due to lack of efficacy	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Discontinued study drug due to other reasons* and last available HIV-1 RNA ≥ 50 copies/mL	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
No virologic data in Week 28 window	3 (5.8%)	2 (3.8%)	3 (5.8%)	0	5 (4.8%)	8 (5.1%)
Discontinued study drug due to adverse event/death	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Discontinued study drug due to other reasons* and last available HIV-1 RNA < 50 copies/mL	2 (3.8%)	1 (1.9%)	3 (5.8%)	0	3 (2.9%)	6 (3.8%)
Missing data during window but on study drug	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
LEN vs BVY						
P value	0.2398	0.1639	0.2307	—	0.1794	0.1916
Difference in percentage (95% CI)	−5.5% (−15.9% to 4.8%)	−7.4% (−18.3% to 3.4%)	−5.7% (−16.3% to 4.9%)	—	−6.9% (−16.1% to 2.4%)	−6.5% (−15.1% to 2.2%)

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); FDA = Food and Drug Administration; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; US = United States

* Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

The Week 28 window is between Days 176 and 231 (inclusive).

The difference in percentage of participants with HIV-1 RNA < 50 copies/mL between each of the LEN-containing treatment groups and the BVY group and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

P value was from the Cochran-Mantel-Haenszel tests stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

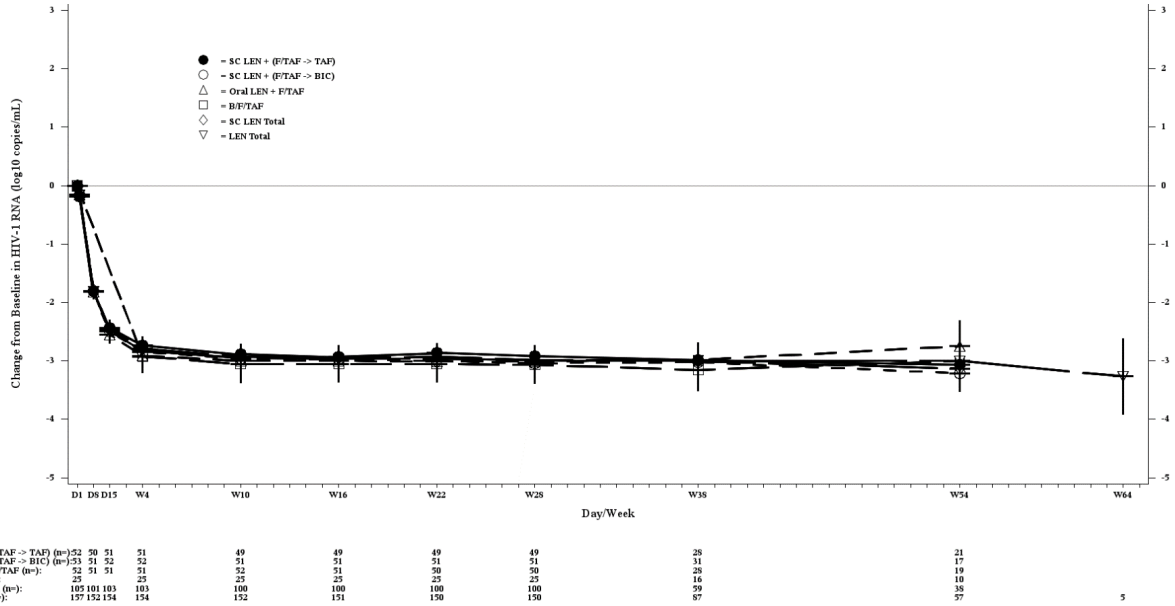
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.8.6

3.2.2.1.2. Change From Baseline in HIV-1 RNA

Mean baseline HIV-1 RNA values and mean changes from baseline in HIV-1 RNA at Week 28 were similar across treatment groups in Study GS-US-200-4334, with no significant differences between each of the LEN-containing groups and the BVY group (Figure 6). Mean (SD) changes from baseline in HIV-1 RNA at Week 28 were as follows:

- LEN total: −2.99 (0.666) $\log_{10}$ copies/mL
- SC LEN + (DVY → TAF): −2.92 (0.649) $\log_{10}$ copies/mL
- SC LEN + (DVY → BIC): −3.04 (0.638) $\log_{10}$ copies/mL
- Oral LEN + DVY: −3.01 (0.716) $\log_{10}$ copies/mL
- BVY: −3.07 (0.774) $\log_{10}$ copies/mL

Figure 6. GS-US-200-4334: Mean (95% CI) Change From Baseline in HIV-1 RNA ($\log_{10}$ copies/mL) by Visit (Full Analysis Set)



B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; Dx = Day x; F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; Wx = Week x
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 28 CSR, Figure 15.9.1

3.2.2.1.3. Change From Baseline in CD4 Cell Count

Mean baseline CD4 cell counts and mean changes from baseline in CD4 cell count at Week 28 were similar across treatment groups in Study GS-US-200-4334, with no significant differences between each of the LEN-containing groups and the BVY group. Mean (SD) changes from baseline in CD4 cell count at Week 28 were as follows:

- LEN total: 179 (166.0) cells/µL
- SC LEN + (DVY → TAF): 172 (178.2) cells/µL
- SC LEN + (DVY → BIC): 158 (164.1) cells/µL
- Oral LEN + DVY: 206 (154.6) cells/µL
- BVY: 163 (157.7) cells/µL

3.2.2.2. Other Efficacy Analyses

3.2.2.2.1. HIV-1 RNA < 50 copies/mL Using Imputation Methods (Missing = Failure and Missing = Excluded)

The M = F analysis of the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 28 in Study GS-US-200-4334 yielded similar results as the analysis using the US FDA-defined snapshot algorithm, with no significant differences between each of the LEN-containing groups and the BVY group, as follows:

- LEN total: 95.5%, 150 of 157 participants
- SC LEN + (DVY → TAF): 94.2%, 49 of 52 participants
- SC LEN + (DVY → BIC): 96.2%, 51 of 53 participants
- Oral LEN + DVY: 96.2%, 50 of 52 participants
- BVY: 100.0%, 25 of 25 participants

For the M = E analysis, all participants in each treatment group had HIV-1 RNA < 50 copies/mL at Week 28 (SC LEN + [DVY → TAF] 49 participants; SC LEN + [DVY → BIC] 51 participants; Oral LEN + DVY 50 participants; BVY 25 participants).

3.3. Comparison of Results in Subpopulations

Statistical methods for subgroup analyses of efficacy data from Studies GS-US-200-4625 and GS-US-200-4334 are described in the statistical analysis plans (GS-US-200-4625 Interim Week 26 CSR, Appendix 16.1.9; GS-US-200-4334 Interim Week 28 CSR, Appendix 16.1.9). Detailed results are presented in the individual CSRs (GS-US-200-4625 Interim Week 26 CSR, Section 9.4; GS-US-200-4334 Interim Week 28 CSR, Section 9.4).

3.3.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

In HTE PWH with multidrug resistance in Study GS-US-200-4625, the percentage of participants with HIV-1 RNA < 50 copies/mL at Week 26 using the US FDA-defined snapshot algorithm was numerically higher in participants aged < 50 years, female participants, participants with a baseline CD4 cell count ≥ 200 cells/μL, and participants with a baseline HIV-1 RNA level ≤ 100,000 copies/mL.

Despite the limitations of the small sample size in some subgroups, the efficacy of LEN by baseline CD4 cell count and HIV-1 RNA level was generally as expected, since low CD4 cell counts and high HIV-1 RNA levels are factors known to limit virologic response (Table 16). However, the general trend of the efficacy analyses by various subgroups based on OBR suggests that the contribution of LEN toward efficacy was clinically meaningful. Specifically, the efficacy of LEN in subgroups of participants who were considered more difficult to treat did not appear to be clinically meaningfully lower than those who were considered not as difficult to treat (ie, those with no fully active agents versus those with fully active agents, those with INSTI resistance versus those without, and those without either dolutegravir or darunavir in the OBR versus those with either).

Table 16. GS-US-200-4625: Number and Proportion of Participants With HIV-1 RNA < 50 copies/mL at Week 26 Using the US FDA-Defined Snapshot Algorithm by Subgroup – All LEN Analysis (Full Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 6)	Total (N = 42)
Baseline CD4 cell count categories (cells/μL)					
< 200	14/16 (87.5%)	7/11 (63.6%)	21/27 (77.8%)	1/2 (50.0%)	22/29 (75.9%)
≥ 200	7/8 (87.5%)	1/1 (100.0%)	8/9 (88.9%)	3/4 (75.0%)	11/13 (84.6%)
Baseline HIV-1 RNA categories (copies/mL)					
≤ 100,000	20/23 (87.0%)	5/6 (83.3%)	25/29 (86.2%)	4/5 (80.0%)	29/34 (85.3%)
> 100,000	1/1 (100.0%)	3/6 (50.0%)	4/7 (57.1%)	0/1	4/8 (50.0%)
Overall susceptibility score based on baseline OBR					
0 to < 1	3/4 (75.0%)	1/2 (50.0%)	4/6 (66.7%)	2/2 (100.0%)	6/8 (75.0%)
1 to < 2	6/6 (100.0%)	5/6 (83.3%)	11/12 (91.7%)	2/3 (66.7%)	13/15 (86.7%)
≥ 2	12/14 (85.7%)	2/4 (50.0%)	14/18 (77.8%)	0/1	14/19 (73.7%)
Number of fully active ARV agents in the baseline OBR					
0	3/4 (75.0%)	1/2 (50.0%)	4/6 (66.7%)	2/2 (100.0%)	6/8 (75.0%)
1	6/7 (85.7%)	6/7 (85.7%)	12/14 (85.7%)	2/3 (66.7%)	14/17 (82.4%)
≥ 2	12/13 (92.3%)	1/3 (33.3%)	13/16 (81.3%)	0/1	13/17 (76.5%)
Resistance categories based on baseline INSTI resistance profile					
With INSTI resistance	19/20 (95.0%)	4/7 (57.1%)	23/27 (85.2%)	3/5 (60.0%)	26/32 (81.3%)
Without INSTI resistance	2/4 (50.0%)	3/4 (75.0%)	5/8 (62.5%)	1/1 (100.0%)	6/9 (66.7%)
Use of DTG and/or DRV					
With DTG and DRV	6/6 (100.0%)	4/6 (66.7%)	10/12 (83.3%)	0/1	10/13 (76.9%)
With DTG, without DRV	4/4 (100.0%)	1/2 (50.0%)	5/6 (83.3%)	2/3 (66.7%)	7/9 (77.8%)
Without DTG, with DRV	5/6 (83.3%)	2/3 (66.7%)	7/9 (77.8%)	1/1 (100.0%)	8/10 (80.0%)
Without DTG or DRV	6/8 (75.0%)	1/1 (100.0%)	7/9 (77.8%)	1/1 (100.0%)	8/10 (80.0%)
Use of IMAB					
With IMAB	8/9 (88.9%)	1/3 (33.3%)	9/12 (75.0%)	0/1	9/13 (69.2%)
Without IMAB	13/15 (86.7%)	7/9 (77.8%)	20/24 (83.3%)	4/5 (80.0%)	24/29 (82.8%)

ARV = antiretroviral; DRV = darunavir; DTG = dolutegravir; FDA = Food and Drug Administration; IMAB = ibalizumab; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; OBR = optimized background regimen; US = United States
The Week 26 window is between Days 184 and 232 (inclusive).
Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the first subcutaneous LEN, was used in this analysis.
Source: GS-US-200-4625 Interim Week 26 CSR, Tables 15.9.2.3, req13058.1, and req13061.1

3.3.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

In treatment-naive PWH in Study GS-US-200-4334, the percentages of participants with HIV-1 RNA < 50 copies/mL at Week 28 in the subgroups based on age (< 50 years or ≥ 50 years), sex (male or female), and race (Black or non-Black) were similar to the results in the overall study population. However, the small size and imbalance of participant numbers within each subgroup preclude meaningful conclusions.

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Rationale for Phase 2 and 2/3 LEN Dosing Regimen

The LEN dosing regimen selected for the ongoing Phase 2 and 2/3 studies in PWH (Studies GS-US-200-4334 and GS-US-200-4625, respectively) was as follows: oral LEN 600 mg on Days 1 and 2, oral LEN 300 mg on Day 8, followed by SC LEN injection 927 mg on Day 15 and every 6 months (26 weeks) thereafter.

The efficacy, safety, and PK of LEN oral and SC formulations have been comprehensively characterized in Phase 1 studies in healthy participants (Studies GS-US-200-4070, GS-US-200-4071, and GS-US-200-4538) and the Phase 1b, dose-ranging, proof-of-concept study in PWH (Study GS-US-200-4072). Using modeling and simulation based on the observed Phase 1 data, the Phase 2 and 2/3 dosing regimen was selected to target an exposure whereby the lower bound of the 90% CI of the C_{trough} is at least 4-fold higher than the in vitro protein-adjusted 95% effective concentration (3.87 ng/mL; MT-4 cells), corresponding to IQ4 (15.5 ng/mL), within a few days of dosing initiation and through the end of the 6-month (26-week) dosing interval. Additional considerations supporting the 14-day oral lead-in period of the selected Phase 2 and 2/3 dosing regimen included rapid achievement of target LEN concentrations (oral dosing on Days 1 and 2) and maintenance of target concentrations (oral dosing on Day 8) during a 14-day period selected to confirm tolerability of LEN prior to administration of the long-acting SC formulation (m2.7.2, Section 3.2.1.1).

Rationale for Proposed LEN Dosing Regimen

In the Phase 2 and 2/3 studies, the selected LEN dosing regimen included a 14-day oral lead-in period that enabled the following: an oral loading (from a PK standpoint); an assessment of the contribution of LEN to the efficacy of an otherwise-failing regimen (during the Functional Monotherapy Period of Study GS-US-200-4625); and an assessment of safety and tolerability of LEN prior to administration of SC LEN injection. However, this specific oral lead-in design can be simplified to improve adherence without compromising efficacy.

Given the established safety profile and lack of exposure-safety relationships for LEN in Studies GS-US-200-4625 and GS-US-200-4334, the following simplified LEN dosing regimen is proposed for the treatment of HTE PWH: oral LEN 600 mg and SC LEN injection 927 mg on Day 1, oral LEN 600 mg on Day 2, followed by SC LEN injection 927 mg every 6 months (26 weeks) thereafter. Simulations using a population PK model indicate that this simplified regimen will yield a comparable LEN PK profile to that of the Phase 2 and 2/3 dosing regimen and should be considered the preferred LEN dosing regimen (m2.7.2, Section 3.2.1.3).

A 4-week dosing window around the every-6-month dose for SC LEN injection is predicted to maintain safe and efficacious LEN exposures based on modeling and simulation results of the Phase 2 and 2/3 dosing regimen (m2.7.2, Section 3.2.1.2).

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

No data are available at this time. Studies GS-US-200-4625 and GS-US-200-4334 are ongoing, and longer-term data will be available in the future.

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7. APPENDIX

7.1. Tabular Summary of Studies Relevant for Efficacy

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-200-4625	To evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for PWH with multidrug resistance	Phase 2/3, randomized, placebo-controlled, multicenter study	Cohort 1: Functional Monotherapy Period: oral LEN 600, 600, and 300 mg or placebo-to-match LEN on Days 1, 2, and 8, respectively, while continuing their failing regimen Maintenance Period: Cohort 1A: SC LEN 927 mg and initiation of an OBR starting on Day 1 SC (14 days after the first dose of oral LEN) and once every 6 months (26 weeks) Cohort 1B: oral LEN 600 mg and initiation of an OBR on Day 15; oral LEN 600 and 300 mg on Days 16 and 22, respectively; SC LEN 927 mg while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks) Cohort 2: Oral Lead-in Period: oral LEN 600 mg and initiation of an OBR on Day 1; oral LEN 600 and 300 mg on Days 2 and 8, respectively, while continuing their OBR Maintenance Period: SC LEN 927 mg while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks)	At least 54 weeks	Enrolled: 72 participants; Cohort 1: 36 participants; Cohort 2: 36 participants	Heavily treatment-experienced adult and adolescent PWH with resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications and plasma HIV-1 RNA ≥ 400 copies/mL at screening while taking a failing regimen	Study ongoing; Interim Week 26 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-200-4334	To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment Group 1 (oral to SC LEN): • Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral DVY 200/25 mg • Maintenance: SC LEN 927 mg and oral TAF 25 mg Treatment Group 2 (oral to SC LEN): • Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral DVY 200/25 mg • Maintenance: SC LEN 927 mg and oral BIC 75 mg Treatment Group 3: oral LEN 600 and 50 mg and oral DVY 200/25 mg Treatment Group 4: oral BVY 50/200/25 mg	At least 80 weeks	Randomized: 183 participants; Safety Analysis Set: 182 participants; SC LEN + (DVY → TAF): 52 participants; SC LEN + (DVY → BIC): 53 participants; Oral LEN + DVY: 52 participants; BVY: 25 participants	Treatment-naive PWH ≥ 18 years of age	Study ongoing; Interim Week 28 CSR

ARV = antiretroviral; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CSR = clinical study report; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); LEN = lenacapavir; OBR = optimized background regimen; PWH = people with HIV; SC = subcutaneous; TAF = tenofovir alafenamide

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY

ADDENDUM

LENACAPAVIR

Gilead Sciences, Inc.

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

A	alemtuzumab
AE	adverse event
ART	ARV therapy
ARV	antiretroviral
B	bendamustine
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
BIC	bictegravir
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated
CD4	clusters of differentiation 4
CI	confidence interval
CRF	case report form
CSR	clinical study report
D	darunavir
Diff	difference
DRV	darunavir
DTG	dolutegravir
DVY	emtricitabine/tenofovir alafenamide (coformulated
EACS	European AIDS Clinical Society
eg	for example
F/TAF	form; DVY = emtricitabine/tenofovir alafenamide
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTR	fostemsavir
Gilead	Gilead Sciences
GS	glutamine synthetase
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HTE	heavily treatment-experienced
ie	that is
IMAB	ibalizumab
IN	integrase
INSTI	integrase strand-transfer inhibitor
ISR	injection site reaction
kg	kilogram
LEN	Lenacapavir
LSM	least squares mean
M = E	missing = excluded
M = F	missing = failure
µL	microliter

max	maximum
Met	metformin
min	minimum
mL	milliliter
N	number of participants
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OBR	optimized background regimen
OL	open label
P	passage
PI	isoelectric point
PK	pharmacokinetics
PP	Per-Protocol
PWH	people with HIV
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
TAF	tenofovir alafenamide
US	United States
vs	versus

1. BACKGROUND AND OVERVIEW

1.1. Background

While combination antiretroviral (ARV) therapy (ART) for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality previously associated with HIV disease, there remains a significant medical need for new, well-tolerated therapies that take into consideration HIV genetic variability, ARV resistance, new options for regimen simplification, as well as the desires of people with HIV (PWH) for alternative, longer-acting options. Some treatment-experienced PWH eventually lose the virologic, immunologic, or clinical benefit from their current regimens. People with HIV who have multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {British HIV Association 2016, European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019, Saag 2020, U. S. Department of Health and Human Services 2015}. Developing safe and effective therapies for heavily treatment-experienced (HTE) PWH with multidrug-resistant HIV remains a priority. For these individuals, newer treatments are needed to control viral replication, preserve immune function, and prevent clinical progression.

Lenacapavir (LEN; GS-6207) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function, which is being developed for the treatment and prevention of HIV-1 infection. Lenacapavir inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

This addendum provides additional efficacy data from the interim analyses of the following studies:

- The primary study, Study GS-US-200-4625 (a Phase 2/3 study in HTE PWH with multidrug resistance) which was conducted after participants in Cohort 1 had completed the Week 52 visit or had prematurely discontinued the study drug and all participants in Cohort 2 had completed their Week 26 visit or had prematurely discontinued the study drug.

- Study GS-US-200-4334 (a Phase 2 study in treatment-naive PWH) which was conducted after all participants had completed the Week 54 visit or had prematurely discontinued the study drug.

1.2. Overview of Clinical Efficacy

1.2.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

The proposed indication for LEN is primarily based on data from a Phase 2/3 study in HTE PWH with multidrug resistance (Study GS-US-200-4625). Information on the study design and population for this study is presented in Table 1.

Results for the primary efficacy end point and secondary end points from the interim Week 26 analysis are described in GS-US-200-4625 Interim Week 26 clinical study report (CSR), Section 9 and in m2.7.3, Section 3.2.1 of the parent m2.7.3 document.

Secondary efficacy end points summarized in this document include the proportions of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 52 using the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm.

Other efficacy end points include the proportions of participants in Cohort 2 with HIV-1 RNA < 50 and < 200 copies/mL at Weeks 26 and 52 (US FDA-defined snapshot algorithm), changes from baseline in HIV-1 RNA and CD4 cell count by visit, and the proportion of participants with HIV-1 RNA < 50 copies/mL by visit using imputation methods (missing = failure [M = F] and missing = excluded [M = E]).

This summary document provides efficacy data from the interim analysis of Cohorts 1 and 2 in Study GS-US-200-4625, which was conducted after all participants in Cohort 1 had completed the Week 52 visit (ie, 52 weeks after the first dose of subcutaneous [SC] LEN injection) or had prematurely discontinued study drug. Statistical methods are described in the statistical analysis plan (GS-US-200-4625 Interim Week 52 CSR addendum, Appendix 16.1.9).

Table 1. Overview of the Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented	Location of Study Narrative and CSR
GS-US-200-4625	Phase 2/3, randomized, placebo-controlled, multicenter study	HTE PWH	**Cohort 1 (N = 36):** ***Cohort 1A (N = 24):*** • Functional Monotherapy Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + failing regimen • Maintenance Period: SC LEN injection 927 mg on Day 1 SC[c] and every 6 months	Efficacy, PK[d], and safety	Section 2.1 GS-US-200-4625 Interim Week 52 Addendum

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented	Location of Study Narrative and CSR
			(26 weeks) thereafter + OBR ***Cohort 1B (N = 12):*** • Functional Monotherapy Period: placebo on Days 1, 2, and 8 + failing regimen • Maintenance Period: oral LEN 600 mg on Days 15 and 16 and 300 mg on Day 22 + SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR **Cohort 2 (N = 36):** • Oral Lead-in Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + OBR • Maintenance Period: SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR		

CSR = clinical study report; HTE = heavily treatment experienced; LEN = lenacapavir; OBR = optimized background regimen; PK = pharmacokinetic(s); PWH = people with HIV; SC = subcutaneous

a Participants who were enrolled and received at least 1 dose of study drug.

b Oral LEN 300 and 600 mg were administered as 1 × 300-mg tablet and 2 × 300-mg tablets, respectively, and SC LEN injection 927 mg (309 mg/mL) was administered as 2 × 1.5-mL injections.

c The Day 1 SC visit occurred 14 days after the first dose of oral LEN.

d Results of the PK analyses are not discussed in the text of the CSR addendum.

1.2.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

Supportive efficacy data for LEN are provided from a Phase 2 study in treatment-naive PWH (Study GS-US-200-4334). Information on the study design and population for this study is presented in Table 2.

Results for secondary end points from the interim Week 28 analysis are described in the GS-US-200-4334 Interim Week 28 CSR, Section 9 and in m2.7.3, Section 3.2.2 of the parent m2.7.3 document.

The primary efficacy end point for Study GS-US-200-4334 (proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the US FDA-defined snapshot algorithm) is summarized in this document.

Secondary efficacy end points summarized in this document include the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 38 and 54 (US FDA-defined snapshot algorithm) and changes from baseline in HIV-1 RNA and CD4 cell count at Weeks 38 and 54. Additionally, the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 using imputation methods (M = F and M = E) is presented.

This summary document provides efficacy data from the interim analysis of Study GS-US-200-4334, which was conducted after all participants had completed the Week 54 visit or had prematurely discontinued study drug. Statistical methods are described in the statistical analysis plan (GS-US-200-4334 Interim Week 54 CSR addendum, Appendix 16.1.9).

Table 2. Overview of Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented	Location of Study Narrative and CSR
GS-US-200-4334	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment-naive PWH	**Treatment Group 1 (SC LEN + [DVY → TAF]) (N = 52):** • Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[c] + SC LEN injection 927 mg on Day 15 • Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months	Efficacy, PK[d], and safety	Section 2.2 GS-US-200-4334 Interim Week 54 Addendum

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented	Location of Study Narrative and CSR
			(26 weeks) thereafter + oral daily TAF 25 mg[c] **Treatment Group 2 (SC LEN + [DVY → BIC]) (N = 53):** • Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[c] + SC LEN injection 927 mg on Day 15 • Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months (26 weeks) thereafter + oral daily BIC 75 mg[c] **Treatment Group 3 (Oral LEN + DVY) (N = 52):** oral LEN 600 mg on Days 1 and 2 and oral daily LEN 50 mg from Day 3 onwards + oral daily DVY (F/TAF 200/25 mg) **Treatment Group 4 (BVY) (N = 25):** oral daily BVY (B/F/TAF 50/200/25 mg)		

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); CSR = clinical study report; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; PK = pharmacokinetic(s); PWH = people with HIV; SC = subcutaneous; TAF = tenofovir alafenamide

a Participants who were randomized and received at least 1 dose of study drug.

b Oral LEN 50, 300, and 600 mg were administered as 1 × 50-mg tablet, 1 × 300-mg tablet, and 2 × 300-mg tablets, respectively, and SC LEN injection 927 mg (309 mg/mL) was administered as 2 × 1.5-mL injections.

c Participants in Treatment Groups 1 or 2 with HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 discontinued DVY at Week 28 and initiated oral daily TAF or BIC, respectively; those with values ≥ 50 copies/mL discontinued study drug at or prior to Week 28.

d Results of the PK analyses are not discussed in the text of the CSR addendum.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Complete study descriptions and results for Studies GS-US-200-4625 and GS-US-200-4334 are available in the individual CSR addenda. Narratives of these studies are presented in the following sections.

2.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

Location:	GS-US-200-4625 Interim Week 52 Addendum
Title:	A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination With an Optimized Background Regimen in Heavily Treatment-Experienced People Living With HIV-1 Infection With Multidrug Resistance
Study Objectives:	The primary objective of this study is as follows: • To evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for PWH with multidrug resistance The secondary objective of this study is as follows: • To evaluate the safety and efficacy of LEN in combination with an optimized background regimen (OBR) at Weeks 26 and 52
Study Design and Participant Population:	This is an ongoing Phase 2/3, randomized, placebo-controlled, multicenter study evaluating the safety and efficacy of LEN in combination with an OBR in HTE PWH with multidrug resistance. Participants who met all eligibility criteria returned to the clinic between 14 and 30 days after the screening visit for a cohort-selection visit. Eligible participants who had both a decline in HIV-1 RNA of < 0.5 $\log_{10}$ copies/mL compared with the screening visit and HIV-1 RNA ≥ 400 copies/mL at the cohort-selection visit were randomized in a blinded fashion and in a 2:1 ratio to receive either oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 (Cohort 1A) or placebo (Cohort 1B) during the Functional Monotherapy Period while they continued their failing regimen. After each participant completed the Functional Monotherapy Period, the participant's treatment assignment was unblinded. During the Maintenance Period, participants in Cohort 1A received SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) and initiated their OBR on Day 1 SC (ie, 14 days after the first dose of oral LEN). Participants in Cohort 1B received oral LEN 600 mg (2 × 300-mg tablets) on Days 15 and 16 and 300 mg (1 × 300-mg tablet) on Day 22 and initiated their OBR on Day 15; they received SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 1 SC (ie, 14 days after the first dose of oral LEN) while continuing their OBR. Eligible participants were enrolled into Cohort 2 if Cohort 1 was fully enrolled or if they did not meet the criteria for randomization into Cohort 1, possibly due to improved adherence after the screening visit. During the Oral Lead-in Period, all participants in Cohort 2 received oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 and initiated their OBR on Day 1. During the Maintenance Period, participants received SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 1 SC (ie, 14 days after the first dose of oral LEN) and continued their OBR. Participants in Cohorts 1 and 2 received their subsequent SC LEN injection at the Week 26 visit. At the Week 52 visit, participants in both cohorts are given the option to receive SC LEN injection and continue in the study to receive SC LEN injection every 6 months (26 weeks) while continuing their OBR, until the product becomes accessible to participants through an access program or until Gilead Sciences (Gilead) elects to discontinue the study in the country. Both the oral LEN tablets and SC LEN injections were administered without regard to food. Eligible participants were HTE PWH aged ≥ 18 years (all sites) or aged ≥ 12 years and weighing ≥ 35 kg (sites in North America and Dominican Republic) who were receiving a stable failing regimen for > 8 weeks before screening and were willing to continue that regimen until Day 1 (or until Day 14 for participants in Cohort 1); had plasma HIV-1 RNA ≥ 400 copies/mL at screening; had resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications (nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, or integrase

	strand-transfer inhibitors [INSTIs]); and had ≤ 2 fully active ARV medications remaining from the 4 main classes that could be effectively combined to form a viable regimen in the opinion of the investigator based on resistance, tolerability, contraindication, safety, drug access, or acceptability to the participant. The CSR addendum describes the interim analysis at Week 52, which was conducted after all participants in Cohort 1 completed the Week 52 visit (ie, 52 weeks after the first dose of SC LEN) or had prematurely discontinued the study drug, and after all participants in Cohort 2 completed the Week 26 visit (ie, 26 weeks after the first dose of SC LEN) or had prematurely discontinued the study drug. Overall in Cohorts 1 and 2, 72 participants were enrolled in the study and were included in the Safety Analysis Set (Cohort 1: LEN, 24 participants; placebo, 12 participants; Cohort 2: LEN + OBR, 36 participants). All 72 participants completed the Functional Monotherapy (Cohort 1: 36 participants) or Oral Lead-in Period (Cohort 2: 36 participants), and all received Day 1 SC LEN. Of the 72 participants who received Day 1 SC LEN, 32 participants (all from Cohort 2) are continuing the study drug in the Main Phase, and 37 participants completed study drug in the Main Phase (Week 52). Three participants discontinued study drug during the Main Phase. Reasons for premature discontinuation were lost to follow-up, investigator's discretion, and death (1 participant each, 1.4%). One participant who decided not to receive SC LEN at Week 52 and not to continue the study completed the study at the Week 52 visit. Thirty-six participants entered into the Extension Phase (Cohort 1: 34 participants; Cohort 2: 2 participants). Of the 36 participants who entered the Extension Phase, 34 participants are continuing the study drug. Two participants discontinued study drug during the Extension Phase. Reasons for premature discontinuation were adverse event (AE) and lost to follow-up (1 participant each, 2.8%).
Summary of Results and Conclusions:	• Consistent with the data reported in the Study GS-US-200-4625 Interim Week 26 CSR, high rates of virologic suppression continued to be maintained through Week 52. • The percentages of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 52 using the US FDA-defined snapshot algorithm were 83.3% (30 of 36 participants) and 86.1% (31 of 36 participants), respectively. • At Week 26, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 80.6% (58 of 72 participants) and 87.5% (63 of 72 participants), respectively. At Week 52, The percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 77.8% (35 of 45 participants) and 82.2% (37 of 45 participants), respectively. • The results were consistent even in participants who had suboptimal baseline OBR (eg, low overall susceptibility score, no or 1 fully active agent, INSTI resistance, no dolutegravir or darunavir), demonstrating a clinically meaningful contribution of LEN towards virologic suppression. • Consistent with the data reported in the Study GS-US-200-4625 Interim Week 26 CSR, there were clinically meaningful increases in CD4 cell count from baseline to Week 52. • LEN remained generally safe and well tolerated. No participant experienced a study drug-related serious adverse reaction. The majority of injection site reactions were Grade 1 or 2 in severity. One participant discontinued LEN at Week 52 (after the Week 26 interim analysis) due to an AE of Grade 1 injection site nodule.

2.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

Location:	GS-US-200-4334 Interim Week 54 Addendum
Title:	A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination With Other Antiretroviral Agents in People Living With HIV
Study Objectives:	The primary objective of this study is as follows: • To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 The secondary objectives of this study are as follows: • To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 • To evaluate the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4 cell count at Weeks 28, 38, 54, and 80 • To evaluate the safety and tolerability of the LEN-containing regimens through 28, 38, 54, and 80 weeks of treatment • To evaluate the pharmacokinetics of LEN, bictegravir (BIC; GS-9883), and tenofovir alafenamide (TAF)
Study Design and Participant Population:	This is an ongoing Phase 2, randomized, open-label, active-controlled, multicenter study evaluating the safety and efficacy of LEN in combination with other ARV agents in treatment-naive PWH. Participants who met all eligibility criteria were randomized in a 2:2:2:1 ratio to 1 of the 4 treatment groups below. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

Treatment Group	Time Period	Study Treatments
1	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 • Oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15
	Maintenance (Weeks 28 through 80)	• SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily TAF 25 mg[a]
2	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 • Oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15
	Maintenance (Weeks 28 through 80)	• SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily BIC 75 mg[a]
3	Day 1 through Week 80	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and oral daily LEN 50 mg (1 × 50-mg tablet) from Day 3 onwards • Oral daily DVY (F/TAF 200/25 mg)
4	Day 1 through Week 80	• Oral daily BVY (B/F/TAF 50/200/25 mg)

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir;
BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy);

	DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide a Participants in Treatment Groups 1 or 2 with HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 discontinued DVY at Week 28 and initiated oral daily TAF or BIC, respectively; those with values ≥ 50 copies/mL discontinued study drug at or prior to Week 28. All study drugs were administered without regard to food.
	At Week 80, participants in Treatment Group 4 will complete the study. Participants willing to continue the study beyond Week 80 in Treatment Groups 1 to 3 will continue to receive SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) every 6 months (26 weeks) (Treatment Groups 1 and 2) or oral daily LEN 50 mg (Treatment Group 3) from Week 80 until the product becomes accessible to participants through an access program or until Gilead elects to discontinue the study in the country. Participants in Treatment Groups 1 to 3 will also receive TAF, BIC, or emtricitabine/tenofovir alafenamide (coformulated; Descovy®; DVY), as applicable. Eligible participants were ARV-naive (no use of any ARV within 1 month of screening) PWH aged ≥ 18 years who had plasma HIV-1 RNA ≥ 200 copies/mL and CD4 cell count ≥ 200 cells/µL at screening. Eligible participants were ARV-naive (no use of any ARV within 1 month of screening) PWH aged ≥ 18 years who had plasma HIV-1 RNA ≥ 200 copies/mL and CD4 cell count ≥ 200 cells/µL at screening. The CSR addendum describes the interim analysis at Week 54, including the primary efficacy end point, which was conducted after all participants completed their Week 54 visit or had prematurely discontinued the study drug. Of the 249 participants screened, 183 were randomized, and 182 received at least 1 dose of study drug. Of these 182 participants, 22 participants (12.1%) prematurely discontinued the study drug during the Main Phase (ie, data collected on or before Week 80): 17 of 105 participants (16.2%) in the SC LEN total group, 4 of 52 participants (7.7%) in the oral LEN group, and 1 of 25 participants (4.0%) in the bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®; BVY) group. The reasons for premature study drug discontinuation in the SC LEN total group were participant decision and lost to follow-up (each 4 participants [3.8%]), investigator's discretion, lack of efficacy, and AE (each 3 participants [2.9%]). The reasons for premature study drug discontinuation in the oral LEN group were lost to follow-up (3 participants [5.8%]) and participant decision (1 participant [1.9%]) and in the BVY group it was participant decision (1 participant [4.0%]).
Summary of Results and Conclusions:	• High rates of virologic suppression continued to be maintained through Week 54. For the primary efficacy end point, overall, 136 of 157 participants (86.6%) who received SC or oral LEN and 23 of 25 participants (92.0%) who received BVY had HIV-1 RNA < 50 copies/mL at Week 54. • For participants with HIV-1 RNA < 50 copies/mL at Week 28, high rates of virologic suppression continued to be maintained through Week 54. Overall, 135 of 147 participants (91.8%) who received SC or oral LEN and 23 of 25 participants (92.0%) who received BVY had HIV-1 RNA < 50 copies/mL at Week 54. • Subcutaneously and orally administered LEN remained generally safe and well tolerated. Similar percentages of participants in the LEN total (total of 157 participants) and BVY (total of 25 participants) groups had any AE by Week 54 (LEN total 87.9%, 138 participants; BVY 84.0%, 21 participants).

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Study Populations

Participant disposition, and analysis populations are presented by study for Studies GS-US-200-4625 and GS-US-200-4334. Detailed results, including demographic and other baseline characteristics are presented in the individual CSRs (GS-US-200-4625 Interim Week 26 CSR, Section 8; GS-US-200-4334 Interim Week 28 CSR, Section 8).

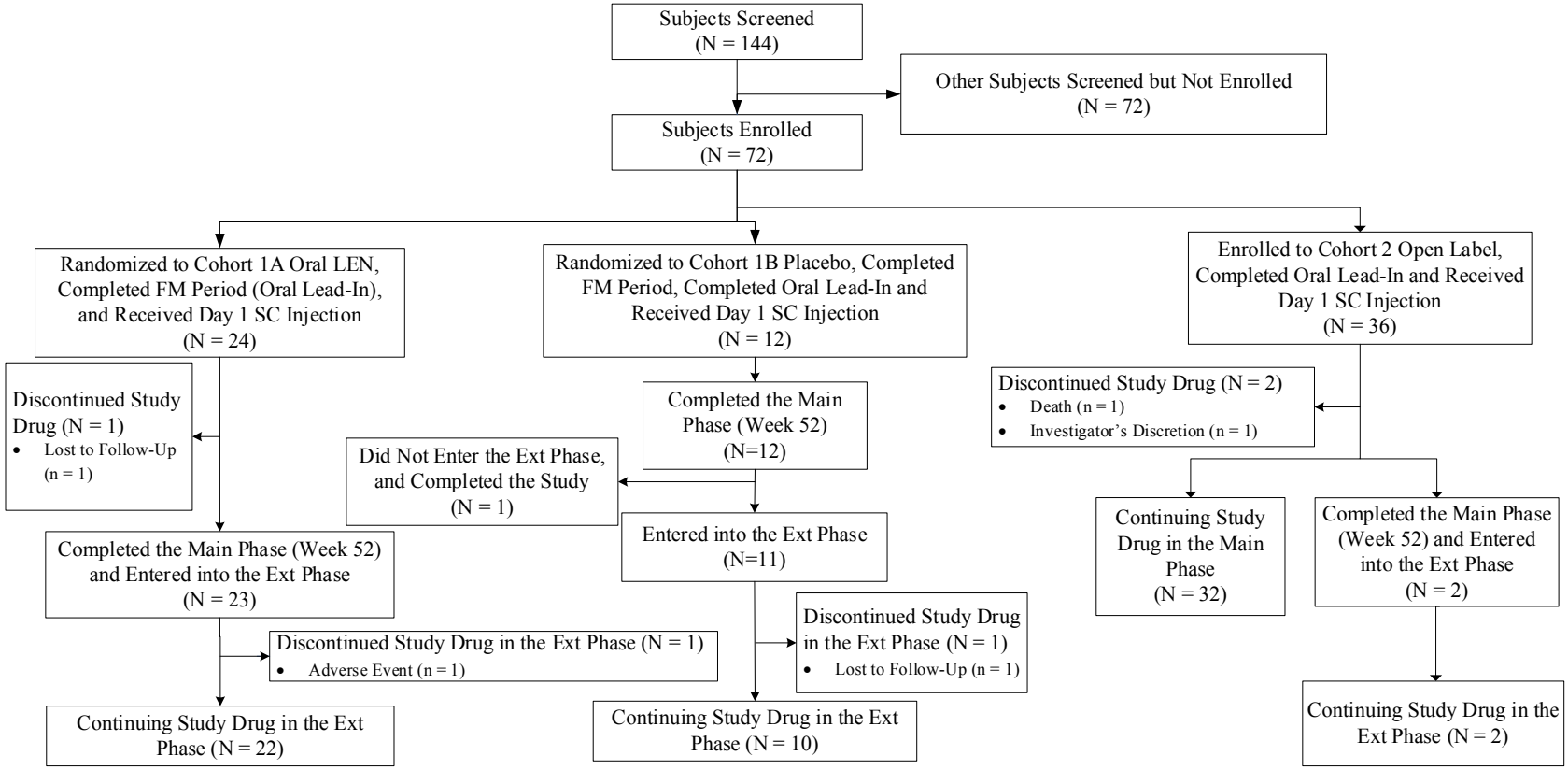
3.1.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

3.1.1.1. Participant Disposition

Overall in Cohorts 1 and 2, 72 participants were enrolled in the study and were included in the Safety Analysis Set (Cohort 1: LEN, 24 participants; placebo, 12 participants; Cohort 2: LEN + OBR, 36 participants). All 72 participants completed the Functional Monotherapy (Cohort 1: 36 participants) or Oral Lead-in Period (Cohort 2: 36 participants), and all received Day 1 SC LEN.

Of the 72 participants who received Day 1 SC LEN, 32 participants (all from Cohort 2) are continuing study drug in the Main Phase, and 37 participants completed study drug in the Main Phase (Week 52). Three participants discontinued study drug during the Main Phase. Reasons for premature discontinuation were lost to follow-up, investigator's discretion, and death (1 participant each, 1.4%). One participant who decided not to receive SC LEN at Week 52 and not to continue the study completed the study at the Week 52 visit. Thirty-six participants entered into the Extension Phase (Cohort 1: 34 participants; Cohort 2: 2 participants). Of the 36 participants who entered the Extension Phase, 34 participants are continuing study drug. Two participants discontinued study drug during the Extension Phase. Reasons for premature discontinuation were AE and lost to follow-up (1 participant each, 2.8%). Disposition of participants is presented in Figure 1 and Table 3.

Figure 1. GS-US-200-4625: Disposition of Participants (All Screened Participants)



CRF = case report form; Ext = extension; FM = Functional Monotherapy; LEN = lenacapavir; SC = subcutaneous
"Main Phase" is defined as data collected through Week 52 (52 weeks from the first dose of SC LEN).
Included CRF data collected up to [redacted] 20[redacted].
One subject in Cohort 1 Placebo group who completed Week 52 visit, and decided not to receive study drug at the visit and not to enter the Extension Phase were counted as completing the Main Phase, and completing the study.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Figure 15.8.1

Table 3. GS-US-200-4625: Disposition of Participants (All Screened Participants)

	Cohort 1				
	LEN	Placebo	Total	Cohort 2	Total
Screened	—	—	—	—	144
Met All Eligibility Criteria but Not Enrolled	—	—	—	—	0
All Enrolled	24	12	36	36	72
Safety Analysis Set	24	12	36	36	72
Study Drug Disposition in Main Phase					
Oral Lead-In Before the First SC Injection					
Completed Study Drug	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Continuing Study Drug	0	0	0	0	0
Prematurely Discontinued Study Drug	0	0	0	0	0
After the First SC Injection (From the First SC Injection Through Week 52 Visit)					
Received Day 1 SC Injection	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Continuing Study Drug	0	0	0	32 (88.9%)	32 (44.4%)
Completed Study Drug	23 (95.8%)	12 (100.0%)	35 (97.2%)	2 (5.6%)	37 (51.4%)
Prematurely Discontinued Study Drug	1 (4.2%)	0	1 (2.8%)	2 (5.6%)	3 (4.2%)
Reason for Prematurely Discontinued Study Drug					
Death	0	0	0	1 (2.8%)	1 (1.4%)
Investigator's Discretion	0	0	0	1 (2.8%)	1 (1.4%)
Lost to Follow-Up	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
Study Drug Disposition in the Extension Phase					
Treated in the Extension Phase	23	11	34	2	36
Continuing Study Drug	22 (95.7%)	10 (90.9%)	32 (94.1%)	2 (100.0%)	34 (94.4%)
Completed Study Drug	0	0	0	0	0

	Cohort 1			Cohort 2	Total
	LEN	Placebo	Total		
Prematurely Discontinued Study Drug	1 (4.3%)	1 (9.1%)	2 (5.9%)	0	2 (5.6%)
Reason for Prematurely Discontinued Study Drug					
Adverse Event	1 (4.3%)	0	1 (2.9%)	0	1 (2.8%)
Lost to Follow-Up	0	1 (9.1%)	1 (2.9%)	0	1 (2.8%)
Study Disposition Throughout the Study					
Continuing Study	22 (91.7%)	10 (83.3%)	32 (88.9%)	34 (94.4%)	66 (91.7%)
Completed Study	0	1 (8.3%)	1 (2.8%)	0	1 (1.4%)
Prematurely Discontinued Study	2 (8.3%)	1 (8.3%)	3 (8.3%)	2 (5.6%)	5 (6.9%)
Reason for Premature Discontinuation					
Adverse Event	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
Death	0	0	0	1 (2.8%)	1 (1.4%)
Investigator's Discretion	0	0	0	1 (2.8%)	1 (1.4%)
Lost to Follow-Up	1 (4.2%)	1 (8.3%)	2 (5.6%)	0	2 (2.8%)

CRF = case report form; LEN = lenacapavir; SC = subcutaneous
"Main Phase" is defined as data collected through Week 52 (including the oral lead-in). Week 52 is defined as 52 weeks from the first dose of SC LEN.
Percentages for study drug disposition and study disposition were calculated based on the number of participants in the Safety Analysis Set.
Percentages for disposition status for the Extension Phase were calculated based on the number of participants treated in the Extension Phase.
Included CRF data collected up to [redacted]20[redacted].
One subject in Cohort 1 Placebo group who completed Week 52 visit, and decided not to receive study drug at the visit and not to enter the Extension Phase were counted as completing the Main Phase, and completing the study.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.8.1.3.1

3.1.1.2. Demographic and Other Baseline Characteristics

Demographic and baseline disease characteristics for Cohort 1 and Cohort 2 are described in the GS-US-200-4625 Interim Week 26 CSR and in m2.7.3, Section 3.1.1.2 of the parent m2.7.3 document.

3.1.1.3. Analysis Populations

For Cohorts 1 and 2, 72 participants received at least 1 dose of LEN (ie, blinded or open-label LEN) and are included in the Full Analysis Set (FAS) and Safety Analysis Set for the All LEN Analysis (Table 4).

Table 4. GS-US-200-4625: Analysis Sets at Week 52 (All Enrolled Analysis Set)

Analysis Set	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)		
All Enrolled Analysis Set	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Full Analysis Set for the All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Safety Analysis Set for the All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
PK Analysis Set	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)

LEN = lenacapavir; PK = pharmacokinetic(s)
Denominator for percentages was the All Enrolled Analysis Set.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.8.5

3.1.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

3.1.2.1. Participant Disposition

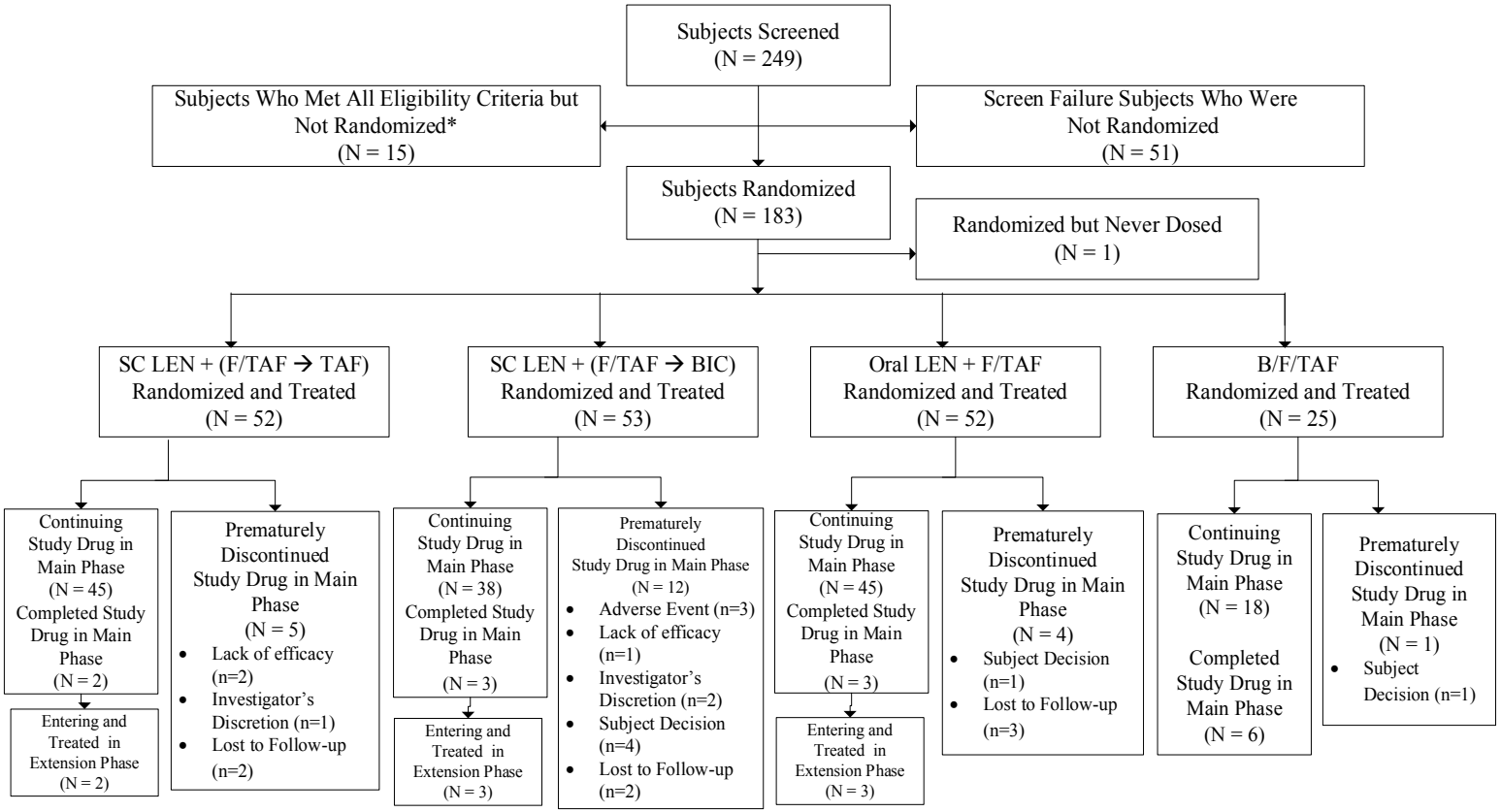
Of the 249 participants screened, 183 were randomized, and 182 received at least 1 dose of study drug (Figure 2 and Table 5). Of these 182 participants, 22 participants (12.1%) prematurely discontinued the study drug during the Main Phase (ie, data collected on or before Week 80): 17 of 105 participants (16.2%) in the SC LEN total group, 4 of 52 participants (7.7%) in the oral LEN group, and 1 of 25 participants (4.0%) in the BVY group.

The reasons for premature study drug discontinuation in the SC LEN total group were participant decision and lost to follow-up (each 4 participants [3.8%]), investigator's discretion, lack of efficacy, and AE (each 3 participants [2.9%]). The reasons for premature study drug discontinuation in the oral LEN group were lost to follow-up (3 participants [5.8%]) and participant decision (1 participant [1.9%]) and in the BVY group it was participant decision (1 participant [4.0%]).

None of these discontinuations affected the overall quality or interpretation of the study data.

As of the Week 54 data cut date, 8 participants entered into the Extension Phase (SC LEN total group, 5 participants; oral LEN group, 3 participants) and were continuing receiving study drug.

Figure 2. GS-US-200-4334: Participant Disposition (All Screened Participants)



BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide
Included case report form data collected up to [redacted]20[redacted]
*Among 15 participants who met all eligibility criteria but not randomized, the reasons (n) were: investigator's discretion (1); withdrew consent (9); lost to follow-up (3); and outside of visit window (1). One participant is not screen failure (missed 2 criteria but met all other criteria) and not enrolled due to lost to follow-up.
Screen failure participants are the participants who did not meet all eligibility criteria.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.8.1

Table 5. GS-US-200-4334: Disposition of Participants (All Screened Analysis Set)

	SC LEN + (DVY -> TAF)	SC LEN + (DVY -> BIC)	Oral LEN + DVY	BVY	SC LEN Total	LEN Total	Total
Subjects Screened							249
Subjects Met All Eligibility Criteria and Not Randomized							15
Adverse Event							0
Investigator's Discretion							1
Withdrew Consent							9
Lost to Follow-Up							3
Outside of Visit Window							1
Study Enrollment Closed							0
Other							0
All Randomized but Never Dosed	0	0	0	1	0	0	1
All Randomized Analysis Set	52	53	52	26	105	157	183
Safety Analysis Set	52	53	52	25	105	157	182
Week 54 Per-Protocol (PP) Analysis Set	47	46	47	22	93	140	162
Study Drug Completion Status in Main Phase							
Continuing Study Drug	45 (86.5%)	38 (71.7%)	45 (86.5%)	18 (72.0%)	83 (79.0%)	128 (81.5%)	146 (80.2%)
Completed Study Drug	2 (3.8%)	3 (5.7%)	3 (5.8%)	6 (24.0%)	5 (4.8%)	8 (5.1%)	14 (7.7%)
Prematurely Discontinued Study Drug	5 (9.6%)	12 (22.6%)	4 (7.7%)	1 (4.0%)	17 (16.2%)	21 (13.4%)	22 (12.1%)
Reason for Premature Discontinuation of Study Drug in Main Phase							
Adverse Event	0	3 (5.7%)	0	0	3 (2.9%)	3 (1.9%)	3 (1.6%)
Death	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Lack of Efficacy	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)	3 (1.6%)
Investigator's Discretion	1 (1.9%)	2 (3.8%)	0	0	3 (2.9%)	3 (1.9%)	3 (1.6%)
Non-Compliance with Study Drug	0	0	0	0	0	0	0
Protocol Violation	0	0	0	0	0	0	0
Subject Decision	0	4 (7.5%)	1 (1.9%)	1 (4.0%)	4 (3.8%)	5 (3.2%)	6 (3.3%)
Lost to Follow-Up	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)	7 (3.8%)

	SC LEN + (DVY -> TAF)	SC LEN + (DVY -> BIC)	Oral LEN + DVY	BVY	SC LEN Total	LEN Total	Total
Study Terminated by Sponsor	0	0	0	0	0	0	0
Entering and treated in the extension phase	2	3	3	0	5	8	8
Study Drug Completion Status in Extension Phase							
Continuing Study Drug	2 (100.0%)	3 (100.0%)	3 (100.0%)	0	5 (100.0%)	8 (100.0%)	8 (100.0%)
Completed Study Drug	0	0	0	0	0	0	0
Prematurely Discontinued Study Drug	0	0	0	0	0	0	0
Study Completion Status							
Continuing Study	48 (92.3%)	42 (79.2%)	48 (92.3%)	18 (72.0%)	90 (85.7%)	138 (87.9%)	156 (85.7%)
Completed Study	1 (1.9%)	0	0	6 (24.0%)	1 (1.0%)	1 (0.6%)	7 (3.8%)
Prematurely Discontinued Study	3 (5.8%)	11 (20.8%)	4 (7.7%)	1 (4.0%)	14 (13.3%)	18 (11.5%)	19 (10.4%)
Reason for Premature Discontinuation of Study							
Adverse Event	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0
Lack of Efficacy	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)	1 (0.5%)
Investigator's Discretion	1 (1.9%)	2 (3.8%)	0	0	3 (2.9%)	3 (1.9%)	3 (1.6%)
Non-Compliance with Study Drug	0	0	0	0	0	0	0
Protocol Violation	0	0	0	0	0	0	0
Withdrew Consent	0	6 (11.3%)	1 (1.9%)	1 (4.0%)	6 (5.7%)	7 (4.5%)	8 (4.4%)
Lost to Follow-Up	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)	7 (3.8%)
Study Terminated by Sponsor	0	0	0	0	0	0	0

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); CRF = case report form; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide
The denominator for percentages is based on the number of participants in the Safety Analysis Set except the categories in the Extension Phase.
The denominator for percentages in the Extension Phase is the number of participants treated in Extension Phase.
Included CRF data collected up to [redacted]20[redacted].
One participant is not screen failure (missed 2 criteria but met all other criteria) and not enrolled due to lost to follow-up.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.8.1.3

3.1.2.2. Demographic and Other Baseline Characteristics

Demographics, general baseline characteristics, and baseline disease characteristics are described in the GS-US-200-4334 Interim Week 28 CSR.and in m2.7.3, Section 3.1.2.2 of the parent m2.7.3 document.

3.1.2.3. Analysis Populations

Overall, 183 participants were randomized and included in the All Randomized Analysis Set and a total of 182 participants received at least 1 dose of the study drug and were included in both the FAS and Safety Analysis Set (Table 6). A total of 162 participants were included in the Per-Protocol Analysis Set.

Table 6. GS-US-200-4334: Analysis Sets (All Randomized Analysis Set)

Analysis set	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 26)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 183)
All Randomized Analysis Set	52	53	52	26	105	157	183
Safety Analysis Set	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (96.2%)	105 (100.0%)	157 (100.0%)	182 (99.5%)
Full Analysis Set	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (96.2%)	105 (100.0%)	157 (100.0%)	182 (99.5%)
Participants in Week 54 Per-Protocol (PP) Analysis Set	47 (90.4%)	46 (86.8%)	47 (90.4%)	22 (84.6%)	93 (88.6%)	140 (89.2%)	162 (88.5%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; PP = per-protocol; SC = subcutaneous; TAF = tenofovir alafenamide
The denominator for percentage is the number of participants in the All Randomized Analysis Set.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.8.5.

3.2. Comparison of Efficacy Results of All Studies

Given the difference in study populations, efficacy results are summarized by study for Studies GS-US-200-4625 and GS-US-200-4334. Detailed efficacy results are presented in the individual CSRs (GS-US-200-4625 Interim Week 52 CSR Addendum, Section 9; GS-US-200-4334 Interim Week 54 CSR Addendum, Section 9).

3.2.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

3.2.1.1. Primary Efficacy End Point: Reduction in HIV-1 RNA of ≥ 0.5 log_{10} copies/mL From Baseline

Results for the primary efficacy end point from the interim Week 26 analysis are described in GS-US-200-4625 Interim Week 26 CSR, Section 9 and in m2.7.3, Section 3.2.1 of the parent m2.7.3 document.

3.2.1.2. Secondary Efficacy End Point

3.2.1.2.1. HIV-1 RNA < 50 and < 200 copies/mL at Week 52 in Cohort 1 (US FDA-Defined Snapshot Algorithm)

Results for the secondary efficacy end point for Cohort 1 at Week 26 are described in the GS-US-200-4625 Interim Week 26 CSR. and in m2.7.3, Section 3.2.1 of the parent m2.7.3 document.

The percentages of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 52 using the US) FDA-defined snapshot algorithm were 83.3% (30 of 36 participants) and 86.1% (31 of 36 participants), respectively (Table 7).

Table 7. GS-US-200-4625: The Proportion of Participants With HIV-1 RNA < 50 and < 200 copies/mL at Week 52 Using the US FDA-Defined Snapshot Algorithm – All LEN Analysis (Full Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 9)	Total (N = 45)
Using HIV-1 RNA Cutoff at 50 copies/mL					
HIV-1 RNA < 50 copies/mL	21 (87.5%)	9 (75.0%)	30 (83.3%)	5 (55.6%)	35 (77.8%)
95% CI	67.6% to 97.3%	42.8% to 94.5%	67.2% to 93.6%	21.2% to 86.3%	62.9% to 88.8%
HIV-1 RNA ≥ 50 copies/mL	2 (8.3%)	3 (25.0%)	5 (13.9%)	3 (33.3%)	8 (17.8%)
HIV-1 RNA ≥ 50 copies/mL in Week 52 Window	2 (8.3%)	3 (25.0%)	5 (13.9%)	2 (22.2%)	7 (15.6%)
Discontinued Study Drug Due To Lack of Efficacy	0	0	0	0	0

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 9)	Total (N = 45)
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA ≥ 50 copies/mL	0	0	0	1 (11.1%)	1 (2.2%)
No Virologic Data in Week 52 Window	1 (4.2%)	0	1 (2.8%)	1 (11.1%)	2 (4.4%)
Discontinued Study Drug Due To AE/Death	0	0	0	1 (11.1%)	1 (2.2%)
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL	1 (4.2%)	0	1 (2.8%)	0	1 (2.2%)
Missing Data During Window But on Study Drug	0	0	0	0	0
Using HIV-1 RNA Cutoff at 200 copies/mL					
HIV-1 RNA < 200 copies/mL	22 (91.7%)	9 (75.0%)	31 (86.1%)	6 (66.7%)	37 (82.2%)
95% CI	73.0% to 99.0%	42.8% to 94.5%	70.5% to 95.3%	29.9% to 92.5%	67.9% to 92.0%
HIV-1 RNA ≥ 200 copies/mL	1 (4.2%)	3 (25.0%)	4 (11.1%)	2 (22.2%)	6 (13.3%)
HIV-1 RNA ≥ 200 copies/mL in Week 52 Window	1 (4.2%)	3 (25.0%)	4 (11.1%)	1 (11.1%)	5 (11.1%)
Discontinued Study Drug Due To Lack of Efficacy	0	0	0	0	0
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA ≥ 200 copies/mL	0	0	0	1 (11.1%)	1 (2.2%)
No Virologic Data in Week 52 Window	1 (4.2%)	0	1 (2.8%)	1 (11.1%)	2 (4.4%)
Discontinued Study Drug Due To AE/Death	0	0	0	1 (11.1%)	1 (2.2%)
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA < 200 copies/mL	1 (4.2%)	0	1 (2.8%)	0	1 (2.2%)
Missing Data During Window But on Study Drug	0	0	0	0	0

AE = adverse event; LEN = lenacapavir

a Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

Cohort 2 ongoing subjects who have missing HIV-1 RNA at Week 52 and have not reached the upper limit of the analysis window for Week 52 are excluded.

The Week 52 window is between Days 324 and 414 (inclusive).

Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the last subcutaneous LEN, was used in this analysis.

The 95% CIs of the percentages of participants with HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Week 52 were calculated based on the Exact method.

Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Tables 15.9.2.2.1 and 15.9.2.2.2

3.2.1.3. Other Efficacy Analyses

Generally, efficacy results reported for Cohort 2 at Week 26 were similar to those reported for Cohort 1 in the Week 26 Interim CSR. Therefore, efficacy results are presented for participants in Cohorts 1 and 2 at both Week 26 and Week 52.

3.2.1.3.1. HIV-1 RNA < 50 and < 200 copies/mL at Week 26 and Week 52

At Week 26, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 80.6% (58 of 72 participants) and 87.5% (63 of 72 participants), respectively (Table 8).

At Week 52, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 77.8% (35 of 45 participants) and 82.2% (37 of 45 participants), respectively (Table 7).

Note that a total of 9 participants in Cohort 2 were included in the Week 52 snapshot analysis (Table 7). However, the study drug disposition (Figure 1 and Table 3) shows 2 participants in Cohort 2 completed the Week 52 visit. Among the 7 additional participants included in the Week 52 snapshot outcome, 4 participants received Week 52 HIV-1 RNA test results after the electronic case report form data cut date ([redacted] 20[redacted]) but before the laboratory data cut date ([redacted] 20[redacted]), 1 participant missed Week 52 SC injection (and received it after the Week 52 analysis window), 1 participant discontinued study drug at Week 4 due to investigator's discretion and 1 participant discontinued study drug at Day 90 due to death.

Table 8. GS-US-200-4625: The Proportion of Participants With HIV-1 RNA < 50 and < 200 copies/mL at Week 26 Using the US FDA-Defined Snapshot Algorithm – All LEN Analysis (Full Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Using HIV-1 RNA Cutoff at 50 copies/mL					
HIV-1 RNA < 50 copies/mL	21 (87.5%)	8 (66.7%)	29 (80.6%)	29 (80.6%)	58 (80.6%)
95% CI	67.6% to 97.3%	34.9% to 90.1%	64.0% to 91.8%	64.0% to 91.8%	69.5% to 88.9%
HIV-1 RNA ≥ 50 copies/mL	3 (12.5%)	4 (33.3%)	7 (19.4%)	6 (16.7%)	13 (18.1%)
HIV-1 RNA ≥ 50 copies/mL in Week 26 Window	3 (12.5%)	4 (33.3%)	7 (19.4%)	5 (13.9%)	12 (16.7%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0	0	0
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA ≥ 50 copies/mL	0	0	0	1 (2.8%)	1 (1.4%)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
No Virologic Data in Week 26 Window	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to AE/Death	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL	0	0	0	0	0
Missing Data During Window but on Study Drug	0	0	0	0	0
Using HIV-1 RNA Cutoff at 200 copies/mL					
HIV-1 RNA < 200 copies/mL	23 (95.8%)	9 (75.0%)	32 (88.9%)	31 (86.1%)	63 (87.5%)
95% CI	78.9% to 99.9%	42.8% to 94.5%	73.9% to 96.9%	70.5% to 95.3%	77.6% to 94.1%
HIV-1 RNA ≥ 200 copies/mL	1 (4.2%)	3 (25.0%)	4 (11.1%)	4 (11.1%)	8 (11.1%)
HIV-1 RNA ≥ 200 copies/mL in Week 26 Window	1 (4.2%)	3 (25.0%)	4 (11.1%)	3 (8.3%)	7 (9.7%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0	0	0
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA ≥ 200 copies/mL	0	0	0	1 (2.8%)	1 (1.4%)
No Virologic Data in Week 26 Window	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to AE/Death	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 200 copies/mL	0	0	0	0	0
Missing Data During Window but on Study Drug	0	0	0	0	0

AE = adverse event; LEN = lenacapavir

a Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

The Week 26 window is between Days 184 and 232 (inclusive).

Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the last SC LEN, was used in this analysis.

The 95% CIs of the proportions of subjects with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 were calculated based on the Exact method.

Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Tables 15.9.2.1.1 and 15.9.2.1.2

3.2.1.3.2. Change From Baseline in HIV-1 RNA at Week 26 and Week 52

Mean (SD) baseline HIV-1 RNA values of participants in Cohorts 1 and 2 was 4.12 (1.028) $\log_{10}$ copies/mL. At Week 26, mean (SD) change from baseline in HIV-1 RNA was −2.53 (1.184) $\log_{10}$ copies/mL (Table 9). At Week 52, mean (SD) change from baseline in HIV-1 RNA was −2.50 (1.145) $\log_{10}$ copies/mL (Table 9).

Table 9. GS-US-200-4625: Change From Baseline in HIV-1 RNA by Visit ($\log_{10}$ copies/mL) – All LEN Analysis (Full Analysis Set)

	Cohort 1				
Analysis Set	**LEN (N = 24)**	**Placebo → LEN (N = 12)**	**All LEN (N = 36)**	**Cohort 2 (N = 36)**	**Total (N = 72)**
Baseline					
N	24	12	36	36	72
Mean (SD)	3.97 (0.922)	4.56 (0.712)	4.17 (0.893)	4.07 (1.158)	4.12 (1.028)
95% CI	(3.58 to 4.36)	(4.11 to 5.02)	(3.86 to 4.47)	(3.67 to 4.46)	(3.87 to 4.36)
Median	4.19	4.60	4.46	4.49	4.47
Q1, Q3	3.20, 4.57	4.39, 5.04	3.68, 4.77	3.28, 4.90	3.35, 4.87
Min, Max	2.33, 5.40	2.61, 5.33	2.33, 5.40	1.28, 5.70	1.28, 5.70
Change at Week 26					
N	24	12	36	34	70
Mean (SD)	−2.52 (1.057)	−2.69 (1.042)	−2.58 (1.040)	−2.47 (1.333)	−2.53 (1.184)
95% CI	(−2.97 to −2.07)	(−3.35 to −2.03)	(−2.93 to −2.23)	(−2.94 to −2.01)	(−2.81 to −2.24)
Median	−2.89	−3.08	−2.96	−2.76	−2.91
Q1, Q3	−3.27, −1.92	−3.24, −1.95	−3.27, −1.92	−3.56, −1.48	−3.32, −1.84
Min, Max	−4.06, −0.36	−4.00, −0.70	−4.06, −0.36	−4.43, 0.28	−4.43, 0.28
Change at Week 52					
N	23	12	35	7	42
Mean (SD)	−2.53 (0.972)	−2.63 (1.118)	−2.57 (1.009)	−2.14 (1.734)	−2.50 (1.145)
95% CI	(−2.96 to −2.11)	(−3.34 to −1.92)	(−2.91 to −2.22)	(−3.75 to −0.54)	(−2.85 to −2.14)
Median	−2.87	−3.11	−2.88	−3.13	−2.89
Q1, Q3	−3.28, −1.84	−3.49, −1.30	−3.30, −1.67	−3.50, −0.04	−3.30, −1.53
Min, Max	−3.88, −0.68	−4.00, −1.00	−4.00, −0.68	−3.95, 0.33	−4.00, 0.33

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SD = standard deviation
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.9.3.2

3.2.1.3.3. Change From Baseline in CD4 Cell Count at Week 26 and Week 52

Mean (SD) baseline CD4 cell count value of participants in Cohorts 1 and 2 at baseline was 212 (226.2) cells/µL. At Week 26, mean (SD) change from baseline was 89 (106.7) cells/µL. At Week 52, mean (SD) change from baseline was 94 (121.5) cells/µL (Table 10).

Table 10. GS-US-200-4625: Mean Changes From Baseline in CD4 Cell Counts at Week 26 and 52 – All LEN Analysis (Full Analysis Set)

	Cohort 1				
Analysis Set	**LEN (N = 24)**	**Placebo → LEN (N = 12)**	**All LEN (N = 36)**	**Cohort 2 (N = 36)**	**Total (N = 72)**
Baseline					
N	24	12	36	36	72
Mean (SD)	199 (166.1)	99 (115.9)	166 (157.0)	258 (273.4)	212 (226.2)
95% CI	(129 to 269)	(25 to 173)	(113 to 219)	(165 to 350)	(159 to 265)
Median	172	64	137	195	152
Q1, Q3	99, 248	40, 121	63, 201	56, 392	61, 306
Min, Max	16, 827	3, 437	3, 827	3, 1296	3, 1296
Change at Week 26					
N	22	12	34	33	67
Mean (SD)	68 (80.1)	105 (141.8)	81 (105.4)	98 (109.0)	89 (106.7)
95% CI	(33 to 104)	(15 to 195)	(44 to 118)	(59 to 136)	(63 to 115)
Median	69	82	72	88	77
Q1, Q3	24, 112	25, 121	24, 112	19, 138	22, 122
Min, Max	−101, 271	−13, 522	−101, 522	−103, 459	−103, 522
Change at Week 52					
N	23	12	35	6	41
Mean (SD)	75 (129.4)	97 (84.6)	83 (115.1)	163 (146.0)	94 (121.5)
95% CI	(19 to 131)	(43 to 150)	(43 to 122)	(10 to 316)	(56 to 133)
Median	56	92	68	107	83
Q1, Q3	3, 138	61, 163	11, 142	74, 269	21, 142
Min, Max	−194, 467	−71, 214	−194, 467	17, 405	−194, 467

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile;; SD = standard deviation
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.9.4

The categorical distributions of CD4 cell counts in Cohorts 1 and 2 at baseline were as follows: < 350 cells/µL: 60 participants (83.3%); < 200 cells/µL: 46 participants (63.9%); < 50 cells/µL: 17 participants (23.6%). At Week 26, the categorical distribution of CD4 cell counts was as follows: < 350 cells/µL: 45 participants (67.2%); < 200 cells/µL: 26 participants (38.8%); < 50 cells/µL: no participants. At Week 52, the categorical distribution of CD4 cell counts was as follows: < 350 cells/µL: 33 participants (80.4%); < 200 cells/µL: 14 participants (34.1%); < 50 cells/µL: 1 participant (2.4%) (Table 11).

Table 11. GS-US-200-4625: CD4 Cell Counts (/uL) in 5 Categories by Visit – All LEN Analysis (Full Analysis Set)

Analysis Set	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Baseline					
N	24	12	36	36	72
< 50	3 (12.5%)	5 (41.7%)	8 (22.2%)	9 (25.0%)	17 (23.6%)
≥ 50 to < 200	13 (54.2%)	6 (50.0%)	19 (52.8%)	10 (27.8%)	29 (40.3%)
≥ 200 to < 350	6 (25.0%)	0	6 (16.7%)	8 (22.2%)	14 (19.4%)
≥ 350 to < 500	1 (4.2%)	1 (8.3%)	2 (5.6%)	4 (11.1%)	6 (8.3%)
≥ 500	1 (4.2%)	0	1 (2.8%)	5 (13.9%)	6 (8.3%)
Week 26					
N	22	12	34	33	67
< 50	0	0	0	0	0
≥ 50 to < 200	8 (36.4%)	9 (75.0%)	17 (50.0%)	9 (27.3%)	26 (38.8%)
≥ 200 to < 350	7 (31.8%)	1 (8.3%)	8 (23.5%)	11 (33.3%)	19 (28.4%)
≥ 350 to < 500	6 (27.3%)	1 (8.3%)	7 (20.6%)	5 (15.2%)	12 (17.9%)
≥ 500	1 (4.5%)	1 (8.3%)	2 (5.9%)	8 (24.2%)	10 (14.9%)
Week 52					
N	23	12	35	6	41
< 50	0	1 (8.3%)	1 (2.9%)	0	1 (2.4%)
≥ 50 to < 200	8 (34.8%)	5 (41.7%)	13 (37.1%)	0	13 (31.7%)
≥ 200 to < 350	10 (43.5%)	5 (41.7%)	15 (42.9%)	4 (66.7%)	19 (46.3%)
≥ 350 to < 500	2 (8.7%)	1 (8.3%)	3 (8.6%)	0	3 (7.3%)
≥ 500	3 (13.0%)	0	3 (8.6%)	2 (33.3%)	5 (12.2%)

LEN = lenacapavir
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table req13265.1.1.1

3.2.1.3.4. HIV-1 RNA < 50 copies/mL Using Imputation Methods (M = F, M = E)

At Week 26 for the M = F analysis, the percentage of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 copies/mL was 80.6% (58 of 72 participants). At Week 52, the percentage of participants with HIV-1 RNA < 50 copies/mL was 77.8% (35 of 45 participants). As 3 participants discontinued study drug by Week 52, similar results were seen for the M = E approach at both Weeks 26 and 52 (Table 12).

Table 12. GS-US-200-4625: Number and Proportion of Participants With HIV-1 RNA < 50 copies/mL for Cohorts 1 and 2 at Week 52 Using Imputation Methods (Missing = Failure and Missing = Excluded) – All LEN Analysis (Full Analysis Set)

Participants With HIV-1 RNA < 50 copies/mL	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Missing = Failure					
Week 26	21/24 (87.5%)	8/12 (66.7%)	29/36 (80.6%)	29/36 (80.6%)	58/72 (80.6%)
Week 52	21/24 (87.5%)	9/12 (75.0%)	30/36 (83.3%)	5/9 (55.6%)	35/45 (77.8%)
Missing = Excluded					
Week 26	21/24 (87.5%)	8/12 (66.7%)	29/36 (80.6%)	29/34 (85.3%)	58/70 (82.9%)
Week 52	21/23 (91.3%)	9/12 (75.0%)	30/35 (85.7%)	5/7 (71.4%)	35/42 (83.3%)

LEN = lenacapavir
For the missing = failure analysis, the denominator for percentages was based on the number of participants in the Full Analysis Set for the All LEN Analysis, excluding ongoing participants who had missing HIV-1 RNA at a visit and had not reached the upper limit of the analysis window for the corresponding visit.
For the missing = excluded analysis, the denominator for percentages was based on the number of participants in the Full Analysis Set for the All LEN Analysis with nonmissing HIV-1 RNA value at each visit. HIV-1 RNA data up to the final data extraction date were included.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Tables 15.9.5.1 and 15.9.5.2

3.2.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

3.2.2.1. Primary Efficacy End Point: Proportion of Participants in the FAS With HIV-1 RNA < 50 copies/mL at Week 54

The proportion of participants in the FAS with HIV-1 RNA < 50 copies/mL at Week 54 using the US FDA-defined snapshot algorithm were similar in each treatment group, with no significant difference between each of the LEN-containing groups and the BVY group (Table 13), as follows:

- LEN total: 136 of 157 participants (86.6%)
- SC LEN + (DVY → TAF): 47 of 52 participants (90.4%)
- SC LEN + (DVY → BIC): 45 of 53 participants (84.9%)
- Oral LEN + DVY: 44 of 52 participants (84.6%)
- BVY: 23 of 25 participants (92.0%)

The proportion of participants in the Week 54 Per-Protocol Analysis Set with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm were consistent with those for the FAS.

Table 13. GS-US-200-4334: Virology Outcome at Week 54 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm) (Full Analysis Set)

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
HIV-1 RNA < 50 copies/mL	47 (90.4%)	45 (84.9%)	44 (84.6%)	23 (92.0%)	92 (87.6%)	136 (86.6%)
HIV-1 RNA ≥ 50 copies/mL	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)
HIV-1 RNA ≥ 50 copies/mL in Week 54 Window	0	0	3 (5.8%)	0	0	3 (1.9%)
Discontinued Study Drug Due to Lack of Efficacy	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
No Virologic Data in Week 54 Window	3 (5.8%)	6 (11.3%)	5 (9.6%)	2 (8.0%)	9 (8.6%)	14 (8.9%)
Discontinued Study Drug Due to AE/Death	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	3 (5.8%)	4 (7.5%)	4 (7.7%)	1 (4.0%)	7 (6.7%)	11 (7.0%)
Missing Data During Window but on Study Drug	0	0	1 (1.9%)	1 (4.0%)	0	1 (0.6%)
LEN vs BVY						
P-value	0.7178	0.3900	0.3797		0.5109	0.4340
Diff in Percentage (95% CI)	−2.6% (−18.4% to 13.2%)	−7.1% (−23.4% to 9.3%)	−7.2% (−23.5% to 9.1%)		−4.7% (−19.2% to 9.7%)	−5.6% (−19.5% to 8.4%)

AE = adverse event; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); CMH = Cochran-Mantel-Haenszel; Diff = difference; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MH = Mantel-Haenszel; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide

The Week 54 window was between Days 323 and 413 (inclusive).

* Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

The difference in percentage of participant with HIV-1 RNA < 50 copies/mL between each of the LEN-containing treatment groups and the BVY group, and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

P-value was from the CMH tests stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.8.6.1

For participants with HIV-1 RNA < 50 copies/mL at Week 28, the proportion with HIV-1 RNA < 50 copies/mL at Week 54 using the US FDA-defined snapshot algorithm were also similar in each treatment group, with no significant difference between each of the LEN-containing groups and the BVY group (Table 14), as follows:

- LEN total: 135 of 147 participants (91.8%)
- SC LEN + (DVY → TAF): 46 of 49 participants (93.9%)
- SC LEN + (DVY → BIC): 45 of 49 participants (91.8%)
- Oral LEN + DVY: 44 of 49 participants (89.8%)
- BVY: 23 of 25 participants (92.0%)

Five participants who had the virologic outcome of HIV-1 RNA < 50 copies/mL at Week 28 had that of HIV-1 RNA ≥ 50 copies/mL at Week 54 using the US FDA-defined snapshot algorithm (SC LEN + [DVY → TAF]: 2 participants [4.1%]; oral LEN + DVY: 3 participants [6.1%]).

Otherwise, the remaining participants who did not have HIV-1 RNA < 50 copies/mL at Week 54 discontinued study drug (SC LEN + [DVY → TAF]: 1 participant [2.0%], SC LEN + [DVY → BIC]: 4 participants [8.2%], oral LEN + DVY: 1 participant [2.0%], and BVY: 1 participant [4.0%]) or had missing data (oral LEN + DVY: 1 participant [2.0%] and BVY: 1 participant [4.0%]).

Table 14. GS-US-200-4334: Virology Outcome at Week 54 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm) For Participants With HIV-1 RNA < 50 copies/mL at Week 28 (Full Analysis Set)

	SC LEN + (DVY -> TAF) (N = 49)	SC LEN + (DVY -> BIC) (N = 49)	Oral LEN + DVY (N = 49)	BVY (N = 25)	SC LEN Total (N = 98)	LEN Total (N = 147)
HIV-1 RNA < 50 copies/mL	46 (93.9%)	45 (91.8%)	44 (89.8%)	23 (92.0%)	91 (92.9%)	135 (91.8%)
HIV-1 RNA ≥ 50 copies/mL	2 (4.1%)	0	3 (6.1%)	0	2 (2.0%)	5 (3.4%)
HIV-1 RNA ≥ 50 copies/mL in Week 54 Window	0	0	3 (6.1%)	0	0	3 (2.0%)
Discontinued Study Drug Due to Lack of Efficacy	2 (4.1%)	0	0	0	2 (2.0%)	2 (1.4%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL	0	0	0	0	0	0
No Virologic Data in Week 54 Window	1 (2.0%)	4 (8.2%)	2 (4.1%)	2 (8.0%)	5 (5.1%)	7 (4.8%)
Discontinued Study Drug Due to AE/Death	0	1 (2.0%)	0	0	1 (1.0%)	1 (0.7%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	1 (2.0%)	3 (6.1%)	1 (2.0%)	1 (4.0%)	4 (4.1%)	5 (3.4%)
Missing Data During Window but on Study Drug	0	0	1 (2.0%)	1 (4.0%)	0	1 (0.7%)
LEN vs. BVY						
P-value	0.8908	1.0000	0.7649		0.9148	0.9465
Diff in Percentage (95% CI)	0.9% (−14.3% to 16.0%)	0.0% (−15.4% to 15.4%)	−2.2% (−17.9% to 13.5%)		0.6% (−13.4% to 14.7%)	−0.4% (−14.1% to 13.3%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); CMH = Cochran-Mantel-Haenszel;
DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MH = Mantel-Haenszel; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide
The Week 54 window is between Days 323 and 413 (inclusive).
* Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
The difference in percentage of participants with HIV-1 RNA < 50 copies/mL between each of the LEN-containing treatment groups and the BVY group, and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).
P-value was from the CMH tests stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table req13250.1

3.2.2.2. Secondary Efficacy End Points

3.2.2.2.1. HIV-1 RNA < 50 copies/mL Using the US FDA-Defined Snapshot Algorithm at Weeks 28 and 38

The secondary efficacy end point of the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 28 as determined by the US FDA-defined snapshot algorithm was presented in the Interim Week 28 CSR. Viral suppression rates were similar in each treatment group, with no significant difference between each of the LEN-containing groups and the BVY group.

The proportion of participants in the FAS with HIV-1 RNA < 50 copies/mL at Week 38 using the US FDA-defined snapshot algorithm were similar in each treatment group, with no significant difference between each of the LEN-containing groups and the BVY group, as follows:

- LEN total: 140 of 157 participants (89.2%)
- SC LEN + (DVY → TAF): 47 of 52 participants (90.4%)
- SC LEN + (DVY → BIC): 47 of 53 participants (88.7%)
- Oral LEN + DVY: 46 of 52 participants (88.5%)
- BVY: 24 of 25 participants (96.0%)

3.2.2.2.2. Change From Baseline in HIV-1 RNA at Weeks 38 and 54

Since the Week 28 analysis, the decrease in the HIV-1 RNA levels from baseline through Weeks 38 and 54 were maintained across treatment groups (Table 15). The mean (SD) changes from baseline in $\log_{10}$ HIV-1 RNA were similar, with no significant differences between each of the LEN-containing groups and the BVY group (Figure 3), as follows:

Week 38

- LEN total: −3.01 (0.681) $\log_{10}$ copies/mL
- SC LEN + (DVY → TAF): −2.96 (0.639) $\log_{10}$ copies/mL
- SC LEN + (DVY → BIC): −3.06 (0.641) $\log_{10}$ copies/mL
- Oral LEN + DVY: −3.02 (0.771) $\log_{10}$ copies/mL
- BVY: −3.04 (0.760) $\log_{10}$ copies/mL

Week 54

- LEN total: −2.98 (0.700) $\log_{10}$ copies/mL
- SC LEN + (DVY → TAF): −2.95 (0.636) $\log_{10}$ copies/mL
- SC LEN + (DVY → BIC): −3.12 (0.589) $\log_{10}$ copies/mL
- Oral LEN + DVY: −2.85 (0.840) $\log_{10}$ copies/mL
- BVY: −3.08 (0.787) $\log_{10}$ copies/mL

Table 15. GS-US-200-4334: Change From Baseline in HIV-1 RNA (log_{10} copies/mL) by Visit (Full Analysis Set)

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Baseline						
N	52	53	52	25	105	157
Mean (SD)	4.18 (0.672)	4.35 (0.670)	4.33 (0.722)	4.35 (0.780)	4.27 (0.673)	4.29 (0.688)
95% CI	(3.9, 4.37)	(4.17, 4.54)	(4.13, 4.53)	(4.03, 4.67)	(4.14, 4.40)	(4.18, 4.40)
Median	4.27	4.32	4.53	4.37	4.32	4.36
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.88, 4.70	3.85, 4.73
Min, Max	2.27, 5.63	2.46, 5.75	2.35, 5.54	2.10, 5.92	2.27, 5.75	2.27, 5.75
LEN vs. BVY						
P-value	0.5267	0.9455	0.8150		0.6826	0.7062
Diff in LSM (95% CI)	−0.09 (−0.38, 0.20)	−0.01 (−0.28, 0.26)	−0.03 (−0.32, 0.26)		−0.05 (−0.30, 0.20)	−0.05 (−0.28, 0.19)
Change at Week 28						
N	49	51	50	25	100	150
Mean (SD)	−2.92 (0.649)	−3.04 (0.638)	−3.01 (0.716)	−3.07 (0.774)	−2.98 (0.643)	−2.99 (0.666)
95% CI	(−3.11, −2.73)	(−3.22, −2.86)	(−3.22, −2.81)	(−3.39, −2.75)	(-3.11, −2.85)	(−3.10, −2.88)
Median	−3.05	−3.03	−3.17	−3.10	−3.04	−3.05
Q1, Q3	−3.36, −2.57	−3.46, −2.68	−3.51, −2.53	−3.49, −2.81	−3.41, −2.65	−3.45, −2.57
Min, Max	−4.35, −0.99	−4.26, −1.18	−4.26, −1.08	−4.56, −0.82	−4.35, −0.99	−4.35, −0.99
LEN vs. BVY						
P-value	0.5755	0.8697	0.7052		0.6732	0.6595
Diff in LSM (95% CI)	0.08 (−0.20, 0.37)	0.02 (−0.25, 0.29)	0.06 (−0.23, 0.35)		0.05 (−0.19, 0.29)	0.05 −0.18, 0.29)

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Change at Week 38						
N	49	51	47	25	100	147
Mean (SD)	−2.96 (0.639)	−3.06 (0.641)	−3.02 (0.771)	−3.04 (0.760)	−3.01 (0.639)	−3.01 (0.681)
95% CI	(−3.14, −2.77)	(−3.24, −2.88)	(−3.24, −2.79)	(−3.36, −2.73)	(−3.13, −2.88)	(−3.12, −2.90)
Median	−3.06	−3.04	−3.26	−3.04	−3.05	−3.11
Q1, Q3	−3.36, −2.59	−3.46, −2.68	−3.59, −2.53	−3.49, −2.81	−3.43, −2.66	−3.46, −2.58
Min, Max	−4.35, −0.99	−4.26, −1.18	−4.26, −1.08	−4.46, −0.82	−4.35, −0.99	−4.35, −0.99
LEN vs. B/F/TAF						
P-value	0.8942	0.9058	0.8129		0.9845	0.9149
Diff in LSM (95% CI)	0.02 (−0.26, 0.30)	−0.02 (−0.28, 0.25)	0.04 (−0.27, 0.35)		0.00 (−0.24, 0.24)	0.01 (−0.23, 0.26)
Change at Week 54						
N	49	47	47	23	96	143
Mean (SD)	−2.95 (0.636)	−3.12 (0.589)	−2.85 (0.840)	−3.08 (0.787)	−3.04 (0.616)	−2.98 (0.700)
95% CI	(−3.14, −2.77)	(−3.30, −2.95)	(−3.10, −2.61)	(−3.42, −2.74)	(−3.16, −2.91)	(−3.09, −2.86)
Median	−3.06	−3.13	−3.03	−3.10	−3.06	−3.06
Q1, Q3	−3.36, −2.59	−3.48, −2.77	−3.51, −2.36	−3.56, −2.81	−3.45, −2.67	−3.45, −2.57
Min, Max	−4.27, −0.99	−4.26, −1.76	−4.08, −0.74	−4.64, −0.82	−4.27, −0.99	−4.27, −0.74
LEN vs. B/F/TAF						
P-value	0.7864	0.7013	0.2753		0.9851	0.5943
Diff in LSM (95% CI)	0.04 (−0.25, 0.33)	−0.05 (−0.31, 0.21)	0.22 (−0.18, 0.62)		0.00 (−0.24, 0.24)	0.08 (−0.21, 0.36)

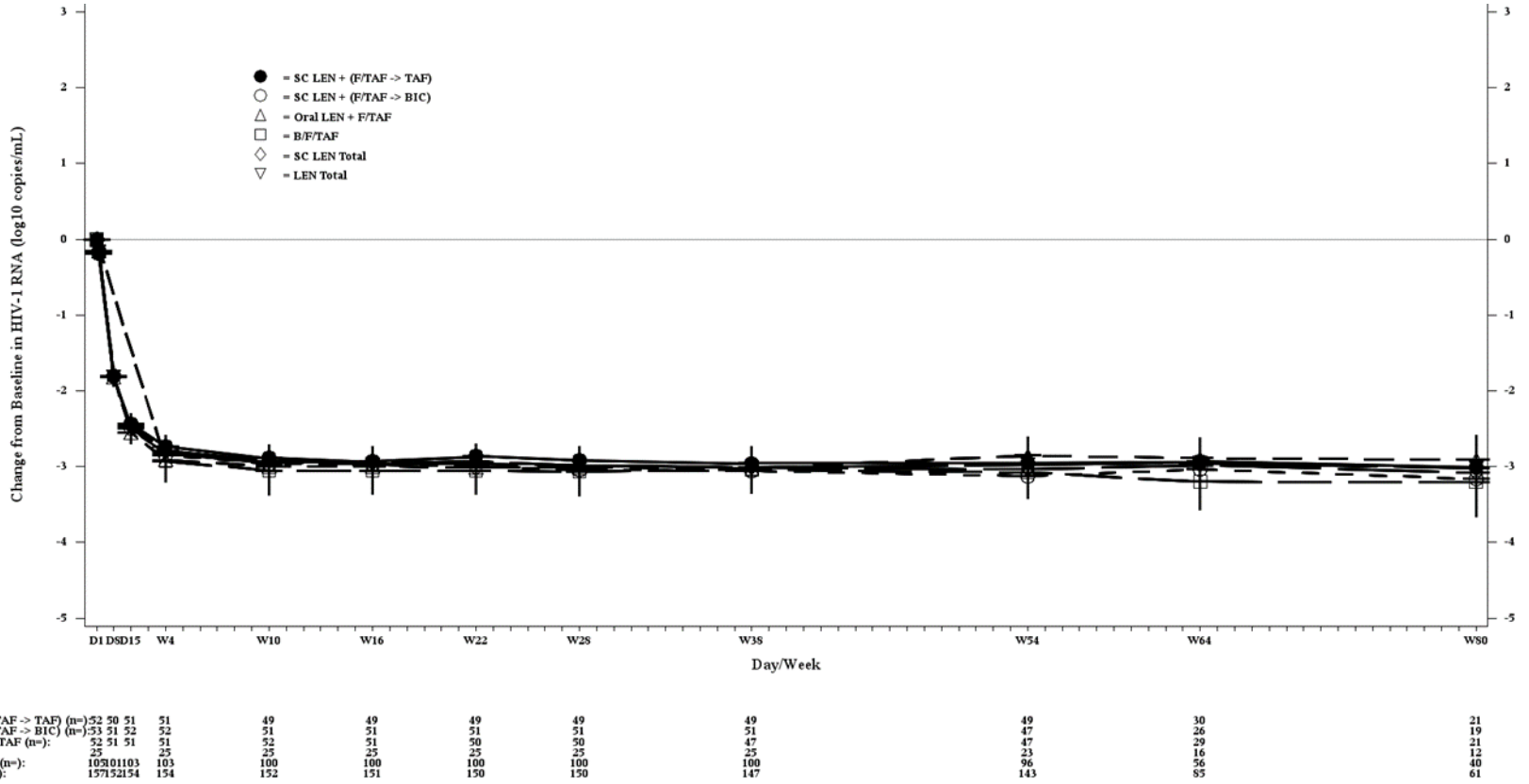
ANOVA = analysis of variance; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); Diff = difference; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; LSM = least squares mean; N = number of participants; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide

HIV-1 RNA results of "No HIV-1 RNA detected" and "< 20 copies/mL HIV-1 RNA Detected" were replaced as 19 copies/mL for analysis purpose.

P-value, difference in least squares means (Diff in LSM), and its 95% CI were from ANOVA model adjusting for the baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.8.7.1

Figure 3. GS-US-200-4334: Mean (95% CI) Change From Baseline in log_{10} HIV-1 RNA by Visit (Full Analysis Set)



SC LEN + (F/TAF -> TAF) (n=):	52	50	51	51	49	49	49	49	49	49	30	21
SC LEN + (F/TAF -> BIC) (n=):	53	51	52	52	51	51	51	51	51	47	26	19
Oral LEN + F/TAF (n=):	52	51	51	51	52	51	50	50	47	47	29	21
B/F/TAF (n=):	25			25	25	25	25	25	25	23	16	12
SC LEN Total (n=):	105	101	103	103	100	100	100	100	100	96	56	40
LEN Total (n=):	157	152	154	154	152	151	150	150	147	143	85	61

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); CI = confidence interval; D = Day; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; W = Week
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Figure 15.9.1

3.2.2.2.3. Change from Baseline in CD4 Cell Count at Weeks 38 and 54

Since the Week 28 analysis, the increase in CD4 cell counts from baseline through Weeks 38 and 54 were maintained across treatment groups (Table 16). The mean (SD) changes from baseline in CD4 cell counts were similar, with no significant differences between each of the LEN-containing groups and the BVY group, as follows:

Week 38

- LEN total: 208 (172.7) cells/µL
- SC LEN + (DVY → TAF): 195 (164.6) cells/µL
- SC LEN + (DVY → BIC): 219 (187.4) cells/µL
- Oral LEN + DVY: 210 (167.1) cells/µL
- BVY: 232 (209.3) cells/µL

Week 54

- LEN total: 213 (182.1) cells/µL
- SC LEN + (DVY → TAF): 206 (187.0) cells/µL
- SC LEN + (DVY → BIC): 212 (187.1) cells/µL
- Oral LEN + DVY: 220 (175.5) cells/µL
- BVY: 193 (191.1) cells/µL

Table 16. GS-US-200-4334: Change From Baseline in CD4 Cell Count (/µL) by Visit (Full Analysis Set)

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Baseline						
N	52	53	52	25	105	157
Mean (SD)	506 (297.0)	490 (209.9)	470 (221.7)	534 (260.0)	498 (255.7)	489 (244.6)
95% CI	(423, 589)	(433, 548)	(408, 532)	(427, 641)	(449, 548)	(450, 527)
Median	404	450	409	482	434	417
Q1, Q3	320, 599	332, 599	301, 600	393, 527	321, 599	320, 599
Min, Max	213, 1846	187, 991	175, 1091	232, 1443	187, 1846	175, 1846
LEN vs. B/F/TAF						
P-value	0.5528	0.4360	0.2744		0.4678	0.3701
Diff in LSM (95% CI)	−41 (−177, 96)	−42 (−149, 65)	−63 (−176, 51)		−40 (−151, 70)	−47 (−150, 56)
Change at Week 28						
N	49	50	50	25	99	149
Mean (SD)	172 (178.2)	158 (164.1)	206 (154.6)	163 (157.7)	165 (170.5)	179 (166.0)
95% CI	(121, 224)	(112, 205)	(162, 250)	(98, 228)	(131, 199)	(152, 206)
Median	143	193	194	155	179	183
Q1, Q3	78, 301	91, 264	99, 306	59, 257	78, 278	89, 283
Min, Max	−230, 556	−331, 457	−129, 573	−88, 488	−331, 556	−331, 573
LEN vs. B/F/TAF						
P-value	0.7751	0.9549	0.2603		0.8778	0.6238
Diff in LSM (95% CI)	12 (−73, 97)	−2 (−79, 75)	44 (−33, 120)		6 (−68, 80)	17 (−53, 88)
Change at Week 38						

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
N	49	51	46	25	100	146
Mean (SD)	195 (164.6)	219 (187.4)	210 (167.1)	232 (209.3)	207 (176.1)	208 (172.7)
95% CI	(148, 242)	(166, 271)	(161, 260)	(146, 318)	(172, 242)	(180, 236)
Median	175	216	184	220	204	194
Q1, Q3	112, 317	91, 363	89, 304	62, 331	107, 327	97, 320
Min, Max	−175, 701	−203, 638	−66, 597	−77, 624	−203, 701	−203, 701
LEN vs. B/F/TAF						
P-value	0.4827	0.7844	0.6082		0.5835	0.5565
Diff in LSM (95% CI)	−31 (−119, 57)	−13 (−106, 81)	−23 (−112, 66)		−22 (−103, 58)	−23 (−98, 53)
Change at Week 54						
N	49	47	47	23	96	143
Mean (SD)	206 (187.0)	212 (187.1)	220 (175.5)	193 (191.1)	209 (186.1)	213 (182.1)
95% CI	(152, 259)	(158, 267)	(169, 272)	(110, 276)	(171, 247)	(183, 243)
Median	180	242	238	177	208	219
Q1, Q3	110, 311	94, 343	102, 293	30, 290	103, 330	102, 318
Min, Max	−291, 673	−301, 631	−74, 603	−59, 749	−301, 673	−301, 673
LEN vs. B/F/TAF						
P-value	0.6614	0.6791	0.5563		0.6393	0.6091
Diff in LSM (95% CI)	21 (−73, 115)	20 (−75, 115)	27 (−65, 120)		20 (−65, 105)	21 (−60, 102)

ANOVA = analysis of variance; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); Diff = difference; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; LSM = least squares mean; N = number of participants; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide

P-value, difference in least squares means (Diff in LSM), and its 95% CI were from ANOVA model adjusting for the baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Figure 15.8.7.2

3.2.2.3. Other Efficacy Analyses

3.2.2.3.1. HIV-1 RNA < 50 copies/mL Using Imputation Methods (M = F and M = E)

The M = F analysis of the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 yielded similar results as the analysis using the US FDA-defined snapshot algorithm, with no significant difference between each of the LEN-containing treatment groups and the BVY treatment group, as follows:

- LEN total: 140 of 157 participants (89.2%)
- SC LEN + (DVY → TAF): 49 of 52 participants (94.2%)
- SC LEN + (DVY → BIC): 47 of 53 participants (88.7%)
- Oral LEN + DVY: 44 of 52 participants (84.6%)
- BVY: 23 of 25 participants (92.0%)

Consistent with the M = F analysis, there were no significant difference between each of the LEN-containing treatment groups and the BVY treatment group in the M = E analysis for participants with HIV-1 RNA < 50 copies/mL. In the M = E analysis, all participants in the SC LEN + (DVY → TAF) (49 participants), SC LEN + (DVY → BIC) (47 participants), and BVY (23 participants) had HIV-1 RNA < 50 copies/mL at Week 54. The M = E analysis of the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 in the oral LEN + DVY group was 93.6% (44 of 47 participants).

3.3. Comparison of Results in Subpopulations

Statistical methods for subgroup analyses of efficacy data from Studies GS-US-200-4625 and GS-US-200-4334 are described in the statistical analysis plans (GS-US-200-4625 Interim Week 52 CSR Addendum, Appendix 16.1.9; GS-US-200-4334 Interim Week 54 CSR Addendum, Appendix 16.1.9). Detailed results are presented in the individual CSRs (GS-US-200-4625 Interim Week 52 CSR Addendum, Section 9.4; GS-US-200-4334 Interim Week 54 CSR Addendum, Section 9.4).

3.3.1. Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

The proportion of participants in Cohorts 1 and 2 with HIV 1 RNA < 50 copies/mL at Week 52 using the US FDA-defined snapshot algorithm based on the FAS was numerically higher in female participants, in non-Black participants, participants in ex-US region, participants with baseline CD4 cell count ≥ 200 cells/μL, and participants with baseline viral load ≤ 100,000 copies/mL.

Despite the limitations of the small sample size in some subgroups, the efficacy of LEN by baseline CD4 cell count and HIV-1 RNA level was generally as expected, since low CD4 cell counts and high HIV-1 RNA levels are factors known to limit virologic response (Table 17).

However, the general trend of the efficacy analyses by various subgroups of baseline OBR suggests that the contribution of LEN toward efficacy was clinically meaningful. Specifically, the efficacy of LEN in subgroups of participants who were considered more difficult to treat did not appear to be clinically meaningfully lower than those who were considered not as difficult to treat (ie, those with no fully active agents versus those with fully active agents, those with INSTI resistance versus those without, those without either dolutegravir or darunavir in the baseline OBR versus those with either).

Table 17. GS-US-200-4625: Number and Proportion of Participants With HIV-1 RNA < 50 Copies/mL at Week 52 (Snapshot Algorithm) by Subgroup – All LEN Analysis (Full Analysis Set)

	Cohort 1			Cohort 2 (N = 9)	Total (N = 45)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Baseline CD4 Cell Count Categories (μL)					
< 200	13/16 (81.3%)	8/11 (72.7%)	21/27 (77.8%)	2/4 (50.0%)	23/31 (74.2%)
≥ 200	8/8 (100.0%)	1/1 (100.0%)	9/9 (100.0%)	3/5 (60.0%)	12/14 (85.7%)
Baseline Viral Load Categories (copies/mL)					
≤ 100,000	20/23 (87.0%)	5/6 (83.3%)	25/29 (86.2%)	4/5 (80.0%)	29/34 (85.3%)
> 100,000	1/1 (100.0%)	4/6 (66.7%)	5/7 (71.4%)	1/4 (25.0%)	6/11 (54.5%)
Overall Susceptibility Score Based on Baseline OBR					
0 to < 1	3/4 (75.0%)	1/2 (50.0%)	4/6 (66.7%)	2/2 (100.0%)	6/8 (75.0%)
1 to < 2	5/6 (83.3%)	5/6 (83.3%)	10/12 (83.3%)	3/4 (75.0%)	13/16 (81.2%)
≥ 2	13/14 (92.9%)	3/4 (75.0%)	16/18 (88.9%)	0/3	16/21 (76.2%)
Number of Fully Active ARV Agents in the Baseline OBR					
0	3/4 (75.0%)	1/2 (50.0%)	4/6 (66.7%)	2/2 (100.0%)	6/8 (75.0%)
1	5/7 (71.4%)	6/7 (85.7%)	11/14 (78.6%)	3/5 (60.0%)	14/19 (73.7%)
≥ 2	13/13 (100.0%)	2/3 (66.7%)	15/16 (93.8%)	0/2	15/18 (83.3%)
Resistance Categories Based on Baseline INSTI Resistance Profile					
With INSTI Resistance	18/20 (90.0%)	4/7 (57.1%)	22/27 (81.5%)	4/7 (57.1%)	26/34 (76.5%)
Without INSTI Resistance	3/4 (75.0%)	4/4 (100.0%)	7/8 (87.5%)	1/2 (50.0%)	8/10 (80.0%)

	Cohort 1			Cohort 2 (N = 9)	Total (N = 45)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Use of DRV and/or DTG					
With DTG and DRV	6/6 (100.0%)	4/6 (66.7%)	10/12 (83.3%)	0/3	10/15 (66.7%)
With DTG, without DRV	3/4 (75.0%)	2/2 (100.0%)	5/6 (83.3%)	2/3 (66.7%)	7/9 (77.8%)
Without DTG, with DRV	6/6 (100.0%)	2/3 (66.7%)	8/9 (88.9%)	1/1 (100.0%)	9/10 (90.0%)
Without DTG or DRV	6/8 (75.0%)	1/1 (100.0%)	7/9 (77.8%)	2/2 (100.0%)	9/11 (81.8%)
Use of IMAB and/or FTR					
With IMAB, regardless of FTR	8/9 (88.9%)	2/3 (66.7%)	10/12 (83.3%)	0/1	10/13 (76.9%)
Without IMAB, regardless of FTR	13/15 (86.7%)	7/9 (77.8%)	20/24 (83.3%)	5/8 (62.5%)	25/32 (78.1%)
Regardless of IMAB, with FTR	3/3 (100.0%)	0/0	3/3 (100.0%)	0/0	3/3 (100.0%)
Regardless of IMAB, without FTR	18/21 (85.7%)	9/12 (75.0%)	27/33 (81.8%)	5/9 (55.6%)	32/42 (76.2%)

ARV = antiretroviral; DRV = darunavir; DTG = dolutegravir; FTR = fostemsavir; IMAB = ibalizumab; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; OBR = optimized background regimen; OL = open label; SC = subcutaneous
The Week 52 window is between Days 324 and 414 (inclusive).
For Cohort 2, the subjects who have not reached the Week 52 visit but are still ongoing are excluded from the snapshot analysis.
Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the last SC LEN, was used in this analysis.
OBR at baseline was defined as any nonstudy drug ARV medications that were started on or prior to Study Day 28 from the first dose of OL LEN and were used for a minimum duration of 28 days, regardless of temporary interruption, on or after the first dose of OL LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Tables 15.9.2.3.1 and 15.9.2.3.2

3.3.2. Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

The percentages of participants in the subgroups by age (< 50 and ≥ 50 years), sex (male and female), and race (Black and non-Black) with HIV-1 RNA < 50 copies/mL at Week 54 using the US FDA-defined snapshot algorithm were similar to the overall results. However, the small size and imbalance of participant numbers within each subgroup preclude meaningful conclusions.

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

No new information is submitted.

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

No data are available at this time. Studies GS-US-200-4625 and GS-US-200-4334 are ongoing, and longer-term data will be available in the future.

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7. APPENDIX

7.1. Tabular Summary of Studies Relevant for Efficacy

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled clinical studies pertinent to the claimed indication	GS-US-200-4625	To evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for PWH with multidrug resistance	Phase 2/3, randomized, placebo-controlled, multicenter study	Cohort 1: Functional Monotherapy Period: oral LEN 600, 600, and 300 mg or placebo-to-match LEN on Days 1, 2, and 8, respectively, while continuing their failing regimen Maintenance Period: Cohort 1A: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) and initiation of an OBR starting on Day 1 SC (14 days after the first dose of oral LEN), and once every 6 months (26 weeks) Cohort 1B: oral LEN 600 mg and initiation of an OBR on Day 15; oral LEN 600 and 300 mg on Days 16 and 22, respectively; SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks) Cohort 2: Oral Lead-in Period: oral LEN 600 mg and initiation of an OBR on Day 1; oral LEN 600 and 300 mg on Days 2 and 8, respectively, while continuing their OBR Maintenance Period: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks)	At least 54 weeks	Enrolled in study: 72 participants; Cohort 1: 36 participants; Cohort 2: 36 participants Completed Main Phase or continued Main Phase: 69 participants Cohort 1: 35 participants Cohort 2: 34 participants	Heavily treatment-experienced adult and adolescent PWH with resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications and plasma HIV-1 RNA ≥ 400 copies/mL at screening while taking a failing regimen	Study ongoing; Interim Week 26 CSR, Interim Week 52 CSR Addendum

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled clinical studies pertinent to the claimed indication	GS-US-200-4334	To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment Group 1 (oral to SC LEN): Induction: oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2 and 300 mg (1 × 300 mg) on Day 8, SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15, and oral DVY 200/25 mg daily from Day 1 for 28 weeks Maintenance: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and once every 6 months (26 weeks) thereafter, and oral TAF 25 mg daily Treatment Group 2 (oral to SC LEN): Induction: oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2 and 300 mg (1 × 300 mg) on Day 8, SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15, and oral DVY 200/25 mg daily from Day 1 for 28 weeks Maintenance: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and once every 6 months (26 weeks) thereafter, and oral BIC 75 mg daily Treatment Group 3: oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2 and 50 mg (1 × 50 mg) daily from Day 3 onwards, and oral DVY 200/25 mg daily Treatment Group 4: oral BVY 50/200/25 mg daily	At least 80 weeks	Randomized in study: 183 participants; Safety Analysis Set: 182 participants; SC LEN + (DVY → TAF): 52 participants; SC LEN + (DVY → BIC): 53 participants; Oral LEN + DVY: 52 participants; BVY: 25 participants Completed Main Phase or continued Main Phase: 160 participants SC LEN + (DVY → TAF): 47 participants SC LEN + (DVY → BIC): 41 participants Oral LEN + DVY: 48 participants BVY: 24 participants	Treatment-naive PWH ≥ 18 years of age	Study ongoing; Interim Week 28 CSR, Interim Week 54 CSR Addendum

ARV = antiretroviral; BIC = bictegravir (GS-9883); BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CSR = clinical study report; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); LEN = lenacapavir (GS-6207); OBR = optimized background regimen; PWH = people with HIV; SC = subcutaneous; TAF = tenofovir alafenamide (Vemlidy®)

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

LENACAPAVIR

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	ARV therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BIC, B	bictegravir (GS-9883)
BMI	body mass index
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CD4	cluster determinant 4
CK	creatine kinase
CSR	clinical study report
CYP	cytochrome P450 enzyme
DAIDS	Division of AIDS7
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FTC, F	emtricitabine (Emtriva®)
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HTE	heavily treatment-experienced
ISR	injection site reaction
ISS	integrated summary of safety
LEN	lenacapavir
MedDRA	Medical Dictionary for Regulatory Activities
OATP	organic anion transporting polypeptide
OBR	optimized background regimen
P-gp	P-glycoprotein
PK	pharmacokinetics
PT	preferred term
PWH	people with HIV
Q1	first quartile
Q3	third quartile

SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	system organ class
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1

1. EXPOSURE TO THE DRUG

1.1. Background

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38 million people with HIV (PWH) worldwide and approximately 26 million on antiretroviral (ARV) treatment {UNAIDS 2020}. Advances in combination ARV therapy (ART) for HIV have led to significant improvements in quality of life among PWH by suppressing viral replication, preserving immunologic function, and averting disease progression to AIDS. Most currently approved ARV drugs target 1 of the following 4 steps of the HIV lifecycle: the inhibition of viral entry, reverse transcription, viral DNA integration, or the proteolysis of viral polyproteins essential for virion maturation. While combination ART for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality previously associated with HIV disease, there remains a significant medical need for new, well-tolerated therapies that take into consideration HIV genetic variability, ARV resistance, new options for regimen simplification, as well as the desires of PWH for alternative, longer-acting options.

Some treatment-experienced PWH eventually lose the virologic, immunologic, or clinical benefit from their current regimens. People with HIV who have multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {British HIV Association 2016, European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019, Saag 2020, U. S. Department of Health and Human Services 2015}. These challenges are also relevant for adolescents, particularly those with perinatal HIV-1 transmission. Developing safe and effective therapies for heavily treatment-experienced (HTE) PWH with multidrug-resistant HIV remains a priority. For these individuals, newer treatments are needed to control viral replication, preserve immune function, and prevent clinical progression.

Lenacapavir (LEN; GS-6207) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function, which is being developed for the treatment and prevention of HIV-1 infection. Lenacapavir inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

1.2. Overall Safety Evaluation Plan and Narratives of Safety Studies

1.2.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

The proposed indication for LEN is primarily based on data from Study GS-US-200-4625, an ongoing Phase 2/3, randomized, placebo-controlled, multicenter study of LEN in combination with an optimized background regimen (OBR) in HTE PWH with multidrug resistance. A majority of participants in this study had a baseline CD4 cell count < 200 cells/μL (a hallmark of severe immune suppression and the criteria to diagnose AIDS).

An overview of Study GS-US-200-4625 is presented in m2.7.3, Section 1.2.1 and a tabular summary of the study design is presented in Appendix 8.1.

This summary document provides safety data from the interim analysis of Cohorts 1 and 2 in Study GS-US-200-4625, which was conducted after all participants in Cohort 1 had completed the Week 26 visit (ie, 26 weeks after the first dose of subcutaneous [SC] LEN injection) or had prematurely discontinued study drug. Safety was evaluated through the incidence of treatment-emergent adverse events (AEs) and treatment-emergent clinical laboratory abnormalities.

1.2.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Supportive safety data for LEN are provided from Study GS-US-200-4334, an ongoing Phase 2, randomized, open-label, active-controlled, multicenter study of LEN in combination with other ARV agents in treatment-naive PWH. Study GS-US-200-4334 uses bictegravir (BIC; B)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (Biktarvy®; BVY) as the active comparator, allowing for comparisons between the LEN-containing regimens with a guideline-recommended initial regimen for treatment-naive PWH {European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019}.

An overview of Study GS-US-200-4334 is presented in m2.7.3, Section 1.2.2 and a tabular summary of the study design is presented in Appendix 8.1.

This summary document provides safety data from the interim analysis of Study GS-US-200-4334, which was conducted after all participants had completed the Week 28 visit or had prematurely discontinued study drug. Safety was evaluated through the incidence of treatment-emergent AEs and treatment-emergent clinical laboratory abnormalities.

1.2.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

Supportive safety data for LEN are provided from an integrated summary of safety (ISS) presenting pooled analyses of 2 Phase 1 studies (GS-US-200-4538 and GS-US-200-5709) evaluating the safety and pharmacokinetics (PK) of LEN in healthy participants.

Study GS-US-200-4538 was a randomized, blinded, placebo-controlled, single center, single-dose Phase 1 study with staggered dose escalations. The study had 8 parts (Parts A to H). Parts A to G were to characterize the PK of single ascending doses of different LEN formulations. Part H was to characterize the impact of injection number and/or volume on PK of a formulation(s) selected for further clinical development.

Study GS-US-200-5709 is an ongoing, Phase 1, open-label, multi cohort, multi dose oral and/or SC LEN study to evaluate the safety and tolerability of multiple-dose oral and SC LEN and to characterize the PK of multiple-dose oral and SC LEN in healthy participants.

Study GS-US-200-5709 evaluated the oral + SC clinical regimen for LEN (2-week oral lead in, followed by 927 mg of 309 mg/mL LEN SC), while Study GS-US-200-4538 evaluated a SC

formulation (927 mg of 309 mg/mL LEN SC), as well as a different SC formulation with similar exposure (927 mg of 155 mg/mL LEN SC).

Safety data from specific cohorts from both studies in which participants received a regimen with comparable exposure to LEN as the planned regimen for commercialization were selected for the ISS analyses. The ISS analysis was conducted based on final data of Cohorts 6, 7, and 10 in Study GS-US-200-4538, and interim data (data cut date: [redacted] 20[redacted]) of Cohort 1 in Study GS-US-200-5709 (Table 1). Safety was evaluated through the incidence of treatment-emergent AEs and treatment-emergent clinical laboratory abnormalities. Pooled analyses are labeled as such in this summary document.

Table 1. Overview of Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

Treatment	Study	Cohort (Dosing)	Number of Participants	Total Number of Participants
LEN	GS-US-200-4538	Cohort 6 (927 mg, 309 mg/mL LEN injection 3 × 1.0 mL)	8	55
		Cohort 7 (927 mg, 309 mg/mL LEN injection 2 × 1.5 mL)	8	
		Cohort 10 (927 mg, 155 mg/mL LEN injection 3 × 2 mL)	8	
	GS-US-200-5709	Cohort 1 (Oral 600, 600, 300 mg on Days 1, 2, and 8 + 927 mg, 309 mg/mL LEN injection 2 × 1.5 mL on Day 15)	31	
Placebo	GS-US-200-4538	2 placebo participants each from 10 dosed cohorts	20	20

LEN = lenacapavir

1.2.4. Safety Analysis Sets

1.2.4.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

The Safety Analysis Set included all participants who were enrolled and received at least 1 dose of study drug in Study GS-US-200-4625. This was the primary analysis set for safety analyses. This analysis set was used to describe baseline information as well as safety summary for the Functional Monotherapy Period analysis and All LEN Analysis.

Functional Monotherapy Period analysis included data collected from participants randomized in the Functional Monotherapy Period. All data collected up to the first dose date of the open-label study drug, defined as the earliest date from SC LEN or open-label oral LEN, were included in this analysis except for data on AEs and death. For AEs and death, only data collected prior to the first dose date of the open-label study drug were included.

All LEN Analysis included data collected from participants who received at least 1 dose of LEN (ie, blinded or open-label oral LEN or SC LEN). Data collected on and after the first dose of LEN were included in this analysis. Data included in this analysis were used to assess efficacy, safety, PK, and patient-reported outcomes of LEN. Results were summarized by cohort and total, unless specified otherwise.

1.2.4.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

The Safety Analysis Set included all participants who were randomized and received at least 1 dose of study drug in Study GS-US-200-4334. This was the primary analysis set for safety analyses. All safety data collected up to the last exposure date for participants who prematurely discontinued study drug or all available data for participants who were still on study drug were included in the safety summary, unless specified otherwise.

1.2.4.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

The Safety Analysis Set included all participants in the All Enrolled Analysis Set who received at least 1 dose of study drug. Participants were grouped by treatment taken:

- **LEN:** this group included participants from selected cohorts who were randomized (Study GS-US-200-4538) or enrolled (Study GS-US-200-5709) to receive LEN.

- **Placebo:** this group included participants who were randomized to placebo in any cohort in Study GS-US-200-4538, including cohorts other than the 3 cohorts in which LEN participants were pooled.

1.2.5. Safety Assessments

Adverse event and clinical laboratory data were summarized by treatment group using descriptive statistics. Adverse events were coded using the MedDRA, Version 23.1. Summaries (number and percentage of participants) of treatment-emergent AEs (by system organ class and preferred term [PT]) were provided by treatment group. Additional summaries included summaries for AEs by grade and investigator's assessment of relationship to study drug.

For the individual Studies GS-US-200-4625 and GS-US-200-4334, additional analysis of AEs was performed for injection site reactions (ISRs) related to study drug, which was defined as an AE related to study drug reported as any event within the MedDRA high-level term of "injection site reactions."

Graded laboratory abnormalities were defined using the grading scheme in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, (corrected Version 2.1, July 2017). Incidences of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline, were summarized by treatment group. Laboratory data that are categorical were summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

Further details on the statistical methods for the individual studies are provided in the statistical analysis plan (SAP) for each study (GS-US-200-4625 Interim Week 26 clinical study report [CSR], Appendix 16.1.9; and GS-US-200-4334 Interim Week 28 CSR, Appendix 16.1.9). Further details on the statistical methods, safety data definitions, and grading scales are provided in the LEN ISS Statistical Analysis Plan (SAP), and are described briefly in this summary, when appropriate.

1.2.6. Summary of Results of Individual Studies

Study narratives, including safety data, for individual clinical pharmacology and efficacy studies are presented in m2.7.2 and m2.7.3, respectively.

1.3. Overall Extent of Exposure

The overall duration on study from Study GS-US-200-4625 and the extent of exposure from Study GS-US-200-4334 are presented in Sections 1.3.1 and 1.3.2, respectively. Detailed results are presented in the individual CSRs (GS-US-200-4625 Interim Week 26 CSR, Section 11.1; GS-US-200-4334 Interim Week 28 CSR, Section 11.1).

Disposition for participants in Studies GS-US-200-4625 and GS-US-200-4334 is described in m2.7.3, Section 3.1.

Detailed results summarizing the disposition for participants and the overall duration of follow-up from the pooled Studies GS-US-200-4538 and GS-US-200-5709 are presented in Section 1.3.3.

1.3.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

During the Functional Monotherapy Period of Study GS-US-200-4625, all 24 participants in Cohort 1 received their scheduled dose of oral LEN on Days 1, 2, and 8.

All LEN Analysis

Of the 72 participants in Cohorts 1 and 2 who received oral LEN, all 72 participants received SC LEN on Day 1 SC and 39 participants (54.2%) (Cohort 1: 36 participants, Cohort 2: 3 participants) received a second dose of SC LEN at Week 26. The median (Q1, Q3) duration on study was 346 (254, 405) days and 156 (106, 191) days for Cohorts 1 and 2, respectively.

1.3.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Exposure to study drugs in Study GS-US-200-4334 was similar across the 4 treatment groups. By Week 28, 96.2% of participants in the LEN total group (151 of 157 participants) and 100.0% of those in the BVY group (25 of 25 participants) had been exposed to study drug for at least 28 weeks. The median (Q1, Q3) duration of exposure to study drug was 43.4 (33.3, 57.4) weeks in the LEN total group (Table 2).

Table 2. GS-US-200-4334: Extent of Study Drug Exposure (Safety Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Total Duration of Exposure to Study Drug (Weeks)						
N	52	53	52	25	105	157
Mean (SD)	44.8 (14.05)	44.6 (13.23)	45.4 (13.49)	48.1 (12.07)	44.7 (13.57)	44.9 (13.51)
Median	42.9	42.3	44.2	52.0	42.3	43.4
Q1, Q3	33.5, 57.9	33.3, 56.3	33.7, 57.9	35.4, 58.3	33.3, 57.3	33.3, 57.4
Min, Max	9.7, 69.0	8.4, 64.4	10.3, 66.1	31.1, 66.4	8.4, 69.0	8.4, 69.0
Cumulative N (%) of Participants Exposed to Study Drug						
≥ 1 Day	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
≥ 2 Days	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
≥ 8 Days	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
≥ 15 Days	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
≥ 4 Weeks (28 Days)	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
≥ 10 Weeks (70 Days)	51 (98.1%)	52 (98.1%)	52 (100.0%)	25 (100.0%)	103 (98.1%)	155 (98.7%)
≥ 16 Weeks (112 Days)	50 (96.2%)	52 (98.1%)	51 (98.1%)	25 (100.0%)	102 (97.1%)	153 (97.5%)
≥ 22 Weeks (154 Days)	50 (96.2%)	52 (98.1%)	51 (98.1%)	25 (100.0%)	102 (97.1%)	153 (97.5%)
≥ 28 Weeks (196 Days)	50 (96.2%)	51 (96.2%)	50 (96.2%)	25 (100.0%)	101 (96.2%)	151 (96.2%)
≥ 38 Weeks (266 Days)	29 (55.8%)	31 (58.5%)	30 (57.7%)	16 (64.0%)	60 (57.1%)	90 (57.3%)
≥ 54 Weeks (378 Days)	22 (42.3%)	20 (37.7%)	23 (44.2%)	12 (48.0%)	42 (40.0%)	65 (41.4%)
≥ 64 Weeks (448 Days)	2 (3.8%)	2 (3.8%)	3 (5.8%)	2 (8.0%)	4 (3.8%)	7 (4.5%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Duration of exposure to study drug = last exposure date − first dose date + 1
For ongoing participants, the last exposure date is defined as the data cut date.
For participants who prematurely discontinued study drug, the last exposure date is defined as the last study date for participants who randomized to LEN treatment group and received SC injection, the minimum of last dose date plus 60 days and last study date for participants who randomized to LEN treatment group and did not receive SC injection, the minimum of last dose date plus 30 days and last study date for participants in BVY treatment group.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.11.1.1.

1.3.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

Participant Disposition

Overall, 75 participants received at least 1 dose of study drug and were included in the Safety Analysis Set for the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 (55 participants in the LEN group and 20 participants in the placebo group) and 74 participants completed study drug. One participant in the LEN group prematurely discontinued study drug due to an AE considered not related to study drug (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test positive).

A total of 8 participants (10.7%) prematurely discontinued from the study (LEN group: 7 participants [12.7%]; placebo group: 1 participant [5.0%]).

The most common reasons for premature study discontinuation were lost to follow-up (LEN group: 3 participants [5.5%]; placebo group: 1 participant [5.0%]), withdrawal of consent (LEN group: 3 participants [5.5%]), and AE (LEN group: 1 participant [1.8%]) (Table 3).

Table 3. GS-US-200-4538 and GS-US-200-5709: Participant Disposition (All Enrolled Analysis Set)

	LEN (N = 55)	Placebo (N = 20)
All Enrolled Analysis Set	55	20
Safety Analysis Set	55 (100.0%)	20 (100.0%)
Study Drug Completion Status		
Completed Study Drug	54 (98.2%)	20 (100.0%)
Prematurely Discontinued Study Drug	1 (1.8%)	0
Reason for Discontinuation of Study Drug		
Adverse Event	1 (1.8%)	0
Death	0	0
Pregnancy	0	0
Investigator's Discretion	0	0
Participant Never Dosed With Study Drug	0	0
Protocol Violation	0	0
Participant Decision	0	0
Lost to Follow-Up	0	0
Study Terminated by Sponsor	0	0
Study Completion Status		
Continuing Study	30 (54.5%)	0
Completed Study	18 (32.7%)	19 (95.0%)
Prematurely Discontinued Study	7 (12.7%)	1 (5.0%)

	LEN (N = 55)	Placebo (N = 20)
Reason for Discontinuation of Study		
Adverse Event	1 (1.8%)	0
Death	0	0
Pregnancy	0	0
Investigator's Discretion	0	0
Protocol Violation	0	0
Withdrew Consent	3 (5.5%)	0
Lost to Follow-Up	3 (5.5%)	1 (5.0%)
Study Terminated by Sponsor	0	0

LEN = lenacapavir
Percentages for the Safety Analysis Set were calculated based on the number of participants in the All Enrolled Analysis Set. All other percentages were based on total number of participants in the Safety Analysis Set.
Source: LEN ISS, Table 1

Duration on Study

The median (Q1, Q3) duration on study treatment for participants in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 was as follows: LEN group 135.0 (27.0, 449.0) days; placebo group 448.5 (335.5, 449.0) days (Table 4).

Table 4. GS-US-200-4538 and GS-US-200-5709: Duration on Study (Safety Analysis Set)

	LEN (N = 55)	Placebo (N = 20)	Total (N = 75)
Duration on Study (Days)			
N	55	20	75
Mean (SD)	208.8 (178.94)	384.4 (111.09)	255.6 (180.68)
Median	135.0	448.5	225.0
Q1, Q3	27.0, 449.0	335.5, 449.0	43.0, 449.0
Min, Max	27.0, 469.0	43.0, 465.0	27.0, 469.0
Duration on Study			
≥ 7 days	55 (100.0%)	20 (100.0%)	75 (100.0%)
≥ 14 days	55 (100.0%)	20 (100.0%)	75 (100.0%)
≥ 21 days	55 (100.0%)	20 (100.0%)	75 (100.0%)
≥ 28 days	39 (70.9%)	20 (100.0%)	59 (78.7%)
≥ 35 days	38 (69.1%)	20 (100.0%)	58 (77.3%)
≥ 42 days	37 (67.3%)	20 (100.0%)	57 (76.0%)
≥ 72 days	37 (67.3%)	19 (95.0%)	56 (74.7%)

	LEN (N = 55)	Placebo (N = 20)	Total (N = 75)
≥ 102 days	37 (67.3%)	19 (95.0%)	56 (74.7%)
≥ 132 days	37 (67.3%)	19 (95.0%)	56 (74.7%)
≥ 162 days	21 (38.2%)	19 (95.0%)	40 (53.3%)
≥ 192 days	20 (36.4%)	19 (95.0%)	39 (52.0%)
≥ 222 days	20 (36.4%)	19 (95.0%)	39 (52.0%)
≥ 252 days	19 (34.5%)	17 (85.0%)	36 (48.0%)
≥ 282 days	18 (32.7%)	17 (85.0%)	35 (46.7%)
≥ 312 days	18 (32.7%)	17 (85.0%)	35 (46.7%)
≥ 342 days	18 (32.7%)	15 (75.0%)	33 (44.0%)
≥ 372 days	18 (32.7%)	13 (65.0%)	31 (41.3%)
≥ 402 days	18 (32.7%)	13 (65.0%)	31 (41.3%)
≥ 432 days	18 (32.7%)	13 (65.0%)	31 (41.3%)
≥ 462 days	1 (1.8%)	1 (5.0%)	2 (2.7%)

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Duration on study was the number of days between Day 1 and the last study date.
Source: LEN ISS, Table 3

1.4. Demographics and Other Characteristics of Study Population

Demographics, general baseline characteristics, and baseline disease characteristics for participants in Studies GS-US-200-4625 and GS-US-200-4334 are described in m2.7.3, Section 3.1.

Demographics and general baseline characteristics for participants in the pooled Studies GS-US-200-4538 and GS-US-200-5709 are summarized below.

1.4.1. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

Demographic and baseline characteristics in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 were generally similar between the LEN and placebo groups (Table 5). The majority of the participants were male (65.3%; 49 of 75 participants), White (73.3%, 55 participants), and Hispanic or Latino (98.7%, 74 participants). Median age was 33 years (range: 20 to 45 years) and median (Q1, Q3) body mass index (BMI) was 26.8 (24.5, 28.8) kg/m^2.

Table 5. GS-US-200-4538 and GS-US-200-5709: Demographics and Baseline Characteristics (Safety Analysis Set)

	LEN (N = 55)	Placebo (N = 20)
Age (years)		
N	55	20
Mean (SD)	33 (6.8)	33 (6.7)
Median	33	33
Q1, Q3	29, 38	31, 38
Min, Max	21, 45	20, 44
Sex at Birth		
Male	35 (63.6%)	14 (70.0%)
Female	20 (36.4%)	6 (30.0%)
Race		
American Indian or Alaska Native	0	0
Asian	0	0
Black	15 (27.3%)	5 (25.0%)
Native Hawaiian or Pacific Islander	0	0
White	40 (72.7%)	15 (75.0%)
Other	0	0
Ethnicity		
Hispanic or Latino	55 (100.0%)	19 (95.0%)
Not Hispanic or Latino	0	1 (5.0%)
Body Mass Index (kg/m^2)		
N	55	20
Mean (SD)	26.2 (2.57)	27.0 (2.90)
Median	26.3	28.0
Q1, Q3	24.3, 28.6	25.0, 29.0
Min, Max	20.7, 30.3	19.8, 30.7

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Denominator for percentage was the Safety Analysis Set.
Age (in years) was calculated from the date of first study drug dosing if dosed, or enrollment if not dosed.
Body Mass Index (kg/m^2) = [Weight (kg)/Height $(cm)^2$]*10,000
Source: LEN ISS, Table 2

2. ADVERSE EVENTS

All AEs and laboratory abnormalities presented in this summary were treatment emergent and are referred to as AEs and laboratory abnormalities throughout this report. Additionally, the relationship of AEs to study drug is investigator assigned.

2.1. Analysis of Adverse Events

Detailed results describing AEs for Studies GS-US-200-4625 and GS-US-200-4334 are provided in the individual CSRs (GS-US-200-4625 Interim Week 26, Section 11.2 and GS-US-200-4334 Interim Week 28, Section 11.2). Detailed results describing the AEs from the pooled Studies GS-US-200-4538 and GS-US-200-5709 are presented in this section.

Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

During the Functional Monotherapy Period for Cohort 1, the percentages of participants who experienced AEs were LEN 37.5% (9 of 24 participants); placebo 25.0% (3 of 12 participants). No deaths, serious adverse events (SAEs), AEs leading to discontinuation of study drug, or Grade 3 or higher AEs were reported in either the LEN or placebo group (Table 6).

Table 6. GS-US-200-4625: Treatment-Emergent Adverse Events: Overall Summary for Cohort 1 (Functional Monotherapy Period Analysis) (Safety Analysis Set)

Number (%) of Participants With Any	LEN (N = 24)	Placebo (N = 12)
TEAE	9 (37.5%)	3 (25.0%)
TEAE With Grade 3 or Higher	0	0
TEAE With Grade 2 or Higher	3 (12.5%)	0
TEAE Related to Study Drug	4 (16.7%)	1 (8.3%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0
TEAE Related to Study Drug With Grade 2 or Higher	2 (8.3%)	0
TE Serious AE	0	0
TE Serious AE Related to Study Drug	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	0
TEAE Leading to Premature Discontinuation of Study	0	0
All Deaths	0	0

AE = adverse event; LEN = lenacapavir; TE = treatment emergent; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAE was defined as an AE that began on or after the first dose date of blinded study drug and prior to the first dose date of the open-label study drug.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Death includes any death that occurred during the Functional Monotherapy Period.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.11.2.1.1.1

All LEN Analysis

In the All LEN Analysis of Study GS-US-200-4625, the percentage of participants who received LEN in Cohorts 1 and 2 who experienced AEs was 91.7% (66 of 72 participants). Four participants (5.6%) (2 in each cohort) experienced SAEs. One participant in Cohort 2 died in the study, experiencing an AE of cancer, not related to study drug. Five participants (13.9%) in Cohort 1 and 8 participants (22.2%) in Cohort 2 experienced Grade 3 or higher AEs (Table 7).

Table 7. GS-US-200-4625: Treatment-Emergent Adverse Events: Overall Summary (All LEN Analysis) (Safety Analysis Set)

Number (%) of Participants With Any	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)		
TEAE	22 (91.7%)	11 (91.7%)	33 (91.7%)	33 (91.7%)	66 (91.7%)
TEAE With Grade 3 or Higher	3 (12.5%)	2 (16.7%)	5 (13.9%)	8 (22.2%)	13 (18.1%)
TEAE With Grade 2 or Higher	12 (50.0%)	5 (41.7%)	17 (47.2%)	22 (61.1%)	39 (54.2%)
TEAE Related to Study Drug	17 (70.8%)	6 (50.0%)	23 (63.9%)	22 (61.1%)	45 (62.5%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0	0	4 (11.1%)	4 (5.6%)
TEAE Related to Study Drug With Grade 2 or Higher	6 (25.0%)	2 (16.7%)	8 (22.2%)	11 (30.6%)	19 (26.4%)
TE Serious AE	1 (4.2%)	1 (8.3%)	2 (5.6%)	2 (5.6%)	4 (5.6%)
TE Serious AE Related to Study Drug	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study	0	0	0	1 (2.8%)	1 (1.4%)
All Deaths	0	0	0	1 (2.8%)	1 (1.4%)

AE = adverse event; LEN = lenacapavir; TE = treatment emergent; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAE is defined as an AE that began on or after the first dose date of LEN.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Death includes any death that occurred on and after the first dose of LEN.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.11.2.1.1.2

Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In Study GS-US-200-4334, similar percentages of participants in the LEN total (total of 157 participants) and BVY (total of 25 participants) groups had any AE by Week 28 (LEN total 86.6%, 136 participants; BVY 84.0%, 21 participants). The percentages of participants with Grade 3 or higher AEs were also similar between the LEN total and BVY groups (LEN total

7.0%, 11 participants; BVY 4.0%, 1 participant). Serious AEs occurred only in the LEN total group (5.1%, 8 participants); none were considered related to study drug (Table 8).

Adverse events related to the study drug occurred at a higher frequency in the SC LEN total group than in the oral LEN + DVY or BVY groups, because of ISRs (SC LEN total 44.8% [47 of 105 participants], Oral LEN + DVY 13.5% [7 of 52 participants], and BVY 16.0% [4 of 25 participants]). Except for 1 participant (1.0%, 1 of 105) in the SC LEN total group with a Grade 3 AE related to study drug (injection site nodule), none of these were Grade 3 or higher.

Adverse events that led to a premature discontinuation of the study drug were ISRs occurring in 2 participants (1.9%) in the SC LEN total group and no participants in the other treatment groups.

Table 8. GS-US-200-4334: Treatment-Emergent Adverse Events: Overall Summary (Safety Analysis Set)

Number (%) of Participants With Any	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
TEAE	50 (96.2%)	44 (83.0%)	42 (80.8%)	21 (84.0%)	94 (89.5%)	136 (86.6%)
TEAE With Grade 3 or Higher	1 (1.9%)	4 (7.5%)	6 (11.5%)	1 (4.0%)	5 (4.8%)	11 (7.0%)
TEAE With Grade 2 or Higher	18 (34.6%)	15 (28.3%)	18 (34.6%)	11 (44.0%)	33 (31.4%)	51 (32.5%)
TEAE Related to Study Drug	27 (51.9%)	20 (37.7%)	7 (13.5%)	4 (16.0%)	47 (44.8%)	54 (34.4%)
TEAE Related to Study Drug With Grade 3 or Higher	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
TEAE Related to Study Drug With Grade 2 or Higher	8 (15.4%)	2 (3.8%)	0	0	10 (9.5%)	10 (6.4%)
TE Serious AE	2 (3.8%)	2 (3.8%)	4 (7.7%)	0	4 (3.8%)	8 (5.1%)
TE Serious AE Related to Study Drug	0	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)
TEAE Leading to Premature Discontinuation of Study	0	0	0	0	0	0
Death	0	0	0	0	0	0

AE = adverse event; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; TE = treatment emergent; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAEs began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.11.2.1.1

Additional Data Supporting the Safety of LEN: (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

The percentages of participants in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 with any AE were as follows: LEN 92.7%, 51 of 55 participants; placebo 85.0%, 17 of 20 participants). The majority of AEs were Grade 1 in severity. Grade 3 or higher AEs were reported as follows: LEN 1.8%, 1 participant; placebo 5.0%, 1 participant.

The incidence of AEs considered related to study drugs was as follows: LEN 83.6%, 46 of 55 participants; placebo 70.0%, 14 of 20 participants. Most were Grade 1 in severity. There were no Grade 3 or higher AEs considered related to study drug.

There were no deaths, and SAEs were reported as follows: LEN 1.8%, 1 participant; placebo 5.0%, 1 participant. No SAE was considered related to study drug. One participant (1.8%) in the LEN group prematurely discontinued study drug due to an AE considered not related to study drug (SARS-CoV-2 test positive).

Table 9. GS-US-200-4538 and GS-US-200-5709: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

Number (%) of Participants With Any	LEN (N = 55)	Placebo (N = 20)
TEAE	51 (92.7%)	17 (85.0%)
TEAE With Grade 3 or Higher	1 (1.8%)	1 (5.0%)
TEAE With Grade 2 or Higher	8 (14.5%)	2 (10.0%)
TEAE Related to Study Drug	46 (83.6%)	14 (70.0%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0
TEAE Related to Study Drug With Grade 2 or Higher	3 (5.5%)	0
TE Serious AE	1 (1.8%)	1 (5.0%)
TE Serious AE Related to Study Drug	0	0
TEAE Leading to Discontinuation of Study Drug	1 (1.8%)	0
TEAE Leading to Discontinuation of Study	1 (1.8%)	0
Death	0	0

AE = adverse event; TE = treatment-emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23.1.
TEAEs began on or after the study drug start date, or led to premature study drug discontinuation.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Death includes any death that occurred during the study.
Source: LEN ISS, Table 4

2.1.1. Common Adverse Events

2.1.1.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

Nausea was the only AE reported in > 1 participant (LEN 12.5%, 3 participants) during the Functional Monotherapy Period for Cohort 1 of Study GS-US-200-4625 (Table 10).

Table 10. GS-US-200-4625: Treatment-Emergent Adverse Events by Preferred Term for Cohort 1 Reported in > 5% of Participants in Either Treatment Group (Functional Monotherapy Period Analysis) (Safety Analysis Set)

	LEN (N = 24)	Placebo (N = 12)
Number (%) of Participants With Any Treatment-Emergent Adverse Event	9 (37.5%)	3 (25.0%)
Nausea	3 (12.5%)	0
Diarrhoea	1 (4.2%)	1 (8.3%)
Abscess limb	0	1 (8.3%)
Neck pain	0	1 (8.3%)
Thrombocytopenia	0	1 (8.3%)
Vomiting	0	1 (8.3%)

AE = adverse event; LEN = lenacapavir; PT = preferred term; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAE was defined as an AE that began on or after the first dose date of blinded study drug and prior to the first dose date of the open-label study drug.
Multiple AEs were counted only once per participant for the highest severity grade for each PT.
PTs were presented by descending order of the total frequencies.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.11.2.1.3.1

All LEN Analysis

The 3 most commonly reported AEs (reported in ≥ 5% of participants overall) were all ISRs, as follows (Table 11):

- Injection site swelling (29.2%, 21 of 72 participants)
- Injection site erythema (26.4%, 19 participants)
- Injection site pain (25.0%, 18 participants)

Three participants had Grade 3 ISRs that were attributed to enfuvirtide.

Table 11. GS-US-200-4625: Treatment-Emergent Adverse Events by Preferred Term for > 5% of Participants Overall (All LEN Analysis) (Safety Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Number (%) of Participants With Any Treatment-Emergent Adverse Events	22 (91.7%)	11 (91.7%)	33 (91.7%)	33 (91.7%)	66 (91.7%)
Injection site swelling	9 (37.5%)	3 (25.0%)	12 (33.3%)	9 (25.0%)	21 (29.2%)
Injection site erythema	7 (29.2%)	2 (16.7%)	9 (25.0%)	10 (27.8%)	19 (26.4%)
Injection site pain	7 (29.2%)	2 (16.7%)	9 (25.0%)	9 (25.0%)	18 (25.0%)
Injection site nodule	8 (33.3%)	4 (33.3%)	12 (33.3%)	2 (5.6%)	14 (19.4%)
Injection site induration	2 (8.3%)	0	2 (5.6%)	7 (19.4%)	9 (12.5%)
Diarrhoea	3 (12.5%)	2 (16.7%)	5 (13.9%)	1 (2.8%)	6 (8.3%)
Nausea	4 (16.7%)	1 (8.3%)	5 (13.9%)	1 (2.8%)	6 (8.3%)
Cough	2 (8.3%)	2 (16.7%)	4 (11.1%)	1 (2.8%)	5 (6.9%)
Headache	2 (8.3%)	0	2 (5.6%)	3 (8.3%)	5 (6.9%)
Pyrexia	1 (4.2%)	2 (16.7%)	3 (8.3%)	2 (5.6%)	5 (6.9%)
Urinary tract infection	2 (8.3%)	0	2 (5.6%)	3 (8.3%)	5 (6.9%)
Abdominal distension	3 (12.5%)	0	3 (8.3%)	1 (2.8%)	4 (5.6%)
Arthralgia	4 (16.7%)	0	4 (11.1%)	0	4 (5.6%)
Back pain	0	1 (8.3%)	1 (2.8%)	3 (8.3%)	4 (5.6%)
Constipation	2 (8.3%)	2 (16.7%)	4 (11.1%)	0	4 (5.6%)
Oral candidiasis	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Rash	2 (8.3%)	0	2 (5.6%)	2 (5.6%)	4 (5.6%)

AE = adverse event; LEN = lenacapavir; PT = preferred term
AEs were coded according to MedDRA Version 23.1.
Treatment-emergent AE was defined as an AE that began on or after the first dose date of LEN.
Multiple AEs were counted only once per participant for the highest severity grade for each PT.
PTs were presented by descending order of the total frequencies.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.11.2.1.3.2

2.1.1.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In Study GS-US-200-4334, the 3 most commonly reported AEs (reported in ≥ 5% of participants overall) by treatment group were as follows (Table 12):

- LEN total (157 participants), excluding ISRs: headache (11.5%, 18 participants), nausea (10.8%, 17 participants), and lymphadenopathy (7.6%, 12 participants)

- SC LEN total (105 participants), only ISRs: injection site swelling (22.9%, 24 participants), injection site erythema (21.0%, 22 participants), and injection site pain (each 21.0%, 22 participants)

- Oral LEN + DVY (52 participants): headache (13.5%, 7 participants), nausea, lymphadenopathy, diarrhea, back pain, and urinary tract infection (each 7.7%, 4 participants)

- BVY (25 participants): syphilis, insomnia, and weight increased (each 12.0%, 3 participants)

Table 12. GS-US-200-4334: Treatment-Emergent Adverse Events by Preferred Term Reported for ≥ 5% of Participants in Any Treatment Group (Safety Analysis Set)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Treatment-Emergent Adverse Events	50 (96.2%)	44 (83.0%)	42 (80.8%)	21 (84.0%)	94 (89.5%)	136 (86.6%)
Injection site swelling	13 (25.0%)	11 (20.8%)	0	0	24 (22.9%)	24 (15.3%)
Injection site erythema	13 (25.0%)	9 (17.0%)	0	0	22 (21.0%)	22 (14.0%)
Injection site pain	13 (25.0%)	9 (17.0%)	0	0	22 (21.0%)	22 (14.0%)
Headache	6 (11.5%)	5 (9.4%)	7 (13.5%)	2 (8.0%)	11 (10.5%)	18 (11.5%)
Nausea	9 (17.3%)	4 (7.5%)	4 (7.7%)	1 (4.0%)	13 (12.4%)	17 (10.8%)
Lymphadenopathy	4 (7.7%)	4 (7.5%)	4 (7.7%)	1 (4.0%)	8 (7.6%)	12 (7.6%)
COVID-19	5 (9.6%)	3 (5.7%)	3 (5.8%)	1 (4.0%)	8 (7.6%)	11 (7.0%)
Back pain	1 (1.9%)	4 (7.5%)	4 (7.7%)	2 (8.0%)	5 (4.8%)	9 (5.7%)
Diarrhoea	2 (3.8%)	4 (7.5%)	4 (7.7%)	1 (4.0%)	6 (5.7%)	10 (6.4%)
Injection site induration	7 (13.5%)	4 (7.5%)	0	0	11 (10.5%)	11 (7.0%)
Injection site nodule	6 (11.5%)	5 (9.4%)	0	0	11 (10.5%)	11 (7.0%)
Syphilis	3 (5.8%)	3 (5.7%)	2 (3.8%)	3 (12.0%)	6 (5.7%)	8 (5.1%)
Depression	1 (1.9%)	5 (9.4%)	3 (5.8%)	0	6 (5.7%)	9 (5.7%)
Arthralgia	1 (1.9%)	3 (5.7%)	2 (3.8%)	2 (8.0%)	4 (3.8%)	6 (3.8%)
Anxiety	1 (1.9%)	2 (3.8%)	3 (5.8%)	1 (4.0%)	3 (2.9%)	6 (3.8%)
Dizziness	3 (5.8%)	1 (1.9%)	2 (3.8%)	1 (4.0%)	4 (3.8%)	6 (3.8%)
Fatigue	0	4 (7.5%)	2 (3.8%)	1 (4.0%)	4 (3.8%)	6 (3.8%)
Hypertension	3 (5.8%)	2 (3.8%)	1 (1.9%)	1 (4.0%)	5 (4.8%)	6 (3.8%)
Insomnia	1 (1.9%)	1 (1.9%)	2 (3.8%)	3 (12.0%)	2 (1.9%)	4 (2.5%)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Pyrexia	3 (5.8%)	2 (3.8%)	1 (1.9%)	1 (4.0%)	5 (4.8%)	6 (3.8%)
Urinary tract infection	1 (1.9%)	1 (1.9%)	4 (7.7%)	1 (4.0%)	2 (1.9%)	6 (3.8%)
Weight increased	2 (3.8%)	0	2 (3.8%)	3 (12.0%)	2 (1.9%)	4 (2.5%)
Cough	3 (5.8%)	1 (1.9%)	0	1 (4.0%)	4 (3.8%)	4 (2.5%)
Proctitis gonococcal	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Rhinitis allergic	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Vomiting	1 (1.9%)	0	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Acarodermatitis	3 (5.8%)	0	0	0	3 (2.9%)	3 (1.9%)
Anal chlamydia infection	0	0	3 (5.8%)	0	0	3 (1.9%)
Constipation	0	0	3 (5.8%)	0	0	3 (1.9%)
Upper respiratory tract infection	1 (1.9%)	0	0	2 (8.0%)	1 (1.0%)	1 (0.6%)
Ligament sprain	0	0	0	2 (8.0%)	0	0

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); COVID-19 = coronavirus disease 2019;
DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple adverse events were counted only once per participant for the highest severity grade for each preferred term.
Preferred terms were presented by descending order of the total frequencies.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.11.2.1.3

2.1.1.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

In the pooled analysis, the 3 most commonly reported AEs (reported in > 5% of participants overall) in each treatment group were all ISRs, as follows (Table 13):

- LEN: injection site induration (72.7%, 40 participants), injection site pain (56.4%, 31 participants), and injection site erythema (47.3%, 26 participants)
- Placebo: injection site bruising (40.0%, 8 participants), injection site induration (30.0%, 6 participants), injection site pain and headache (25.0%, 5 participants each)

Table 13. GS-US-200-4538 and GS-US-200-5709: Treatment-Emergent Adverse Events by Preferred Term for > 5% of Participants in Either Treatment Group (Safety Analysis Set)

	LEN (N = 55)	Placebo (N = 20)
Number (%) of Participants With Any Treatment-Emergent Adverse Event	51 (92.7%)	17 (85.0%)
Number (%) of Participants With Any Treatment-Emergent Adverse Event by Preferred Term		
Injection site induration	40 (72.7%)	6 (30.0%)
Injection site pain	31 (56.4%)	5 (25.0%)
Injection site erythema	26 (47.3%)	0
Headache	11 (20.0%)	5 (25.0%)
Injection site bruising	7 (12.7%)	8 (40.0%)
Injection site swelling	13 (23.6%)	2 (10.0%)
Injection site nodule	10 (18.2%)	0
Upper respiratory tract infection	3 (5.5%)	3 (15.0%)
SARS-CoV-2 test positive	5 (9.1%)	0
Hypersensitivity	3 (5.5%)	1 (5.0%)
Oropharyngeal pain	3 (5.5%)	1 (5.0%)
Back pain	3 (5.5%)	0
Injection site pruritus	3 (5.5%)	0

AEs = adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; PT = preferred term
AEs were coded according to MedDRA Version 23.1.
Treatment-emergent AEs began on or after the study drug start date, or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant for each PT.
PTs were presented by descending order of total frequencies.
Source: LEN ISS, Table 5.2

2.1.2. Adverse Events by Severity

2.1.2.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

During the Functional Monotherapy Period for Cohort 1 of Study GS-US-200-4625, all AEs were Grade 1 or 2 in severity.

All LEN Analysis

The majority of AEs in the All LEN Analysis of Study GS-US-200-4625 were Grade 1 or 2 in severity.

Grade 3 or higher AEs were reported for 13 participants (18.1%). Grade 3 or higher AEs reported for ≥ 2 participants were all ISRs: injection site erythema (5.6%, 4 participants), injection site edema, injection site pain, and injection site swelling (2.8%, 2 participants each). Three participants had Grade 3 ISRs that were attributed to enfuvirtide.

Four participants experienced Grade 3 or higher AEs considered related to study drug: rash and abdominal abscess, injection site swelling and injection site erythema, injection site pain, and hepatic function abnormal (1 participant each).

2.1.2.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In Study GS-US-200-4334, the majority of AEs were Grade 1 or 2 in severity.

The percentage of participants with Grade 3 or higher AEs was 7.0% (11 of 157 participants) in the LEN total group and 4.0% (1 of 25 participants) in the BVY group. No Grade 3 or higher AEs were reported for > 1 participant in any treatment group (Table 14).

Table 14. GS-US-200-4334: Grade 3 or Higher Treatment-Emergent Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Grade 3 or Higher Treatment-Emergent Adverse Events	1 (1.9%)	4 (7.5%)	6 (11.5%)	1 (4.0%)	5 (4.8%)	11 (7.0%)
Anal fissure	0	0	1 (1.9%)	0	0	1 (0.6%)
Anxiety	0	0	1 (1.9%)	0	0	1 (0.6%)
Back pain	0	0	1 (1.9%)	0	0	1 (0.6%)
Bipolar disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Deep vein thrombosis	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Dyspnoea	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Hypertriglyceridaemia	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Injection site nodule	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Insomnia	0	0	1 (1.9%)	0	0	1 (0.6%)
Lymphadenopathy mediastinal	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Major depression	0	0	1 (1.9%)	0	0	1 (0.6%)
Metastases to central nervous system	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Nephrolithiasis	0	0	1 (1.9%)	0	0	1 (0.6%)
Non-small cell lung cancer	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pleural effusion	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumocystis jirovecii pneumonia	0	0	1 (1.9%)	0	0	1 (0.6%)
Pneumonia	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumothorax	0	0	1 (1.9%)	0	0	1 (0.6%)
Poisoning	0	0	1 (1.9%)	0	0	1 (0.6%)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Psychotic disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Substance-induced psychotic disorder	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Transient ischaemic attack	0	0	0	1 (4.0%)	0	0
Vomiting	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple adverse events were counted only once per participant for the highest severity grade for each preferred term.
Preferred terms were presented by descending order of the total frequencies.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.11.2.2.2.2

2.1.2.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

In the pooled analysis, the majority of AEs were Grade 1 in severity (Table 9). Grade 3 or higher AEs were reported for 1 participant (1.8%) in the LEN group (tibia fracture) and 1 participant (5.0%) in the placebo group (sepsis) (LEN ISS, Table 6.2). All Grade 3 or higher AEs were considered not related to study drug.

2.1.3. Adverse Events by Relationship to Study Drug

2.1.3.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

During the Functional Monotherapy Period for Cohort 1 of Study GS-US-200-4625, AEs considered related to study drugs that was reported in > 1 participant was nausea (8.3%, 2 participants in the LEN group).

All LEN Analysis

Overall, 62.5% (45 of 72 participants) in the All LEN Analysis of Study GS-US-200-4625 experienced treatment-related AEs. The 3 most commonly reported treatment-related AEs were all ISRs: injection site swelling (26.4%, 19 participants), injection site erythema (23.6%, 17 participants), and injection site pain (19.4%, 14 participants).

2.1.3.2. Other Data Supporting the Safety of LEN: (Study GS-US-200-4334)

In Study GS-US-200-4334, AEs considered related to study drug were as follows:

- LEN total (157 participants): 34.4% (54 participants)
- SC LEN total (105 participants): 44.8% (47 participants)
- Oral LEN + DVY (52 participants): 13.5% (7 participants)
- BVY (25 participants): 16.0% (4 participants)

The higher frequency of treatment-related AEs in the SC LEN total group was due to ISRs, as reflected in the most common AEs considered related to study drugs:

- LEN total group (157 participants), excluding ISRs: nausea (4.5%, 7 participants), diarrhea (2.5%, 4 participants), fatigue, and headache (each 1.9%, 3 participants)
- SC LEN total group (105 participants), only ISRs: injection site swelling (18.1%, 19 participants), injection site erythema (16.2%, 17 participants), injection site pain (15.2%, 16 participants)

- Oral LEN + DVY (52 participants): nausea (3.8%, 2 participants), diarrhea (3.8%, 2 participants), fatigue, headache, dyspepsia, flatulence, vomiting, weight increased, overdose, and hot flush (each 1.9%, 1 participant)

- BVY (25 participants): dyspepsia, salivary hypersecretion, insomnia, and weight increased (4.0%, 1 participant)

2.1.3.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

Adverse events considered related to study drug for participants in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 were as follows: LEN 83.6%, 46 of 55 participants; Placebo 70.0%, 14 of 20 participants (LEN ISS, Table 8.2).

Most study drug-related AEs were Grade 1 in severity. There were no Grade 3 or higher AEs considered related to study drugs (Table 9).

The 3 most commonly reported AEs considered related to study drug in each treatment group were all ISRs as follows:

- LEN: injection site induration (70.9%, 39 participants), injection site pain (56.4%, 31 participants), and injection site erythema (45.5%, 25 participants)

- Placebo: injection site bruising (40.0%, 8 participants), injection site induration (30.0%, 6 participants), and injection site pain (20.0%, 4 participants)

2.1.4. Deaths

2.1.4.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

There were no deaths in the Functional Monotherapy Period for Cohort 1 of Study GS-US-200-4625.

All LEN Analysis

One participant in Cohort 2 died on Study Day 90; the cause of death was cancer.

2.1.4.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

There were no deaths by Week 28 in Study GS-US-200-4334.

2.1.4.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

There were no deaths in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 (LEN ISS, Table 13 and Listing 5).

2.1.5. Serious Adverse Events

2.1.5.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

No SAEs were reported during the Functional Monotherapy Period for Cohort 1 of Study GS-US-200-4625.

All LEN Analysis

Serious AEs were reported for 5.6% (4 of 72 participants) in the All LEN Analysis of Study GS-US-200-4625; no SAEs were reported in > 1 participant. All SAEs were considered not related to study drug. One SAE of cancer resulted in death.

2.1.5.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In Study GS-US-200-4334, SAEs were reported for 5.1% (8 of 157 participants) in the LEN total group and no participants in the BVY group (Table 15). None of the SAEs were reported for > 1 participant in any treatment group, and none were considered related to the study drugs.

Multiple SAEs were reported in the MedDRA psychiatric disorders SOC. One participant with SAEs of bipolar disorder and major depression and a second participant with an SAE of psychotic disorder had relevant psychiatric medical histories that could have predisposed them to these SAEs, while a third participant experienced an SAE of substance-induced psychotic disorder.

Table 15. GS-US-200-4334: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Treatment-Emergent Serious Adverse Events	2 (3.8%)	2 (3.8%)	4 (7.7%)	0	4 (3.8%)	8 (5.1%)
Blood and lymphatic system disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Lymphadenopathy mediastinal	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Gastrointestinal disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Vomiting	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Infections and infestations	2 (3.8%)	2 (3.8%)	1 (1.9%)	0	4 (3.8%)	5 (3.2%)
Escherichia infection	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Perirectal abscess	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Pneumocystis jirovecii pneumonia	0	0	1 (1.9%)	0	0	1 (0.6%)
Pneumonia	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Staphylococcal infection	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Injury, poisoning and procedural complications	0	0	1 (1.9%)	0	0	1 (0.6%)
Poisoning	0	0	1 (1.9%)	0	0	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Metastases to central nervous system	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Non-small cell lung cancer	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Psychiatric disorders	0	1 (1.9%)	2 (3.8%)	0	1 (1.0%)	3 (1.9%)
Bipolar disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Major depression	0	0	1 (1.9%)	0	0	1 (0.6%)

System Organ Class Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Psychotic disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Substance-induced psychotic disorder	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	0	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Dyspnoea	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pleural effusion	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumothorax	0	0	1 (1.9%)	0	0	1 (0.6%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; PT = preferred term; SC = subcutaneous; SOC = system organ class; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple adverse events were counted only once per participant for the highest severity grade for each SOC and PT.
SOCs were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.11.3.1.

2.1.5.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

In the pooled analysis, SAEs were reported for 1 participant (1.8%) in the LEN group (tibia fracture) and 1 participant (5.0%) in the placebo group (sepsis). Neither of the SAEs were considered related to study drug or led to discontinuation of study drug. (LEN ISS, Table 11.2 and Listing 4).

2.1.6. Discontinuation Due to Adverse Events

2.1.6.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

No participant in the Functional Monotherapy Period or in the All LEN Analysis (N = 72) discontinued study drug due to an AE in Study GS-US-200-4625.

2.1.6.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In Study GS-US-200-4334, 2 of 105 participants (1.9%) in the SC LEN total group discontinued study drug prematurely due to AEs of injection site induration. Both occurrences were nonserious and Grade 1 in severity.

2.1.6.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

In the pooled analysis, 1 participant (1.8%; 1 of 55 participants) in the LEN group discontinued study drug and the study due to an AE (SARS-CoV-2 test positive) (LEN ISS, Table 15.2 and Listing 7 to 8).

2.1.7. Study Drug-Related Injection Site Reactions

2.1.7.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

For the All LEN Analysis in Study GS-US-200-4625, 40 participants (55.6%) experienced a study drug–related ISR. All were Grade 1 or 2 with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR which resolved after a few days. Three participants with Grade 3 ISRs were attributed to enfuvirtide. The median (Q1, Q3) total duration of any study drug-related ISR was 8 (3, 57) days. The most frequently reported ISRs (in ≥ 10% of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site swelling (26.4%, 19 participants), 11 (5, 20) days
- Injection site erythema (23.6%, 17 participants), 6 (3, 8) days
- Injection site pain (19.4%, 14 participants), 3 (2, 6) days
- Injection site nodule (18.1%, 13 participants), 153 (72, 232) days
- Injection site induration (12.5%, 9 participants), 71 (29, 171) days

Following the Day 1 SC dose of LEN in a total of 72 participants, the most frequently reported ISRs (reported in ≥ 10% of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site swelling (26.4%, 19 participants), 10 (4, 21) days
- Injection site erythema (23.6%, 17 participants), 6 (3, 8) days
- Injection site pain (19.4%, 14 participants), 3 (2, 6) days
- Injection site nodule (18.1%, 13 participants), 156 (71, 279) days
- Injection site induration (11.1%, 8 participants), 66 (22, 169) days

2.1.7.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In Study GS-US-200-4334, 40 of 103 participants (38.8%) who received SC LEN had a study drug-related ISR; all were Grade 1 or 2, except for 1 participant with a Grade 3 injection site nodule. The most frequently reported ISRs (≥ 10% of participants in the SC LEN total group) and their duration in median (Q1, Q3) days for the 221 total number of doses administered were as follows:

- Injection site swelling (18.4%, 19 participants); 10 (5, 14) days
- Injection site erythema (16.5%, 17 participants), 5 (2, 11) days
- Injection site pain (15.5%, 16 participants), 4 (1, 10) days
- Injection site induration (10.7%, 11 participants), 143 (74, 213) days
- Injection site nodule (10.7%, 11 participants), 189 (123, 338) days

After the Day 15 SC LEN injection, the most frequently reported ISRs (≥ 5% of participants in the SC LEN total group) and their duration in median (Q1, Q3) days for the 103 doses administered were as follows:

- Injection site erythema (13.6%, 14 participants), 5 (2, 11) days
- Injection site swelling (13.6%, 14 participants), 10 (5, 30) days
- Injection site pain (12.6%, 13 participants), 4 (1, 10) days
- Injection site nodule (9.7%, 10 participants), 318 (136, 362) days
- Injection site induration (8.7%, 9 participants), 202 (143, 257) days

2.1.8. Hypersensitivity Reactions

Preferred terms for defining hypersensitivity reactions were identified from the narrow Standardized MedDRA Query (SMQ) of "Hypersensitivity." Across Studies GS-US-200-4625, GS-US-200-4334 and the pooled Studies GS-US-200-4538 and GS-US-200-5709, no AEs matching PTs in this SMQ were SAEs and none resulted in study drug discontinuation.

2.1.8.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

During the Functional Monotherapy Period of Study GS-US-200-4625, Grade 1 AEs of rhinitis allergic and rash were reported for 1 participant each (4.2%) in the LEN group. Neither AE was considered related to study drug.

All LEN Analysis

For the All LEN Analysis in Study GS-US-200-4625, AEs that occurred in > 1 participant were rash (5.6%, 4 participants), and rash pruritic and rash papular (2.8%, 2 participants each).

Adverse events considered related to study drug were rash macular and rash papular reported for 1 participant each (1.4%) and rash for 2 participants (2.8%), all of which resolved and did not recur with ongoing LEN exposure. All AEs were Grade 1 or 2 in severity except for a Grade 3 AE of rash, reported as "exanthema", occurring concurrently with Grade 2 AEs of pyrexia and influenza like illness, all starting on Day 11 and resolving with ongoing LEN exposure and switch from Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate [TDF]) to Truvada (emtricitabine/TDF) in the OBR.

2.1.8.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In the LEN total group of Study GS-US-200-4334, 1 participant developed Grade 2 urticaria on Day 153, and 3 participants (1.9%) experienced the PT of hypersensitivity, reported as Grade 1"allergy," Grade 1 "allergic reaction," and Grade 2 "allergic reaction on face" on Days 190, 65, and 24, respectively. The participant who experienced "allergic reaction in face" also experienced a concurrent AE of food poisoning on the same day.

Other AEs that occurred in > 1 participant were rhinitis allergic (2.5%, 4 participants), rash (1.9%, 3 participants), and rash macular (1.3%, 2 participants). All rash events were Grade 1 and each resolved and did not recur with ongoing LEN exposure.

None of the AEs were considered related to study drug.

2.1.8.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

In the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709, AEs of hypersensitivity (reported term of "environmental allergy") were reported for 3 participants in

the LEN group (5.5%) and in 1 participant in the placebo group (5.0%). None of the AEs were considered related to study drug.

2.2. Narratives

Narratives for deaths, SAEs, and discontinuations due to AEs are provided in the relevant CSRs.

3. CLINICAL LABORATORY EVALUATIONS

All laboratory abnormalities discussed in the following sections were treatment-emergent and are referred to as laboratory abnormalities.

Detailed clinical laboratory evaluation results are described and provided in the individual CSRs (GS-US-200-4625 Interim Week 26, Section 11.6 and GS-US-200-4334 Interim Week 28, Section 11.6).

There were no clinically relevant changes from baseline in median values for hematology, clinical chemistry (including metabolic parameters) in Studies GS-US-200-4625, GS-US-200-4334 and the pooled Studies GS-US-200-4538 and GS-US-200-5709 (LEN ISS, Tables 16.1.1 to 16.2.5).

3.1. Graded Laboratory Abnormalities

Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Functional Monotherapy Period

The majority of participants in the Functional Monotherapy Period of Study GS-US-200-4625 had at least 1 graded laboratory abnormality (LEN 75.0% [18 of 24 participants]; placebo 75.0% [9 of 12 participants]). The majority of abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 3 participants (12.5%) in the LEN group (increased creatinine, hyperglycemia [nonfasting], and increased lipase) and no participants in the placebo group. No participants experienced Grade 4 laboratory abnormalities.

All LEN Analysis

For the All LEN Analysis of Study GS-US-200-4625, the majority of the participants had at least 1 graded laboratory abnormality (91.7%, 66 of 72 participants). The majority of abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 15 participants (20.8%) and Grade 4 laboratory abnormalities were reported for 4 participants (5.6%) (Table 16).

For both the Functional Monotherapy Period and All LEN Analysis, none of the laboratory abnormalities reported were considered clinically relevant; all were transient, improved on subsequent visits despite continued exposure to the study drug, or participants had previous underlying conditions such as diabetes. No participants had Grade 3 or higher increase in creatine kinase (CK) or CK-associated AEs such as rhabdomyolysis during the study.

Table 16. GS-US-200-4625: Grade 3 or 4 Laboratory Abnormalities Reported in ≥ 2 Participants – All LEN Analysis (Safety Analysis Set)

Maximum Postbaseline Toxicity Grade	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)		
Participants With Postbaseline Value	24	12	36	36	72
Grade 3 or 4	8 (33.3%)	4 (33.3%)	12 (33.3%)	7 (19.4%)	19 (26.4%)
Grade 3	8 (33.3%)	3 (25.0%)	11 (30.6%)	4 (11.1%)	15 (20.8%)
Grade 4	0	1 (8.3%)	1 (2.8%)	3 (8.3%)	4 (5.6%)
Chemistry					
Creatinine, High	24	12	36	36	72
Grade 3 or 4	4 (16.7%)	0	4 (11.1%)	2 (5.6%)	6 (8.3%)
Grade 3	4 (16.7%)	0	4 (11.1%)	1 (2.8%)	5 (6.9%)
Grade 4	0	0	0	1 (2.8%)	1 (1.4%)
Creatinine Clearance or eGFR, Low	24	12	36	36	72
Grade 3 or 4	3 (12.5%)	2 (16.7%)	5 (13.9%)	2 (5.6%)	7 (9.7%)
Grade 3	3 (12.5%)	2 (16.7%)	5 (13.9%)	2 (5.6%)	7 (9.7%)
Grade 4	0	0	0	0	0
Hyperglycemia, Fasting	20	9	29	26	55
Grade 3 or 4	1 (5.0%)	2 (22.2%)	3 (10.3%)	0	3 (5.5%)
Grade 3	1 (5.0%)	1 (11.1%)	2 (6.9%)	0	2 (3.6%)
Grade 4	0	1 (11.1%)	1 (3.4%)	0	1 (1.8%)
Hyperglycemia, Nonfasting	17	8	25	25	50
Grade 3 or 4	2 (11.8%)	1 (12.5%)	3 (12.0%)	0	3 (6.0%)
Grade 3	2 (11.8%)	1 (12.5%)	3 (12.0%)	0	3 (6.0%)
Grade 4	0	0	0	0	0
Urinalysis					
Glycosuria (Dipstick)	24	12	36	36	72
Grade 3 or 4	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Grade 3	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Grade 4	0	0	0	0	0
Proteinuria (Dipstick)	24	12	36	36	72
Grade 3 or 4	1 (4.2%)	1 (8.3%)	2 (5.6%)	0	2 (2.8%)
Grade 3	1 (4.2%)	1 (8.3%)	2 (5.6%)	0	2 (2.8%)
Grade 4	0	0	0	0	0

eGFR = estimated glomerular filtration rate; LEN = lenacapavir
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
For summary over all laboratory tests, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline.
For Urinalysis (ie, urine glucose, urine protein, the highest grade is up to Grade 3.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.11.6.4.2.2

Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

The majority of participants in Study GS-US-200-4334 had at least 1 graded laboratory abnormality (LEN total 94.9% [149 of 157 participants]; BVY 100.0% [25 of 25 participants]). The majority of laboratory abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 19 participants (12.1%) in the LEN total group and 3 participants (12.0%) in the BVY group.(Table 17).

Grade 4 laboratory abnormalities were reported for 7 participants (4.5%) in the LEN total group only and included high creatine kinase (3 participants).

None of the laboratory abnormalities were considered clinically relevant; all were transient or unconfirmed, or participants had a medical history of underlying conditions such as diabetes. Grade 3 or higher abnormalities of high CK were isolated and infrequent, improved on subsequent visits despite continued exposure to the study drug and were attributed to strenuous activity, dehydration, or use of creatine. There were no CK-associated AEs such as rhabdomyolysis during the study.

Table 17. GS-US-200-4334: Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities for ≥ 3 Participants in Any Treatment Group (Safety Analysis Set)

Maximum Postbaseline Toxicity Grade	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Participants With Postbaseline Value	52	53	52	25	105	157
Grade 3 or 4	8 (15.4%)	10 (18.9%)	8 (15.4%)	3 (12.0%)	18 (17.1%)	26 (16.6%)
Grade 3	6 (11.5%)	8 (15.1%)	5 (9.6%)	3 (12.0%)	14 (13.3%)	19 (12.1%)
Grade 4	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)
Chemistry						
AST (SGOT), High	52	53	52	25	105	157
Grade 3 or 4	1 (1.9%)	1 (1.9%)	2 (3.8%)	0	2 (1.9%)	4 (2.5%)
Grade 3	1 (1.9%)	1 (1.9%)	2 (3.8%)	0	2 (1.9%)	4 (2.5%)
Grade 4	0	0	0	0	0	0
Creatine Kinase, High	52	53	52	25	105	157
Grade 3 or 4	3 (5.8%)	2 (3.8%)	2 (3.8%)	0	5 (4.8%)	7 (4.5%)
Grade 3	2 (3.8%)	1 (1.9%)	1 (1.9%)	0	3 (2.9%)	4 (2.5%)
Grade 4	1 (1.9%)	1 (1.9%)	1 (1.9%)	0	2 (1.9%)	3 (1.9%)
Creatinine, High	52	53	52	25	105	157
Grade 3 or 4	1 (1.9%)	2 (3.8%)	0	1 (4.0%)	3 (2.9%)	3 (1.9%)
Grade 3	1 (1.9%)	2 (3.8%)	0	1 (4.0%)	3 (2.9%)	3 (1.9%)
Grade 4	0	0	0	0	0	0
Creatinine Clearance or eGFR, Low	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	3 (5.7%)	1 (1.9%)	2 (8.0%)	5 (4.8%)	6 (3.8%)
Grade 3	2 (3.8%)	3 (5.7%)	1 (1.9%)	2 (8.0%)	5 (4.8%)	6 (3.8%)
Grade 4	0	0	0	0	0	0

Maximum Postbaseline Toxicity Grade	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Hyperglycemia, Fasting	48	51	50	21	99	149
Grade 3 or 4	1 (2.1%)	1 (2.0%)	1 (2.0%)	0	2 (2.0%)	3 (2.0%)
Grade 3	1 (2.1%)	1 (2.0%)	1 (2.0%)	0	2 (2.0%)	3 (2.0%)
Grade 4	0	0	0	0	0	0
Triglycerides (Fasting)	46	51	46	21	97	143
Grade 3 or 4	0	3 (5.9%)	0	1 (4.8%)	3 (3.1%)	3 (2.1%)
Grade 3	0	2 (3.9%)	0	1 (4.8%)	2 (2.1%)	2 (1.4%)
Grade 4	0	1 (2.0%)	0	0	1 (1.0%)	1 (0.7%)
Lipase, High	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)
Grade 3	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)
Grade 4	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Hyperglycemia, Nonfasting	41	37	33	18	78	111
Grade 3 or 4	2 (4.9%)	1 (2.7%)	0	0	3 (3.8%)	3 (2.7%)
Grade 3	2 (4.9%)	0	0	0	2 (2.6%)	2 (1.8%)
Grade 4	0	1 (2.7%)	0	0	1 (1.3%)	1 (0.9%)
Urinalysis						
Glycosuria (Dipstick)	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	1 (1.9%)	0	3 (2.9%)	4 (2.5%)
Grade 3	2 (3.8%)	1 (1.9%)	1 (1.9%)	0	3 (2.9%)	4 (2.5%)
Grade 4	0	0	0	0	0	0

AST = aspartate aminotransferase; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); eGFR = estimated glomerular filtration rate; LEN = lenacapavir; SC = subcutaneous; SGOT = serum glutamic oxaloacetic transaminase; TAF = tenofovir alafenamide

Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (corrected Version 2.1, July 2017).
For summary over all laboratory tests, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last exposure date.
The fourth generation low-density lipoprotein is derived from Friedewald formula: total cholesterol – high-density lipoprotein – triglyceride/5.
For Urinalysis (ie, urine glucose), the highest grade is up to Grade 3.
Source: GS-US-200-4334 Interim Week 28 CSR, Table 15.11.6.4.2

Additional Data Supporting Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

The majority of participants in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 had at least 1 graded laboratory abnormality (LEN 80.0% [44 of 55 participants]; placebo 90.0% [18 of 20 participants]) (LEN ISS, Table 17). The majority of abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 8 participants (14.5%) in the LEN group and 4 participants (20.0%) in the placebo group (Table 18).

Grade 4 laboratory abnormalities were reported for 2 of 55 participants (3.6%) who received LEN (increased fasting triglycerides) and 1 of 20 participants (5.0%) who received placebo (increased CK).

None of the laboratory abnormalities were considered clinically relevant, as they were transient or unconfirmed, or participants had a medical history of underlying conditions (eg, diabetes). Grade 3 or higher abnormalities of increased CK occurred in 1 participant (1.8%) in the LEN group and 3 participants (15.0%) in the placebo group, all abnormalities improved on subsequent visits despite continued exposure to the study drug and were attributed to strenuous activity, dehydration or use of creatine. There were no CK-associated AEs such as rhabdomyolysis.

Although not part of the ISS analysis for Studies GS-US-200-4538 and GS-US-200-5709, in Cohort 3 of Study GS-US-200-4329, evaluating the safety, tolerability, PK, metabolism, and excretion of LEN following a single IV dose in healthy participants, 1 participant who received LEN 20 mg had a Grade 4 SAE of rhabdomyolysis which was considered related to study drug and resolved during continued exposure to LEN. The participant was confined at the time and there were no reports of recent strenuous exercise, trauma, illicit substance use, or prior CK elevations. The time of onset of the rhabdomyolysis (Day 22) for this participant was 21 days after the C_{max} of LEN was reached (within 1 hour of dosing), and the LEN concentration was approximately 150-fold lower on Day 22 than C_{max} on Day 1 (Day 1: 210 ng/mL; Day 22: 1.43 ng/mL). In addition, CK levels for this participant continued to decrease in the presence of ongoing LEN exposure (GS-US-200-4329 Final CSR, Section 11.4).

Table 18. GS-US-200-4538 and GS-US-200-5709: Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

	LEN (N = 55)	Placebo (N = 20)
Participants With Postbaseline Value	55	20
Any Grade 3 or Above	10 (18.2%)	5 (25.0%)
Grade 3	8 (14.5%)	4 (20.0%)
Grade 4	2 (3.6%)	1 (5.0%)
Hematology		
Hemoglobin (Decreased)	55	20
Any Grade 3 or Above	1 (1.8%)	0
Grade 3	1 (1.8%)	0
Grade 4	0	0

	LEN (N = 55)	Placebo (N = 20)
Chemistry		
AST (Increased)	55	20
Any Grade 3 or Above	0	1 (5.0%)
Grade 3	0	0
Grade 4	0	1 (5.0%)
CPK (Increased)	55	20
Any Grade 3 or Above	1 (1.8%)	3 (15.0%)
Grade 3	1 (1.8%)	2 (10.0%)
Grade 4	0	1 (5.0%)
Creatinine Clearance (Decreased)	55	20
Any Grade 3 or Above	0	1 (5.0%)
Grade 3	0	1 (5.0%)
Grade 4	0	0
Serum Glucose (Fasting, Hypoglycemia)	55	20
Any Grade 3 or Above	1 (1.8%)	0
Grade 3	1 (1.8%)	0
Grade 4	0	0
LDL (Fasting, Increased)	55	20
Any Grade 3 or Above	3 (5.5%)	1 (5.0%)
Grade 3	3 (5.5%)	1 (5.0%)
Grade 4	0	0
Triglycerides (Fasting, Increased)	55	20
Any Grade 3 or Above	5 (9.1%)	0
Grade 3	3 (5.5%)	0
Grade 4	2 (3.6%)	0
Lipase (Increased)	31	1
Any Grade 3 or Above	0	1 (100.0%)
Grade 3	0	0
Grade 4	0	1 (100.0%)

AST = aspartate aminotransferase; CPK = creatine phosphokinase; LDL = low-density lipoprotein; LEN = lenacapavir
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
For maximum postdose toxicity grade, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from predose.
Source: LEN ISS, Table 18

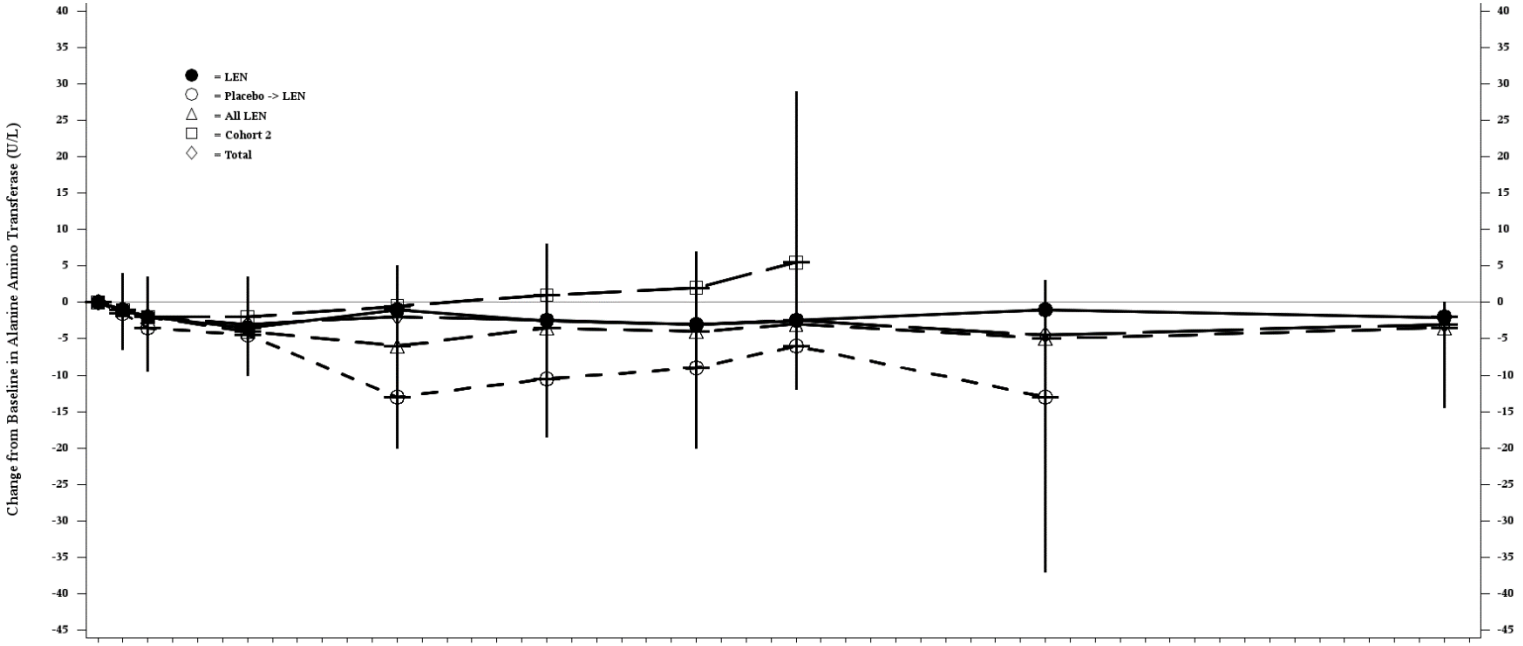
3.1.1. Hepatobiliary Laboratory Parameters

3.1.1.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

For the All LEN Analysis in Study GS-US-200-4625, there were no clinically relevant changes from baseline in ALT, AST (Figure 1 and Figure 2), or total bilirubin. One participant (2.8%) experienced a Grade 3 increase in ALT and a Grade 4 increase in AST, which were reported as an AE of immune reconstitution inflammatory syndrome considered as associated with an ongoing medical history of chronic hepatitis B.

There was no clinically relevant change from baseline in alkaline phosphatase (Figure 3). No participants experienced Grade 3 or Grade 4 increases in alkaline phosphatase.

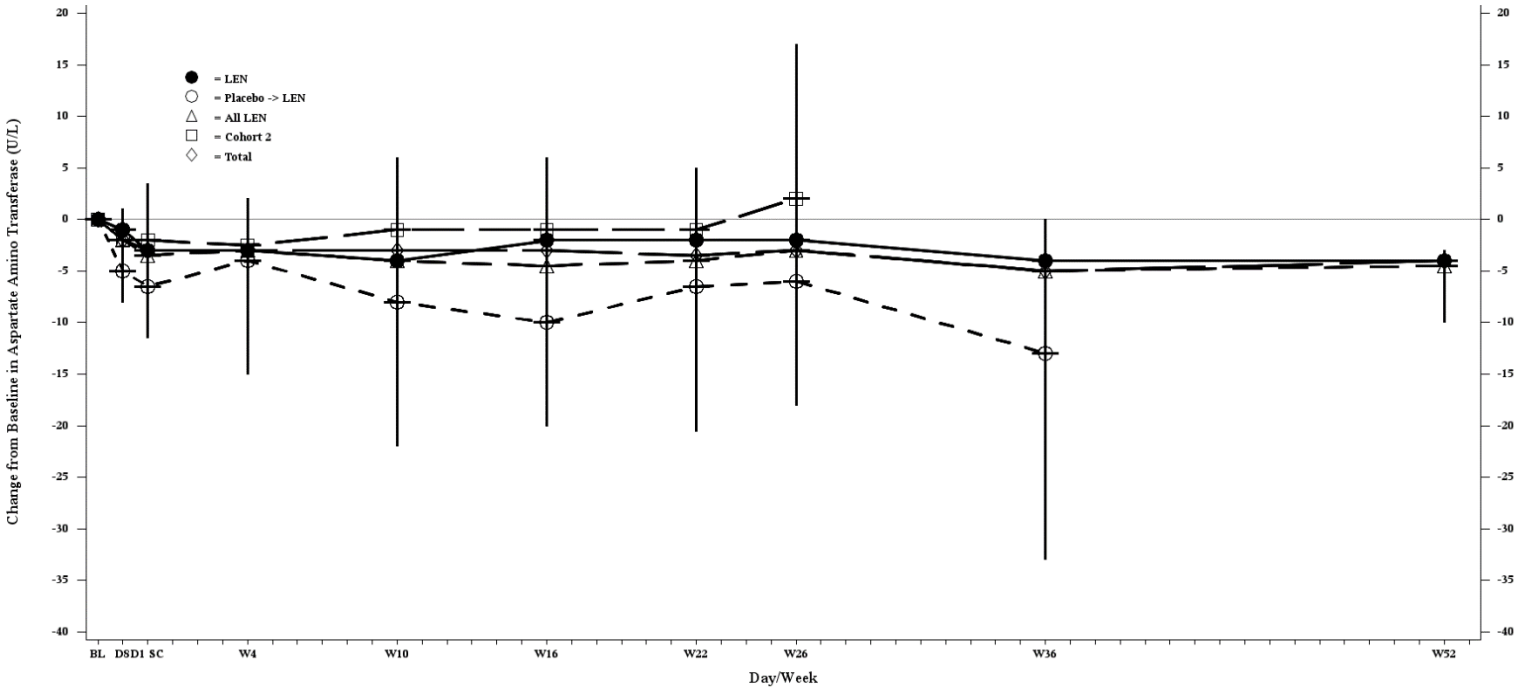
Figure 1. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Alanine Amino Transferase (U/L) by Visit-All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	24	24	24	24	23	24	14	8
Placebo -> LEN (n=):	12	12	12	12	11	12	12	12	7	
All LEN (n=):	36	36	36	36	35	36	35	36	21	12
Cohort 2 (n=):	36	36	36	36	32	22	13	6		
Total (n=):	72	72	72	72	67	58	48	42	22	13

BL = baseline; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 26 CSR, Figure 15.11.6.4.8

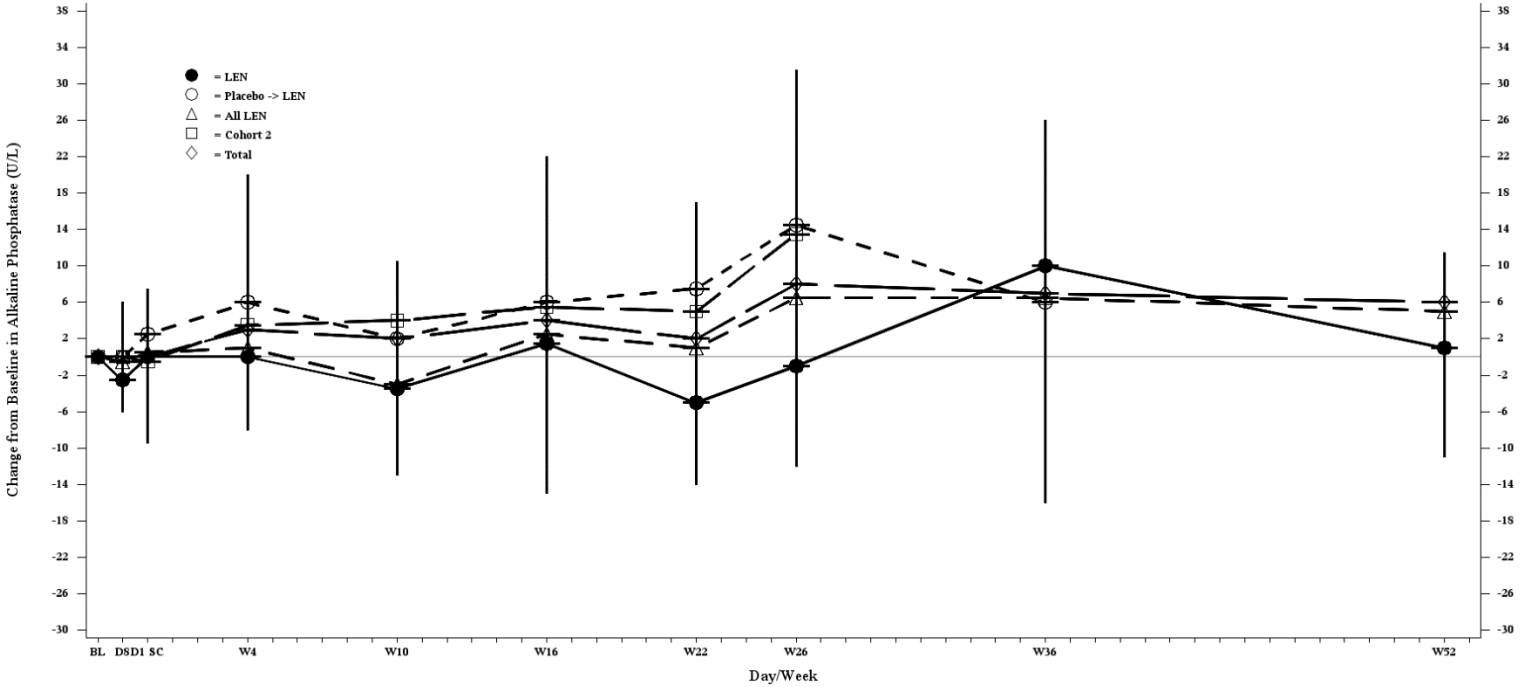
Figure 2. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Aspartate Amino Transferase (U/L) by Visit – All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	24	23	24	24	23	23	15	8
Placebo -> LEN (n=):	12	11	12	12	11	12	12	12	7	
All LEN (n=):	36	35	36	35	35	36	35	35	22	12
Cohort 2 (n=):	36	35	36	36	32	21	13	6		
Total (n=):	72	70	72	71	67	57	48	41	23	13

BL = baseline; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 26 CSR, Figure 15.11.6.4.9

Figure 3. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Alkaline Phosphatase (U/L) by Visit – All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	24	24	24	24	23	24	15	8
Placebo -> LEN (n=):	12	12	12	12	11	12	12	12	7	
All LEN (n=):	36	36	36	36	35	36	35	36	22	12
Cohort 2 (n=):	36	36	36	36	32	22	13	6		
Total (n=):	72	72	72	72	67	58	48	42	23	13

BL = baseline; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 26 CSR, Figure 15.11.6.4.7

3.1.1.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

There were no clinically relevant changes from baseline in ALT, AST, and alkaline phosphatase (Figure 4, Figure 5, and Figure 6) in Study GS-US-200-4334.

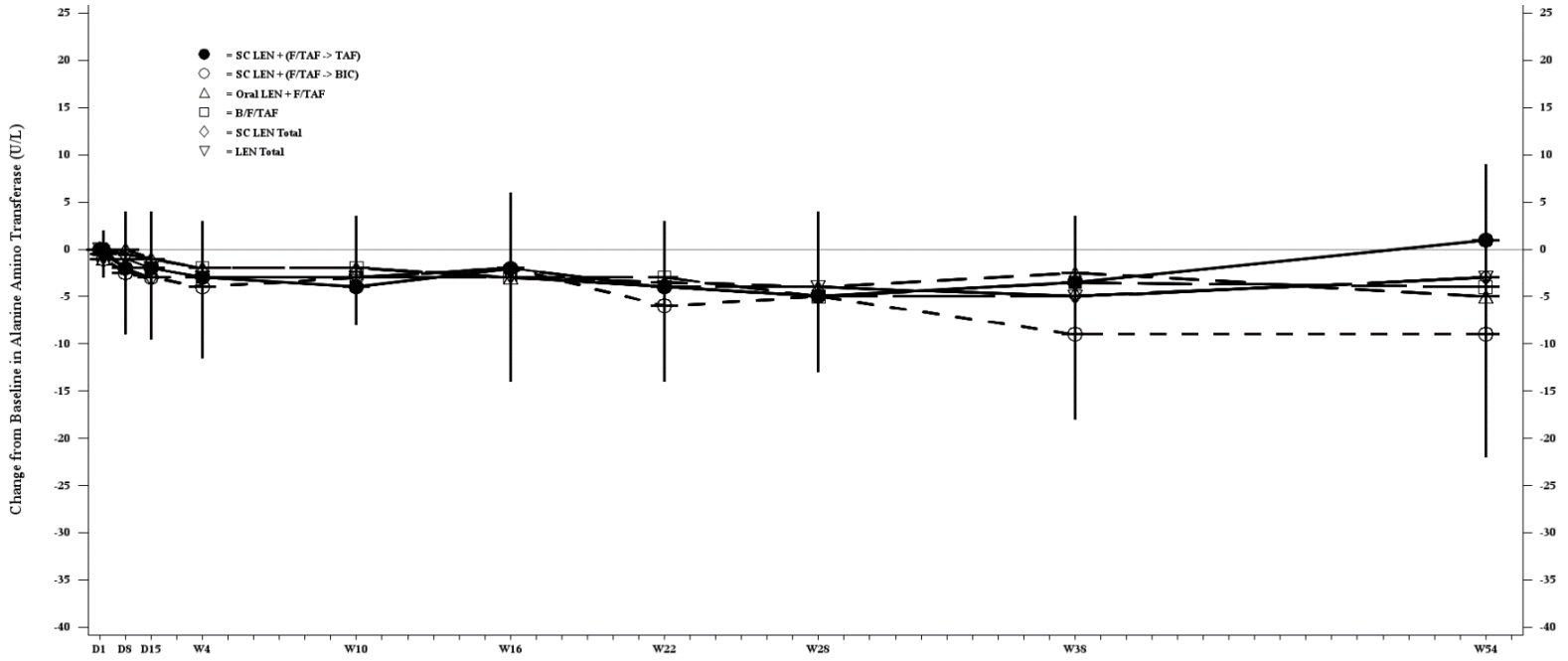
Grade 3 or higher laboratory abnormalities in the LEN total group (157 participants) and the BVY group (25 participants) included the following:

- High ALT: 2 participants (1.3%) and 0 participants, respectively
- High AST: 4 participants (2.5%) and 0 participants, respectively
- Hyperbilirubinemia: 1 participant (0.6%) and 1 participant (4.0%), respectively

For all participants, Grade 3 or higher laboratory abnormalities either improved or returned to normal.

No Grade 3 or higher alkaline phosphatase laboratory abnormalities were reported for any treatment group.

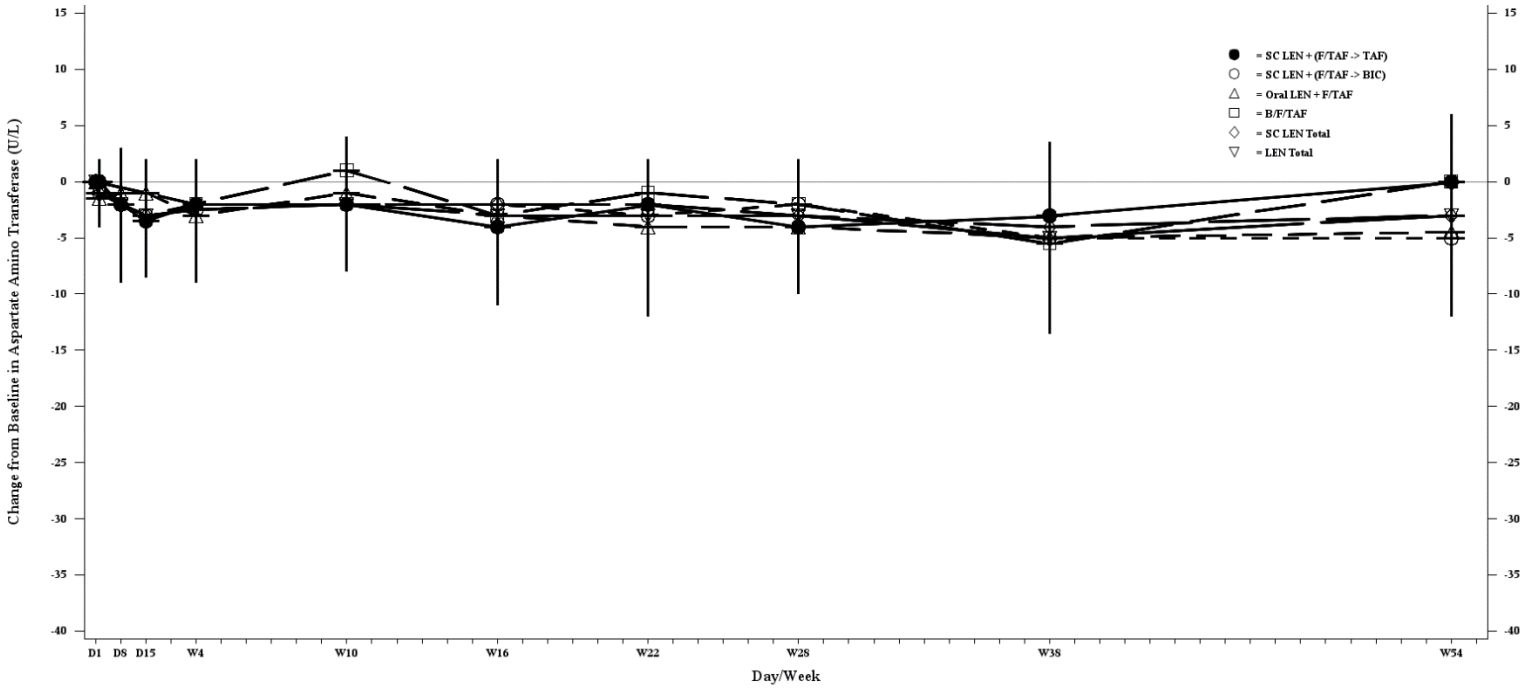
Figure 4. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Alanine Amino Transferase (U/L) by Visit (Safety Analysis Set)



SC LEN + (F/TAF -> TAF) (n=):	52	52	51	51	49	49	50	49	28	21
SC LEN + (F/TAF -> BIC) (n=):	53	52	52	52	52	51	51	51	31	17
Oral LEN + F/TAF (n=):	52	51	51	51	52	51	50	49	28	20
B/F/TAF (n=):	25			25	25	25	25	25	16	11
SC LEN Total (n=):	105	104	103	103	101	100	101	100	59	38
LEN Total (n=):	157	155	154	154	153	151	151	149	87	58

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 28 CSR, Figure 15.11.2.8

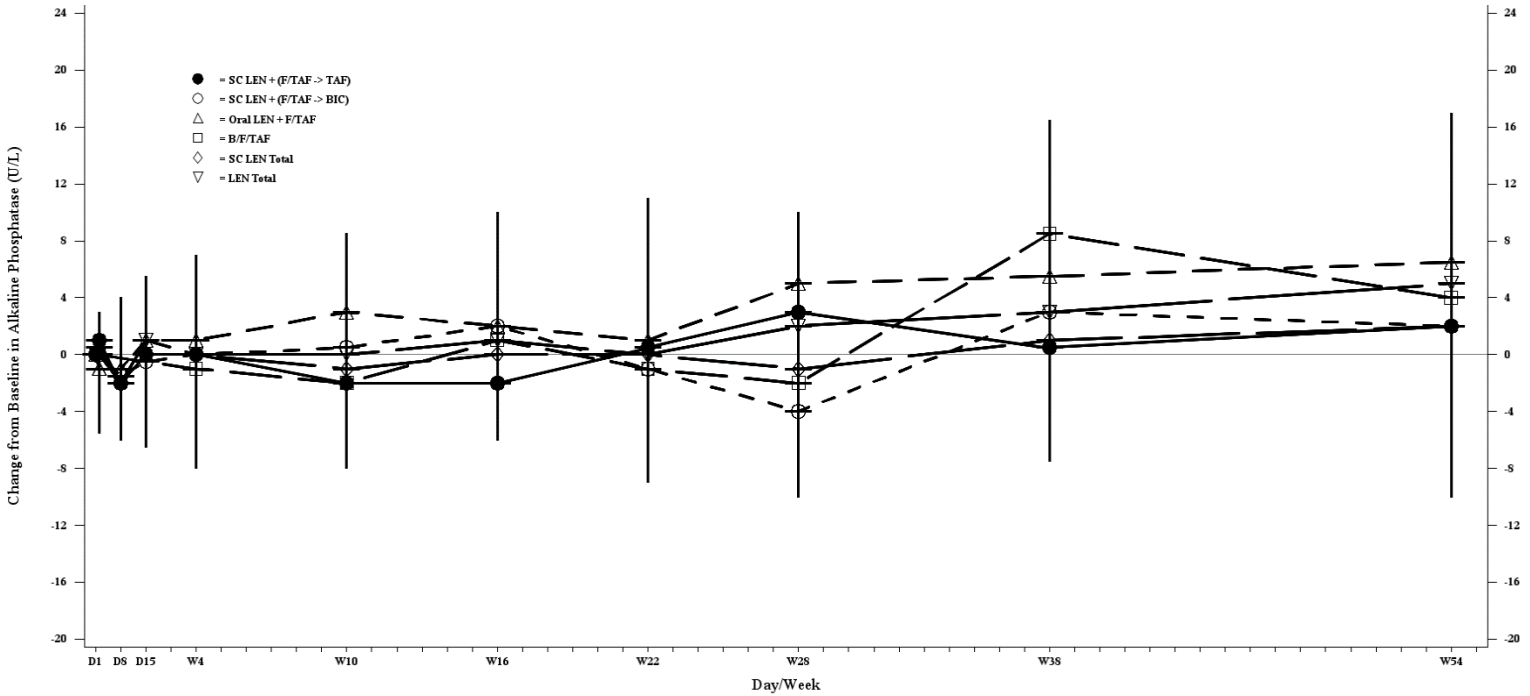
Figure 5. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Aspartate Amino Transferase (U/L) by Visit (Safety Analysis Set)



SC LEN + (F/TAF -> TAF) (n=):	52	52	50	50	49	49	50	49	28	21
SC LEN + (F/TAF -> BIC) (n=):	53	51	52	52	52	51	51	51	31	17
Oral LEN + F/TAF (n=):	52	51	51	50	52	51	50	49	28	20
B/F/TAF (n=):	25			25	25	25	25	25	16	11
SC LEN Total (n=):	105	103	102	102	101	100	101	100	59	38
LEN Total (n=):	157	154	153	152	153	151	151	149	87	58

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 28 CSR, Figure 15.11.2.9

Figure 6. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Alkaline Phosphatase (U/L) by Visit Safety Analysis Set (Safety Analysis Set)



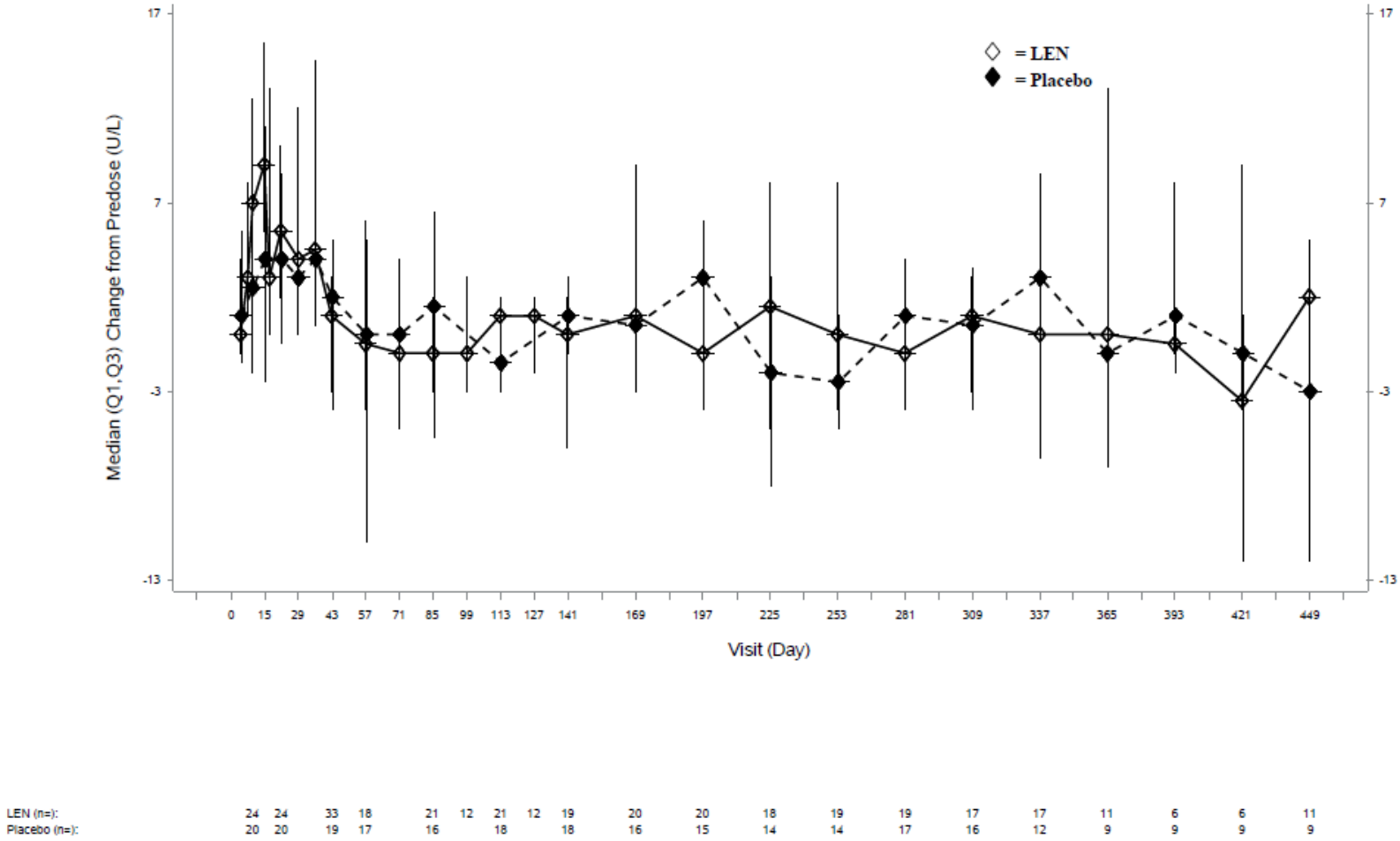
SC LEN + (F/TAF -> TAF) (n=):	52	52	51	51	49	49	50	49	28	21
SC LEN + (F/TAF -> BIC) (n=):	53	52	52	52	52	51	51	51	31	17
Oral LEN + F/TAF (n=):	52	51	51	51	52	51	50	50	28	20
B/F/TAF (n=):	25			25	25	25	25	25	16	11
SC LEN Total (n=):	105	104	103	103	101	100	101	100	59	38
LEN Total (n=):	157	155	154	154	153	151	151	150	87	58

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY) LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 28 CSR, Figure 15.11.2.7

3.1.1.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

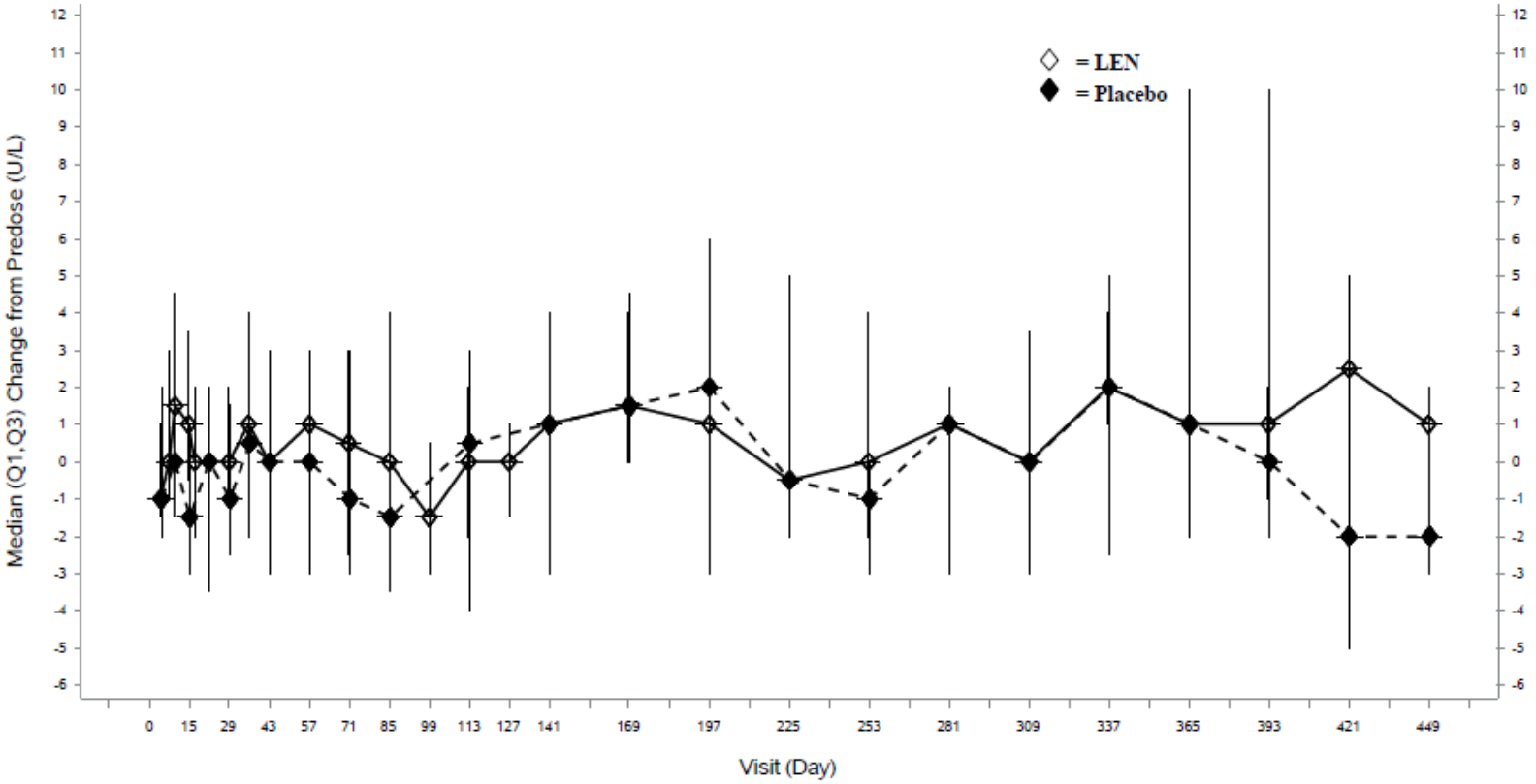
There were no clinically relevant changes from baseline in ALT, AST, total bilirubin, and alkaline phosphatase (Figure 7, Figure 8, Figure 2.7, and Figure 9 and Tables 16.1.3, 16.1.4, 16.1.7, and 16.1.2, respectively).

Figure 7. **GS-US-200-4538 and GS-US-200-5709: Median (Q1, Q3) ALT (U/L) Change From Predose Versus Time (Safety Analysis Set)**



ALT = alanine aminotransferase; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Source: LEN ISS, Figure 2.3

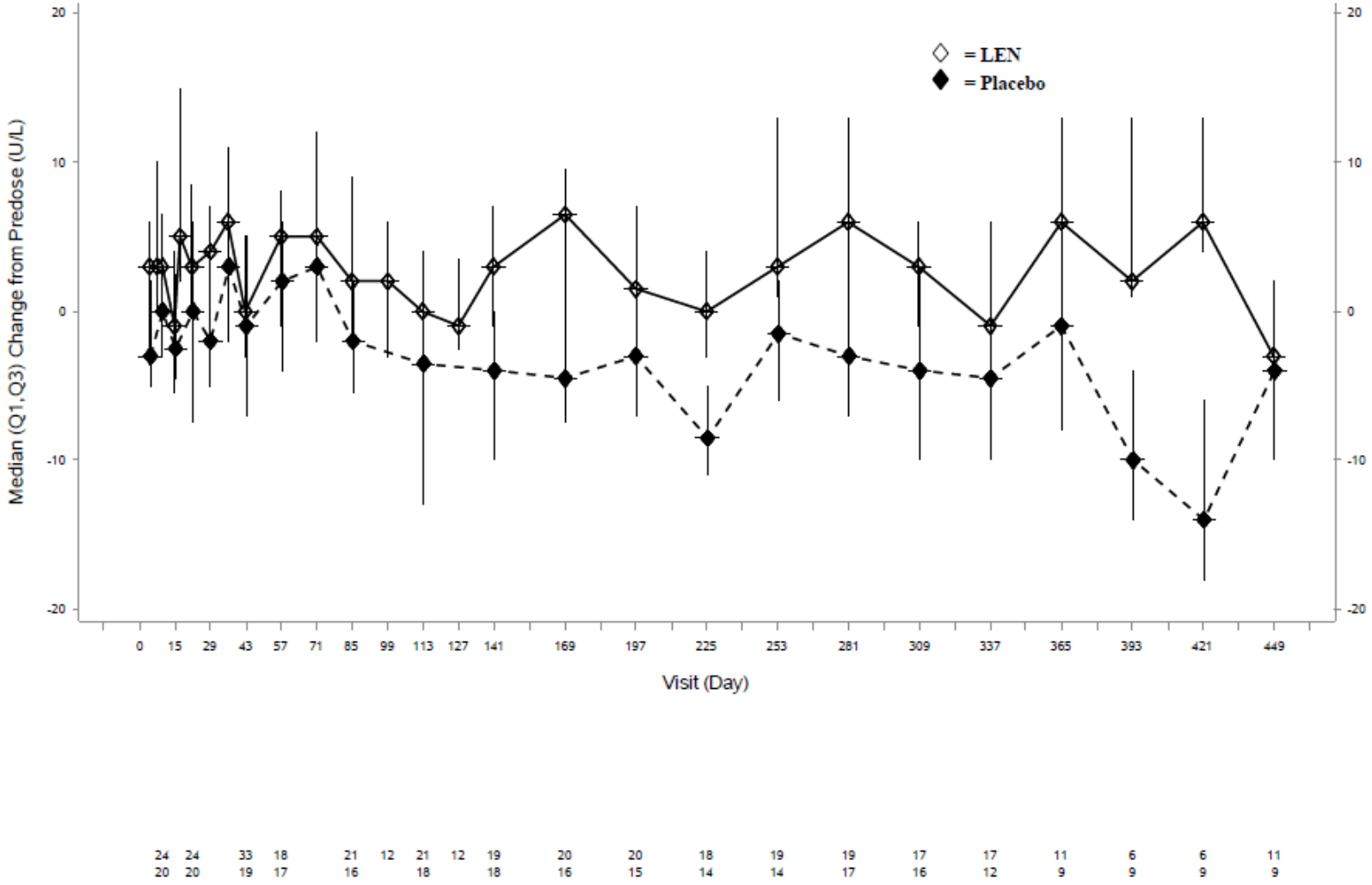
Figure 8. **GS-US-200-4538 and GS-US-200-5709: Median (Q1, Q3) AST (U/L) Change From Predose Versus Time (Safety Analysis Set)**



LEN (n=):	24	24	33	18	21	12	21	12	19	20	20	18	19	19	17	17	11	6	6	11
Placebo (n=):	20	20	19	17	16		18		18	16	15	14	14	17	16	12	9	9	9	9

AST = aspartate aminotransferase; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Source: LEN ISS, Figure 2.4

Figure 9. **GS-US-200-4538 and GS-US-200-5709: Median (Q1, Q3) Alkaline Phosphatase (U/L) Change From Predose Versus Time (Safety Analysis Set)**



LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Source: LEN ISS, Figure 2.2

3.1.2. Renal Laboratory Parameters

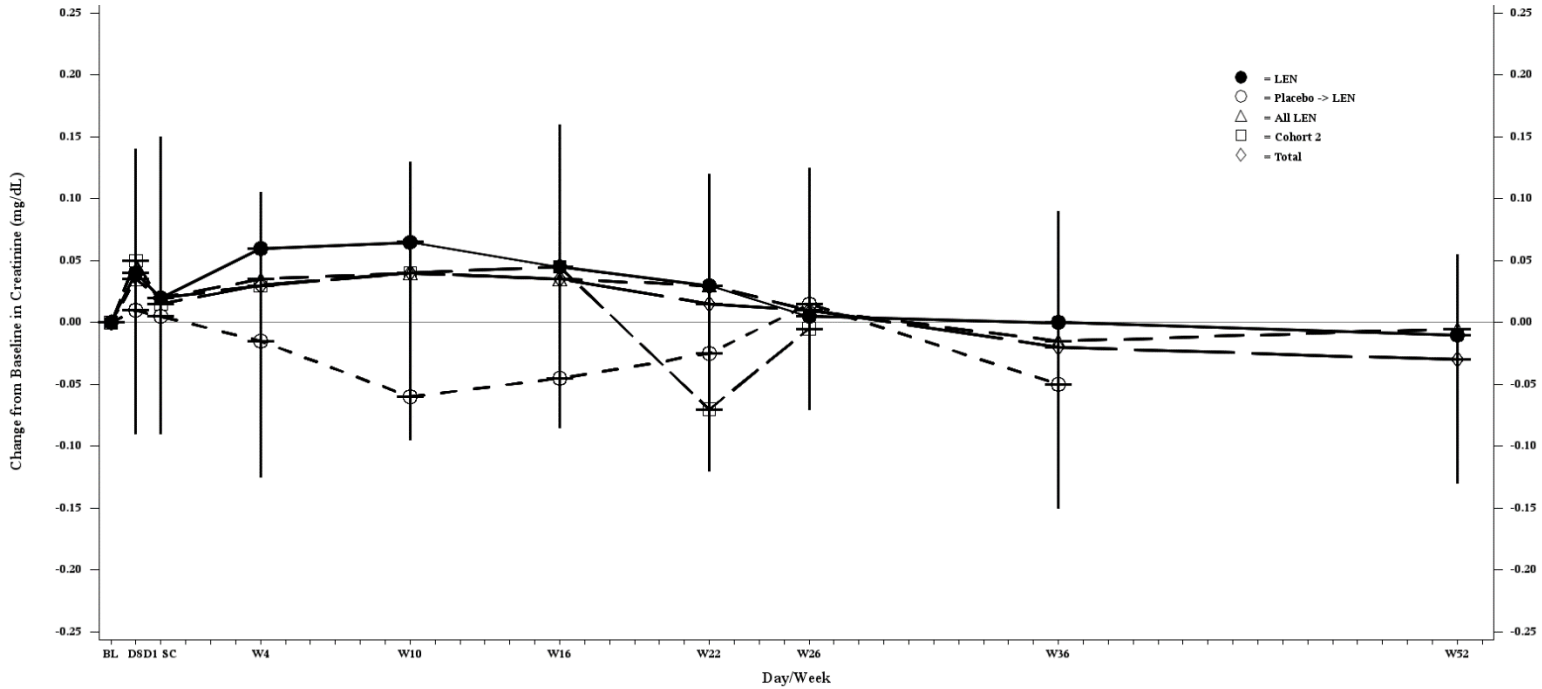
3.1.2.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

There were no clinically relevant changes in serum creatinine and eGFR by Cockcroft-Gault ($eGFR_{CG}$) from baseline (Figure 10 and Figure 11). Grade 3 or higher renal laboratory abnormalities for the All LEN Analysis were reported as follows:

- Grade 3 increased creatinine: 5 participants (6.9%)
- Grade 3 low creatinine clearance or eGFR: 7 participants (9.7%)
- Grade 4 increased creatinine: 1 participant (1.4%)

For most participants, the abnormalities either improved or returned to normal during the study.

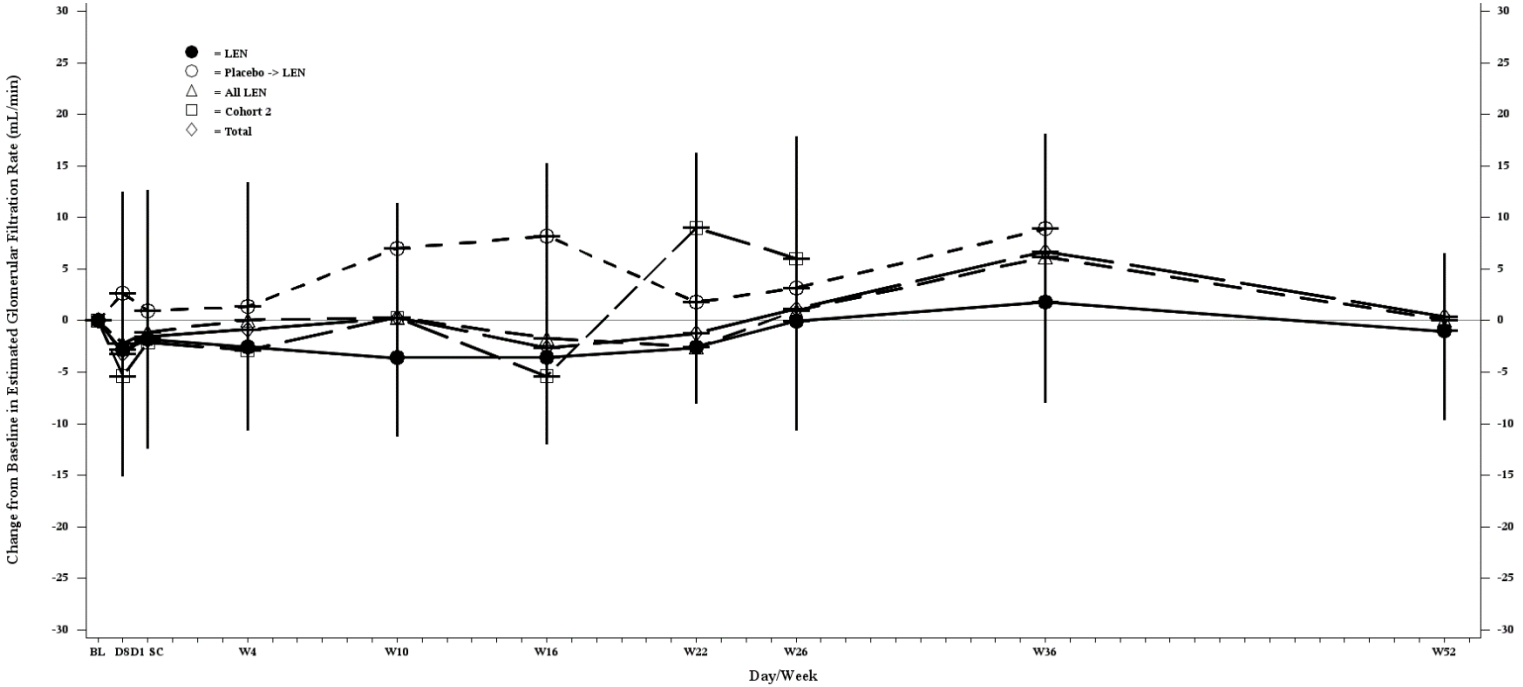
Figure 10. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Creatinine (mg/dL) by Visit – All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	24	24	24	24	23	24	15	8
Placebo -> LEN (n=):	12	12	12	12	11	12	12	12	7	
All LEN (n=):	36	36	36	36	35	36	35	36	22	12
Cohort 2 (n=):	36	36	36	36	32	22	13	6		
Total (n=):	72	72	72	72	67	58	48	42	23	13

BL = baseline; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 26 CSR, Figure 15.11.6.4.4

Figure 11. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Estimated Glomerular Filtration Rate (mL/min) by Visit – All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	24	24	24	24	23	24	15	8
Placebo -> LEN (n=):	12	12	12	12	11	12	12	12	7	
All LEN (n=):	36	36	36	36	35	36	35	36	22	12
Cohort 2 (n=):	36	36	36	36	32	22	13	6		
Total (n=):	72	72	72	72	67	58	48	42	23	13

BL = baseline; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source GS-US-200-4625 Interim Week 26 CSR, Figure 15.11.6.4.5

3.1.2.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

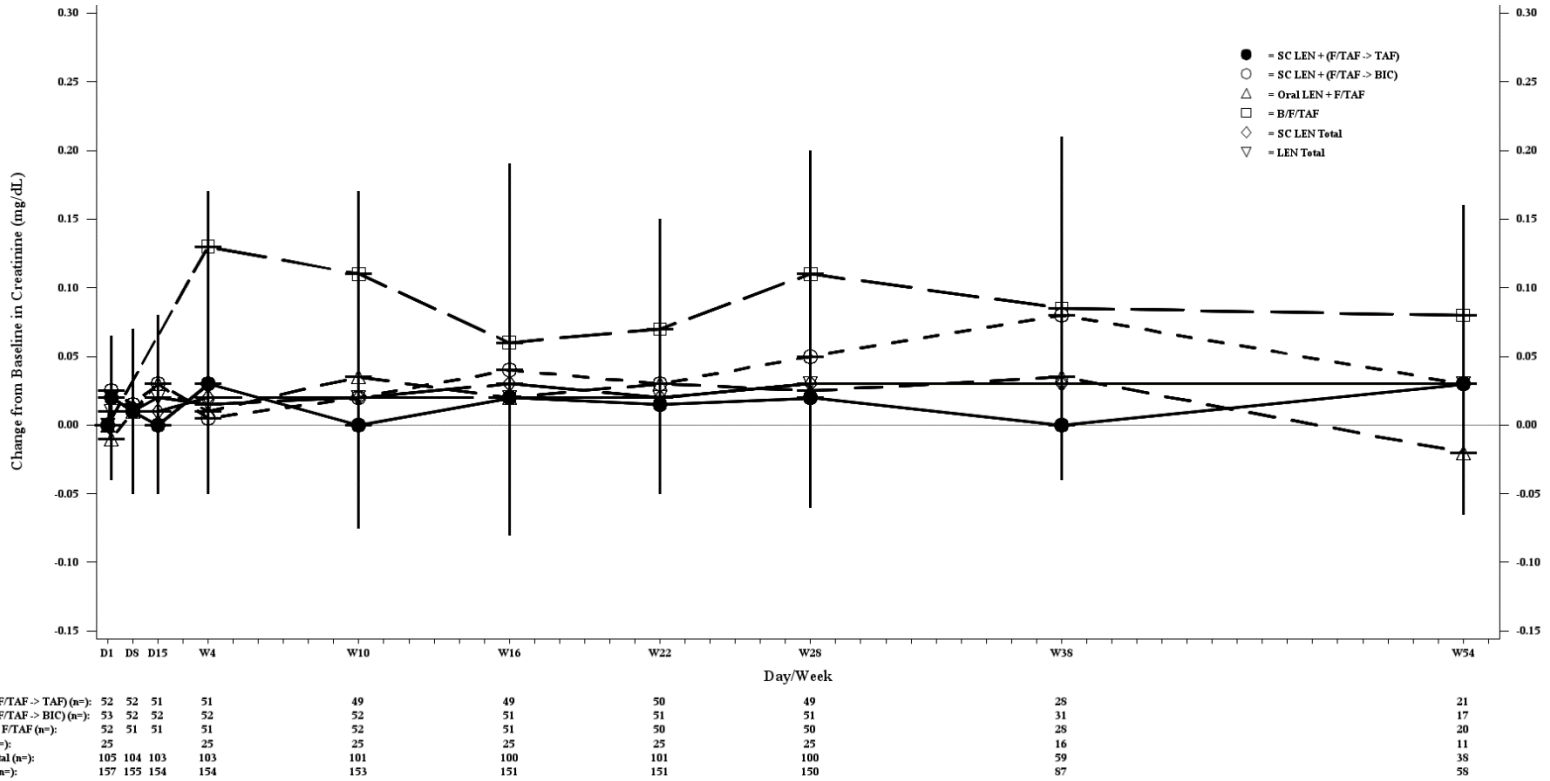
There were no clinically relevant changes in serum creatinine and $eGFR_{CG}$ from baseline in participants treated with LEN (Figure 12 and Figure 13). Median creatinine increased and median eGFR decreased in participants receiving BVY, consistent with previously described effects on the tubular excretion of creatinine {BIKTARVY 2021}.

Grade 3 or higher laboratory abnormalities in the LEN total group (157 participants) and the BVY group (25 participants) were reported as follows:

- High creatinine: 3 participants (1.9%) and 1 participant (4.0%), respectively
- Low creatinine clearance or eGFR: 6 participants (3.8%) and 2 participants (8.0%), respectively

For all participants, the laboratory abnormalities either improved or returned to normal during the study.

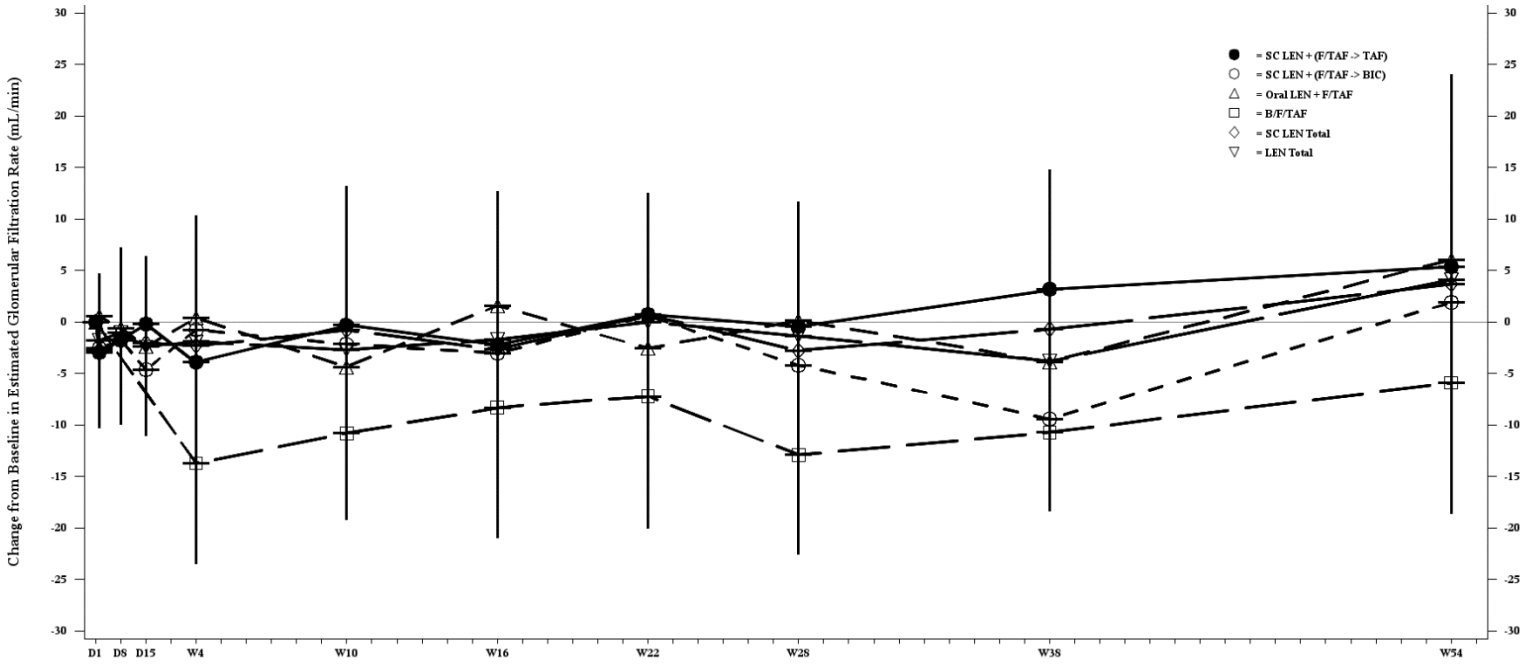
Figure 12. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Creatinine (mg/dL) by Visit (Safety Analysis Set)



SC LEN + (F/TAF -> TAF) (n=):	52	52	51	51	49	49	50	49	28	21
SC LEN + (F/TAF -> BIC) (n=):	53	52	52	52	52	51	51	51	31	17
Oral LEN + F/TAF (n=):	52	51	51	51	52	51	50	50	28	20
B/F/TAF (n=):	25			25	25	25	25	25	16	11
SC LEN Total (n=):	105	104	103	103	101	100	101	100	59	38
LEN Total (n=):	157	155	154	154	153	151	151	150	87	58

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 28 CSR, Figure 15.11.2.4

Figure 13. GS-US-200-4334: Change From Baseline in Estimated Glomerular Filtration Rate (mL/min) by Visit (Safety Analysis Set)



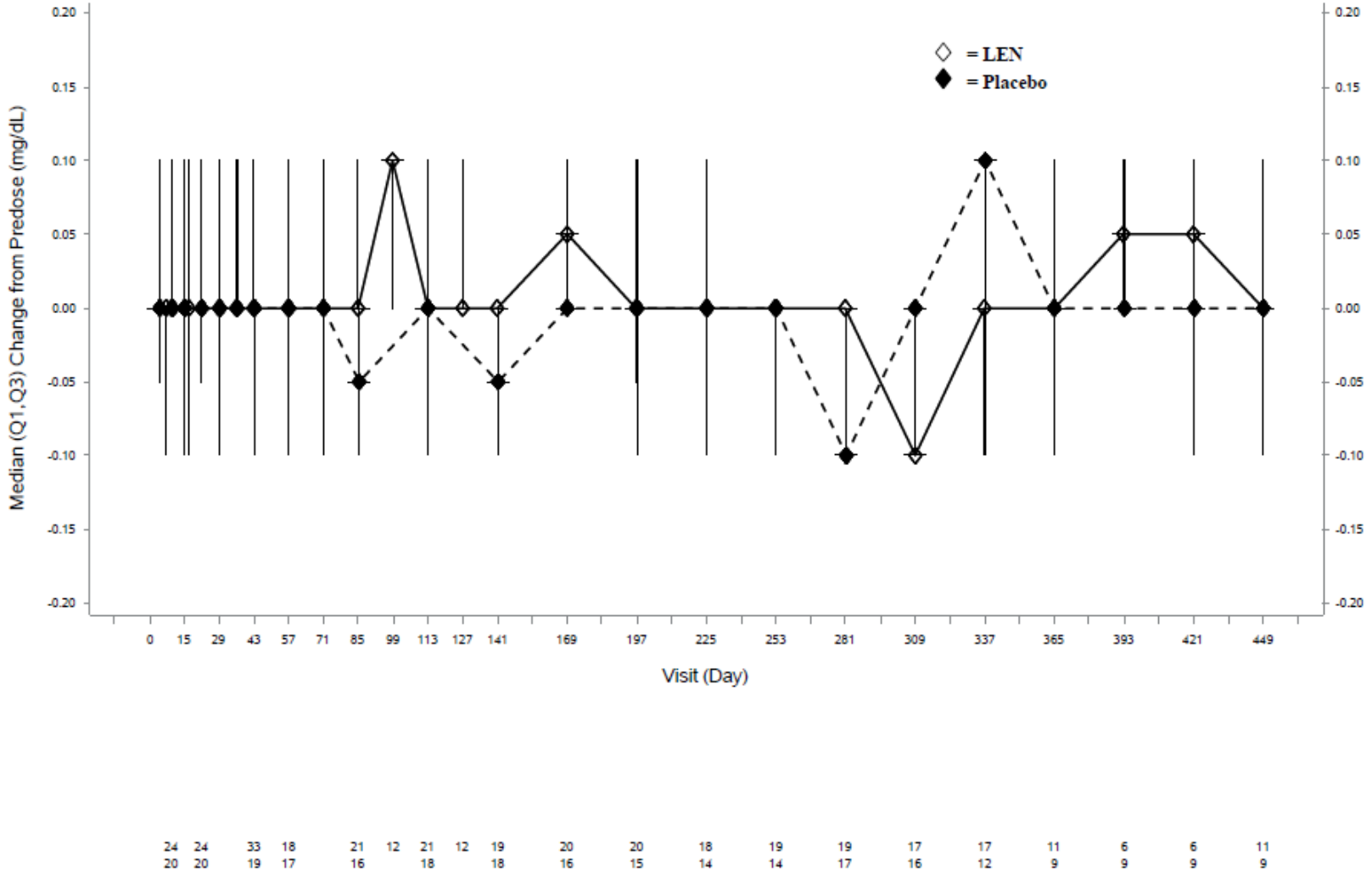
SC LEN + (F/TAF -> TAF) (n=):	52	52	51	51	49	49	50	49	28	21
SC LEN + (F/TAF -> BIC) (n=):	53	52	52	52	52	51	51	51	31	17
Oral LEN + F/TAF (n=):	52	51	51	51	52	51	50	50	28	20
B/F/TAF (n=):	25			25	25	25	25	25	16	11
SC LEN Total (n=):	105	104	103	103	101	100	101	100	59	38
LEN Total (n=):	157	155	154	154	153	151	151	150	87	58

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Baseline value was the last available value collected on or prior to first dose of study drug.
Source GS-US-200-4334 Interim Week 28 CSR, Figure 15.11.2.5

3.1.2.3. Additional Data Supporting the Safety of LEN (Pooled Studies GS-US-200-4538 and GS-US-200-5709)

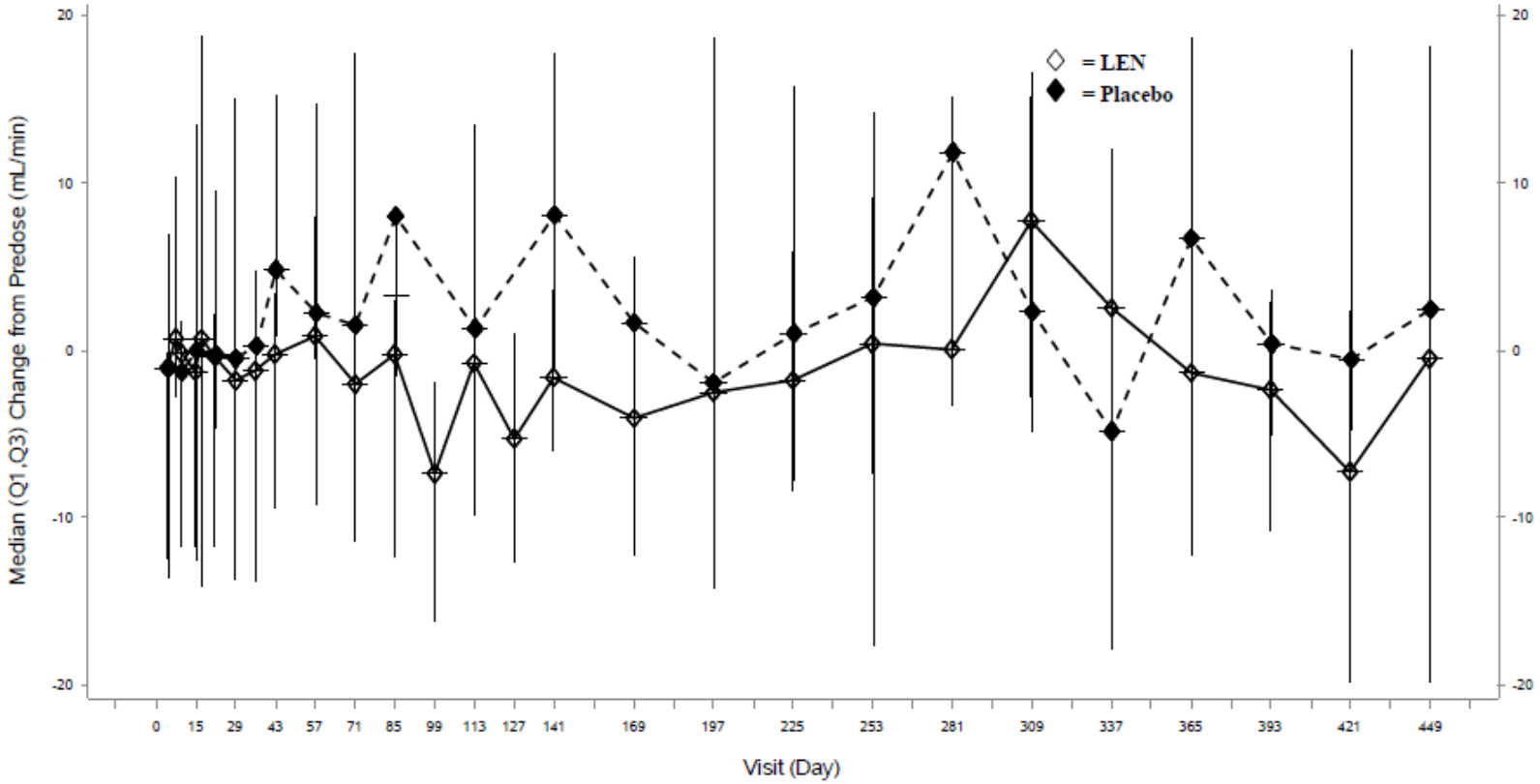
There were no clinically relevant changes in serum creatinine and creatinine clearance from baseline in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 (Figure 14 and Figure 15, and Tables 16.1.5 and 16.1.6).

Figure 14. **GS-US-200-4538 and GS-US-200-5709: Median (Q1, Q3) Creatinine (mg/dL) Change From Predose Versus Time (Safety Analysis Set)**



LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Source: LEN ISS, Figure 2.5

Figure 15. **GS-US-200-4538 and GS-US-200-5709: Median (Q1, Q3) Creatinine Clearance (mL/min) Change From Predose Versus Time (Safety Analysis Set)**



LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Source: LEN ISS, Figure 2.6

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

A detailed description and summary of vital signs, physical findings, and other observations related to safety are provided in the individual CSRs (GS-US-200-4625 Interim Week 26, Section 11.7 and GS-US-200-4334 Interim Week 28, Section 11.7).

4.1. Vital Signs and Body Weight

In both the primary study supporting LEN safety (All LEN Analysis of Study GS-US-200-4625) or other data supporting LEN safety (Study GS-US-200-4334), there were no clinically relevant changes from baseline or in median values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, or body temperature.

The median (Q1, Q3) increase in body weight by study was as follows:

- Study GS-US-200-4625 at Week 26: 2.0 (−0.9, 5.5) kg.
- Study GS-US-200-4334 by Week 28: LEN total group 2.3 (−0.2, 4.8) kg; BVY group 2.7 (0, 4.8) kg in the BVY group.

4.2. ECG Findings

In Studies GS-US-200-4625, GS-US-200-4334, and the pooled Studies GS-US-200-4538 and GS-US-200-5709, there were no clinically significant abnormal ECGs at screening or post-treatment.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

No impact of age, sex, and race was identified on the PK of LEN (m2.7.2, Section 3.1.6.4).

Summaries of AE incidence by subgroup are provided by age group, sex, and race in the individual CSRs (GS-US-200-4625 Interim Week 26 CSR, Tables 15.11.2.1.4.1 to 15.11.2.1.4.3 and GS-US-200-4334 Interim Week 28 CSR, Tables 15.11.2.1.4.1 to 15.11.2.1.4.3).

No clinically meaningful conclusions can be made due to the low number of participants in each subgroup; however based on the available data, there is no difference in the safety profile of LEN due to age, sex, or race.

5.2. Extrinsic Factors

5.2.1. Region

5.2.1.1. Study GS-US-200-4625

A summary of AE incidence by subgroup is provided by region in the CSR for Study GS-US-200-4625 (GS-US-200-4625 Interim Week 26 CSR, Table 15.11.2.1.4.4). No clinically meaningful conclusions can be made due to the low number of participants in the subgroups by region.

5.3. Drug Interactions

The drug-drug interaction (DDI) potential of LEN with coadministered drugs that may be used by people with HIV-1 infection has been evaluated in DDI clinical studies. A detailed summary of drug interaction potential and management of known interactions is provided in m2.7.2, Section 3.1.7.2.

Lenacapavir is a substrate of cytochrome P450 enzyme 3A (CYP3A), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Strong inducers of CYP3A, P-gp, and UGT1A1, such as rifampin, may significantly decrease plasma concentrations of LEN. As such, rifampin is contraindicated with LEN. Moderate inducers of CYP3A and P-gp, such as efavirenz, may also significantly decrease plasma concentrations of LEN, and as such, are not recommended with LEN.

Strong CY3A4 inhibitors alone (eg, voriconazole) or strong inhibitors of CYP3A4 and P-gp together (eg, cobicistat) do not result in a clinically meaningful increase in LEN exposures. Strong inhibitors of CYP3A, P-gp and UGT1A1 together (ie, all 3 pathways), such as atazanavir/cobicistat, may significantly increase plasma concentrations of LEN, and as such, are not recommended with LEN.

Lenacapavir is a moderate inhibitor of CYP3A. Caution is advised if LEN is coadministered with a sensitive CYP3A substrate with a narrow therapeutic index (eg, midazolam). Lenacapavir is not a clinically meaningful inhibitor of P-gp and BCRP and does not inhibit OATP.

5.4. Use in Pregnancy and Lactation

5.4.1. Pregnancy

No clinical studies of LEN have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of LEN with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development.

No formal DDI studies between LEN and hormonal contraceptives have been conducted. Based on in vitro and in vivo DDI liability assessments, clinically significant DDIs between LEN and hormonal contraceptives are not anticipated.

5.4.1.1. Pregnancies Reported in Phase 1, 2, and 2/3 LEN Studies

No pregnancies were reported in Phase 1, 2, and 2/3 studies of LEN.

5.4.2. Lactation

No new information is submitted.

5.5. Overdose

No new safety issues regarding overdose have been identified from the available data.

5.6. Drug Abuse

No safety issues concerning the abuse or misuse of LEN tablets or injections have been identified from the available data.

5.7. Withdrawal and Rebound

No formal clinical studies for withdrawal or rebound effects of LEN have been conducted.

5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been conducted to evaluate the effects of LEN on the ability to drive or operate machinery.

6. POSTMARKETING DATA

No postmarketing safety data are included in this submission.

7. REFERENCES

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8. APPENDIX

8.1. Tabular Summary of Studies Relevant for Safety

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-200-4070	To assess the safety and tolerability of escalating single SC doses of LEN compared with placebo in healthy participants To assess the PK of LEN in healthy participants	Phase 1, randomized, blinded, placebo-controlled, SAD study	Participants were randomized to receive LEN or placebo (4:1 ratio per cohort). Cohort 1: 30 mg Cohort 2: 100 mg Cohort 3: 300 mg Cohort 4: 450 mg Cohort 5 (not enrolled): up to 600 mg	1 day	Randomized: 40 participants; Completed: 38 participants	Healthy male and nonpregnant, nonlactating female participants	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-200-4071	To evaluate the safety and tolerability of escalating single and multiple oral doses of LEN To characterize the single- and multiple-dose PK of oral LEN To evaluate the effect of concomitant food intake on oral LEN PK	Phase 1, randomized, blinded, placebo-controlled, single and multiple ascending dose study in participants	For Study Parts A to C, participants were randomized to receive LEN or placebo (4:1 ratio per cohort).Study Part D involved open-label, parallel-group, single-dose cohorts. Study Part A (SAD/MAD; Formulation 1: LEN 50-mg/mL solution in capsule, free acid): Cohort 1: 30 mg (50 mg/mL) Cohort 2: 100 mg (50 mg/mL) Study Part B (SAD; Formulations 1 and 2: LEN 50- or 100-mg/mL solution in capsule, free acid):	Less than or equal to 11 days	Randomized: 106 participants; Completed: 102 participants	Healthy male and nonpregnant, nonlactating female participants	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				Cohort 3: 300 mg (100 mg/mL) Cohort 4: 75 mg (100 mg/mL) Cohort 5: 300 mg (50 mg/mL) Cohort 6 (not enrolled): up to 900 mg (100 mg/mL) Study Part C (SAD; Formulation 3: LEN 50- or 300-mg tablet): Cohort 7: 300 mg (1 × 300-mg tablet) Cohort 8: 900 mg (3 × 300-mg tablet) Cohort 9: 1800 mg (6 × 300-mg tablet) Cohort 10: 50 mg (1 × 50-mg tablet) Cohort 11 (not enrolled): up to 1800 mg Study Part D (Food Effect; Formulation 3: LEN 50- or 300-mg tablet): Cohort 12: 300 mg (1 × 300-mg tablet) with high-fat/high-calorie meal Cohort 13: 300 mg (1 × 300-mg tablet) with light meal Cohorts 14 to 17 (not enrolled): up to 1800 mg with high-				

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				fat/high-calorie (Cohort 15), moderate-fat (Cohorts 14 and 17), or light (Cohort 16) meal				
Healthy Subject PK and Initial Tolerability	GS-US-200-4329	To evaluate the PK of LEN (and metabolites, if applicable) following single ascending IV doses of LEN or a single IV dose of radiolabeled [^{14}C]LEN To determine the mass balance of LEN following administration of a single IV dose of radiolabeled [^{14}C]LEN	Part A: Phase 1, randomized, blinded, placebo-controlled, SAD study Part B: Phase 1, open-label, single-center, mass-balance study	Part A: Cohort 1: single dose of LEN 10 mg or placebo Cohort 2 (not enrolled): single dose of LEN up to 30 mg or placebo Part B: Cohort 3: single IV dose of LEN 20 mg containing a mixture of unlabeled LEN and [^{14}C]LEN (equivalent to approximately 200 µCi)	1 day	Enrolled: 21 participants; Completed: 11 participants	Healthy nonsmoking (≥ 90 days) male and nonpregnant, nonlactating female participants	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-200-4538	To assess the safety and tolerability of escalating single doses of SC LEN injectable solutions compared with placebo in healthy participants To assess the PK of SC injectable solutions of LEN in healthy participants	Phase 1, randomized, blinded, placebo-controlled, SAD study	Participants were randomized to receive LEN or placebo (4:1 ratio per cohort). Part A (SAD; Formulation 1: LEN 300 mg/mL, free acid): Cohort 1: 300 mg Cohort 2 (not enrolled): up to 900 mg Cohorts 3 and 4 (not enrolled): up to 1200 mg	1 day	Randomized: 100 participants; Completed: 78 participants	Healthy male and nonpregnant, nonlactating female participants	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				Part B (SAD; Formulation 2: LEN 309 mg/mL, sodium salt): Cohort 5: 309 mg Cohorts 6 and 7: 927 mg Cohort 8 (not enrolled): up to 2472 mg Part C (SAD; Formulation 3: LEN 155 mg/mL, sodium salt): Cohort 9: 309 mg Cohort 10: 927 mg Cohorts 11 and 12 (not enrolled): up to 1236 mg Part D (SAD; Formulation 4: LEN 300 mg/mL, sodium salt with poloxamer): Cohort 13: 900 mg Cohorts 14 to 16 (not enrolled): up to 2400 mg Part E (SAD; Formulation 5: LEN 150 mg/mL, sodium salt with poloxamer): Cohort 17 (not enrolled): 900 mg Cohorts 18 to 20 (not enrolled): up to 1200 mg				

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				Part F (SAD; Formulation 6: LEN 75 mg/mL, sodium salt with poloxamer): Cohort 21: 75 mg Cohort 22: 225 mg Cohorts 23 and 24 (not enrolled): up to 600 mg Part G (SAD; Formulation 7: LEN 50 mg/mL, sodium salt with poloxamer): Cohort 25: 50 mg Cohort 26 (not enrolled): up to 150 mg Cohorts 27 and 28 (not enrolled): up to 400 mg Part H: Cohorts 29 to 32 (not enrolled): up to 1200 mg (Formulations 1, 3, and 5); up to 2400 mg (Formulations 2 and 4); up to 600 mg (Formulation 6); or up to 400 mg (Formulation 7)				

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-200-5709	To characterize the PK of multiple-dose oral and SC LEN To evaluate the safety and tolerability of multiple-dose oral and SC LEN	Phase 1, open-label, multiple-cohort, multiple-dose study	Cohort 1: Treatment A: oral tablets of LEN on Day 1 (600 mg; 2 × 300 mg tablets), Day 2 (600 mg; 2 × 300 mg tablets), Day 8 (300 mg; 1 × 300 mg tablet), SC LEN on Day 15 (927 mg; 2 × 1.5 mL of LEN injection), all administered under fed conditions. Cohort 2: Treatment B: SC LEN (927 mg; 2 × 1.5 mL of LEN injection) and oral 600 mg (2 × 300 mg tablets) on Day 1 followed by oral 600 mg on Day 2 (2 × 300 mg tablets), all administered under fed conditions. Cohort 3: Treatment C: oral LEN twice daily on Days 1 to 10 (600 mg; 2 × 300 mg tablets), and last dose of LEN (600 mg; 2 × 300 mg tablets) in the morning on Day 11, all administered under fed conditions	Cohort 1: 4 days Cohort 2: 2 days Cohort 3: 11 days	Enrolled: 60 participants; Cohort 1: 31 participants Cohort 2: 14 participants Cohort 3: 15 participants	Healthy male and nonpregnant, nonlactating female participants	Study ongoing; Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Patient PK and Initial Tolerability	GS-US-200-4072	Part A: To evaluate the short-term antiviral activity of LEN compared with placebo with respect to the maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Days 1 through 10 in adult PWH who were ARV treatment naive or were experienced but CAI naive Part B: To evaluate the short-term antiviral activity of TAF with respect to the maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Day 1 through Day 10 in adult PWH who were ARV treatment naive or were experienced but without resistance to TAF	Phase 1b, randomized, double-blind, placebo-controlled, multicohort study	Part A: Cohort 1: LEN 150 mg or placebo Cohort 2: LEN 50 mg or placebo Cohort 3: LEN 450 mg or placebo Cohort 4: LEN 20 mg or placebo Cohort 5: LEN 750 mg or placebo Part B: Cohort 6: TAF 200 mg Cohort 7: TAF 600 mg Cohort 8 (not enrolled): TAF up to 600 mg	1 day	Part A: Randomized: 41 participants; Completed: 38 participants Part B: Enrolled: 12 participants; Completed: 12 participants	Adult PWH who were ARV treatment naive or were experienced but CAI and INSTI naive (Part A only), had not received any ART within 12 weeks of screening, and had genotypic sensitivity to BVY	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Intrinsic Factor PK	GS-US-200-4330	To evaluate the single-dose PK of LEN in participants with severe renal impairment or matched healthy controls with normal renal function	Phase 1, open-label, single-dose, parallel-group study	Single dose of LEN 300 mg(1 × 300-mg tablet)	1 day	Enrolled: 20 participants (10 with severe renal impairment and 10 matched healthy participants with normal renal function); Completed: 20 participants	Participants with severe renal impairment classification ($15 \leq CL_{cr} \leq 29$ mL/min) at screening and matched healthy participants with normal renal function ($CL_{cr} \geq 90$ mL/min)	Study completed; Final CSR
Intrinsic Factor PK	GS-US-200-4331	To evaluate the single-dose PK of LEN in participants with normal or moderately impaired hepatic function	Phase 1, open-label, multicenter, single-dose, parallel-group study	Single dose of LEN 300 mg (1 × 300-mg tablet)	1 day	Enrolled: 20 participants (10 with moderate hepatic impairment and 10 matched healthy controls with normal hepatic function); Completed: 19 participants	Male and nonpregnant, nonlactating female participants with moderately impaired and normal hepatic function	Study completed; Final CSR
Extrinsic Factor PK	GS-US-200-4333	To evaluate the effect of a CYP3A inhibitor, a mixed CYP3A/P-gp inhibitor, and a mixed CYP3A/P-gp/ UGT1A1 inhibitor on the PK of LEN To evaluate the effect of an inducer of CYP3A/P-gp/UGT and an inducer of CYP3A/P-gp on	Phase 1, open-label, single-center, parallel-design, single- and multiple-dose, multicohort study	LEN 300 mg (6 × 50-mg capsules): Cohort 1: LEN Cohort 2: COBI 150 mg and LEN Cohort 3: DRV/COBI 800/150 mg and LEN LEN 300 mg (1 × 300-mg tablet): Cohort 4: LEN Cohort 5: VORI 400 mg, VORI 200 mg, and LEN Cohort 6: LEN (under	Cohorts 1, 4, 6, and 10: 1 day Cohorts 2 and 3: up to 90 days Cohort 5: 25 days Cohort 7: 60 days Cohorts 8 and 9: 25 days Cohort 11: 27 days	Enrolled: 291 participants; Completed: 272 participants	Healthy male and nonpregnant, nonlactating female participants	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
		the PK of LEN To evaluate the effect of an H2RA on the PK of LEN To evaluate the effect of LEN on the PK of an OATP substrate, a BCRP substrate, a P-gp substrate, and a CYP3A substrate		fed conditions) Cohort 7: ATV/COBI 300/150 mg and LEN Cohort 8: RIF 600 mg and LEN Cohort 9: EFV 600 mg and LEN Cohort 10: FAM 40 mg and LEN LEN 600 mg (2 × 300-mg tablets): Cohort 11: PIT 2 mg, ROS 5 mg, TAF 25 mg, MDZ 2.5 mg, and LEN				
Healthy Subject PD and PK/PD	GS-US-200-4332	To evaluate the effect of LEN on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, double-blinded, randomized, placebo- and positive-controlled, 3-sequence, parallel (with nested crossover), multiple-dose study	Treatment A (Positive Control): Single oral dose of 400 mg MOXI (1 × 400-mg tablet), under fed conditions, in the morning Treatment B (Placebo Control-1): Single oral dose of placebo-to-match MOXI (1 tablet), under fed conditions, in the morning Treatment C (Therapeutic and Supratherapeutic Exposure to LEN): Twice-daily 600 mg of LEN (2 × 300-mg tablet) for 8 days, under fed conditions	10 days	Randomized: 97 participants; Completed: 95 participants	Healthy male and nonpregnant, nonlactating female participants	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				Treatment D (Placebo Control-2): Twice-daily placebo for LEN (2 tablets) for 8 days, under fed conditions				
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-200-4334	To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment Group 1 (oral to SC LEN): Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral DVY 200/25 mg Maintenance: SC LEN 927 mg and oral TAF 25 mg Treatment Group 2 (oral to SC LEN): Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral DVY 200/25 mg Maintenance: SC LEN 927 mg and oral BIC 75 mg Treatment Group 3: oral LEN 600 and 50 mg and oral DVY 200/25 mg Treatment Group 4: oral BVY 50/200/25 mg	At least 80 weeks	Randomized: 183 participants; Safety Analysis Set: 182 participants; SC LEN + (DVY -> TAF): 52 participants; SC LEN + (DVY-> BIC): 53 participants; Oral LEN + DVY: 52 participants; BVY: 25 participants	Treatment-naive PWH ≥ 18 years of age	Study ongoing; Interim Week 28 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-200-4625	To evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for PWH with multidrug resistance	Phase 2/3, randomized, placebo-controlled, multicenter study	Cohort 1: Functional Monotherapy Period: oral LEN 600, 600, and 300 mg or placebo-to-match LEN on Days 1, 2, and 8, respectively, while continuing their failing regimen Maintenance Period: Cohort 1A: SC LEN 927 mg and initiation of an OBR starting on Day 1 SC (14 days after the first dose of oral LEN), and once every 6 months (26 weeks) Cohort 1B: oral LEN 600 mg and initiation of an OBR on Day 15; oral LEN 600 and 300 mg on Days 16 and 22, respectively; SC LEN 927 mg while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks) Cohort 2: Oral Lead-in Period: oral LEN 600 mg and initiation of an OBR on Day 1; oral LEN 600 and 300 mg on Days 2 and 8, respectively, while	At least 54 weeks	Enrolled: 72 participants; Cohort 1: 36 participants; Cohort 2: 36 participants	Heavily treatment-experienced adult and adolescent PWH with resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications and plasma HIV-1 RNA ≥ 400 copies/mL at screening while taking a failing regimen	Study ongoing; Interim Week 26 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				continuing their OBR Maintenance Period: SC LEN 927 mg while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks)				

ARV = antiretroviral; ART = antiretroviral therapy; ATV = atazanavir; BCRP = breast cancer resistance protein; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CAI = capsid inhibitor; CL_{cr} = creatinine clearance; COBI = cobicistat (Tybost®); CSR = clinical study report; CYP = cytochrome P450 enzyme; DRV = darunavir; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); EFV = efavirenz; FAM = famotidine; H2RA = histamine 2 receptor antagonist; INSTI = integrase strand-transfer inhibitor; IV = intravenous; LEN = lenacapavir; MAD = multiple ascending dose; MDZ = midazolam; MOXI = moxifloxacin; OATP = organic anion transporting polypeptide; OBR = optimized background regimen; PD = pharmacodynamic(s); P-gp = P-glycoprotein; PIT = pitavastatin; PK = pharmacokinetic(s); PWH = people with HIV; QTcF = QT interval corrected for heart rate using the Fridericia formula; RIF = rifampin; ROS = rosuvastatin; SAD = single ascending dose; SC = subcutaneous; TAF = tenofovir alafenamide (Vemlidy®); UGT = uridine diphosphate glucuronosyltransferase; VORI = voriconazole

8.2. Additional Safety Analysis for the Study Population

Outputs from the ISS for Studies GS-US-200-4538 and GS-US-200-5709 are described in the LEN ISS SAP and are included in this submission.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

ADDENDUM

Lenacapavir

Gilead Sciences, Inc.

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BIC; B	bictegravir (GS-9883)
BVY	bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF)
CD4	clusters of differentiation 4
CK	creatine kinase
COVID-19	coronavirus disease 2019
CSR	clinical study report
CYP3A	cytochrome P450 enzyme 3A
DAIDS	Division of AIDS
DDI	drug-drug interaction
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
F	emtricitabine (Emtriva®);
FTC	emtricitabine (Emtriva®)
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HTE	heavily treatment-experienced
ie	that is
ISR	injection site reaction
LDL	low-density lipoprotein
LEN	lenacapavir (GS-6207)
m	Module
MedDRA	Medical Dictionary for Regulatory Activities
N	number of participants
OATP	organic anion transporting polypeptide
OBR	optimized background regimen
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PT	preferred term
PWH	people with HIV

Q1	first quartile
Q3	third quartile
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA Query
TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate (Viread®)
TE	treatment emergent
TEAE	treatment-emergent adverse event
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1

1. EXPOSURE TO THE DRUG

1.1. Background

While combination antiretroviral therapy (ART) for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality previously associated with HIV disease, there remains a significant medical need for new, well-tolerated therapies that take into consideration HIV genetic variability, antiretroviral (ARV) resistance, new options for regimen simplification, as well as the desires of people with HIV (PWH) for alternative, longer-acting options.

Some treatment-experienced PWH eventually lose the virologic, immunologic, or clinical benefit from their current regimens. People with HIV who have multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {British HIV Association 2016, European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019, Saag 2020, U. S. Department of Health and Human Services 2015}. Developing safe and effective therapies for heavily treatment-experienced (HTE) PWH with multidrug-resistant HIV remains a priority. For these individuals, newer treatments are needed to control viral replication, preserve immune function, and prevent clinical progression.

Lenacapavir (LEN; GS-6207) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function, which is being developed for the treatment and prevention of HIV-1 infection. Lenacapavir inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and physicochemical properties well suited for extended-release parenteral or oral formulations.

This addendum provides additional cumulative safety data from the interim analyses of the following studies:

- The primary study, Study GS-US-200-4625 (a Phase 2/3 study in HTE PWH with multidrug resistance) which was conducted after participants in Cohort 1 had completed the Week 52 visit and all participants in Cohort 2 had completed their Week 26 visit.

- Study GS-US-200-4334 (a Phase 2 study in treatment-naive PWH) which was conducted after all participants had completed the Week 54 visit.

- Study GS-US-200-5709 (an ongoing, Phase 1, open-label, multicohort, multidose oral and/or subcutaneous [SC] LEN study in healthy participants) which was conducted based on interim data (data cut date: [redacted] 20[redacted]) of the ongoing cohorts (Cohorts 1 and 2).

1.2. Overall Safety Evaluation Plan and Narratives of Safety Studies

1.2.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

The proposed indication for LEN is primarily based on data from Study GS-US-200-4625, an ongoing Phase 2/3, randomized, placebo-controlled, multicenter study of LEN in combination with an optimized background regimen (OBR) in HTE PWH with multidrug resistance. The majority of participants in this study had a baseline CD4 cell count less than 200 cells/µL (a hallmark of severe immune suppression and the criteria to diagnose AIDS).

An overview of Study GS-US-200-4625 is presented in m2.7.3, Section 1.2.1 and a tabular summary of the study design is presented in Appendix 8.1.

This summary document provides cumulative safety data from the interim analysis at Week 52 of Cohorts 1 and 2 in Study GS-US-200-4625, which was conducted after all participants in Cohort 1 completed the Week 52 visit (ie, 52 weeks after the first dose of SC LEN) or had prematurely discontinued the study drug, and after all participants in Cohort 2 completed the Week 26 visit (ie, 26 weeks after the first dose of SC LEN) or had prematurely discontinued the study drug. Safety was evaluated through the incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities.

1.2.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Supportive safety data for LEN are provided from Study GS-US-200-4334, an ongoing Phase 2, randomized, open-label, active-controlled, multicenter study of LEN in combination with other ARV agents in treatment-naive PWH. Study GS-US-200-4334 uses bictegravir (BIC; B)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (Biktarvy®; BVY) as the active comparator, allowing for comparisons between the LEN-containing regimens with a guideline-recommended initial regimen for treatment-naive PWH {European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019}.

An overview of Study GS-US-200-4334 is presented in m2.7.3, Section 1.2.2 and a tabular summary of the study design is presented in Appendix 8.1.

This summary document provides cumulative safety data from the interim analysis of Study GS-US-200-4334, which was conducted after all participants had completed the Week 54 visit or had prematurely discontinued study drug. Safety was evaluated through the incidence of TEAEs and treatment-emergent clinical laboratory abnormalities.

1.2.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

Supportive safety data for LEN are provided from Study GS-US-200-5709, an ongoing, Phase 1, open-label, multicohort, multidose oral and/or SC LEN study to evaluate the safety and tolerability of multiple-dose oral and SC LEN and to characterize the pharmacokinetics (PK) of multiple-dose oral and SC LEN in healthy participants. Study GS-US-200-5709 evaluated the oral + SC clinical regimen for LEN (2 week oral lead in, followed by 927 mg of 309 mg/mL LEN SC).

A narrative of Study GS-US-200-5709 is presented in m2.7.2, Section 2.1.1 and a tabular summary of the study design is presented in Appendix 8.1.

This summary document provides cumulative safety data from the interim analysis of Study GS-US-200-5709, which was conducted based on interim data (data cut date: [redacted] 20[redacted]) of the ongoing cohorts (Cohorts 1 and 2) in Study GS-US-200-5709. Safety was evaluated through the incidence of TEAEs and treatment-emergent clinical laboratory abnormalities.

1.2.4. Safety Assessments

Adverse events (AEs)and clinical laboratory data were summarized by treatment group using descriptive statistics. Adverse events were coded using MedDRA, Version 23.1. Summaries (number and percentage of participants) of TEAEs (by system organ class and preferred term [PT]) were provided by treatment group. Additional summaries included summaries for AEs by grade and investigator's assessment of relationship to study drug.

For the individual Studies GS-US-200-4625 and GS-US-200-4334, additional analysis of AEs was performed for injection site reactions (ISRs) related to study drug, which was defined as an AE related to study drug reported as any event with a PT within the MedDRA high-level term of "injection site reactions."

Graded laboratory abnormalities were defined using the grading scheme in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, (corrected Version 2.1, July 2017). Incidences of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline, were summarized by treatment group. Laboratory data that are categorical were summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

Further details on the statistical methods for the individual studies are provided in the statistical analysis plan (SAP) for each study (GS-US-200-4625 Interim Week 52 clinical study report [CSR] Addendum, Appendix 16.1.9; GS-US-200-4334 Interim Week 54 CSR Addendum, Appendix 16.1.9, and GS-US-200-5709 Interim CSR Addendum, Appendix 16.1.9).

1.2.5. Summary of Results of Individual Studies

Study narratives, including safety data, for individual clinical pharmacology and efficacy studies are presented in m2.7.2 and m2.7.3, respectively.

1.3. Overall Extent of Exposure

The overall duration on study from Study GS-US-200-4625 and the extent of exposure from Study GS-US-200-4334 are presented in Sections 1.3.1 and 1.3.2, respectively. Detailed results are presented in the individual CSRs (GS-US-200-4625 Interim Week 52 CSR, Section 11.1; GS-US-200-4334 Interim Week 54 CSR, Section 11.1).

Disposition for participants in Studies GS-US-200-4625 and GS-US-200-4334 is described in m2.7.3, Section 3.1.

Detailed results summarizing the disposition for participants and the overall duration of follow up from the Study GS-US-200-5709 is presented in Section 1.3.3.

1.3.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Of the 72 participants in Cohorts 1 and 2 who received oral LEN, 72 participants received SC LEN on Day 1 SC, 70 participants (Cohort 1: 36 participants, Cohort 2: 34 participants) received a second dose of SC LEN at Week 26, and 36 participants (Cohort 1: 34 participants, Cohort 2: 2 participants) received a third dose of SC LEN at Week 52. The median (first quartile [Q1], third quartile [Q3]) duration on study was 484 (411, 559) and 317 (267, 352) days for Cohorts 1 and 2, respectively.

1.3.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Exposure to the study drugs was similar across the 4 treatments groups and is summarized in Table 1. By Week 54, 89.2% of participants in the LEN total group (140 of 157 participants) and 96.0% of those in the BVY group (24 of 25 participants) had been exposed to study drug for at least 54 weeks.

Table 1. GS-US-200-4334: Extent of Study Drug Exposure (Safety Analysis Set)

	SC LEN + (DVY →TAF) (N = 52)	SC LEN + (DVY →BIC) (N = 53)	Oral LEN + DVY (N = 52)	DVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Total Duration of Exposure to Study Drug (Weeks)						
N	52	53	52	25	105	157
Mean (SD)	67.5 (17.43)	64.7 (16.90)	67.5 (17.62)	70.5 (12.90)	66.1 (17.14)	66.6 (17.26)
Median	67.0	61.3	68.4	76.1	64.1	66.3
Q1, Q3	57.4, 81.5	56.3, 80.3	57.5, 82.1	58.4, 80.4	56.6, 80.6	57.4, 81.1
Min, Max	9.7, 93.1	8.4, 88.6	10.3, 90.3	38.1, 89.3	8.4, 93.1	8.4, 93.1
Cumulative N (%) of Participants Exposed to Study Drug						
>= 1 Day	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
>= 2 Days	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
>= 8 Days	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
>= 15 Days	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
>= 4 Weeks (28 Days)	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (100.0%)	105 (100.0%)	157 (100.0%)
>= 10 Weeks (70 Days)	51 (98.1%)	52 (98.1%)	52 (100.0%)	25 (100.0%)	103 (98.1%)	155 (98.7%)
>= 16 Weeks (112 Days)	50 (96.2%)	52 (98.1%)	51 (98.1%)	25 (100.0%)	102 (97.1%)	153 (97.5%)
>= 22 Weeks (154 Days)	50 (96.2%)	52 (98.1%)	51 (98.1%)	25 (100.0%)	102 (97.1%)	153 (97.5%)
>= 28 Weeks (196 Days)	50 (96.2%)	51 (96.2%)	50 (96.2%)	25 (100.0%)	101 (96.2%)	151 (96.2%)
>= 38 Weeks (266 Days)	49 (94.2%)	50 (94.3%)	48 (92.3%)	25 (100.0%)	99 (94.3%)	147 (93.6%)
>= 54 Weeks (378 Days)	47 (90.4%)	45 (84.9%)	48 (92.3%)	24 (96.0%)	92 (87.6%)	140 (89.2%)
>= 64 Weeks (448 Days)	28 (53.8%)	25 (47.2%)	29 (55.8%)	16 (64.0%)	53 (50.5%)	82 (52.2%)
>= 80 Weeks (560 Days)	18 (34.6%)	15 (28.3%)	18 (34.6%)	8 (32.0%)	33 (31.4%)	51 (32.5%)
>= 90 Weeks (630 Days)	1 (1.9%)	0	1 (1.9%)	0	1 (1.0%)	2 (1.3%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; N = number of participants; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard abbreviation; TAF = tenofovir alafenamide

Duration of exposure to study drug = last exposure date − first dose date + 1

For ongoing participants, the last exposure date is defined as the data cut date.

For participants who prematurely discontinued study drug, the last exposure date is defined as the last study date for participants who randomized to LEN treatment group and received SC injection, the minimum of last dose date plus 60 days and last study date for participants who randomized to LEN treatment group and did not receive SC injection, the minimum of last dose date plus 30 days and last study date for participants in BVY treatment group.

Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.1.1

1.3.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

Cohort 1

A total of 31 participants were enrolled in Cohort 1 and received at least 1 dose of study drug. As of [redacted] 20[redacted], the median (Q1, Q3) duration of follow up was 264 (145, 372) days (Table 2).

Cohort 2

A total of 14 participants were enrolled in Cohort 2 and received at least 1 dose of study drug. As of [redacted] 20[redacted], the median (Q1, Q3) duration of follow up was 136 (136, 150) days (Table 2).

Table 2. GS-US-200-5709: Duration on Study (Safety Analysis Set)

	Cohort 1 (N = 31)	Cohort 2 (N = 14)
Duration on study (Days)		
N	31	14
Mean (SD)	252 (113.3)	141 (7.0)
Median	264	136
Q1, Q3	145, 372	136, 150
Min, max	32, 372	136, 150
Duration on study		
≥ 7 Days	31 (100.0%)	14 (100.0%)
≥ 14 Days	31 (100.0%)	14 (100.0%)
≥ 21 Days	31 (100.0%)	14 (100.0%)
≥ 51 Days	29 (93.5%)	14 (100.0%)
≥ 81 Days	26 (83.9%)	14 (100.0%)
≥ 111 Days	25 (80.6%)	14 (100.0%)
≥ 141 Days	25 (80.6%)	5 (35.7%)
≥ 171 Days	23 (74.2%)	0
≥ 201 Days	23 (74.2%)	0
≥ 231 Days	23 (74.2%)	0
≥ 261 Days	22 (71.0%)	0
≥ 291 Days	10 (32.3%)	0
≥ 321 Days	10 (32.3%)	0
≥ 351 Days	10 (32.3%)	0
≥ 381 Days	0	0

Q1 = first quartile; Q3 = third quartile; N = number of participants; SD = standard deviation
Duration on study was the number of days between Day 1 and [redacted] 20[redacted] for Cohort 1 and Cohort 2.
Source: GS-US-200-5709 Interim CSR Addendum, Table 15.11.1.1

1.4. Demographic and Other Characteristics of Study Population

Demographics, general baseline characteristics, and baseline disease characteristics for participants in Studies GS-US-200-4625 and GS-US-200-4334 are described in the GS-US-200-4625 Interim Week 26 CSR and in the GS-US-200-4334 Interim Week 28 CSR, respectively. Demographics and general baseline characteristics for participants in Study GS-US-200-5709 are described in the GS-US-200-5709 Interim CSR.

2. ADVERSE EVENTS

All AEs and laboratory abnormalities presented in this summary were treatment emergent and are referred to as AEs and laboratory abnormalities throughout this report. Additionally, the relationship of AEs to study drug is investigator assigned.

2.1. Analysis of Adverse Events

Detailed results describing AEs for Studies GS-US-200-4625 and GS-US-200-4334 are provided in the individual CSRs (GS-US-200-4625 Interim Week 52 CSR Addendum, Section 11.2, GS-US-200-4334 Interim Week 54 CSR Addendum, Section 11.2, and GS-US-200-5709 Interim CSR Addendum, Section 11.2).

Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

The percentage of participants who received LEN in Cohorts 1 and 2 and experienced AEs was 93.1% (67 of 72 participants) (Table 3). Overall, 8 participants (11.1%) (5 in Cohort 1 and 3 in Cohort 2) experienced serious adverse events (SAEs). Since the Interim Week 26 analysis, 4 additional participants experienced SAEs of coronavirus disease 2019 (COVID-19) (2 participants), septic shock, renal impairment, shock (1 participant), pneumonia (1 participant), and 2 participants who previously experienced SAEs experienced additional SAEs of anal squamous cell carcinoma, impaired healing, anal cancer (1 participant), and angina pectoris (1 participant). None of these SAEs led to discontinuation of study drug and none were considered related to study drug. One participant in Cohort 2 died on Study Day 90, experiencing an SAE of cancer with a fatal outcome also reported as leading to premature discontinuation from the study. The event was previously reported in the Week 26 analysis and was considered not related to study drug. No additional deaths were reported beyond Week 26. While no participant discontinued study drug due to AE at the Week 26 analysis, 1 participant (1.4%) discontinued study drug due to Grade 1 AE of injection site nodule during the Extension Phase after receiving the Week 52 LEN SC injection. Overall, 16 participants (22.2%) had Grade 3 or higher AEs (Cohort 1: 6 participants, 16.7%; Cohort 2: 10 participants, 27.8%). Since the Interim Week 26 analysis, 3 additional participants had Grade 3 or higher AEs and 16 new terms of Grade 3 or higher AEs were reported.

Table 3. GS-US-200-4625: Treatment-Emergent Adverse Events: Overall Summary – All LEN Analysis (Safety Analysis Set)

Number (%) of Participants With Any	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo LEN (N = 12)	Total (N = 36)		
TEAE	22 (91.7%)	12 (100.0%)	34 (94.4%)	33 (91.7%)	67 (93.1%)
TEAE With Grade 3 or Higher	3 (12.5%)	3 (25.0%)	6 (16.7%)	10 (27.8%)	16 (22.2%)
TEAE With Grade 2 or Higher	14 (58.3%)	7 (58.3%)	21 (58.3%)	25 (69.4%)	46 (63.9%)
TEAE Related to Study Drug	17 (70.8%)	6 (50.0%)	23 (63.9%)	25 (69.4%)	48 (66.7%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0	0	4 (11.1%)	4 (5.6%)
TEAE Related to Study Drug With Grade 2 or Higher	7 (29.2%)	3 (25.0%)	10 (27.8%)	12 (33.3%)	22 (30.6%)
TE Serious AE	2 (8.3%)	3 (25.0%)	5 (13.9%)	3 (8.3%)	8 (11.1%)
TE Serious AE Related to Study Drug	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
TEAE Leading to Premature Discontinuation of Study	1 (4.2%)	0	1 (2.8%)	1 (2.8%)	2 (2.8%)
All Deaths	0	0	0	1 (2.8%)	1 (1.4%)

AE = adverse event; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; TE = treatment emergent; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAE was defined as an AE that began on or after the first dose date of LEN.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017).
Death includes any death that occurred on and after the first dose of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.2.1.1

Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Similar percentages of participants in the LEN total (total of 157 participants) and BVY (total of 25 participants) groups had any AE by Week 54 (LEN total 87.9%, 138 participants; BVY 84.0%, 21 participants). The percentages of participants with Grade 3 or higher AEs were also similar between the LEN total and BVY groups (LEN total 8.3%, 13 participants; BVY 8.0%, 2 participants). Serious AEs (SAEs) occurred only in the LEN total group (6.4%, 10 participants) (Table 4). None of the SAEs were considered related to the study drugs.

Adverse events related to the study drug occurred at a higher frequency in the SC LEN total group than in the Oral LEN + emtricitabine/tenofovir alafenamide (F/TAF; DVY) or BVY groups, mainly because of ISRs (SC LEN total 58.1% [61 of 105 participants], Oral LEN + DVY 15.4% [8 of 52 participants], and BVY 16.0% [4 of 25 participants]). Except for 1 participant (1.0%, 1 of 105) in the SC LEN total group with a Grade 3 AE related to study drug (injection site nodule), no other AEs related to study drug were Grade 3 or higher.

Since the Week 28 analysis, 2 additional AEs of Grade 3 or higher were reported in the LEN total group (SC LEN + [DVY → TAF] group: 1 participant; SC LEN + [DVY → BIC] group: 1 participant]) and 1 additional AE of Grade 3 or higher was reported in the BVY group (1 participant).

Adverse events that led to a premature discontinuation of the study drug occurred in 3 participants (2.9%) in the SC LEN total group and no participants in the other treatment groups. Since the Week 28 analysis, 1 participant in the SC LEN total group had experienced AEs of injection site erythema and injection site swelling that led to premature discontinuation of study drug. Both occurrences were nonserious and Grade 1 in severity.

Table 4. GS-US-200-4334: Treatment-Emergent Adverse Events: Overall Summary (Safety Analysis Set)

Number (%) of Participants With Any	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
TEAE	50 (96.2%)	45 (84.9%)	43 (82.7%)	21 (84.0%)	95 (90.5%)	138 (87.9%)
TEAE With Grade 3 or Higher	2 (3.8%)	5 (9.4%)	6 (11.5%)	2 (8.0%)	7 (6.7%)	13 (8.3%)
TEAE With Grade 2 or Higher	20 (38.5%)	17 (32.1%)	21 (40.4%)	13 (52.0%)	37 (35.2%)	58 (36.9%)
TEAE Related to Study Drug	34 (65.4%)	27 (50.9%)	8 (15.4%)	4 (16.0%)	61 (58.1%)	69 (43.9%)
TEAE Related to Study Drug With Grade 3 or Higher	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
TEAE Related to Study Drug With Grade 2 or Higher	9 (17.3%)	2 (3.8%)	0	0	11 (10.5%)	11 (7.0%)
TE Serious AE	3 (5.8%)	3 (5.7%)	4 (7.7%)	0	6 (5.7%)	10 (6.4%)
TE Serious AE Related to Study Drug	0	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	3 (5.7%)	0	0	3 (2.9%)	3 (1.9%)
TEAE Leading to Premature Discontinuation of Study	0	0	0	0	0	0
Death	0	0	0	0	0	0

AE = adverse event; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide; TE = treatment-emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.2.1.1

Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

Cohort 1

In the interim CSR, AEs were reported for 27 of 31 participants (87.1%) in Cohort 1. Adverse events considered related to study drug were reported for 22 participants (71.0%).
One participant (3.2%) had an AE leading to premature discontinuation (Grade 1 AE of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] test positive). No Grade 3 or 4 AEs, deaths, or SAEs were reported for Cohort 1 participants. There was no change to the overall number of participants with AEs in Cohort 1 in this CSR addendum (Table 5).

Cohort 2

In the interim CSR, AEs were reported for all participants (14 of 14 participants, 100.0%) in Cohort 2. Adverse events considered related to study drug were reported for all participants (100.0%). No Grade 3 or 4 AEs, deaths, SAEs, or AEs leading to premature discontinuation of study drug or the study were reported in Cohort 2. There was no change to the overall number of participants with AEs in Cohort 2 in this CSR addendum (Table 5).

Table 5. GS-US-200-5709: Overall Summary of Adverse Events (Safety Analysis Set)

Number (%) of Participants With Any	Cohort 1 Overall (N = 31)	Cohort 2 Overall (N = 14)
TEAE	27 (87.1%)	14 (100.0%)
TEAE With Grade 2 or higher	4 (12.9%)	6 (42.9%)
TEAE With Grade 3 or higher	0	0
TEAE related to study drug	22 (71.0%)	14 (100.0%)
TEAE related to study procedures	0	0
TEAE related to study drug With Grade 2 or higher	3 (9.7%)	6 (42.9%)
TEAE related to study drug With Grade 3 or higher	0	0
TE serious AE	0	0
TE serious AE related to study drug	0	0
TEAE leading to premature discontinuation of study drug	1 (3.2%)	0
TEAE leading to premature discontinuation of study	1 (3.2%)	0
TE injection site reaction (excluding injection site abscess) AEs	22 (71.0%)	14 (100.0%)
Death	0	0

AE = adverse event; DAIDS = Division of AIDS; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; TE = treatment-emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the study drug start date or led to premature study drug discontinuation.
Severity grades were defined by DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
Death included any death that occurred during the study.
Source: GS-US-200-5709 Interim CSR Addendum, Table 15.11.2.1.1

2.1.1. Common Adverse Events

2.1.1.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

The 3 most commonly reported AEs by participants who received at least 1 dose of LEN were as follows (Table 6):

- Injection site pain (37.5%, 27 of 72 participants)
- Injection site swelling (33.3%, 24 of 72 participants)
- Injection site erythema (27.8%, 20 of 72 participants)

Three participants experienced Grade 3 ISRs that were attributed to enfuvirtide.

Table 6. GS-US-200-4625: Treatment-Emergent Adverse Events by Preferred Term for > 5% of Participants Overall – All LEN Analysis (Safety Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Number (%) of Participants With Any Treatment-Emergent Adverse Events	22 (91.7%)	12 (100.0%)	34 (94.4%)	33 (91.7%)	67 (93.1%)
Injection site pain	11 (45.8%)	3 (25.0%)	14 (38.9%)	13 (36.1%)	27 (37.5%)
Injection site swelling	9 (37.5%)	4 (33.3%)	13 (36.1%)	11 (30.6%)	24 (33.3%)
Injection site erythema	7 (29.2%)	2 (16.7%)	9 (25.0%)	11 (30.6%)	20 (27.8%)
Injection site nodule	9 (37.5%)	4 (33.3%)	13 (36.1%)	5 (13.9%)	18 (25.0%)
Injection site induration	2 (8.3%)	0	2 (5.6%)	9 (25.0%)	11 (15.3%)
Diarrhoea	4 (16.7%)	2 (16.7%)	6 (16.7%)	3 (8.3%)	9 (12.5%)
Nausea	6 (25.0%)	1 (8.3%)	7 (19.4%)	2 (5.6%)	9 (12.5%)
COVID-19	3 (12.5%)	1 (8.3%)	4 (11.1%)	4 (11.1%)	8 (11.1%)
Abdominal distension	5 (20.8%)	0	5 (13.9%)	2 (5.6%)	7 (9.7%)
Constipation	4 (16.7%)	2 (16.7%)	6 (16.7%)	1 (2.8%)	7 (9.7%)
Cough	3 (12.5%)	3 (25.0%)	6 (16.7%)	1 (2.8%)	7 (9.7%)
Arthralgia	4 (16.7%)	0	4 (11.1%)	2 (5.6%)	6 (8.3%)
Back pain	1 (4.2%)	1 (8.3%)	2 (5.6%)	4 (11.1%)	6 (8.3%)
Headache	2 (8.3%)	0	2 (5.6%)	4 (11.1%)	6 (8.3%)
Pyrexia	1 (4.2%)	2 (16.7%)	3 (8.3%)	3 (8.3%)	6 (8.3%)
Urinary tract infection	2 (8.3%)	0	2 (5.6%)	4 (11.1%)	6 (8.3%)

	Cohort 1				
	LEN (N = 24)	**Placebo → LEN (N = 12)**	**Total (N = 36)**	**Cohort 2 (N = 36)**	**Total (N = 72)**
Rash	2 (8.3%)	0	2 (5.6%)	3 (8.3%)	5 (6.9%)
Dizziness	2 (8.3%)	0	2 (5.6%)	2 (5.6%)	4 (5.6%)
Fatigue	3 (12.5%)	1 (8.3%)	4 (11.1%)	0	4 (5.6%)
Oral candidiasis	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Vomiting	1 (4.2%)	0	1 (2.8%)	3 (8.3%)	4 (5.6%)

AE = adverse event; COVID-19 = coronavirus disease 2019; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; PT = preferred term
AEs were coded according to MedDRA Version 23.1.
Treatment-emergent AE was defined as an AE that began on or after the first dose date of LEN.
Multiple AEs were counted only once per participant for the highest severity grade for each PT.
PTs were presented by descending order of the total frequencies.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.2.1.3

2.1.1.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

The most commonly reported AEs were as follows (Table 7):

- LEN total (157 participants), excluding ISRs: headache and nausea (each 13.4%, 21 participants), COVID-19 (9.6%, 15 participants), and syphilis and lymphadenopathy (each 8.9%, 14 participants)
- SC LEN total (105 participants), only ISRs: injection site erythema (31.4%, 33 participants), injection site swelling (27.6%, 29 participants), and injection site pain (23.8%, 25 participants)
- Oral LEN + DVY (52 participants): headache (13.5%, 7 participants), nausea and lymphadenopathy (each 11.5%, 6 participants) and COVID-19, syphilis, diarrhea, and influenza (each 9.6%, 5 participants)
- BVY (25 participants): syphilis and arthralgia (each 16.0%, 4 participants) and headache, COVID-19, back pain, weight increased, upper respiratory tract infection, and insomnia (each 12.0%, 3 participants)

Table 7. GS-US-200-4334: Treatment-Emergent Adverse Events by Preferred Term Reported Overall for ≥ 5% of Participants in Any Treatment Group (Safety Analysis Set)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Treatment-Emergent Adverse Events	50 (96.2%)	45 (84.9%)	43 (82.7%)	21 (84.0%)	95 (90.5%)	138 (87.9%)
Injection site erythema	21 (40.4%)	12 (22.6%)	0	0	33 (31.4%)	33 (21.0%)
Injection site swelling	16 (30.8%)	13 (24.5%)	0	0	29 (27.6%)	29 (18.5%)
Injection site pain	15 (28.8%)	10 (18.9%)	0	0	25 (23.8%)	25 (15.9%)
Headache	9 (17.3%)	5 (9.4%)	7 (13.5%)	3 (12.0%)	14 (13.3%)	21 (13.4%)
Nausea	10 (19.2%)	5 (9.4%)	6 (11.5%)	1 (4.0%)	15 (14.3%)	21 (13.4%)
COVID-19	5 (9.6%)	5 (9.4%)	5 (9.6%)	3 (12.0%)	10 (9.5%)	15 (9.6%)
Syphilis	5 (9.6%)	4 (7.5%)	5 (9.6%)	4 (16.0%)	9 (8.6%)	14 (8.9%)
Injection site nodule	9 (17.3%)	8 (15.1%)	0	0	17 (16.2%)	17 (10.8%)
Lymphadenopathy	4 (7.7%)	4 (7.5%)	6 (11.5%)	1 (4.0%)	8 (7.6%)	14 (8.9%)
Injection site inflammation	10 (19.2%)	4 (7.5%)	0	0	14 (13.3%)	14 (8.9%)
Diarrhoea	3 (5.8%)	4 (7.5%)	5 (9.6%)	1 (4.0%)	7 (6.7%)	12 (7.6%)
Injection site induration	8 (15.4%)	5 (9.4%)	0	0	13 (12.4%)	13 (8.3%)
Arthralgia	2 (3.8%)	4 (7.5%)	2 (3.8%)	4 (16.0%)	6 (5.7%)	8 (5.1%)
Back pain	1 (1.9%)	4 (7.5%)	4 (7.7%)	3 (12.0%)	5 (4.8%)	9 (5.7%)
Depression	1 (1.9%)	6 (11.3%)	3 (5.8%)	1 (4.0%)	7 (6.7%)	10 (6.4%)
Influenza	4 (7.7%)	2 (3.8%)	5 (9.6%)	0	6 (5.7%)	11 (7.0%)
Nasopharyngitis	4 (7.7%)	4 (7.5%)	3 (5.8%)	0	8 (7.6%)	11 (7.0%)
Anxiety	2 (3.8%)	2 (3.8%)	3 (5.8%)	2 (8.0%)	4 (3.8%)	7 (4.5%)
Fatigue	0	6 (11.3%)	2 (3.8%)	1 (4.0%)	6 (5.7%)	8 (5.1%)
Oropharyngeal pain	2 (3.8%)	4 (7.5%)	3 (5.8%)	0	6 (5.7%)	9 (5.7%)
Pyrexia	3 (5.8%)	2 (3.8%)	2 (3.8%)	2 (8.0%)	5 (4.8%)	7 (4.5%)
Dizziness	3 (5.8%)	2 (3.8%)	2 (3.8%)	1 (4.0%)	5 (4.8%)	7 (4.5%)
Gonorrhoea	2 (3.8%)	2 (3.8%)	3 (5.8%)	1 (4.0%)	4 (3.8%)	7 (4.5%)
Hypertension	3 (5.8%)	3 (5.7%)	1 (1.9%)	1 (4.0%)	6 (5.7%)	7 (4.5%)
Vitamin D deficiency	0	4 (7.5%)	3 (5.8%)	1 (4.0%)	4 (3.8%)	7 (4.5%)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Vomiting	3 (5.8%)	1 (1.9%)	4 (7.7%)	0	4 (3.8%)	8 (5.1%)
Weight increased	2 (3.8%)	1 (1.9%)	2 (3.8%)	3 (12.0%)	3 (2.9%)	5 (3.2%)
Abdominal pain	4 (7.7%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	5 (4.8%)	6 (3.8%)
Upper respiratory tract infection	2 (3.8%)	0	2 (3.8%)	3 (12.0%)	2 (1.9%)	4 (2.5%)
Urinary tract infection	1 (1.9%)	1 (1.9%)	4 (7.7%)	1 (4.0%)	2 (1.9%)	6 (3.8%)
Cough	3 (5.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	4 (3.8%)	5 (3.2%)
Insomnia	1 (1.9%)	0	2 (3.8%)	3 (12.0%)	1 (1.0%)	3 (1.9%)
Onychomycosis	3 (5.8%)	1 (1.9%)	2 (3.8%)	0	4 (3.8%)	6 (3.8%)
Oropharyngeal gonococcal infection	1 (1.9%)	1 (1.9%)	3 (5.8%)	1 (4.0%)	2 (1.9%)	5 (3.2%)
Rash	1 (1.9%)	0	3 (5.8%)	2 (8.0%)	1 (1.0%)	4 (2.5%)
Acarodermatitis	3 (5.8%)	0	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)
Anogenital warts	0	1 (1.9%)	3 (5.8%)	1 (4.0%)	1 (1.0%)	4 (2.5%)
Abdominal pain upper	2 (3.8%)	0	0	2 (8.0%)	2 (1.9%)	2 (1.3%)
Anal chlamydia infection	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Proctitis gonococcal	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Rhinitis allergic	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Constipation	0	0	3 (5.8%)	0	0	3 (1.9%)
Hypertriglyceridaemia	0	3 (5.7%)	0	0	3 (2.9%)	3 (1.9%)
Otitis media	0	0	1 (1.9%)	2 (8.0%)	0	1 (0.6%)
Ligament sprain	0	0	0	2 (8.0%)	0	0

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); COVID-19 = coronavirus disease 2019;
DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple adverse events were counted only once per participant for the highest severity grade for each preferred term.
Preferred terms were presented by descending order of the total frequencies.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.2.1.3

2.1.1.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

Cohort 1

The most commonly reported AEs in Cohort 1 were injection site nodule (22 of 31 participants, 71.0%), injection site induration (16 of 31 participants, 51.6%), and injection site pain (12 of 31 participants, 38.7%). For the most commonly reported AEs, only the incidence of injection site nodule had increased since the interim CSR (6 of 31 participants [19.4%] versus 22 of 31 participants [71.0%]) (Table 8).

Cohort 2

In the interim CSR, the most commonly reported AEs in Cohort 2 were injection site induration (100.0%, 14 of 14 participants), injection site erythema (35.7%, 5 of 14 participants), and injection site pain (4 of 14 participants, 28.6%). There was no change to the number of participants with the most commonly reported AEs in Cohort 2 since the interim CSR (Table 8).

Table 8. GS-US-200-5709: Adverse Events Reported for at Least 2 Participants Overall in Either Cohort (Safety Analysis Set)

Adverse Events by Preferred Term	Cohort 1 Overall (N = 31)	Cohort 2 Overall (N = 14)
Number (%) of participants With any AE	27 (87.1%)	14 (100.0%)
Injection site induration	16 (51.6%)	14 (100.0%)
Injection site nodule	22 (71.0%)	0
Injection site pain	12 (38.7%)	4 (28.6%)
Injection site erythema	10 (32.3%)	5 (35.7%)
SARS-CoV-2 test positive	10 (32.3%)	0
Headache	2 (6.5%)	2 (14.3%)
Abdominal pain	2 (6.5%)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; PT = preferred term
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the study drug start date or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant for each PT.
Source: GS-US-200-5709 Interim CSR Addendum, Table 15.11.2.1.3

2.1.2. Adverse Events by Severity

2.1.2.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

The majority of AEs were Grade 1 or 2 in severity.

Grade 3 or higher AEs were reported for 16 participants (22.2%). Since the Interim Week 26 analysis, 3 additional participants had Grade 3 or higher AEs and 16 new terms of Grade 3 or

higher AEs were reported. Grade 3 or higher AEs that were reported for at least 2 participants were injection site erythema (5.6%, 4 participants), injection site edema, injection site pain, and injection site swelling (2.8%, 2 participants each). Three participants with Grade 3 ISRs were attributed to enfuvirtide.

Four participants experienced Grade 3 or higher AEs that were considered related to study drug: rash and abdominal abscess, injection site swelling and injection site erythema, injection site pain, and immune reconstitution inflammatory syndrome (1 participant each). The AE of abdominal abscess was an abscess at the injection site due to secondary infection most likely because the participant scratched the injection site.

2.1.2.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

The majority of the AEs reported in the 4 treatment groups were Grade 1 or 2 in severity.

The percentage of participants with AEs of Grade 3 or higher was 8.3% (13 of 157 participants) in the LEN total group and 8.0% (2 of 25 participants) in the BVY group (Table 9). No AEs of Grade 3 or higher were reported for more than 1 participant in any treatment group.

Since the Week 28 analysis, 2 additional AEs of Grade 3 or higher were reported in the LEN total group (uterine leiomyoma in the SC LEN + [DVY → TAF] group: 1 participant; hepatitis A in the SC LEN + [DVY → BIC] group: 1 participant]) and 1 additional AE of Grade 3 or higher (anogenital warts) was reported in the BVY group (1 participant). None of these events were considered related to study drug.

Table 9. GS-US-200-4334: Grade 3 or Higher Treatment-Emergent Adverse Events Overall by Preferred Term (Safety Analysis Set)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Grade 3 or Higher Treatment-Emergent Adverse Events	2 (3.8%)	5 (9.4%)	6 (11.5%)	2 (8.0%)	7 (6.7%)	13 (8.3%)
Anal fissure	0	0	1 (1.9%)	0	0	1 (0.6%)
Anogenital warts	0	0	0	1 (4.0%)	0	0
Anxiety	0	0	1 (1.9%)	0	0	1 (0.6%)
Back pain	0	0	1 (1.9%)	0	0	1 (0.6%)
Bipolar disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Deep vein thrombosis	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Dyspnoea	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Hepatitis A	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hypertriglyceridaemia	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Injection site nodule	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Insomnia	0	0	1 (1.9%)	0	0	1 (0.6%)
Lymphadenopathy mediastinal	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Major depression	0	0	1 (1.9%)	0	0	1 (0.6%)
Mental disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Metastases to central nervous system	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Nephrolithiasis	0	0	1 (1.9%)	0	0	1 (0.6%)
Non-small cell lung cancer	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pleural effusion	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumocystis jirovecii pneumonia	0	0	1 (1.9%)	0	0	1 (0.6%)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Pneumonia	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumothorax	0	0	1 (1.9%)	0	0	1 (0.6%)
Poisoning	0	0	1 (1.9%)	0	0	1 (0.6%)
Psychotic disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Substance-induced psychotic disorder	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Syncope	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Transient ischaemic attack	0	0	0	1 (4.0%)	0	0
Uterine leiomyoma	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Vomiting	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple adverse events were counted only once per participant for the highest severity grade for each preferred term.
Preferred terms were presented by descending order of the total frequencies.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.2.2.2.2

2.1.2.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

Cohort 1

In the interim CSR, Grade 1 AEs were reported for 23 of 31 participants (74.2%) and Grade 2 AEs were reported for 4 of 31 participants (12.9%). No Grade 3 or 4 AEs were reported. There was no change in the number of participants with AEs reported by severity in Cohort 1 in the CSR addendum.

Cohort 2

In the interim CSR, Grade 1 AEs were reported for 8 of 14 participants (57.1%) and Grade 2 AEs were reported for 6 of 14 participants (42.9%). No Grade 3 or 4 AEs were reported. There was no change in the number of participants with AEs reported by severity in Cohort 2 in the CSR addendum.

2.1.3. Adverse Events by Relationship to Study Drug

2.1.3.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Overall, 66.7% (48 of 72 participants) experienced treatment-related AEs. The most commonly reported treatment-related AEs were injection site pain and injection site swelling (30.6%, 22 participants each), injection site erythema (25.0%, 18 participants), and injection site nodule (23.6%, 17 participants).

2.1.3.2. Other Data Supporting the Safety of LEN: (Study GS-US-200-4334)

The percentages of participants with treatment-related AEs overall were as follows:

- LEN total (157 participants): 43.9% (69 participants)
- SC LEN total (105 participants): 58.1% (61 participants)
- Oral LEN + DVY (52 participants): 15.4% (8 participants)
- BVY (25 participants): 16.0% (4 participants)

The higher frequency of treatment-related AEs in the SC LEN total group was mainly because of ISRs, as reflected in the most common AEs considered related to study drugs:

- LEN total group (157 participants), excluding ISRs: nausea (5.1%, 8 participants), diarrhea and headache (each 2.5%, 4 participants), and fatigue (1.9%, 3 participants)
- SC LEN total group (105 participants), only ISRs: injection site erythema (26.7%, 28 participants), injection site swelling (22.9%, 24 participants), injection site pain (19.0%, 20 participants)

- Oral LEN + DVY (52 participants): nausea and diarrhea (each 3.8%, 2 participants), fatigue, headache, dyspepsia, flatulence, vomiting, weight increased, influenza, overdose, and hot flush (each 1.9%, 1 participant)

- BVY (25 participants): dyspepsia, salivary hypersecretion, insomnia, and weight increased (4.0%, 1 participant)

2.1.3.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

Cohort 1

In the interim CSR, treatment-related AEs were reported for 22 of 31 participants (71.0%). There was no change in the number of participants with treatment-related AEs reported in Cohort 1 in the CSR addendum. All ISRs were considered related to study drug.

Cohort 2

In the interim CSR, treatment-related AEs were reported for all participants (100.0%). There was no change in the number of participants with treatment-related AEs reported in Cohort 2 in this CSR addendum. All ISRs were considered related to study drug. Injection site reactions accounted for all the treatment-related AEs in Cohort 2.

2.1.4. Deaths

2.1.4.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

One participant in Cohort 2 died on Study Day 90; the cause of death was cancer. No additional deaths were reported beyond Week 26.

2.1.4.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

No deaths were reported by Week 54.

2.1.4.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

There were no deaths during the study.

2.1.5. Serious Adverse Events

2.1.5.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Serious AEs were reported for 11.1% (8 of 72 participants). Since the Interim Week 26 analysis, 4 additional participants experienced SAEs of COVID-19, (2 participants), septic shock, renal impairment, shock (1 participant), pneumonia (1 participant), and 2 participants who previously experienced SAEs experienced additional SAEs of anal squamous cell carcinoma, impaired healing, anal cancer (1 participant), and angina pectoris (1 participant). The only SAE that was reported for more than 1 participant was COVID-19 (2.8%, 2 participants). None of these SAEs led to discontinuation of study drug and none were considered related to study drug.

2.1.5.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Serious AEs were reported for 6.4% (10 of 157 participants) in the LEN total group and none of the participants in the BVY group (Table 10). None of the SAEs were reported for more than 1 participant in any treatment group, and all were considered not related to the study drugs.

Since the Week 28 analysis, 1 additional SAE was reported in the SC LEN + (DVY → TAF) group (uterine leiomyoma) and 1 additional SAE was reported in the SC LEN + (DVY → BIC) total group (hepatitis A).

Table 10. GS-US-200-4334: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Treatment-Emergent Serious Adverse Events	3 (5.8%)	3 (5.7%)	4 (7.7%)	0	6 (5.7%)	10 (6.4%)
Blood and lymphatic system disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Lymphadenopathy mediastinal	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Gastrointestinal disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Vomiting	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Infections and infestations	2 (3.8%)	3 (5.7%)	1 (1.9%)	0	5 (4.8%)	6 (3.8%)
Escherichia infection	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hepatitis A	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Perirectal abscess	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Pneumocystis jirovecii pneumonia	0	0	1 (1.9%)	0	0	1 (0.6%)
Pneumonia	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Staphylococcal infection	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Injury, poisoning, and procedural complications	0	0	1 (1.9%)	0	0	1 (0.6%)
Poisoning	0	0	1 (1.9%)	0	0	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Metastases to central nervous system	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Non-small cell lung cancer	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Uterine leiomyoma	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)

System Organ Class Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Psychiatric disorders	0	1 (1.9%)	2 (3.8%)	0	1 (1.0%)	3 (1.9%)
Bipolar disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Major depression	0	0	1 (1.9%)	0	0	1 (0.6%)
Mental disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Psychotic disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Substance-induced psychotic disorder	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	0	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Dyspnoea	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pleural effusion	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumothorax	0	0	1 (1.9%)	0	0	1 (0.6%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; PT = preferred term; SC = subcutaneous; SOC = system organ class; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple adverse events were counted only once per participant for the highest severity grade for each SOC and PT.
SOCs were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.3.1

2.1.5.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

There were no SAEs reported during the study.

2.1.6. Discontinuation Due to Adverse Events

2.1.6.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

While no participant discontinued study drug due to AE at the Week 26 analysis, 1 participant (1.4%) in Cohort 1 experienced a Grade 1 AE of injection site nodule during the Extension Phase, leading to premature discontinuation from the study after receiving the Week 52 LEN SC injection. The event was considered related to study drug.

2.1.6.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Three of 105 participants (2.9%) in the SC LEN total group discontinued study drug due to AEs (injection site induration, injection site erythema, and injection site swelling). All were nonserious and Grade 1 in severity.

Since the Week 28 analysis, 1 participant in the SC LEN total group had experienced AEs of injection site erythema and injection site swelling that led to premature discontinuation of study drug after the week 52 LEN SC injection. Both occurrences were nonserious and Grade 1 in severity.

2.1.6.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

A summary of AEs leading to premature discontinuation of study drug and study (by system organ class and PT]) during each dosing period and overall is provided in GS-US-200-5709 Interim CSR Addendum in Tables 15.11.5.1 and 15.11.5.2, respectively.

Cohort 1

In the interim CSR, 1 participant (3.2%) prematurely discontinued study drug and study due to an AE (SARS-CoV-2 test positive). This AE was considered not serious and not related to study drug. A narrative for this participant is provided in the interim CSR. No new study drug discontinuations were reported for this CSR addendum.

Cohort 2

No participant discontinued study drug or the study due to AEs.

2.1.7. Study Drug-Related Injection Site Reactions

2.1.7.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Overall, 45 participants (62.5%) experienced a study drug-related ISR. All were Grade 1 or 2 with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR which resolved after a few days. No new Grade 3 or 4 ISRs were reported beyond Week 26. The median (Q1, Q3)

total duration of any study drug-related ISR was 8 (3, 67) days (Table 11). The most frequently reported study drug-related ISRs (reported in ≥ 10% of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site swelling (30.6%, 22 participants), 12 (6, 30) days
- Injection site pain (30.6%, 22 participants), 3 (2, 7) days
- Injection site nodule (23.6%, 17 participants), 180 (111, 330) days
- Injection site erythema (25.0%, 18 participants), 6 (3, 8) days
- Injection site induration (15.3%, 11 participants), 118 (15, 182) days

Following the Day 1 SC dose of LEN in a total of 72 participants, the most frequently reported ISRs (reported in ≥ 10% of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site swelling (26.4%, 19 participants), 10 (4, 21) days
- Injection site erythema (23.6%, 17 participants), 6 (3, 8) days
- Injection site pain (22.2%, 16 participants), 3 (1, 6) days
- Injection site nodule (22.2%, 16 participants), 235 (72, 422) days
- Injection site induration (11.1%, 8 participants), 99 (22, 224) days

A numerically lower percentage of participants had ISRs after the second LEN injection compared with the first injection. Following the Week 26 SC dose of LEN in a total of 70 participants, the most frequently reported ISRs (reported in ≥ 5% of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site pain (21.4%, 15 participants), 4 (3, 8) days
- Injection site swelling (12.9%, 9 participants), 14 (8, 16) days
- Injection site nodule (11.4%, 8 participants), 188 (111, 314) days
- Injection site erythema (11.4%, 8 participants), 6 (4, 8) days
- Injection site induration (10%, 7 participants), 118 (13, 168) days

Following the Week 52 SC dose of LEN in a total of 36 participants, the most frequently reported ISRs (reported in ≥ 5% of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site nodule (16.7%, 6 participants), 140 (132,169) days
- Injection site pain (13.9%, 5 participants), 2 (1, 3) days
- Injection site swelling (11.1%, 4 participants), 48 (45, 48) days

Table 11. GS-US-200-4625: Study Drug-related Injection Site Reactions – All LEN Analysis (Safety Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Number of Participants Who Received At Least 1 Injection	24	12	36	36	72
Number (%) of Participants With Any Study Drug-Related ISRs	17 (70.8%)	6 (50.0%)	23 (63.9%)	22 (61.1%)	45 (62.5%)
Grade 1	14 (58.3%)	4 (33.3%)	18 (50.0%)	12 (33.3%)	30 (41.7%)
Grade 2	3 (12.5%)	2 (16.7%)	5 (13.9%)	8 (22.2%)	13 (18.1%)
Grade 3	0	0	0	2 (5.6%)	2 (2.8%)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Number (%) of Participants With Any Study Drug-Related ISRs by Preferred Term					
Injection site swelling	8 (33.3%)	4 (33.3%)	12 (33.3%)	10 (27.8%)	22 (30.6%)
Injection site pain	9 (37.5%)	1 (8.3%)	10 (27.8%)	12 (33.3%)	22 (30.6%)
Injection site nodule	9 (37.5%)	4 (33.3%)	13 (36.1%)	4 (11.1%)	17 (23.6%)
Injection site erythema	6 (25.0%)	2 (16.7%)	8 (22.2%)	10 (27.8%)	18 (25.0%)
Injection site induration	2 (8.3%)	0	2 (5.6%)	9 (25.0%)	11 (15.3%)
Injection site pruritus	2 (8.3%)	0	2 (5.6%)	1 (2.8%)	3 (4.2%)
Injection site extravasation	1 (4.2%)	0	1 (2.8%)	1 (2.8%)	2 (2.8%)
Injection site discomfort	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
Injection site mass	0	1 (8.3%)	1 (2.8%)	0	1 (1.4%)
Injection site haematoma	0	0	0	1 (2.8%)	1 (1.4%)
Injection site oedema	0	0	0	1 (2.8%)	1 (1.4%)
Injection site ulcer	0	0	0	1 (2.8%)	1 (1.4%)
Total Duration of Any Study Drug-Related ISRs					
N	80	37	117	79	196
Mean (SD)	94 (156.9)	74 (91.9)	88 (139.6)	39 (75.3)	68 (120.2)
Median	10	50	14	6	8
Q1, Q3	3, 147	7, 111	4, 111	3, 41	3, 67
Min, Max	1, 552	1, 337	1, 552	1, 422	1, 552

ISR = injection site reaction; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard deviation
Adverse events were coded according to MedDRA Version 23.1.

Study drug-related ISR is defined as an adverse event marked as "Related" on the adverse event electronic case report form with high-level term = "injection site reactions."
Denominator for percentage calculation for the injection visit of interest is the number of participants received injection for that visit.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017).
Preferred terms were presented by descending order of the total frequencies.
Each SC dose consists of 2 SC injections into the abdomen.
Duration = stop date − onset date + 1. For ongoing ISRs, stop date was imputed as last study date or data cut date, whichever is the earliest.
Participants may receive more than 1 SC injection.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Tables 15.11.2.4.1 and 15.11.2.4.2

2.1.7.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Overall, 57 of 103 participants (55.3%) who received SC LEN had a study drug-related ISR; all were Grade 1 or Grade 2, except for 1 participant with a Grade 3 injection site nodule (Table 12). There were no new Grade 3 or higher ISRs reported since the Week 28 analysis. The most frequently of reported ISRs (≥ 10% in SC LEN total group) and their duration in median (Q1, Q3) days were as follows:

- Injection site erythema (27.2%, 28 participants), 5 (2, 11) days
- Injection site swelling (23.3%, 24 participants), 11 (6, 29) days
- Injection site pain (19.4%, 20 participants), 4 (1, 9) days
- Injection site nodule (14.6%, 15 participants), 195 (122, 301) days
- Injection site inflammation (13.6%, 14 participants), 3 (1, 8) days
- Injection site induration (12.6%, 13 participants), 202 (101, 361) days

Following the Day 15 SC LEN injection, the most frequently reported ISRs (≥ 5% in SC LEN total group) and their duration in median (Q1, Q3) days were as follows:

- Injection site pain (14.6%, 15 participants), 4 (1, 9) days
- Injection site erythema (13.6%, 14 participants), 5 (2, 11) days
- Injection site swelling (13.6%, 14 participants), 10 (5, 30) days
- Injection site nodule (10.7%, 11 participants), 301 (140, 369) days
- Injection site induration (8.7%, 9 participants), 213 (143, 445) days

Following the Week 28 SC LEN injection, the most frequently reported ISRs (≥ 5% in SC LEN total group) and their duration in median (Q1, Q3) days were as follows:

- Injection site erythema (17.9%, 17 participants), 5 (3, 11) days

- Injection site inflammation (14.7%, 14 participants), 3 (1, 8) days
- Injection site swelling (11.6%, 11 participants), 10 (5, 14) days
- Injection site pain (9.5%, 9 participants), 2 (1, 3) days
- Injection site nodule (8.4%, 8 participants), 222 (175, 278) days
- Injection site induration (6.3%, 6 participants), 236 (145, 262) days

A numerically lower percentage of participants had ISRs after their Week 54 SC LEN injections than after their Day 15 and Week 28 injections. Following the Week 54 SC LEN injection, the most frequently reported ISRs (≥ 5% in SC LEN total group) and their duration in median (Q1, Q3) days were as follows:

- Injection site swelling (13.3%, 12 participants), 14 (6, 69) days
- Injection site nodule (10.0%, 9 participants), 100 (44, 157) days
- Injection site erythema (6.7%, 6 participants), 4 (2, 9) days
- Injection site pain (6.7%, 6 participants), 8 (3, 20) days

Table 12. GS-US-200-4334: Study Drug-Related Injection Site Reactions (Safety Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	SC LEN Total (N = 105)
Number of Participants Who Received at Least One Injection	51	52	103
Number (%) of Participants With Any Study Drug-Related ISRs	32 (62.7%)	25 (48.1%)	57 (55.3%)
Grade 1	26 (51.0%)	23 (44.2%)	49 (47.6%)
Grade 2	6 (11.8%)	1 (1.9%)	7 (6.8%)
Grade 3	0	1 (1.9%)	1 (1.0%)
Grade 4	0	0	0
Grade 5	0	0	0
Number (%) of Participants With Any Study Drug-Related ISRs by Preferred Term			
Injection site erythema	18 (35.3%)	10 (19.2%)	28 (27.2%)
Injection site swelling	13 (25.5%)	11 (21.2%)	24 (23.3%)
Injection site pain	12 (23.5%)	8 (15.4%)	20 (19.4%)
Injection site nodule	8 (15.7%)	7 (13.5%)	15 (14.6%)
Injection site inflammation	10 (19.6%)	4 (7.7%)	14 (13.6%)
Injection site induration	8 (15.7%)	5 (9.6%)	13 (12.6%)
Injection site mass	2 (3.9%)	2 (3.8%)	4 (3.9%)
Injection site bruising	1 (2.0%)	0	1 (1.0%)
Injection site haematoma	0	1 (1.9%)	1 (1.0%)
Injection site paraesthesia	1 (2.0%)	0	1 (1.0%)
Injection site pruritus	0	1 (1.9%)	1 (1.0%)
Injection site warmth	1 (2.0%)	0	1 (1.0%)
Number of Participants Who Received Injection at Day 15 SC Visit	51	52	103
Number (%) of Participants With Any Study Drug-Related ISRs Following Day 15 SC Injection	22 (43.1%)	17 (32.7%)	39 (37.9%)
Grade 1	18 (35.3%)	16 (30.8%)	34 (33.0%)
Grade 2	4 (7.8%)	1 (1.9%)	5 (4.9%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	SC LEN Total (N = 105)
Number (%) of Participants With Any Study Drug-Related ISRs by Preferred Term Following Day 15 SC Injection			
Injection site pain	9 (17.6%)	6 (11.5%)	15 (14.6%)
Injection site erythema	9 (17.6%)	5 (9.6%)	14 (13.6%)
Injection site swelling	7 (13.7%)	7 (13.5%)	14 (13.6%)
Injection site nodule	7 (13.7%)	4 (7.7%)	11 (10.7%)
Injection site induration	5 (9.8%)	4 (7.7%)	9 (8.7%)
Injection site mass	2 (3.9%)	1 (1.9%)	3 (2.9%)
Injection site bruising	1 (2.0%)	0	1 (1.0%)
Injection site paraesthesia	1 (2.0%)	0	1 (1.0%)
Injection site warmth	1 (2.0%)	0	1 (1.0%)
Number of Participants Who Received Injection at Week 28 SC Visit	48	47	95
Number (%) of Participants With Any Study Drug-Related ISRs Following Week 28 SC Injection	24 (50.0%)	18 (38.3%)	42 (44.2%)
Grade 1	23 (47.9%)	17 (36.2%)	40 (42.1%)
Grade 2	1 (2.1%)	0	1 (1.1%)
Grade 3	0	1 (2.1%)	1 (1.1%)
Grade 4	0	0	0
Grade 5	0	0	0
Number (%) of Participants With Any Study Drug-Related ISRs by Preferred Term Following Week 28 SC Injection			
Injection site erythema	11 (22.9%)	6 (12.8%)	17 (17.9%)
Injection site inflammation	10 (20.8%)	4 (8.5%)	14 (14.7%)
Injection site swelling	6 (12.5%)	5 (10.6%)	11 (11.6%)
Injection site pain	5 (10.4%)	4 (8.5%)	9 (9.5%)
Injection site nodule	3 (6.3%)	5 (10.6%)	8 (8.4%)
Injection site induration	6 (12.5%)	0	6 (6.3%)
Injection site haematoma	0	1 (2.1%)	1 (1.1%)
Injection site mass	0	1 (2.1%)	1 (1.1%)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	SC LEN Total (N = 105)
Number of Participants Who Received Injection at Week 54 SC Visit	47	43	90
Number (%) of Participants With Any Study Drug-Related ISRs Following Week 54 SC Injection	12 (25.5%)	11 (25.6%)	23 (25.6%)
Grade 1	11 (23.4%)	11 (25.6%)	22 (24.4%)
Grade 2	1 (2.1%)	0	1 (1.1%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Number (%) of Participants With Any Study Drug-Related ISRs by Preferred Term Following Week 54 SC Injection			
Injection site swelling	9 (19.1%)	3 (7.0%)	12 (13.3%)
Injection site nodule	4 (8.5%)	5 (11.6%)	9 (10.0%)
Injection site erythema	5 (10.6%)	1 (2.3%)	6 (6.7%)
Injection site pain	4 (8.5%)	2 (4.7%)	6 (6.7%)
Injection site induration	3 (6.4%)	1 (2.3%)	4 (4.4%)
Injection site mass	0	1 (2.3%)	1 (1.1%)
Injection site pruritus	0	1 (2.3%)	1 (1.1%)

BIC, B = bictegravir; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); ISR = injection site reaction; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Study drug-related ISR is defined as an adverse event marked as "Related" on the adverse event electronic case report form with high-level term = "Injection Site Reactions."
Denominator for percentage calculation for the injection visit of interest is the number of participants received injection for that visit.
Source: GS-US-200-4334 Interim CSR Addendum, Table 15.11.5.1

2.1.7.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

In both Cohort 1 and Cohort 2, all ISRs were considered related to study drug. Injection site reactions accounted for all the treatment-related AEs in Cohort 2. All ISRs were Grade 1 or 2 in severity.

2.1.8. Study Drug-Related Injection Site Nodule and Induration

2.1.8.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Overall, 17 participants (23.6%) experienced study drug-related injection site nodule, and 11 participants (15.3%) experienced study drug-related injection site induration (Table 13). All events were Grade 1 or 2.

Injection site nodules and indurations due to Day 1 SC injection:

Participant level analysis:

- Nodules: Ongoing (9/16 [56.3%]); Resolved (7/16 [43.8%])
- Indurations: Ongoing (1/8 [12.5%]); Resolved (7/8 [87.5%])

Event level analysis:

- Nodules: Ongoing (9/23 [39.1%]); Resolved (14/23 [60.9%])
- Indurations: Ongoing (1/8 [12.5%]); Resolved (7/8 [87.5%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration due to Day 1 SC injection was 107 (70, 227) days and 43 (15, 196) days, respectively.

Injection site nodules and indurations due to second LEN injection at Week 26:

Participant level analysis:

- Nodules: Ongoing (6/8 [75.0%%]); Resolved (2/8 [25.0%])
- Indurations: Ongoing (3/7 [42.9%]); Resolved (4/7 [57.1%])

Event level analysis:

- Nodules: Ongoing (12/14 [85.7%]); Resolved (2/14 [14.3%])
- Indurations: Ongoing (3/7 [42.9%]); Resolved (4/7 [57.1%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration after the second LEN injection at Week 26 was 92 (3, 180) days and 38 (9, 123) days, respectively.

Table 13. GS-US-200-4625: Ongoing and Resolved Study Drug-related Injection Site Nodules and Indurations – All LEN Analysis (Safety Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Participant Level Analysis					
Number of Participants Who Received at Least One Injection	24	12	36	36	72
Number of Participants With Any Injection Site Nodule	9	4	13	4	17
Ongoing	7 (77.8%)	2 (50.0%)	9 (69.2%)	4 (100.0%)	13 (76.5%)
Resolved	2 (22.2%)	2 (50.0%)	4 (30.8%)	0	4 (23.5%)
Number of Participants With Any Injection Site Induration	2	0	2	9	11
Ongoing	1 (50.0%)	0	1 (50.0%)	3 (33.3%)	4 (36.4%)
Resolved	1 (50.0%)	0	1 (50.0%)	6 (66.7%)	7 (63.6%)
Number of Participants Who Received Day 1 SC Injection	24	12	36	36	72
Number of Participants With Any Injection Site Nodule Due to Day 1 SC Injection	9	3	12	4	16
Ongoing	5 (55.6%)	1 (33.3%)	6 (50.0%)	3 (75.0%)	9 (56.3%)
Resolved	4 (44.4%)	2 (66.7%)	6 (50.0%)	1 (25.0%)	7 (43.8%)
Number of Participants With Any Injection Site Induration Due to Day 1 SC Injection	1	0	1	7	8
Ongoing	1 (100.0%)	0	1 (100.0%)	0	1 (12.5%)
Resolved	0	0	0	7 (100.0%)	7 (87.5%)
Number of Participants Who Received Week 26 SC Injection	24	12	36	34	70
Number of Participants With Any Injection Site Nodule Due to Week 26 SC Injection	4	3	7	1	8
Ongoing	3 (75.0%)	2 (66.7%)	5 (71.4%)	1 (100.0%)	6 (75.0%)
Resolved	1 (25.0%)	1 (33.3%)	2 (28.6%)	0	2 (25.0%)
Number of Participants With Any Injection Site Induration Due to Week 26 SC Injection	1	0	1	6	7
Ongoing	0	0	0	3 (50.0%)	3 (42.9%)
Resolved	1 (100.0%)	0	1 (100.0%)	3 (50.0%)	4 (57.1%)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Event Level Analysis					
Total Number of SC LEN Doses Administered	77	37	114	73	187
Injection Site Nodule	24	14	38	7	45
Ongoing	15 (62.5%)	8 (57.1%)	23 (60.5%)	5 (71.4%)	28 (62.2%)
Resolved	9 (37.5%)	6 (42.9%)	15 (39.5%)	2 (28.6%)	17 (37.8%)
Injection Site Induration	2	0	2	13	15
Ongoing	1 (50.0%)	0	1 (50.0%)	3 (23.1%)	4 (26.7%)
Resolved	1 (50.0%)	0	1 (50.0%)	10 (76.9%)	11 (73.3%)
Number of Day 1 SC Injections	24	12	36	36	72
Injection Site Nodule Due to Day 1 SC Injection	12	6	18	5	23
Ongoing	5 (41.7%)	1 (16.7%)	6 (33.3%)	3 (60.0%)	9 (39.1%)
Resolved	7 (58.3%)	5 (83.3%)	12 (66.7%)	2 (40.0%)	14 (60.9%)
Injection Site Induration Due to Day 1 SC Injection	1	0	1	7	8
Ongoing	1 (100.0%)	0	1 (100.0%)	0	1 (12.5%)
Resolved	0	0	0	7 (100.0%)	7 (87.5%)
Number of Week 26 SC Injections	24	12	36	34	70
Injection Site Nodule Due to Week 26 SC Injection	6	6	12	2	14
Ongoing	5 (83.3%)	5 (83.3%)	10 (83.3%)	2 (100.0%)	12 (85.7%)
Resolved	1 (16.7%)	1 (16.7%)	2 (16.7%)	0	2 (14.3%)
Injection Site Induration Due to Week 26 SC Injection	1	0	1	6	7
Ongoing	0	0	0	3 (50.0%)	3 (42.9%)
Resolved	1 (100.0%)	0	1 (100.0%)	3 (50.0%)	4 (57.1%)
Duration (Days) of Resolved Injection Site Nodule Due to Day 1 SC Injection					
N	7	5	12	2	14
Mean (SD)	215 (143.0)	97 (73.1)	166 (129.6)	91 (70.7)	155 (123.8)
Median	155	72	114	91	107
Q1, Q3	70, 367	57, 72	70, 240	41, 141	70, 227
Min, Max	70, 436	57, 227	57, 436	41, 141	41, 436
Duration (Days) of Resolved Injection Site Induration Due to Day 1 SC Injection					
N	0	0	0	7	7
Mean (SD)				99 (100.2)	99 (100.2)
Median				43	43

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Q1, Q3				15, 196	15, 196
Min, Max				3, 252	3, 252
Duration (Days) of Resolved Injection Site Nodule Due to Week 26 SC Injection					
N	1	1	2	0	2
Mean (SD)	3	180	92 (125.2)		92 (125.2)
Median	3	180	92		92
Q1, Q3	3, 3	180, 180	3, 180		3, 180
Min, Max	3, 3	180, 180	3, 180		3, 180
Duration (Days) of Resolved Injection Site Induration Due to Week 26 SC Injection					
N	1	0	1	3	4
Mean (SD)	182		182	27 (31.4)	66 (81.6)
Median	182		182	13	38
Q1, Q3	182, 182		182, 182	5, 63	9, 123
Min, Max	182, 182		182, 182	5, 63	5, 182

ISR = injection site reaction; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard deviation
Study drug-related ISR is defined as an adverse event marked as "Related" on the adverse event electronic case report form with high-level term = "injection site reactions."
Each SC dose consists of 2 SC injections into the abdomen.
Each injection site reaction was counted in the total. One participant could have multiple ISRs.
If a participant had more than one injection site induration or nodule events, the participant will be counted in the "Ongoing" category unless all study drug-related injection site induration or nodule events have been resolved.
Duration = stop date − onset date + 1
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Tables 15.11.2.4.3, 15.11.2.4.4, and 15.11.2.4.5

2.1.8.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Overall, 15 of 103 participants had an AE of injection site nodule and 13 of 103 participants had an AE of injection site induration. All were Grade 1 or Grade 2, except for 1 participant with a Grade 3 injection site nodule.

Information about ongoing and resolved injection site indurations and nodules are presented in Table 14.

Injection site reactions after the first SC LEN injection at Day 15:

Participant-level analysis:

- Nodules: Ongoing (1 of 11 [9.1%]); Resolved (10 of 11 [90.9%])
- Indurations: Ongoing (6 of 9 [66.7%]); Resolved (3 of 9 [33.3%])

Event-level analysis:

- Nodules: Ongoing (1 of 13 [7.7%]); Resolved (12 of 13 [92.3%])
- Indurations: Ongoing (6 of 9 [66.7%]); Resolved (3 of 9 [33.3%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration was 278 (136, 366) days and 202 (101, 213) days, respectively.

Injection site reactions after the second SC LEN injection at Week 28:

Participant-level analysis:

- Nodules: Ongoing (5 of 8 [62.5%]); Resolved (3 of 8 [37.5%])
- Indurations: Ongoing (3 of 6 [50.0%]); Resolved (3 of 6 [50.0%])

Event-level analysis:

- Nodules: Ongoing (5 of 8 [62.5%]); Resolved (3 of 8 [37.5%])
- Indurations: Ongoing (3 of 6 [50.0%]); Resolved (3 of 6 [50.0%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration was 152 (123, 240) days and 145 (4, 258) days, respectively.

Table 14. GS-US-200-4334: Ongoing and Resolved Study Drug-related Injection Site Nodules and Indurations (Safety Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	SC LEN Total (N = 105)
Participant-level Analysis			
Number of Participants Who Received at Least One Injection	51	52	103
Number of Participants With Any Injection Site Nodule	8	7	15
Ongoing	4 (50.0%)	5 (71.4%)	9 (60.0%)
Resolved	4 (50.0%)	2 (28.6%)	6 (40.0%)
Number of Participants With Any Injection Site Induration	8	5	13
Ongoing	6 (75.0%)	4 (80.0%)	10 (76.9%)
Resolved	2 (25.0%)	1 (20.0%)	3 (23.1%)
Number of Participants Who Received Day 15 SC Injection	51	52	103
Number of Participants With Any Injection Site Nodule Due to Day 15 SC Injection	7	4	11
Ongoing	1 (14.3%)	0	1 (9.1%)
Resolved	6 (85.7%)	4 (100.0%)	10 (90.9%)
Number of Participants With Any Injection Site Induration Due to Day 15 SC Injection	5	4	9
Ongoing	3 (60.0%)	3 (75.0%)	6 (66.7%)
Resolved	2 (40.0%)	1 (25.0%)	3 (33.3%)
Number of Participants Who Received Day Week 28 SC Injection	48	47	95
Number of Participants With Any Injection Site Nodule Due to Week 28 SC Injection	3	5	8
Ongoing	2 (66.7%)	3 (60.0%)	5 (62.5%)
Resolved	1 (33.3%)	2 (40.0%)	3 (37.5%)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	SC LEN Total (N = 105)
Number of Participants With Any Injection Site Induration Due to Week 28 SC Injection	6	0	6
Ongoing	3 (50.0%)	0	3 (50.0%)
Resolved	3 (50.0%)	0	3 (50.0%)
Event-level Analysis			
Total Number of SC LEN Doses Administered	161	153	314
Injection Site Nodule	16	14	30
Ongoing	5 (31.3%)	6 (42.9%)	11 (36.7%)
Resolved	11 (68.8%)	8 (57.1%)	19 (63.3%)
Injection Site Induration	14	5	19
Ongoing	8 (57.1%)	4 (80.0%)	12 (63.2%)
Resolved	6 (42.9%)	1 (20.0%)	7 (36.8%)
Number of Day 15 SC Injections	51	52	103
Injection Site Nodule Due to Day 15 SC Injection	9	4	13
Ongoing	1 (11.1%)	0	1 (7.7%)
Resolved	8 (88.9%)	4 (100.0%)	12 (92.3%)
Injection Site Induration Due to Day 15 SC Injection	5	4	9
Ongoing	3 (60.0%)	3 (75.0%)	6 (66.7%)
Resolved	2 (40.0%)	1 (25.0%)	3 (33.3%)
Number of Week 28 SC Injections	48	47	95
Injection Site Nodule Due to Week 28 SC Injection	3	5	8
Ongoing	2 (66.7%)	3 (60.0%)	5 (62.5%)
Resolved	1 (33.3%)	2 (40.0%)	3 (37.5%)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	SC LEN Total (N = 105)
Injection Site Induration Due to Week 28 SC Injection	6	0	6
Ongoing	3 (50.0%)	0	3 (50.0%)
Resolved	3 (50.0%)	0	3 (50.0%)
Duration (Days) of Resolved Injection Site Nodule Due to Day 15 SC Injection			
N	8	4	12
Mean (SD)	262 (127.5)	260 (186.5)	261 (140.9)
Median	278	250	278
Q1, Q3	195, 349	103, 417	136, 366
Min, Max	26, 424	75, 464	26, 464
Duration (Days) of Resolved Injection Site Induration Due to Day 15 SC Injection			
N	2	1	3
Mean (SD)	157 (79.2)	202	172 (61.7)
Median	157	202	202
Q1, Q3	101, 213	202, 202	101, 213
Min, Max	101, 213	202, 202	101, 213
Duration (Days) of Resolved Injection Site Nodule Due to Week 28 SC Injection			
N	1	2	3
Mean (SD)	240	138 (20.5)	172 (60.9)
Median	240	138	152
Q1, Q3	240, 240	123, 152	123, 240
Min, Max	240, 240	123, 152	123, 240

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	SC LEN Total (N = 105)
Duration (Days) of Resolved Injection Site Induration Due to Week 28 SC Injection			
N	3	0	3
Mean (SD)	136 (127.3)		136 (127.3)
Median	145		145
Q1, Q3	4, 258		4, 258
Min, Max	4, 258		4, 258

AE = adverse event; BIC, B = bictegravir; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); ISR = injection site reaction; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard deviation; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Study drug-related ISR is defined as an adverse event marked as "Related" on the AE electronic case report form with high-level term = "injection site reactions."
Each SC dose consists of 2 SC injections into the abdomen.
Participants may have received more than one SC injection. Each SC injection may have more than one ISRs
Duration (days) = stop date − onset date + 1.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Tables 15.11.5.3, 15.11.5.4, and 15.11.5.5

2.1.9. Hypersensitivity Reactions

Preferred terms for defining hypersensitivity reactions were identified from the narrow Standardized MedDRA Query (SMQ) of "Hypersensitivity." Across Studies GS-US-200-4625, GS-US-200-4334 and GS-US-200-5709, no AEs matching PTs in this SMQ were SAEs, and none resulted in study drug discontinuation.

2.1.9.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

Adverse events that occurred in more than 1 participant at Week 52 were rash (6.9%, 5 participants), rhinitis allergic (2.8%, 2 participants), and rash pruritic and rash papular (2.8%, 2 participants each). No TEAEs of hypersensitivity were reported.

Treatment-emergent adverse events considered related to study drug were rash macular and rash papular reported for 1 participant each (1.4%) and rash for 2 participants (2.8%), all of which resolved and did not recur with ongoing LEN exposure. All TEAEs were Grade 1 or 2 in severity except for a Grade 3 AE of rash in 1 participant, reported as general maculopapular exanthema, itchy when touched, covering chest and back, occurring concurrently with Grade 2 AEs of pyrexia and influenza like illness. All events started on Day 11 and resolved with ongoing LEN exposure and after a switch from Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate [TDF]) to Truvada (emtricitabine/TDF) in the OBR. The investigator suspected that the allergic reaction occurred due to the OBR, in particular doravirine, and the participant proceeded to receive SC LEN on Day 15 with no recurrence of the rash.

None of the reported TEAEs led to discontinuation of study drug or the study.

Since the Week 26 Interim analysis, 1 additional participant experienced an unrelated Grade 1 AE of rash (reported term "rash on nose"). Study drug was continued.

2.1.9.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

In the LEN total group of Study GS-US-200-4334, AEs that occurred in more than 1 participant at Week 54 were hypersensitivity (3.2%, 5 participants), rhinitis allergic (2.5%, 4 participants), rash (2.5%, 4 participants), and rash macular (1.3%, 2 participants).

Since the Week 28 analysis, 2 additional participants experienced AEs of hypersensitivity (reported terms "allergy in body" and "allergy"), and 1 additional participant experienced the AE of rash (reported term "skin rash"). None of the additional rash or hypersensitivity AEs were considered related to study drug by the investigator, or led to discontinuation, and all AEs were Grade 1 and resolved during continued exposure to study drug.

2.1.9.3. Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

In Cohorts 1 and 2 of GS-US-200-5709, one TEAE of hypersensitivity ("environmental allergy") was reported and was not considered related to study drug.

2.2. Narratives

Narratives for deaths, SAEs, and discontinuations due to AEs are provided in the relevant CSRs.

3. CLINICAL LABORATORY EVALUATIONS

All laboratory abnormalities discussed in the following sections were treatment emergent and are referred to as laboratory abnormalities.

Detailed clinical laboratory evaluation results are described and provided in the individual CSRs (GS-US-200-4625 Interim Week 52 CSR Addendum, Section 11.6, GS-US-200-4334 Interim Week 54 CSR Addendum, Section 11.6, and GS-US-200-5709 Interim CSR Addendum, Section 11.6).

There were no clinically relevant changes from baseline in median values for hematology, clinical chemistry (including metabolic parameters) in Studies GS-US-200-4625, GS-US-200-4334, and GS-US-200-5709.

3.1. Graded Laboratory Abnormalities

Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

The majority of the participants had at least 1 graded laboratory abnormality (97.2%, 70 of 72 participants). The majority of abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 16 participants (22.2%) and Grade 4 laboratory abnormalities were reported for 5 participants (6.9%). Grade 3 and 4 laboratory abnormalities reported for at least 2 participants are presented in Table 15.

Since the Interim Week 26 analysis, 1 additional participant had Grade 3 laboratory abnormalities and 1 additional participant had Grade 4 laboratory abnormalities.

These laboratory abnormalities were either transient, returned to baseline, improved on subsequent visits despite continued exposure to the study drug, or occurred in participants with underlying conditions expected in the population (eg, diabetes, alcohol abuse, viral hepatitis).

Table 15. GS-US-200-4625: Grade 3 or 4 Laboratory Abnormalities Reported in ≥ 2 Participants – All LEN Analysis (Safety Analysis Set)

	Cohort 1				
Maximum Postbaseline Toxicity Grade	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Participants With Postbaseline Value	24	12	36	36	72
Grade 3 or 4	9 (37.5%)	4 (33.3%)	13 (36.1%)	8 (22.2%)	21 (29.2%)
Grade 3	8 (33.3%)	3 (25.0%)	11 (30.6%)	5 (13.9%)	16 (22.2%)
Grade 4	1 (4.2%)	1 (8.3%)	2 (5.6%)	3 (8.3%)	5 (6.9%)
Chemistry					
ALT (SGPT), High	24	12	36	36	72
Grade 3 or 4	0	0	0	2 (5.6%)	2 (2.8%)
Grade 3	0	0	0	2 (5.6%)	2 (2.8%)
Grade 4	0	0	0	0	0

Maximum Postbaseline Toxicity Grade	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)		
AST (SGOT), High	24	12	36	36	72
Grade 3 or 4	0	0	0	2 (5.6%)	2 (2.8%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	2 (5.6%)	2 (2.8%)
Creatinine, High	24	12	36	36	72
Grade 3 or 4	5 (20.8%)	1 (8.3%)	6 (16.7%)	3 (8.3%)	9 (12.5%)
Grade 3	4 (16.7%)	1 (8.3%)	5 (13.9%)	2 (5.6%)	7 (9.7%)
Grade 4	1 (4.2%)	0	1 (2.8%)	1 (2.8%)	2 (2.8%)
Creatinine Clearance or eGFR, Low	24	12	36	36	72
Grade 3 or 4	5 (20.8%)	2 (16.7%)	7 (19.4%)	3 (8.3%)	10 (13.9%)
Grade 3	4 (16.7%)	2 (16.7%)	6 (16.7%)	3 (8.3%)	9 (12.5%)
Grade 4	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
Direct Bilirubin, High	24	12	36	36	72
Grade 3 or 4	0	0	0	2 (5.6%)	2 (2.8%)
Grade 3	0	0	0	2 (5.6%)	2 (2.8%)
Grade 4	0	0	0	0	0
Hyperglycemia, Fasting	20	9	29	26	55
Grade 3 or 4	1 (5.0%)	2 (22.2%)	3 (10.3%)	0	3 (5.5%)
Grade 3	1 (5.0%)	1 (11.1%)	2 (6.9%)	0	2 (3.6%)
Grade 4	0	1 (11.1%)	1 (3.4%)	0	1 (1.8%)
Hyperglycemia, Nonfasting	18	9	27	27	54
Grade 3 or 4	2 (11.1%)	1 (11.1%)	3 (11.1%)	0	3 (5.6%)
Grade 3	2 (11.1%)	1 (11.1%)	3 (11.1%)	0	3 (5.6%)
Grade 4	0	0	0	0	0
Urinalysis					
Glycosuria (Dipstick)	24	12	36	36	72
Grade 3 or 4	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Grade 3	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Grade 4	0	0	0	0	0
Proteinuria (Dipstick)	24	12	36	36	72
Grade 3 or 4	1 (4.2%)	1 (8.3%)	2 (5.6%)	0	2 (2.8%)
Grade 3	1 (4.2%)	1 (8.3%)	2 (5.6%)	0	2 (2.8%)
Grade 4	0	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate;
LEN = lenacapavir; N = number of participants; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017).
For summary over all laboratory tests, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time after baseline.
For Urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.6.4.2.2

Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

The majority of the participants had at least 1 graded laboratory abnormality (LEN total 94.9% [149 of 157 participants]; BVY 100.0% [25 of 25 participants]). The majority of the laboratory abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 16.6% of participants (26 of 157) in the LEN total group and 24.0% of participants (6 of 25) in the BVY group. Grade 4 laboratory abnormalities were reported for 8.3% of participants (13 of 157) in the LEN total group only (Table 16).

Since the Week 28 analysis, Grade 3 laboratory abnormalities were reported for an additional 9 participants (LEN total group: 6 participants; BVY group: 3 participants) and Grade 4 laboratory abnormalities were reported for an additional 6 participants in the LEN total group only.

None of these laboratory abnormalities were clinically relevant, as they were transient or unconfirmed, participants had a medical history of underlying conditions (eg, diabetes), or there was an alternative explanation (eg, creatine kinase or aspartate aminotransferase [AST] elevation after strenuous activity).

Table 16. GS-US-200-4334: Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities for ≥ 3 Participants in Any Treatment Group (Safety Analysis Set)

Maximum Postbaseline Toxicity Grade	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Participants With Postbaseline Value	52	53	52	25	105	157
Grade 3 or 4	11 (21.2%)	15 (28.3%)	13 (25.0%)	6 (24.0%)	26 (24.8%)	39 (24.8%)
Grade 3	6 (11.5%)	11 (20.8%)	9 (17.3%)	6 (24.0%)	17 (16.2%)	26 (16.6%)
Grade 4	5 (9.6%)	4 (7.5%)	4 (7.7%)	0	9 (8.6%)	13 (8.3%)
Hematology						
Absolute Neutrophil Count (ANC), Low	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Grade 3	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Chemistry						
ALT (SGPT), High	52	53	52	25	105	157
Grade 3 or 4	0	2 (3.8%)	3 (5.8%)	0	2 (1.9%)	5 (3.2%)
Grade 3	0	1 (1.9%)	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Grade 4	0	1 (1.9%)	2 (3.8%)	0	1 (1.0%)	3 (1.9%)
AST (SGOT), High	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)
Grade 3	2 (3.8%)	1 (1.9%)	3 (5.8%)	0	3 (2.9%)	6 (3.8%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hyperbilirubinemia	52	53	52	25	105	157
Grade 3 or 4	0	1 (1.9%)	1 (1.9%)	1 (4.0%)	1 (1.0%)	2 (1.3%)
Grade 3	0	0	0	1 (4.0%)	0	0
Grade 4	0	1 (1.9%)	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Creatine Kinase, High	52	53	52	25	105	157
Grade 3 or 4	6 (11.5%)	2 (3.8%)	3 (5.8%)	1 (4.0%)	8 (7.6%)	11 (7.0%)
Grade 3	2 (3.8%)	1 (1.9%)	2 (3.8%)	1 (4.0%)	3 (2.9%)	5 (3.2%)
Grade 4	4 (7.7%)	1 (1.9%)	1 (1.9%)	0	5 (4.8%)	6 (3.8%)
Creatinine, High	52	53	52	25	105	157
Grade 3 or 4	1 (1.9%)	4 (7.5%)	1 (1.9%)	2 (8.0%)	5 (4.8%)	6 (3.8%)
Grade 3	1 (1.9%)	3 (5.7%)	1 (1.9%)	2 (8.0%)	4 (3.8%)	5 (3.2%)

Maximum Postbaseline Toxicity Grade	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Creatinine Clearance or eGFR, Low	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	7 (13.2%)	3 (5.8%)	3 (12.0%)	9 (8.6%)	12 (7.6%)
Grade 3	2 (3.8%)	6 (11.3%)	3 (5.8%)	3 (12.0%)	8 (7.6%)	11 (7.0%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Triglycerides (Fasting)	48	51	49	23	99	148
Grade 3 or 4	0	4 (7.8%)	0	1 (4.3%)	4 (4.0%)	4 (2.7%)
Grade 3	0	3 (5.9%)	0	1 (4.3%)	3 (3.0%)	3 (2.0%)
Grade 4	0	1 (2.0%)	0	0	1 (1.0%)	1 (0.7%)
Lipase, High	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)
Grade 3	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)
Grade 4	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Hyperglycemia, Nonfasting	45	43	39	18	88	127
Grade 3 or 4	2 (4.4%)	1 (2.3%)	0	1 (5.6%)	3 (3.4%)	3 (2.4%)
Grade 3	2 (4.4%)	0	0	1 (5.6%)	2 (2.3%)	2 (1.6%)
Grade 4	0	1 (2.3%)	0	0	1 (1.1%)	1 (0.8%)
Urinalysis						
Glycosuria (Dipstick)	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)
Grade 3	2 (3.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LEN = lenacapavir; N = number of participants; SC = subcutaneous; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TAF = tenofovir alafenamide
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017.
For summary over all laboratory tests, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last exposure date.
The fourth generation LDL is derived from Friedewald formula: total cholesterol-HDL- triglyceride/5.
For Urinalysis (eg, urine glucose), the highest grade is up to Grade 3.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.6.4.2

Additional Data Supporting the Safety of LEN (Study GS-US-200-5709)

Cohort 1

In the interim CSR, laboratory abnormalities were reported for 23 of 31 participants (74.2%). For this CSR addendum, graded laboratory abnormalities were reported for 26 of 31 participants (83.9%). The maximum abnormality grade for most of the participants was Grade 1 or 2. Five of 31 participants (16.1%) had Grade 3 laboratory abnormalities and 1 of 31 participants (3.2%) had a Grade 4 laboratory abnormality (Table 17). Since the interim CSR, 3 additional participants had Grade 3 laboratory abnormalities (increases in creatine kinase (CK), fasting urine glucose, and fasting creatinine, respectively), and none were reported as AEs.

Cohort 2

In the interim CSR, laboratory abnormalities were reported for 7 of 14 participants (50.0%). For this CSR addendum, graded laboratory abnormalities were reported for 12 of 14 participants (85.7%). The maximum abnormality grade for most of the participants was Grade 1 or 2. Three of 14 participants (21.4%) had Grade 3 laboratory abnormalities and no participants had a Grade 4 laboratory abnormality (Table 17). Since the interim CSR, 2 additional participants had Grade 3 laboratory abnormalities (increases in CK and fasting triglycerides, respectively), and neither were reported as AEs.

Table 17. GS-US-200-5709: Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

Maximum Postbaseline Toxicity Grade 3 or 4	Cohort 1 Overall (N = 31)	Cohort 2 Overall (N = 14)
Participants With Postbaseline Value	31	14
Any Grade 3 or above	6 (19.4%)	3 (21.4%)
Grade 3	5 (16.1%)	3 (21.4%)
Grade 4	1 (3.2%)	0
Creatine kinase (increased)	31	14
Any Grade 3 or above	1 (3.2%)	1 (7.1%)
Grade 3	1 (3.2%)	1 (7.1%)
Grade 4	0	0
Creatinine (increased)	31	14
Any Grade 3 or above	1 (3.2%)	0
Grade 3	1 (3.2%)	0
Grade 4	0	0
LDL (fasting, increased)	31	14
Any Grade 3 or above	0	1 (7.1%)
Grade 3	0	1 (7.1%)
Grade 4	0	0

Maximum Postbaseline Toxicity Grade 3 or 4	Cohort 1 Overall (N = 31)	Cohort 2 Overall (N = 14)
Total cholesterol (fasting, hypercholesterolemia)	31	14
Any Grade 3 or above	0	1 (7.1%)
Grade 3	0	1 (7.1%)
Grade 4	0	0
Triglycerides (fasting, increased)	31	14
Any Grade 3 or above	3 (9.7%)	1 (7.1%)
Grade 3	2 (6.5%)	1 (7.1%)
Grade 4	1 (3.2%)	0
Urine glucose (glycosuria)	31	14
Any Grade 3 or above	1 (3.2%)	0
Grade 3	1 (3.2%)	0
Grade 4	0	0

DAIDS = Division of AIDS; LDL = low-density lipoprotein; LEN = lenacapavir; N = number of participants
Severity grades were defined by DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
For maximum postdose toxicity grade, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from predose at any time postdose.
Source: GS-US-200-5709 Interim CSR Addendum, Table 15.11.6.4.2

3.1.1. Hepatobiliary Laboratory Parameters

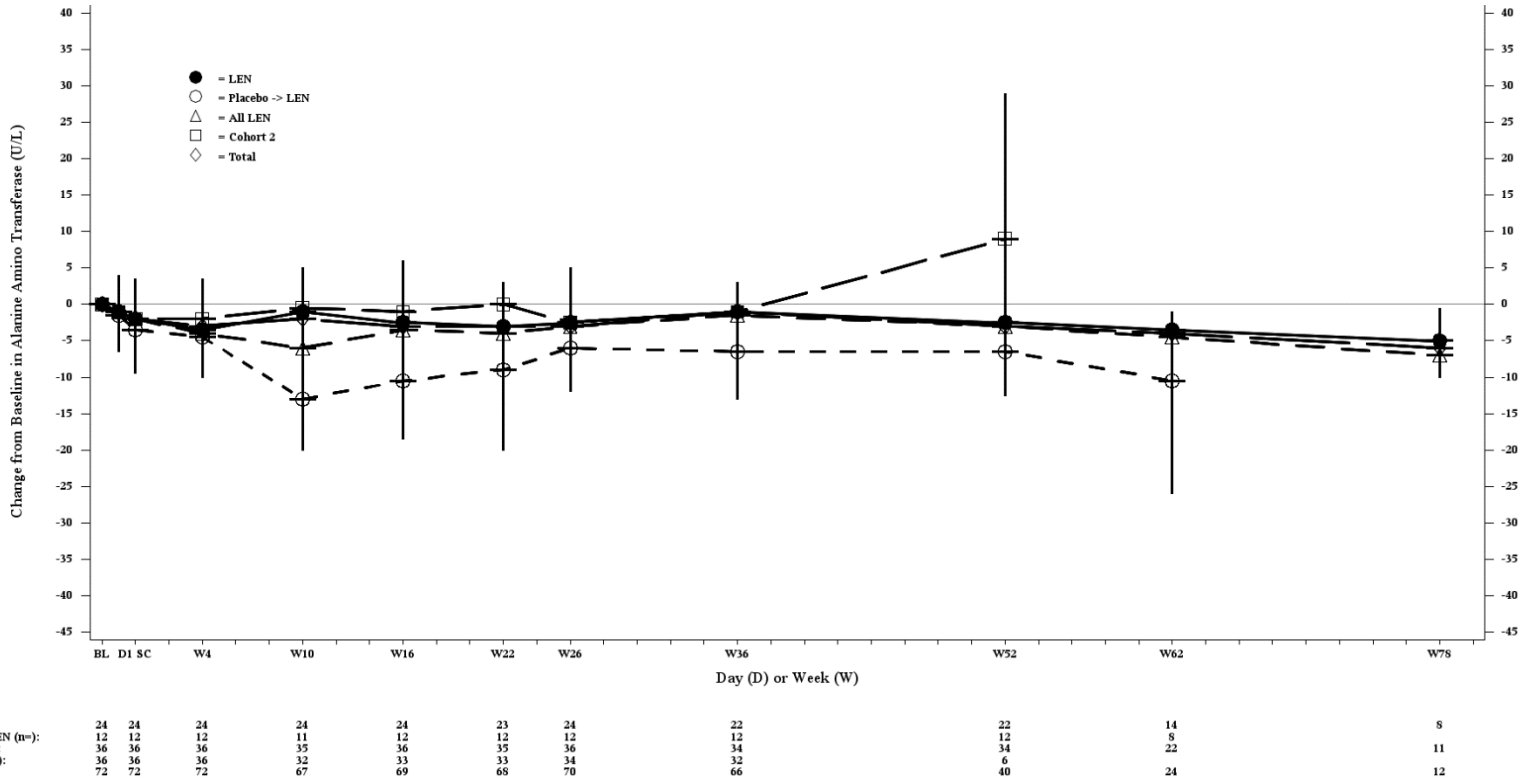
3.1.1.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

There were no clinically relevant changes from baseline in alanine aminotransferase (ALT), AST, or total bilirubin (Figure 1 and Figure 2).

Overall, 2 participants in Cohort 2 experienced a Grade 3 increase in ALT and a Grade 4 increase in AST each. Both participants had concurrent alternative etiologies. The first participant, who was hepatitis B surface antigen (HBsAg) positive with Grade 2 ALT and AST elevations at baseline, previously reported a TEAE of immune reconstitution inflammatory syndrome, and the other participant had a medical history of chronic hepatitis B and AE of alcohol abuse.

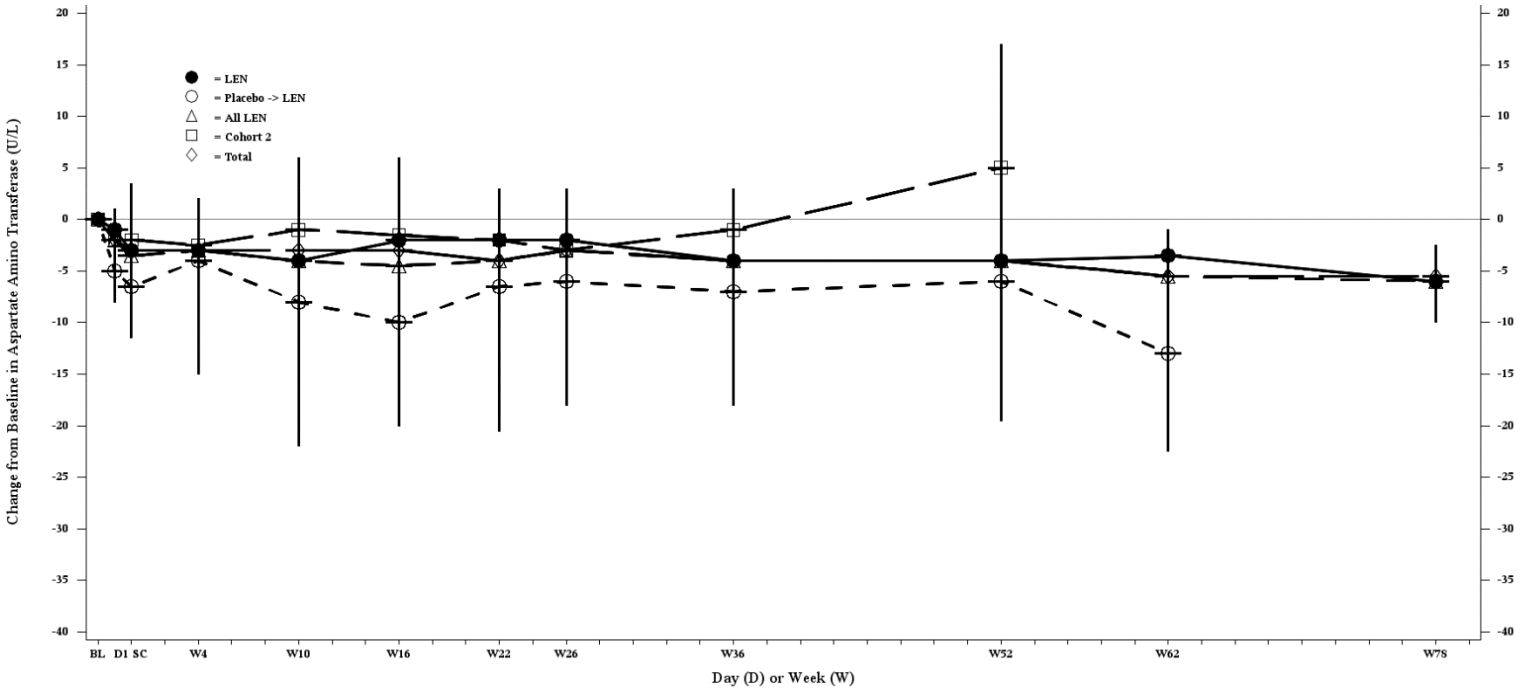
There was no clinically relevant change from baseline in alkaline phosphatase (Figure 3). No participants experienced Grade 3 or Grade 4 increases in alkaline phosphatase.

Figure 1. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Alanine Amino Transferase (U/L) by Visit – All LEN Analysis (Safety Analysis Set)



BL = baseline; Dx = Day x; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; Wx = Week x
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Figure 15.11.6.4.8

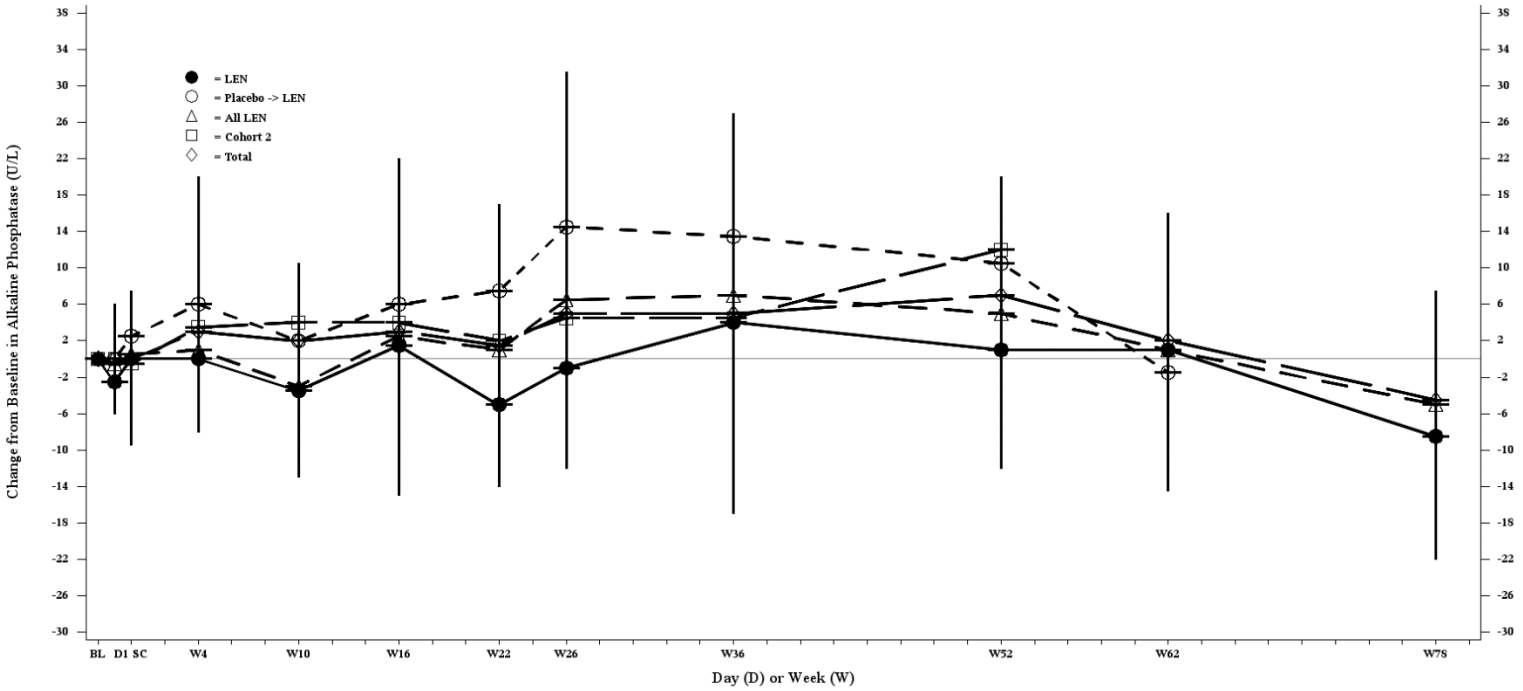
Figure 2. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Aspartate Amino Transferase (U/L) by Visit – All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	23	24	24	23	23	23	22	14	8
Placebo -> LEN (n=):	12	12	12	11	12	12	12	12	12	8	
All LEN (n=):	36	36	35	35	36	35	35	35	34	22	11
Cohort 2 (n=):	36	36	36	32	32	31	34	32	6		
Total (n=):	72	72	71	67	68	66	69	67	40	24	12

BL = baseline; Dx = Day x; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; Wx = Week x
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Figure 15.11.6.4.9

Figure 3. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Alkaline Phosphatase (U/L) by Visit – All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	24	24	24	23	24	23	22	14	8
Placebo -> LEN (n=):	12	12	12	11	12	12	12	12	12	8	
All LEN (n=):	36	36	36	35	36	35	36	35	34	22	11
Cohort 2 (n=):	36	36	36	32	33	33	34	32	6		
Total (n=):	72	72	72	67	69	68	70	67	40	24	12

BL = baseline; Dx = Day x; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; Wx = Week x
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Figure 15.11.6.4.7

3.1.1.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

Changes in alanine aminotransferase (ALT), AST, and total bilirubin from baseline are presented in Figure 4 and Figure 5.

Grade 3 or 4 laboratory abnormalities involving hepatic safety in the LEN total group (157 participants) and the BVY group (25 participants) include the following:

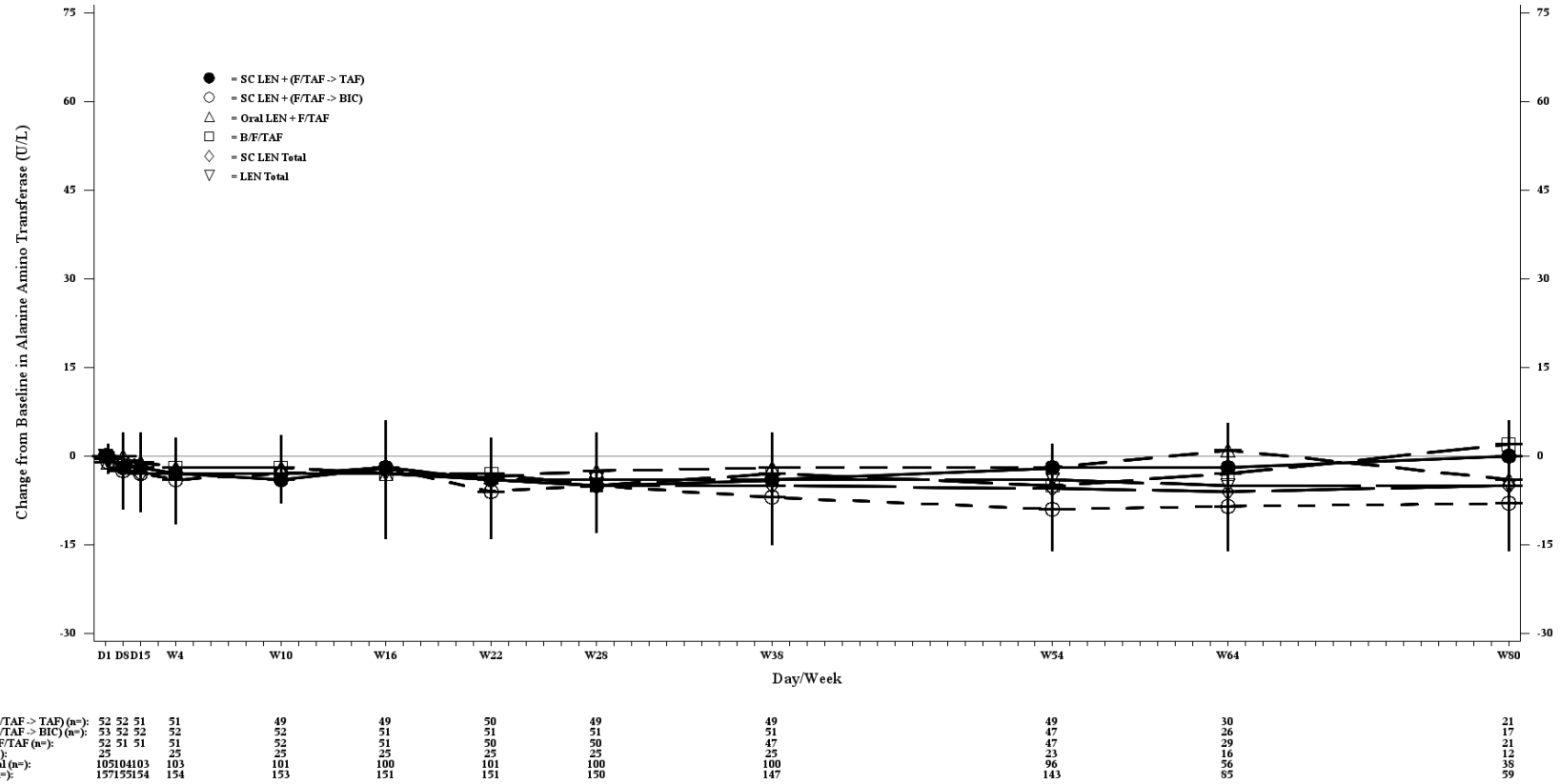
- High ALT: 5 participants (3.2%) and 0 participants, respectively
- High AST: 7 participants (4.5%) and 0 participants, respectively
- Hyperbilirubinemia: 2 participants (1.3%) and 1 participant (4.0%), respectively

Since the Week 28 analysis, an additional 3 participants experienced Grade 3 or 4 high ALT. Two of these 3 participants also experienced high AST, and 1 of these 3 participants also experienced hyperbilirubinemia and had an AE of hepatitis A.

For all participants, the laboratory abnormalities either improved or returned to normal while on study drug. There were no clinically relevant changes in median ALT or AST during the study.

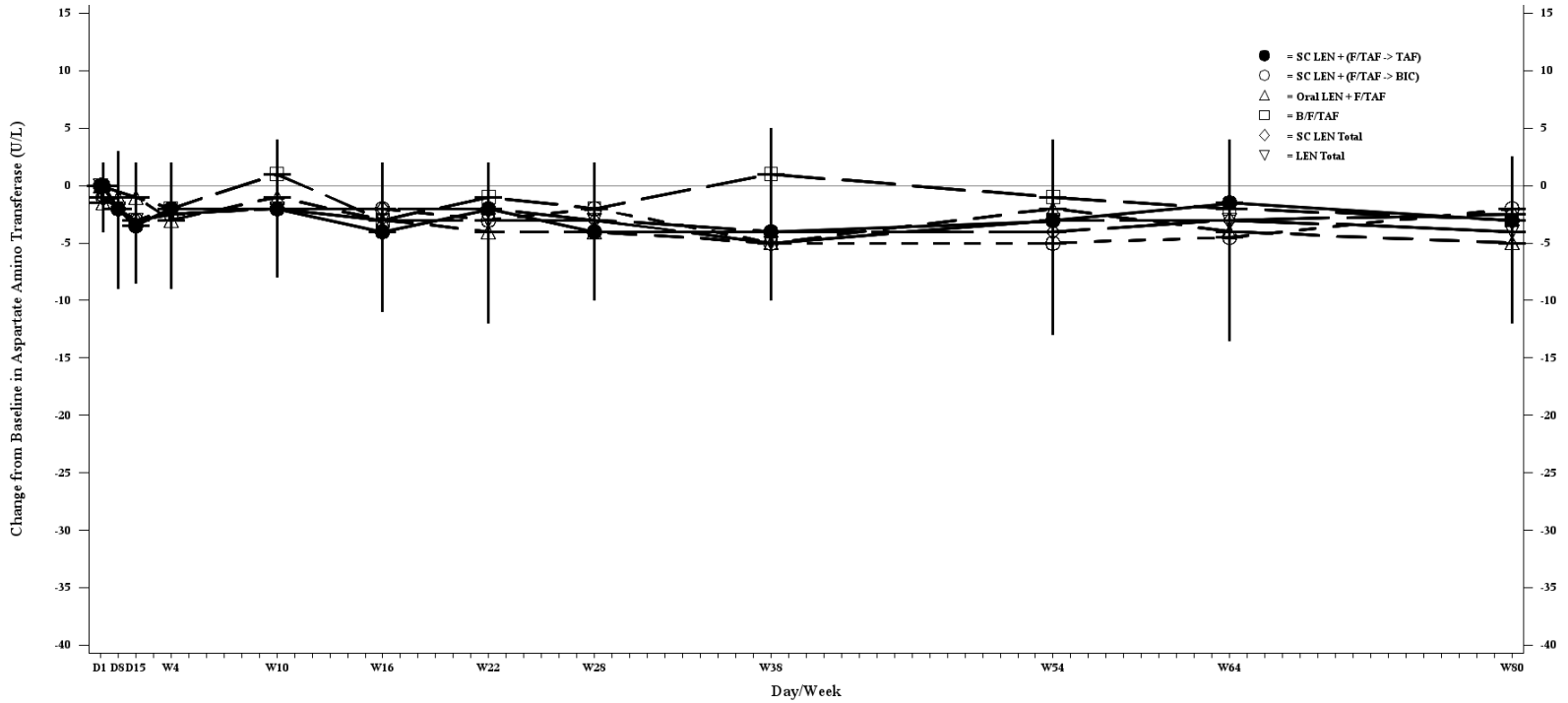
There were no clinically relevant changes from baseline in alkaline phosphatase (Figure 6). No Grade 3 or 4 high alkaline phosphatase laboratory abnormalities were reported for any treatment group

Figure 4. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Alanine Amino Transferase (U/L) by Visit (Safety Analysis Set)



BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); D = Day; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide; W = Week
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Figure 15.11.2.8

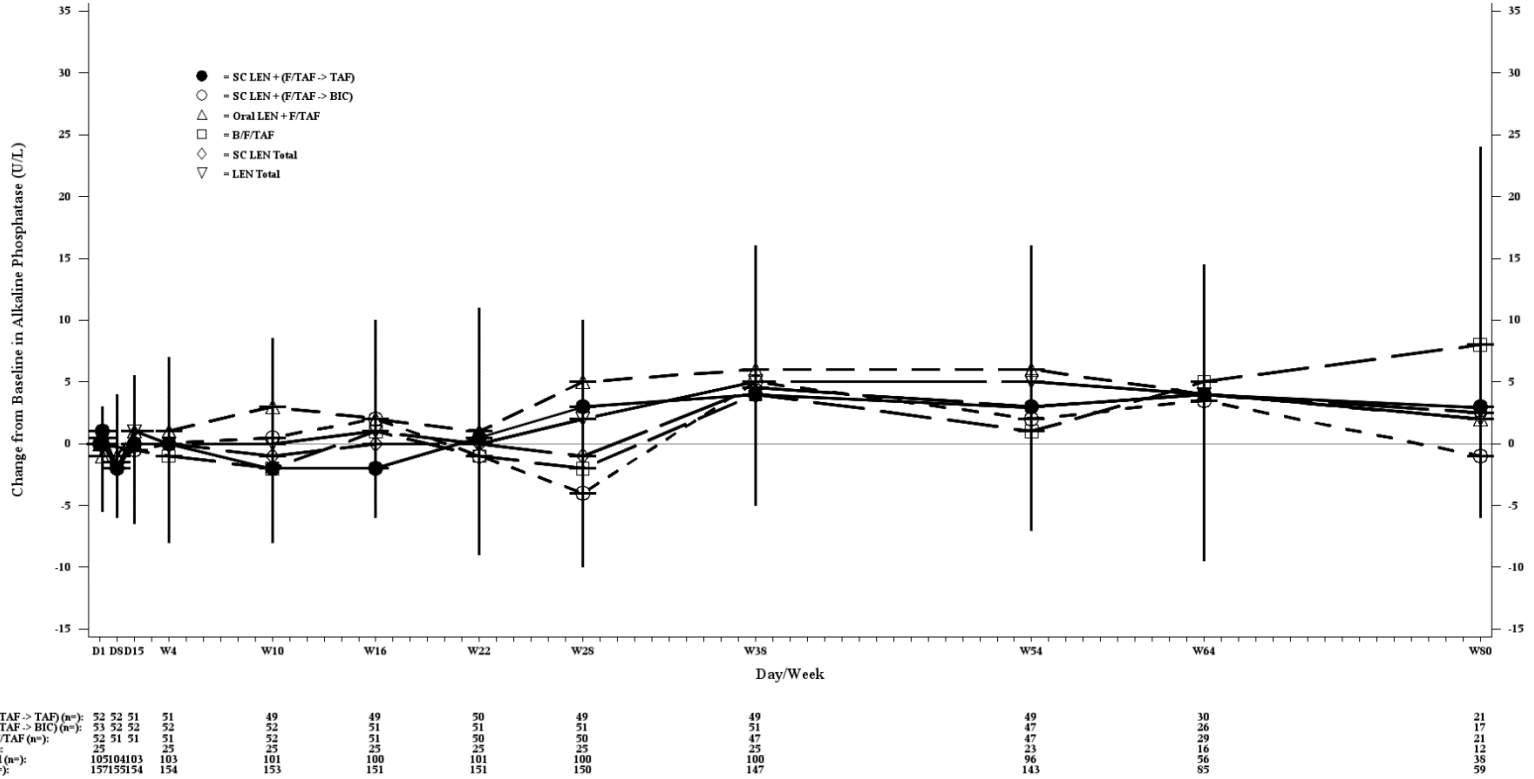
Figure 5. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Aspartate Amino Transferase (U/L) by Visit (Safety Analysis Set)



SC LEN + (F/TAF -> TAF) (n=):	52	52	50	50	49	49	50	49	49	49	30	21
SC LEN + (F/TAF -> BIC) (n=):	53	51	52	52	52	51	51	51	51	47	26	17
Oral LEN + F/TAF (n=):	52	51	51	50	52	51	50	49	47	48	29	21
B/F/TAF (n=):	25			25	25	25	25	25	25	23	16	12
SC LEN Total (n=):	105	103	102	102	101	100	101	100	100	96	56	38
LEN Total (n=):	157	154	153	152	153	151	151	149	147	144	85	59

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); D = Day; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide; W = Week
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Figure 15.11.2.9

Figure 6. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Alkaline Phosphatase (U/L) by Visit Safety Analysis Set (Safety Analysis Set)



BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); D = Day; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY) LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide; W = Week
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Figure 15.11.2.7

3.1.2. Renal Laboratory Parameters

3.1.2.1. Primary Study Supporting the Safety of LEN (Study GS-US-200-4625)

There were no clinically relevant changes in serum creatinine and estimated glomerular filtration rate (eGFR) by Cockcroft-Gault ($eGFR_{CG}$) from baseline. Change in serum creatinine and estimated $eGFR_{CG}$ from baseline are presented in Figure 7 and Figure 8, respectively. Grade 3 or 4 renal laboratory abnormalities for the All LEN Analysis were reported as follows (Table 17):

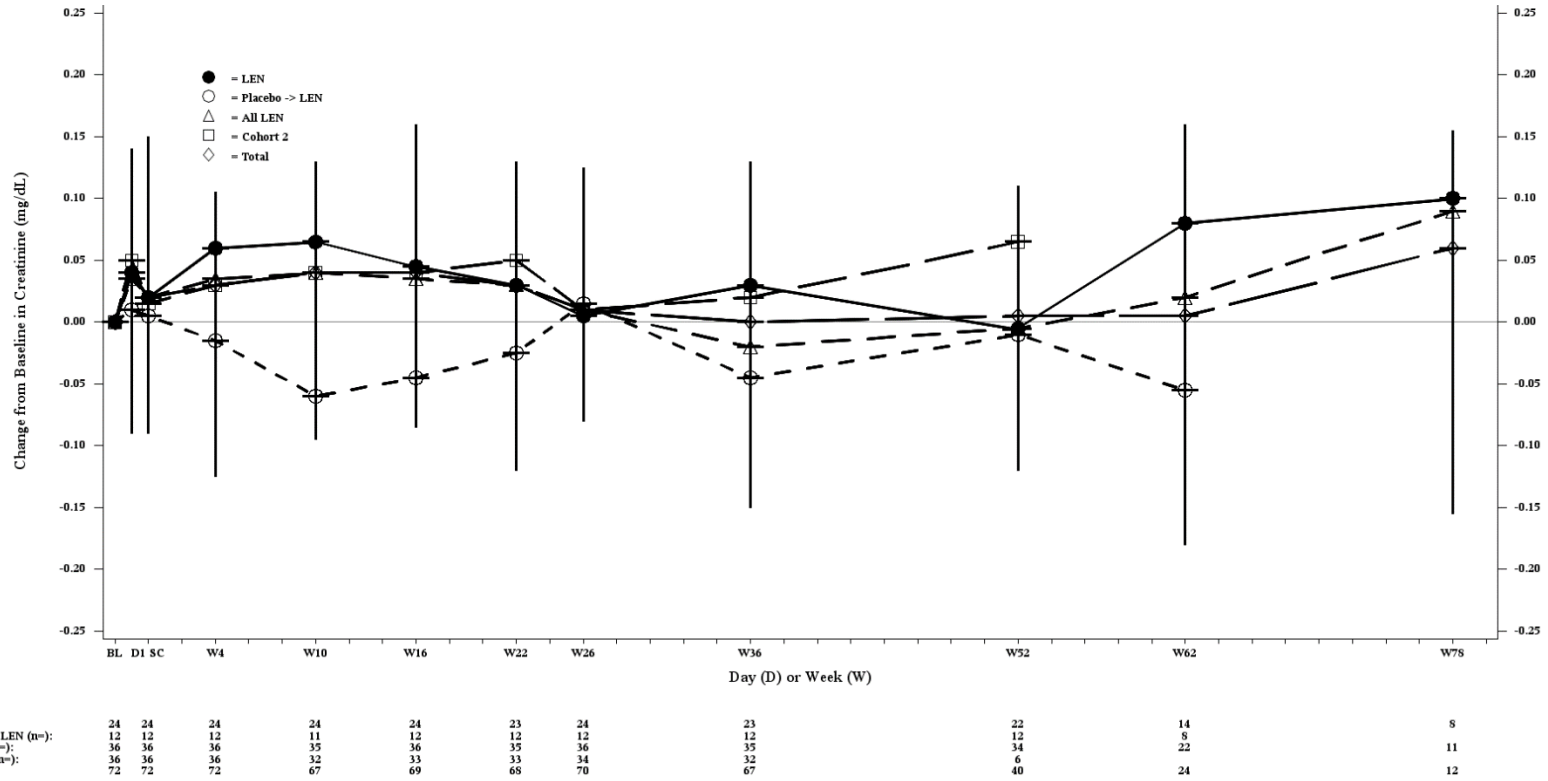
- Grade 3 increased creatinine: 7 participants (9.7%)
- Grade 3 low creatinine clearance or eGFR: 9 participants (12.5%)
- Grade 4 increased creatinine: 2 participants (2.8%)
- Grade 4 low creatinine clearance or eGFR: 1 participant (1.4%)

Since the Interim Week 26 analysis, 1 additional participant experienced Grade 3 increased creatinine and Grade 3 low creatinine clearance or eGFR, and 1 additional participant experienced Grade 4 increased creatinine and Grade 4 low creatinine clearance or eGFR. Two participants who previously experienced laboratory abnormalities experienced additional events of Grade 3 increased creatinine (1 participant) and Grade 3 low creatinine clearance or eGFR (1 participant).

For most participants, both events of increased serum creatinine and low creatinine clearance were reported and the abnormalities either improved or returned to normal within 6 weeks.

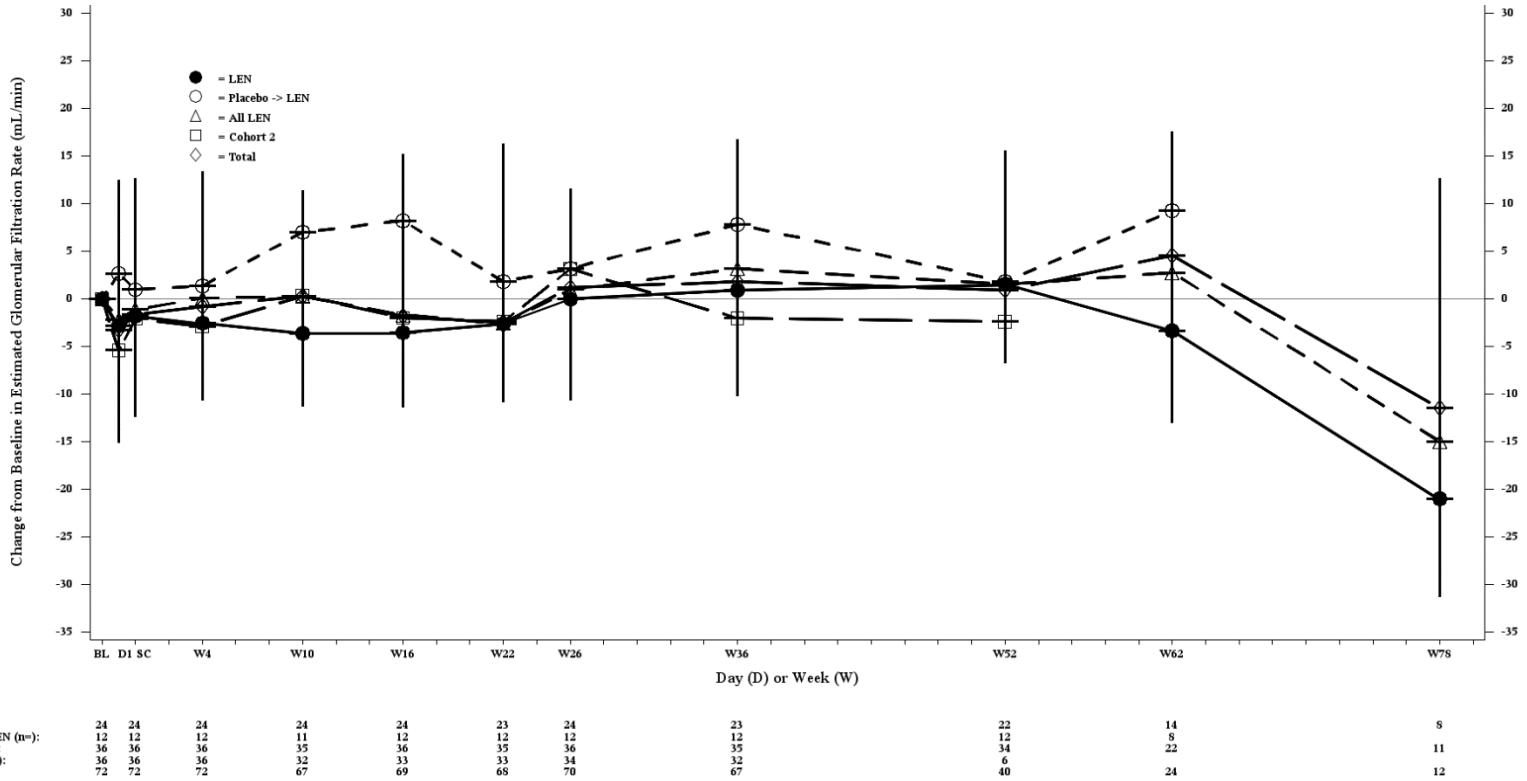
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Figure 7. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Creatinine (mg/dL) by Visit – All LEN Analysis (Safety Analysis Set)



BL = baseline; Dx = Day x; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; Wx = Week x
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Figure 15.11.6.4.4

Figure 8. GS-US-200-4625: Median (Q1, Q3) Change From Baseline in Estimated Glomerular Filtration Rate (mL/min) by Visit – All LEN Analysis (Safety Analysis Set)



LEN (n=):	24	24	24	24	24	23	24	23	22	14	8
Placebo -> LEN (n=):	12	12	12	11	12	12	12	12	12	8	
All LEN (n=):	36	36	36	35	36	35	36	35	34	22	11
Cohort 2 (n=):	36	36	36	32	33	33	34	32	6		
Total (n=):	72	72	72	67	69	68	70	67	40	24	12

BL = baseline; Dx = Day x; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; Wx = Week x
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Figure 15.11.6.4.5

3.1.2.2. Other Data Supporting the Safety of LEN (Study GS-US-200-4334)

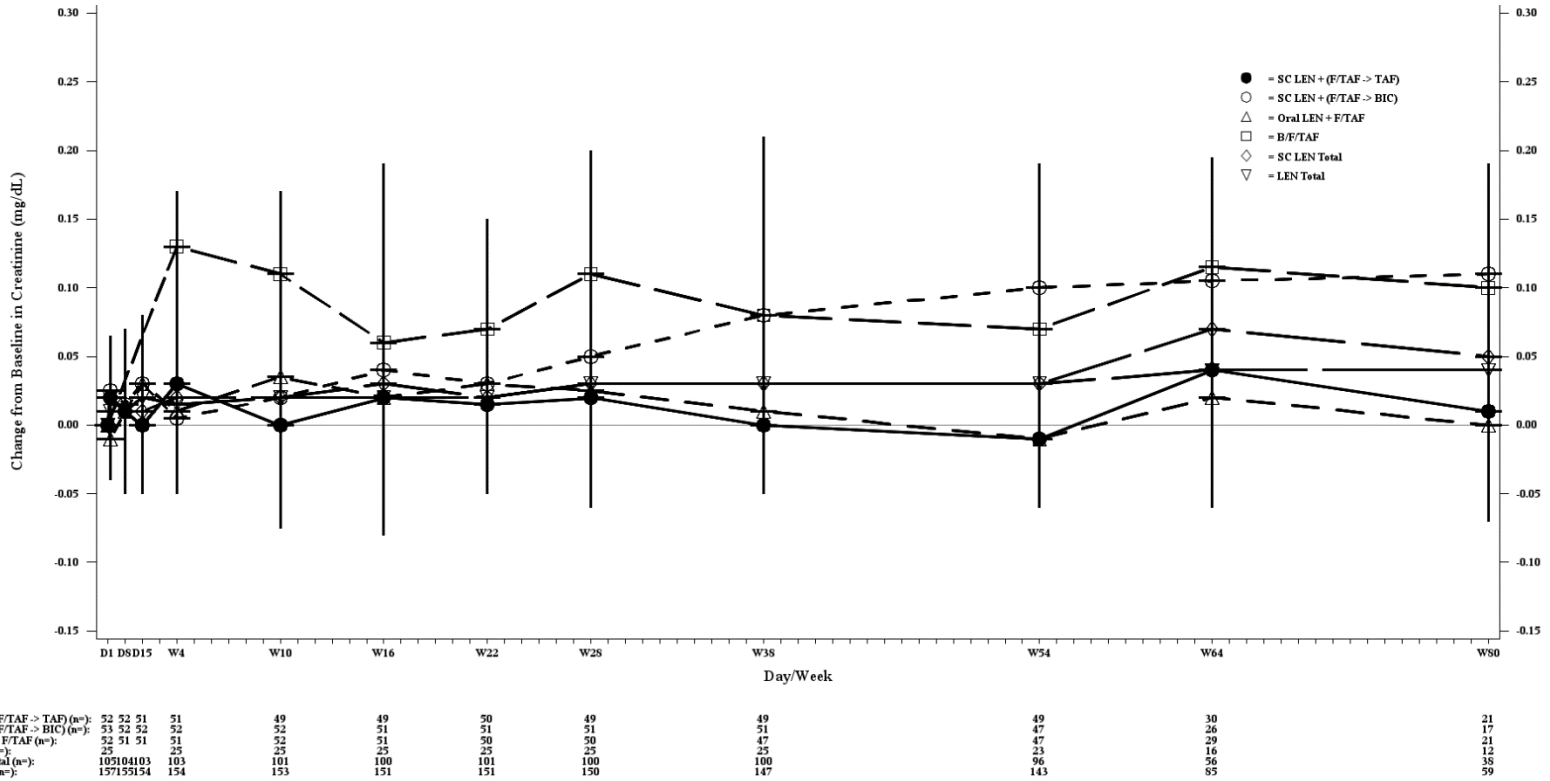
Changes in serum creatinine and estimated glomerular filtration rate (eGFR) from baseline are presented in Figure 9 and Figure 10. Grade 3 or 4 laboratory abnormalities in the LEN total group (157 participants) and the BVY group (25 participants) were reported as follows:

- High creatinine: 6 participants (3.8%) and 2 participants (8.0%), respectively
- Low creatinine clearance or eGFR: 12 participants (7.6%) and 3 participants (12.0%), respectively

Since the Week 28 analysis, an additional 4 participants experienced Grade 3 or 4 high creatinine (LEN total group: 3 participants; BVY group: 1 participant) and 7 additional participants experienced Grade 3 or 4 low creatinine clearance or eGFR (LEN total group: 6 participants; BVY group: 1 participant).

For all participants, the laboratory abnormalities either improved or returned to normal. There were no clinically relevant changes in median creatinine or creatine clearance in participants treated with LEN during the study. Median creatinine increased and median eGFR decreased in participants receiving BVY and those switching to SC LEN + (DVY → BIC) through Week 54, which is consistent with previously described effects on the tubular secretion of creatinine without affecting renal function {BIKTARVY 2021}.

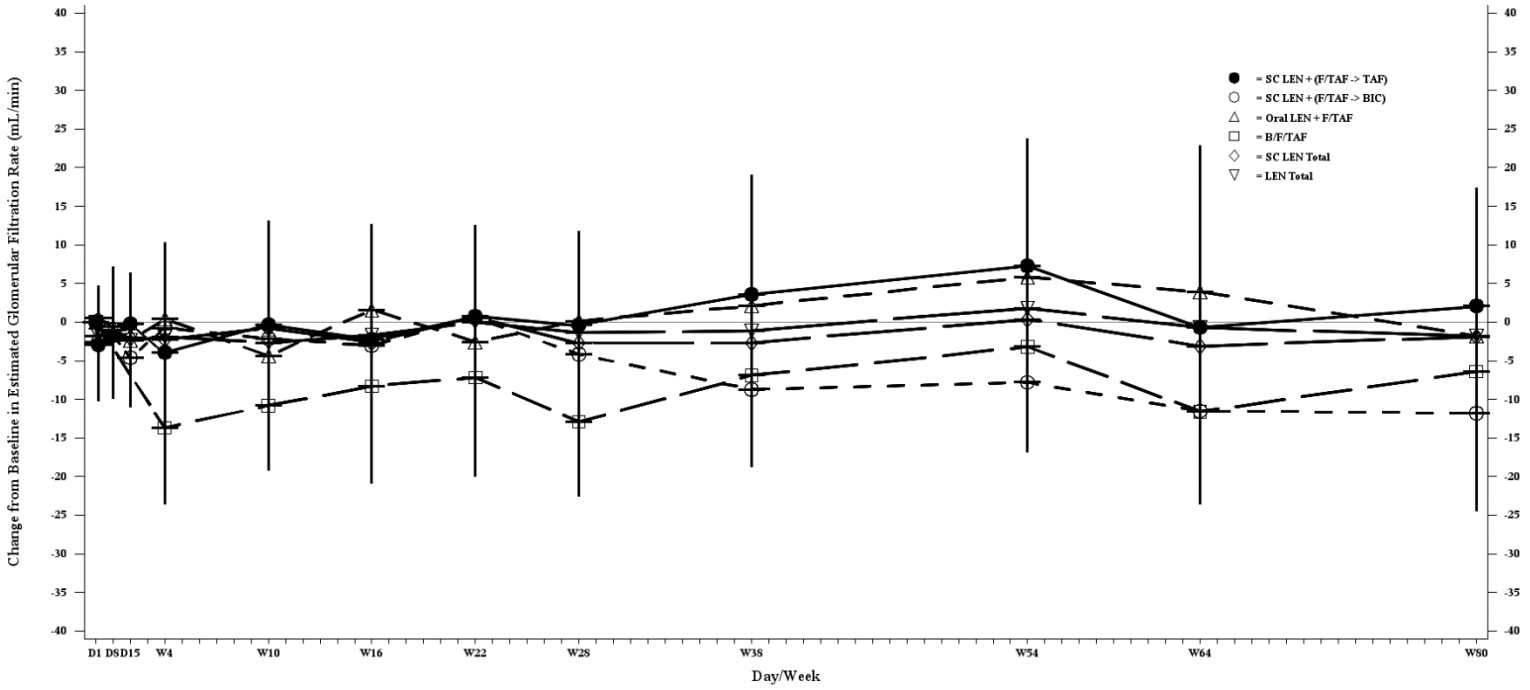
Figure 9. GS-US-200-4334: Median (Q1, Q3) Change From Baseline in Creatinine (mg/dL) by Visit (Safety Analysis Set)



SC LEN + (F/TAF -> TAF) (n=):	52	52	51	51	49	49	50	49	49	49	30	21
SC LEN + (F/TAF -> BIC) (n=):	53	52	52	52	52	51	51	51	51	47	26	17
Oral LEN + F/TAF (n=):	52	51	51	51	52	51	50	50	47	47	29	21
B/F/TAF (n=):	25			25	25	25	25	25	25	23	16	12
SC LEN Total (n=):	105	104	103	103	101	100	101	100	100	96	56	38
LEN Total (n=):	157	155	154	154	153	151	151	150	147	143	85	59

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); D = Day; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide; W = Week
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Figure 15.11.2.4

Figure 10. GS-US-200-4334: Change From Baseline in Estimated Glomerular Filtration Rate (mL/min) by Visit (Safety Analysis Set)



SC LEN + (F/TAF -> TAF) (n=):	52	52	51	51	49	49	50	49	49	49	30	21
SC LEN + (F/TAF -> BIC) (n=):	53	52	52	52	52	51	51	51	51	47	26	17
Oral LEN + F/TAF (n=):	52	51	51	51	52	51	50	50	47	47	29	21
B/F/TAF (n=):	25			25	25	25	25	25	25	23	16	12
SC LEN Total (n=):	105	104	103	103	101	100	101	100	100	96	56	38
LEN Total (n=):	157	155	154	154	153	151	151	150	147	143	85	59

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); D = Day; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; W = Week
Baseline value was the last available value collected on or prior to first dose of study drug.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Figure 15.11.2.5

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

A detailed description and summary of vital signs, physical findings, and other observations related to safety are provided in the individual CSRs (GS-US-200-4625 Interim Week 52 CSR Addendum, Section 11.7, GS-US-200-4334 Interim Week 54 CSR Addendum, Section 11.7, and GS-US-200-5709 Interim CSR Addendum, Section 11.7).

4.1. Vital Signs and Body Weight

In both the primary study supporting LEN safety (All LEN Analysis of Study GS-US-200-4625) or other data supporting LEN safety (Study GS-US-200-4334 and GS-US-200-5709), there were no clinically relevant changes from baseline or in median values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, or body temperature.

The median (Q1, Q3) increase in body weight by study was as follows:

- Study GS-US-200-4625 at Week 52: 2.2 (−1.6, 3.6) kg.
- Study GS-US-200-4334 by Week 54: LEN total group 2.6 (0.2, 6.8) kg; BVY group 2.3 (−3.1, 7.3) kg in the BVY group.

4.2. Electrocardiogram Findings

In Studies GS-US-200-4625, GS-US-200-4334, and GS-US-200-5709, there were no clinically significant abnormal electrocardiograms (ECGs) at screening or posttreatment.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

No impact of age, sex, and race was identified on the PK of LEN (m2.7.2, Section 3.1.6.4).

Summaries of AE incidence by subgroup are provided by age group, sex, and race in the individual CSRs (GS-US-200-4625 Interim Week 52 CSR Addendum, Tables 15.11.2.1.4.1 to 15.11.2.1.4.3 and GS-US-200-4334 Interim Week 54 CSR Addendum, Tables 15.11.2.1.4.1 to 15.11.2.1.4.3).

No clinically meaningful conclusions can be made due to the low number of participants in each subgroup; however based on the available data, there is no difference in the safety profile of LEN due to age, sex, or race.

5.2. Extrinsic Factors

5.2.1. Region

5.2.1.1. Study GS-US-200-4625

A summary of AE incidence by subgroup is provided by region in the CSR for Study GS-US-200-4625 (GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.2.1.4.4). No clinically meaningful conclusions can be made due to the low number of participants in the subgroups by region.

5.3. Drug Interactions

The drug-drug interaction (DDI) potential of LEN with coadministered drugs that may be used by people with HIV-1 infection has been evaluated in DDI clinical studies. A detailed summary of drug interaction potential and management of known interactions is provided in m2.7.2, Section 3.1.7.2. No new significant drug interactions have been identified since the initial submission.

Lenacapavir is a substrate of cytochrome P450 enzyme 3A (CYP3A), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Strong inducers of CYP3A, P-gp, and UGT1A1, such as rifampin, may significantly decrease plasma concentrations of LEN. As such, rifampin is contraindicated with LEN. Moderate inducers of CYP3A and P-gp, such as efavirenz, may also significantly decrease plasma concentrations of LEN, and as such, are not recommended with LEN.

Strong CY3A4 inhibitors alone (eg, voriconazole) or strong inhibitors of CYP3A4 and P-gp together (eg, cobicistat) do not result in a clinically meaningful increase in LEN exposures. Strong inhibitors of CYP3A, P-gp and UGT1A1 together (ie, all 3 pathways), such as atazanavir/cobicistat, may significantly increase plasma concentrations of LEN, and as such, are not recommended with LEN.

Lenacapavir is a moderate inhibitor of CYP3A. Caution is advised if LEN is coadministered with a sensitive CYP3A substrate with a narrow therapeutic index (eg, midazolam). Lenacapavir is not a clinically meaningful inhibitor of P-gp and breast cancer resistance protein (BCRP) and does not inhibit organic anion transporting polypeptide (OATP).

5.4. Use in Pregnancy and Lactation

5.4.1. Pregnancy

No clinical studies of LEN have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of LEN with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development.

No formal DDI studies between LEN and hormonal contraceptives have been conducted. Based on in vitro and in vivo DDI liability assessments, clinically significant DDIs between LEN and hormonal contraceptives are not anticipated.

5.4.1.1. Pregnancies Reported in Phase 1, 2, and 2/3 LEN Studies

No pregnancies were reported in Phase 1, 2, and 2/3 studies of LEN.

5.4.2. Lactation

No new information is submitted.

5.5. Overdose

No new safety issues regarding overdose have been identified from the available data.

5.6. Drug Abuse

No safety issues concerning the abuse or misuse of LEN tablets or injections have been identified from the available data.

5.7. Withdrawal and Rebound

No formal clinical studies for withdrawal or rebound effects of LEN have been conducted.

5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been conducted to evaluate the effects of LEN on the ability to drive or operate machinery.

6. POSTMARKETING DATA

No postmarketing safety data are included in this submission.

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8. APPENDIX

8.1. Tabular Summary of Studies Relevant for Safety

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy participant PK and initial tolerability	GS-US-200-5709	• To characterize the PK of multiple-dose oral and SC LEN • To evaluate the safety and tolerability of multiple-dose oral and SC LEN	Phase 1, open-label, multiple-cohort, multiple-dose study	Cohort 1: Treatment A: oral tablets of LEN on Day 1 (600 mg; 2 × 300 mg tablets), Day 2 (600 mg; 2 × 300 mg tablets), Day 8 (300 mg; 1 × 300 mg tablet), and SC LEN on Day 15 (927 mg; 2 × 1.5 mL LEN injection), all administered under fed conditions Cohort 2: Treatment B: SC LEN (927 mg; 2 × 1.5 mL LEN injection) and oral 600 mg (2 × 300 mg tablets) on Day 1 followed by oral 600 mg on Day 2 (2 × 300 mg tablets), all administered under fed conditions Cohort 3: Treatment C: oral LEN (600 mg; 2 × 300 mg tablets) twice daily (in the morning and afternoon) on Days 1 to 10, and last dose of LEN (600 mg; 2 × 300 mg tablets) in the morning on Day 11, all administered under fed conditions	Cohort 1: 4 days Cohort 2: 2 days Cohort 3: 11 days	Enrolled in study: 60 participants; Cohort 1: 31 participants Cohort 2: 14 participants Cohort 3: 15 participants Completed study: 51 participants; Cohort 1: 22 participants Cohort 2: 14 participants Cohort 3: 15 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Interim CSR; Interim CSR Addendum

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled clinical studies pertinent to the claimed indication	GS-US-200-4334	To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment Group 1 (oral to SC LEN): Induction: oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2 and 300 mg (1 × 300 mg) on Day 8, SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15, and oral DVY 200/25 mg daily from Day 1 for 28 weeks Maintenance: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and once every 6 months (26 weeks) thereafter, and oral TAF 25 mg daily Treatment Group 2 (oral to SC LEN): Induction: oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2 and 300 mg (1 × 300 mg) on Day 8, SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15, and oral DVY 200/25 mg daily from Day 1 for 28 weeks Maintenance: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and once every 6 months (26 weeks) thereafter, and oral BIC 75 mg daily Treatment Group 3: oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2 and 50 mg (1 × 50 mg) daily from Day 3 onwards, and oral DVY 200/25 mg daily Treatment Group 4: oral BVY 50/200/25 mg daily	At least 80 weeks	Randomized in study: 183 participants; Safety Analysis Set: 182 participants; SC LEN + (DVY → TAF): 52 participants; SC LEN + (DVY → BIC): 53 participants; Oral LEN + DVY: 52 participants; BVY: 25 participants Completed Main Phase or continued Main Phase: 160 participants SC LEN + (DVY → TAF): 47 participants SC LEN + (DVY → BIC): 41 participants Oral LEN + DVY: 48 participants BVY: 24 participants	Treatment-naive PWH ≥ 18 years of age	Study ongoing; Interim Week 28 CSR; Interim Week 54 CSR Addendum

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled clinical studies pertinent to the claimed indication	GS-US-200-4625	To evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for PWH with multidrug resistance	Phase 2/3, randomized, placebo-controlled, multicenter study	Cohort 1: Functional Monotherapy Period: oral LEN 600, 600, and 300 mg or placebo-to-match LEN on Days 1, 2, and 8, respectively, while continuing their failing regimen Maintenance Period: Cohort 1A: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) and initiation of an OBR starting on Day 1 SC (14 days after the first dose of oral LEN), and once every 6 months (26 weeks) Cohort 1B: oral LEN 600 mg and initiation of an OBR on Day 15; oral LEN 600 and 300 mg on Days 16 and 22, respectively; SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks) Cohort 2: Oral Lead-in Period: oral LEN 600 mg and initiation of an OBR on Day 1; oral LEN 600 and 300 mg on Days 2 and 8, respectively, while continuing their OBR Maintenance Period: SC LEN 927 mg (309 mg/mL; 2 × 1.5 mL) while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks)	At least 54 weeks	Enrolled in study: 72 participants; Cohort 1: 36 participants; Cohort 2: 36 participants Completed Main Phase or continued Main Phase: 69 participants Cohort 1: 35 participants Cohort 2: 34 participants	Heavily treatment-experienced adult and adolescent PWH with resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications and plasma HIV-1 RNA ≥ 400 copies/mL at screening while taking a failing regimen	Study ongoing; Interim Week 26 CSR; Interim Week 52 CSR Addendum

ARV = antiretroviral; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CSR = clinical study report; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); LEN = lenacapavir (GS-6207); OBR = optimized background regimen; PK = pharmacokinetic(s); PWH = people with HIV; SC = subcutaneous; TAF = tenofovir alafenamide (Vemlidy®)

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.5—LITERATURE REFERENCES

LENACAPAVIR

Gilead Sciences

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SECTION 2.7.6— SYNOPSES OF INDIVIDUAL STUDIES

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LISTING OF CLINICAL STUDIES

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-200-4070	• To assess the safety and tolerability of escalating single SC doses of LEN compared with placebo in healthy volunteers • To assess the PK of LEN in healthy volunteers	Phase 1, randomized, blinded, placebo-controlled, SAD study	Participants were randomized to receive LEN or placebo (4:1 ratio per cohort). • Cohort 1: 30 mg • Cohort 2: 100 mg • Cohort 3: 300 mg • Cohort 4: 450 mg • Cohort 5 (not enrolled): up to 600 mg	1 day	Randomized: 40 participants; Completed: 38 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-200-4071	• To evaluate the safety and tolerability of escalating single and multiple oral doses of LEN • To characterize the single- and multiple-dose PK of oral LEN • To evaluate the effect of concomitant food intake on oral LEN PK	Phase 1, randomized, blinded, placebo-controlled, single and multiple ascending dose study in volunteers	For Study Parts A to C, participants were randomized to receive LEN or placebo (4:1 ratio per cohort).Study Part D involved open-label, parallel-group, single-dose cohorts. Study Part A (SAD/MAD; Formulation 1: LEN 50-mg/mL solution in capsule, free acid): • Cohort 1: 30 mg (50 mg/mL) • Cohort 2: 100 mg (50 mg/mL) Study Part B (SAD; Formulations 1 and 2: LEN 50- or 100-mg/mL solution in	Less than or equal to 11 days	Randomized: 106 participants; Completed: 102 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				capsule, free acid): • Cohort 3: 300 mg (100 mg/mL) • Cohort 4: 75 mg (100 mg/mL) • Cohort 5: 300 mg (50 mg/mL) • Cohort 6 (not enrolled): up to 900 mg (100 mg/mL) Study Part C (SAD; Formulation 3: LEN 50- or 300-mg tablet): • Cohort 7: 300 mg (1 × 300-mg tablet) • Cohort 8: 900 mg (3 × 300-mg tablet) • Cohort 9: 1800 mg (6 × 300-mg tablet) • Cohort 10: 50 mg (1 × 50-mg tablet) • Cohort 11 (not enrolled): up to 1800 mg Study Part D (Food Effect; Formulation 3: LEN 50- or 300-mg tablet): • Cohort 12: 300 mg (1 × 300-mg tablet) with high-fat/high-calorie meal				

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				• Cohort 13: 300 mg (1 × 300-mg tablet) with light meal • Cohorts 14 to 17 (not enrolled): up to 1800 mg with high-fat/high-calorie (Cohort 15), moderate-fat (Cohorts 14 and 17), or light (Cohort 16) meal				
Healthy Subject PK and Initial Tolerability	GS-US-200-4329	• To evaluate the PK of LEN (and metabolites, if applicable) following single ascending IV doses of LEN or a single IV dose of radiolabeled [14C]LEN • To determine the mass balance of LEN following administration of a single IV dose of radiolabeled [14C]LEN	Part A: Phase 1, randomized, blinded, placebo-controlled, SAD study Part B: Phase 1, open-label, single-center, mass-balance study	Part A: • Cohort 1: single dose of LEN 10 mg or placebo • Cohort 2 (not enrolled): single dose of LEN up to 30 mg or placebo Part B: • Cohort 3: single IV dose of LEN 20 mg containing a mixture of unlabeled LEN and [^{14}C]LEN (equivalent to approximately 200 µCi)	1 day	Enrolled: 21 participants; Completed: 11 participants	Healthy nonsmoking (≥ 90 days) male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-200-4538	• To assess the safety and tolerability of escalating single doses of SC LEN injectable solutions compared with placebo in healthy volunteers • To assess the PK of SC injectable solutions of LEN in healthy volunteers	Phase 1, randomized, blinded, placebo-controlled, SAD study	Participants were randomized to receive LEN or placebo (4:1 ratio per cohort). Part A (SAD; Formulation 1: LEN 300 mg/mL, free acid): • Cohort 1: 300 mg • Cohort 2 (not enrolled): up to 900 mg • Cohorts 3 and 4 (not enrolled): up to 1200 mg Part B (SAD; Formulation 2: LEN 309 mg/mL, sodium salt): • Cohort 5: 309 mg • Cohorts 6 and 7: 927 mg • Cohort 8 (not enrolled): up to 2472 mg Part C (SAD; Formulation 3: LEN 155 mg/mL, sodium salt): • Cohort 9: 309 mg • Cohort 10: 927 mg • Cohorts 11 and 12 (not enrolled): up to 1236 mg Part D (SAD; Formulation 4: LEN 300 mg/mL, sodium salt with poloxamer): • Cohort 13:	1 day	Randomized: 100 participants; Completed: 78 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				900 mg • Cohorts 14 to 16 (not enrolled): up to 2400 mg Part E (SAD; Formulation 5: LEN 150 mg/mL, sodium salt with poloxamer): • Cohort 17 (not enrolled): 900 mg • Cohorts 18 to 20 (not enrolled): up to 1200 mg Part F (SAD; Formulation 6: LEN 75 mg/mL, sodium salt with poloxamer): • Cohort 21: 75 mg • Cohort 22: 225 mg • Cohorts 23 and 24 (not enrolled): up to 600 mg Part G (SAD; Formulation 7: LEN 50 mg/mL, sodium salt with poloxamer): • Cohort 25: 50 mg • Cohort 26 (not enrolled): up to 150 mg • Cohorts 27 and 28 (not enrolled): up to 400 mg Part H: Cohorts 29 to 32 (not enrolled): up to 1200 mg (Formulations 1, 3, and 5); up to 2400 mg (Formulations				

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				2 and 4); up to 600 mg (Formulation 6); or up to 400 mg (Formulation 7)				
Healthy Subject PK and Initial Tolerability	GS-US-200-5709	• To characterize the PK of multiple-dose oral and SC LEN • To evaluate the safety and tolerability of multiple-dose oral and SC LEN	Phase 1, open-label, multiple-cohort, multiple-dose study	Cohort 1: Treatment A: oral tablets of LEN on Day 1 (600 mg; 2 × 300 mg tablets), Day 2 (600 mg; 2 × 300 mg tablets), Day 8 (300 mg; 1 × 300 mg tablet), SC LEN on Day 15 (927 mg; 2 × 1.5 mL of LEN injection), all administered under fed conditions. Cohort 2: Treatment B: SC LEN (927 mg; 2 × 1.5 mL of LEN injection) and oral 600 mg (2 × 300 mg tablets) on Day 1 followed by oral 600 mg on Day 2 (2 × 300 mg tablets), all administered under fed conditions. Cohort 3: Treatment C: oral LEN twice daily on Days 1 to 10 (600 mg; 2 × 300 mg tablets), and last dose of LEN (600 mg; 2 × 300 mg tablets) in the morning on Day 11, all administered under fed conditions	Cohort 1: 4 days Cohort 2: 2 days Cohort 3: 11 days	Enrolled: 60 participants; Cohort 1: 31 participants Cohort 2: 14 participants Cohort 3: 15 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study ongoing; Interim CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Patient PK and Initial Tolerability	GS-US-200-4072	Part A: • To evaluate the short-term antiviral activity of LEN compared with placebo with respect to the maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Days 1 through 10 in adult PWH who were ARV treatment naive or were experienced but CAI naive Part B: • To evaluate the short-term antiviral activity of TAF with respect to the maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Day 1 through Day 10 in adult PWH who were ARV	Phase 1b, randomized, double-blind, placebo-controlled, multicohort study	Part A: • Cohort 1: LEN 150 mg or placebo • Cohort 2: LEN 50 mg or placebo • Cohort 3: LEN 450 mg or placebo • Cohort 4: LEN 20 mg or placebo • Cohort 5: LEN 750 mg or placebo Part B: • Cohort 6: TAF 200 mg • Cohort 7: TAF 600 mg • Cohort 8 (not enrolled): TAF up to 600 mg	1 day	Part A: Randomized: 41 participants; Completed: 38 participants Part B: Enrolled: 12 participants; Completed: 12 participants	Adult PWH who were ARV treatment naive or were experienced but CAI and INSTI naive (Part A only), had not received any ART within 12 weeks of screening, and had genotypic sensitivity to BVY	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
		treatment naive or were experienced but without resistance to TAF						
Intrinsic Factor PK	GS-US-200-4330	To evaluate the single-dose PK of LEN in participants with severe renal impairment or matched healthy controls with normal renal function	Phase 1, open-label, single-dose, parallel-group study	Single dose of LEN 300 mg(1 × 300-mg tablet)	1 day	Enrolled: 20 participants (10 with severe renal impairment and 10 matched healthy volunteers with normal renal function); Completed: 20 participants	Participants with severe renal impairment classification ($15 \leq CL_{cr} \leq 29$ mL/min) at screening and matched healthy participants with normal renal function ($CL_{cr} \geq 90$ mL/min)	Study completed; Final CSR
Intrinsic Factor PK	GS-US-200-4331	To evaluate the single-dose PK of LEN in participants with normal or moderately impaired hepatic function	Phase 1, open-label, multicenter, single-dose, parallel-group study	Single dose of LEN 300 mg (1 × 300-mg tablet)	1 day	Enrolled: 20 participants (10 with moderate hepatic impairment and 10 matched healthy controls with normal hepatic function); Completed: 19 participants	Male and nonpregnant, nonlactating female participants with moderately impaired and normal hepatic function	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Extrinsic Factor PK	GS-US-200-4333	• To evaluate the effect of a CYP3A inhibitor, a mixed CYP3A/P-gp inhibitor, and a mixed CYP3A/P-gp/ UGT1A1 inhibitor on the PK of LEN • To evaluate the effect of an inducer of CYP3A/P-gp/UGT and an inducer of CYP3A/P-gp on the PK of LEN • To evaluate the effect of an H2RA on the PK of LEN • To evaluate the effect of LEN on the PK of an OATP substrate, a BCRP substrate, a P-gp substrate, and a CYP3A substrate	Phase 1, open-label, single-center, parallel-design, single- and multiple-dose, multicohort study	LEN 300 mg (6 × 50-mg capsules): • Cohort 1: LEN • Cohort 2: COBI 150 mg and LEN • Cohort 3: DRV/COBI 800/150 mg and LEN LEN 300 mg (1 × 300-mg tablet): • Cohort 4: LEN • Cohort 5: VORI 400 mg, VORI 200 mg, and LEN • Cohort 6: LEN (under fed conditions) • Cohort 7: ATV/COBI 300/150 mg and LEN • Cohort 8: RIF 600 mg and LEN • Cohort 9: EFV 600 mg and LEN • Cohort 10: FAM 40 mg and LEN LEN 600 mg (2 × 300-mg tablets): • Cohort 11: PIT 2 mg, ROS 5 mg, TAF 25 mg, MDZ 2.5 mg, and LEN	Cohorts 1, 4, 6, and 10: 1 day Cohorts 2 and 3: up to 90 days Cohort 5: 25 days Cohort 7: 60 days Cohorts 8 and 9: 25 days Cohort 11: 27 days	Enrolled: 291 participants; Completed: 272 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PD and PK/PD	GS-US-200-4332	To evaluate the effect of LEN on time-matched, baseline-adjusted, placebo-corrected QTcF	Phase 1, double-blinded, randomized, placebo- and positive-controlled, 3-sequence, parallel (with nested crossover), multiple-dose study	Treatment A (Positive Control): Single oral dose of 400 mg MOXI (1 × 400-mg tablet), under fed conditions, in the morning Treatment B (Placebo Control-1): Single oral dose of placebo-to-match MOXI (1 tablet), under fed conditions, in the morning Treatment C (Therapeutic and Supratherapeutic Exposure of LEN): Twice-daily 600 mg of LEN (2 × 300-mg tablet) for 8 days, under fed conditions Treatment D (Placebo Control-2): Twice-daily placebo for LEN (2 tablets) for 8 days, under fed conditions	10 days	Randomized: 97 participants; Completed: 95 participants	Healthy male and nonpregnant, nonlactating female volunteers	Study completed; Final CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-200-4334	To evaluate the efficacy of LEN-containing regimens in PWH as determined by the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment Group 1 (oral to SC LEN): • Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral DVY 200/25 mg • Maintenance: SC LEN 927 mg and oral TAF 25 mg • Treatment Group 2 (oral to	At least 80 weeks	Randomized: 183 participants; Safety Analysis Set: 182 participants; SC LEN + (DVY -> TAF): 52 participants; SC LEN + (DVY-> BIC): 53 participants; Oral LEN + DVY:	Treatment-naive PWH ≥ 18 years of age	Study ongoing; Interim Week 28 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				SC LEN): • Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral DVY 200/25 mg • Maintenance: SC LEN 927 mg and oral BIC 75 mg Treatment Group 3: oral LEN 600 and 50 mg and oral DVY 200/25 mg Treatment Group 4: oral BVY 50/200/25 mg		52 participants; BVY: 25 participants		
Controlled Clinical Studies Pertinent to the Claimed Indication	GS-US-200-4625	To evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for PWH with multidrug resistance	Phase 2/3, randomized, placebo-controlled, multicenter study	Cohort 1: Functional Monotherapy Period: oral LEN 600, 600, and 300 mg or placebo-to-match LEN on Days 1, 2, and 8, respectively, while continuing their failing regimen Maintenance Period: Cohort 1A: SC LEN 927 mg and initiation of an OBR starting on Day 1 SC (14 days after the first dose of oral LEN), and once every 6 months (26 weeks) Cohort 1B: oral LEN 600 mg and initiation of an OBR on Day 15; oral LEN 600 and 300 mg on Days 16	At least 54 weeks	Enrolled: 72 participants; Cohort 1: 36 participants; Cohort 2: 36 participants	Heavily treatment-experienced adult and adolescent PWH with resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications and plasma HIV-1 RNA ≥ 400 copies/mL at screening while taking a failing regimen	Study ongoing; Interim Week 26 CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Participants	Study Population/ Entry Criteria	Study Status; Type of Report
				and 22, respectively; SC LEN 927 mg while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks) Cohort 2: Oral Lead-in Period: oral LEN 600 mg and initiation of an OBR on Day 1; oral LEN 600 and 300 mg on Days 2 and 8, respectively, while continuing their OBR Maintenance Period: SC LEN 927 mg while continuing their OBR starting on Day 1 SC and once every 6 months (26 weeks)				

ARV = antiretroviral; ART = antiretroviral therapy; ATV = atazanavir; BCRP = breast cancer resistance protein; BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CAI = capsid inhibitor; CL_{cr} = creatinine clearance; COBI = cobicistat (Tybost®); CSR = clinical study report; CYP = cytochrome P450 enzyme; DRV = darunavir; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); EFV = efavirenz; FAM = famotidine; H2RA = histamine 2 receptor antagonist; INSTI = integrase strand-transfer inhibitor; IV = intravenous; LEN = lenacapavir; MAD = multiple ascending dose; MDZ = midazolam; MOXI = moxifloxacin; OATP = organic anion transporting polypeptide; OBR = optimized background regimen; PD = pharmacodynamic(s); P-gp = P-glycoprotein; PIT = pitavastatin; PK = pharmacokinetic(s); PWH = people with HIV; QTcF = QT interval corrected for heart rate using the Fridericia formula; RIF = rifampin; ROS = rosuvastatin; SAD = single ascending dose; SC = subcutaneous; TAF = tenofovir alafenamide (Vemlidy®); UGT = uridine diphosphate glucuronosyltransferase; VORI = voriconazole