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RESEARCH**

APPLICATION NUMBER:

215973Orig1s000

215974Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information (NDA 215973)

Category	Application Information
Application type	NDA
Application number(s)	215973
Priority or standard	Priority
Submit date(s)*	6/27/2022
Received date(s)	6/27/2022
PDUFA goal date	12/27/2022
Division/office	Division of Antivirals (DAV)
Review completion date	12/21/2022
Established/proper name	Lenacapavir
(Proposed) proprietary name	Sunlenca
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1) capsid inhibitor
Code name	GS-6207
Applicant	Gilead Sciences, Inc.
Dosage form(s)/formulation(s)	Injection, for subcutaneous use
Dosing regimen	Initiation Option 1: 927 mg by subcutaneous injection (2×1.5 mL injections) and 600 mg orally (2 tablets) on Day 1; 600 mg orally (2 tablets) on Day 2. Tablets may be taken without regard to food. Initiation Option 2: 600 mg orally (2 tablets) on Day 1; 600 mg orally (2 tablets) on day 2; 300 mg orally (1 tablet) on Day 8; 927 mg by subcutaneous injection (2×1.5 mL injections) on Day 15. Maintenance: 927 mg by subcutaneous injection (2×1.5 mL injections) every 6 months (26 weeks) from the date of the last injection ±2 weeks. Missed Dose: If more than 28 weeks since last injection and clinically appropriate to continue Sunlenca, restart initiation from Day 1, using either Option 1 or Option 2.
Applicant proposed indication(s)/ population(s)	(b) (4)
Proposed SNOMED indication	(b) (4)
Regulatory action	Approval
Approved dosage (if applicable)	Initiation with one of two options [see dosing regimen above] followed by once every 6-months maintenance dosing. Tablets may be taken without regard to food.
Approved indication(s)/ population(s) (if applicable)	Sunlenca, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Approved SNOMED term for indication (if applicable)	40780007: Human immunodeficiency virus I infection (disorder)

*Second cycle NDA resubmission. First cycle NDA submission date: June 28, 2021. First cycle Complete Response date: February 28, 2022.

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 2. Administrative Application Information (NDA 215974)

Category	Application Information
Application type	NDA
Application number(s)	215974
Priority or standard	Priority
Submit date(s)*	6/27/2022
Received date(s)	6/27/2022
PDUFA goal date	12/27/2022
Division/office	Division of Antivirals (DAV)
Review completion date	12/21/2022
Established/proper name	Lenacapavir
(Proposed) proprietary name	Sunlenca
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1) capsid inhibitor
Code name	GS-6207
Applicant	Gilead Sciences, Inc.
Dosage form(s)/formulation(s)	Tablets, for oral use
Dosing regimen	Initiation Option 1: 927 mg by subcutaneous injection (2×1.5 mL injections) and 600 mg orally (2 tablets) on Day 1; 600 mg orally (2 tablets) on Day 2. Tablets may be taken without regard to food. Initiation Option 2: 600 mg orally (2 tablets) on Day 1; 600 mg orally (2 tablets) on Day 2; 300 mg orally (1 tablet) on Day 8; 927 mg by subcutaneous injection (2×1.5 mL injections) on Day 15. Maintenance: 927 mg by subcutaneous injection (2×1.5 mL injections) every 6 months (26 weeks) from the date of the last injection ±2 weeks. Missed Dose: If more than 28 weeks since last injection and clinically appropriate to continue Sunlenca, restart initiation from Day 1, using either Option 1 or Option 2.
Applicant proposed indication(s)/ population(s)	(b) (4)
Proposed SNOMED indication	(b) (4)
Regulatory action	Approval
Approved dosage (if applicable)	Initiation with one of two options [see dosing regimen above] followed by once every 6-months maintenance dosing. Tablets may be taken without regard to food.
Approved indication(s)/ population(s) (if applicable)	Sunlenca, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Approved SNOMED term for indication (if applicable)	40780007: Human immunodeficiency virus I infection (disorder)

*Second cycle NDA resubmission. First cycle NDA submission date: June 28, 2021. First cycle Complete Response date: February 28, 2022.

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Glossary

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
BIC	bictegravir
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated tablet)
CA	capsid
CD	cluster of differentiation
COVID-19	coronavirus disease 2019
CR	Complete Response
DDD	Division of Dermatology and Dentistry
DILI	drug-induced liver injury
DVY	emtricitabine/tenofovir alafenamide coformulated; Descovy
FDA	Food and Drug Administration (also, the <i>Agency</i>)
FMP	functional monotherapy period
F/TAF	emtricitabine/tenofovir alafenamide (coformulated tablet)
HIV	human immunodeficiency virus
HTE	heavily treatment-experienced
INSTI	integrase strand-transfer inhibitor
ISR	injection site reaction
LEN	lenacapavir
MDR	multidrug-resistant
NDA	new drug application
NGS	next-generation sequencing
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OBR	optimized background regimen
PEG	polyethylene glycol
PK	pharmacokinetics

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PLWH	people living with HIV
PMR	postmarketing requirement
Q	quartile
RT	reverse transcriptase
SAE	serious adverse event
SC	subcutaneous
	(b) (4)
SEM-EDX	scanning electron microscopy-energy dispersive x-ray
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
USP	United States Pharmacopeia
VF	virologic failure
w/w	weight by weight

I. Executive Summary

1. Summary of Regulatory Action

These new drug applications (NDAs) for oral (NDA 215974) and injectable (NDA 215973) formulations of lenacapavir (LEN) were submitted by Gilead Sciences. LEN is a first-in-class human immunodeficiency type 1 (HIV-1) capsid inhibitor with Breakthrough Therapy Designation. These NDAs were initially submitted on June 28, 2021 and reviewed by the interdisciplinary review team.

The intended indication for LEN is to be used in combination with other antiretroviral(s) for the treatment of HIV-1 infection in heavily treatment-experienced adult patients with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

The product quality deficiencies identified in the first cycle review were: (1) product quality information to support the proposed container presentation in borosilicate glass vials was not acceptable for commercial use due to delamination of the vial containers and concern for glass particulate contamination, and (2) the data supporting aluminosilicate glass vials as an alternative were insufficient for full review. The Product Quality assessment team recommended a complete response based on these deficiencies. On February 28, 2022, Complete Response (CR) letters were issued to NDAs 215973 and 215974 due to product quality deficiencies.

On June 27, 2022, the Applicant resubmitted both NDAs with additional product quality, nonclinical and additional long-term data from clinical Study GS-US-200-4625 (Study 4625). The Clinical, Clinical Virology, Clinical Pharmacology, Pharmacology/Toxicology, Statistics, Product Quality, and Regulatory disciplines did not identify issues that preclude approval.

I, the signatory authority for these applications, agree that the benefit-risk assessment favors approval as described in the Benefit-Risk Framework below. The proposed proprietary name, Sunlenca, was found acceptable.

The Applicant submitted one adequately designed phase 2/3 study, Study 4625, that provided substantial evidence of efficacy for the proposed indication. Supportive evidence of efficacy was provided by Study GS-US-200-4334 (Study 4334).

The available safety data from the clinical trials demonstrate that LEN is safe for its intended use in the heavily treatment-experienced population. Based on the additional nonclinical and clinical data submitted for this second cycle review, I concur that the risks identified in the review of the clinical studies' data can be mitigated through labeling and further evaluated via routine pharmacovigilance and issuance of postmarketing commitments and postmarketing requirements. The risk of persistent injection site nodules and indurations was added to the Warnings and Precautions section of the proposed label, and a subsection for injection site reactions (ISRs) was included in the Adverse Reactions section in labeling. Additionally, the prolonged residual exposure of LEN is an important consideration for potential drug-drug interactions and development of resistance, and these risks have been clearly conveyed in product labeling.

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NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Additional information is needed to understand the contributing factors of ISRs with LEN, particularly the mechanism driving the persistence of injection site nodules and indurations in some subjects. The Clinical team has recommended a postmarketing requirement for further long-term assessment of ISRs.

[REDACTED] (b) (4)

Based on our assessment of the relevant nonclinical and clinical data, we determined that [REDACTED] (b) (4) particulates are unlikely to be responsible for the development or persistence of ISRs and do not pose an unacceptable safety risk for the indicated population. However, the Product Quality team has recommended three postmarketing commitments to further assess vial and [REDACTED] (b) (4) compatibility, and to evaluate an alternative device and/or procedure for withdrawing the LEN injection from the vial to consistently reduce the presence of [REDACTED] (b) (4) particulates in the drug product solution.

For detailed information supporting the basis for the benefit-risk assessment, please refer to the details in this Integrated Assessment document and the Review Cycle 1 Integrated Review.

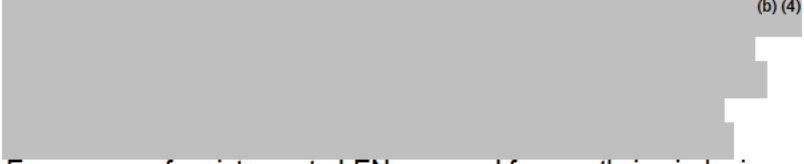
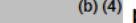
2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Human immunodeficiency virus type 1 (HIV-1) is a transmissible virus that attacks and weakens the immune system. Without effective antiretroviral therapy (ART), HIV-1 infection leads to progressive destruction of the immune system, acquired immunodeficiency syndrome (AIDS)-defining illnesses, and premature death in almost all cases. - The U.S. Centers for Disease Control and Prevention estimates that approximately 1.2 million people in the United States are living with HIV. In 2019, there were 15,815 deaths among people diagnosed with HIV (CDC 2022). - Maximal and durable suppression of HIV-1 RNA restores and/or preserves the immune system and reduces HIV-associated morbidity and mortality. Most treatment-adherent patients with limited previous HIV treatment experience can maximally and durably suppress HIV-1 RNA using a combination of two or more commercially available drugs from different drug classes. - Treatment failure occurs as a result of drug resistance, drug intolerance, and suboptimal adherence. Resistance-associated substitution(s) selected by one drug often confer(s) resistance to other drugs within that drug class, which further limits treatment options. - Heavily treatment-experienced (HTE) patients have limited remaining options for constructing a fully suppressive antiretroviral (ARV) regimen due to multidrug resistance, intolerance, or safety considerations.	HTE patients with limited treatment options and evidence of ongoing HIV replication despite ART are at high risk of AIDS-related morbidity and mortality.
Current Treatment Options	- For patients with multidrug-resistant (MDR) HIV-1 infection, providers must individually tailor combination treatment regimens based on previous ARV exposure, cumulative viral resistance testing, drug safety and tolerability, and comorbid conditions. - The resulting ARV regimens are often burdensome, less well-tolerated, and associated with inadequate HIV-1 RNA suppression.	HTE patients with limited treatment options need new and effective therapies that lack cross-resistance with commercially available products, have a favorable tolerability profile, and allow for convenient dosing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Efficacy of lenacapavir (LEN) in HTE patients with multidrug resistance (MDR) who were failing treatment due to resistance, intolerance, or safety considerations was established in Study GS-US-200-4625 (Study 4625), a phase 2/3 study conducted in two cohorts. • The Study 4625 design was consistent with FDA’s Guidance for Industry (FDA 2015). • Cohort 1 of Study 4625 was divided into two periods. During the first period, the Functional Monotherapy Period (FMP), 36 subjects in Study 4625 were randomized 2:1 to receive 14 days of oral LEN or placebo, respectively, in addition to their failing regimen. During the second period, the Maintenance Period, all subjects were unblinded and dosed with LEN (via subcutaneous injection following the 14-day oral lead-in) plus an optimized background regimen (OBR) through at least 52 weeks of follow-up. A second cohort enrolled 36 subjects, all of whom received open-label LEN plus an OBR, in parallel with Cohort 1. • The primary efficacy endpoint for Study 4625 was the proportion of subjects in Cohort 1 achieving a reduction in HIV-1 RNA of $\geq 0.5 \log_{10}$ copies/mL from baseline at the end of the 14-day FMP. The difference in proportions in HIV-1 RNA $\log_{10}$ copies/mL from Day 1 to Day 14 (LEN minus placebo) was -70.8 (95% confidence interval, $-34.9, -90.0$), demonstrating statistical superiority of LEN compared to placebo. • Early HIV-1 RNA decreases of $>0.5 \log_{10}$ copies/mL in prior trials have been associated with reduction in clinical disease progression according to the FDA’s Guidance for Industry (FDA 2015). • The key secondary efficacy endpoints assessed durability of virologic response following the FMP. After 26 and 52 weeks, 81% and 83% of participants continued to have HIV-1 RNA suppression (<50 copies/mL), respectively. • Supplemental efficacy data were provided by a phase 2 trial, Study GS-US-200-4334 (Study 4334). A total of 183 treatment-naïve people living with HIV (PLWH) was randomized to receive one of three regimens containing LEN or an active comparator (bictegravir/emtricitabine/tenofovir alafenamide coformulated [B/F/TAF]). At the Week 54 analysis, 87% (136/157) of the subjects who received a regimen containing LEN and 92% (23/25) of the	• LEN has demonstrated virologic activity in HTE patients with MDR HIV-1 infection who have limited treatment options. • The clinical study design and endpoints were appropriate for the HTE population with limited treatment options. • Reductions in HIV-1 RNA levels are highly predictive of meaningful clinical benefit, and LEN functional monotherapy was superior to placebo for reducing HIV-1 RNA over 14 days. • Study 4625 was uncontrolled during the maintenance period, so there are limitations in performing comparative analyses. However, the Week 52 analysis suggests that LEN contributes to the durability of virologic response when added to an OBR. • Availability of LEN would provide a new and effective first-in-class treatment option for HTE patients with multidrug resistant HIV-1 infection and limited alternative options due to resistance, intolerance, or safety considerations. Patients who achieve virologic suppression with LEN plus an OBR would have a reduced risk of HIV/AIDS-related morbidity and mortality. • (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	subjects who received B/F/TAF maintained HIV-1 RNA <50 copies/mL. - Study 4625 enrolled 72 subjects from the HTE patient population, and the safety database included 195 PLWH exposed to at least one 927 mg subcutaneous dose of LEN with the same proposed formulation for marketing. This safety database is smaller than the minimum recommended sample size of 300 to 500, as outlined by FDA’s Guidance for Industry (FDA 2015); however, the overall clinical experience with any LEN formulation in PLWH and healthy volunteers was over 1200. - The most common adverse drug reactions during treatment with LEN were injection site reactions (ISRs). Most ISRs were mild to moderate in severity. There was one discontinuation due to an ISR (injection site nodule) in Study 4625. Injection site pain, swelling, and erythema were the most common specific ISRs reported, and typically lasted no more than a few days; however, indurations and nodules were reported to have longer durations, including several nodules that have persisted over 1 year of follow-up.  (b) (4) - Emergence of resistance to LEN occurred frequently in virologic failures (9/22; 41%). The M66I capsid substitution emerged most frequently, alone or in combination with other LEN resistance-associated capsid substitutions including substitutions at Q67, K70, N74, A105, and T107. Virologic failure isolates with emergent LEN resistance-associated substitutions showed 6- to 1428-fold decreased susceptibility to LEN.	- Based on the available data, LEN has an acceptable safety profile. Additional information, however, is needed to understand the contributing factors of ISRs with LEN, particularly the mechanism driving the persistence of injection site nodules and indurations in some subjects. The risk of persistent injection site nodules and indurations was added to the Warnings and Precautions section of the proposed label, and a subsection for ISRs was included in the Adverse Reactions section. This issue will be further addressed via routine pharmacovigilance and the issuance of a PMR. - Based on an assessment of the relevant nonclinical and clinical data, FDA determined that  (b) (4) particulates are unlikely to be responsible for the development or persistence of ISRs and do not pose an unacceptable safety risk for the indicated population. This issue will be further addressed via the issuance of PMCs. - LEN resistance emerges readily in virologic failures, thus it is important to use LEN as a component of a complete active ARV regimen. - LEN resistance substitutions do not confer cross-resistance to other currently FDA-approved ARVs.

2.2. Conclusions Regarding Benefit-Risk

Infection with HIV-1 continues to be a significant public health concern both domestically and internationally. Although the HIV treatment armamentarium is robust, additional effective antiretroviral (ARV) treatment options that provide greater flexibility in meeting patients’ individual needs and facilitating their tolerance for and adherence to lifelong HIV-1 treatment are needed. Heavily treatment-experienced patients infected with MDR HIV-1 represent a rare but important subset of patients living with HIV. Patients

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

with multidrug-resistant HIV-1 who cannot achieve complete virologic suppression with antiretroviral therapy (ART) are at high risk for AIDS-related morbidity and mortality. This population needs new and effective ARV products that lack cross-resistance with commercially available products, have a favorable tolerability profile, and allow for convenient dosing. LEN, a first-in-class HIV-1 capsid inhibitor with Breakthrough Therapy Drug designation, is one such product. The injectable formulation of LEN provides an option with the advantage of providing a new mechanism of action and maintenance dosing every 6 months following a lead-in with oral tablets. However, the prolonged residual exposure is an important consideration for potential drug-drug interactions and risk of development of resistance.

The submitted evidence demonstrates LEN is effective in patients with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. The pivotal study, Study 4625 (CAPELLA), demonstrated superiority of LEN compared to placebo, when added to a failing regimen, for the proportion of subjects achieving a reduction in HIV-1 RNA of $\geq 0.5 \log_{10}$ copies/mL after 14 days of treatment. The lack of a control group after Day 14 in Study 4625 limits the ability to precisely quantify the contribution of LEN to long-term virologic suppression. However, the contribution of LEN is reflected by the relatively high rate of virologic suppression achieved with LEN plus an optimized background regimen (OBR) through the Week 52 analysis in a population previously unable to achieve virologic suppression. Additional supportive data from the phase 2 study in treatment-naïve people living with HIV, Study 4334, demonstrated that regimens containing LEN achieved and maintained comparable virologic suppression through the Week 54 analysis to a standard-of-care control arm based on the results of the primary endpoint.

The safety evaluation for LEN was adequate and the demonstrated clinical safety profile of LEN is acceptable for the proposed indication. With the exception of local injection site reactions and the risk of treatment-emergent resistance to LEN, the safety profile of LEN was generally favorable. While generally reported as mild to moderate in severity, injection site indurations and nodules remained persistent in several cases and were a cause of study drug discontinuations in Studies 4625 and 4334. Additional information, however, is needed to understand the contributing factors of ISRs with LEN, particularly the mechanism driving the persistence of injection site nodules and indurations in some subjects. These issues will be further addressed via routine pharmacovigilance and the issuance of a clinical PMR. Resistance to LEN emerges readily in virologic failures, thus it is important to use LEN as a component of a complete active ARV regimen.

Based upon review of all available efficacy and safety data, the benefits of LEN, in combination with other ARVs, clearly outweigh the risks for treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations. The availability of LEN will provide a new and effective treatment option for this patient population.

II. Interdisciplinary Assessment

3. Introduction

Refer to Section 3 of the Integrated Review dated February 28, 2022 from the first cycle, and to Section [12](#) for additional regulatory history.

The Applicant resubmitted two new drug applications (NDAs) in parallel for the two dosage forms of lenacapavir (LEN) (injection [NDA 215973] and tablet [NDA 215974]) and is seeking the indication of (b) (4)

LEN is a first-in-class HIV-1 capsid (CA) inhibitor and has been formulated for subcutaneous (SC) injection and as a tablet for oral use. The Applicant previously submitted an original investigational new drug application in 2017 to investigate LEN for injection and in 2018 to investigate LEN for oral use for the treatment of HIV-1 infection. (Refer to Section [12](#) for additional regulatory history.) This interdisciplinary assessment combines the review of NDA 215973 for LEN SC injection and NDA 215974 for LEN oral tablets.

The Applicant conducted two clinical studies in support of the findings of safety and efficacy for LEN, Study GS-US-200-4625 (Study 4625, also referred to as CAPELLA) and Study GS-US-200-4334 (Study 4334, also referred to as CALIBRATE). Study 4625 is an ongoing phase 2/3 study designed to evaluate the antiviral activity of LEN administered as an add-on to a failing regimen (functional monotherapy) for heavily treatment-experienced (HTE) people living with HIV (PLWH). Study 4334 is a phase 2 study conducted in a treatment-naïve patient population and serves as supplementary support for the efficacy and safety evaluation of LEN for the indication of treating the HTE HIV-1 population. Of note, the results of Studies 4625 and 4334 have been published [Week 26, ([Segal-Maurer et al. 2022](#))] and presented at the Conference on Retroviral and Opportunistic Infections 2022 [Week 52, ([Ogbuagu et al. 2022](#)) and Week 54, ([Gupta et al. 2022](#))], respectively.

Other currently available therapies used as part of the standard of care for the treatment of HIV-1 are discussed in more detail in Section [2](#). When constructing an ARV regimen for HTE PLWH, as noted by the U.S. HIV Treatment Guidelines ([DHHS 2022a](#)), the expected potency and whether a new drug as part of a complete regimen has a new mechanistic action are important considerations. Currently, no other ARV product in the CA inhibitor class for HIV-1 has been approved, nor have any been approved with a dosing interval as long as every 6 months ([DHHS 2022b](#)).

At the conclusion of the first NDA review cycle for NDAs 215973 and 215974 on February 28, 2022, Complete Response letters were issued to the Applicant as a result of product quality deficiencies including: 1) Incompatibility between drug product and borosilicate glass vials, and 2) incomplete information with respect to Container Closure Integrity Testing. On May 24, 2022, a Type A, postaction teleconference was held between the Applicant and the Food and Drug Administration (FDA; also, *the Agency*) for NDAs 215973 and 215974; the purpose of this

meeting was to discuss the deficiencies noted in the Complete Response letters and to obtain feedback on the Applicant's plan for resubmission of NDAs 215973 and 215974. On June 27, 2022, Gilead resubmitted NDAs 215973 and 215974.

The primary efficacy results from Study 4625 were confirmed during the first NDA review cycle. Superiority of LEN compared to placebo was demonstrated for the proportion of HIV-1 RNA reduction $\geq 0.5 \log_{10}$ from baseline to the end of the functional monotherapy period (FMP) at Day 14. The Week 26 and Week 52 HIV-1 RNA were planned to be evaluated as secondary endpoints; however, the majority of subjects did not complete the Week 52 assessment at the time of the original NDA submissions. The resubmissions of NDAs 215973 and 215974 provide additional long-term safety and efficacy data (Week 52) from Study 4625, as well as safety and efficacy data from other ongoing and completed clinical studies with LEN.

3.1. Review Issue List

Refer to Section 3.1 of the Integrated Review dated February 28, 2022 from the first cycle. During the first cycle, the review team identified five review issues relevant to the evaluation of benefit and three review issues relevant to the evaluation of risk.

Key Review Issues Related to Evaluation of Benefit (First Cycle)

- The baseline imbalances of HIV-1 RNA level and cluster of differentiation (CD) 4⁺ cell count for Cohort 1 between the two randomized arms. The conclusion was that these baseline imbalances did not impact the interpretability of the primary efficacy result.
- The Applicant proposed a simplified dosing regimen that was not studied during the LEN clinical development program. The review team concluded that the simplified dosing regimen was acceptable, and the label should include recommendations for both the simplified regimen and the regimen used in Study 4625.
- In a clinical study designed for study in an HTE patient population, it is important to determine if the subjects are truly failing on their pre-study ARV regimen rather than due to nonadherence to the ARV drugs with no evidence of resistance in their supposed "failing" regimen. If subjects are nonadherent to the regimen and do not have resistance to the "failing" regimen during the LEN functional monotherapy period, it will be difficult to determine the contribution of LEN to efficacy in the background of other active or partially active ARVs. Supplementary sensitivity efficacy analyses removing subjects that had evidence they were not failing on their background regimens at study entry confirmed the primary endpoint analysis of LEN.
- The proposed subcutaneous maintenance dosing interval and the approach to missed doses outside of the recommended window (± 2 weeks). The review team concluded that the optimal dosing interval for SC LEN injection is 26 weeks, and the ± 2 -week dosing window is acceptable to provide flexibility and facilitate adherence to the SC LEN regimen.

-  (b) (4)

Key Review Issues Related to Evaluation of Risk (First Cycle)

- Emergence of resistance was assessed in virologic failures (VFs) of a LEN-containing ARV regimen. The review team concluded that LEN resistance emerges readily in VFs and thus it is important to use LEN as a component of a complete active ARV regimen. LEN resistance substitutions do not confer cross-resistance to other ARVs, but longer-term data from all subjects are required to determine durability of LEN and the other ARVs in the optimized background regimen (OBR).
- Injection site reactions (ISRs) were identified as the most common adverse drug reaction (ADR) among subjects who received SC injections of LEN; however, long-term experience of subjects after multiple injections was limited in Studies 4625 and 4334. The review team concluded that additional information is needed to understand the contributing factors of ISRs with LEN, particularly for subjects who have prolonged time to resolution of nodules and indurations.
- The risk of suprathreshold LEN exposures when LEN is combined with a background regimen containing boosted protease inhibitors was not prospectively assessed in Study 4625. The review team conducted a post hoc analysis and concluded that labeling for LEN should include the recommendation against concomitant administration of atazanavir/cobicistat or atazanavir/ritonavir. No clinically significant drug interactions were observed with darunavir/cobicistat.

For the NDA resubmissions, the review team identified one review issue relevant to the evaluation of benefit (Section [6.3](#)) and two review issues relevant to the evaluation of risk (Section [7.7](#)).

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Extended Efficacy Data From Study 4625 (Week 52 Interim Analyses for Cohorts 1 and 2)

The assessment of the durability of virologic response in HTE subjects is an important component of understanding the overall efficacy of LEN.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Resistance Assessments of Virologic Failures at Week 52

The assessment of resistance emergence in VFs of an LEN-containing ARV regimen is critical to interpreting the overall risk-benefit of LEN and understanding the durability of LEN as a component of an ARV regimen in a HTE patient population.

3.1.2.2. Injection Site Reactions

ISRs were identified as the most commonly reported ADRs among subjects who received SC LEN injections; however, the long-term experience of subjects with multiple SC LEN injections was limited in Studies 4625 and 4334.

3.2. Approach to the Review

[Table 4](#) provides an overview of the clinical studies that substantially contributed to the benefit and risk assessment for LEN. Data from Study 4625 (CAPELLA) were the primary clinical study data submitted in support of efficacy. Study 4334 (CALIBRATE) provided additional descriptive support for the evaluation of safety and efficacy.

Additional phase 1 studies, such as Study GS-US-200-5709 (Study 5709), were used to support the simplified dosing regimen, as well as adding supportive safety experience to the overall safety database.

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Lenacapavir

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	No. of Centers and Countries
GS-US-200-4625 (CAPELLA) [NCT04150068]	HTE adult and adolescent subjects with MDR HIV-1 infection (Note: although eligible, no adolescents actually enrolled)	Control type: Placebo controlled during FMP only Randomization: Cohort 1: Randomized 2:1 (LEN:PBO) during FMP Cohort 2: Single-arm, not randomized Blinding: Cohort 1 (FMP only): Blinded Cohort 1 (Maintenance only) and Cohort 2: Open-label	Dosage: Cohort 1: Cohort 1A: (N=24) FMP 1-2 weeks Oral LEN 600 mg (Days 1 and 2) + 300 mg (Day 8) + Failing Regimen Maintenance: Week 3-54 SC LEN (927 mg) + OBR. Cohort 1B: (N=12). FMP Weeks 1-2: Pb + Failing Regimen Oral dosing Weeks 3-4: Oral LEN 600 mg (Days 1 and 2) + 300 mg (Day 8) + OBR Maintenance Weeks 5-54: SC Len (927 mg) + OBR Cohort 2: Oral LEN 600 mg + OBR on Day 1; oral LEN 600 and 300 mg on Days 2 and 8, respectively, + OBR Maintenance: SC LEN (927 mg) + OBR Number treated: 72 Duration: ≥54 wk	Primary: The proportion of subjects in Cohort 1 achieving a reduction in HIV-1 RNA of ≥0.5 log ₁₀ copies/mL from baseline at the end of the FMP Secondary: The proportion of subjects in Cohort 1 with plasma HIV-1 RNA <50 copies/mL and <200 copies/mL at Weeks 26 and 52 of treatment based on the FDA-defined snapshot algorithm	Planned: 100 Actual: 72 Cohort 1: 36 Cohort 1A: 24 Cohort 1B: 12 Cohort 2: 36	Centers: 31 Countries: 11

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	No. of Centers and Countries
GS-US-200-4334 (CALIBRATE) [NCT04143594]	Treatment-naïve people with HIV ≥18 years of age	Control type: Active control Randomization: Randomized Blinding: Open-label	<u>Dosage: Treatment Group 1 (oral to SC LEN):</u> Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral F/TAF 200/25 mg Maintenance: SC LEN 927 mg and oral TAF 25 mg <u>Treatment Group 2 (oral to SC LEN):</u> Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral F/TAF 200/25 mg Maintenance: SC LEN 927 mg and oral BIC 75 mg <u>Treatment Group 3:</u> oral LEN 600 and 50 mg and oral F/TAF 200/25 mg <u>Treatment Group 4:</u> Oral B/F/TAF 50/200/25 mg Number treated: 175 Duration: ≥80 wk	Primary: The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 54 as determined by the FDA-defined snapshot algorithm Secondary: The proportion of subjects with HIV-1 RNA <50 copies/mL at Weeks 28, 38, and 80 as determined by the FDA-defined snapshot algorithm	Planned: 175 Actual: 183 SC LEN + (F/TAF→TAF): 52 SC LEN + (F/TAF→BIC): 53 Oral LEN + F/TAF: 52 B/F/TAF: 25	Centers: 41 Countries: 3

Source: Reviewer's summary.

¹ Includes all submitted phase 2/3 clinical studies, except for phase 1 and pharmacokinetic studies.

Abbreviations: ARV, antiretroviral; BIC, bicitregavir; B/F/TAF, bicitregavir/emtricitabine/tenofovir alafenamide (coformulated tablet); BID, twice daily; DB, double-blind; F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); FDA, Food and Drug Administration; FMP, functional monotherapy period; HIV, human immunodeficiency virus; HTE, heavily treatment-experienced; LEN, lenacapavir; LTE, long-term extension study; MC, multicenter; MDR, multidrug resistant; N, number of subjects; NCT, National Clinical Trials; OL, open-label; OBR, optimized background regimen; PBO, placebo; PC, placebo-controlled; PG, parallel group; RNA, ribonucleic acid; SC, subcutaneous; TAF, tenofovir alafenamide; wk, weeks

4. Patient Experience Data

Patient experience data have not yet been submitted. Study 4625 is ongoing, but the protocol has included collection of patient-reported outcomes. Subjects ≥ 18 years of age will complete the following, if available:

- Symptoms Distress Module, Short Form Health Survey, EQ-5D-5L at Day 1, and at Weeks 4, 16, 26, and 52.
- The Numeric Pain Rating Scale at Day 1 SC, and Weeks 26 and 52.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Please refer to the Clinical Pharmacology review in Section 5 of the Integrated Review dated February 28, 2022 from the first cycle. No additional data were submitted in this review cycle.

6. Assessment of Effectiveness

Please refer to the Statistical review in Section 6 of the Integrated Review dated February 28, 2022 from the first cycle. For this cycle, the Applicant submitted extended efficacy data for both Studies 4625 and 4334.

6.1. Results of Analyses of Clinical Trial Intended to Demonstrate Efficacy, Study 4625

Disposition

The study data are updated through Week 52. All subjects completed the Week 52 visit or prematurely discontinued the study ([Table 6](#)).

Table 6. Patient Disposition Updated to Week 52, Study 4625

Parameter	Cohort 1			Cohort 2
	LEN	PBO to LEN	Total	Total
Randomized	24	12	36	36
Maintenance period (to Week 52)				
Completed maintenance period	24 (100%)	12 (100%)	36 (100%)	36 (100%)
Completed study drug	23 (95.8%)	12 (100%)	35 (97.2%)	32 (88.9%)
Prematurely discontinued study drug	1 (4.2%)	0	1 (2.8%)	4 (11.1%)
Reason: death	0	0	0	1 (2.8%)
Reason: lost to follow-up	1 (4.2%)	0	1 (2.8%)	2 (5.6%)
Reason: investigator's discretion	0	0	0	1 (2.8%)

Source: Statistical Reviewer's analysis.

Abbreviations: LEN, lenacapavir; PBO, placebo

Efficacy Endpoints

The primary endpoint for Study 4625 was the proportion of subjects in Cohort 1 who achieved HIV-1 RNA reduction of ≥ 0.5 log₁₀ copies/mL from baseline at the end of the monotherapy period. This result has been evaluated during the first cycle.

Week 26 and Week 52 HIV-1 RNA levels are planned to be evaluated as secondary endpoints. During the last review cycle, only six subjects in Cohort 2 completed the Week 26 visit. For this cycle, all subjects completed Week 52 visit. At Week 52, the proportions of subjects who achieved HIV-1 RNA <50 copies/mL in both Cohort 1 and Cohort 2 are reasonably consistent compared to those at Week 26 ([Table 7](#) and [Table 8](#)).

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 7. Secondary Endpoints at Week 26 for Cohort 2, Study 4625

Week 26	Cohort 2
HIV-1 RNA $\geq$ 50 copies/mL	6/36 (16.7%)
HIV-1 RNA <50 copies/mL	29/36 (80.6%)
No virologic data	1/36 (2.8%)
Discontinued study due to AE or death	1/36 (2.8%)
Discontinued study for other reasons	0/36 (0.0%)
On study but missing data in window	0/36 (0.0%)

Source: Statistical Reviewer's analysis.

FDA snapshot algorithm was used.

Abbreviations: AE, adverse event; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; RNA, ribonucleic acid

Table 8. Secondary Endpoints at Week 52, Study 4625

Week 52	Cohort 1			Cohort 2
	LEN	PBO to LEN	Total	
HIV-1 RNA $\geq$ 50 copies/mL	2/24 (8.3%)	3/12 (25.0%)	5/36 (13.9%)	6/36 (16.7%)
HIV-1 RNA <50 copies/mL	21/24 (87.5%)	9/12 (75.0%)	30/36 (83.3%)	26/36 (72.2%)
No virologic data	1/24 (4.2%)	0/12 (0.0%)	1/36 (2.8%)	4/36 (11.1%)
Discontinued study due to AE or death	0/24 (0.0%)	0/12 (0.0%)	0/36 (0.0%)	1/36 (2.8%)
Discontinued study for other reasons	1/24 (4.2%)	0/12 (0.0%)	1/36 (2.8%)	2/36 (5.6%)
On study but missing data in window	0/24 (0.0%)	0/12 (0.0%)	0/36 (0.0%)	1/36 (2.8%)

Source: Statistical Reviewer's analysis.

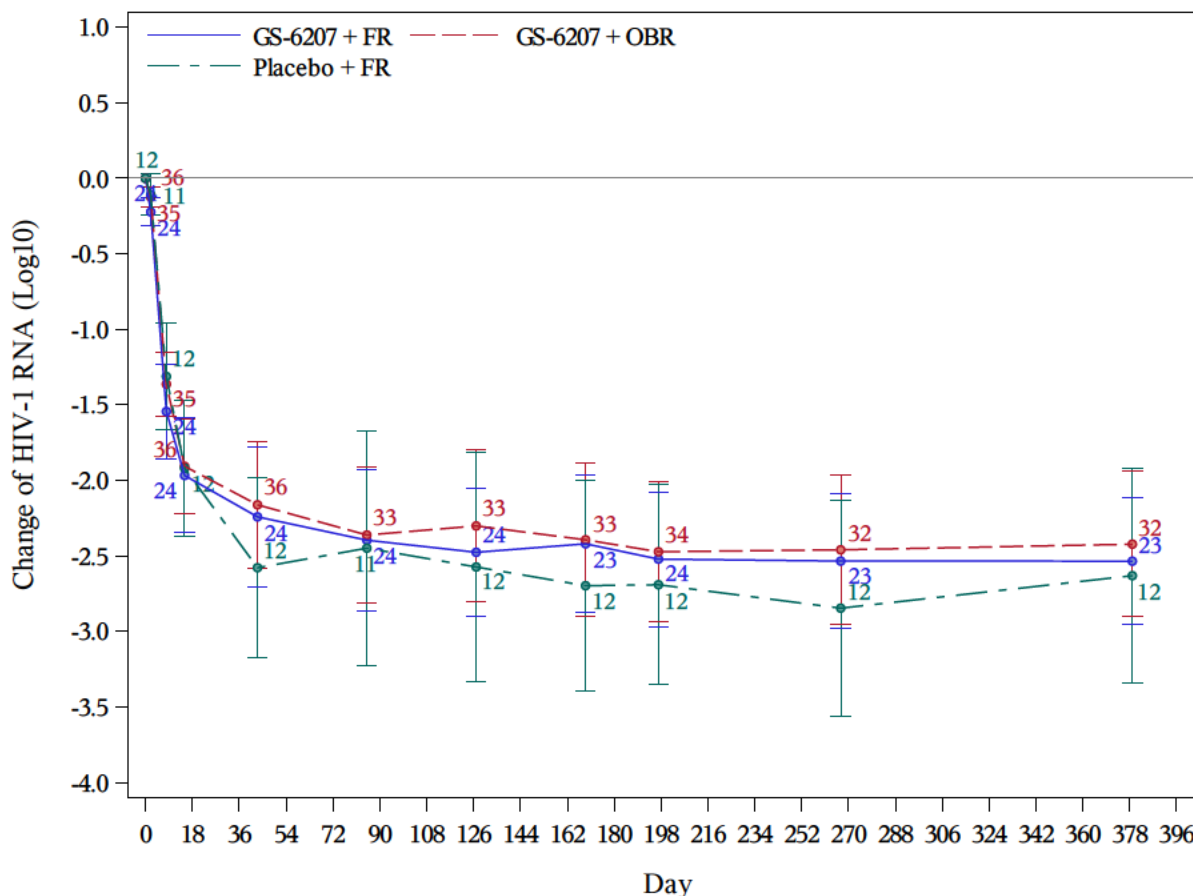
FDA snapshot algorithm was used.

Abbreviations: AE, adverse event; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; LEN, lenacapavir; PBO, placebo; RNA, ribonucleic acid

Viral Load and Immunologic Response

Changes of the HIV-1 RNA level and CD4⁺ cell count over time through Week 52 for Cohort 1 (presented as two arms) and Cohort 2 subjects are shown in [Figure 1](#) and [Figure 2](#). All treatment arms received LEN + OBR (following the FMP in Cohort 1). The 95% CI bars are wide because of a small sample sizes. Differences between arms, therefore, are likely random variation.

Figure 1. Mean Change and 95% CI of HIV-1 RNA for Subjects after Receiving LEN (Cohorts 1 and 2), Study 4625

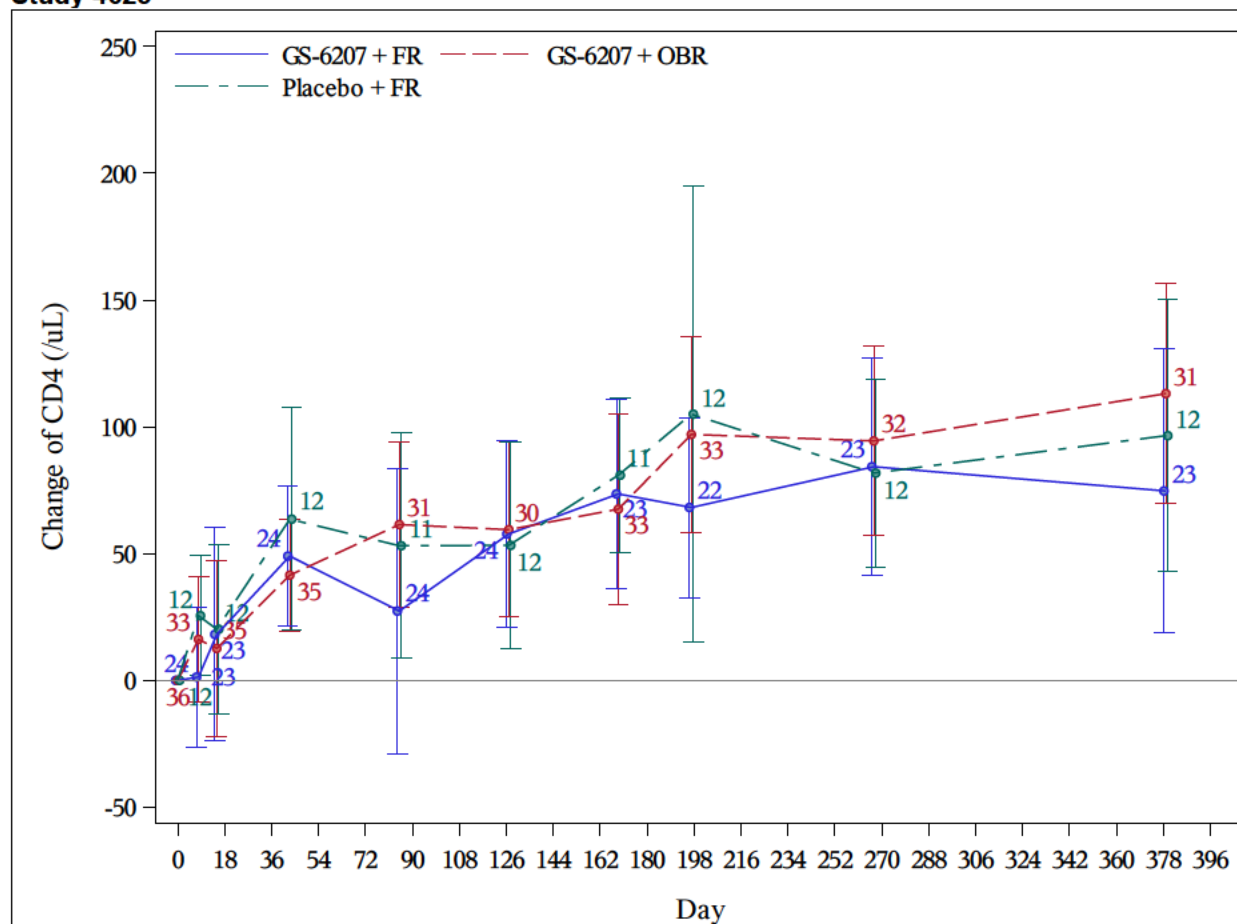


Source: Statistical reviewer's analysis.

GS-6207+FR indicates subjects randomized to the LEN arm in Cohort 1; placebo+FR indicates subjects randomized to the placebo arm in Cohort 1 (Day 0 for this arm was the day immediately prior to LEN administration); and GS-6207+OBR indicates subjects enrolled in Cohort 2. Numbers indicate sample sizes at the indicated timepoints.

Abbreviations: CI, confidence interval; FR, failing regimen; GS-6207/Len, lenacapavir; HIV, human immunodeficiency virus; OBR, optimized background regimen; RNA, ribonucleic acid

Figure 2. Mean Change and 95% CI of CD4 for Subjects after Receiving LEN (Cohorts 1 and 2), Study 4625



Source: Statistical reviewer's analysis.

GS-6207+FR indicates subjects randomized to the LEN arm in Cohort 1; placebo+FR indicates subjects randomized to the placebo arm in Cohort 1 (Day 0 for this arm was the day immediately prior to LEN administration); and GS-6207+OBR indicates subjects enrolled in Cohort 2. Numbers indicate sample sizes at the indicated timepoints.

Abbreviations: CD, cluster of differentiation; CI, confidence interval; FR, failing regimen; GS-6207/Len, lenacapavir; HIV, human immunodeficiency virus; OBR, optimized background regimen; RNA, ribonucleic acid

6.2. Results of Analyses of Clinical Trial Intended to Supplement Efficacy, Study 4334

Disposition

For this cycle, all subjects completed the Week 54 visit or prematurely discontinued the study. More subjects in the SC LEN arm discontinued study drug prematurely compared to the oral LEN arm, and more subjects in the LEN-containing arm discontinued study drug prematurely compared to the bicitgravir/emtricitabine/tenofovir alafenamide coformulated (B/F/TAF) arm ([Table 9](#)).

Table 9. Patient Disposition, Study 4334

Parameter	SC LEN + (F/TAF→TAF)	SC LEN + (F/TAF→BIC)	Oral LEN + F/TAF	B/F/TAF
Randomized and received dose	52	53	52	25
Study drug completion status				
Continuing study drug	45 (86.5%)	38 (71.7%)	45 (86.5%)	18 (72.0%)
Completed study drug	2 (3.8%)	3 (5.7%)	3 (5.8%)	6 (24.0%)
Prematurely discontinued study drug	5 (9.6%)	12 (22.6%)	4 (7.7%)	1 (4.0%)
Reason: adverse event	0	3 (5.7%)	0	0
Reason: lack of efficacy	2 (3.8%)	1 (1.9%)	0	0
Reason: investigator's discretion	1 (1.9%)	2 (3.8%)	0	0
Reason: subject decision	0	4 (7.5%)	1 (1.9%)	1 (4.0%)
Reason: lost to follow-up	2 (3.8%)	2 (3.8%)	3 (5.8%)	0

Source: Statistical Reviewer's analysis.

Abbreviations: BIC, bicitegravir; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); LEN, lenacapavir; SC, subcutaneous; TAF, tenofovir alafenamide

Efficacy Endpoints

The primary endpoint for this study was the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 54. For virologic suppression (HIV-1 RNA <50 copies/mL), the LEN combined arm had a similar response rate with Study 4625, which support the efficacy results of Study 4625; the difference between the LEN and BVY arms had a wide 95% CI with the lower bound at -17.3. For VF (HIV-1 RNA ≥50 copies/mL), the LEN combined arm had a significantly worse result compared to the B/F/TAF arm. Also, the difference between the two arms was greater than that at Week 28 ([Table 10](#)).

Table 10. Efficacy Endpoints at Week 54, Study 4334

Parameter	LEN Combined	B/F/TAF	Difference (95% CI)
HIV-1 RNA <50 copies/mL	136/157 (86.6%)	23/25 (92.0%)	-5.3 (-17.3, 6.7)
HIV-1 RNA ≥50 copies/mL	7/157 (4.5%)	0/25 (0.0%)	4.4 (1.2, 7.6)
No virologic data	14/157 (8.9%)	2/25 (8.0%)	
Discontinued study due to AE or death	2/157 (1.3%)	0/25 (0.0%)	
Discontinued study for other reasons	11/157 (7.0%)	1/25 (4.0%)	
On study but missing data in window	1/157 (0.6%)	1/25 (4.0%)	

Source: Statistical Reviewer's analysis.

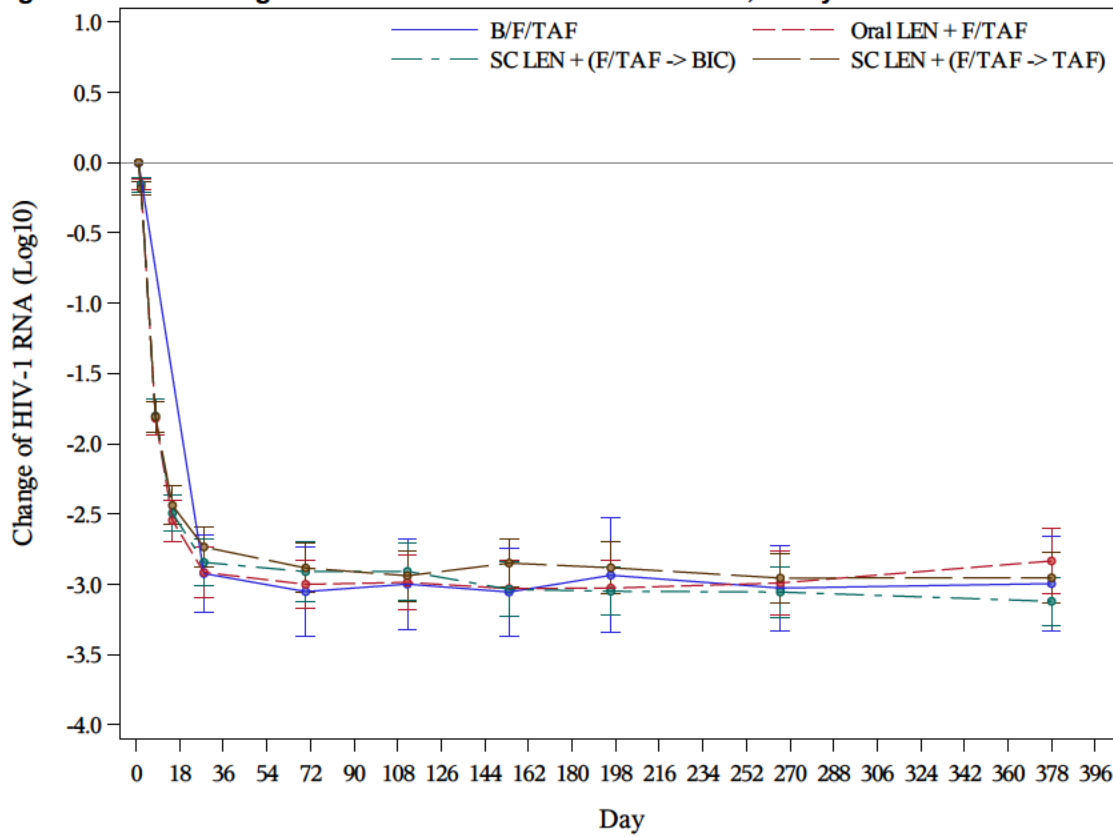
FDA snapshot algorithm was used. Stratified Cochran–Mantel–Haenszel test with baseline HIV-1 RNA level (≤100,000 or >100,000 copies/mL) as the stratification factor was used to calculate risk differences and the associated 95% CI.

Abbreviations: AE, adverse event; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); CI, confidence interval; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; LEN, lenacapavir; RNA, ribonucleic acid

Viral Load and Immunologic Response

Changes of the HIV-1 RNA level and the CD4⁺ cell count over time through Week 54 are shown in [Figure 3](#) and [Figure 4](#).

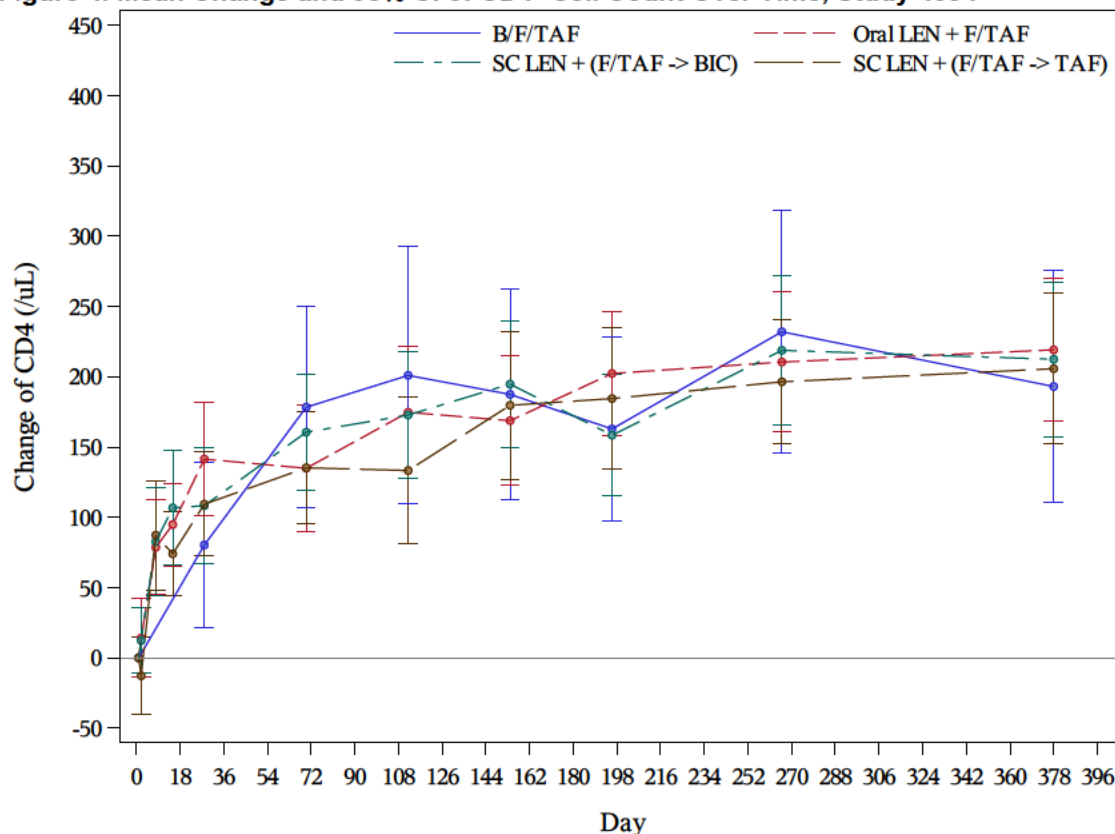
Figure 3. Mean Change and 95% CI of HIV-1 RNA Over Time, Study 4334



Source: Statistical Reviewer's analysis.

Abbreviations: BIC, bicitgravir; B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide (coformulated tablet); CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); HIV, human immunodeficiency virus; RNA, ribonucleic acid; SC, subcutaneous; TAF, tenofovir alafenamide

Figure 4. Mean Change and 95% CI of CD4⁺ Cell Count Over Time, Study 4334



Source: Statistical Reviewer's analysis.

Abbreviations: BIC, bictegravir; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); CD, cluster of differentiation; CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); HIV, human immunodeficiency virus; RNA, ribonucleic acid; SC, subcutaneous; TAF, tenofovir alafenamide

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Extended Efficacy Data From Study 4625 (Week 52 Interim Analyses for Cohorts 1 and 2)

Issue

Do the efficacy data from the Week 52 interim analysis demonstrate durability of the contribution of LEN?

Background

Prior to enrollment, the HTE population in Study 4625 had not been able to achieve virologic suppression with currently available therapy. Therefore, assessing the durability of virologic response in HTE subjects is an important component of understanding the overall efficacy of LEN.

Assessment

From Day 14 onward, all subjects in Cohort 1 were transitioned from their initial (failing) background regimen to an optimized regimen in combination with open-label LEN. There was no comparator arm during the maintenance period, and the interim analysis included follow-up through Week 52.

The proportion of subjects in Cohort 1 who achieved HIV-1 RNA <50 copies/mL was 81% at Week 26 (presented at Cycle 1 of the review), and 83% at Week 52. The durability of virologic response was maintained. Details of the analyses for virologic outcomes at Week 52 for Cohorts 1 and 2 are presented in [Table 8](#). Additional extended follow-up is anticipated (optional through 104 weeks).

Comparing the virologic response of LEN to other drugs indicated for the HTE population, proportions of subjects who achieved HIV-1 RNA <40 copies/mL was 54% at Week 48 for fostemsavir, and proportions of subjects who achieved HIV-1 RNA <50 copies/mL was 43% at Week 25 for ibalizumab-uiyk. These comparisons across these different studies, however, should be considered with caution.

Conclusion

Despite the limitations in the assessment of extended efficacy data, such as the lack of a comparator arm during the maintenance period and uncertainties associated with cross-study comparisons, the available data suggest that LEN contributes to the durable antiretroviral effect as part of an optimized background regimen.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Refer to Section 7.1 of the Integrated Review dated February 28, 2022 from the first cycle. Please also refer to Section [13](#). No new potential risks were identified based on the Pharmacology Toxicology review of additional nonclinical data.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Refer to Section 7.2 of the Integrated Review dated February 28, 2022 from the first cycle.

LEN is the first in a new class of antiretroviral drugs; therefore, no previously described clinical experience is available to inform any specific safety concern regarding CA inhibitors.

Immune reconstitution syndrome has been reported with combination antiretroviral therapy, particularly in the initial phase of treatment, in patients whose immune systems develop an inflammatory response to indolent or residual opportunistic infections. This is also often particularly relevant in a HTE patient population.

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Loss of virologic response because of drug-drug interactions has been included as a warning in labeling for other ARVs.

For other ARVs that are administered in an injectable form, such as CABENUVA (a long-acting formulation of two drugs, cabotegravir and rilpivirine), ISRs are the most commonly reported adverse reactions. The most commonly reported ISR that is included in the CABENUVA labeling is pain/discomfort (71% to 79% of subjects). The CABENUVA labeling also includes the following other ISRs: nodules (10% to 17% of subjects), induration (7% to 12% of subjects), swelling (5% to 8% of subjects), erythema (2% to 4% of subjects), pruritus (4% to 5% of subjects), bruising/discoloration (2% to 3% of subjects), and warmth (1% to 2% of subjects) ([ViiV-Healthcare 2022](#)).

7.3. Potential Safety Concerns Identified Through Postmarket Experience

During the current review cycle, the European Medicines Agency granted Marketing Authorization to LEN on August 17, 2022 ([EMA 2022](#)). Per the Applicant, (b) (4)

no potential safety concerns have been identified through postmarket experience at this time. Following the priority review of New Drug Submissions, Sunlenca (LEN) was granted marketing authorization (Notice of Compliance) in Canada on November 2, 2022 ([Health-Canada 2022](#)).

7.4. FDA Approach to the Safety Review

Refer to Section 7.4 of the Integrated Review dated February 28, 2022 from the first cycle.

In the original NDA submissions, the primary safety data for LEN were derived from an ongoing phase 2/3 study of LEN in combination with an OBR in HTE PLWH (Study 4625). In addition, supportive safety data were derived from an ongoing phase 2 study of LEN in combination with other ARVs in treatment-naïve PLWH (Study 4334), and an Integrated Summary of Safety presenting a pooled analysis of two phase 1 studies evaluating the safety of LEN in healthy subjects (Study GS-US-200-4538 [Study 4538] and Study 5709). Of the two phase 1 studies, only Study 5709 was ongoing at the time of the original submission. Study 4538 had been completed, and the full clinical study report was included in the original NDA submissions.

The review team did not identify any major data quality or integrity issues that preclude performing a safety review. No major issues were identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in Studies 4625 and 4334 were reviewed and were found to be acceptable.

This review summarizes the NDA resubmissions, which included additional longer-term safety data from the two studies included in the original NDA submissions:

- The primary study, Study 4625 (a phase 2/3 study in HTE PLWH with multidrug resistance): analyses were conducted after all subjects in both Cohorts 1 and 2 had completed the Week 52 visit or prematurely discontinued study drug (February 2022 data cut date).

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

- Study 4334 (a phase 2 study in treatment-naïve PLWH): Analyses were conducted after all subjects had completed the Week 54 visit (September 2021 data cut date).

In addition, the Applicant included a summary of overall LEN exposure from all ongoing and completed studies.

In the NDA resubmissions safety update report, updated cumulative safety data from the first dose of study drug through the safety update data cut date were provided for Studies 4625, 4334, and 5709. For Study 4625, the NDA resubmission safety update data-cut date was in February 2022, after all subjects in both Cohorts 1 and 2 had completed their Week 52 visit (i.e., 52 weeks after their first dose of SC LEN) or prematurely discontinued study drug. In addition, the safety update included safety data from six phase 1 studies with LEN that were not included in the original NDA submissions; these studies are evaluating the safety of SC, intramuscular, and oral LEN in healthy adult subjects. One of the six phase 1 studies (Study GS-US-536-5816 [Study 5816]) is evaluating the safety of SC LEN in combination with two broadly neutralizing anti-HIV-1 antibodies in virologically suppressed adults with HIV-1 infection. The studies providing data for this safety report are listed in [Table 11](#).

Table 11. Studies in the Lenacapavir NDA Resubmissions Safety Update Report

Study	Original NDA Submission Data Cut Date	NDA Resubmission Data Cut Date
Phase 3 studies		
GS-US-200-4625	April 01, 2021 Interim Week 24 analysis, last subject last observation	February 03/07, 2022 Interim Week 52 analysis, last subject last observation ¹
GS-US-200-4334	March 26, 2021 Interim Week 28 analysis, last subject last observation	September 30, 2021 Interim Week 54 analysis, last subject last observation
Phase 1 studies		
GS-US-200-4540	Not included in the original NDA	December 22, 2021
GS-US-200-5709	October 31, 2020 (Cohort 1); February 24, 2021 (Cohort 2)	December 13, 2021
GS-US-200-5710	Not included in the original NDA	December 31, 2021
GS-US-200-5717	Not included in the original NDA	December 31, 2021
GS-US-200-5977	Not included in the original NDA	March 03, 2022
GS-US-536-5816	Not included in the original NDA	March 04, 2022
GS-US-563-6148	Not included in the original NDA	March 02, 2022

Source: Applicant's NDA Resubmission Safety Update, Applicant's Statistical Analysis Plan.

¹ February 03, 2022 was the data cut date for all subjects except one, for whom the data cut date was February 07, 2022.

Abbreviation: NDA, new drug application

For the phase 1 studies, Study 5709 was included in the original NDA submissions; the other studies are newly added to the NDA resubmissions and were not included in the original NDA submissions. The Integrated Summary of Safety submitted for the original NDA submissions included pooled data from Studies 4538 and 5709. Study 4538 and Study 5709 Cohort 3 had completed and final data were used in the original NDA submissions; therefore, there was no new update.

Approach to Assessment of Clinical Trial Data

The review approach for assessment of risk consisted of the evaluation of safety data from Study 4625 and Study 4334 separately, as well as the pooled safety data from phase 1 studies. These

studies were reviewed separately because the studies enrolled different patient populations. Study 4625 enrolled an HTE population, whereas Study 4334 enrolled a treatment-naïve population, and the phase 1 studies enrolled healthy adults. Results of individual studies are highlighted where important differences may have emerged.

Clinical-study data from Studies 4635 and 4334 were independently analyzed using JMP v. 16.2.0, Analysis Studio v. 1.6.0, and JMP Clinical v. 8.0. Additional analyses were provided by the Clinical Data Scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. Prespecified hypothesis testing was not proposed for safety outcomes in Study 4625 or 4334; comparisons are therefore based on descriptive analyses.

Comparisons across arms in Study 4625 were limited because assessment during the randomized portion of the study were limited to the 14-day FMP with only the oral administration of LEN. As a general approach, attribution of events due to LEN comparisons across study arms were derived largely from Study 4334 and selected cohorts from phase 1. For relevance to the proposed SC dosing, study arms that included SC LEN were combined and compared to another active control arm randomized to B/F/TAF. Because the pooled phase 1 data were placebo-controlled in healthy volunteers, comparisons across arms were generally more acceptable for the purpose of assessing contribution of LEN; however, the overall sample size achieved in this analysis was small and duration of follow-up was shorter.

In the Applicant's proposed labeling for LEN, Adverse Reactions (Section 6.1) included only data from Study 4625 as this study included the relevant patient population (HTE) for the proposed indication, whereas Study 4334 included treatment-naïve subjects anticipated to have significant differences in underlying disease severity and comorbid conditions.

7.5. Adequacy of the Clinical Safety Database

Refer to Section 7.5 of the Integrated Review dated February 28, 2022 from the first cycle.

Overall, the safety database is adequate to assess the safety of LEN for the proposed indication, dosage regimen, and patient population (HTE).

At the time of the NDA resubmissions, 1508 subjects were enrolled in clinical studies and received at least one dose of LEN, regardless of route (SC, by mouth, or intravenous), formulation, or population (healthy, PLWH). Excluding subjects who received LEN or LEN placebo for two ongoing blinded studies, the total number of subjects are at least 1272. A total of 797 subjects (healthy, PLWH) have received at least one subcutaneous dose of LEN, and a total of 303 subjects with HIV have received LEN (any route). The total number of PLWH who received one dose of 927 mg SC LEN, with the same proposed SC formulation or equivalent oral dose that is expected to achieve the targeted exposure for at least 6 months, was 195 ([Table 12](#)).

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 12. Number of Subjects With HIV Who Received at Least One Dose of SC LEN at the Proposed Dose/Duration

Study Number	Study Status and Description	Number of SC LEN Subjects
GS-US-200-4334	Ongoing, phase 2, randomized, open-label, active-controlled, multicenter study in treatment-naïve PLWH	103
GS-US-200-4625	Ongoing, phase 2/3, randomized, placebo-controlled, multicenter study in heavily treatment-experienced PLWH	72
GS-US-536-5816	Ongoing, blinded, phase 1b, randomized, two-dose study	20
Total		195

Source: Applicant's Summary of Clinical Safety Addendum (Table 4, p. 88).

Abbreviations: HIV, human immunodeficiency virus; LEN, lenacapavir; PLWH, people living with HIV; SC, subcutaneous

Study 4625 Clinical Safety Experience

The median duration on-study was 84 and 64 weeks for Cohorts 1 and 2, respectively; this period of exposure enabled the review team to identify both early- and late-onset adverse events (AEs). [Table 13](#) summarizes the exposure periods for Study 4625, which is ongoing. A total of 72 subjects in Cohorts 1 and 2 received at least one dose of SC LEN. Safety comparisons between randomized subjects, however, were limited to 36 subjects in Cohort 1 during the 14-day FMP, 24 of whom received oral doses of LEN. During the maintenance phase of Study 4625, during which all subjects received SC LEN:

- Week 26: 70 subjects received a second dose of SC LEN
 - Cohort 1: N=36, Cohort 2: N=34
- Week 52: 53 subjects received a third dose of SC LEN
 - Cohort 1: N=34, Cohort 2: N=19

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 13. Duration of Treatment Exposure, Safety Population, Study 4625 (Week 52 Analysis)

Parameter	Cohort 1			Cohort 2 N=36 n (%)	All Subjects N=72 n (%)
	PBO→LEN N=12 n (%)	LEN N=24 n (%)	All LEN N=36 n (%)		
Duration of treatment, weeks					
Mean (SD)	83.5 (15.4)	86.1 (14.6)	85.2 (14.7)	59.9 (16.6)	72.5 (20.1)
Median (Q1, Q3)	83.6 (74.2, 94.9)	86.6 (77.5, 96.5)	84.4 (76.2, 96)	63.5 (56.3, 68.6)	71.1 (60.3, 86.2)
Minimum, maximum	54.1, 105.6	41.7, 110.6	41.7, 110.6	12.9, 100.6	12.9, 110.6
Total exposure (person-years)	19	40	59	41	100
Patients treated, by duration, n (%)					
<10 Weeks	0	0	0	0	0
≥10 to <16 Weeks	0	0	0	2 (5.6)	2 (2.8)
≥16 to <22 Weeks	0	0	0	0	0
≥22 to <26 Weeks	0	0	0	0	0
≥26 to <36 Weeks	0	0	0	2 (5.6)	2 (2.8)
≥36 to <52 Weeks	0	1 (4.2)	1 (2.8)	0	1 (1.4)
≥52 to <58 Weeks	1 (8.3)	0	1 (2.8)	8 (22.2)	9 (12.5)
≥58 to <64 Weeks	0	0	0	7 (19.4)	7 (9.7)
≥64 to <72 Weeks	2 (16.7)	1 (4.2)	3 (8.3)	14 (38.9)	17 (23.6)
≥72 to <80 Weeks	2 (16.7)	7 (29.2)	9 (25.0)	1 (2.8)	10 (13.9)
≥80 to <88 Weeks	2 (16.7)	3 (12.5)	5 (13.9)	1 (2.8)	6 (8.3)
≥88 to <96 Weeks	2 (16.7)	6 (25.0)	8 (22.2)	0	8 (11.1)
≥96 to <104 Weeks	2 (16.7)	5 (20.8)	7 (19.4)	1 (2.8)	8 (11.1)
≥104 Weeks	1 (8.3)	1 (4.2)	2 (5.6)	0	2 (2.8)

Source: Clinical Data Scientist's review of the adex.xpt and adsl.xpt datasets; software: R.

Exposure duration calculated using treatment duration days (TRTDURD) provided by the Applicant.

Abbreviations: LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PBO, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation

Study 4334 Clinical Safety Experience

[Table 14](#) summarizes the exposure periods for Study 4334, which is ongoing. A total of 157 subjects received at least one dose of LEN, among whom 105 subjects received at least one dose of SC LEN. The median duration on study was 66 weeks for the LEN total group; this period of exposure enabled the review team to identify both early- and late-onset AEs.

Table 14. Duration of Treatment Exposure, Safety Population, Study 4334 (Week 54 Analysis)

Parameter	SC LEN + (F/TAF→TAF) N=52 n (%)	SC LEN + (F/TAF→BIC) N=53 n (%)	SC LEN Total N=105 n (%)	Oral LEN + F/TAF N=52 n (%)	LEN Total N=157 n (%)	B/F/TAF N=25 n (%)
Duration of treatment, weeks						
Mean (SD)	67.5 (17.4)	64.7 (16.9)	66.1 (17.1)	67.5 (17.6)	66.6 (17.3)	70.5 (12.9)
	67	61.3	64.1	68.4	66.3	76.1
Median (Q1, Q3)	(57.4, 81.5)	(56.3, 80.3)	(56.6, 80.6)	(57.5, 81.8)	(57.4, 81.1)	(58.4, 80.4)
Minimum, maximum	9.7, 93.1	8.4, 88.6	8.4, 93.1	10.3, 90.3	8.4, 93.1	38.1, 89.3
Total exposure (person-years)	67	66	133	67	200	34
Patients treated, by duration, n (%)						
<4 Weeks	0	0	0	0	0	0
≥4 to <16 Weeks	2 (3.8)	1 (1.9)	3 (2.9)	1 (1.9)	4 (2.5)	0
≥16 to <28 Weeks	0	1 (1.9)	1 (1.0)	1 (1.9)	2 (1.3)	0
≥28 to <54 Weeks	3 (5.8)	6 (11.3)	9 (8.6)	2 (3.8)	11 (7.0)	1 (4.0)
≥54 to <80 Weeks	29 (55.8)	30 (56.6)	59 (56.2)	30 (57.7)	89 (56.7)	16 (64.0)
≥80 to <90 Weeks	17 (32.7)	15 (28.3)	32 (30.5)	17 (32.7)	49 (31.2)	8 (32.0)
≥90 weeks	1 (1.9)	0	1 (1.0)	1 (1.9)	2 (1.3)	0

Source: Clinical Data Scientist's review of the adex.xpt and adsl.xpt datasets; software: R.

Exposure duration calculated using treatment duration days (LEXP DURD) provided by the Applicant.

Abbreviations: BIC, bicitegravir; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide coformulated tablet; F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with a given treatment duration; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

The demonstrated safety profile of LEN in HTE subjects with MDR HIV-1 infection is acceptable at the proposed doses by mouth and SC. Overall, there is no clear pattern of LEN-related safety issues considered severe or life-threatening (Grade 3 or 4). Deaths were uncommon, and there were no patterns observed among serious adverse events (SAEs). None of the deaths nor SAEs were considered to be study-drug related in Studies 4625 and 4334. A small number of subjects from Studies 4625 and 4334 experienced ISRs resulting in discontinuation of LEN, which is consistent with a long-acting injectable drug.

7.6.1. Safety Findings and Concerns, Studies 4625 and 4334

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Studies 4625 and 4334

An overview of treatment-emergent adverse events (TEAEs) in Study 4625 through at least the Week 52 visit date is shown in [Table 15](#). Overall, 96% of subjects in the total LEN group experienced at least one TEAE.

An overview of the TEAEs in Study 4334 through at least the Week 54 visit date is shown in [Table 16](#). Overall, 88% of subjects in the total LEN group, and 84% of subjects in the B/F/TAF group experienced at least one TEAE.

Across Studies 4625 and 4334, there were no drug-related SAEs, very few discontinuations because of AEs, and very few Grade ≥ 3 AEs considered by the investigator to be study drug-related. Differences in AEs reported across these two studies likely reflect underlying differences in the patient populations.

Table 15. Overview of Treatment-Emergent Adverse Events, Study 4625 (Week 52 Analysis)

Event Category	Total LEN N=72 n (%)
Any treatment-emergent AE ¹	69 (95.8)
Study-drug related TEAE ²	51 (70.8)
Severe or potentially life-threatening TEAE (Grade 3-4) ³	19 (26.4)
Study-drug related TEAE (Grade 3-4) ^{2,3}	5 (6.9)
Death	2 (2.8)
Any SAE	10 (13.9)
Study drug-related SAE ²	0
SAE with fatal outcome	2 (2.8)

Event Category	Total LEN N=72 n (%)
AE leading to discontinuation of study drug	1 (1.4)
AEs leading to dose modification of study drug	0
AE leading to interruption of study drug	0
AE leading to reduction of study drug	0
AE leading to dose delay of study drug	0

Source: Clinical Data Scientist's and Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.

¹ Treatment-emergent AE defined as an AE that began on or after the first dose date of LEN. For participants who discontinued from oral LEN, only AEs collected up to 60 days after the last dose date were considered treatment emergent.

² Relatedness as determined by the investigator.

³ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AE, adverse event; LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 16. Overview of Treatment-Emergent Adverse Events, Study 4334 (Week 54 Analysis)

Event Category	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
Any treatment-emergent AE ¹	95 (90.5)	138 (87.9)	21 (84.0)
Study-drug related TEAE ²	61 (58.1)	69 (43.9)	4 (16.0)
Severe or potentially life-threatening TEAEs (Grade 3-4) ³	7 (6.7)	13 (8.3)	2 (8.0)
Study-drug related TEAE (Grade 3-4) ^{2,3}	1 (1.0)	1 (0.6)	0
Death	0	0	0
Any SAE	6 (5.7)	10 (6.4)	0
Study drug-related SAE ²	0	0	0
SAE with fatal outcome	0	0	0
AE leading to discontinuation of study drug	3 (2.9)	3 (1.9)	0
AE leading to dose modification of study drug	0	0	0
AE leading to interruption of study drug	0	0	0
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0

Source: Clinical Data Scientist's and Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.

¹ Treatment-emergent AE defined as an event that 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.

² Relatedness as determined by the investigator.

³ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Analysis of clinical safety outcomes by demographic subgroups were intentionally not included here because of the small sample sizes anticipated with Studies 4625 and 4334, which would hamper meaningful interpretation of the analyses.

7.6.1.2. Deaths, Studies 4625 and 4334

In Study 4625, one additional death was reported after the Week 26 interim analysis (original NDA submissions); this subject died on Day 568 of hypoxemic respiratory failure and mycoplasma pneumonia. In total from Study 4625, two subjects who received LEN died; none of the events were considered to be study drug-related by the investigators; the clinical reviewer agrees with these assessments. Details of the two deaths are provided in Section [7.6.3.2](#).

There were no deaths reported in Study 4334 by Week 54.

Clinical Reviewer’s Assessment: The one additional death reported in Study 4625 since the original NDA submissions does not represent a new safety concern and does not change the overall safety profile of LEN.

7.6.1.3. Serious Adverse Events, Studies 4625 and 4334

In Study 4625, since the Week 26 interim analysis (original NDA submissions), six additional subjects experienced the following SAEs: coronavirus disease 2019 (COVID-19; two subjects), genital herpes simplex (one subject), pneumonia (one subject), pneumonia mycoplasmal, pancytopenia, dehydration, and acute respiratory failure (one subject), and septic shock, renal impairment, shock (one subject).

In Study 4334, after the Week 28 interim analysis (original NDA submissions), one subject experienced an SAE of uterine leiomyoma (SC LEN + emtricitabine/tenofovir alafenamide coformulated [F/TAF]→tenofovir alafenamide [TAF] group), and one subject experienced an SAE of hepatitis A (LEN + [F/TAF→bictegravir [BIC] group), which is discussed further in Section [7.6.4.6](#).

An overview of all the SAEs in Study 4625 through at least the Week 52 visit dates is shown in [Table 17](#). An overview of the SAEs in Study 4334 through at least the Week 54 visit dates is shown in [Table 18](#). None of the SAEs was considered to be study-drug related in Studies 4625 and 4334. See Section [17.2](#) for additional details.

Clinical Reviewer’s Assessment: Overall, no events were disproportionately reported as SAEs to suggest a pattern. Treatment-emergent SAEs were the most commonly reported within the Infections SOC in Studies 4625 and 4334; however, these SAEs are reflective of the patient population rather than the safety profile of LEN.

Table 17. Treatment-Emergent SAEs by SOC and PT, Study 4625 (Week 52 Analysis)

System Organ Class Preferred Term ¹	Total LEN N=72 n (%)
Any treatment-emergent ² SAE	10 (13.9)
Infections and infestations (SOC)	7 (9.7)
<i>Clostridium difficile</i> colitis	1 (1.4)
COVID-19	2 (2.8)
Pneumonia	1 (1.4)
Genital herpes simplex	1 (1.4)
Pneumonia mycoplasmal	1 (1.4)
Septic shock	1 (1.4)
Gastrointestinal disorders (SOC)	2 (2.8)
Abdominal pain	1 (1.4)
Pancreatic mass	1 (1.4)
Proctalgia	1 (1.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps) (SOC)	2 (2.8)
Anal cancer	1 (1.4)
Anal squamous cell carcinoma	1 (1.4)
Neoplasm malignant	1 (1.4)
Blood and lymphatic system disorders (SOC)	1 (1.4)
Pancytopenia	1 (1.4)

System Organ Class Preferred Term¹	Total LEN N=72 n (%)
Cardiac disorders (SOC)	1 (1.4)
Angina pectoris	1 (1.4)
General disorders and administration site conditions (SOC)	1 (1.4)
Impaired healing	1 (1.4)
Injury, poisoning and procedural complications (SOC)	1 (1.4)
Femoral neck fracture	1 (1.4)
Metabolism and nutrition disorders (SOC)	1 (1.4)
Dehydration	1 (1.4)
Nervous system disorders (SOC)	1 (1.4)
Dizziness	1 (1.4)
Renal and urinary disorders (SOC)	1 (1.4)
Renal impairment	1 (1.4)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (1.4)
Acute respiratory failure	1 (1.4)
Vascular disorders (SOC)	1 (1.4)
Shock	1 (1.4)

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

² A treatment-emergent AE is defined as an AE beginning on or after the first dose date of LEN. Multiple AEs were counted only once per subject for each SOC and PT. Listed in descending order of frequency by SOC.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SAE, serious adverse event; SOC, system organ class

Table 18. Treatment-Emergent SAEs by SOC and PT, Study 4334 (Week 54 Analysis)

System Organ Class Preferred Term¹	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
Any treatment-emergent ² SAE	6 (5.7)	10 (6.4)	0
Infections and infestations (SOC)	5 (4.8)	6 (3.8)	0
Pneumonia	1 (1.0)	1 (0.6)	0
Staphylococcal infection	1 (1.0)	1 (0.6)	0
<i>Escherichia</i> infection	1 (1.0)	1 (0.6)	0
Hepatitis A	1 (1.0)	1 (0.6)	0
Perirectal abscess	1 (1.0)	1 (0.6)	0
<i>Pneumocystis jirovecii</i> pneumonia	0	1 (0.6)	0
Psychiatric disorders (SOC)	1 (1.0)	3 (1.9)	0
Bipolar disorder	0	1 (0.6)	0
Major depression	0	1 (0.6)	0
Mental disorder	0	1 (0.6)	0
Psychotic disorder	0	1 (0.6)	0
Substance-induced psychotic disorder	1 (1.0)	1 (0.6)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC)	2 (1.9)	2 (1.3)	0
Metastases to central nervous system	1 (1.0)	1 (0.6)	0
Non-small cell lung cancer	1 (1.0)	1 (0.6)	0
Uterine leiomyoma	1 (1.0)	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (1.0)	2 (1.3)	0
Dyspnea	1 (1.0)	1 (0.6)	0
Pleural effusion	1 (1.0)	1 (0.6)	0
Pneumothorax	0	1 (0.6)	0
Blood and lymphatic system disorders (SOC)	1 (1.0)	1 (0.6)	0
Lymphadenopathy mediastinal	1 (1.0)	1 (0.6)	0

System Organ Class Preferred Term ¹	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
	Gastrointestinal disorders (SOC)	1 (1.0)	1 (0.6)
Vomiting	1 (1.0)	1 (0.6)	0
Injury, poisoning and procedural complications (SOC)	0	1 (0.6)	0
Poisoning	0	1 (0.6)	0

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

² A treatment-emergent AE is defined as an AE beginning on or after the first dose date of LEN. Multiple AEs were counted only once per subject for each SOC and PT. Listed in descending order of frequency by SOC for total LEN.

Abbreviations: AE, adverse event; B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide (coformulated tablet); LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SAE, serious adverse event; SOC, system organ class

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Studies 4625 and 4334

In Study 4625, after the Week 26 interim analysis (original NDA submissions), one subject (1.4%) in Cohort 1 experienced a nonserious TEAE of injection site nodule (Grade 1) after receiving the Week 52 SC LEN injections, which lead to premature discontinuation of LEN during the Extension Phase (data collected after Week 52). The TEAE of injection site nodule was assessed as related to LEN by the investigator and had not resolved by the data cut date. At the time of the original NDA submission, no subject had prematurely discontinued study drug because of an AE; however, this subject's premature discontinuation was included in the 90-Day Safety Update from the original NDA submissions. See Sections [7.6.3.4](#) and [7.7.2](#).

In Study 4334, after the Week 28 interim analysis (original NDA submissions), one subject in the total SC LEN group experienced nonserious TEAEs of injection site erythema (Grade 1) and injection site swelling (Grade 1) that led to premature discontinuation of LEN. In total, 3 of 105 subjects (2.9%) in the SC LEN total group discontinued study drug due to ISRs (injection site induration [2 subjects], injection site erythema [1 subject], and injection site swelling [1 subject]); all the ISRs were nonserious and Grade 1 in severity. See Section [7.7.2](#).

Clinical Reviewer's Assessment: Nonserious, Grade 1 ISRs were the only AEs that led to the discontinuation of LEN in Studies 4625 and 4334. The LEN labeling includes the one subject from Study 4625 who discontinued LEN because of an AE (Grade 1 injection site nodule); in addition, ISRs are adequately described as adverse drug reactions (ADRs) associated with SC LEN in labeling. See Section [7.7.2](#) for details.

7.6.1.5. Treatment-Emergent Adverse Events, Studies 4625 and 4334

In Study 4625, a TEAE was defined as an AE that began on or after the first dose date of LEN; for participants who discontinued from the oral LEN, only AEs collected up to 60 days after the last dose date were considered treatment emergent. In Study 4334, 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.

A combination of data from Studies 4625 and 4334 were used to assess the general AE profile of LEN. Although details of safety information from Study 4334 will not be presented in the LEN

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

labeling, Study 4334 was important in this assessment because it serves as supplementary support for the safety evaluation of LEN.

In this section, adverse drug reactions (ADRs), or TEAEs considered by the investigator to be related to study drug, are discussed. [Table 19](#) summarizes ADRs occurring in at least 3% of subjects in Study 4625. [Table 20](#) and [Table 21](#) summarize ADRs occurring in Study 4334.

Table 19. ADRs Occurring in at Least 3% of Total LEN Subjects, All Grades, Study 4625 (Week 52 Analysis)

	Total LEN N=72 n (%)
Preferred Term¹	
Any treatment-related AE	51 (70.8)
Any injection site reaction ²	47 (65.3)
Injection site swelling	26 (36.1)
Injection site erythema	22 (30.6)
Injection site pain	22 (30.6)
Injection site nodule	18 (25.0)
Injection site induration	11 (15.3)
Injection site pruritus	4 (5.6)
Nausea	3 (4.2)

Source: Clinical Data Scientist's review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

² Discomfort, erythema, extravasation, hematoma, induration, mass, nodule, edema, pain, pruritus, swelling, or ulcer
 Abbreviations: ADR, adverse drug reaction; AE, adverse event; LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 20. ADRs (Excluding Injection Site Reactions) Occurring in at Least 2% of Total LEN Subjects, All Grades, Study 4334 (Week 54 Analysis)

	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
Preferred Term¹			
Any treatment-related AE	61 (58.1)	69 (43.9)	4 (16.0)
Nausea	6 (5.7)	8 (5.1)	0
Diarrhea	2 (1.9)	4 (2.5)	0
Headache	3 (2.9)	4 (2.5)	0
Dyspepsia	0	0	1 (4.0)
Insomnia	0	0	1 (4.0)
Salivary hypersecretion	0	0	1 (4.0)
Weight increased	0	0	1 (4.0)

Source: Clinical Data Scientist's review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

Abbreviations: ADR, adverse drug reaction; AE, adverse event; B, bicitegravir; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous

Table 21. Adverse Drug Reactions (Only Injection Site Reactions) Occurring in at Least 2% of LEN Subjects, All Grades, Study 4334 (Week 54 Analysis)

Preferred Term ¹	Total SC LEN
	N=103 ² n (%)
Any injection site reaction ³	57 (55.3)
Injection site erythema	28 (27.2)
Injection site swelling	24 (23.3)
Injection site pain	20 (19.4)
Injection site nodule	15 (14.6)
Injection site inflammation	14 (13.6)
Injection site induration	13 (12.6)
Injection site mass	4 (3.9)

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

² Of 105 subjects, 103 received at least one LEN injection.

³ Injection site bruising, erythema, hematoma, induration, inflammation, mass, nodule, pain, paresthesia, pruritis, swelling, warmth
 Abbreviations: LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with adverse event; SC, subcutaneous

Clinical Reviewer's Assessment: ISRs were the most commonly reported ADRs in Studies 4625 and 4334. For the reasons previously discussed, only information from Study 4625 will be presented in the LEN labeling, which includes ADRs reported in ≥3% of subjects. After negotiation with the Applicant, ISRs associated with SC LEN are adequately described in the LEN labeling under Warnings and Precautions, and under ADRs in a subsection titled Injection-Associated Adverse Reactions. See Section 7.7.2 for details.

7.6.2. Laboratory Findings Studies 4625 and 4334

Most laboratory abnormalities in Studies 4625 and 4334 were generally not clinically significant (Grade 1 or 2), and occurred in subjects who had previous underlying conditions (e.g., diabetes), or there was an alternative explanation (e.g., creatine kinase elevation after strenuous activity).

In Study 4625, Grade 3 laboratory abnormalities were reported in 18 (25.0%) of 72 subjects. Grade 4 laboratory abnormalities were reported in 5 (6.9%) of 72 subjects. Grade 3 or 4 abnormalities that occurred in more than two subjects included high creatinine, high fasting glucose, high nonfasting glucose, glycosuria, and proteinuria. The frequency of subjects with Grade 3 or Grade 4 laboratory abnormalities at Week 52 (23 subjects; 31.9%) was similar to Week 26 (19 subjects; 26.4%). See the discussion in Section 7.6.3.6.

In Study 4334, Grade 3 laboratory abnormalities were reported in 26 (16.6%) of 157 subjects who received LEN (the total LEN group) and 6 (24.0%) of the 25 subjects in the B/F/TAF group. Grade 4 laboratory abnormalities were reported in 13 (8.3%) of 157 subjects in the total LEN group and no subjects in the B/F/TAF group. Grade 4 laboratory abnormalities were reported in 13 (8.3%) of 157 subjects in the total LEN group, including the following in more than one subject: high creatine kinase, high alanine aminotransferase (ALT), hyperbilirubinemia, and glycosuria. The frequency of subjects with Grade 3 or Grade 4 laboratory abnormalities at Week 54 (39 subjects; 24.8%) was similar to Week 28 (26 subjects; 16.6%). See the discussion in Section 7.6.4.6.

Trends in vital signs and body weight in Studies 4625 (Week 52 analysis) and 4334 (Week 54 analysis) were also reviewed. 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. In Study 4625, the median (quartile 1, quartile 3) increase in body weight was 1.3 (–2.0, 4.3) kg; only one subject had an ADR of weight increased (Grade 1). In Study 4334, the median increase in body weight was 2.6 (0.2, 6.8) kg and 2.3 (–3.1, 7.3) kg in the total LEN group and the B/F/TAF group, respectively; two subjects receiving LEN had ADRs of weight increased (oral LEN + F/TAF [Grade 1]; SC LEN + [F/TAF→TAF] [Grade 2]), and 1 subject receiving B/F/TAF had an ADR of weight increased (Grade 1).

7.6.3. Safety Findings and Concerns, Study 4625

7.6.3.1. Overall Treatment-Emergent Adverse Event Summary

An overview of TEAEs for Study 4625 was discussed in Section 7.6.1.1. Table 22 lists the TEAEs experienced during the FMP only. One of the limitations of Study 4625 is the lack of a comparator beyond the FMP. Because the two cohorts were not randomized to different regimens during the maintenance period (and all subjects in Cohort 1 received SC LEN following the FMP), comparisons across treatment arms were not expected to provide trends that demonstrate the impact of LEN on safety outcomes (Table 23).

Table 22. TEAEs, FMP Only, Study 4625, Cohort 1 (Week 52 Analysis)

Event Category	FMP LEN + FR	FMP PBO + FR
	N=24 n (%)	N=12 n (%)
Any TEAE ¹	9 (37.5)	4 (33.3)
Study-drug related TEAE	4 (16.7)	1 (8.3)
Severe or potentially life-threatening TEAE (Grade 3-4) ²	0	0
Death	0	0
Any SAE	0	0
AE leading to discontinuation of study drug	0	0
AEs leading to dose modification of study drug	0	0
AE leading to interruption of study drug	0	0
AE leading to reduction of study drug	0	0
AE leading to dose delay of study drug	0	0

Source: Clinical Reviewer; adae.xpt; software, JMP v. 16.2.0.

¹ Treatment-emergent adverse events defined as an AE that began on or after the first dose date of blinded study drug.

² Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 (NIH 2017).

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; FMP, functional monotherapy period; FR, failing regimen; LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 23. TEAEs, Maintenance and Extension Phases, Study 4625 (Week 52 Analysis)

Event Category	Cohort 1 N=36 n (%)	Cohort 2 N=36 n (%)	Total LEN N=72 n (%)
Any TEAE ¹	34 (94.4)	35 (97.2)	69 (95.8)
Study-drug related TEAE ²	24 (66.7)	27 (75.0)	50 (69.4)
Severe or potentially life-threatening TEAE (Grade 3-4) ³	7 (19.4)	12 (33.3)	19 (26.4)
Severe or potentially life-threatening TEAE (Grade 3-4) ^{2,3}	0	5 (13.9)	5 (6.9)
Death	0	2 (5.6)	2 (2.8)
Any SAE	6 (16.7)	4 (11.1)	10 (13.9)
Study drug-related SAE ²	0	0	0
SAEs with fatal outcome	0	2 (5.6)	2 (2.8)
AE leading to discontinuation of study drug	1 (2.8)	0	1 (1.4)
AEs leading to dose modification of study drug	0	0	0
AE leading to interruption of study drug	0	0	0
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0

Source: Clinical Data Scientist's and Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.

¹ TEAEs defined as an AE that began on or after the first dose date of blinded study drug.

² Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

³ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; FMP, functional monotherapy period; FR, failing regimen; LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.3.2. Deaths

After the Week 26 interim analysis (original NDA submissions), one additional death was reported and is summarized below; this death was not considered related to LEN by the investigator. In total, from both cohorts of Study 4625, two subjects (2.8%) who received LEN died ([Table 24](#)).

Subject (b) (6)

This was a 48-year-old female in the United States with an extensive ongoing medical history that included the following: hypertension, asthma, hyperlipidemia, colitis, depression, and esophageal candidiasis. At baseline, HIV-1 RNA was 880 copies/mL and CD4⁺ cell count was 495/ μ L (15.8%). The subject's HIV-1 background regimen included doravirine, BIC, emtricitabine (FTC), and TAF. On Study Day 514, experienced mycoplasma pneumonia (Grade 3, assessed as not related); Study Day 528, developed pancytopenia (Grade 3, assessed as not related); Study Day 543, developed dehydration (Grade 3, assessed as not related); and Study Day 553, developed acute respiratory failure (Grade 5, assessed as not related). The subject died on Day 568 of hypoxemic respiratory failure and mycoplasma pneumonia. Autopsy findings revealed "consolidated lungs with superimposed severe acute bronchopneumonia on pre-existing acute and organizing acute respiratory distress syndrome leading to respiratory failure and sepsis."

Table 24. All Individual Patient Deaths, Safety Population, Study 4625 (Week 52 Analysis)

Subject ID	Age/Sex	Study Day of Death	Cause of Death		LEN- Related: Investigator Assessment	LEN- Related: Clinical Reviewer Assessment
			Preferred Term	Verbatim Term		
(b) (6)	48/F	568	Acute respiratory failure	Acute hypoxic respiratory failure	No	No
(b) (6)	61/M	90	Neoplasm malignant	Cancer	No	No

Source: Clinical Data Scientist's and Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.
 Treatment-emergent adverse events defined as any AE with an onset date on or after the study drug start date.
 Abbreviations: F, female; ID, identifier; LEN, lenacapavir; M, male

7.6.3.3. Serious Adverse Events

Since the Week 26 interim analysis (original NDA submissions), six additional subjects experienced the following treatment-emergent SAEs: COVID-19 (two subjects), genital herpes simplex (one subject), pneumonia (one subject), pneumonia mycoplasmal, pancytopenia, dehydration, and acute respiratory failure (one subject), and septic shock, renal impairment, and shock (one subject). In addition, two subjects in Cohort 1 who had previously experienced treatment-emergent SAEs, experienced additional SAEs of anal squamous cell carcinoma, impaired healing, anal cancer (one subject), and angina pectoris (one subject).

In total, from both cohorts of Study 4625, 10 subjects (13.9% [6 subjects in Cohort 1; 4 subjects in Cohort 2]) who received LEN experienced a treatment-emergent SAE. None of the SAEs was assessed as related to LEN by the investigator. The only treatment-emergent SAE that was reported for more than one subject was COVID-19 (two subjects [2.8%]). All SAEs from Study 4625 are presented in [Table 25](#).

Table 25. Treatment-Emergent Serious Adverse Events, Study 4625 (Week 52 Analysis)

Subject ID	Cohort/ Treatment	Age/ Sex	Preferred Term ¹	Event Onset	LEN-Related: Investigator Assessment
(b) (6)	1/LEN	54/M	Anal cancer	Day 479	No
			Anal squamous cell carcinoma	Day 257	No
			Impaired healing	Day 351	No
			Proctalgia	Day 288	No
	1/PBO→ LEN	54/M	Abdominal pain	Day 77	No
			Angina pectoris	Day 367	No
			<i>Clostridium difficile</i> colitis	Day 240	No
			Pancreatic mass	Day 36	No
	2/LEN	48/F	Acute respiratory failure ³	Day 553	No
			Dehydration	Day 543	No
			Pancytopenia	Day 528	No
			Pneumonia mycoplasmal	Day 514	No
	2/LEN	61/M	Dizziness	Day 38	No
Neoplasm malignant ³			Day 80	No	
1/LEN	24/M	COVID-19	Day 266	No	
1/LEN	68/M	Genital herpes simplex	Day 467	No	
1/PBO→ LEN	55/M	COVID-19	Day 403	No	
2/LEN	34/M	Femoral neck fracture	Day 83	No	
2/LEN	51/F	Renal impairment	Day 221	No	
		Septic shock	Day 177	No	
		Shock	Day 221	No	
1/PBO→ LEN	50/M	Pneumonia	Day 465	No	

Source: Clinical Reviewer's summary of Applicant's Narratives of Serious Adverse Events, Deaths, AE Leading to Discontinuation and Snapshot Failures and analysis (JMP v. 16.2.0) of the adae.xpt dataset.

¹ Coded as Medical Dictionary for Regulatory Activities preferred terms.

² Subjects with a serious adverse event since the Week 26 interim analysis and the Applicant's 90-Day Safety Update.

³ Fatal outcome, as described in Section 7.6.3.2.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; F, female; LEN, lenacapavir; M, male; N, number of subjects in group; n, number of subjects with at least one event; PBO, placebo; SAE, serious adverse event

As discussed in Section 7.6.3.2, two subjects experienced treatment-emergent SAEs that resulted in death. Details of the subjects with additional nonfatal, treatment-emergent SAEs since the Week 26 interim analysis are provided below.

- Subject (b) (6) (Cohort 1), who had previously experienced SAEs, experienced additional SAEs of anal squamous cell carcinoma, impaired healing, and anal cancer. The subject experienced an SAE of proctalgia (Days 288 to 289), considered unrelated to study drug, which was reported in the original submissions, and the additional unrelated SAEs of anal squamous cell carcinoma (Days 257 to 259), impaired healing (Days 351 to 358), and anal cancer (Days 479 to 483) since the original NDA submissions. None of the SAEs were assessed by the investigator as related to LEN.
- Subject (b) (6) (Cohort 1), who had previously experienced SAEs, experienced an additional SAE of angina pectoris. SAEs of pancreatic mass (Day 36, ongoing), abdominal pain (Days 77 to 115), and *Clostridium difficile* colitis (Days 240 to 242) had been reported in the original NDA submission, and were followed by an unrelated SAE of angina pectoris

(Days 367 to 368). The SAE of angina pectoris resolved and was assessed by the investigator as not related to LEN.

- Subject (b) (6) (Cohort 1) experienced an SAE of COVID-19 (Days 266 to 275); this SAE resolved and was assessed by the investigator as not related to LEN. This event was submitted in the Applicant's 90-Day Safety Update and was assessed in the Integrated Review dated February 28, 2022 from the first cycle.
- Subject (b) (6) (Cohort 1) experienced an SAE of genital herpes simplex (Days 467 to 505); this SAE resolved and was assessed by the investigator as not related to LEN.
- Subject (b) (6) (Cohort 1) experienced an SAE of COVID-19 (Days 403 to 423); this SAE resolved and was assessed by the investigator as not related to LEN.
- Subject (b) (6) (Cohort 2) experienced SAEs of septic shock (Days 177 to 197) and renal impairment and shock (both Days 221 to 236); the SAEs resolved and were assessed by the investigator as not related to LEN. These events were submitted in the Applicant's 90-Day Safety Update and were assessed in the Integrated Review dated February 28, 2022 from the first cycle.
- Subject (b) (6) (Cohort 1) experienced an SAE of pneumonia (Days 465 to 467); this SAE resolved and was assessed by the investigator as not related to LEN. This event was submitted in the Applicant's 90-Day Safety Update and was assessed in the Integrated Review dated February 28, 2022 from the first cycle.

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events

Since the Week 26 interim analysis (original NDA submissions), one subject (1.4%) in Cohort 1 experienced a nonserious, LEN-related TEAE of injection site nodule and is described below. At the time of the original NDA submissions, no subject had prematurely discontinued LEN because of a TEAE in Study 4625. The ISR in this subject is detailed below and is also summarized in Section [7.7.2](#).

- Subject (b) (6) (Cohort 1); This was a 56-year-old female in the United States who experienced a nonserious, Grade 1 injection site nodule (reported term: right-sided injection site nodules) on Day 18. On Day 380, after receiving the Week 52 SC LEN injections, the subject experienced a nonserious, Grade 1 injection site nodule (reported term: right abdomen injection site nodules) and discontinued LEN. The injection site nodules were assessed by the investigator as related to LEN and were ongoing as of the data cut date. This subject's premature discontinuation of study drug was included in the 90-Day Safety Update from the original NDA submissions.

7.6.3.5. Treatment-Emergent Adverse Events

[Table 26](#) lists the TEAEs reported only during the FMP in subjects of Cohort 1. Nausea and decreased appetite were the only AEs reported in more than one subject. TEAEs considered by the investigator to be related to study drug (i.e., ADRs) are discussed in Section [7.6.1.5](#).

Table 26. TEAEs Occurring During the FMP, Study 4625, Cohort 1 (Week 52 Analysis)

Preferred Term ¹	FMP LEN + FR	FMP PBO + FR
	N=24 n (%)	N=12 n (%)
Any TEAE	9 (37.5)	4 (33.3)
Nausea	3 (12.5)	0
Decreased appetite	2 (8.3)	0
Abdominal pain	1 (4.2)	0
Abdominal pain lower	1 (4.2)	0
Arthralgia	1 (4.2)	0
Cough	1 (4.2)	0
Diarrhea	1 (4.2)	1 (8.3)
Ecchymosis	1 (4.2)	0
Fatigue	1 (4.2)	0
Flatulence	1 (4.2)	0
Hemoptysis	1 (4.2)	0
Headache	1 (4.2)	0
Myalgia	1 (4.2)	0
Photophobia	1 (4.2)	0
Pyrexia	1 (4.2)	0
Rash	1 (4.2)	0
Rhinitis allergic	1 (4.2)	0
Urinary tract infection	1 (4.2)	0
Vessel puncture site hemorrhage	1 (4.2)	0
Abscess limb	1 (4.2)	1 (8.3)
Fatigue	1 (4.2)	1 (8.3)
Neck pain	1 (4.2)	1 (8.3)
Thrombocytopenia	1 (4.2)	1 (8.3)
Vomiting	1 (4.2)	1 (8.3)

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

Listed in descending order of frequency in the FMP LEN + FR arm.

Abbreviations: AE, adverse event; FMP, functional monotherapy period; FR, failing regimen; LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event; PBO, placebo; TEAE, treatment-emergent adverse event

[Table 27](#) lists the TEAEs occurring at $\geq 5\%$ frequency in Study 4625 (Week 52). The most common TEAEs were ISRs; other frequent non-ISR TEAEs in Study 4625 included diarrhea, nausea, constipation, COVID-19, cough, and pyrexia.

Table 27. Treatment-Emergent AEs Occurring at ≥5% Frequency (All Subjects) in Study 4625 (Week 52 Analysis)

Preferred Term ¹	Cohort 1			Cohort 2	Total
	PBO to LEN N=12 n (%)	LEN N=24 n (%)	All LEN N=36 n (%)	N=36 n (%)	All Subjects N=72 n (%)
Any AE	12 (100)	22 (91.7)	34 (94.4)	35 (97.2)	69 (95.8)
Injection site swelling	4 (33.3)	10 (41.7)	14 (38.9)	14 (38.9)	28 (38.9)
Injection site pain	3 (25.0)	11 (45.8)	14 (38.9)	13 (36.1)	27 (37.5)
Injection site erythema	2 (16.7)	8 (33.3)	10 (27.8)	14 (38.9)	24 (33.3)
Injection site nodule	4 (33.3)	10 (41.7)	14 (38.9)	6 (16.7)	20 (27.8)
Injection site induration	0	2 (8.3)	2 (5.6)	9 (25.0)	11 (15.3)
Diarrhea	2 (16.7)	4 (16.7)	6 (16.7)	4 (11.1)	10 (13.9)
Nausea	1 (8.3)	6 (25.0)	7 (19.4)	3 (8.3)	10 (13.9)
Constipation	2 (16.7)	4 (16.7)	6 (16.7)	3 (8.3)	9 (12.5)
COVID-19	1 (8.3)	3 (12.5)	4 (11.1)	5 (13.9)	9 (12.5)
Cough	3 (25.0)	3 (12.5)	6 (16.7)	2 (5.6)	8 (11.1)
Pyrexia	2 (16.7)	1 (4.2)	3 (8.3)	5 (13.9)	8 (11.1)
Abdominal distension	0	5 (20.8)	5 (13.9)	2 (5.6)	7 (9.7)
Back pain	1 (8.3)	2 (8.3)	3 (8.3)	4 (11.1)	7 (9.7)
Headache	0	2 (8.3)	2 (5.6)	5 (13.9)	7 (9.7)
Arthralgia	0	4 (16.7)	4 (11.1)	2 (5.6)	6 (8.3)
Rash	0	2 (8.3)	2 (5.6)	4 (11.1)	6 (8.3)
Urinary tract infection	0	2 (8.3)	2 (5.6)	4 (11.1)	6 (8.3)
Dizziness	0	3 (12.5)	3 (8.3)	2 (5.6)	5 (6.9)
Fatigue	1 (8.3)	3 (12.5)	4 (11.1)	1 (2.8)	5 (6.9)
Herpes zoster	2 (16.7)	0	2 (5.6)	3 (8.3)	5 (6.9)
Vomiting	1 (8.3)	1 (4.2)	2 (5.6)	3 (8.3)	5 (6.9)
Abdominal pain	1 (8.3)	1 (4.2)	2 (5.6)	2 (5.6)	4 (5.6)
Injection site pruritus	0	2 (8.3)	2 (5.6)	2 (5.6)	4 (5.6)
Insomnia	0	1 (4.2)	1 (2.8)	3 (8.3)	4 (5.6)
Neck pain	3 (25.0)	1 (4.2)	4 (11.1)	0	4 (5.6)
Oral candidiasis	2 (16.7)	1 (4.2)	3 (8.3)	1 (2.8)	4 (5.6)
Pneumonia	2 (16.7)	1 (4.2)	3 (8.3)	1 (2.8)	4 (5.6)
Weight increased	1 (8.3)	1 (4.2)	2 (5.6)	2 (5.6)	4 (5.6)

Source: Clinical Data Scientist Review; adae.xpt; software: R.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; LEN, lenacapavir; N, number of patients in treatment arm; n, number of patients with adverse event; PBO, placebo

7.6.3.6. Laboratory Findings

Most laboratory abnormalities in Study 4625 were generally not clinically significant (Grade 1 or 2), and occurred in subjects who had previous underlying conditions such as diabetes.

In Study 4625, Grade 3 laboratory abnormalities were reported in 15 (21%) of 72 subjects. Grade 4 laboratory abnormalities were reported in 4 (6%) of 72 subjects. Grade 3 and 4 abnormalities that occurred in more than two subjects included high creatinine and high fasting glucose.

Since the Week 28 analysis, Grade 3 laboratory abnormalities were reported for an additional nine subjects (LEN total group: six subjects; B/F/TAF group: three subjects) and Grade 4 laboratory abnormalities were reported for an additional six subjects in the LEN total group. No Grade 4 laboratory abnormalities were reported in the B/F/TAF group. None of these laboratory

abnormalities were clinically relevant, as they were transient, subjects had a medical history of underlying conditions (e.g., diabetes), or there was an alternative explanation (e.g., creatine kinase or aspartate aminotransferase [AST] elevation after strenuous activity).

The laboratory findings in [Table 28](#) reflect postbaseline laboratory abnormalities that will be included in LEN labeling (Grades 3 to 4 occurring in at least 2% of subjects in Study 4625).

Table 28. Treatment-Emergent¹ Grade 3 or 4 Laboratory Abnormalities Reported in ≥2 Subjects, Study 4625 (Week 52 Analysis)

Laboratory Parameter	Cohort 1			Cohort 2	Total
	PBO to LEN N=12 n (%)	LEN N=24 n (%)	All LEN N=36 n (%)	N=36 n (%)	All Subjects N=72 n (%)
Chemistry					
ALT, high	12	24	36	36	72
Grade 1	3 (25.0)	1 (4.2)	4 (11.1)	3 (8.3)	7 (9.7)
Grade 2	0	1 (4.2)	1 (2.8)	1 (2.8)	2 (2.8)
Grade 3	0	0	0	2 (5.6)	2 (2.8)
Grade 4	0	0	0	0	0
AST, high	12	24	36	36	72
Grade 1	1 (8.3)	1 (4.2)	2 (5.6)	3 (8.3)	5 (6.9)
Grade 2	0	0	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	2 (5.6)	2 (2.8)
Creatinine, high	12	24	36	36	72
Grade 1	1 (8.3)	2 (8.3)	3 (8.3)	3 (8.3)	6 (8.3)
Grade 2	3 (25.0)	2 (8.3)	5 (13.9)	5 (13.9)	10 (13.9)
Grade 3	1 (8.3)	4 (16.7)	5 (13.9)	2 (5.6)	7 (9.7)
Grade 4	0	1 (4.2)	1 (2.8)	1 (2.8)	2 (2.8)
Direct bilirubin, high	12	24	36	36	72
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0
Grade 3	0	0	0	2 (5.6)	2 (3.5)
Grade 4	0	0	0	0	0
Glucose, fasting, high	9	20	29	28	57
Grade 1	3 (33.3)	2 (10.0)	5 (17.2)	7 (25.0)	12 (21.1)
Grade 2	0	3 (15.0)	3 (10.3)	5 (17.9)	8 (14.0)
Grade 3	1 (11.1)	1 (5.0)	2 (6.9)	0	2 (3.5)
Grade 4	1 (11.1)	0	1 (3.4)	0	1 (1.8)

Laboratory Parameter	Cohort 1			Cohort 2	Total
	PBO to LEN N=12 n (%)	LEN N=24 n (%)	All LEN N=36 n (%)	N=36 n (%)	All Subjects N=72 n (%)
Urinalysis					
Glycosuria ² (dipstick)	12	24	36	36	72
Grade 1	0	0	0	1 (2.8)	1 (1.4)
Grade 2	0	0	0	0	0
Grade 3	2 (16.7)	1 (4.2)	3 (8.3)	1 (2.8)	4 (5.6)
Proteinuria ² (dipstick)	12	24	36	36	72
Grade 1	3 (25.0)	4 (16.7)	7 (19.4)	10 (27.8)	17 (23.6)
Grade 2	2 (16.7)	1 (4.2)	3 (8.3)	1 (2.8)	4 (5.6)
Grade 3	1 (8.3)	1 (4.2)	2 (5.6)	1 (2.8)	3 (4.2)

Source: Table 15.11.6.4.1.2 in the Applicant's Efficacy and Safety Summary for Study 4625 (Cohort 1 and Cohort 2, Week 52).

¹ A treatment-emergent laboratory abnormality was defined as an increase of at least one toxicity grade from baseline at any time postbaseline (and up to 60 days after the last dose date if subjects discontinue from oral LEN). Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 (NIH 2017). For each laboratory test, the most severe graded abnormality for that test was counted for a subject.

² Highest grade is Grade 3.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; AST, aspartate transaminase; CRCL, creatinine clearance; FR, failing regimen; LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event; PBO, placebo

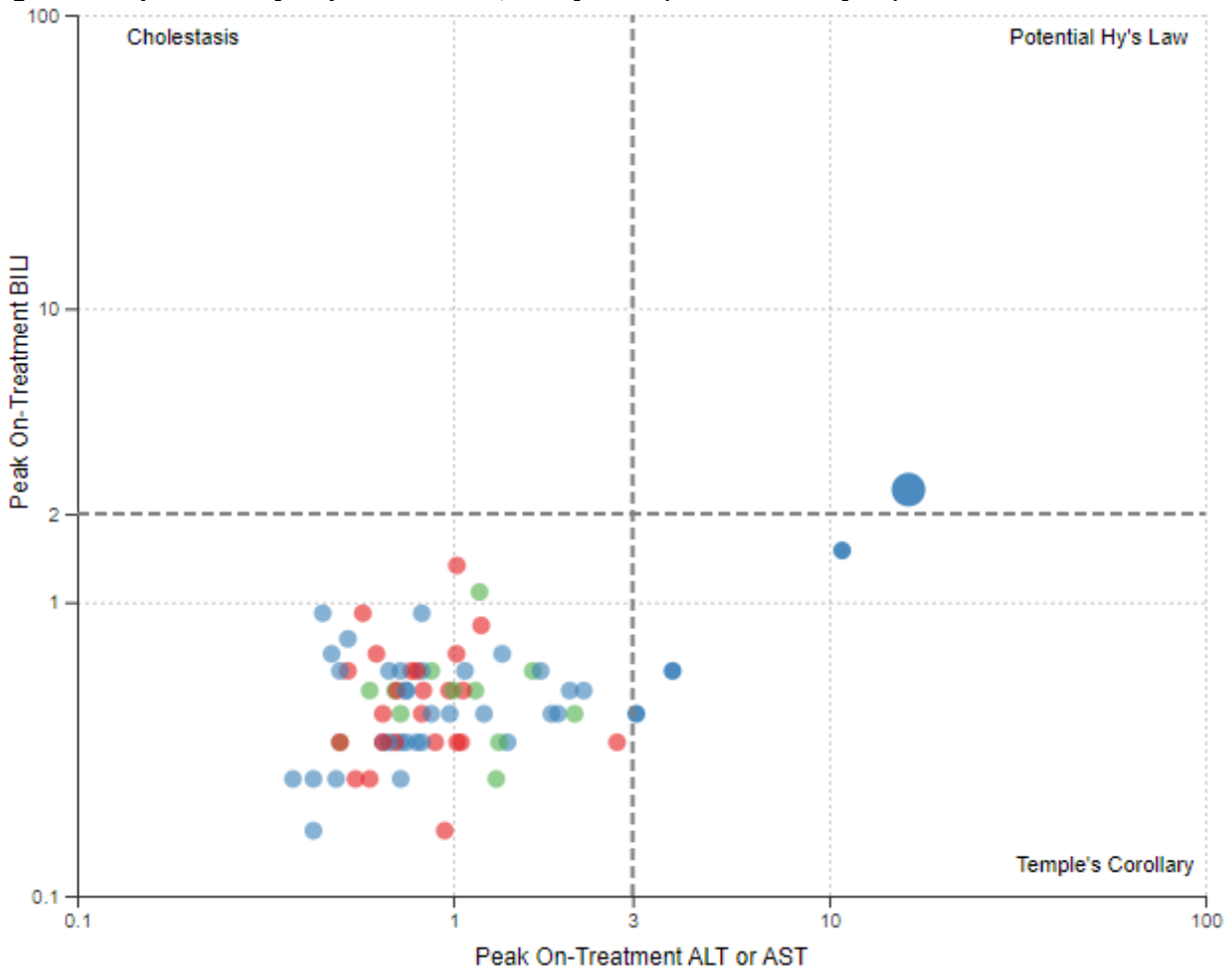
Hepatic Safety

Overall, there were no clinically relevant changes from baseline in ALT, AST, or total bilirubin. Subjects with marked elevations in hepatic transaminases and/or bilirubin were evaluated for potential drug-induced liver injury (DILI). The subjects were reviewed to determine the etiology of the biochemistry elevations. If no other likely causes of DILI could be found, the case could be attributed to LEN.

Overall, two subjects in Cohort 2 (one in the Week 26 interim analysis and the other in the Week 52 interim analysis) each experienced a Grade 3 increase in ALT and a Grade 4 increase in AST. Both subjects had concurrent alternative etiologies and are described below.

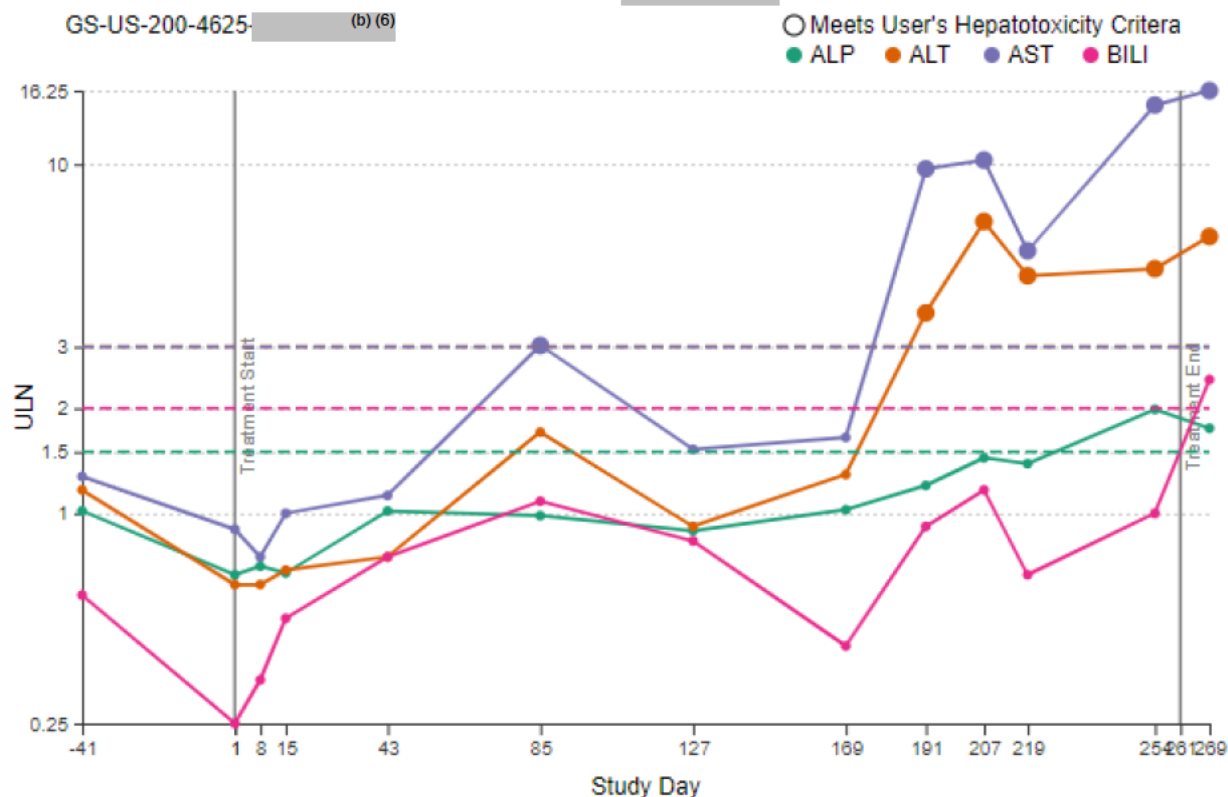
In a screening analysis for DILI from all subjects during Study 4625, one subject ((b) (6)) in Cohort 2 (large blue dot [•] in Figure 5, who was a 27-year-old Asian male, experienced a Grade 4 increase in AST, a Grade 3 increase in ALT, and a Grade 2 increase in total bilirubin; these increases were also reported as one TEAE of alcohol abuse (Grade 3) and three TEAEs of alcoholic hepatitis (Grade 2/3). Laboratory trends are shown in Figure 6. The increases in ALT, AST, and ratio of AST to ALT were not considered related to LEN by the investigator. Although not shown in Figure 6, additional information provided by the Applicant showed improvement in AST, ALT, and total bilirubin when the subject abstained from alcohol while LEN continued. Because of the alternative cause reported, the increases in ALT, AST, and total bilirubin were not considered related to LEN.

Figure 5. Hepatotoxicity Exploration Plot, Study 4625 (Week 52 Analysis)



Source: Clinical Reviewer's analysis, Analysis Studio (adsl.xpt and lb.xpt).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin

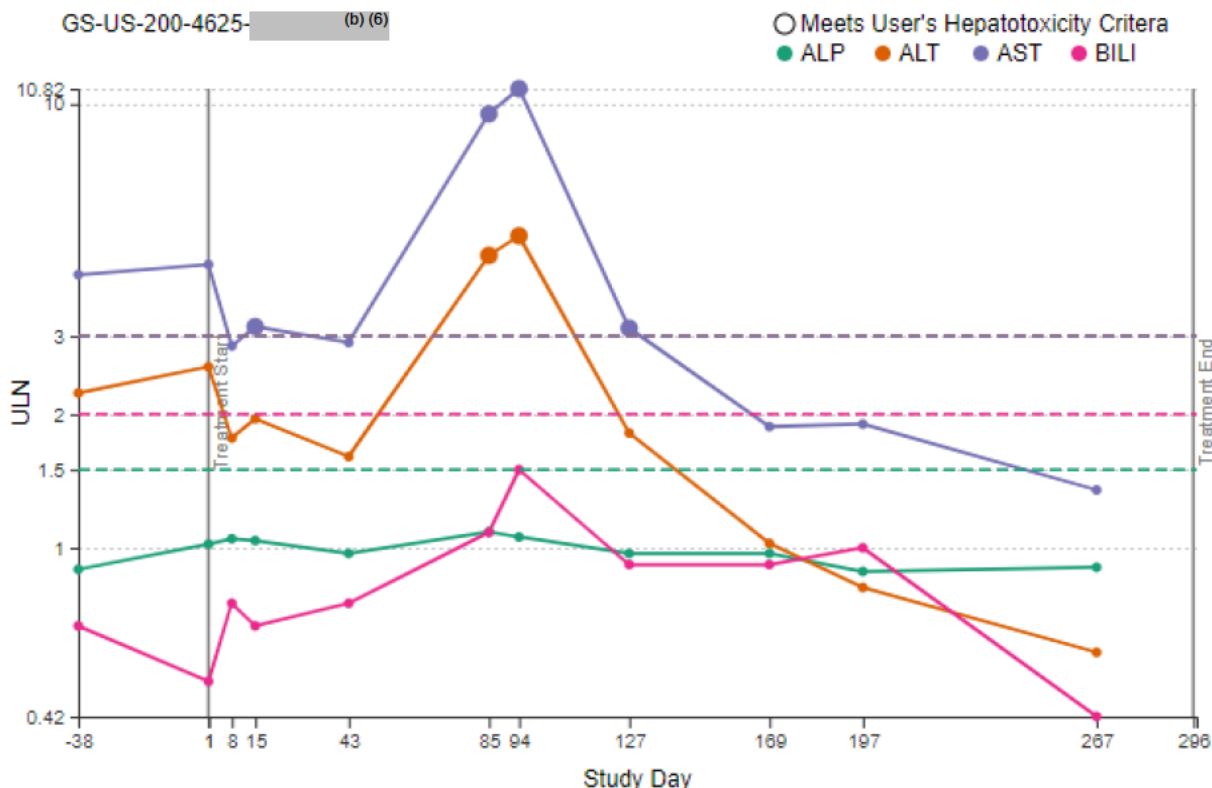
Figure 6. Hepatic Laboratory Values for Subject # (b) (6), Study 4625 (Week 52 Analysis)



Source: Clinical Reviewer's analysis, Analysis Studio (adsl.xpt and lb.xpt).
 Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal

The second subject ((b) (6)) was reviewed in the Week 26 interim analysis (original NDA submissions). This was a 51-year-old Asian female who experienced a Grade 4 increase in AST and a Grade 3 increase in ALT. These increases were also reported as an AE of immune reconstitution inflammatory syndrome associated with an ongoing medical history of chronic hepatitis B. Laboratory trends are shown in [Figure 7](#). Because of the alternative cause reported, these increases in ALT and AST were not considered directly related to LEN.

Figure 7. Hepatic Laboratory Values for Subject # [REDACTED] (b) (6), Study 4625 (Week 52 Analysis)



Source: Clinical Reviewer's analysis, Analysis Studio (adsl.xpt and lb.xpt).
 Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal

7.6.4. Safety Findings and Concerns, Study 4334

7.6.4.1. Overall Adverse Event Summary

An overview of TEAEs for Study 4334 was discussed in Section 7.6.1.1. Serious AEs occurred only in the total LEN group; 10 subjects (6.4%), 6 of whom were randomized to receive SC LEN. TEAEs related to the study drug occurred at a higher frequency in the total SC LEN group than in the oral LEN or B/F/TAF group, primarily because of ISRs.

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 29. TEAEs, Study 4334 (Week 54 Analysis)

Event Category	SC LEN + (F/TAF→TAF)	SC LEN + (F/TAF→BIC)	Oral LEN + F/TAF	Total SC LEN	Total LEN	B/F/TAF
	N=52 n (%)	N=53 n (%)	N=52 n (%)	N=105 n (%)	N=157 n (%)	N=25 n (%)
Any TEAE ¹	50 (96.2)	45 (84.9)	43 (82.7)	95 (90.5)	138 (87.9)	21 (84.0)
Study-drug related TEAE ²	34 (65.4)	27 (50.9)	8 (15.4)	61 (58.1)	69 (43.9)	4 (16)
Severe or potentially life-threatening TEAEs (Grade 3-4) ³	2 (3.8)	5 (9.4)	6 (11.5)	7 (6.7)	13 (8.3)	2 (8.0)
Study-drug related TEAE (Grade 3-4) ^{2,3}	0	1 (1.9)	0	1 (1.0)	1 (0.6)	0
Death	0	0	0	0	0	0
Any SAE	3 (5.8)	3 (5.7)	4 (7.7)	6 (5.7)	10 (6.4)	0
Study drug-related SAE ²	0	0	0	0	0	0
SAEs with fatal outcome	0	0	0	0	0	0
AE leading to discontinuation of study drug	0	3 (5.7)	0	3 (2.9)	3 (1.9)	0

Source: Clinical Data Scientist's and Clinical Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.

¹ Includes treatment-emergent AE defined as events that 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.

² Relatedness as determined by the investigator.

³ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; BIC, bicitegravir; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.4.2. Deaths

No subjects died during Study 4334 as of the Week 54 interim analysis data cut date.

7.6.4.3. Serious Adverse Events

Since the Week 28 interim analysis (original NDA submissions), treatment-emergent SAEs were reported for two additional subjects (1.3%) in the total LEN group; these were uterine leiomyoma (worsening; Days 240 to 249) in one subject in the SC LEN + F/TAF→TAF group, and hepatitis A (Days 572 to 573) in one subject in the SC LEN + F/TAF→BIC group (discussed further in Section 7.6.4.6). An additional subject in the Oral LEN + F/TAF group, who had experienced previous SAEs of concurrent bipolar disorder and major depression (Days 67 to 77), had an additional SAE of mental disorder (Days 534 to 543). None of the SAEs were considered related to LEN by the investigator, and none were disproportionately reported as SAEs to suggest a pattern. None of the subjects in the B/F/TAF group experienced any SAEs.

In total, SAEs were reported in 10 subjects (6.4%) in the total LEN group and none of the subjects in the B/F/TAF group. None of the SAEs were reported in more than one subject in any treatment group, and all SAEs were considered not related to the study drug by the investigator. All SAEs from Study 4334 are presented in [Table 30](#).

Table 30. Treatment-Emergent SAEs, Study 4334 (Week 54 Analysis)

Subject ID	Cohort/ Treatment	Age/ Sex	Preferred Term ¹	Event Onset	LEN-Related: Investigator Assessment
(b) (6)	Oral LEN + F/TAF	46/ Male	<i>Pneumocystis jirovecii</i> pneumonia	27	No
			Pneumothorax	40	No
	Oral LEN + F/TAF	36/ Male	Psychotic disorder	43	No
	Oral LEN + F/TAF	34/ Male	Poisoning	207	No
	SC LEN + (F/TAF→ TAF)	51/ Female	Uterine leiomyoma	240	No
	SC LEN + (F/TAF→ BIC)	26/ Male	<i>Escherichia</i> infection	41	No
			Substance-induced psychotic disorder	89	No
	SC LEN + (F/TAF → BIC)	33/ Male	Perirectal abscess	32	No
	Oral LEN + F/TAF	28/ Male	Bipolar disorder	67	No
			Major depression	67	No
		Mental disorder	534	No	
SC LEN + (F/TAF→ TAF)	29/ Male	<i>Staphylococcal</i> infection	36	No	

Subject ID	Cohort/ Treatment	Age/ Sex	Preferred Term ¹	Event Onset	LEN-Related: Investigator Assessment
(b) (6) 2	SC LEN + (F/TAF→ BIC)	42/ Male	Hepatitis A	572	No
	SC LEN + (F/TAF→ TAF)	40/ Male	Dyspnea	216	No
			Lymphadenopathy mediastinal	216	No
			Pneumonia	216	No
			Vomiting	216	No
			Pleural effusion	217	No
			Non-small cell lung cancer	219	No
			Metastases to central nervous system	229	No

Source: Clinical Reviewer Summary of Applicant's Narratives of Serious Adverse Events, Deaths, AE Leading to Discontinuation and Snapshot Failures.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

² Subjects with a serious adverse event since the Week 28 interim analysis.

Abbreviations: AE, adverse event; BIC, bicitregavir; COVID-19, coronavirus disease 2019; F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); ID, identifier; LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event; SC, subcutaneous; TAF, tenofovir alafenamide

7.6.4.4. Dropouts and/or Discontinuations Due to Adverse Events

Since the Week 28 interim analysis (original NDA submissions), one additional subject in the total SC LEN group experienced TEAEs of injection site erythema and injection site swelling (Days 196 to 206; following the second LEN injection at Week 28) that led to premature discontinuation of study drug; both events were non-serious and Grade 1 in severity. Details of the ISRs in this subject are provided in Section 7.7.2.

In total, three subjects (2.9%) in the total SC LEN group discontinued study drug due to TEAEs that were also ISRs (Table 31). Details of the ISRs in the three subjects are provided in Section 7.7.2.

Table 31. Subjects With AEs Leading to Treatment Discontinuation from Study Drug, Safety Population, Study 4334 (Week 54 Analysis)

Study Arm	Subject ID	Preferred Term	Verbatim Term	SAE	AE Study Day of Onset/Stop	Study Day of Last Dose of Study Drug	Study Day of Discontinuation	Investigator's Assessment of Relatedness
SC LEN Total	(b) (6)	Injection site induration	Injection site induration from SC injection day 15	No	15, 575	602	602	RELATED
SC LEN Total	(b) (6)	Injection site induration	Induration of injection site	No	15, 157	157	157	RELATED

Study Arm	Subject ID	Preferred Term	Verbatim Term	SAE	AE Study Day of Onset/Stop	Study Day of Last Dose of Study Drug	Study Day of Discontinuation	Investigator's Assessment of Relatedness
SC LEN Total	(b) (6)	Injection site erythema	Injection site reaction redness (bilateral)	No	196, 206	399	399	RELATED
		Injection site swelling	Injection site reaction swelling (bilateral)	No	196, 206	399	399	RELATED

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as either: 1) Any AE that began on or after the date of first dose of study drug (subcutaneous lenacapavir treatment groups), or 2) any AE that began on or after the date of first dose of study drug and up to 60 days and 30 days, respectively, after the last dose date or any AE leading to study drug discontinuation (B/F/TAF and oral LEN). SAE defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Abbreviations: AE, adverse event; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); ID, identifier; LEN, lenacapavir; SAE, serious adverse event; SC, subcutaneous

7.6.4.5. Treatment-Emergent Adverse Events

Table 32. Treatment-Emergent Adverse Events Occurring at ≥5% in the Total LEN Population, Study 4625 (Week 54 Analysis)

Preferred Term ¹	SC LEN + (F/TAF→TA F) N=52 n (%)	SC LEN + (F/TAF→BIC) N=53 n (%)	Oral LEN + F/TAF N=52 n (%)	B/F/TAF N=25 n (%)	Total SC LEN N=105 n (%)	Total LEN (N=157) n (%)
	Any AE	50 (96.2)	45 (84.9)	43 (82.7)	21 (84.0)	95 (90.5)
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)
Injection site nodule	9 (17.3)	8 (15.1)	0	0	17 (16.2)	17 (10.8)
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)
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)
Injection site induration	8 (15.4)	5 (9.4)	0	0	13 (12.4)	13 (8.3)
Diarrhea	3 (5.8)	4 (7.5)	5 (9.6)	1 (4.0)	7 (6.7)	12 (7.6)

Preferred Term ¹	SC LEN + (F/TAF→TA F) N=52	SC LEN + (F/TAF→BIC) N=53	Oral LEN + F/TAF N=52	B/F/TAF N=25	Total SC LEN N=105	Total LEN (N=157)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
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)
Depression	1 (1.9)	6 (11.3)	3 (5.8)	1 (4.0)	7 (6.7)	10 (6.4)
Back pain	1 (1.9)	4 (7.5)	4 (7.7)	3 (12.0)	5 (4.8)	9 (5.7)
Oropharyngeal pain	2 (3.8)	4 (7.5)	3 (5.8)	0	6 (5.7)	9 (5.7)
Arthralgia	2 (3.8)	4 (7.5)	2 (3.8)	4 (16.0)	6 (5.7)	8 (5.1)
Fatigue	0	6 (11.3)	2 (3.8)	1 (4.0)	6 (5.7)	8 (5.1)

Source: Clinical Data Scientist's and Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

Abbreviations: AE, adverse event; BIC, bicitegravir; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); COVID-19, coronavirus disease 2019; F/TAF, emtricitabine/tenofovir alafenamide (coformulated tablet); LEN, lenacapavir; SC, subcutaneous; TAF, tenofovir alafenamide

7.6.4.6. Laboratory Findings

Since the Week 28 interim analysis (original NDA submissions), Grade 3 laboratory abnormalities were reported for an additional nine subjects (total LEN group, six subjects; B/F/TAF group, three subjects) and Grade 4 laboratory abnormalities were reported for an additional six subjects in the total LEN group only.

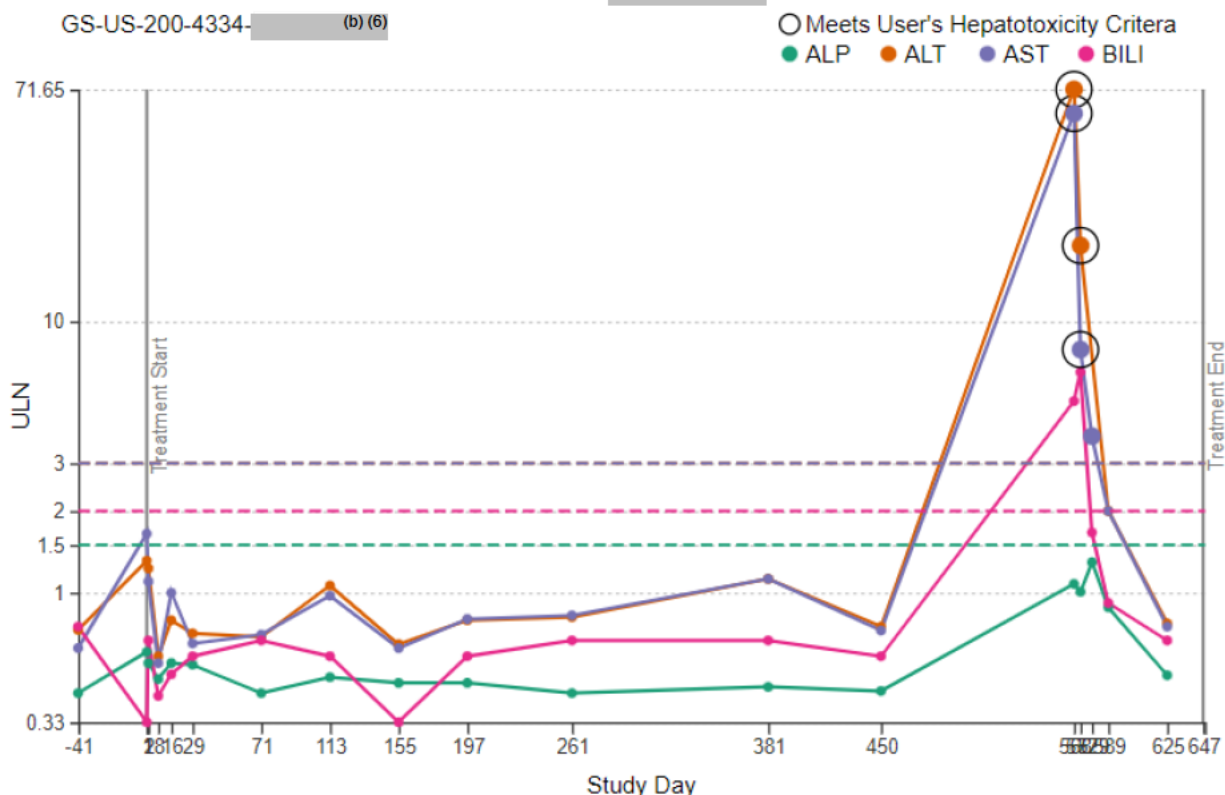
None of these laboratory abnormalities were clinically relevant, as they were transient, subjects had a medical history of underlying conditions (e.g., diabetes), or there was an alternative explanation (e.g., creatine kinase or elevation after strenuous activity).

Hepatic Safety

Subjects with marked elevations in hepatic transaminases and/or bilirubin were evaluated for potential DILI. The subjects were reviewed to determine the etiology of the biochemistry elevations. If no other causes could be found, the case would be attributed to LEN. Since the Week 28 analysis, an additional three subjects experienced Grade 3 or 4 high ALT. Two of the three subjects also experienced high AST, and one of the three subjects also experienced hyperbilirubinemia and had a Grade 3 TEAE of hepatitis A (Subject # (b) (6); [Figure 8](#)). For all subjects, the laboratory abnormalities either improved or returned to normal while on study drug.

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Figure 8. Hepatic Laboratory Values for Subject # [REDACTED] (b) (6), Study 4334 (Week 54 Analysis)



Source: Reviewer's analysis, Analysis Studio (adsl.xpt and lb.xpt).
 Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin;
 ULN, upper limit of normal

7.6.5. Safety Findings and Concerns, Phase 1 Studies Not Submitted in the Original NDA

7.6.5.1. Overall Assessment

No new safety concerns for LEN were identified after reviewing the safety data from the phase 1 studies with LEN that were submitted in the NDA resubmissions safety update (not included in the original NDA submissions). The overall safety profile of LEN remains consistent with those in the original NDA submissions and previous NDA 90-Day Safety Update Report.

7.6.5.2. Deaths

No deaths were reported to the respective NDA resubmission safety update report data cut dates for Studies 5709, GS-US-200-4540 (Study 4540), GS-US-200-5710 (Study 5710), GS-US-200-5717 (Study 5717), GS-US-200-5977 (Study 5977), 5816, or GS-US-563-6148 (Study 6148).

7.6.5.3. Serious Adverse Events

No SAEs were reported through the respective NDA resubmission safety update report data-cut dates for Studies 5709, 4540, 5977, 5816, or 6148.

A single SAE was reported for one subject in each of Studies 5710 and 5717; both events were assessed as not related to study drug by the investigator and are summarized below:

- In Study 5710, Grade 2 cholecystitis (Days 50 to 53) was reported as an SAE for one subject in Cohort 4 with underlying cholelithiasis; the subject received a single 100 mg dose of SC LEN injection on Day 1.
- In Study 5717, Grade 3 back pain (Days 153 to 312) was reported as an SAE for one subject in Cohort 2; the subject received a single 600 mg dose of SC LEN injection on Day 1. The subject had a previous Grade 1 nonserious AE of back pain (Days 70 to 72).

7.6.5.4. Discontinuations Due to Adverse Events

In Study 5709, there were no further premature discontinuations of study drug due to an AE were reported through the NDA resubmission safety update data cut date.

No subject prematurely discontinued study drug because of an AE in any of the Phase 1 studies not included in the original NDA submissions or previous NDA 90-day safety update report.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Resistance Assessments of Virologic Failures (VFs) at Week 52

Issue

The assessment of resistance emergence in VFs of a LEN-containing ARV regimen is critical to interpreting the overall risk-benefit of LEN and understanding the durability of LEN as a component of an ARV regimen in an HTE patient population.

Background

Genotypic and phenotypic analyses of the HIV-1 protease, reverse transcriptase (RT), integrase, and capsid (CA) proteins were performed at screening for all subjects enrolled in Study 4625.

Resistance testing at postscreening timepoints was performed for any subject meeting the criteria of the resistance analysis, which included any subject who received at least one dose of study drug and met one of the following VF criteria:

- HIV-1 RNA ≥ 50 copies/mL and $< 1 \log_{10}$ HIV-1 RNA reduction from the start of oral LEN at the Week 4 visit, confirmed at a scheduled or unscheduled visit at least 2 weeks following Week 4.
- 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 log₁₀ increase in HIV-1 RNA from the nadir, which was subsequently confirmed at the following scheduled or unscheduled visit.
- Any study subject with HIV-1 RNA ≥ 50 copies/mL at the study endpoint or study discontinuation who did not meet any of the criteria above.

Monogram Biosciences, Inc. (South San Francisco, CA, USA) was the designated reference laboratory for all resistance analyses at screening and virologic failure. The PhenoSense GT[®] assay (Monogram Biosciences), which determines the genotype for the entire HIV-1 protease and amino acids 1 to 305 of RT and measures the drug susceptibility of all marketed protease and RT inhibitors based on that sequence, was performed for all subjects at screening. The GeneSeq Integrase assay was used to determine the sequence of the entire IN protein, and the PhenoSense Integrase assay measured the drug susceptibility of all marketed integrase strand-transfer inhibitors (INSTIs) based on that sequence (Monogram Biosciences). In cases of assay failure, alternative assays such as GeneSeq, GenoSure mg, or GenoSure Integrase (Monogram Biosciences) were used to obtain genotypic information.

HIV-1 CA genotype was determined using the GenoSure Gag-Pro assay, which uses next-generation sequencing (NGS) to detect codon variants present at $>10\%$ frequency (Monogram Biosciences). The PhenoSense Gag-Pro assay (Monogram Biosciences) was used to assess phenotypic response to LEN.

The phenotypic susceptibility of screening samples from enrolled subjects to entry inhibitors (enfuvirtide, fostemsavir, ibalizumab, maraviroc) was analyzed at the end of the enrollment period. These analyses were conducted using a combination of the Trofile and PhenoSense Entry assays (Monogram Biosciences), which determine the coreceptor tropism and the susceptibility to the inhibitors, respectively, based on the HIV-1 envelope from the subject's sample.

Assessment

Week 52 Clinical Resistance Emergence

In Study 4625, 31% (22 of 72) met the criteria for resistance analyses through Week 52 (HIV-1 RNA ≥ 50 copies/mL at confirmed VF [suboptimal virologic response at Week 4, virologic rebound, or viremia at last visit]) ([Table 33](#) and [Table 34](#); see also [Table 54](#)). The 22 confirmed VFs had postbaseline CA genotypic resistance data, comprising 11 from Cohort 1 (six in the LEN arm and five in the placebo arm) and 11 from Cohort 2. LEN resistance-associated substitutions in CA emerged in 41% (9 of 22) of the VFs ([Table 33](#) and [Table 34](#)). The LEN resistance-associated CA substitution M66I was observed most frequently in six confirmed VFs (five with HIV-1 subtype B, one with HIV-1 subtype AE), alone or with other substitutions including Q67Q/H, Q67Q/H/K/N, K70K/R, K70N/S, N74D, N74N/H, A105T, and T107A. The other three VFs had emergent LEN resistance-associated CA substitutions Q67K+K70H, Q67H+K70R+T107S, and Q67Q/H. An independent assessment of NGS data was performed and in general, corroborated the genotypic results submitted in the NDA.

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 33. Virologic Failures in Study 4625

Parameter	LEN Functional Monotherapy Cohort 1A n=24	Placebo Functional Monotherapy Cohort 1B n=12	LEN + OBR Cohort 2 N=36
Virologic failures at Week 26	6 (25%)	5 (42%)	8 (22%)
Virologic failures at Week 52	6 (25%)	5 (42%)	11 (31%)
Virologic failure >400 copies/mL	2	4	6
With postbaseline resistance data	6	5	11
Emergent capsid RAS ¹	1	3	5
Emergent CA M66I	1	3	2
Emergent OBR resistance	0	1	3
No active drugs in OBR	0	2	2

Source: FDA Analysis.

¹ M66I, Q67Q/H, Q67K, Q67Q/H/K/N, K70H, K70R, K70K/R, K70N/S, N74D, A105T, T107A, T107S, and T107T/C/S.

Abbreviations: CA, capsid; LEN, lenacapavir; OBR, optimized background regimen; RAS, resistance-associated substitution

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 34. Summary of Resistance Emergence in Virologic Failures, Study 4625, Cohorts 1 and 2

PID	Arm	OBR	Timepoint	HIV RNA Copies/mL	Emergent Capsid RAS	Emergent OBR RAS	Phenotypic Resistance
(b) (6)	LEN	DTG DRV/r TDF	WK10	28,900 Suppressed at WK26	S41A T54M (M66M/I @WK4) K70N/S N74N/H V191V/I R229R/K		LEN AF
	Placebo	DTG DRV/C LAM ENF MVC	WK22	(5440 at WK10) 206 Resuppressed at WK26	S41A H87Q M66I Q67Q/H N74D H87Q A105T		DTG >196 DRV 474 LAM >65 ENF-R MVC-R LEN >1428
	Placebo	DTG DRV FTC TAF IBL	WK52	2970	S41T Q50A M66I A77A/S A105T T107S		DTG 137 DRV 215 FTC >68 TAF 1.1 IBL-R LEN 111
	Placebo	DTG DRV/C RPV TAF FTC	WK52	11,400	M66I N74D A78S A105T	RT: K65R S68N from BL mixtures	DTG 0.91 DRV 0.63 RPV 1.84 FTC >100 TAF 1.74 LEN 1064
	Placebo	DTG LAM IBL MVC	WK26	91	T107A		LEN 0.61
	LEN+OBR	ATV BIC FTC TAF DOR	WK4	424 Resuppressed		PI: M36M/I/V RT: K103K/N M184I/V	DOR 0.21 FTC 28 TDF 0.6 BIC AF ATV 1.2 LEN 1.5
	LEN+ OBR	DTG FTC TAF FTR IBL	WK10	68,100	V11V/I M66M/I Q67Q/H/K/N K70K/R T107T/C/S	PI: V82I/M	DTG AF (BL: 126) FTC AF (BL: >55) TAF AF (BL: 0.7) FTR-R IBL-R LEN 12.2

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	OBR	Timepoint	HIV RNA Copies/mL	Emergent Capsid RAS	Emergent OBR RAS	Phenotypic Resistance
(b) (6)	LEN+ OBR	DRV/C DTG	WK52	28,800	@WK10: A105A/T T107T/N K70H @WK52: Q67K K70H		DRV 1.7 DTG 0.81 LEN 342
	LEN+ OBR	DOR FTR IBL	WK10	6220 Resuppressed	M66I T107A	NNRTI: V106M from mixture	DOR >95 FTR-R IBL-R LEN 239
	LEN+ OBR	DTG DRV BIC FTC TAF	WK4	75,500	H67H K70R T107S		DRV 2.7 DTG 0.81 DOR 104 FTC 3.2 TDF 0.76 IBL-R LEN 15
	LEN+ OBR	DRV/C DTG FTC TDF	WK52	137	T107S	NRTI: K65K/R V106V/M	AF
	LEN+ OBR	DRV/C DTG FTC TAF RPV	WK52	4480	Q67Q/H		LEN 6.6

Source: FDA Analysis.

Bold: Resistance-associated substitutions, resistant phenotype.

¹ Subjects not included as having emergent LEN resistance-associated capsid substitutions because T107A or T107S alone showed no decreased phenotypic susceptibility to LEN.

All subjects had HIV-1 subtype B except Subject (b) (6), who had HIV-1 subtype AE.

Abbreviations: AF, assay failure; ATV, atazanavir; BIC, bictegravir; BL, baseline; DOR, doravirine; DRV, darunavir; DRV/C, darunavir; DTG, dolutegravir; ENF, enfurvitide; FTC, emtricitabine; HIV, human immunodeficiency virus; IBL, ibalizumab; LAM, lamivudine; LEN, lenacapavir; MVC, maraviroc; OBR, optimized background regimen; PID, patient identifier; -R, resistant; RAS, resistance-associated substitution; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; WK, week

In one of the VFs ((b) (6)), the R229R/K substitution was only observed transiently, and its potential role in CA resistance is unknown. Residue R229 is located outside of the LEN-binding site, near the C-terminus of the CA protein. The emergence of S41A from S41T at baseline was seen in VFs (b) (6) and (b) (6), and its role in resistance to LEN is unknown. The S41A substitution alone showed no effect on LEN resistance in cell culture (fold change of 1.2 compared to the wild-type control).

Among the nine VFs who developed LEN resistance-associated substitutions in CA, four ((b) (6)) received LEN in combination with a background regimen with no fully active ARVs based on the baseline genotypic and/or phenotypic resistance and were therefore at a higher risk of developing resistance against the sole active agent, LEN, in their treatment regimen (Table 33 and Table 34). Three VFs ((b) (6)) had a rebound back to baseline level after development of LEN resistance although they were receiving active drugs in their regimen, suggestive of potential treatment adherence issues. The remaining two VFs ((b) (6)) had HIV-1 RNA resuppression with no change in their OBR 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.

Phenotypic analyses of the confirmed VF isolates with emergent LEN resistance substitutions showed 6- to >1428-fold decreases in LEN susceptibility compared to wild-type (Table 34).

Emergence of Resistance Substitutions in Protease, RT, and Integrase

Four virologic failures had emerging resistance substitutions to OBR components (Table 34):

- Subject (b) (6) developed the K103N/S and M184M/I/V RT resistance substitutions while receiving an OBR composed of the non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine along with the INSTI/nucleoside reverse transcriptase inhibitor (NRTI) fixed-dose combination of BIC, FTC, and TAF. This subject met the criteria for resistance analysis due to suboptimal virologic response at Week 4 but was resuppressed to <50 copies/mL by Week 52.
- Subject (b) (6) had the emergent NNRTI-resistance substitution V106M in addition to the LEN resistance substitutions M66I+T107A with doravirine plus FTC and ibalizumab in their OBR.
- Subject (b) (6) had the emergent resistance substitution K65K/R at Week 52 on a regimen including tenofovir disoproxil fumarate (TDF) (darunavir, dolutegravir, FTC, and TDF) as well as the emergent CA substitution T107S.
- Subject (b) (6) had emergent NRTI resistance substitutions K65R and S68N from mixtures at baseline in addition to the LEN resistance substitution M66I with TDF, plus FTC, dolutegravir, darunavir/cobicistat, and rilpivirine in their OBR and had 11,400 copies/mL HIV-1 RNA at Week 52.

The Applicant stated that Subject (b) (6) developed the V82V/A resistance substitution in protease at Week 26 while receiving an OBR including the protease inhibitor darunavir along with the NNRTI doravirine, the NRTIs FTC and TAF, and the INSTI dolutegravir. However, this could not be confirmed in the submitted dataset. The subject was resuppressed to <50 copies/mL at subsequent visits.

NGS Analysis

An independent resistance assessment was performed using the NGS data derived from subjects in Study 4625 who were determined to be VFs. Several CA amino acid substitutions were identified as treatment-emergent among multiple subjects from different genotypes and subgroups who experienced VF, including substitutions at positions M66 (six subjects: five B and one AE), Q67 (five subjects: three B, one BF, and one C), K70 (five subjects: three B, one AE, and one BF), N74 (four subjects: two B, one AE, and one C), A105 (four subjects: three B and one AE), and T107 (two subjects: two B). These treatment-emergent CA substitutions identified in the independent analysis were also reported by the Applicant and the phenotypic data were provided in the NDA submissions.

Conclusion

In Study 4625, 31% (22 of 72) of HTE subjects met the criteria for resistance analyses through Week 52 (HIV-1 RNA $\geq$ 50 copies/mL at confirmed VF [suboptimal virologic response at Week 4, virologic rebound, or viremia at last visit]) and were analyzed for LEN-associated substitution emergence. LEN resistance-associated CA substitutions were found in 41% (n=9) of the confirmed VF subjects with postbaseline CA genotypic resistance data (n=22). The M66I CA substitution was observed in 27% (6 of 22) of subjects, alone or in combination with other LEN resistance-associated CA substitutions, including Q67Q/H, Q67Q/H/K/N, K70K/R, K70N/S, N74D, N74N/H, A105T, and T107A. The other three VFs had emergent LEN resistance-associated CA substitutions Q67K +K70H, Q67H+K70R+T107S, and Q67Q/H. The treatment-emergent CA resistance substitutions were confirmed by FDA independent analyses.

The VF isolates with emergent CA resistance-associated substitutions had reduced LEN susceptibility of 6- to >1428-fold.

Four VF subjects had emergent resistance substitutions to components of the OBR. Additionally, among the nine VFs who developed LEN resistance substitutions in CA, four received LEN in combination with a background regimen with no fully active ARVs based on the baseline genotypic and/or phenotypic resistance. Therefore, given the higher risk of developing resistance to LEN, careful consideration should be given to inclusion of active drugs in addition to LEN in the treatment regimen.

- LEN resistance emerges readily in VFs and thus it is important to use LEN as a component of a complete active ARV regimen.
- LEN resistance substitutions do not confer cross-resistance to other ARVs.

7.7.2. Injection Site Reactions

Issue

ISRs were identified as the most commonly reported ADRs among subjects who received SC injections of LEN; however, long-term experience of subjects after multiple SC injections of LEN was limited in Studies 4625 and 4334.

Background

For other ARVs administered in an injectable form, such as CABENUVA (a long-acting formulation of two drugs, cabotegravir and rilpivirine), ISRs are the most commonly reported ADRs. ISRs associated with intramuscular CABENUVA were most commonly described as localized pain/discomfort (71% to 79% of subjects). The CABENUVA label also includes the following other ISRs: nodules (10% to 17% of subjects), induration (17% to 12% of subjects), swelling (5% to 8% of subjects), erythema (2% to 4% of subjects), pruritus (4% to 5% of subjects), bruising/discoloration (2% to 3% of subjects), and warmth (1% to 2% of subjects). Anesthesia, abscess, cellulitis, and hemorrhage at the injection site were each reported in less than 1% of subjects ([ViiV-Healthcare 2022](#)). Serious postinjection reactions were reported within minutes after the injection of rilpivirine and began to resolve within a few minutes after the injection (<1% of subjects). These reactions were characterized by signs and symptoms including dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and back pain (e.g., back and chest). These events may have been associated with accidental intravenous administration during the intramuscular injection procedure ([ViiV-Healthcare 2022](#)).

Injection site nodules have been reported with a number of other drug classes, including glucagon-like peptide 1 receptor agonists used for treatment of patients with type 2 diabetes. General ISRs (e.g., erythema, pain, or rash) have been reported with all commercially available glucagon-like peptide 1 receptor agonists (i.e., exenatide, lixisenatide, liraglutide, dulaglutide, and semaglutide) ([Hearn and Sherman 2021](#)). Injection site nodules have rarely been described with other long-acting or extended-release drug products, such as exenatide. Although the mechanism for development of such nodules is not entirely clear, available histopathology data reveal the presence of eosinophils and granuloma at these sites, and therefore, hypersensitivity to the formulation is a plausible mechanism ([Jones et al. 2015](#)). Surgical excision or some other medical intervention, such as serial intralesional corticosteroid injections, may be required for treatment of persistent lesions.

LEN is a CA inhibitor with not only a new mechanism of action but also unique, albeit not fully understood, physical properties when injected (b) (4)

Assessment

ISRs were the most commonly reported ADRs with SC LEN injections. Preferred terms related to ISRs in Studies 4625 and 4334 are listed in [Table 35](#). Injection site swelling, erythema, pain, nodule, and induration were the most frequently (>10%) reported preferred terms. None of the ISRs was considered serious.

- In Study 4625, 47 of 72 (65.3%) subjects experienced ISRs assessed as related to SC LEN; most ISRs were Grade 1 or 2 in severity. Three subjects (4.2%) experienced nonserious, Grade 3 ISRs that were considered by the investigator to be related to SC LEN and are described below:
 - Subject (b) (6) experienced two Grade 3 ISRs: “bilateral swelling at injection site max diameter cm 10” reported on Day 16 and ending on Day 19 (Injection site swelling); “bilateral redness at the injection site max diameter cm 10” reported on Day 16 and ending on Day 23 (Injection site erythema).

- Subject (b) (6) experienced two Grade 3 ISRs: “pain at injection site (1st)” on Day 16 and ending on Day 16 (Injection site pain); “pain at injection site (2nd)” on Day 16 and ending on Day 16 (Injection site pain).
- Subject (b) (6) experienced five Grade 3 ISRs: “injection site redness” on Day 380 and ending Day 394 (Injection site erythema); “injection site redness” on Day 380 and ending Day 394 (Injection site erythema); “injection site pain bilateral” on Day 380 and ending Day 394 (Injection site pain); “swelling dx injection site” on Day 380 and ending Day 394 (Injection site swelling); “swelling sx injection site” on Day 380 and ending Day 394 (Injection site swelling).
- One subject (1.4%) reported nonserious, Grade 1 injection site nodules that led to SC LEN discontinuation and is described below:
 - Subject (b) (6) experienced two Grade 1 ISRs: “right sided injection site nodules” reported on Day 18 and are ongoing (*Injection site nodule*); “right abdomen injection site nodules” on Day 380 and are ongoing (*Injection site nodule*).
- In Study 4334, 57 of 103 (55.3%) of subjects who received SC LEN experienced ISRs assessed as related to SC LEN; most ISRs were Grade 1 or 2 in severity. One subject (1.0%) experienced a nonserious, Grade 3 ISR that was considered by the investigator to be related to SC LEN and is described below:
 - Subject (b) (6) experienced one Grade 3 ISR: “injection site nodule” reported on Day 194 and is ongoing (*Injection site nodule*).
- Three subjects (2.9%) in Study 4334, all in the SC LEN + (F/TAF→BIC) group, reported ISRs that led to SC LEN discontinuation.
 - Subject (b) (6) experienced one Grade 1 ISR: “injection site induration from SC injection Day 15” on Day 15 and is ongoing (*Injection site induration*).
 - Subject (b) (6) experienced one Grade 1 ISR: “induration of injection site” on Day 15 and is ongoing (*Injection site induration*).
 - Subject (b) (6) experienced two Grade 1 ISRs: “injection site reaction redness (bilateral)” reported on Day 196 and ending Day 206 (*Injection site erythema*); “injection site reaction swelling (bilateral)” on Day 196 and ending Day 206 (*Injection site swelling*).

Table 35. LEN-Related Injection Site Reactions, Studies 4625 (Week 52 Analysis) and 4334 (Week 54 Analysis)

Preferred Term ¹	Study 4625	Study 4334
	Total LEN N=72 n (%)	Total SC LEN N=103 n (%)
Any injection site reaction	47 (65.3)	57 (55.3)
Injection site swelling	26 (36.1)	24 (23.3)
Injection site erythema	22 (30.6)	28 (27.2)
Injection site pain	22 (30.6)	20 (19.4)
Injection site nodule	18 (25.0)	15 (14.6)
Injection site induration	11 (15.3)	13 (12.6)
Injection site pruritus	4 (5.6)	1 (1.0)
Injection site extravasation	2 (2.8)	0
Injection site mass	2 (2.8)	4 (3.9)
Injection site discomfort	1 (1.4)	0
Injection site hematoma	1 (1.4)	1 (1.0)
Injection site edema	1 (1.4)	0
Injection site ulcer	1 (1.4)	0
Injection site bruising	0	1 (1.0)
Injection site granuloma	0	0
Injection site paresthesia	0	1 (1.0)
Injection site warmth	0	1 (1.0)

Source: Clinical Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.

¹ Listed in descending order of frequency by preferred term for total LEN.

Abbreviations: LEN, lenacapavir; SC, subcutaneous

The durations of ISRs by specific preferred terms in Studies 4625 and 4334 are summarized in [Table 36](#). The durations of induration and nodules were much longer (approximately 3 to 12 months) than other injection site reactions (e.g., erythema, pain and swelling; approximately <1 to 3 weeks).

Table 36. LEN-Related Injection Site Reaction Duration, Studies 4625 (Week 52 Analysis) and 4334 (Week 54 Analysis)

Preferred Term ¹	Study 4625	Study 4334
	Total LEN Median Duration (Q1, Q3); Range	Total SC LEN Median Duration (Q1, Q3); Range
Injection site nodule	253 days (111, 365); 3-727	195 days (117, 310); 14-550
Injection site induration	112 days (36, 227); 3-655	202 days (101, 361); 4-561
Injection site swelling	11 days (5, 16); 1-71	11 days (6, 29); 1-550
Injection site erythema	5 days (3, 8); 1-58	5 days (2, 11); 1-92
Injection site pain	3 days (2, 5); 1-58	4 days (1, 9); 1-178

Source: Clinical Reviewer's analysis (JMP 16.2.0) of the adae.xpt dataset.

¹ Coded as Medical Dictionary for Regulatory Activities Preferred Terms.

Abbreviations: LEN, lenacapavir; Q1, first quartile; Q3, third quartile; SC, subcutaneous

The ISRs included in the following section from Study 4625 reflect those that will be included in labeling. Further analyses of ISRs from Studies 4624 and 4334 can be found in [Section 17.4](#).

In Study 4625, 18 subjects (25.0%) experienced injection site nodules assessed as related to SC LEN, and 11 subjects (15.3%) experienced injection site indurations assessed as related to SC LEN; all events were Grade 1 or 2 in severity. Because the longest available follow-up information was after the first SC LEN injections, the review team focused on resolved and

ongoing injection site nodules and injection site indurations reported as a result of the first SC LEN injections as follows (if a subject had more than one injection site induration or nodule event, the subject was counted in the ongoing category; [Table 37](#)):

- Subject-level analysis:
 - Nodules
 - Ongoing: 7 of 16 subjects (43.8%); resolved: 9 of 16 subjects (56.3%)
 - Indurations
 - Ongoing: 1 of 8 subjects (12.5%); resolved: 7 of 8 subjects (87.5%)
- Event-level analysis:
 - Nodules
 - Ongoing 7 of 23 events (30.4%); resolved: 16 of 23 events (69.6%)
 - Indurations
 - Ongoing 1 of 8 events (12.5%); resolved: 7 of 8 events (87.5%)

Table 37. LEN-Related Injection Site Nodules and Indurations After the First Injection, Study 4625 (Week 52 Analysis)

Parameter	Study 4625 Total LEN
Subjects who received at least one injection	72
Injection site indurations	
Subjects with injection site indurations after first injection, n (%)	8 (11.1)
Subjects with ongoing indurations after first injection, n (%)	1 (1.4)
Mean duration (SD); ongoing (days)	655
Median duration; ongoing (IQR) (days)	655
Minimum, maximum; ongoing (days)	N/A
Subjects with resolved indurations after first injection, n (%)	7 (9.7)
Mean duration (SD); resolved (days)	105 (97)
Median duration; resolved (IQR) (days)	70 (15, 196)
Minimum, maximum; resolved (days)	3, 252
Injection site nodules	
Subjects with injection site nodules after first injection, n (%)	16 (22.2)
Subjects with ongoing nodules after first injection, n (%)	7 (9.7)
Mean duration (SD); ongoing (days)	494 (174)
Median duration; ongoing (IQR) (days)	552 (337, 624)
Minimum, maximum; ongoing (days)	181, 680
Subjects with resolved nodules after first injection, n (%)	9 (12.5)
Mean duration (SD); resolved (days)	204 (188)
Median duration; resolved (IQR) (days)	148 (70, 334)
Minimum, maximum; resolved (days)	41, 727

Source: Clinical Reviewer's analysis (JMP v. 16.2.0) of the adae.xpt dataset.

Study drug-related AE is defined as an adverse event marked as *Related* on the adverse event electronic case report form.

Abbreviations: AE, adverse event; IQR, interquartile range; LEN, lenacapavir; N/A, not applicable; SC, subcutaneous; SD, standard deviation

Nodules and indurations were seen commonly across studies in the development program, affecting subjects in a generally similar way to that seen in the pivotal Study 4625 (nodules [25%], indurations [15%]); nodules and indurations generally persisted longer than other ISRs.

Review of the Applicant's nonclinical data for LEN, clinical data for LEN, and clinical data of other approved ARVs did not identify a clear association between high formulation pH and duration of nodules and indurations. The Division of Dermatology and Dentistry (DDD) was previously consulted during the first cycle, and DDD was reconsulted for the NDA resubmissions to review and assess the Applicant's Cumulative Review of Injection Site Reactions, including the Applicant's assessment of high pH formulations and ISRs, and to provide recommendations for the communication of ISRs in the LEN labeling.

During the review of the original NDA submissions, photographic documentation of injection site indurations or injection site nodules from Studies 5709, 4334, and 4625 were provided in response to the Agency's information request dated September 08, 2021. Refer to Section 7.7.2 of the Integrated Review dated February 28, 2022 from the first cycle. During the first cycle, DAV requested that the Applicant obtain human histopathology (e.g., punch biopsy), and specimens should be examined by an independent dermatopathologist where clinically indicated, at the discretion of an independent dermatologist. Investigators had generally described most induration and nodules similarly as palpable with elongated shape, not painful, and not associated with any redness. Nodules were more visible in subjects who were leaner with little fat tissue in the abdomen. The maximum size for the majority of injection site nodules and indurations was approximately 1 to 4 cm.

In the initial second cycle NDA resubmissions, no additional photographic reports from Study 5709, 4334, or 4625 were included. The Applicant reported that although a few investigators were contacted regarding ongoing injection site nodules or injection site indurations, the investigators did not refer the study subjects for dermatological consultations because the ISRs had resolved or were not warranted. See Section [17.4.2](#) for additional information.

Due to the concern about ISRs during the second cycle review, the Quality Assessment team requested additional assessment of the vial compatibility. Although there was no evidence of glass incompatibility of the LEN formulation with the proposed aluminosilicate glass vials,

 (b) (4)
Please refer to Section [9](#) and the Integrated Quality review, for additional details. To further evaluate the potential risk of  (b) (4) particulates, DAV requested additional information from the Applicant.

In response to an information request dated November 29, 2022, the Applicant provided updated photographic documentation, biopsy reports, and independent dermatologist assessments of injection site indurations or nodules between June 15, 2022 and November 29, 2022, for participants who had AEs of ISRs related to SC LEN administered from borosilicate vials that are Grade 3 or higher, or did not resolved within 24 weeks from a LEN injection. Photographic documentation was provided for two subjects in Study 4625; however, the investigators did not note the exact location of the injection site nodule or induration. No additional photographic documentations of injection site indurations or nodules were available from the following: Study 4334, phase 3 HIV-1 prevention studies, or phase 1 studies. The Applicant received dermatologist assessments without biopsy for two subjects, and biopsy reports (with or without dermatologist assessment) for eight subjects who had ISRs that were not resolved within 24 weeks from LEN treatment and prevention clinical programs ([Table 38](#)). Of note, none of the 10 subjects discontinued LEN. See Section [17.4.2](#) for additional information.

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Table 38. Available Biopsy Reports and Dermatology Evaluations for Subjects in Studies With Subcutaneous LEN Who Met the ISR Criteria for Dermatological Assessment (Between June 15, 2022 and November 29, 2022)

Subject ID	Injection Site Reaction	Study Biopsy Grade	Day Performed	Biopsy	Summary of Biopsy/Dermatology Evaluation Report
Study GS-US-200-4625 (CAPELLA)					
(b) (6)	Injection site nodule	1	15	Yes	- Granulomatous foreign body reaction in adipose panicle - Fatty tissue necrosis changes - Findings compatible with clinical orientation of foreign body panniculitis
	Injection site induration	2	204	No	Dermatology evaluation: area is palpable; no erythema or swelling observed
	Injection site nodule	1	15, 215	No	Dermatology evaluation: abdominal injection scars; 4 subcutaneous indurations were found, 2 on each side of abdomen
Study GS-US-200-4334 (CALIBRATE)					
(b) (6)	Injection site swelling	1	561	Yes	- Focal dermal fibrosis; findings could represent the edge of an old rupture cyst or folliculitis - Focal areas of granulomatous inflammation surrounding small collections of amorphous material - Findings consistent with a granulomatous reaction to the injected medication
	Injection site nodule	1	380	Yes	- Subcutaneous nodules of the periumbilical region; apparent on deep palpation of skin - No tenderness upon palpation - No overlying skin changes - No granulomatous inflammation of foreign body reaction - No evidence of panniculitis - No birefringent material is identified with polarized light
	Injection site nodule	1	463	Yes	- Fibrosis and giant cell reaction, subcutaneous; compatible with injection site reaction - Polarizable foreign material not seen in association with the reaction

Subject ID	Injection Site Reaction	Study Biopsy Grade	Biopsy Day Performed	Summary of Biopsy/Dermatology Evaluation Report
Study GS-US-412-5624 (PURPOSE 1, for HIV PrEP)				
(b) (6)	Injection site nodule	1	7 Yes	- Multiple levels of the biopsy were examined and showed occasional inflammatory cells within the dermis - No evidence of a foreign body reaction
(b) (6)	Injection site nodule	1	1 Yes	- Epidermis showed no evidence of ulceration - Deeper subcutis showed evidence of a foreign body giant cell response - Amorphous eosinophilic material present and surrounded by a foreign body giant cell response
(b) (6)	Injection site nodule	1	1 Yes	- Evidence of a prominent foreign body type reaction in the deep subcutis - Amorphous eosinophilic material also present with an associated foreign body type giant cell response
Study GS-US-536-5816 (Phase 1b, LEN + broadly neutralizing antibodies)				
(b) (6)	Injection site nodule	1	3 Yes	- Dermatopathology report from biopsies at two different injection sites showed deep dermal multinucleated giant cell reaction with associated amphophilic material; suggestive of injection site reaction - Polarizable foreign material not seen in either part - Increased eosinophils to suggest a drug reaction or dermal hypersensitivity reaction not seen

Source: Applicant's Response to FDA Information Request dated November 29, 2022.

Abbreviations: HIV, human immunodeficiency virus; ID, identifier; ISR, injection site reaction; LEN, lenacapavir; PrEP, pre-exposure prophylaxis

In Study 4625, a total of three subjects had biopsies performed. Two of the three subjects (injection site induration and injection site nodule) had biopsies that were consistent with foreign body granuloma, and the third subject (injection site nodule) likely had secondary amyloidosis associated with SC injections of enfuvirtide ([Table 53](#) in Section [17.4.2](#) for additional detail).

In Study 4334, a total three subjects had biopsies performed. Two of the three subjects (injection site swelling and injection site nodule) had biopsies that were consistent with foreign body granuloma.

The Applicant provided their assessment on the role of physical and chemical characteristics of LEN on ISRs; this included an assessment of nonclinical and clinical data for LEN and other ARVs. In summary, the Applicant stated that their review of ISRs and pH for various SC ARVs as well as other LEN formulations did not identify a clear association between high pH of a formulation and ISRs. The Applicant states that their available nonclinical data suggest that chronic granulomatous inflammation and foreign body response at the SC injection site are expected to occur due to the presence of a SC drug depot, and irrespective of the pH of the formulation. Finally, the Applicant believes that the ISRs observed in clinical studies with SC LEN, including nodules and indurations, are likely associated with the expected host foreign

body response to the presence of a SC LEN drug depot, and not because of the potential presence of (b) (4) particulate matter.

On December 14, 2022, the Applicant responded to another request for information regarding any available information of ISRs. Additional follow-up was presented through Week 80 of Study 4334, Week 26 of Study GS-US-536-5816 (phase 1b, LEN + broadly neutralizing antibodies), and Week 8 of Study GS-US-412-5624 (LEN for PrEP in cisgender women). Overall, the findings were consistent with prior assessments as discussed above. In the Week 80 analysis of Study 4334, there were no new Grade 3 or higher ISRs reported. One additional subject discontinued due to an ISR (induration, Grade 1); making a total of 4 subjects that discontinued due to a LEN-related ISR.

Conclusion

ISRs can be characterized as having a short-term phase lasting a few days (e.g., pain, swelling, and erythema) or a long-term phase (e.g., indurations and nodules), some of which were still resolving over a period of weeks to months. Indurations and nodules were generally described as palpable and elongated (1 to 4 cm), not painful, and not associated with any erythema. Nodules were more visible in subjects who were leaner with little fat tissue in the abdomen. Several subjects in Study 4625 had indurations or nodules that had not fully resolved at the time of the interim data cut dates. Overall, it appears nodules tend to resolve more slowly than indurations; however, there may be overlap in choice of preferred terms used by investigators that could also be characterized similarly by terms such as “mass” or “granuloma”. Due to the lack of understanding of the histopathology at the injection sites in patients who experienced longer times to resolution of indurations and nodules, and the relationship with the unique properties of the drug product solution, it is unclear what is driving persistence in some subjects. Given the concern about the incompatibility of LEN with the borosilicate glass, compatibility with the (b) (4) was further evaluated. The available nonclinical and clinical data do not support that the presence of particulates are responsible for the development or persistence of ISRs. The available dermatopathology has revealed expected responses to foreign body that are also expected from the presence of the SC LEN drug depot.

Overall, DDD agrees with the Applicant’s assessment, that ISRs most likely the result of the presence of the drug depot, and the proposed labeling describing ISRs, including injection site nodules and indurations. In addition, DDD continues to recommend that human histopathology (e.g., punch biopsy) be obtained in ongoing or future clinical trials; the presence of findings such as necrosis, hypersensitivity, granulomas, foreign bodies, fibrous tissue, etc. can aid in understanding the pathophysiology of nodule formation. Additionally, where possible, injection site nodules should be followed to resolution or stabilization. Please also refer to the DDD Memorandum completed November 18, 2022 for additional details.

During the initial exchange of updates to the draft labeling in the first cycle for LEN, DAV requested additional description of ISRs similar to the presentation in the Cabenuva labeling ([ViiV-Healthcare 2022](#)), with the additional description of nodules and induration and details of time to resolution provided as a separate subsection entitled “Injection-Associated Adverse Reactions” in Section 6 (Adverse Reactions) of the proposed label. During the NDA resubmissions, a similar exchange of updates to the draft labeling for LEN occurred. Initially, DAV requested the additional description of ongoing and resolved injection site nodules and

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indurations, including the time to resolution in Section 6 (Adverse Reactions). Later in the review cycle, DAV requested the addition of ISRs in Section 5 (Warnings and Precautions) to address the concern of persistent injection site nodules and indurations. The Product Quality team has also recommended that the provider carefully inspect the syringe after withdrawing the LEN solution from the vial for visible particulates.

Based upon our assessment of the available data, including the addendum submitted by the Applicant on December 14, 2022, the potential of risk of ISRs associated with SC LEN do not outweigh the benefit for the treatment of MDR HIV-1 infection in HTE subjects with the appropriate labeling as mentioned above. From a clinical safety perspective, however, additional information is needed to fully understand if there are any contributing factors of injection site reactions with LEN, particularly for subjects who have prolonged resolution with nodules and indurations. The Clinical team has recommended a PMR to assess the completion of long-term follow-up of ISRs in Studies 4625 and 4334, and the Product Quality team has recommended postmarketing commitments (PMCs) to further assess vial and (b) (4) compatibility, and evaluate an alternative device for withdrawing the LEN injection from the vial.

8. Therapeutic Individualization

Please refer to the Clinical Pharmacology review in Section 8 of the Integrated Review dated February 28, 2022 from the first cycle. No additional data were submitted in this review cycle.

9. Product Quality

NDA 215973 and 215974 were found to be approvable from a drug product perspective. Please refer to the summary of the Product Quality review in Section 9 of the Integrated Review dated February 28, 2022 from the first cycle. The summary of the second cycle Product Quality review is provided below. Please also refer to the Integrated Quality Reviews for additional detail.

NDA 215973

Summary

NDA 215973 is recommended for approval from the product quality perspective. Lenacapavir (LEN) Injection, 309 mg/mL is a sterile, preservative-free, yellow solution for subcutaneous administration. The formulation composition is of (b) (4) % active ingredient (b) (4) % water and (b) (4) polyethylene glycol (PEG) 300. The pH of the proposed drug product is around 10, and the drug product manufacturing process involves (b) (4).

The proposed dosing regimen of LEN includes (Option 1) an initial dose of 927 mg of LEN by subcutaneous injection (2×1.5 mL injections) and 600 mg orally (2 LEN tablets, NDA 215974 drug product) on Day 1; 600 mg orally (2 LEN tablets) on Day 2, followed by a maintenance doses of 927 mg by subcutaneous injection (2×1.5 mL injections) every 6 months; or (Option 2) starting dose of 600 mg orally on Days 1 and 2, 300 mg orally on Day 8, and 927 mg by subcutaneous injection (2×1.5 mL injections) on Day 15 followed by 927 mg by subcutaneous maintenance doses and every 6 months. After administration the drug (b) (4).

(b) (4) release lenacapavir to the circulatory system (b) (4). This application was submitted simultaneously with NDA 215974, the submission for a tablet formulation of lenacapavir proposed for initial loading doses, both originally and in this resubmission.

This is the second CMC review of this NDA. In the original submission, Gilead proposed borosilicate and aluminosilicate glass vials for the packaging of LEN injection. However, the proposed drug product formulation was found incompatible with borosilicate glass vials, leading to the generation of glass lamellae. Due to the lack of sufficient data to support the compatibility of lenacapavir injection with aluminosilicate vials, a CR was issued.

The delamination is suspected to occur as a result of (b) (4) of the formulation (b) (4). Significant pitting was observed with the originally proposed borosilicate vials, (b) (4). Scanning electron microscopy and optical microscopy images were submitted late in the previous review cycle to support the use of the aluminosilicate vials; however, unexplained particles were observed and the data was not sufficient to mitigate concerns for the potential interaction of the formulation with the vials.

In addition, the stability data submitted in the first review cycle for the aluminosilicate vials only included 9 months long-term (and 6 months accelerated) results, which did not allow final assessment of the proposed drug product expiry period.

The deficiency included in the CR for vial incompatibility is as follows: “Your data demonstrate that the drug product solution is incompatible with the proposed commercial borosilicate glass vials. The data provided in support of the compatibility of the alternative aluminosilicate glass vials are incomplete and ambiguous. As evidenced by your data and glass particles found in the clinical batches, glass containers are (b) (4). In order to resolve this deficiency, we require a comprehensive study report with unambiguous data and fully validated methods to demonstrate the compatibility of the drug product solution with your proposed primary container closure system.”

In the resubmission, Gilead submitted the vial compatibility data (optical microscopy, scanning electron microscopy, and inductively coupled plasma-mass spectrometry) data for three registration batches stored in aluminosilicate glass vials for up to 18 months under long term storage conditions (30°C/75% relative humidity). The data do not show any evidence of glass incompatibility of LEN formulation with the proposed aluminosilicate glass vials. In addition, the FDA Office of Translational Research laboratory analysis (report no. FY22-114-OTR-DPQR-T) of registration and clinical batches also demonstrated the compatibility of proposed vials with LEN injection. The proposed analytical methods were also found acceptable. The additional data from registration stability batches and three production batches will be reviewed as it will be submitted postapproval as CBE-0 supplements to further confirm the suitability of the proposed vials with the LEN injection solution.

During the review, (b) (4)

The safety risk of these (b) (4) particulates was discussed within the review team, and found to be acceptable based on nonclinical and clinical studies and

the overall risk-benefit profile of the product for the particular indication within heavily treatment-experienced patients with multidrug resistance. However, a PMC was requested and agreed by the applicant to evaluate an alternative device/procedure for withdrawal of the vial contents (b) (4).

Based upon the 18-month long-term storage data, Gilead proposed the shelf life of 24 months for the drug product. The proposed shelf life is acceptable. The proposed storage condition for drug product is “Store at 20°C to 25°C (68°F to 77°F), excursions permitted 15°C to 30°C (59°F to 86°F), protect from light.” The photostability data demonstrate that the secondary packaging ((b) (4) tray with paperboard carton) protects LEN injection from photodegradation. The supporting in-use stability data to confirm the stability of LEN injection during the proposed in-use period in the clear glass vials and syringe is provided in the NDA. The proposed drug product label also includes a statement in Section 16; i.e., ‘*keep the vials in the original carton until just prior to preparation of the injections, in order to protect from light*’.

Drug Substance

The drug substance review was adequate in the previous review cycle, and no new drug substance information was provided in the resubmission. The NDA is recommended for approval from the drug substance perspective.

Drug Product

The submission is adequate from a drug product perspective. LEN Injection is sterile, preservative-free, for subcutaneous administration. Marketing of a single strength is proposed (463.5 mg/1.5 mL [309 mg/mL]) in a glass vial. The dosage strength is based on the lenacapavir free acid. Each vial contains a nominal 1.5 mL clear, yellow (b) (4) solution consisting of 473.1 mg of lenacapavir sodium, 896.3 mg polyethylene glycol 300, and (b) (4) water for injection. Each vial contains sufficient volume ((b) (4) mL with (b) (4) mL overfill) to allow withdrawal of 1.5 mL.

Drug product kit: The proposed container closure system for the drug product consists of a single-dose, clear glass vial. Each vial is sealed with an (b) (4) closure and aluminum overseal with flip-off cap. The drug product is supplied as a co-packaged kit which includes all the components needed for healthcare professionals to administer the injection; i.e., two lenacapavir filled vials, two vial access devices, two disposable syringes, and two injection safety needles.

Devices

All components (devices) of the proposed kit are 510(k) cleared; therefore, the CDRH determined that no additional review is needed. Gilead had previously submitted the device validation studies in Section 3.2.R, therefore, the DMEPA team was also consulted during the first review cycle and determined that a human factor study and results were not required for NDA submission. There is no change in the device design since that determination (February 2021), thus no additional review was needed from the DMEPA team and their review will be limited to the labeling.

Specifications

In the current review cycle, Gilead updated drug product specifications to include controls for (b) (4) apparent pH, and to tighten the acceptance criterion for the appearance test. The pH measurement is reported to be distorted (b) (4)

(b) (4). The Applicant originally did not include a pH specification as a result. However, United States Pharmacopeia (USP) <791> allows the usage of term ‘apparent’ for pH values of partially aqueous solutions, which applies to the lenacapavir injection. Therefore, the specification for “apparent pH” was requested, and the applicant complied, adding a test and acceptance limits of (b) (4) based on batch history.

Compatibility of Drug Product Solution With Container Closure Components

The available optical microscopy, scanning electron microscopy, and elemental analysis data from registration and clinical batches indicate that the proposed aluminosilicate glass vials are compatible with LEN injection up to 18 months under long-term storage conditions. The Office of Translational Research laboratory analysis and inspection by the FDA team of the Gilead La Verne site also support the vial compatibility.

The proposed vial compatibility test methods were found acceptable. However, because Gilead made significant updates to the proposed test methods during current review cycle, and limited data is available as per the revised procedures, Gilead was requested to provide the vial compatibility data for upcoming stability time points for three registration batches and the first three production batches as CBE-0 supplement/s, per an agreed postmarketing commitment.

(b) (4)
Gilead agreed to the above requests and included written agreement in Section 3.2.P.8.2.

During the course of the resubmission review, (b) (4) particulates were reported in the filtrate of samples used to evaluate for glass compatibility. However, these were determined to be generated as a result of the sample preparation, (b) (4)

(b) (4). Therefore, (b) (4) particles should not be present at any point in the product nor pose any patient safety concerns.

During the review, for the studies evaluating the compatibility of the product with the glass vials, the presence of (b) (4)

No visible particulates were observed in 21-month long-term stability samples of the registration batches when following the IFU. In addition, no (b) (4) particles due to storage of LEN injection vials in the inverted orientation was observed, and no apparent

relationship between storage time was observed in data from two (5.5 months, 21 months) stability time points, which indicate that (b) (4) does not appear to be occurring. Since data are limited, additional stability data was agreed by Gilead per the PMC to be provided postapproval.

The proposed (b) (4) (b) (4)) meets the USP <381> criterion for fragmentation per information from the applicant, and the vial access device is 510(k) cleared. Although USP <1> and <790> state that the finished injectable drug products are expected to be essentially free of visible particulates, USP <381> allow for a certain number (<5 per 12 vials) of potentially visible particles greater than 50 µm. In fact, other injectable products are not typically required to meet USP <381> requirements following preparation for administration. These considerations were discussed during the review cycle with the Office of New Drugs review team, including the Clinical and Pharmacology-Toxicology teams as well as Office of New Drugs leadership.

In addition to the above factors, the review discussions highlighted the following relevant factors for consideration:

- Nonclinical studies were performed using container closures using borosilicate vials with a synthetic (b) (4) (b) (4) (b) (4), and demonstrated injection site reactions (chronic granulomatous inflammations) for dose groups but not vehicle control groups in the same container closures. This suggests that (b) (4) particulates are not responsible for the ISRs in animal studies, although it does not rule out that glass lamellae could have contributed. To note, the studies used a needle to withdraw the vial contents.
- Phase 1 clinical studies, although some were conducted with a different formulation/pH and not all subjects were followed to resolution, were all performed with a container closure sealed with a (b) (4) and demonstrated a decreased frequency and duration of injection site nodules and induration in patients who received placebo versus in patients who received lenacapavir. This again suggests that (b) (4) particulates may not be responsible for the ISRs. Likewise, if (b) (4) is responsible for the glass delamination observed in borosilicate vials, the ISRs may not be related to glass lamellae but rather drug depot formation or other characteristics of the formulation.
- Although evidence of foreign body reaction were obtained in available biopsy results, the above studies indicate that the subcutaneous depot of the drug may be responsible.
- The intended population for the product is treatment of HIV-1 infection in heavily treatment experienced patients with multi-drug resistance, for which the product has breakthrough designation.

Based on the above considerations, (b) (4) (b) (4), were determined not to represent unacceptable risk to patients. Since it does not appear that Gilead explored other options besides the vial access device, it is possible that (b) (4) (b) (4). Therefore, a PMC was requested and agreed by Gilead to evaluate an alternative device/s (i.e., vial access device, needle, etc.) and/or procedure for withdrawing the LEN injection from the vial, (b) (4).

(b) (4)
inspection of the syringe during administration was included in the following statement in the dosage and administration section (Section 2.3) of the USPI and IFU; i.e., “visually inspect the solution in the vials and prepared syringe for particulate matter and discoloration prior to administration.... Do not use SUNLENCA injection if the solution is discolored or if it contains particulate matter.”

Postmarketing Commitments (PMCs)

PMC 1

Complete the vial compatibility study (i.e., (b) (4)) for the remaining time points of the registration stability batches and three production batches and submit the report as a CBE-0 supplement.

PMC 2

Evaluate the upcoming stability time points of the registration batches and first three production batches (at release and over stability studies) of lenacapavir injection using the proposed instructions for use (IFU) for (b) (4) particulates in both visible and subvisible size ranges (i.e., 10 µm to 25 µm; 25 µm to 50 µm; 50 µm to 100 µm; 100 µm to 150 µm and >150 µm). Submit the optical microscopy and SEM-EDX analysis data for the vials stored in both inverted and upright orientations. Report any trend or increase in particulates with vial orientation, time etc. and provide explanation including details of any investigation into the source of the increase. Also, submit optical microscopy and SEM-EDX data from multiple batches (e.g., three batches) of the control vials (filled with polyethylene glycol and water mixture) prepared using both vial decrimping and proposed instructions for use (IFU) procedures. Submit the interim and final study reports as CBE-0 supplements.

PMC 3

Evaluate an alternative device/s (i.e., vial access device, needle, etc.) and/or procedure for withdrawing the lenacapavir injection from the vial, which consistently reduces the presence of (b) (4) particulates in the drug product solution to (b) (4) per 12 vials as measured by optical microscopy, (b) (4)

(b) (4) Provide supporting data (e.g., optical microscopy, SEM-EDX, USP <788> subvisible particulates data etc.) from multiple drug product batches (e.g., three batches) tested at release and multiple time points over stability studies (long-term and accelerated storage conditions) under both upright and inverted orientation to support the alternative device/procedure.

Manufacturing

Two testing facilities were added in the resubmission. Gilead Sciences, Inc. (FEI: 3013189568) is proposed as stability tester facility (physical–glass lamellae and glass corrosion) of LEN injection. A preapproval inspection was performed on September 12 to 16 2022, and a one-item

form FDA 483 was issued. The recommendation from the preapproval inspection was to approve the site to support NDA 215973. Based on the preapproval inspection recommendation, the facility is found acceptable to perform the proposed responsibilities. (b) (4) is proposed as a release and stability tester (chemical- (b) (4)) for the drug product. The firm has significant experience with chemical testing responsibilities of similar drug product and adequate compliance history. Hence, the firm is found acceptable to perform the proposed responsibilities as release/stability tester of the drug product. There are no changes related to process and previously approved facilities.

The proposed manufacturing process involves (b) (4)

No scale-up is proposed; the applicant manufactured ten clinical and stability batches with batch sizes ranging from (b) (4) kg to (b) (4) kg, whereas the proposed commercial manufacturing scale is (b) (4) kg.

The drug product manufacturing facility, (b) (4), is found acceptable to perform the proposed responsibilities based on district recommendation, experience with the proposed operations, and adequate compliance history. Gilead Alberta ULC (FEI: 3001027806, CSN) is found acceptable to perform the proposed responsibilities as drug substance manufacturer and tester based on district recommendation. (b) (4)

(b) (4), IDD, DKA) is proposed as secondary packager (kitting, labeler of co-package kit) and it is found acceptable to perform the proposed responsibilities based on district recommendation, experience with the proposed operations, and adequate compliance status. The following testing sites are found acceptable to perform the proposed responsibilities in support of NDA 215973: (b) (4), LCP & LMS) and Gilead Sciences, Inc. (FEI: 1000523075, LCP). The overall manufacturing recommendation is adequate.

Biopharmaceutics

No new biopharmaceutics information was included in the resubmission. NDA 215973 remains approvable from the biopharmaceutics perspective.

Microbiology

In the CR of the original submission dated February 28 2022, the microbiology deficiency below was included:

- The information request response provided on December 29, 2021, regarding the Container Closure Integrity Testing performed with aluminosilicate vials with batches GB2007B, GB2008B, and GB2009B is acknowledged. However, this response is incomplete and additional information is needed to assess acceptability of aluminosilicate vials: a) Provide the spectrophotometric data with all results from the Container Closure Integrity Testing dye ingress studies reported to be performed with 20 intact vials sourced from each of batches GB2007B, GB2008B, and GB2009B, respectively.

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The Applicant provided a response to this deficiency in the resubmission, provided evaluation of three registration batches of the drug product (lots GB2007B, GB2008B, and GB2009B) for container closure integrity after 12 and 15 months of storage at 30°C/75% relative humidity in the inverted orientation. Two process validation batches exposed to target (b) (4) conditions (lots P112406PV and P112407PV) and three development batches exposed to worst-case (b) (4) conditions (lots P112409PV/DV-B, P112409PV/DV-M, and P112409PV/DV-E) were also evaluated for container closure integrity. The results met the acceptance criteria and are acceptable. The Applicant's verification of container closure integrity is consistent with regulatory expectations for a sterile pharmaceutical product. The NDA is adequate from a microbiology perspective.

NDA 215974

Summary

NDA 215974 is recommended for approval from the product quality perspective. LEN tablets are 300 mg strength immediate release tablet proposed as the initial loading dose for LEN injection – the subject of the concurrent NDA 215973. During the drug product manufacturing process, (b) (4)

(b) (4) In the first review cycle, the applicant's proposal to measure the drug product expiry period from (b) (4) was found acceptable.

The proposed drug product has low oral bioavailability (<10%), (b) (4)

Drug Substance

See the information under NDA 215973 [above](#).

Drug Product

LEN tablet is an immediate-release dosage form containing 300 mg LEN, present as 306.8 mg lenacapavir sodium. The drug substance is (b) (4)

The proposed container closure system for the drug product consists of a blister card with four (4) or five (5) tablets, fitted between two (2) paperboard cards, (b) (4). The blister cards are packaged in a sealed (b) (4)-laminated pouch with three (3) grams of silica gel desiccant. The packaging materials are identical for the proposed commercial 4- and 5-count configurations.

Stability results from 18 months long-term and 6 months accelerated storage for three drug product batches packaged with 5-count blister packaging configuration, along with 3-month stability data for three DP batches packaged with 4-count blister pack was provided. In addition,

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12 to 18 months of long-term stability data for two drug product batches manufactured using (b) (4) were provided.

Based on the available stability data, a 24-month shelf life of the drug product is acceptable. The proposed drug product storage conditions are 'Store at 25°C, excursions permitted 15 to 30°C.'

(b) (4)
This agreement is included in 3.2.P.3.4.

The NDA remains approvable from a drug product perspective.

Manufacturing

(b) (4)

The facilities involved in the current submission are as follow:

- Gilead Alberta ULC, FEI: 3001027806: DS manufacture
- (b) (4) release/stability testing for DS/DP
- Gilead Sciences, Inc, FEI: 1000523075: release/stability testing for DS/DP
- (b) (4)
- (b) (4): DP manufacture

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

- (b) (4) DP packaging

All sites have experience with the proposed responsibilities and thus, no PAI was recommended for any of these facilities. All facilities currently remain compliant.

Biopharmaceutics

No new biopharmaceutics was included in the second cycle submission. NDA 215974 remains approvable from the biopharmaceutics perspective.

9.1. Device or Combination Product Considerations

Refer to Section 9.1 of the Integrated Review dated February 28, 2022 from the first cycle.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Refer to Section 10 of the Integrated Review dated February 28, 2022 from the first cycle.

11. Advisory Committee Summary

This application was not taken to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and there were no controversial issues that would benefit from discussion by an advisory committee.

III. Appendices

12. Summary of Regulatory History

Refer to the Review Cycle 1 Integrated Review for complete Summary of Regulatory History prior to submission of the initial new drug applications (NDAs) on June 28, 2021.

On February 28, 2022, Complete Response letters were issued to NDAs 215973 and 215974 due to product quality deficiencies including 1) incompatibility between drug product and borosilicate glass vials, and 2) incomplete information with respect to container closure integrity testing.

On May 24, 2022, a Type A, postaction teleconference was held between Gilead and the Food and Drug Administration (FDA or the Agency). The purpose of this meeting was to discuss the deficiencies noted in the Complete Response letters and to obtain feedback on Gilead's plan for resubmission of the NDAs. The Agency agreed with the plan to submit data from nonclinical Study TX-200-2068 and additional long-term data from clinical Study 4625 in the resubmission. In addition, Gilead's approach to responding to the product quality issues seemed acceptable.

On June 27, 2022, Gilead submitted their resubmissions to NDAs 215973 and 215974.

On July 27, 2022, the Agency acknowledged receipt of the applications and notified Gilead that the submissions had be classified as Class 2 Resubmissions.

13. Pharmacology Toxicology: Additional Information and Assessment

Please refer to Section 13 of the Integrated Review dated February 28, 2022 for the Nonclinical review from the first cycle. Additional data submitted in this cycle include a 26-week carcinogenicity study in transgenic mouse and a single-dose intramuscular local tolerance study in rabbit.

13.1. Carcinogenicity

GS-6207^{(b) (4)}: A 26-Week Subcutaneous Carcinogenicity Study in 001178-T (Hemizygous) RasH2 Mice (TX-200-2068)

The carcinogenic potential of lenacapavir (LEN) was tested via subcutaneous (SC) administration in a 26-week mouse study. RasH2 hemizygous mice were administered 0, 30, 100, or 300 mg/kg/dose of LEN formulated in ^{(b) (4)}% polyethylene glycol (PEG)-300 and ^{(b) (4)}% sterile water for injection once every 13 weeks for 26 weeks (two total doses).

There were no variations of tumor incidences considered related to administration of LEN based on the FDA statistical review. The Executive Carcinogenicity Assessment Committee concurred that this study was negative.

13.2. Other Toxicology Studies

A Single-Dose Intramuscular Injection Local Tolerance Study of GS-6207^{(b) (4)} in Male New Zealand White Rabbits with a 28- or 90-Day Observation Period (TX-200-2074)

The effects of three formulations of LEN on local tolerance were evaluated in male rabbits via a single intramuscular injection followed by a 28- or 90-day observation period. The vehicle control formulations were as follows: ^{(b) (4)}

There were no marked differences among the different vehicle formulations.

Injection site reactions of granulomatous inflammation and minimal to slight mineralization were detected in all animals across doses and controls 28 days postdose (necropsy 1). Slight to moderated myofiber necrosis and minimal to slight hemorrhage was detected at 400 mg/kg LEN.

At necropsy 2, granulomatous inflammation at dosing-site B was still detected but at a lower incidence and severity compared to necropsy 1. Other histopathology findings detected at necropsy 1 were no longer detected at necropsy 2.

14. Clinical Pharmacology: Additional Information and Assessment

Please refer to the Clinical Pharmacology review in Section 14 of the Integrated Review dated February 28, 2022 from the first cycle. No additional data were submitted in this review cycle.

15. Trial Design: Additional Information and Assessment

Refer to Section 15 of the Integrated Review dated February 28, 2022 from the first cycle.

16. Efficacy: Additional Information and Assessment

Please refer to the Statistical, Clinical and Clinical Virology reviews for details.

17. Clinical Safety: Additional Information and Assessment

Refer to Section 17 of the Integrated Review dated February 28, 2022 from the first cycle.

Analysis of clinical safety outcomes by demographic subgroups were specifically not included here because of the small sample sizes anticipated with Studies 4625 and 4334, which would limit meaningful interpretation of the analyses.

17.1. Extent of Exposure, Phase 1 Studies

17.1.1. Phase 1 Studies Included in the Original NDA Submissions

17.1.1.1. Study 5709

Study 5709 is an ongoing, phase 1, open-label, multiple-cohort, multiple-dose study in healthy subjects.

- Cohort 1:
 - For the original NDA submission, 31 subjects were enrolled and had received ≥ 1 dose of study drug; the median (quartile [Q] 1, Q3) duration on-study was 27 (27, 135) days.
 - At the NDA resubmission safety update data cut date, the median duration on-study was 435 days ([Table 39](#)).
- Cohort 2:
 - For the original NDA submission, 14 subjects were enrolled and had received ≥ 1 dose of study drug; the median (Q1, Q3) duration on-study was 15 (15, 29) days. At the NDA resubmission safety update data cut date, the median duration on-study for the 14 subjects enrolled in Cohort 2, each of whom had received ≥ 1 dose of study drug, was 307 days ([Table 39](#)).

Table 39. Study 5709: Duration on Study (Safety Analysis Set)

Parameter	Cohort 1	Cohort 2	Total (N=45)
	SC LEN 927 mg (N=31)	SC LEN 927 mg (N=14)	
Duration on study, days	31	14	45
Mean (SD)	355 (159)	290 (79)	335 (142)
Median	435	307	417
Q1, Q3	249, 463	307, 321	307, 435
Minimum, maximum	32, 463	18, 321	18, 463

Parameter	Cohort 1	Cohort 2	Total (N=45)
	SC LEN 927 mg (N=31)	SC LEN 927 mg (N=14)	
Duration on study			
≥7 Days	31 (100.0%)	14 (100.0%)	45 (100.0%)
≥14 Days	31 (100.0%)	14 (100.0%)	45 (100.0%)
≥21 Days	31 (100.0%)	13 (92.9%)	44 (97.8%)
≥51 Days	29 (93.5%)	13 (92.9%)	42 (93.3%)
≥81 Days	26 (83.9%)	13 (92.9%)	39 (86.7%)
≥111 Days	25 (80.6%)	13 (92.9%)	38 (84.4%)
≥141 Days	25 (80.6%)	13 (92.9%)	38 (84.4%)
≥171 Days	24 (77.4%)	13 (92.9%)	37 (82.2%)
≥201 Days	24 (77.4%)	13 (92.9%)	37 (82.2%)
≥231 Days	24 (77.4%)	13 (92.9%)	37 (82.2%)
≥261 Days	23 (74.2%)	13 (92.9%)	36 (80.0%)
≥291 Days	23 (74.2%)	13 (92.9%)	36 (80.0%)
≥321 Days	23 (74.2%)	4 (28.6%)	27 (60.0%)
≥351 Days	23 (74.2%)	0	23 (51.1%)
≥381 Days	23 (74.2%)	0	23 (51.1%)
≥411 Days	23 (74.2%)	0	23 (51.1%)
≥441 Days	9 (29.0%)	0	9 (20.0%)
≥481 Days	0	0	0

Source: Applicant's NDA Resubmission Safety Update (p. 23).

Abbreviations: LEN, lenacapavir; NDA, new drug application; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

17.1.2. Phase 1 Studies Not Included in the Original NDA Submissions

The following phase 1 studies were not included in the original NDA submissions or the previous NDA 90-day safety update report. The provided information is based on the NDA resubmission safety update data cut date.

17.1.2.1. Study 4540

Study 4540 is an ongoing, phase 1, open-label study to evaluate the pharmacokinetics (PK), safety, and tolerability of SC LEN in healthy adult subjects, who received a single dose of SC LEN (927 mg as the sodium salt) on Day 1, administered into alternative injection sites (thigh [Cohort 1] and upper arm [Cohort 2]) in comparison with the abdomen (Cohort 3) as the reference site. A total of 30 subjects was enrolled in the study, 10 in each of Cohorts 1, 2, and 3, all of whom received a single dose (927 mg) of SC LEN.

17.1.2.2. Study 5710

Study 5710 is an ongoing, phase 1, open-label, multiple-cohort study to evaluate the PK, safety, and tolerability of single doses of SC and intramuscular (IM) LEN formulations containing different concentrations of both LEN and (b) (4), administered to healthy adult subjects, with or without an optional oral LEN loading dose as determined prior to cohort initiation based on available data. Dose escalation through cohorts was performed in an adaptive manner. A total of 98 subjects was enrolled in Cohorts 1 (1200 mg; n=22), 3 (300 mg; n=21), 4

(100 mg; n=12), 7 (125 mg; n=11), 10 (150 mg; n=12), and 13 (300 mg; n=20), and each had received the protocol-specified single SC LEN injection on Day 1, with doses ranging from 100 to 1200 mg containing up to [REDACTED] ^{(b) (4)}. No optional oral loading dose was required to be administered to subjects in Cohort 1, 3, 4, 7, or 10, whereas subjects in Cohort 13 were administered a protocol-required 600 mg oral LEN loading dose on Days 1 and 2. All subjects in the specified cohorts completed study drug and there were no premature study drug discontinuations due to an adverse event (AE). Not all cohorts had enrolled.

17.1.2.3. Study 5717

Study 5717 is an ongoing, phase 1, open-label, multiple-cohort study to evaluate the PK, safety, and tolerability of single doses of SC or IM LEN formulations containing different concentrations of both LEN and [REDACTED] ^{(b) (4)}, administered to healthy adult subjects, with or without an optional oral LEN loading dose for subjects receiving an IM LEN injection, depending on cohort and based upon available data. A total of 57 subjects had been enrolled variously in Cohorts 1 (2400 mg; n=20), 2 (2400 mg; n=10), 4 (3200 mg; n=10), 6 (2400 mg; n=7), and 11 (2400 mg; n=10). Subjects in Cohorts 1, 2, 4, and 6 had received the protocol-specified single SC LEN injection on Day 1, with doses ranging from 2400 mg to 3200 mg, while subjects in Cohort 11 had received a single IM LEN injection on Day 1 with no protocol requirement for an optional oral loading dose. All subjects in the cohorts identified completed study drug, and there were no premature discontinuations from study drug because of an AE. Not all cohorts had enrolled.

17.1.2.4. Study 5977

Study 5977 was a phase 1, open-label study to evaluate the PK, safety, and tolerability of oral LEN in healthy adult subjects, who received a single oral dose of LEN (25 mg) on Day 1 (Cohort 1), or multiple oral doses of LEN (25 mg) once daily for 56 days (Cohort 2). A total of 34 subjects was enrolled in the study, Cohort 1 (n=8) and Cohort 2 (n=26), all of whom received at least one dose of study drug. There were no discontinuations due to AEs.

17.1.2.5. Study 5816

Study 5816 is an ongoing phase 1, randomized, blinded, proof-of-concept study to evaluate the safety and efficacy of the broadly neutralizing antibodies GS-5423 and GS-2872 in combination with LEN in virologically suppressed adults with human immunodeficiency virus type 1 (HIV-1) infection. Subjects were randomized in a 1:1 ratio into one of two treatment groups, each of which received on Day 1 a loading dose of oral LEN 600 mg, followed by SC LEN 927 mg, followed by intravenous infusions of, first, GS-5423 30 mg/kg body weight, and, second, GS-2872 at a dose of 10 or 30 mg/kg depending on treatment group. A further loading dose of oral LEN 600 mg was administered on Day 2. A total of 21 subjects was randomized and received at least one dose of study drug. No subject discontinued study drug due to an AE.

17.1.2.6. Study 6148

Study 6148 was a phase 1, open-label, parallel-design, single-dose, three-cohort study to evaluate the potential drug-drug interaction between islatravir (ISL) and LEN in healthy adult subjects who received coadministered oral ISL 20 mg and oral LEN 600 mg (Cohort 1), oral islatravir 20 mg (Cohort 2), or oral LEN 600 mg (Cohort 3) under fasted conditions on the morning of Day 1. A total of 55 subjects was enrolled in the study, 18 in each of Cohorts 1 and 2, and 19 in Cohort 3; each subject received their assigned single dose(s) of study drug. No subject prematurely discontinued study drug due to an AE.

17.2. Supplemental Data for the Safety Review: Results From Study 4625

17.2.1. Laboratory Abnormalities

The majority of laboratory abnormalities have been discussed in previous sections, either in the context of organ-specific safety issues, or in Section 7.6.3.6, which outlines laboratory abnormalities included in the LEN labeling. The remainder of the laboratory abnormalities are presented here for completeness (Table 40, Table 41, Table 42, and Table 43); these are not included in labeling because they did not meet the frequency deemed clinically meaningful.

Table 40. Subjects Meeting Chemistry Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4625 (Week 52 Analysis)

Grade	All Subjects
	N=72 n (%)
Sodium, high (mEq/L)	
Any grade	10 (13.9)
Grade 1	10 (13.9)
Sodium, low (mEq/L)	
Any grade	15 (20.8)
Grade 1	15 (20.8)
Potassium, high (mEq/L)	
Any grade	4 (5.6)
Grade 1	3 (4.2)
Grade 2	0 (0)
Grade 3	1 (1.4)
Potassium, low (mEq/L)	
Any grade	4 (5.6)
Grade 1	4 (5.6)
Bicarbonate, low (mEq/L)	
Any grade	26 (36.1)
Grade 1	24 (33.3)
Grade 2	2 (2.8)
Glucose (fasting), high (mg/dL)	
Any grade	23 (40.4)
Grade 1	12 (21.1)
Grade 2	8 (14.0)
Grade 3	2 (3.5)
Grade 4	1 (1.8)

Grade	All Subjects N=72 n (%)
Glucose (fasting), low (mg/dL)	
Any grade	2 (3.8)
Grade 1	1 (1.8)
Grade 2	1 (1.8)
Calcium, high (mg/dL)	
Any grade	3 (4.2)
Grade 1	2 (2.8)
Grade 2	1 (1.4)
Magnesium, low (mg/dL)	
Any grade	5 (6.9)
Grade 1	5 (6.9)
Phosphate, low (mg/dL)	
Any grade	4 (5.6)
Grade 1	2 (2.8)
Grade 2	2 (2.8)
Albumin, low (g/dL)	
Any grade	3 (4.2)
Grade 1	1 (1.4)
Grade 2	2 (2.8)
Creatine kinase, high (U/L)	
Any grade	3 (4.2)
Grade 1	3 (4.2)
Lipase, high (U/L)	
Any grade	10 (13.9)
Grade 1	4 (5.6)
Grade 2	5 (6.9)
Grade 3	1 (1.4)

Source: Applicant Table 15.11.6.4.1.2: Treatment-Emergent Laboratory Abnormalities.

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AIDS, acquired immunodeficiency syndrome; N, number of patients in treatment arm; n, number of patients meeting criterion

Table 41. Subjects Meeting Chemistry (Renal) Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4625 (Week 52 Analysis)

Laboratory Parameter	All Subjects N=72 n (%)
Creatinine, high (mg/dL)	
Any grade	25 (34.7)
Grade 1	6 (8.3)
Grade 2	10 (13.9)
Grade 3	7 (9.7)
Grade 4	2 (2.8)
Creatinine clearance or eGFR, low	
Any grade	34 (47.2)
Grade 1	0 (0)
Grade 2	22 (30.6)
Grade 3	11 (15.3)
Grade 4	1 (1.4)

Source: Applicant Table 15.11.6.4.1.2: Treatment-Emergent Laboratory Abnormalities.

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AIDS, acquired immunodeficiency syndrome; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criterion

Table 42. Subjects Meeting Chemistry (Hepatic) Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4625 (Week 52 Analysis)

Laboratory Parameter	All Subjects
	N=72 n (%)
Alkaline phosphatase, high (U/L)	
Any grade	7 (9.7)
Grade 1	6 (8.3)
Grade 2	1 (1.4)
Alanine aminotransferase, high (U/L)	
Any grade	11 (15.3)
Grade 1	7 (9.7)
Grade 2	2 (2.8)
Grade 3	2 (2.8)
Aspartate aminotransferase, high (U/L)	
Any grade	7 (9.7)
Grade 1	5 (6.9)
Grade 2	0 (0)
Grade 3	0 (0)
Grade 4	2 (2.8)
Bilirubin, total, high (mg/dL)	
Any grade	4 (5.6)
Grade 1	3 (4.2)
Grade 2	1 (1.4)
Direct bilirubin, high (mg/dL)	
Any grade	2 (2.8)
Grade 1	0 (0)
Grade 2	0 (0)
Grade 3	2 (2.8)

Source: Applicant Table 15.11.6.4.1.2: Treatment-Emergent Laboratory Abnormalities.

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AIDS, acquired immunodeficiency syndrome; N, number of patients in treatment arm; n, number of patients meeting criterion

Table 43. Subjects Meeting Chemistry (Hematologic) Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4625 (Week 52 Analysis)

Laboratory Parameter	All Subjects
	N=72 n (%)
WBC, low (cells/ μ L)	
Any grade	1 (1.4)
Grade 1	1 (1.4)
Grade 2	0 (0)
Grade 3	0 (0)
Hemoglobin, low (g/dL)	
Any grade	9 (12.5)
Grade 1	5 (6.9)
Grade 2	3 (4.2)
Grade 3	1 (1.4)

Laboratory Parameter	All Subjects N=72 n (%)
Platelets, low (cells/ μ L)	
Any grade	4 (5.6)
Grade 1	3 (4.2)
Grade 2	1 (1.4)
Absolute neutrophil count, low	
Any grade	1 (1.4)
Grade 1	0 (0)
Grade 2	0 (0)
Grade 3	1 (1.4)

Source: Applicant Table 15.11.6.4.1.2: Treatment-Emergent Laboratory Abnormalities.

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 (NIH 2017).

Abbreviations: AIDS, acquired immunodeficiency syndrome; N, number of patients in treatment arm; n, number of patients meeting criterion; WBC, white blood cells

17.3. Supplemental Data for the Safety Review: Results From Study 4334

The majority of laboratory abnormalities have been discussed in previous sections, either in the context of organ-specific safety issues, or in Section 7.6.4.6, which outlines laboratory abnormalities included in labeling. The remainder of the laboratory abnormalities are presented here for completeness (Table 44, Table 45, Table 46, and Table 47). These are not included in labeling because they did not meet the frequency deemed clinically meaningful.

Table 44. Subjects Meeting Chemistry Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4334 (Week 54 Analysis)

Grade	LEN Total N=157 n (%)	B/F/TAF N=25 or Nw (%)
Sodium, high (mEq/L)		
Any grade	11 (7.0)	0 (0)
Grade 1	11 (7.0)	0 (0)
Sodium, low (mEq/L)		
Any grade	16 (10.2)	1 (4.0)
Grade 1	16 (10.2)	1 (4.0)
Potassium, high (mEq/L)		
Any grade	5 (3.2)	0 (0)
Grade 1	3 (1.9)	0 (0)
Grade 2	0 (0)	0 (0)
Grade 3	2 (1.3)	0 (0)
Potassium, low (mEq/L)		
Any grade	1 (0.6)	0 (0)
Grade 1	1 (0.6)	0 (0)
Bicarbonate, low (mEq/L)		
Any grade	23 (14.6)	3 (12.0)
Grade 1	23 (14.6)	3 (12.0)
Glucose (fasting), high (mg/dL)		
Any grade	52/151 (34.4)	7/23 (30.4)
Grade 1	33/151 (21.9)	6/23 (26.1)
Grade 2	16/151 (10.6)	1/23 (4.3)
Grade 3	3/151 (2.0)	0/23 (0)
Grade 4	0/151 (0)	0/23 (0)

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Grade	LEN Total N=157 n (%)	B/F/TAF N=25 or Nw (%)
Glucose (fasting), low (mg/dL)		
Any grade	8/151 (5.3)	0/23 (0)
Grade 1	5/151 (3.3)	0/23 (0)
Grade 2	3/151 (2.0)	0/23 (0)
Calcium, low (mg/dL)		
Any Grade	4 (2.5)	1 (4.0)
Grade 1	2 (1.3)	1 (4.0)
Grade 2	1 (0.6)	0 (0)
Grade 3	1 (0.6)	0 (0)
Magnesium, low (mg/dL)		
Any grade	8 (5.1)	2 (8.0)
Grade 1	6 (3.8)	2 (8.0)
Grade 2	0 (0)	0 (0)
Grade 3	2 (1.3)	0 (0)
Phosphate, low (mg/dL)		
Any grade	11 (7.0)	1 (4.0)
Grade 1	7 (4.5)	0 (0)
Grade 2	4 (2.5)	1 (4.0)
Albumin, low (g/dL)		
Any grade	1 (0.6)	0 (0)
Grade 1	0 (0)	0 (0)
Grade 2	1 (0.6)	0 (0)
Creatine kinase, high (U/L)		
Any grade	27 (17.2)	3 (12.0)
Grade 1	7 (4.5)	1 (4.0)
Grade 2	9 (5.7)	1 (4.0)
Grade 3	5 (3.2)	1 (4.0)
Grade 4	6 (3.8)	0 (0)
Lipase, high (U/L)		
Any grade	15 (9.6)	1 (4.0)
Grade 1	7 (4.5)	0 (0)
Grade 2	5 (3.2)	1 (4.0)
Grade 3	2 (1.3)	0 (0)
Grade 4	1 (0.6)	0 (0)

Source: Applicant Table 15.11.6.4.1: Treatment-Emergent Laboratory Abnormalities.

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AIDS, acquired immunodeficiency syndrome; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide (coformulated tablet); LEN, lenacapavir; N, number of patients in treatment arm; n, number of patients meeting criterion; Nw, number of patients with data; WBC, white blood cells

Table 45. Subjects Meeting Chemistry (Renal) Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4334 (Week 54 Analysis)

Laboratory Parameter	LEN Total N=157 n (%)	B/F/TAF N=25 n (%)
Creatinine, high (mg/dL)		
Any grade	27 (17.2)	10 (40.0)
Grade 1	2 (1.3)	2 (8.0)
Grade 2	19 (12.1)	6 (24.0)
Grade 3	5 (3.2)	2 (8.0)
Grade 4	1 (0.6)	0 (0)

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Laboratory Parameter	LEN Total N=157 n (%)	B/F/TAF N=25 n (%)
Creatinine clearance or eGFR, low		
Any grade	94 (47.2)	19 (76.0)
Grade 1	0 (0)	0
Grade 2	82 (52.2)	16 (64.0)
Grade 3	11 (7.0)	3 (12.0)
Grade 4	1 (0.6)	0 (0)

Source: Applicant Table 15.11.6.4.1: Treatment-Emergent Laboratory Abnormalities.

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AIDS, acquired immunodeficiency syndrome; B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide (coformulated tablet); eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criterion

Table 46. Subjects Meeting Chemistry (Hepatic) Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4334 (Week 54 Analysis)

Laboratory Parameter	LEN Total N=157 n (%)	B/F/TAF N=25 n (%)
Alkaline phosphatase, high (U/L)		
Any grade	7 (4.5)	2 (8.0)
Grade 1	6 (3.8)	2 (8.0)
Grade 2	1 (0.6)	0 (0)
Alanine aminotransferase, high (U/L)		
Any grade	27 (17.2)	1 (4.0)
Grade 1	15 (9.6)	1 (4.0)
Grade 2	7 (4.5)	0 (0)
Grade 3	2 (1.3)	0 (0)
Grade 4	3 (1.9)	
Aspartate aminotransferase, high (U/L)		
Any grade	33 (21.0)	2 (8.0)
Grade 1	17 (10.8)	2 (8.0)
Grade 2	9 (5.7)	0 (0)
Grade 3	6 (3.8)	0 (0)
Grade 4	1 (0.6)	0 (0)
Bilirubin, total, high (mg/dL)		
Any grade	28 (17.8)	5 (20.0)
Grade 1	18 (11.5)	2 (8.0)
Grade 2	8 (5.1)	2 (8.0)
Grade 3	0 (0)	1 (4.0)
Grade 4	2 (1.3)	0 (0)
Direct bilirubin, high (mg/dL)		
Any grade	2 (1.3)	0 (0)
Grade 1	0 (0)	0 (0)
Grade 2	0 (0)	0 (0)
Grade 3	2 (1.3)	0 (0)

Source: Applicant Table 15.11.6.4.1: Treatment-Emergent Laboratory Abnormalities

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AIDS, acquired immunodeficiency syndrome; B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide (coformulated tablet); N, number of patients in treatment arm; n, number of patients meeting the criterion

Table 47. Subjects Meeting Chemistry (Hematologic) Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Study 4334 (Week 54 Analysis)

Laboratory Parameter	LEN Total N=157 n (%)	B/F/TAF N=25 n (%)
WBC, low (cells/ μ L)		
Any grade	1 (4.0)	4 (2.5)
Grade 1	1 (4.0)	4 (2.5)
Grade 2	0 (0)	0 (0)
Grade 3	0 (0)	0 (0)
Hemoglobin, low (g/dL)		
Any grade	2 (1.3)	1 (4.0)
Grade 1	1 (0.6)	1 (4.0)
Grade 2	0 (0)	0 (0)
Grade 3	1 (0.6)	0 (0)
Platelets, low (cells/ μ L)		
Any grade	3 (1.9)	0 (0)
Grade 1	2 (1.3)	0 (0)
Grade 2	1 (0.6)	0 (0)
Absolute neutrophil count (ANC), low		
Any grade	10 (6.4)	1 (4.0)
Grade 1	6 (3.8)	1 (4.0)
Grade 2	2 (1.3)	0 (0)
Grade 3	2 (1.3)	0 (0)

Source: Applicant Table 15.11.6.4.1: Treatment-Emergent Laboratory Abnormalities.

¹ Severity grades were defined by the Division of AIDS Table, corrected Version 2.1, July 2017 ([NIH 2017](#)).

Abbreviations: AIDS, acquired immunodeficiency syndrome; B/F/TAF, bicitregavir/emtricitabine/tenofovir alafenamide (coformulated tablet); N, number of patients in treatment arm; n, number of patients meeting criterion; WBC, white blood cells

17.4. Supplemental Data for the Safety Review: Injection Site Reactions

17.4.1. Resolved and Ongoing Injection Site Indurations and Injection Site Nodules by Study

As requested by the Agency, the Applicant submitted a cumulative review of injection-site reactions (ISRs), including ongoing and resolved injection site nodules and indurations and general updates on all types of ISRs from LEN studies (as appropriate and feasible, that include SC dosing regardless of the specific formulation, dose or injection volume).

Study 4625: LEN–Related Injection Site Nodules and Indurations

Overall, 18 of 72 subjects (25.0%) experienced study drug–related injection site nodules, and 11 subjects (15.3%) experienced study drug–related injection site indurations; all events were Grade 1 or 2 in severity.

The duration of nodules and indurations occurring as a result of the first SC LEN injections was longer than those occurring as a result of the second LEN SC injections (since their follow-up was longer) and longer for ongoing ones (compared to resolved ones).

Study 4625: Injection Site Reactions After the First SC LEN Injections

After the first SC LEN injections, 42 of 72 subjects (58.3%) experienced LEN–related ISRs. The injection site nodules and indurations reported because of the first SC LEN injections included the following:

- Subject-level analysis:
 - Nodules
 - Ongoing: 7 of 16 (43.8%); resolved: 9 of 16 (56.3%)
 - Indurations
 - Ongoing: 1 of 8 (12.5%); resolved: 7 of 8 (87.5%)
- Event-level analysis ([Table 48](#))

Table 48. Event-Level Analysis of Ongoing and Resolved LEN–Related Injection Site Nodules and Indurations Due to the First Lenacapavir Injection, Study 4625 (Week 52)

Parameter	SC LEN n (%)
Number of subjects who received injections (Day 1)	72
Injection site nodules	23
Ongoing	7 (30.4)
Resolved	16 (69.6)
Injection site indurations	8
Ongoing	1 (12.5)
Resolved	7 (87.5)
Duration of ongoing injection site nodules, days	
N	7
Mean (SD)	494 (174)
Median	552
IQR	337, 624
Minimum, maximum	181, 680
Duration of resolved injection site nodules, days	
N	16
Mean (SD)	204 (188)
Median	148
IQR	70, 334
Minimum, maximum	41, 727
Duration of ongoing injection site indurations, days	
N	1
Mean (SD)	655
Median	655
IQR	655, 655
Minimum, maximum	655, 655

Parameter	SC LEN n (%)
Number of subjects who received injections (Day 1)	72
Duration of resolved injection site indurations, days	
N	7
Mean (SD)	105 (97)
Median	70
IQR	15, 196
Minimum, maximum	3, 252

Source: Clinical Reviewer's Analysis (JMP v. 16.2.0) of the adae dataset.

Adverse events were coded according to MedDRA v. 24.1.

Study drug-related ISR is defined as an adverse event marked as related on the Adverse Event Electronic Case Report Form with the high-level term, injection site reactions.

Each SC dose consisted of two SC injections into the abdomen.

Each injection site reaction was counted in the total. One subject could have multiple ISRs.

If a subject had more than one injection site induration or nodule events, the subject 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.

Abbreviations: IQR, interquartile range; ISR, injection site reaction; LEN, lenacapavir (GS-6207); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Study 4625: ISRs After the Second SC LEN Injections (Week 26)

After the first SC LEN injections, 30 of 70 subjects (42.9%) experienced LEN-related ISRs. The injection site nodules and indurations reported because of the second LEN injections at Week 26 included the following:

- Subject-level analysis:
 - Nodules:
 - Ongoing: 4 of 8 (50.0%); resolved: 4 of 8 (50.0%)
 - Indurations:
 - Ongoing: 2 of 7 (28.6%); resolved: 5 of 7 (71.4%)
- An event-level analysis is summarized in [Table 49](#).

Table 49. Event-Level Analysis of Ongoing and Resolved LEN-Related Injection Site Nodules and Indurations Due to the Second LEN Injection, Study 4625 (Week 52)

Parameter	SC LEN n (%)
Number of subjects who received injections (Week 26)	70
Injection site nodules	14
Ongoing	7 (50.0)
Resolved	7 (50.0)
Injection site indurations	7
Ongoing	2 (28.6)
Resolved	5 (71.4)

Parameter	SC LEN n (%)
Duration of ongoing injection site nodules, days	
N	7
Mean (SD)	274 (165)
Median	324
IQR	111, 442
Minimum, maximum	111, 498
Duration of resolved injection site nodules, days	
N	7
Mean (SD)	215 (150)
Median	180
IQR	113, 365
Minimum, maximum	3, 366
Duration of ongoing injection site indurations, days	
N	2
Mean (SD)	271 (35)
Median	271
IQR	246, 296
Minimum, maximum	246, 296
Duration of resolved injection site indurations, days	
N	5
Mean (SD)	97 (99)
Median	63
IQR	9, 201
Minimum, maximum	5, 220

Source: Clinical Reviewer's analysis (JMP v. 16.2.0) of the adae dataset.

Adverse events were coded according to MedDRA v. 24.1.

Study drug-related injection site reaction is defined as an adverse event marked as *Related* on the Adverse Event Electronic Case Report Form with the high-level term, injection site reactions.

Each SC dose consists of two SC injections into the abdomen.

Each injection site reaction was counted in the total; one subject could have multiple ISRs.

If a subject had more than one injection site induration or nodule event, the subject was counted in the *Ongoing* category.

Abbreviations: IQR, interquartile range; LEN, lenacapavir; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with an event; N, number of subjects; SC, subcutaneous; SD, standard deviation

Study 4334: LEN-Related Injection Site Nodules and Indurations

In the Week 54 analysis of Study 4334, 15 of 103 subjects (14.6%) experienced study drug-related injection site nodules, and 13 of 103 subjects (12.6%) experienced study drug-related injection site indurations ([Table 50](#)). All events were Grade 1 or 2 in severity, except for one subject with Grade 3 injection site nodules.

The duration of nodules and indurations occurring as a result of the first SC LEN injections dose was longer than those occurring as a result of the second LEN SC injections (since their follow-up was longer) and longer for ongoing ones (compared to resolved ones).

Study 4334: Injection Site Reactions After the First SC LEN Injections

After the first SC LEN injections, 39 of 103 subjects (37.9%) experienced LEN-related ISRs. The injection site nodules and indurations reported because of the first SC LEN injections included the following:

- Subject-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%)
- An event-level analysis is summarized in [Table 50](#).

Table 50. Event-Level Analysis of Ongoing and Resolved LEN–Related Injection Site Nodules and Indurations Due to the First LEN Injections, Study 4334 (Week 54)

Parameter	SC LEN n (%)
Number of subjects who received injections	103
Injection site nodules	13
Ongoing	1 (7.7)
Resolved	12 (92.3)
Injection site indurations	9
Ongoing	6 (66.7)
Resolved	3 (33.3)
Duration of ongoing injection site nodules, days	
N	1
Mean (SD)	550
Median	550
IQR	550, 550
Minimum, maximum	550, 550
Duration of resolved injection site nodules, days	
N	12
Mean (SD)	261 (141)
Median	278
IQR	133, 367
Minimum, maximum	26, 464
Duration of ongoing injection site indurations, days	
N	6
Mean (SD)	341 (197)
Median	412
IQR	122, 485
Minimum, maximum	57, 561

Parameter	SC LEN n (%)
Number of subjects who received injections	103
Duration of resolved injection site indurations, days	
N	3
Mean (SD)	172 (62)
Median	202
IQR	101, 213
Minimum, maximum	101, 213

Source: Clinical Reviewer's Analysis (JMP 16.2.0) of the adatae dataset.

Adverse events were coded according to MedDRA v. 24.1.

Study drug-related ISR is defined as an adverse event marked as related on the Adverse Event Electronic Case Report Form with the high-level term, injection site reactions.

Each SC dose consisted of two SC injections into the abdomen.

Each ISR was counted in the total. One subject could have multiple ISRs.

If a subject had more than one injection site induration or nodule event, the subject 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.

Abbreviations: IQR, interquartile range; ISR, injection site reaction; LEN, lenacapavir (GS-6207); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Study 4334: Injection Site Reactions After the Second SC LEN Injections

After the first SC LEN injections, 42 of 95 subjects (44.2%) experienced LEN-related ISRs. The injection site nodules and indurations reported because of the second SC LEN injections included the following:

- Subject-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%)
- An event-level analysis is summarized in [Table 51](#).

Table 51. Event-Level Analysis of Ongoing and Resolved LEN-Related Injection Site Nodules and Indurations Because of the Second LEN Injections, Study 4334 (Week 54)

Parameter	SC LEN n (%)
Number of subjects who received injections	95
Injection site nodules	8
Ongoing	5 (62.5)
Resolved	3 (37.5)
Injection site indurations	6
Ongoing	3 (50.0)
Resolved	3 (50.0)

Parameter	SC LEN n (%)
Number of subjects who received injections	95
Duration of ongoing injection site nodules, days	
N	5
Mean (SD)	260 (61)
Median	268
IQR	201, 316
Minimum, maximum	198, 343
Duration of resolved injection site nodules, days	
N	3
Mean (SD)	172 (61)
Median	152
IQR	123, 240
Minimum, maximum	123, 240
Duration of ongoing injection site indurations, days	
N	3
Mean (SD)	279 (75)
Median	262
IQR	214, 361
Minimum, maximum	214, 361
Duration of resolved injection site indurations, days	
N	3
Mean (SD)	136 (127)
Median	145
IQR	4, 258
Minimum, maximum	4, 258

Source: Clinical Reviewer's Analysis (JMP v. 16.2.0) of the adae dataset.

Adverse events were coded according to MedDRA v. 24.1.

Study drug-related ISR is defined as an adverse event marked as related on the Adverse Event Electronic Case Report Form with the high-level term, injection site reactions.

Each SC dose consisted of two SC injections into the abdomen.

Each injection site reaction was counted in the total. One subject could have multiple ISRs.

If a subject had more than one injection site induration or nodule events, the subject 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.

Abbreviations: IQR, interquartile range; ISR, injection site reaction; LEN, lenacapavir (GS-6207); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

17.4.2. Photographic and Dermatopathological Reports

During the review of the original NDA submissions, photographic documentation of injection site indurations or injection site nodules from Studies 5709, 4334, and 4625 were provided in response to the Agency's information request dated September 08, 2021. Refer to Section 7.7.2 of the Integrated Review dated February 28, 2022 from the first cycle.

For the NDA resubmissions, no additional photographic reports from Study 5709, 4334, or 4625 were included. The Applicant reported that although a few investigators were contacted regarding ongoing injection site nodules or injection site indurations, the investigators did not refer the study subjects for dermatological consultations because the ISRs had resolved or were not warranted. See [Table 52](#).

Table 52. Investigator Responses to Injection Site Nodules or Injection Site Indurations (Not Referred for Dermatologic Consultation), Studies 4625 and 4334

Subject ID	Injection Site Reaction	Grade	Onset Day	Investigator's Response
Study 4625				
(b) (6)	Injection site nodule	1	197	The investigator did not feel the subject needed to be referred for a dermatology consultation and was concerned that a biopsy could cause more harm than good in the current state of the nodules.
(b) (6)	Injection site nodule	1	198	The nodules had shrunk to the point that they could be felt but not really seen. The provider did not think it would be appropriate to refer him for a dermatology consultation for the current state of the nodules.
Study 4334				
(b) (6)	Injection site nodule	1	379	ISR completely resolved by (b) (6). No pictures were taken; No dermatologic consults or biopsies performed.
	Injection site nodule	1	197	Subject declined to see a dermatologist.
	Injection site induration	1	15	Subject declined to see a dermatologist.
	Injection site induration	1	198	
	Injection site induration	1	16	Subject declined to see a dermatologist.

Source: Adapted from the Applicant's Cumulative Review of Injection Site Reactions (Table 22, p. 55).
 Abbreviations: ID, identifier; ISR, injection site reaction

An updated safety monitoring plan, including dermatological assessment of ISRs of Grade ≥ 3 , or that did not resolve within 24 weeks, was communicated to investigators for all LEN studies that include SC dosing in February 2022. As of June 15 2022, the Applicant had received dermatologist assessments for two subjects from Study 4625 who met the aforementioned ISR criteria; a summary of the biopsy reports is provided in [Table 53](#).

Table 53. Summary of Available Biopsy Reports for Subjects Meeting Injection Site Reaction Criteria for Dermatological Assessment, Study 4625

Subject ID	Injection Site Reaction	Grade	Onset Day (Applicant)	Summary of Biopsy Report (Applicant)	Clinical Comment (Applicant)
(b) (6)	Injection site induration Injection site induration	1 1	15 561	The dermatopathology report from three different injection sites showed multinucleated foreign body-type giant cell reactions present within the deep dermis and SC space. No significant polarizable foreign body material, such as glass, was seen in any of the available samples.	These findings are consistent with the nonclinical findings in animals, as described in “Nonclinical data for LEN and other ARVs”
(b) (6)	Injection site nodule	1	562	Histochemical staining with Congo red supports diagnosis of amyloidosis. Secondary amyloidosis is triggered by the trauma of receiving an injection.	The subject received SC enfuvirtide twice a day for >3 years. The investigator stated that biopsy of the enfuvirtide injection site cannot be ruled out. “Pharmaceutical amyloidosis” associated with the use of SC enfuvirtide has been described ¹

Source: Adapted from the Applicant’s Cumulative Review of Injection Site Reactions (Table 22, p. 56).

¹ Morilla et al. (2009).

Abbreviations: ARV, antiretroviral; ID, identifier; LEN, lenacapavir; SC, subcutaneous

17.4.3. Assessment of the Role of the Physical and Chemical Characteristics of Lenacapavir in ISRs

The Applicant provided their assessment on the role of physical and chemical characteristics of LEN on ISRs; this included an assessment of nonclinical and clinical data for LEN and other antiretrovirals (ARVs). In summary, the Applicant states that their review of ISRs and pH for various SC ARVs as well as other LEN formulations did not identify a clear association between high pH of a formulation and ISRs. In addition, the Applicant believes that the ISRs observed in clinical studies with SC LEN, including nodules and indurations, are likely associated with the presence of a SC LEN depot.

The Applicant states that their available nonclinical data suggest that chronic granulomatous inflammation and foreign body response at the SC injection site are expected to occur for an antiretroviral compound, including LEN, due to the presence of a SC drug depot, and irrespective of the pH of the formulation.

Clinical Reviewer’s Comment: Based on the information provided, the review team agrees that the Applicant’s conclusions are reasonable.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Refer to Section 18 of the Integrated Review dated February 28, 2022 from the first review cycle.

19. Clinical Virology

Table 54. Virologic Failures at Week 52 (N=6 LEN Cohort 1A; N=5 Placebo Cohort 1B; N=11 Cohort 2)

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	LEN+FR	BIC FTC TAF		DAY1	259 not failing on regimen	L172L/I	M46I I47V F53L I54L K55R V82A L90M	M41L D67N L74V K101H/Q Y181C M184V L210W T215Y K219N L228H	L74M T97A Y143R G163R	BIC 0.6 FTC >75 TDF 1.3 LEN 1.0
			BIC FTC TAF	WK26 WK52	150 <20	None	AF	AF	AF	AF
(b) (6)	LEN+FR	BIC FTC TDF DOR IBL		DAY1	75,200	None	L33F M46I I54L G73S L76V I84V L90M	D67N K70R A98S V106M V108I Y181V M184V T215F K219E	L74I/M Q95Q/K E138E/K S147S/G M154L N155H E157E/Q	BIC 52 FTC >80 TDF 1.5 DOR >85 IBL-R LEN 0.76
				WK4	293	AF		D67N T69N K70R A98S Y181V M184V T215F K219E	L74L/I E138E/D M154L N155H/H K157E/Q	
			BIC FTC TAF DOR IBL	WK26	342	None	AF	AF	E96G M154L	AF
				WK52	574	AF	None	AF	AF	AF

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	LEN+FR	DRV/C FTC TDF		DAY1	884 not failing on regimen	H87Q	A71T	M41L D67G T69D V75M L100I K103N M184V L210W T215D K219R	E157Q	DRV 0.81 FTC >79 TDF 0.56 LEN 0.93
			DRV/c FTC TDF DOR	WK4 WK26 WK52	156 39 54	H87Q	AF	AF	AF	AF
(b) (6)	LEN+FR	DTG DRV MVC		DAY1	214 not failing on regimen	None	L33F F53L I54V	M41L E138K Y181C G190E T215C K219R		DTG >0.69 DRV 0.82 LEN 0.87
			BIC FTC TAF DRV MVC	WK4 WK26 WK52	186 81 45	None	None	Y181C T215C	I161T	DRV 0.9 BIC >0.52 FTC 1.3 TDF 0.87
										LEN 0.89 DRV 0.86 BIC AF FTC 1.1 TDF 0.82
(b) (6)	LEN+FR	LAM		DAY1	71,700	S41T T54M	M46I I54V V82A L89M	D67N K70R M184V T215F/I K219E	G140A Q148R	LAM >89 DRV 1.65 DTG AF LEN 0.91
			DTG DRV/r TDF	WK4	25,200	S41T T54M M66M/I K70K/N/ R/S V191V/I R229R/ K	AF	AF	AF	LEN AF
			DTG DRV/r TDF	WK10	28,900	S41A V59V/I K70N/S N74N/H	M36V	None	None	AF

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	LEN+FR	DRV/C FTC TDF		DAY1	377 not failing on regimen	S41T V191V/I	M46I L76V I84I/V	K101K/Q K103E/G/ R Y181Y/C T215F// S		DRV 1.1 FTC 1.2 TDF 0.73 LEN AF
			BIC FTC TAF	WK4	137	S41T N139N/ D V191I	N88N/K	None	V113I K136K/E G140D	LEN AF
				WK26 WK52	164 67	H120N	M46M/I I54I/L L76L/V I84I/V	None	AF AF	LEN AF LEN 1.72 FTC 0.98 TDF 0.91 BIC AF
(b) (6)	Placebo	DTG DRV/C LAM ENF MVC		DAY1	102,000	S41T H87Q	V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41M/L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	DTG >89 DRV 386 LAM >89 ENF-R MVC-R LEN 0.85
			DTG DRV/C LAM ENF MVC	WK10	5440	S41A/T H87Q M66I N74D A105T	V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	DTG >196 DRV 474 LAM >65 ENF-R MVC-R LEN >1428
				WK22	206	S41A M66I Q67Q/H N74D H87Q A105T	V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	AF
				WK26	19		V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	AF

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	Placebo	DTG ABC LAM		DAY1	52,400 (Day 2)	S41A	T74T/A	M41M/L K101Q K103R Y181Y/C M184M/V L210L/W T215C	T97T/A E138E/K S147S/G N155N/H K156N	DTG 1.4 ABC 2.8 LAM >91 LEN 1.04
			DRV/C FTC TAF	WK4	6380	S41A I115I/V	H69H/Q	M41M/L K43K/T K101Q K103R Y181Y/C M184M/V L210L/W T215C	AF	DRV 0.73 FTC 3.9 TDF 0.96 LEN 0.71
				WK52	3340	I115I/V G225G/ S		M41M/L K101Q K103R Y181Y/C M184M/V L210L/W T215C	T97T/A S147S/G N155N/H L156N	LEN 0.67 DRV 0.95 TDF 0.84 FTC 2.8
(b) (6)	Placebo	FTC TDF IBL		DAY1	62,100	S41T Q50A/S T107S	M46I I47V I50V K55R A71V G73E L76V V82T L89V	M41L D67N L74I A98A/G L100I K103N V108V/I M184V L210W T215Y K219N L228H	T97A E138K G140S Q148H G163S	FTC >83 TDF 1.8 IBL-R LEN 1.33
			DTG DRV FTC TAF IBL	WK4	2150	S41T Q50A T107S M66M/I	M36M/I M46I I47V I50V K55R A71V G73E L76V V82T L89V	M41L D67N L74I L100I K103N K104K/R V108I M184V L210W T215Y K219N L228H	T97A E138K G140S Q148H G163S A175A/T	DTG 137 DRV 215 FTC >68 TDF 1.1 IBL-R
				WK26	2420	S41T Q50A M66M/I A105A/ T T107S	M36M/I M46I I47V I50V K55R A71V G73E L76V V82T L89V	M41L D67N L74I L100I K103N K104K/R V108I M184V L210W T215Y K219N L228H	AF	TDF 1.4 LEN 46

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
				Wk52	2970	M66I A77A/V A105T T107S			M50M/T T97A E138K G140S Q148H G163G/S	LEN 111
(b) (6)	Placebo	DRV/C FTC TDF		DAY1	193,000	None	V77I	K65K/R S68S/G Y181C M184M/V	E92Q	DRV 0.83 FTC >100 TDF 0.58 LEN 0.9
		DTG DRV/C RPV TAF FTC		Wk26	561	M66I A78S	V77I	K65R S68N Y181C		DTG >0.51 DRV 0.77 RPV 2.2 LEN 138
				Wk52	11,400	M66I N74D A78S A105T		K65R S68N R199K		LEN 1064 DTG 0.91 DRV 0.63 RPV 1.84 FTC >100 TDF 1.74
(b) (6)	Placebo	DRV/ FTC		DAY1	175,000	E75D	V32I L33M M46L I54L K55K/R G73S T74P I84V I85V L89V L90M	A62V D67E T69G/S A98G V106I Y181F M184V Y188L L210W T215Y		DRV >568 FTC >68 LEN 0.89 DTG 0.61
		DTG LAM IBL MVC		Wk4	260			V32I L33M M46L I54L G73S T74P I84V I85V L89V L90M	E96E/G	DTG AF LAM >49 IBL AF MVC AF
				Wk26	91	E75D				LEN 0.61
(b) (6)	LEN+ OBR	EVG/C FTC TAF		DAY1	1230	H87Q I91V		Y188L	K156N	TDF 1.1 DRV 0.72 DTG AF LEN AF
		DTG TDF DRV/C		Wk10	1280					TDF 1.1 DRV 0.92 DTG AF LEN AF
				Wk26	2350					
				Wk52	2630	H87Q I91V		Y188L	K156N	TDF 1.1 DRV 0.7 DTG AF LEN AF

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	LEN+ OBR	BIC FTC TAF DOR		DAY1	880 (not failing regimen)	H87H/Q I91V		D67N T69N K70E K101E V106I E138E/K H221Y	G140G/S Q148Q/H	DOR 26 FTC 5.6 TDF 1.1 BIC 1.1 ATV 1.4 LEN 1.1
			ATV BIC FTC TAF DOR	WK4 WK52 WK62	424 26 188	H87H/Q I91V	M36M// V	D67N T69N K70E K103N/S M184I/V H221H/Y	AF	DOR 0.21 FTC 28 TDF 0.6 BIC AF ATV 1.2 LEN 1.5
(b) (6)	LEN+ OBR	DTG FTC TAF FTR IBL		DAY1	112,000	T107T/S	V32I L33M M36I M46I I47V I50V I54T A71I G73D V77I V82I/L I85V L89V L90M	M41L D67N K70R K103S V118I E138Q V179I Y181C M184V H208Y L210W Y215Y K219E L228H	T97A E138T G140S Q148H K156K/N	DTG 126 FTC >55 TDF 0.7 FTR-R IBL-R LEN 1.0
			DTG FTC TAF FTR IBL	WK4	101,000	V11V/I M66M/I Q67Q/H /K/N T107T/S I124I/V	AF	AF	AF	
				WK10	68,100	V11V/I M66M/I Q67Q/H /K/N K70K/R T107T/ C/S	V32I L33M M36I M46I I47V I50V I54T A71I G73D V77I V82I/M I85V L89V L90M	M41L D67N K70R K103S V118I E138Q V179I Y181C M184V H208Y L210W Y215Y K219E L228H	AF	DTG AF FTC AF TDF AF FTR-R IBL-R LEN 12.2

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	LEN+ OBR	RAL TDF AZT		DAY1	506,000	None	M36I K43R M46I V82F L89I	D67N K70R	Y143C	DRV 0.55 DTG AF FTC 2.1 TDF 2.3 AZT 14 AF
			DRV/C DTG FTC TDF	WK36	137	AF	AF	AF	AF	AF
				WK52	161	T107S	D30D/G M36I K43K/R M46M/I V82V/F I89I	K65K/R D67D/N K70K/R V106V/M V118V/I Q151Q/R	V151V/I D167D/E	AF
(b) (6)	LEN+ OBR	DRV DTG		DAY1	23,800	None	M36I I54V	D67D/N K70K/N K101E K103R E138K T215C		DRV 1.9 DTG 0.6 LEN 1.3
			DRV/C DTG	WK10	100,500	K70H A105A/ S/T T107T/ N		K101E K103R E138K T215C		DRV 1.7 DTG 0.99 LEN 265
				WK36	32,700	Q67K	M36I	K101E	None	DRV 1.7
				WK52	28800	K70H	I54V	K103R E138K T215C		DTG 0.81 LEN 342
(b) (6)	LEN+ OBR	DRV DTG FTC TAF ETR ENF		DAY1	10,400	None	V32I L33V M36I M46I I54M G73D I84V L89V L90M	M41L D67N K70R K103N V108I V179I Y181C M184V T215F K219E L228H		DRV 329 DTG 0.5 FTC >68 TDF 1.4 ETR 19 ENF-S LEN AF
			DRV DTG FTC TAF ETR ENF	WK26	108	None	V32I L33V M36I	M41L D67N K70R		DRV 337 DTG AF FTC >56 TDF 1.5
				WK36 (resuppr essed)	21		M46I I54M G73D I84V L89V L90M	K103N V108I V179I Y181C M184V T215F K219E L228H		ETR 18 ENF-S LEN 0.8
				WK52	112	AF	AF	AF	AF	LEN 0.61

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	LEN+	DOR		DAY1	43,900	None	V32I	M41L	E138A	DOR >86
	OBR	FTR IBL					L33F M36I I54L A71V T74P V82L I84V I85V L89V L90M	K65R S68G T69I V75I F77L V106I/M V118I Q151M V179I Y181C P225Y L228R	G140A S147G Q148R N155H E157Q	FTR-R IBL-R LEN 1.2
(b) (6)			DOR	WK10	6220	M66I T107A	V32I	M41L	E138A	DOR >95 FTR-R IBL-R LEN 239
		FTR IBL	WK22 WK36	30,200 30	I54L A71V T74P V82L I84V I85V L89V L90M		K65R S68G T69I V75I F77L K104R V106M V118I Q151M V179I Y181C P225Y L228R	G140A S147G Q148R N155H E157Q		
(b) (6)	LEN+	DRV DTG		DAY1	4590	None	D30N	D67N	E138T	DRV 1.3
	OBR	DOR FTC TAF FTR					M36I A71A/T N88D	K70R V90I K103N V106I V118I V179I Y181C	G140S Q148H	DTG ND DOR 19 FTC 2.2 TDF 0.99 FTR-R LEN 1.05
(b) (6)			DRV	WK16	5410	None	D30N	D67N	E138T	DRV 1.3
			DTG IBL	WK26 WK36 (resuppressed)	<20 <20		M36I N88D	K70R V90I K103N V118I V179I Y181C	G140S Q148H	DTG 11 DOR 2.2 FTC 2.6 TDF 1.2 FTR-R LEN AF
(b) (6)	LEN+	DRV FTC		DAY1	20,400	None	M36I	D67N	V151V/I	DRV 0.62
	OBR	TDF					L89M	K70R L74I A98G K101H V108I M184V G190A K219Q	N155H	FTC >68 TDF 1.14 LEN 1.5
(b) (6)			DRV	WK26	116	None	AF	AF	AF	LEN 1.6
			FTC TDF	WK36	40					

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

PID	Arm	Failing BGRD Regimen	OBR	Timept	HIV VL	Capsid RAS	PI RAS	RT RAS	INSTI RAS	Phenotypic Resistance
(b) (6)	LEN+ OBR	DRV DTG DOR FTC TAF IBL		DAY1	191,000	T107T/S	V32I L33L/F M36I I47V A71V V77V/I V82V/I	D67N T69D K70K/R V106V/M E138E/G V179D// N Y181F// N T215T/I K219Q	NONE	DRV 2.7 DTG 0.81 DOR 104 FTC 3.2 TDF 0.76 IBL-R LEN 1.1
			DTG DRV BIC FTC TAF	WK4	75,500	Q67H K70R T107S	AF	AF	AF	DRV 2.7 DTG 0.81 DOR 104 FTC 3.2 TDF 0.76 IBL-R LEN 15
(b) (6)	LEN+ OBR	DRV/C DTG FTC TAF RPV		DAY 1	63800		M36L G48T T74T/A I84V	L74A K103K/N V106M M184V G190G/A	T66I G118R E157Q	
			DRV/C DTG FTC TAF RPV	WK52	4480	Q67Q/H	M36L	None	T66I G118R E157Q	LEN 6.6

Source: FDA.
 Bolded PIDs indicate subjects with emergent resistance to LEN and/or OBR; bolded text indicates RAS or phenotypic resistance. None, no emergent RAS.
 Abbreviations: ABC, abacavir; AF, assay failure; ATV, atazanavir; AZT, azidothymidine; BGRD, background; BIC, bicitgravir; BL, baseline; DOR, doravirine; DRV, darunavir; DRV/C, darunavir; DTG, dolutegravir; ENF, enfurvitide; ETR, etravirine; EVG, elvitegravir; FR, failing regimen; FTC, emtricitabine; FTR, fostemsavir; HIV, human immunodeficiency virus; IBL, ibalizumab; INSTI, integrase strand transfer inhibitor; LAM, lamivudine; MVC, maraviroc; OBR, optimized background regimen; PI, protease inhibitor; PID, patient identifier; -R, resistant; RAL, raltegravir; RAS, resistance-associated substitution; RPV, rilpivirine; RT, reverse transcriptase; -S, sensitive; TAF, tenofovir alafenamide; TDF, tenofovir alafenamide fumarate; timept, timepoint; VL, viral load; WK, week

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Refer to Section 20 of the Integrated Review dated February 28, 2022 from the first cycle.

21. Labeling Summary of Considerations and Key Additional Information

Initial comments on the Applicant's proposed labeling were conveyed on October 18, 2022 and the Applicant responded on October 24, 2022.

United States Prescribing Information Labeling Review

Overview of Major Labeling Changes

- Highlighted below are significant changes made to the prescribing information from the Applicant's proposed labeling submitted on June 28, 2021 for Sunlenca (lenacapavir).
- HIGHLIGHTS and TABLE OF CONTENTS were revised for consistency with the full Prescribing Information.

1 INDICATIONS AND USAGE

- The indications statement was modified (b) (4)
[Redacted]
 - The indication statement was modified (b) (4)
[Redacted]
- Associated changes have also been made in Section (b) (4). Refer to Section (b) (4) of the previous, February 28, 2022 review.

2 DOSAGE AND ADMINISTRATION

- The final approved labeling will include two options for initiation. Option 1, as initially proposed by the applicant; and Option 2, an 'oral' lead-in option, agreed to with the Applicant through the course of the review. Refer to Section 6.3.2. of the previous, February 28, 2022 review.
- [Redacted] (b) (4)
- Instructions to inspect for particulates has been expanded to include inspection of the prepared syringe in addition to the drug vial. This addition added in consideration of the potential for particulates (b) (4).

3 CONTRAINDICATIONS

- The contraindication initially proposed (b) (4) has been revised to contraindicate use with 'strong CYP3A inducers'. Refer to Section 8.2.2. of the previous, February 28, 2022 review.

4 WARNINGS AND PRECAUTIONS

- A new Warnings and Precautions subsection has been added to discuss the long-acting properties and potential associated risks with SUNLENCA. This new subsection addresses the risk of viral resistance if not transitioned to alternative therapy as well as the potential for adverse reactions through interaction with sensitive CYP3A substrates with narrow therapeutic indices for up to 9 months after the last subcutaneous dose. Refer to Section [6.2](#) of the previous, February 28, 2022 review.
- A new Warnings and Precautions subsection has been added to discuss the risk of injection site reactions (ISRs). This new subsection has been added in consideration of the long duration of nodules and indurations, relatively high incidence of ISRs and discontinuations seen as a result in the clinical studies. Refer to Section [7.7.2](#) of this review.

5 ADVERSE REACTIONS

- Discussion has been added to Section 6.1 to discuss local injection site reactions. Refer to Section [7.7.2](#) of this review.

6 DRUG INTERACTIONS

- A section regarding Narcotic Analgesic/Treatment of Opioid Dependence has been added to the drug interactions table.

-  (b) (4)

7 CLINICAL PHARMACOLOGY

- Exposure-response data have been added to Section 12.2.
- Information regarding In Vitro Studies of drug interactions was added.

8 CLINICAL STUDIES

- Upon submission of the second review cycle of this application, 52 week data were added.

22. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) will be issued under NDA 215973 at the time of approval.

- Pediatric Research Equity Act PMR 4351-1: Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of lenacapavir in treatment-experienced children living with HIV-1 infection who are less than 18 years of age and weighing at least 35 kg. The safety and antiviral activity of lenacapavir in pediatric subjects must be evaluated for a minimum of 24 weeks.
 - PMR Milestones:

▪ Draft Protocol submission:	August 2023
▪ Final Protocol submission:	November 2023
▪ Study completion:	March 2027
▪ Final Report submission:	September 2027
- 4351-2: Conduct a 2-year carcinogenicity study in rat to assess the carcinogenic potential of lenacapavir.
 - PMR Milestones:

▪ Final Protocol submission:	March 2020 (submitted)
▪ Study completion:	August 2023
▪ Final Report submission:	September 2023

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- 4351-3: Submit final study reports with datasets from Studies GS-US-200-4625 and GS-US-200-4334. Provide comprehensive assessments of injection site nodules and indurations associated with the first subcutaneous injections, which must be followed until resolution or until study completion, in the final study reports.
 - PMR Milestones:
 - Final Protocol submission: September 2019 (completed)
 - Trial completion: October 2023
 - Final Report submission: June 2024

The following postmarketing requirements (PMRs) will be issued under NDA 215974 at the time of approval.

- Pediatric Research Equity Act PMR 4365-1: Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of lenacapavir in treatment-experienced children living with HIV-1 infection who are less than 18 years of age and weighing at least 35 kg. The safety and antiviral activity of lenacapavir in pediatric subjects must be evaluated for a minimum of 24 weeks.
 - PMR Milestones:
 - Draft Protocol submission: August 2023
 - Final Protocol submission: November 2023
 - Study completion: March 2027
 - Final Report submission: September 2027
- 4365-2: Conduct a 2-year carcinogenicity study in rats to assess the carcinogenic potential of lenacapavir.
 - PMR Milestones:
 - Final Protocol submission: March 2020 (submitted)
 - Study completion: August 2023
 - Final Report submission: September 2023

The following postmarketing commitments (PMCs) will be issued at the time of approval under NDA 215973.

- 4351-4: Complete the vial compatibility study (i.e., (b) (6)) for the remaining time points of the registration stability batches and three production batches and submit the report as a CBE-0 supplement.
 - PMC milestones:
 - Interim Report submission: (b) (4) (March 30, 2023); (b) (4) (March 30, 2024)
 - Final Report submission: November 30, 2024

- 4351-5: Evaluate the upcoming stability time points of the registration batches and first three production batches (at release and over stability studies) of lenacapavir injection using the proposed instructions for use (IFU) for (b) (4) particulates in both visible and subvisible size ranges (i.e., 10 µm to 25 µm; 25 µm to 50 µm; 50 µm to 100 µm; 100 µm to 150 µm and >150 µm) Submit the optical microscopy and SEM-EDX analysis data for the vials stored in both inverted and upright orientations. Report any trend or increase in particulates with vial orientation, time etc. and provide explanation including details of any investigation into the source of the increase. Also, submit optical microscopy and SEM-EDX data from multiple batches (e.g., three batches) of the control vials (filled with polyethylene glycol and water mixture) prepared using both vial decrimping and proposed IFU procedures. Submit the interim and final study reports as CBE-0 supplements.
 - PMC milestones:
 - Interim Report submission: (b) (4) (b) (4) (March 30, 2023); (b) (4) (March 30, 2024)
 - Final Report submission: November 30, 2024
- 4351-6: Evaluate an alternative device/s (i.e., vial access device, needle, etc.) and/or procedure for withdrawing the lenacapavir injection from the vial, which consistently reduces the presence of (b) (4) particulates in the drug product solution to (b) (4).

(b) (4)

Provide supporting data (e.g., optical microscopy, SEM-EDX, USP <788> subvisible particulates data etc.) from multiple drug product batches (e.g., three batches) tested at release and multiple time points over stability studies (long-term and accelerated storage conditions) under both upright and inverted orientation to support the alternative device/procedure.

 - PMC milestone:
 - Final Report submission: August 30, 2023

23. Financial Disclosure

Refer to Section 23 of the Integrated Review dated February 28, 2022 from the first cycle.

24. References

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25. Review Team

Refer to Section 25 of the Integrated Review dated February 28, 2022 from the first cycle.

Table 55. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Kevin Allen, MS
Nonclinical Reviewer	Deacquinta Diggs, PhD
Nonclinical Team Leader	L. Peyton Myers, PhD, DABT
Office of Clinical Pharmacology Reviewers	Jenny Zheng, PhD Xing Jing, PhD Elyes Dahmane, PhD
Office of Clinical Pharmacology Team Leader(s)	Mario Sampson, PharmD Justin Earp, PhD
Clinical Reviewer	Timothy Jancel, PharmD, MHS
Clinical Team Leader	Benjamin Lorenz, MD
Clinical Virology Reviewers	Lisa Naeger, PhD Eric Donaldson, PhD
Clinical Virology Team Leader	Jules J O'Rear, PhD
Statistical Reviewer	Hengrui Sun, PhD
Statistical Team Leader	Thamban Valappil, PhD
Associate Director for Labeling (OCHEN)	Michael Monteleone, MS, RAC
Cross-Disciplinary Team Leader	Benjamin Lorenz, MD
Division Director (DPTID)	Hanan Ghantous, PhD
Associate Director for Therapeutic Review (OCP/DIDP)	Vikram Arya, PhD, FCP
Division Director (OB)	Dionne Price, PhD
Deputy Division Director (acting, clinical)	Wendy Carter, DO
Division Director (clinical)	Debra Birnkrant, MD
Office Director (or designated signatory authority)	Adam Sherwat, MD

Abbreviations: DDPD, Division of Infectious Disease Pharmacology; DPTID, Division of Pharm/Tox for Infectious Diseases; OB, Office of Biostatistics; OCHEN, Office of Cardiology, Hematology, Endocrinology and Nephrology; OCP, Office of Clinical Pharmacology

NDA 215973 Sunlenca (lenacapavir) injection, for subcutaneous use
 NDA 215974 Sunlenca (lenacapavir) tablets, for oral use

Table 56. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
CMC ATL	Peter Guerrieri, PhD
Drug Product	Shalini Anand, PhD
Drug Substance	Karina Zuck, PhD
Biopharmaceutics	Qi Zhang, PhD Elsbeth Chikhale, PhD
Process/Facility (NDA 215973)	David Acevedo, PhD Steve Rhieu, PhD
Process/Facility (NDA 215974)	Abdollah Koolivand, PhD Hang Guo, PhD
Microbiology	Sallie Crenshaw, PhD Erika Pfeiler, PhD
RBPM	Erica Keafer
OPDP	Wendy Lubarsky, PharmD
OSI	Elena Boley, MD Phillip Kronstein, MD
OSE/DEPI	Natasha Pratt, PhD Yan Li, PhD
OSE/DMEPA	Melina Fanari, RPh Madhuri Patel, PharmD
OSE/DRM	Laura Zendal, PharmD Theresa Ng, PharmD
DMPP	Jessica Chung, PharmD Barbara Fuller, RN
DDD	Patricia Brown, MD Kevin Clark, MD Shari Targum, MD

Abbreviations: ATL, Application Technical Lead; CMC, chemistry, manufacturing, and controls; DDD, Division of Dermatology and Dentistry; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DRM, Division of Risk Management; NDA, new drug application; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; RBPM, Regulatory Business Project Manager

Table 57 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Deacquita L. Diggs, PhD	OND/OID/DPTID	☒ Authored 13; 13.1; ☐ Approved 13.2
Reviewer	Signature: Deacquita L. Diggs -S Digitally signed by Deacquita L. Diggs -S Date: 2022.11.30 13:37 35 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Laine Peyton Myers, PhD, DABT	OND/OID/DPTID	☐ Authored ☒ Approved
Team Leader	Signature: Laine P. Myers -S Digitally signed by Laine P. Myers -S Date: 2022.11.30 14:59:46 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Hanan Ghantous, PhD, DABT	OND/OID/DPTID	☐ Authored ☒ Approved
Division Director	Signature: Hanan N. Ghantous -S Digitally signed by Hanan N. Ghantous -S Date: 2022.11.30 22:42:00 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Virology	Lisa Naeger, PhD	OND/OID/DAV	2.1; 7.7.1; 19 ☒ Authored ☐ Approved
Reviewer	Signature: Lisa K. Naeger -S Digitally signed by Lisa K. Naeger -S Date: 2022.11.30 15:48 53 -05'00'		

¹ Include “IA” for authors who contributed to the Interdisciplinary Assessment.
 Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Virology	Eric Donaldson, PhD	OND/OID/DAV	☒ Authored ☐ Approved Contributed to Section 7.7.1
Secondary Reviewer	Signature: Eric F. Donaldson -S  Digitally signed by Eric F. Donaldson -S Date: 2022.11.30 17:04:04 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Virology	Jules O'Rear, PhD	OND/OID/DAV	2.1; 7.7.1; 19 ☒ Authored ☒ Approved
Team Leader	Signature: Julian J. O'rear -S  Digitally signed by Julian J. O'rear -S Date: 2022.12.01 07:03:55 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Jenny Zheng, PhD	OTS/OCP/DIDP	Section 21 ☒ Authored ☐ Approved
Reviewer	Signature: Huimin Zheng -S  Digitally signed by Huimin Zheng -S Date: 2022.12.01 09:23:28 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Xing Jing, PhD	OTS/OCP/DIDP	Section 21 ☒ Authored ☐ Approved
Reviewer	Signature: Xing Jing -S (Affiliate)  Digitally signed by Xing Jing -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=9.2342.19200300.100.1.1 2001331871, cn=Xing Jing -S (Affiliate) Date: 2022.12.01 10:03:43 -05'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
 Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Cross-Disciplinary	Adam Sherwat, MD	OND/OID	☐ Authored ☒ Approved
Signatory Authority	See DARRTS signature below		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

BENJAMIN D LORENZ
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ADAM I SHERWAT
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY IND ASSESSMENT AND EVALUATION

Application Number*: NDA 215973; 215974
Supporting Document Number/s: 38; 29
CDER Receipt Date: June 27, 2022
Sponsor: Gilead Sciences, Inc.
Product: Lenacapavir (GS-6207)
Pharmacologic Class: Inhibitor of HIV capsid
Indication: Treatment of HIV-1 infection
Therapeutic area: Anti-viral
Clinical Review Division: Division of Antivirals (DAV)
Pharm/Tox Division: Division of Pharm/Tox for Infectious
Diseases (DPT-ID)
Reviewer: Deacquinta L. Diggs, Ph.D.
Supervisor/Team Leader: L. Peyton Myers, Ph.D., DABT
Project Manager: Kevin Allen, M.S.
Purpose of Review: Study Report Review

- 26-Week Carcinogenicity study in
RasH2 Mice

Reviewer Completion Date: November 4, 2022

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3 Studies Submitted

3.1 Studies Reviewed

Study no. TX-200-2068 GS-6207^{(b) (4)}: A 26-Week Subcutaneous Carcinogenicity Study in 001178-T (Hemizygous) RasH2 Mice

8 Carcinogenicity

8.1 Study Title*: GS-6207^{(b) (4)}: A 26-Week Subcutaneous Carcinogenicity Study in 001178-T (Hemizygous) RasH2 Mice

Study no.: TX-200-2068
Study report location: Lorenze docuBridge 4.2.3.4.1
Study initiation date: August 20, 2020
Conducting laboratory and location: ^{(b) (4)}
GLP compliance: Yes
Drug, lot #, and % purity: GS-6207^{(b) (4)}, Lot no. 6207^{(b) (4)}-BC-1P, 99.7% pure
Prior Exec CAC Dose Concurrence: Y
Basis for Dose Selection: The high dose was the maximum tolerated dose based on potential liver toxicity. The mid- and low- doses were selected to provide adequate AUC spacing between dose levels.

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings:

No test article-related effects were noted in the incidence of neoplastic or non-neoplastic findings.

Methods

Doses:	0, 30, 100, and 300 mg/kg/dose
Frequency of dosing:	Once every 13 weeks (2 total doses)
Number/Sex/Group:	25/sex/group
Dose volume:	1000 µl/kg (0 and 300 mg/kg groups); 100 µl/kg (30 mg/kg group); 333 µl/kg (100 mg/kg group)
Formulation/Vehicle:	(b) (4) % w/w PEG-300 and (b) (4) % w/w sterile water for injection
Route of administration:	SUBCUTANEOUS
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2)
Age:	9 to 10 weeks
Comment on Study Design and Conduct:	The CAC agreed to the proposed doses but also recommended the addition of a saline control group because the concentrations of the formulation contents differed from those used in the repeat dose toxicology studies. The sponsor did not include the recommended saline control group.
Dosing Comments (Dose Adjustments or Early Termination):	On day 85 a positive control animal was necropsied prior to its scheduled termination. No other protocol deviations effected data interpretation.
Dosing Solution Analysis:	Dosing solutions met acceptance criteria. The test article was not detected in the control solution.

Table 1: Study Design

Group ^a	Dose Level ^b (mg/kg/dose)	Dose Concentration ^b (mg/mL)	Number of Animals	
			Males	Females
1 (Vehicle Control)	0	0	25	25
2 (Low)	30	300	25	25
3 (Intermediate)	100	300	25	25
4 (High)	300	300	25	25
5 (Positive Control) ^c	75	7.5	10	10

NA = Not applicable.

a Group 1 were administered vehicle control only.

b Animals in Groups 1 and 4 were dosed at a volume of 1000 µL/kg. Animals in Group 2 were dosed at a volume of 100 µL/kg. Animals in Group 3 were dosed at a dose volume of 333 µL/kg.

c Group 5 were dosed with one intraperitoneal administration of N-methyl-N-nitrosourea (MNU) on Day 1 of the dosing phase. These animals were included as positive controls to ensure animals supplied appropriately expressed oncogenes and responded to the carcinogenic insult.

Observations and Results

Mortality

Animals were checked twice daily for mortality and signs of pain or distress. The survival rates are presented in **Table 1**. The animal was found dead or sacrificed early due to its moribund condition were noted as the causes of death. The overall lowest survival rate (76%) was in males dosed with 100 mg/kg, whereas, in high dosed males (300 mg/kg), the survival rate was 92% which is similar to that seen in control males (96% survival). The higher incident of mortality in males at 100 mg/kg is unlikely related to the test article because the mortality incidence in males at 300 mg/kg was similar to controls and this effect was not seen in females.

Table 2: Overall Survival Rates

Daily Dose (mg/kg/dose)	0 (Control)		30 (Low)		100 (Intermediate)		300 (High)	
Gender: Number of Animals	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25	M: 25	F: 25
Died or sacrificed moribund ^a	1	1	1	1	6	4	2	3
Terminal sacrifice	24	24	24	24	19	21	23	22
Survival (%)	96	96	96	96	76	84	92	88

F = female; M = male

^aNo GS-6207-related effect on survival was noted.

Clinical Signs

Cageside observations were conducted once daily. Detailed observations were conducted at predose, prior to dosing on day 1, and weekly throughout the study.

Test article administration resulted in injection site reactions of raised areas at dosing site A in 12 out of 25 males at 100 mg/kg and in 10 out of 25 males at 300 mg/kg. Additionally at dosing site B, the area was raised in 12 out of 25 males at 100 mg/kg and in 19 out of 25 males at 300 mg/kg. The raised areas had pale discoloration.

Similar to males, test article administration in females resulted in a raised area at dosing site A in 1 out of 25 females at 100 mg/kg and in 15 out of 25 females at 300 mg/kg. At dosing site B, the area was raised in 7 out of 25 females at 100 mg/kg and in 18 out of 25 females at 300 mg/kg. The raised areas had pale discoloration.

Body Weights

Animals were weighed once during predose, prior to dosing on day 1, and weekly thereafter. There were no test article related effects.

Feed Consumption

Food intake was recorded weekly. Any wet or spilled food was also noted. There were no test article related effects.

Gross Pathology

Animals were necropsied at the end of the study on day 183 via isoflurane inhalation.

There was a dose related increase in injection site reactions (raised area) for both injections sites A and B in males and females. This finding correlates to the pseudocyst finding noted during histopathology analysis.

All other findings were considering sporadic or incidental due to their low incidences, presence in dosed and control animals, or common in this animal model.

Histopathology

Peer Review Conducted: Yes

(b) (4)

Historical Control Provided for Tumor Incidence: The sponsor did not provide historical control data from the lab where the study was conducted but stated that findings were within historical control ranges from the lab as well as published incidence data in RasH2 mice (Paranjpe et al., 2019)

Subcutaneous Injection site A:

Pseudocyst: There was a dose dependent increase in males at 100 and 300 mg/kg only. In females there was a dose dependent increase across doses. This finding correlated with injection site reactions noted during gross pathology.

Subcutaneous Injection site B:

Pseudocyst: There was a dose dependent increase in males and females across doses. This finding correlated with injection site reactions noted during gross pathology.

Skin:

There was one skin papilloma noted in a single female dosed 300 mg/kg that was terminated early due to its moribund condition at week 15. The sponsor stated this finding was within historical control. This finding is unlikely related to the test article because it was a single incidence and animals that reached their scheduled necropsy of 27 weeks did not have this finding.

Neoplastic

There were no statistically significant GS-6207-related findings.

Non Neoplastic

There were no statistically significant GS-6207-related findings.

12 References

Paranjpe MG, Belich JL, Mann PC, et. Al. (2019). A comparison of spontaneous tumors in Tg.rasH2 mice in 26-week carcinogenicity studies conducted at a single test facility during 2004 to 2012 and 2013 to 2018. Toxicol Pathol; 47(1):18-25.

The following 14 pages have been withheld in full as duplicate text of Statistical Review and Evaluation, Carcinogenicity Study. Please see document on page 192 of this review.

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES

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M E M O R A N D U M

Date: November 17, 2022
From: Patricia Brown, MD, Medical Officer, Division of Dermatology and Dentistry (DDD)
Through: Kevin Clark, MD, Acting Clinical Team Leader, DDD
Shari Targum, MD, Deputy Division Director, DDD
To: Dr. Tim Jancel, OID/DAV (Division of Antivirals) (*Senior Clinical Analyst*)
Kevin Allen, CSO, OID/DAV
CC: Margaret Kober, CPMS
Re: DDD Consult #2133: Lenacapavir (NDA 215973, NDA 215974)

Lenacapavir (LEN) is currently under review as an NME under two NDAs, 215973 [injectable (SC) (b) (4)] and 215974 (tablets). The proposed indication by the Applicant is (b) (4)

The Division of Dermatology and Dentistry was previously consulted because injection site reactions (ISRs) were the most common adverse reaction with lenacapavir subcutaneous injection. Based on preclinical histology in rats, rabbits and dogs these reactions were observed to be inflammatory granulomas. One of DAV’s concerns was that injection site nodules and indurations can possibly last several weeks/months, and the longer-term safety data included in the resubmissions may help to further describe and understand injection site reactions associated with LEN.

DAV is requesting DDD’S review and assessment of the Applicant’s Cumulative Review of Injection Site Reactions, including the Applicant’s assessment of high pH formulations and ISRs. DAV requests any recommendations for communication of ISRs in labeling.

Additionally, per email dated July 18, 2022: DAV requests a review of Applicant's responses to FDA additional comments in complete response letters dated, February 28, 2022 (2.2.1 Comment 6).

Materials Reviewed:

- NDA 215973 (Supporting Document # 1: 06/28/2021):
 - Section 2.5: Clinical Overview
 - Section 5.3.5.1:
 - Study GS-US-200-4625 Interim Week 26 Clinical Study Report
 - Narratives – Interim Week 26
 - Amendment: 90-Day Safety Update Report (SD# 11 received 9/24/2021)
- Responses to Information Requests:
 - Response (9/23/2021- SD# 9) to Information Request submitted (9/8/2021)
 - Response (10/26/2021- SD# 16) to Information Request submitted (10/12/2021)
- NDA 215973 (Supporting Document # 38: 06/27/2022 – Class 2 Resubmission)
 - Module 1.11.3 Response to FDA Additional Comments in Complete Response Letters dated 28 February 2022
 - 2.2.1 Comment 6
 - Section 2.7.4:
 - Summary of Clinical Safety Addendum
 - Section 5.3.5.3:
 - Resubmission Safety Update - Report
 - Resubmission Safety Update – Cumulative Review of ISRs
- FDA product labeling:
 - BYDUREON BCISE® (exenatide extended-release) injectable suspension, for subcutaneous use. Initial U.S. Approval: 2005
 - CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension, co-packaged for intramuscular use. Initial U.S. Approval: 2021
 - FUZEON® (enfuvirtide) for Injection. Initial U.S. Approval: 2003
- Literature references (see Appendix B)

Questions for DDD

1. We request your review and assessment of the Applicant's Cumulative Review of Injection Site Reactions, including the Applicant's assessment of high pH formulations and ISRs.
2. (Per email dated July 18, 2022) Review of Applicant's Responses to FDA Additional Comments in Complete Response Letters dated February 28, 2022: 2.2.1 Clinical Comment 6
“Please submit a complete assessment of the extent to which glass particulate contamination, including sub-visible particles, may be associated with injection site nodules and indurations or other clinical effects.”
3. We request any recommendations for communication of ISRs in labeling, specifically a response to the Applicant's rationale to (b) (4) to describe the duration of ISRs, nodules, and indurations.

DDD Response:

1. Review and assessment of the Applicant's Cumulative Review of Injection Site Reactions, including the Applicant's assessment of high pH formulations and ISRs.
 - Review and assessment of the Applicant's Cumulative Review of Injection Site Reactions (Focused on nodules and indurations):

Nodules and indurations were seen commonly across trials in the development program, affecting subjects in a fashion generally similar to that seen in the pivotal trial **GS-US-200-4625** [nodules (25%), indurations (15%)]. Nodules and indurations generally persisted longer than other injection site reactions.

- Conclusion regarding the Applicant's assessment of high pH formulations:
Review of the Applicant's presented nonclinical data for LEN, clinical data for LEN and clinical data of other approved ARVs does not identify a clear association between high formulation pH and duration of nodules and indurations.
 - DDD reiterates that in ongoing or future trials, where possible, injection site nodules be followed to resolution or stabilization. In addition, DDD continues to recommend that human histopathology be obtained (e.g., punch biopsy in a few subjects). The presence of findings such as necrosis, hypersensitivity, granulomas, foreign bodies, fibrous tissue, etc. can aid in understanding the pathophysiology of nodule formation. This in turn can increase understanding of which treatments are most likely to be useful.
2. Assessment of the extent to which glass particulate contamination, including sub-visible particles, may be associated with injection site nodules and indurations or other clinical effects.
- Information submitted (literature and nonclinical and clinical evidence from injectable ARVs) indicates that ISRs, including nodules and induration, most likely result from the presence of the drug depot rather than the potential presence of subvisible glass particulates in the closure system with borosilicate glass vials.
3. Recommendations for communication of ISRs in labeling
- DDD agrees with DAV proposed edits to labeling for LEN in Section 6 of labeling.
 - The Applicant's rationale to [REDACTED]^{(b) (4)} is acceptable. The use of [REDACTED]^{(b) (4)} to describe the duration of ISRs, nodules, and indurations is not recommended since it is not commonly used in clinical practice and not easily interpreted by prescribers. FDA proposes use of range [REDACTED]^{(b) (4)}. See also details of labeling communications.

Background:

From Consult Request:

"Lenacapavir (LEN) is currently under review as an NME under two NDAs, 215973 [injectable (SC) [REDACTED]^{(b) (4)}] and 215974 (tablets). The proposed indication by the Applicant is [REDACTED]^{(b) (4)}

[REDACTED]
"

Complete response letters (CRLs) for NDAs 215973 and 215974 were issued by the Agency on February 28, 2022, primarily related to issues with Chemistry, Manufacturing, and Controls (CMC). On June 27, 2022, the NDA 215973 and 215974 resubmissions were submitted, which respond to the issues and deficiencies identified in the CRLs. The application also includes longer-

term safety and efficacy data from the pivotal phase 3 trial (GS-US-200-4625), as well as safety data from other on-going and completed clinical studies with LEN.

The Division of Dermatology and Dentistry was previously consulted because injection site reactions (ISRs) were the most common adverse reaction with lenacapavir subcutaneous injection. Based on preclinical histology in rats, rabbits and dogs these reactions were observed to be inflammatory granulomas. One of DAV's concerns is that injection site nodules and indurations can possibly last several weeks/months, and the longer-term safety data included in the resubmissions may help to further describe and understand injection site reactions associated with LEN.

DAV is requesting DDD'S review and assessment of the Applicant's Cumulative Review of Injection Site Reactions, including the Applicant's assessment of high pH formulations and ISRs. DAV requests any recommendations for communication of ISRs in labeling, specifically a response to the Applicant's rationale to (b) (4) to (b) (4) describe the duration of ISRs, nodules, and indurations.

Review:

Histopathology:

Clinical Histopathology:

At the time of first submission of application, there was no human histopathology included in the pivotal Phase 2/3 trial (GS-US-200-4625) to support NDA 215973. The Applicant notes that; "no dermatologist consultations or skin biopsies for ISRs were conducted for participants in these studies as these were not required per study protocols and would have been done only at the investigator's discretion as part of clinical management." (Page 56, Cumulative Review of Injection Site Reactions, June 23, 2022)

An updated safety monitoring plan, including dermatological assessment of ISRs that are Grade 3 or higher, or that are not resolved within 24 weeks, was communicated to investigators for all LEN studies that include subcutaneous (SC) dosing in late February 2022.

The Applicant notes that a few investigators who were contacted regarding the ongoing nodules or indurations mentioned that they did not refer their subjects for dermatological consultations because those ISRs had resolved or they were not considered warranted (trial **GS-US-200-4625**, subjects (b) (6) (nodule-not warranted) and (b) (6) (nodule-decreased in size); trial **GS-US-200-4334**, subjects (b) (6) (nodule-resolved), (b) (6) (nodule-participant declined), (b) (6) (nodule-participant declined), (b) (6) (nodule-participant declined).

As of June 15, 2022, Gilead had received dermatologist assessments for two subjects who met the ISR criteria described above. The Applicant notes that additional assessments will be submitted at a later date.

Summary of Available Biopsy Reports for Participants in Study GS-US-200-4625 Who Met the ISR Criteria for Dermatological Assessment

Participant ID	Injection Site Reaction	Grade	Onset Day	Summary of Biopsy Report	Clinical Comment
(b) (6)	Injection site induration	1	Day 15	The dermatopathology report from 3 different injection sites showed multinucleated foreign body-type giant cell reactions present within the deep dermis and subcutaneous space. No significant polarizable foreign body material, such as glass, was seen in any of the available samples.	These findings are consistent with the nonclinical findings in animals, as described in "Non-clinical data for LEN and other ARVs"
		1	Day 561		
(b) (6)	Injection site nodule	1	Day 562	Histochemical staining with congo red supports diagnosis of amyloidosis. Secondary amyloidosis is triggered by the trauma of receiving an injection.	The participant received SC enfuvirtide (T-20) twice a day for more than 3 years (b) (6). The investigator stated that biopsy of the T-20 injection site cannot be ruled out. "Pharmaceutical amyloidosis" associated with the use of SC enfuvirtide has been described {Morilla M. E 2009}

ARV = antiretroviral; LEN = lenacapavir (GS-6207); ID = identification; ISR = injection site reaction; SC = subcutaneous

Table 23, p 56 Cumulative Review of Injection Site Reactions

• Dermatology Assessment/Office Notes:

1) Subject (b) (6), age 57 male

"Patient has a Chief Complaint nodule post subcutaneous injections located on his lower abdomen. New patient referred by OIC for inflammation from previous subcutaneous injection for the treatment of HIV. Patient admits to being in the trial for 2 years. Patient states it is two subcutaneous injections every 6 months. Patient states he's had a total of 6 injections thus far. Patient states one day post injection he experiences a round red circle around the injection site. He states it looks as if it were a welt from the needle. Patient states it will last about a week."

Pathology Report: (three 4mm punch biopsies)

DIAGNOSIS:

1. SKIN, LEFT LOWER ABDOMEN-
MULTINUCLEATED FOREIGN BODY-TYPE GIANT CELL REACTION, FAVOR INJECTION SITE REACTION -
SEE NOTE.
2. SKIN, RIGHT LOWER MEDIAL ABDOMEN-
MULTINUCLEATED FOREIGN BODY-TYPE GIANT CELL REACTION, FAVOR INJECTION SITE REACTION -
SEE NOTE.
3. SKIN, RIGHT LOWER LATERAL ABDOMEN-
MULTINUCLEATED FOREIGN BODY-TYPE GIANT CELL REACTION, FAVOR INJECTION SITE REACTION -
SEE NOTE.

NOTE (1-3): THE HISTOLOGIC FINDINGS ARE SIMILAR IN ALL THREE PARTS. THE GIANT CELL REACTION IS PRESENT WITHIN THE DEEP DERMIS AND SUBCUTANEOUS SPACE. SIGNIFICANT POLARIZABLE FOREIGN MATERIAL, SUCH AS GLASS, IS NOT SEEN IN THE AVAILABLE SAMPLES.



2) Subject (b)(6), age 29 male

“Pt states he is engaging in a study for HIV therapy with (b)(6). He states he has had a subcutaneous induration or nodule at abdominal site of an injection of investigational HIV drug lenacapavir. This nodule has persisted for more than 6 months.

Pt states he was given his most recent injection on (b)(6). Pt states he began to get reaction to the injection after (b)(6). Pt states his reaction has been improving. Pt denies any tenderness to the area. Pt requests evaluation and treatment at this time.”

Pathology Report: (two 4mm punch biopsies)

DIAGNOSIS:

1. SKIN, LEFT LOWER ABDOMEN-
AMYLOIDOSIS, MULTIPLE PIECES.
2. SKIN, RIGHT LOWER ABDOMEN-
AMYLOIDOSIS, MULTIPLE PIECES.

NOTE (1-2): HISTOCHEMICAL STAINING SUPPORTS THE ABOVE DIAGNOSIS. CLINICAL CORRELATION IS RECOMMENDED. POLARIZABLE FOREIGN MATERIAL OR HISTOLOGIC FEATURES OF AN INJECTION SITE REACTION ARE NOT SEEN IN EITHER SAMPLE.



Clinical Histopathology

The dermatologist assessments for two subjects who met the ISR criteria described above from trial GS-US-200-4625 included two biopsy reports, one for each of the two subjects.

For subject (b)(6), the dermatopathology report included 3 different injection sites (described clinically as smooth skin-colored papules, well-formed with assessment: rule

out foreign object (glass) vs injection site reaction) The report showed multinucleated foreign body-type giant cell reactions present within the deep dermis and subcutaneous space. No significant polarizable foreign body material was seen in the material sampled.

For subject (b) (6), the dermatopathology report included two sites (described clinically as nodules/irregular lesions with assessment: neoplasm of uncertain behavior rule out injection site reaction vs. foreign body). The report showed histochemical staining supporting the diagnosis of amyloidosis. The Investigator noted that the subject had received injections of enfuvirtide BID for more than 3 years. The amyloidosis was interpreted as possibly being secondary to injections with enfuvirtide. This supported by a report in the literature (Morilla 2009¹) of a case of localized amyloidosis associated with injection of enfuvirtide.

- It is observed that clinical histopathology received in the current submission includes one case (from trial GS-US-200-4625) demonstrating multinucleated foreign body-type giant cell reactions at injection sites.

Nonclinical Histopathology:

The Applicant notes that nonclinical studies of rats (TX-200-2014), rabbits (TX-200-2033) and dogs (TX-200-2047) showed microscopic findings of granulomatous inflammation at subcutaneous (SC) injection sites. The Applicant notes further that granulomatous inflammation has been observed after SC and intramuscular implantation of bioactive material, including those for HIV treatment and concludes that inflammation and foreign body response to the lenacapavir (LEN) SC depot is an expected host response. (IR response received 9/23/2021, p. 12)

Discussion of Injection Site Reactions/Nodules:

There was no standardized definition of nodule or induration provided to Investigators for the pivotal clinical trial, GS-US-200-4625 or for the supportive trial, GS-US-200-4334.

The Applicant, however, included the following definitions of induration and nodule in Injection site manuals for the Phase 1 trials: GS-US-4070, GS-US-200-4538. (IR response received 10/26/2021, pp. 41/65 and 49/65)

Induration: (Palpable thickening, firmness, or hardening of soft tissue). Usually well demarcated with palpable borders, can be visible (raised or sunken compared to surrounding skin), is often ‘woody’ to touch and has a flat shape (versus the rounder shape of a nodule); it can best be described by palpation.²

Nodule: Discrete or well-demarcated soft tissue mass or lump that is firm.³

¹ Morilla ME, Kocher J, Harmaty M. Localized amyloidosis at the site of enfuvirtide injection. *Ann Intern Med.* 2009 Oct 6;151(7):515-6. doi: 10.7326/0003-4819-151-7-200910060-00017. PMID: 19805777.

² Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, Heath P, Hennig R, Rothstein E, Schuind A, Varricchio F; Brighton Collaboration Local Reactions Working Group for Induration at or near Injection Site. Induration at or near injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine.* 2007 Aug 1;25(31):5839-57. doi: 10.1016/j.vaccine.2007.04.062. Epub 2007 May 8. PMID: 17553602.

³ Rothstein E, Kohl KS, Ball L, Halperin SA, Halsey N, Hammer SJ, Heath PT, Hennig R, Kleppinger C, Labadie J, Varricchio F, Vermeer P, Walop W; Brighton Collaboration Local Reaction Working Group. Nodule at injection site

- In the current submission, the Applicant states that...” ‘nodule’ has a commonly understood clinical definition¹ with size range (a larger [0.5- to 5.0-cm], firm lesion raised above the surface of the surrounding skin).”
- Review of widely used dermatology/internal medicine references is supportive of the Applicant’s statement that nodule has a commonly understood clinical definition.

Harrison's Principles of Internal Medicine²

Nodule: A larger (0.5–5.0 cm), firm lesion raised above the surface of the surrounding skin. This differs from a papule only in size (e.g., a large dermal nevomelanocytic nevus).

Papule: A small, solid lesion, <0.5 cm in diameter, raised above the surface of the surrounding skin and thus palpable (e.g., a closed comedone, or whitehead, in acne).

Bologna, Jean, L. et al. Dermatology³

Nodule

- Palpable, circumscribed
- Larger volume than papule, usually >1 cm in diameter
- Involves the dermis and/or the subcutis
- Greatest portion may be beneath the skin surface or exophytic

Papule

- Elevated (palpable), circumscribed
- <1 cm in diameter
- Elevation due to increased thickness of the epidermis and/or cells or deposits within the dermis
- May have secondary changes (e.g., scale, crust)
- The profile can be flat-topped (lichenoid), dome-shaped, umbilicated, or verrucous

Fitzpatrick's Dermatology⁴

Nodule

A nodule is a palpable lesion greater than 1 cm with a domed, spherical or ovoid shape. They may be solid or cystic. Depending on the anatomic component(s) primarily involved, nodules are of 5 main types: (1) epidermal, (2) epidermal–dermal, (3) dermal, (4) dermal–subdermal, and (5)

as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine*. 2004 Jan 26;22(5-6):575-85. doi: 10.1016/j.vaccine.2003.09.005. PMID: 14741147.

¹ Alterations in the Skin. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. *Harrison's Principles of Internal Medicine*, 20e. McGraw Hill; 2018. Accessed November 30, 2021.

<https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=159213808>

² Yancey KB, Lawley TJ. Approach to the Patient with a Skin Disorder. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. eds. *Harrison's Principles of Internal Medicine*, 21e. McGraw Hill; 2022. Accessed August 22, 2022. <https://accessmedicine-mhmedical-com.fda.idm.oclc.org/content.aspx?bookid=3095&sectionid=263362154>

³ Bologna, Jean, L. et al. *Dermatology*. Available from: Elsevier eBooks+, (4th Edition). Elsevier - OHCE, 2017. Section One Overview of Basic Science Whitney A. High, Carlo Francesco Tomasini, Giuseppe Argenziano, Iris Zalaudek, 1.e1/2674

⁴ Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. *Fitzpatrick's Dermatology*, 9e. McGraw Hill; 2019. Accessed August 22, 2022. <https://accessmedicine-mhmedical-com.fda.idm.oclc.org/content.aspx?bookid=2570&sectionid=210413306>, Chapter 1: Fundamentals of Clinical Dermatology: Morphology and Special Clinical Considerations - Erin H. Amerson; Susan Burgin; Kanade Shinkai

subcutaneous. Texture is an important additional feature of nodules: firm, soft, boggy, fluctuant, etc. Similarly, different surfaces of nodules, such as smooth, keratotic, ulcerated, or fungating, also help direct diagnostic considerations. *Tumor*, also sometimes included under the heading of nodule, may be used to describe a more irregularly shaped mass, benign or malignant.

Papule

A papule is an elevated or depressed lesion less than 1 cm in size, which may be solid or cystic. Among other characteristics, papules may be further described by their topography. Some examples include papules that are sessile, pedunculated, dome-shaped, flat-topped, filiform, mamillated, acuminate (conical), or umbilicated.

➤ **Regarding the current NDAs under review: 215973, 215974**

The primary study that supports the safety and efficacy of LEN is the Phase 2/3 study in HTE (heavily treatment experienced) people with HIV (PWH) (Study GS-US-200-4625), which is further supported by a Phase 2 study of LEN in treatment-naive PWH (Study GS-US-200-4334).

Supportive safety data are also provided from 2 Phase 1 studies in healthy participants (Studies GS-US-200-4538 and GS-US-200-5709); these Phase 1 studies also contributed to the characterization of the pharmacokinetic (PK) profiles of LEN and its metabolites, supporting the clinical pharmacology of LEN and the dosing interval.

The primary data (for establishing safety and efficacy) is based on 26-week data from **GS-US-200-4625** (CAPELLA), described by the Applicant as a “partially randomized, placebo-controlled, double-blind multicenter trial.” The proposed indication, as of the time of this consult (11/17/22 – labeling sent to applicant 11/04/2022), is “the treatment of (HIV-1) infection in heavily treatment experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.”

Study Endpoints:

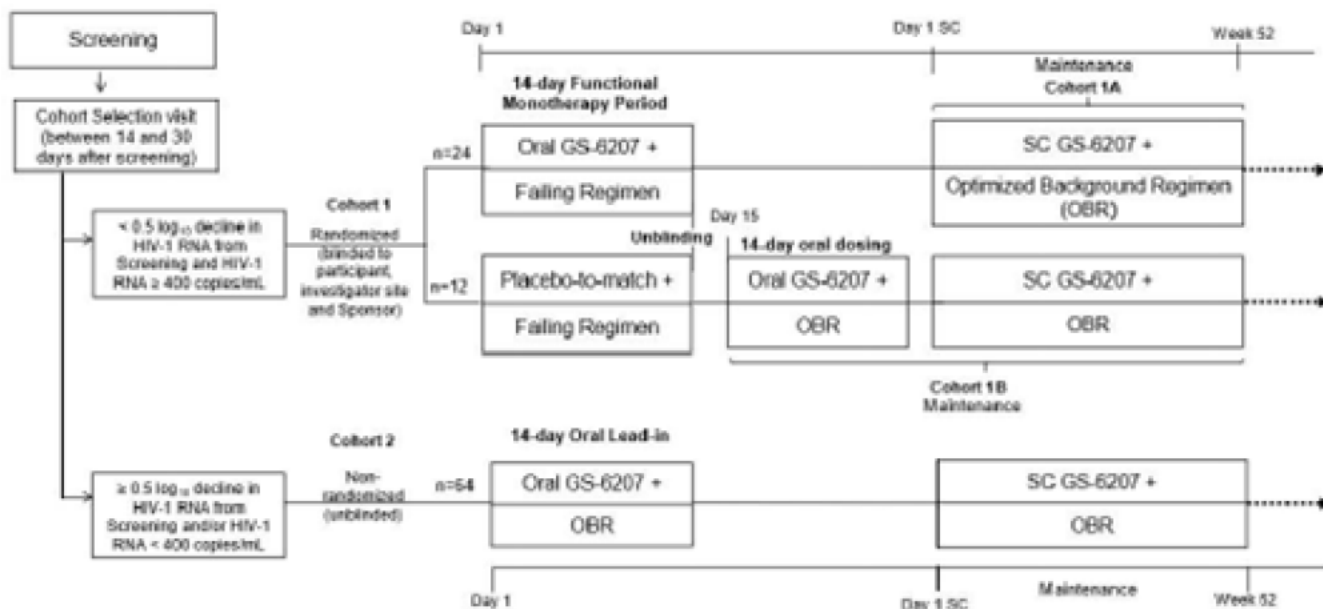
The primary efficacy endpoint was the proportion of subjects in Cohort 1 achieving $\geq 0.5 \log_{10}$ copies/mL reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period.

The secondary efficacy endpoint was the proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 of treatment based on the US Food and Drug Administration (FDA)-defined snapshot algorithm

Trial Outline:

Study Design Schema

BEST AVAILABLE COPY



This trial design shows that there is no arm where active injected drug is compared with placebo injected drug. There are two enrolled cohorts: Cohort 1, if subjects had a $< 0.5 \log_{10}$ HIV-1 RNA decline compared to the screening visit and Cohort 2, if subjects had a $\geq 0.5 \log_{10}$ HIV-1 RNA decline compared to the screening visit or after Cohort 1 reached its planned sample size. Regarding Cohort 1, in the 14-day functional monotherapy period, subjects in Cohort 1 were randomized in a 2:1 ratio in a blinded fashion to receive either drug product or placebo, while continuing their failing regimen.

- **Cohort 1A** subjects received subcutaneous (SC) LEN on day 1 SC (14 days after 1st dose of oral LEN) and once every 6 months (26 weeks). Also initiate their OBR
- **Cohort 1B** subjects received placebo for 14 days, then oral LEN for and initiate their OBR on Day 15, then SC LEN at Day 1 SC (14 days after 1st dose of oral LEN and 28 days into trial) and once every 6 months (26 weeks).
- **Cohort 2:** received oral LEN for 14 days, then SC LEN at Day 1 SC (14 days after 1st dose of oral LEN) and once every 6 months (26 weeks).

➤ Of note, for trial GS-US-200-4625, no specific instructions were given to the various trial sites on how to report injection site reactions.

The adverse event (AE) toxicity scale used was DAIDS (Division of AIDS) version 2.1 (see **Appendix A**). See following table for summary information on study design for trials GS-US-200-5709, GS-US-200-4625 (primary trial) and GS-US-200-4334.

Table 8. GS-US-200-5709, -4625, and -4334: Differences in Study design and Other Relevant Factors between Studies

	Study 5709	Study 4625	Study 4334
Objectives	Phase 1 to evaluate PK in healthy participants	Phase 2/3 to evaluate efficacy and safety in heavily treatment experienced PWH	Phase 2 to evaluate efficacy and safety in treatment naïve PWH
Number of investigators	1	42	41
Number of sites	1	31	41
Countries	US	9 countries (US, Thailand, Italy, Dominican Republic, Spain, France, Canada, Taiwan, and South Africa)	2 countries (US and Dominican Republic),
Specific instructions describing the SC injection technique given to sites	No (However, similar Phase 1 studies were being conducted at the same time under the same investigator, for which pharmacy manual was given out)	Yes (Pharmacy manual - Appendix 4)	Yes (Pharmacy manual - Appendix 3)

	Study 5709	Study 4625	Study 4334
Specific instructions on how to report injection site reactions given to sites	No (However, similar Phase 1 studies were being conducted at the same time under the same investigator, for which ISR manual was given out)	No	No
Confinement required per protocol	(For intensive PK sample collection) Cohort 1: 17 days Cohort 2: 15 Days	None	None
Complete or symptom-driven physical examination post SC LEN per protocol	Cohort 1: Days 1-17 (daily), 18, 20, 22, 24, 29, 36, 43, 50, 57, 71, 85, 99, 127, 155, 169, 183, 197, 211, 225, 239, 267, 295, 323, 351, 379, 407, 435, and 463; Cohort 2: Days 1-15 (daily), 16, 17, 18, 20, 22, 24, 29, 36, 43, 50, 57, 71, 85, 99, 127, 155, 169, 183, 197, 211, 225, 239, 267, 295, 323, 351, 379, 407, 435, 463, 519, 575, 631, 687, and 743	Weeks 4, 10, 16, 22, 26, 36 and 52	Weeks 4, 10, 16, 22, 28, 38, 54, 64 and 80
AE toxicity scale	DAIDS version 2.1	DAIDS version 2.1	DAIDS version 2.1

AE = adverse events; DAIDS = Division of AIDS; ISR(s) = injection site reaction(s); LEN = lenacapavir; PK = pharmacokinetics; PWH = people with HIV; SC = subcutaneous; US = United States

Response to IR of 10/12/2021 received 10/26/2021, p.15

- Of note, active assessment of injection site reactions was not performed.
 - 7.3.1. Adverse Events (Protocol GS-US-200-4625:** Final Amendment 2, Sept 1, 2020, p 65)
Following initiation of study medication, all AEs, regardless of cause or relationship, throughout the duration of the study, including the protocol-defined follow-up visit, must be reported on the eCRFs as instructed. All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.
 - 11.2.1 Study GS-US-200-4625 Interim Week 26 Clinical Study Report Final,** p 87
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.

For Trial GS-US-200-4625:

Lenacapavir 927 mg injection (309 mg/mL) was administered in the abdomen via SC route on Day 1 SC, Weeks 26, 52, and every 6 months (26 weeks) thereafter (Week 26 Clinical Study for trial GS-US-200-4625 Report, p. 32).

Note: Each SC dose consists of 2 SC injections into the abdomen (Week 26 Clinical Study Report for trial GS-US-200-4625, p. 349). See also below:

4.0 LEN Subcutaneous Injection

All participants will receive 2 x 1.5 mL LEN Injections (927 mg) at their Day 1 SC visit i.e. 14 days after their first dose of oral LEN (14 days after Day 15 visits for participants in Cohort 1 who received PTM for the first 14 days). They will continue to receive LEN injections every 6 months during their participation in the study.

Two vials will be dispensed by the IWRS system to prepare and administer two injections (1.5 mL each). Injections should be administered at different abdominal sites, no more than 15 minutes apart. Injections should be prepared and administered according to the instructions below.

Note: Study drug preparation and administration should be completed by appropriately trained and delegated site staff.

1.5 mL Injection Preparation and Administration Instructions:

13. With one hand, pinch a fold of skin where the injection is to be given. The initial injection should be given in the right lower quadrant of the abdomen. If a subject has a tattoo or scar in the right lower quadrant, another quadrant may be used. For the second injection, rotate injection site clockwise, ensuring the subsequent injection is at least 4 inches away from the previous injection site. For additional injections, rotate injection sites clockwise, ensuring subsequent injections are at least 4 inches away from the other injection site(s). The injection site location(s) should be noted in the source documents.

From Pharmacy Manual (p. 4/5) for Trial GS-US-200-4625: Response to IR of 10/12/2021 received 10/26/2021.

➤ **Primary Study Supporting the Safety of LEN (Study GS-US-200-4625) Summary of Clinical Safety Addendum (2.7.4 p.11/88)**

A total of 72 participants were enrolled, 36 into Cohort 1 and 36 into Cohort 2.

Per Applicant:

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
- 53 participants (Cohort 1: 34 participants, Cohort 2: 19 participants) received a third dose of SC LEN at Week 52.

The median (first quartile [Q1], third quartile [Q3]) duration on study was 591 (532, 675) and 445 (394, 480) days for Cohorts 1 and 2, respectively.

Premature Study Drug Withdrawal: Prior to April 1, 2021, the original NDA data cut-off date, no study subjects had discontinued study drug due to an AE. However, since that date, one participant (██████████^{(b) (6)}) in Study GS-US-200-4625 prematurely discontinued study drug (day 379) due to treatment-emergent AEs of injection site nodules. The subject was a 56-year-old black female in the USA. The subject experienced an injection site nodule on Day 18 and on Day 380. Both nodules were Grade 1 (defined as 2.5 to < 5 cm in diameter OR 6.25 to < 25 cm² surface area AND symptoms causing no or minimal interference with usual social and functional activities see also DAIDS Table in Appendix) and were ongoing (GS-US-200-4625, 90-Day Safety Update, Listing 4). The investigator reported that “the nodules were uncomfortable, and the subject did not want the nodules to return.”

Update per **Summary of Clinical Safety Addendum** (2.7.4 p 33/88)

Trial 4625: One subject ((b) (6)) (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 by the investigator. This is the same subject noted in the (GS-US-200-4625, 90-Day Safety Update, Listing 40.

Trial 4334: Three of 105 participants (2.9%) in the SC LEN total group discontinued study drug due to AEs (injection site induration (b) (6); injection site erythema and injection site swelling (b) (6)). All were nonserious and Grade 1 in severity. Per Summary of Clinical Safety Addendum (2.7.4 p.33/88) and Listing 16.2.7.5.1 Supportive **Trial GS-US-4334**)

GS-US-200-4625: Study Drug–related Injection Site Reactions – All LEN Analysis (Safety Analysis Set)

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Number of Participants Who Received At Least 1 Injection	24	12	36	36	72
Injection site nodule	9 (37.5%)	4 (33.3%)	13 (36.1%)	5 (13.9%)	18 (25.0%)

Study GS-US-200-4625 Cohorts 1 and 2 Week 52 Summary, Tables 15.11.2.4.1 and 15.11.2.4.2 adapted from Table 21- Section 2.7.4 – Summary of Clinical Safety Addendum, p. 35/88

Overall Trial GS-US-200-4625: (per **Summary of Clinical Safety Addendum** 2.7.4 p.34/88) Of 72 subjects receiving ≥ one injection

- Injection site nodules were the **4th** most frequently reported ISR (reported in ≥ 10% of subjects overall), (25.0%, 18 subjects): 253 (111, 365) days Median (Q1,Q3)
- Injection site induration was the **5th** most frequently reported ISR (reported in ≥ 10% of subjects overall), (15.3%, 11 subjects): 112 (43, 220) days Median (Q1,Q3)

❖ For more details about nodules and indurations in Trial GS-US-200-4625, see table in **Appendix F**.

FDA proposed labeling:

The ISRs reported in more than 1% of subjects were swelling (36%), pain (31%), erythema (31%), *nodule* (25%), *induration* (15%), pruritus (6%), extravasation (3%) and mass (3%). ISRs reported in 1% of subjects included discomfort, hematoma, edema, and ulcer.

(Italics used for emphasis)

Following the **Day 1 SC dose** of LEN in a total of 72 subjects:

4th most frequently reported ISR: Injection site nodule (22.2%, 16 subjects), 227 (72, 529) days (tied with pain)

5th most frequently reported ISR: Injection site induration (11.1%, 8 subjects), 113 (29, 224) days

Following the **Week 26 SC dose** of LEN in a total of 70 subjects:

4th most frequently reported ISR: Injection site nodule (11.4%, 8 subjects), 252 (111, 365) days

5th most frequently reported ISR: Injection site induration (10%, 7 subjects), 182 (13, 246) days

Following the **Week 52 SC dose** of LEN in a total of 53 subjects:

4th most frequently reported ISR: Injection site nodule (13.2%, 7 subjects), 260 (190, 275) days

5th most frequently reported ISR: Injection site induration (3.8%, 2 subjects), 112 (108, 115) days

- Therefore, in Trial GS-US-200-4625, regardless of the timing of the injections, injection site nodules and indurations, were respectively, the 4th and 5th most frequently reported injection site reactions.
- Data reported from the supportive trial, **GS-US-200-4334** are similar. Overall, injection site nodules and indurations, were respectively, the 4th and 6th most frequently reported injection site reactions.

Of **103** subjects receiving $\geq$ one injection

- Injection site nodules were the **4th** most frequently reported ISR (reported in $\geq$ 10% of subjects in SC LEN total group). (14.6%, 15 subjects), 195 (122, 301) - Median (Q1,Q3) days
- Injection site induration was the **6th** most frequently reported ISR (reported in $\geq$ 10% of subjects in SC LEN total group). (12.6%, 13 subjects), 202 (101, 361) Median (Q1,Q3) days

Additional information regarding Study Drug-related Injection Site Nodules and Indurations

Per Section 2.7.4 – Summary of Clinical Safety: Addendum, p 43/88

Primary Trial **GS-US-200-4625**)

Overall, 18 of 72 subjects (25.0%) experienced study drug–related injection site nodules, and 11 of 72 subjects (15.3%) experienced study drug–related injection site induration. All events were Grade 1 or 2.

The Applicant notes that the duration of induration/nodules occurring as a result of the first SC dose tended to be longer than those occurring as a result of later SC doses (since their follow-up was longer) and longer for ongoing ones (than resolved ones).

- Injection site nodules and indurations due to Day 1 SC injection:

Participant-level analysis:

Nodules: Ongoing (7/16 subjects having a nodule [43.8%]); 7/72 total subjects (9.87%)

Indurations: Ongoing (1/8 [12.5%]); 1/72 total subjects (1.3%)

Event-level analysis:

Nodules: Ongoing (7/23 [30.4%])

Indurations: Ongoing (1/8 [12.5%])

- The median (Q1, Q3) duration of resolved injection site nodule and injection site induration due to Day 1 SC injection was 148 (70, 307) days (among 16 events) and 70 (15, 196) days (among 7 events), respectively.

- **FDA proposed labeling:** “The median time to resolution of nodules and indurations associated with the first injections of SUNLENCA was 148 range: 41 to 727 and 70 range: 3 to 252 days, respectively. After a median follow up of 553 days, 30% of nodules and 13% of indurations (in 10% and 1% of subjects, respectively) associated with the first injections of SUNLENCA had not fully resolved.”
- The median (Q1, Q3) duration of ongoing injection site nodule and injection site induration due to Day 1 SC injection was 552 (337, 624) days (among 7 events) and 665 (665, 665) days (among 1 event), respectively.

(Italics added by reviewer.)

● Injection site nodules and indurations due to second LEN injection at Week 26:

Participant-level analysis:

Nodules: Ongoing (4/8 [50.0%])

Indurations: Ongoing (2/7 [28.6%])

Event-level analysis:

Nodules: Ongoing (7/14 [50.0%])

Indurations: Ongoing (2/7 [28.6%])

- The median (Q1, Q3) duration of resolved injection site nodule and injection site induration after the second LEN injection at Week 26 was 180 (113, 365) days (among 7 events) and 63 (13, 182) days (among 5 events), respectively.
- The median (Q1, Q3) duration of ongoing injection site nodule and injection site induration after the second LEN injection at Week 26 was 324 (111, 442) days (among 7 events) and 271 (246, 296) days (among 2 events), respectively.

● Injection site nodules and indurations due to third LEN injection at Week 52:

Participant-level analysis:

Nodules: Ongoing (6/7 [85.7%])

Indurations: Ongoing (2/2 [100.0%])

Event-level analysis:

Nodules: Ongoing (8/9 [88.9%])

Indurations: Ongoing (2/2 [100.0%])

- The median (Q1, Q3) duration of resolved injection site nodule after the third LEN injection at Week 52 was 3 (3, 3) days (among 1 event). No events of injection site indurations had resolved.
- The median (Q1, Q3) duration of ongoing injection site nodule and injection site induration after the third LEN injection at Week 52 was 260 (225, 275) days (among 8 events) and 112 (108, 115) days (among 2 events), respectively.

(Per Section 2.7.4 – Summary of Clinical Safety: Addendum, p 50/88)

➤ **Supportive Trial GS-US-200-4334**

Overall, **15** of 103 (15%) subjects had an AE of injection site nodule and **13** of 103 (13%) subjects had an AE of injection site induration. All were Grade 1 or Grade 2, except for 1 subject with a Grade 3 injection site nodule, reported at week 28 analysis in the 1st submission)

● Injection site reactions after the first SC LEN injection at Day 15

Participant-level analysis:

Nodules: Ongoing (1 of 11 [9.1%]); 1/105 total subjects (.95%)

Indurations: Ongoing (6 of 9 [66.7%]); 6/105 total subjects (5.7%)

Event-level analysis:

Nodules: Ongoing (1 of 13 [7.7%])

Indurations: Ongoing (6 of 9 [66.7%])

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.

Observation: As compared with the pivotal trial, subjects overall in the supportive trial (GS-US-200-4334), reported fewer nodules 15/103 (15%) versus 18/72 subjects (25.0%), respectively, in the pivotal trial GS-US-200-4625. Subjects reporting indurations were roughly comparable indurations 13/103 (13%) versus 11/72 subjects (15.3%). In the pivotal trial, the median time to resolution of nodules and indurations associated with the first injections of SUNLENCA was 148 and 70 days respectively. In the supportive trial the median times to resolution for nodules and indurations was longer, 278 and 202 days, respectively. For the supportive trial, associated with the Day 15 injections, as of the week 54 analysis (Oct 21, 2021), 7.7% of nodules and 66.7 % of indurations (in 1% and 6% of subjects, respectively) had not fully resolved.

- **Review and assessment of the Applicant's Cumulative Review of Injection Site Reactions, including the Applicant's assessment of high pH formulations and ISRs. (Focusing on nodules and indurations)**

Overall Conclusion (nodules and indurations):

Nodules and indurations were seen commonly across trials in the development program, affecting subjects in a fashion generally similar to that seen in the pivotal trial **GS-US-200-4625** [nodule (25%), induration (15%)]. Nodules and indurations generally persisted longer than other injection site reactions.

More details are provided in Appendix D.

Overall conclusion regarding the Applicant's assessment of high pH formulations

Review of the applicant's presented nonclinical data for LEN, clinical data for LEN and clinical data of other approved ARVs does not identify a clear association between high formulation pH and duration of nodules and indurations.

More details are provided in Appendix D.

➤ **Review of Applicant’s Responses to FDA Additional Comments in Complete Response Letters dated February 28, 2022: 2.2.1 Clinical Comment 6**

The Applicant states that information submitted (literature and nonclinical and clinical evidence from injectable ARVs) support the position that ISRs, including nodules and induration, most likely result from the presence of the drug depot rather than the potential presence of subvisible glass particulates in the closure system with borosilicate glass vials.

This reviewer agrees that this is a reasonable conclusion. More details are provided in Appendix E.

➤ **Applicant’s assessment of injection site reactions in “Cumulative Review of Injection Site Reactions”** (Seq 0015, m1.11.3, Section 2.2, p 62)

The Applicant states that: “Given the majority of ISRs are of low grade, rarely lead to discontinuation, and frequently resolve over a short period of time, the benefit:risk of LEN remains favorable and consistent with Gilead’s overall assessment of ISRs previously provided to the Agency (Seq 0015, m1.11.3, Section 2.2).” (Response to IR of 10/12/2021 received 10/26/202, pp. 11, 12). **See below for Applicant’s previously provided overall assessment:**

“To summarize, we have conducted a comprehensive assessment of injection site reactions (ISRs) across the LEN program, including detailed review of individual cases with the investigators. Our overall assessment is as follows. In Studies GS-US-200-4625 and GS-US-200-4334, approximately half or fewer of the participants (55.6% and 38.8%, respectively) experienced at least 1 AEs of LEN-related ISRs, which were mostly non-serous, Grade 1 or 2, and rarely led to study drug discontinuation. Most AEs of ISRs resolved within days, but those of induration and nodules lasted longer (as described in Gilead's previous response, Seq 0008). These AEs of induration or nodules were generally small (less than a few centimeters), not visible to the participant or the investigator, not causing persistent discomfort to participants, and only detectable upon deep palpation. There were rarely any gross inflammatory components, such as tenderness or erythema, to these AEs of induration or nodules, and when there was coincident pain or erythema, they resolved quickly. There were no reports of tissue destruction (e.g., necrosis), or, upon careful review, suggestion of other more serious reactions such as sterile abscess or persistent tissue damage. No participants appeared to have any safety signal suggesting that LEN was being administered into a deeper tissue than the intended subcutaneous space (e.g., muscle). In written, verbal, and video communication with investigators who took care of participants with AEs of persistent induration or nodule, none were concerned with any potential long term permanent adverse effect, none felt the AEs required additional consultation (e.g., with a dermatologist), and all agreed that those AEs were resolving slowly over time. In general investigators commented on the benign nature of nodules, with some noting that nodules might be more visible in a person who is lean and self-conscious of body image.”

Nodules:

“Based on the totality of Gilead's nonclinical assessment, the induration or nodules after SC LEN injection appears to be a normal and expected tissue body response, manifesting as chronic granulomatous inflammation histologically, to a foreign body (i.e., a drug depot)

without permanent adverse effect. We have not found evidence of injection site nodules or induration being reflective of more serious complications, or resulting from aberrant injections, nor have we found evidence that nodules are related to body habitus or immunologic status.... In summary, our assessment is that nodules that rise to the level of AE reporting occur in a subset of individuals receiving LEN, represent subcutaneous deposition of the drug itself and expected tissue reaction, and are not associated with adverse clinical or pharmacologic consequences.”

- This reviewer finds the Applicant’s assessment, especially as it relates to injection site nodules and indurations, reasonable.

- **Labeling:**

- ❖ **Labeling: Other Products**

- Approved Drug Product Labeling:**

- Approved FDA labeling for a number of drug products includes the adverse reaction of injection site nodules. For some products information regarding injection site nodules is present in Warnings and Precautions. Among the most extensive descriptions of injection site nodules occurs in approved FDA labeling for exenatide injection, suspension, extended-release product BYDUREON BCISE[®] (see Appendix B).

- Approved labeling **CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension) 1/2021: Section 6.1 Clinical Trials Experience**

- “The most commonly reported ISR was localized pain/discomfort (79%) regardless of severity or relatedness. Other manifestations of ISR’s reported in more than 1% of subjects over the duration of the analysis period included *nodules* (14%), *induration* (12%), swelling (8%), erythema (4%), pruritus (4%), bruising (3%), warmth (2%), and hematoma (2%).”

- Approved labeling **FUZEON (enfuvirtide) 8/2019: Section 6.1 Clinical Trials Experience**

- “The majority of ISRs were associated with erythema, induration, the presence of nodules or cysts, and mild to moderate pain at the injection site (Table 2)”: pain/discomfort (96%), *induration* (90%), erythema (91%), *nodules and cysts* (80%), pruritus (65%), and ecchymosis (52%), including participants with Grade 3 or 4 ISRs.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Medical Officer
Division of Dermatology and Dentistry
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Appendix A: DAIDS (Division of AIDS) Version 2.1:
Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Injection Site Pain or Tenderness <i>Report only one</i>	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function <u>OR</u> Hospitalization indicated
Injection Site Erythema or Redness¹² <i>Report only one</i> <i>> 15 years of age</i>	2.5 to < 5 cm in diameter <u>OR</u> 6.25 to < 25 cm ² surface area <u>AND</u> Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter <u>OR</u> ≥ 25 to < 100 cm ² surface area <u>OR</u> Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter <u>OR</u> ≥ 100 cm ² surface area <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage <u>OR</u> Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
<i>≤ 15 years of age</i>	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling <i>Report only one</i> <i>> 15 years of age</i>	Same as for Injection Site Erythema or Redness , > 15 years of age	Same as for Injection Site Erythema or Redness , > 15 years of age	Same as for Injection Site Erythema or Redness , > 15 years of age	Same as for Injection Site Erythema or Redness , > 15 years of age
<i>≤ 15 years of age</i>	Same as for Injection Site Erythema or Redness , ≤ 15 years of age	Same as for Injection Site Erythema or Redness , ≤ 15 years of age	Same as for Injection Site Erythema or Redness , ≤ 15 years of age	Same as for Injection Site Erythema or Redness , ≤ 15 years of age
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized <u>OR</u> Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

¹² Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Appendix B: Examples of Labeling Related to Injection Site Nodules

BYDUREON BCISE® (exenatide extended-release) injectable suspension, for subcutaneous use. Initial U.S. Approval: 2005

5.9 Injection-Site Reactions There have been postmarketing reports of serious injection-site reactions (e.g., abscess, cellulitis, and necrosis), with or without subcutaneous nodules, with the use of BYDUREON [see Adverse Reactions (6.3)]. Isolated cases required surgical intervention.

6.1 Clinical Trial Experience

Table 1 summarizes the adverse reactions with an incidence $\geq 5\%$ occurring in BYDUREON BCISE-treated adult patients in the pooled data from the controlled and extension phases, including 10 weeks of follow-up, of the two comparator-controlled 28-week clinical trials. Adverse reactions were identified based on known adverse reactions associated with BYDUREON.

Table 1: Adverse Reactions Reported in $\geq 5\%$ of BYDUREON BCISE-Treated Patients from Pooled Clinical Trial Data in Patients with Type 2 Diabetes Mellitus

	BYDUREON BCISE 2 mg N = 526 %
Injection site nodule	10.5
Nausea	8.2

Note: Percentages are based on the number of patients who were randomized and received at least one dose of BYDUREON BCISE.

Adverse Reactions Leading to Discontinuation of Therapy

The incidence of discontinuation of therapy due to adverse reactions was 3.9% for BYDUREON BCISE-treated patients in the two comparator-controlled 28-week trials in adults. The most common classes of adverse reactions leading to discontinuation of therapy for BYDUREON BCISE-treated patients were Gastrointestinal Disorders 2.0% and General Disorders and Administration Site Conditions 1.2%. For BYDUREON BCISE-treated patients, the most frequent adverse reactions leading to discontinuation of therapy within each of these respective classes were diarrhea (0.7%), nausea (0.7%), vomiting (0.5%) and injection-site nodule (0.5%).

Injection-Site Adverse Reactions In the two comparator-controlled 28-week trials in adults, injection site reactions (including injection site nodule, injection site pruritus, injection site bruising) were observed in 23.9% of patients treated with BYDUREON BCISE. The formation of subcutaneous nodules is consistent with the properties of the microspheres used in BYDUREON BCISE.

Other drug products having labeling describing injection site nodules in **Section 5: Warnings and Precautions** include; granisetron (SUSTOL), enfuvirtide (FUZEON), and medroxyprogesterone acetate (DEPO-SUBQ-PROVERA).

- Drug products having labeling describing injection site nodules in **Section 6: Adverse Reactions** include; cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (CABENUVA), enoxaparin sodium injection (LOVENOX), insulin human injection

(HUMULIN R), asfotase alfa (STRENSIQ), collagenase clostridium histolyticum-aaes (QWO), degarelix (FIRMAGON), among others.

An example follows:

**CABENUVA (cabotegravir extended-release injectable; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use
Initial U.S. Approval: 2021**

Section 6.1 Clinical Trials Experience

Injection-Associated Adverse Reactions

Local Injection Site Reactions (ISRs): The most frequent adverse reactions associated with the intramuscular administration of CABENUVA were ISRs. After 14,682 injections, 3,663 ISRs were reported. One percent (1%) of subjects discontinued treatment with CABENUVA because of ISRs. Most ISRs were mild (Grade 1, 75%) or moderate (Grade 2, 36%). Four percent (4%) of subjects experienced severe (Grade 3) ISRs, and no subjects experienced Grade 4 ISRs. The most commonly reported ISR was localized pain/discomfort (79%) regardless of severity or relatedness. Other manifestations of ISRs reported in more than 1% of subjects over the duration of the analysis period included **nodules (14%)***, induration (12%), swelling (8%), erythema (4%), pruritus (4%), bruising (3%), warmth (2%), and hematoma (2%). Abscess and cellulitis at the injection site were each reported in less than 1% of subjects. The median duration of ISR events was 3 days.

*Bolded by reviewer for emphasis

Appendix C: Literature References

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Appendix D: Cumulative Review of Injection Site Reactions

Consult request: Review and assessment of the Applicant's Cumulative Review of Injection Site Reactions, including the Applicant's assessment of high pH formulations and ISRs: submitted in module 5.3.5.3 in the submission dated 6, 27, 2022 (SDN#38). The document "Cumulative Review of Injection Site Reactions" includes resolved and ongoing injection site indurations and nodules by study, and it includes an assessment of the role of physical and chemical characteristics of lenacapavir on injection site reactions.

A listing of LEN studies utilizing subcutaneous dosing follows:

Phase 1 studies:

Single dose

- **GS-US-200-4070:** non-commercial formulation: SC aqueous formulation of LEN free acid suspension (pH 7.1)
 - *This trial will be discussed only in reference to pH effect of formulation.*
- **GS-US-200-4072:** non-commercial formulation: SC aqueous formulation of LEN free acid suspension (pH 7.1)
 - *This trial will be discussed only in reference to pH effect of formulation.*
- **GS-US-200-4538:** Noncommercial and Commercial Formulations.
 - *This trial will be discussed only briefly due to small numbers of subjects studied on commercial formulation.*
- **GS-US-200-4540:** Same dose, same formulation = commercial (not in original NDA submission)
- **GS-US-200-5710:** Noncommercial formulation; different doses (not in original NDA submission)
- **GS-US-200-5717:** Noncommercial formulations; different doses (not in original NDA submission)
 - *These trials (5710 and 5717) will not be commented upon here since noncommercial formulations and different doses were examined.*
- **GS-US-536-5816:** Same dose, same method, same formulation = commercial (not in original NDA submission)
- **GS-US-200-5709:** Same dose, same formulation = commercial

Multiple dose

• Phase 2 trial

[GS-US-200-4334](#)

• Phase 2/3 trial

[GS-US-200-4625](#)

❖ **Discussion of single dose trials:**

➤ **GS-US-200-4538: Healthy subject PK and initial tolerability**

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

Multiple formulations were used.

Observation:

Part B evaluated (SAD Formulation 2, 309 mg/mL, sodium salt [NaS]): Commercial formulation. Specifically, cohorts 6 and 7 explored commercial dose, but with slightly different dosing regimens. Cohort 6: 927 mg (3 x1 mL, 309 mg/mL and cohort 7: 927 mg (2 x 1.5 mg/mL)

Injection site induration was very common in cohorts 6 and 7, affecting 100% of subjects. Nodules affected 3 (37.5%) and 1 (12.5%) in cohorts 6 and 7, respectively. It is noted that numbers are small (N = 8 for both cohorts).

➤ **GS-US-200-4540:**

Phase 1 Single SC Dose of LEN in Healthy Subjects Using Commercial LEN Formulation

Overall, 29 participants (96.7%) experienced a study drug-related ISR. All were Grade 1 or 2 ISRs (Study GS-US-200-4540, Listing 7). The median (Q1, Q3) total duration of any study drug-related ISR was 5 (2, 9) days (Table 8). 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 (Table 13602.3.1):

- Injection site pain (90.0%, 27 subjects), 2 (2, 5) days
- Injection site *induration* (86.7%, 26 subjects), 14 (6, 49) days
- Injection site erythema (76.7%, 23 subjects), 4 (3, 6) days
- Injection site swelling (16.7%, 5 subjects), 2 (2, 2) days
- Injection site bruising (10.0%, 3 subjects), 5 (3, 6) days

GS-US-200-4540: Study Drug-related Injection Site Nodules and Indurations at Time of Data Cut (as of Dec 21, study ongoing: CRF data collected up to 22DEC2021 are included in the safety data analysis)

Overall, no participant (0%) experienced study drug-related injection site nodules, and 26 participants (86.7%) experienced study drug-related injection site indurations (Table 9). All events were Grade 1 or 2 in severity (Study GS-US-200-4540, Listing 7).

The injection site indurations reported due to Day 1 SC injection were as follows:

Participant-level analysis:

- *Indurations:* Ongoing (3/26 [11.5%]); Resolved (23/26 [88.5%])

Event-level analysis:

- *Indurations:* Ongoing (5/62 [8.1%]); Resolved (57/62 [91.9%])

The median (Q1, Q3) duration of resolved injection site indurations due to Day 1 SC injection was 14 (6, 49) days. The median (Q1, Q3) duration of unresolved injection site indurations due

to Day 1 SC injection was 15 (13, 15) days.

Observation:

Indurations were experienced by a large number (26 or 86.7%) of subjects. No subjects experienced injection site nodules. It is noted that these were healthy subjects. In trial **GS-US-200-4538**, injection site nodules were noted in healthy subjects: 3 (37.5%) and 1 (12.5%) in cohorts 6 and 7. Also in trial **GS-US-200-5709**: Phase 1 Single and Multiple-Dose SC and Oral LEN in healthy subjects, many subjects experienced injections site nodules.

For GS-US-200-5709:

The most frequently reported study drug– related ISRs (reported in $\geq 10\%$ of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site *induration* (66.7%, 30 subjects), 27 (17, 27) days
- Injection site *nodule* (48.9%, 22 subjects), 396 (102, 421) days

➤ **Study GS-US-536-5816: Phase 1b Single-Dose SC LEN in Virologically Suppressed Adults With HIV-1 Infection Using Commercial LEN Formulation**

Overall, 16 participants (80.0%) experienced a study drug–related ISR. All were Grade 1 or 2 with the exception of 2 participants (10.0%) who experienced Grade 3 ISRs (injection site erythema and injection site cellulitis) (Study GS-US-536-5816, Listing 7). The median (Q1, Q3) total duration of any study drug–related ISR was 36 (12, 123) days (Table 16). The most frequently reported study drug–related ISRs (reported in $\geq 10\%$ of participants overall) and their duration in median (Q1, Q3) days were as follows (Table Req13608.1.1):

- Injection site pain (45.0%, 9 subjects), 13 (5, 15) days
- Injection site erythema (30.0%, 6 subjects), 32 (13, 39) days
- Injection site *nodule* (30.0%, 6 subjects), 129 (85, 184) days
- Injection site *induration* (25.0%, 5 subjects), 173 (128, 191) days
- Injection site *mass* (20.0%, 4 subjects), 117 (99, 144) days

GS-US-536-5816: Study Drug–related Injection Site Nodules and Indurations at Time of Data Cut (Trial is ongoing: Included CRF data collected up to 04 March 2022.)

The injection site nodules and indurations reported due to Day 1 SC injection were as follows:

Participant-level analysis:

- Nodules: Ongoing (5/6 [83.5%]); Resolved (1/6 [16.7%])
- Indurations: Ongoing (5/5 [100.0%]); Resolved (0/5 [0.0%])

Event-level analysis:

- Nodules: Ongoing (7/9 [77.8%]); Resolved (2/9 [22.2%])
- Indurations: Ongoing (7/7 [100.0%]); Resolved (0/7 [0.0%])

The median (Q1, Q3) duration of resolved injection site nodules and injection site indurations due to Day 1 SC injection was 85 (85, 85) days and 0 (0, 0) days, respectively. The median (Q1, Q3) duration of unresolved injection site nodules and injection site indurations due to Day 1 SC injection was 184 (87, 227) days and 173 (128, 191) days, respectively.

Observation:

Nodules and indurations were observed in trial **GS-US-536-5816** roughly in same number of subjects as in pivotal trial **GS-US-200-4625** and persisted longer than other injection site reactions.

➤ **Study GS-US-200-5709: Phase 1 Single and Multiple-Dose SC and Oral LEN in Healthy Participants Using Commercial LEN Formulation**

Overall, 36 participants (80.0%) experienced a study drug–related ISR. All were Grade 1 or 2 ISRs (Study GS-US-200-5709, Listing 7). The median (Q1, Q3) total duration of any study drug–related ISR was 27 (6, 64) days (Table 10). 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 (Table 13602.4.1):

- Injection site *induration* (66.7%, 30 subjects), 27 (17, 27) days
- Injection site *nodule* (48.9%, 22 subjects), 396 (102, 421) days; Denominator = 45
- Injection site pain (35.6%, 16 subjects), 6 (6, 7) days
- Injection site erythema (33.3%, 15 subjects), 4 (4, 6) days

GS-US-200-5709: Study Drug–related Injection Site Nodules and Indurations at Time of Data Cut (13Dec2021: trial is ongoing)

Overall, 22 participants (50.0% Denominator = 44) experienced study drug–related injection site nodules, and 29 participants (65.9%) experienced study drug–related injection site indurations (Table 11). All events were Grade 1 or 2 in severity (Study GS-US-200-5709, Listing 7).

The injection site nodules and indurations reported due to Day 1 SC injection were as follows:

Participant-level analysis:

- Nodules: Ongoing (12/22 [54.5%]); Resolved (10/22 [45.5%])
- Indurations: Ongoing (1/29 [3.4%]); Resolved (28/29 [96.6%])

Event-level analysis:

- Nodules: Ongoing (19/41 [46.3%]); Resolved (22/41 [53.7%])
- Indurations: Ongoing (2/52 [3.8%]); Resolved (50/52 [96.2%])

The median (Q1, Q3) duration of resolved injection site nodules and injection site indurations due to Day 1 SC injection was 421 (113, 421) days and 27 (15, 27) days, respectively. The median (Q1, Q3) duration of unresolved injection site nodules and injection site indurations due to Day 1 SC injection was 393 (29, 416) days and 18 (18, 18) days, respectively).

Observation:

Nodules and indurations observed roughly in somewhat higher number of subjects compared with pivotal trial **GS-US-200-4625** and, as in the pivotal trial, nodules and indurations persisted longer than other injection site reactions.

Phase 2 trial

➤ **GS-US-200-4334: Phase 2, Multiple-Dose SC LEN in PWH Using Commercial LEN Formulation**

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 nodules (Table 18

and Study GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.2.3.2.2). There were no new Grade 3 or higher ISRs reported since the Week 28 analysis. The most frequently of reported ISRs ($\geq 10\%$ in SC LEN total group) and their duration in median (Q1, Q3) days were as follows (Study GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.5.2):

- Injection site erythema (27.2%, 28 subjects), 5 (2, 11) days
- Injection site swelling (23.3%, 24 subjects), 11 (6, 29) days
- Injection site pain (19.4%, 20 subjects), 4 (1, 9) days
- Injection site *nodule* (14.6%, 15 subjects), 195 (122, 301) days
- Injection site inflammation (13.6%, 14 subjects), 3 (1, 8) days
- Injection site *induration* (12.6%, 13 subjects), 202 (101, 361) days

Injection site reactions after the first SC LEN dose at Day 15:

Participant-level analysis:

- Nodules: Ongoing (1 of 11 subjects having nodule [9.1%]); 1/105 total subjects (.95%) Resolved (10 of 11 [90.9%])
- Indurations: Ongoing (6 of 9 subjects having induration [66.7%]); 6/105 total subjects (5.7%) 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 nodules and injection site indurations was 278 (136, 366) days and 202 (101, 213) days, respectively.

Observation:

Nodules and indurations observed roughly in a somewhat lower number of subjects compared with pivotal trial **GS-US-200-4625** however, as in the pivotal trial, nodules and indurations generally persisted longer than other injection site reactions.

Phase 2/3 trial: GS-US-200-4625

➤ Study GS-US-200-4625: Phase 2/3, Multiple-Dose SC LEN in PWH With Multi-Drug Resistance Using Commercial LEN Formulation

Overall, 47 participants (65.3%) experienced a study drug-related ISR. All were Grade 1 or 2 in severity with the exception of 3 participants (4.2%) who experienced a Grade 3 ISR. The median (Q1, Q3) total duration of any study drug-related ISR was 8 (4, 59) days. The most frequently reported study drug-related ISRs (reported in $\geq 10\%$ of 72 participants who received ≥ 1 injection) and their duration in median (Q1, Q3) days were as follows (Study GS-US-200-4625 Cohorts 1 and 2 Week 52 Summary, Tables 15.11.2.4.1 and 15.11.2.4.2):

- Injection site swelling (36.1%, 26 subjects), 11 (5, 16) days
- Injection site pain (30.6%, 22 subjects), 3 (2, 5) days
- Injection site erythema (30.6%, 22 subjects), 5 (3, 8) days
- Injection site *nodule* (25.0%, 18 subjects), 253 (111, 365) days
- Injection site *induration* (15.3%, 11 subjects), 112 (43, 220) days

● Injection site nodules and indurations due to Day 1 SC injection:

Participant-level analysis:

Nodules: Ongoing (7/16 subjects having a nodule [43.8%]); 7/72 total subjects (9.87%)

Indurations: Ongoing (1/8 [12.5%]); 1/72 (1.3%)

Event-level analysis:

Nodules: Ongoing (7/23 [30.4%])

Indurations: Ongoing (1/8 [12.5%])

- The median (Q1, Q3) duration of resolved injection site nodule and injection site induration due to Day 1 SC injection was 148 (70, 307) days (among 16 events) and 70 (15,196) days (among 7 events), respectively.

Labeling as of 11/9/22:

(b) (4)

➤ **Comments Regarding the Effects of Formulation pH:**

The question arises whether high pH could be contributing to long duration of indurations and nodules.

The applicant's assessment of high pH formulations and ISRs: submitted in module 5.3.5.3 in the submission dated 6, 27, 2022 (SDN#38) includes:

- Nonclinical Data for LEN
- Clinical Data for LEN:
- Clinical Data of Other Approved antiretrovirals (ARVs):

Nonclinical Data for LEN

The applicant describes a number of non-clinical studies regarding the effect of pH on chronic granulomatous inflammation and foreign body response at the SC injection sites.

- A single-dose SC injection local tolerance study (**TX-200-2019**) of LEN using a solution of LEN free acid (approximately **pH 7**) and LEN sodium (approximately **pH 9.5**) was conducted in rabbits. Edema correlated with macroscopic observation of thickening at the injection site and microscopic observation of granulomatous inflammation were observed on Day 92. The macroscopic and microscopic findings did not differ between the different LEN formulations (approximately pH 7 or approximately pH 9.5). The granulomatous inflammation decreased in incidence and/or severity by Day 183 and Day 274, suggestive of a process of maturation or recovery.

- A single- (Day 1) and second-dose (Day 1 and Day 92) SC injection toxicity study with a 13-week observation period (**TX-200-2014**) of LEN using a solution of LEN free acid (approximately **pH 7.0**) and LEN sodium (approximately **pH 9.5**) was conducted in rats. LEN-related edema (very slight to moderate), macroscopic thickening and/or tan discoloration, correlative granulomatous inflammation (minimal to moderate; with or without necrosis), and macrophage infiltrate were present at the SC injection sites of animals administered either formulation of LEN (approximately pH 7 and approximately pH 9.5). Evidence of LEN-related granulomatous inflammation reversibility included decreased severity relative to SC injection site(s) used more recently, and/or resolution to a minimal macrophage infiltrate.

- A 9-month (once monthly) SC injection toxicity study (**TX-200-2017**) of LEN using a solution of LEN free acid (approximately **pH 7.0**) and LEN sodium (approximately **pH 9.5**) was conducted in dogs. Lenacapavir-related microscopic observations of necrosis, granulomatous

inflammation, mixed cell inflammation, and/or macrophage infiltrate were observed at the SC injection sites of animals administered either formulation of LEN (approximately pH 7.0 and approximately pH 9.5). At each sacrifice interval, granulomatous inflammation, with variable central necrosis, was generally observed in all but the last site dosed and was considered indicative of the maturation/recovery process. In the oldest injection sites, inflammation had recovered to a macrophage infiltrate in some animals. Overall, an increased interval since dosing was generally associated with a successive decrease in the overall incidence/severity of microscopic findings.

- A SC injection local tolerance study (**TX-200-2033**) of LEN using a solution of LEN free acid (**pH 7.1**) and LEN sodium (pH 9.4) was conducted in rabbits. On Day 4, LEN-related microscopic findings at the injection site consisted of slight to marked necrosis, minimal to moderate mixed cell inflammation, and minimal to slight mononuclear cell infiltrates, that correlated with the macroscopic observation of thickening in all animals administered LEN with either formulation (pH 7.1 and pH 9.4). On Day 29, LEN-related microscopic findings of marked granulomatous inflammation and slight to marked necrosis correlated with the macroscopic observation of thickening in all animals administered LEN. Overall, the incidence and severity of mixed cell and/or granulomatous inflammation and necrosis were similar between dose levels and formulations, regardless of pH. LEN-related edema correlated with the macroscopic observation of thickening and the microscopic observations of mixed cell or granulomatous inflammation, necrosis, and mononuclear cell infiltrates at the SC injection site of animals administered LEN.

● A SC injection local tolerance study (**TX-200-2010**) of LEN (LEN was suspended in vehicle (b) (4) **pH 7.4**) was conducted in rabbits (NDA 215973, Seq 0001, m4.2.3.6).

Lenacapavir-related dermal observations of very slight edema, very slight to well-defined erythema, and desquamation were noted on Day 4; these findings were resolved by Day 29. These observations were minor and recovered by the end of the study; therefore, they were considered not adverse. On Day 4, LEN-related microscopic findings included slight or marked granulomatous inflammation of the subcutis and slight to moderate granulomatous inflammation of the dermis. SC granulomatous inflammation correlated with the macroscopic observation of white discoloration. On Day 29, LEN-related findings of minimal to moderate granulomatous inflammation of the subcutis and was correlated with the macroscopic observation of white discolorations. Minimal mixed cell infiltrates of the dermis were present. No granulomatous inflammation of the dermis was present, indicating reversal.

Non-clinical conclusion:

The Applicant states that their available nonclinical data suggest that chronic granulomatous inflammation and foreign body response at the SC injection site are expected to occur for any antiretroviral compound including LEN due to the presence of a SC drug depot, and irrespective of the pH of the formulation.

This reviewer agrees this is a reasonable conclusion.

Clinical Data for LEN:

From Applicant presented information:

The same SC formulation of LEN 309 mg/mL (2 x 1.5 mL injection – 927mg, initial (**pH = 9.0 to 10.0**))

was used in a total of 219 participants across a Phase 1 study in healthy participants (Study GS-US-200-**5709**, n = 44), a Phase 2 study in treatment-naïve PWH (Study GS-US-200-**4334**, n = 103) and a Phase 2/3 study in heavily treatment-experienced PWH with multidrug resistance (Study GS-US-200-**4625**, n = 72).

Most AEs of ISRs resolved within days, but those of indurations and nodules lasted longer (median [Q1, Q3]: for resolved = 70 [15, 196] and 148 [70, 307] days in Study GS-US-200-**4625**, for resolved = 278 [136, 366] and 202 [101, 213] days in Study GS-US-200-**4334**, and for resolved = 27 [15, 127] and 421 [113, 421] in Study GS-US-200-**5709**, respectively). There were rarely any gross inflammatory components, such as tenderness or erythema, to these AEs of indurations or nodules, and when there was coincident pain or erythema, they resolved quickly. Investigators treating participants with AEs of persistent indurations or nodules reported that those AEs were resolving slowly over time. In general, investigators commented on the benign nature of the nodules.

A SC aqueous formulation of LEN free acid suspension (**pH 7.1**) was used in a total of 61 participants in one Phase 1 trial in healthy participants (Study GS-US-200-**4070**, n = 32), and a Phase 1b proof-of-concept trial in treatment-naïve PWH (Study GS-US-200-**4072**, n = 29). In trial GS-US-200-**4070**, single doses 30 mg, 100mg, 300mg, and 450 mg were examined. In trial GS-US-200-**4072**, single doses 150mg, 50 mg, 20 mg, and multiple doses 450 mg, and 750 mg were examined.

Nodules and indurations were reported in 28.1% and 25.0% of participants in Study GS-US-200-4070, and 20.7% and 24.1% of participants in Study GS-US-200-4072, respectively. Median (Q1, Q3) duration (days) of resolved indurations and nodules was 4 (2, 12), 51 (7, 169) in Study GS-US-200-4070 and 7 (6, 45), 49 (4, 225) in Study GS-US-200-4072.

Clinical conclusion:

Regarding nodules and indurations, the data from the trials described above is suggestive that nodules and indurations persist longer in the trials with initially higher pH (initial pH = 9.0 to 10.0). However, doses examined in in the lower pH trials were generally lower than those examined in the higher pH trials. Additionally, the number of subjects (sample size) in the lower pH trials is smaller, 61 versus 219, for the higher pH trials. It is noted also that non-clinical findings presented by the applicant do not show a significant pH effect.

Clinical Data of Other Approved ARVs:

The Applicant notes that other approved ARVs for SC or intramuscular (IM) injections have been associated with similar or greater incidence of ISRs.

- Approved labeling **CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)** 1/2021: **Section 6.1 Clinical Trials Experience**

“The most commonly reported ISR was localized pain/discomfort (79%) regardless of severity or relatedness. Other manifestations of ISR’s reported in more than 1% of subjects over the duration of the analysis period included *nodules (14%), induration (12%),* swelling (8%), erythema (4%), pruritus (4%), bruising (3%), warmth (2%), and hematoma (2%).”

- Approved labeling **FUZEON (enfuvirtide)** 8/2019: **Section 6.1 Clinical Trials Experience**

“The majority of ISRs were associated with erythema, induration, the presence of nodules or cysts, and mild to moderate pain at the injection site (Table 2)”: pain/discomfort (96%), *induration (90%),* erythema (91%), *nodules and cysts (80%),* pruritus (65%), and ecchymosis (52%), including participants with Grade 3 or 4 ISRs.

Data for Other SC Administered Alkaline Products

The Applicant notes that limited data are available in the published literature describing the safety risk to patients who have received SC injections of an alkaline product.

Labeling for Lenacapavir as of 11/9/22:

(b) (4)

Overall Conclusion regarding effect of pH:

Review of the applicant's presented nonclinical data for LEN, clinical data for LEN and clinical data of other approved ARVs does not identify a clear association between high formulation pH and duration of nodules and indurations.

- **Appendix E:** Review of Response to FDA Additional Comments (specifically Comment 6) in Complete Response Letters dated 28 February 2022 (included in consult email dated 7/18/22)

2.2.1. Comment 6

Please submit a complete assessment of the extent to which glass particulate contamination, including sub-visible particles, may be associated with injection site nodules and indurations or other clinical effects. In addition, submit independent dermatologist evaluation assessments for subjects in Study GS-US-200-4625 or Study GS-US-200-4334 who met Grade 3 or higher adverse event injection site reaction criteria, or who had any injection site reactions (particularly indurations or nodules) that are not resolved within 24 weeks.

- The Applicant provided a response that includes:
- Evidence from the literature
 - Nonclinical data for LEN and other antiretrovirals (ARVs)
 - Assessment of ISRs from clinical studies of LEN and other ARVs.

● **Literature:**

Pertinent information provided by the applicant includes a study (Dorris¹) wherein dogs were randomized to control (with in-line filtration) and experimental (without in-line filtration) groups and received concentrated solutions of particles. When particles were injected by the SC route, no inflammatory response was observed in either group.

The Applicant also provided information that includes the observation that granulomatous inflammation has been observed after SC and IM implantation of bioactive material, including those for HIV treatment (Anderson 1997², Shah 2017³, Van't Klooster 2010⁴).

● **Non-clinical data for LEN and other ARVs:**

A single-dose SC injection local tolerance study (Gilead Sciences: TX-200-2019) of LEN in rabbits was conducted using LEN formulations which were pharmacy compounded at the site (b) (4), and therefore were not expected to contain any intrinsic glass particulates resulting from an interaction between the LEN injection formulation and the borosilicate glass vials. Non-adverse edema correlated with macroscopic observation of thickening at the injection site and microscopic observation of granulomatous inflammation observed on Day 92. The granulomatous inflammation decreased in incidence and/or severity by Day 183 and Day 274, indicative of the maturation/recovery process.

¹ Dorris GG, Bivins BA, Rapp RP, Weiss DL, DeLuca PP, Ravin MB. Inflammatory potential of foreign particulates in parenteral drugs. *Anesth Analg.* 1977 May-Jun;56(3):422-8. doi: 10.1213/00000539-197705000-00022. PMID: 559445.

² Shive MS, Anderson JM. Biodegradation and biocompatibility of PLA and PLGA microspheres. *Adv Drug Deliv Rev.* 1997 Oct 13;28(1):5-24. doi: 10.1016/s0169-409x(97)00048-3. PMID: 10837562.

³ Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. *J Clin Tuberc Other Mycobact Dis.* 2017 Feb 10;7:1-12. doi: 10.1016/j.jctube.2017.02.001. PMID: 31723695; PMCID: PMC6850266.

⁴ van 't Klooster G, Hoeben E, Borghys H, Looszova A, Bouche MP, van Velsen F, Baert L. Pharmacokinetics and disposition of rilpivirine (TMC278) nanosuspension as a long-acting injectable antiretroviral formulation. *Antimicrob Agents Chemother.* 2010 May;54(5):2042-50. doi: 10.1128/AAC.01529-09. Epub 2010 Feb 16. PMID: 20160045; PMCID: PMC2863620.

A single-dose SC injection local tolerance study (Gilead Sciences: TX-144-2071) of bicitegravir (IND (b) (4)) was conducted in cynomolgus monkeys. On Day 92, bicitegravir-related macroscopic (thick skin) and microscopic inflammatory changes (moderate to marked granulomatous or pyogranulomatous inflammation with central pseudocyst, mild to marked capsular fibrosis, and/or minimal to moderate pigmented macrophages) were noted at the site of bicitegravir administration.

A single-dose SC injection local tolerance study (Gilead Sciences: TX-485-2002) of tenofovir alafenamide (TAF) (IND (b) (4)) was conducted in dogs. On Day 57, TAF-related microscopic findings at the injection site consisted of minimal to slight granulomatous inflammation and mononuclear cell infiltrates, moderate to marked adipose tissue necrosis and minimal to moderate fibrosis. Except for the granulomatous inflammation, the incidence and severity of these findings generally decreased on Day 57 compared with Day 29. The pyogranulomatous and neutrophil inflammation noted on Day 29 were not noted on Day 57.

For both bicitegravir and TAF, (b) (4)
(b) (4). The storage time for these formulations in the vials is short and they are not expected to contain any intrinsic glass particles.

Conclusion regarding non-clinical data:

The Applicant concludes that the available non-clinical data from local tolerance studies of ARV agents presented above suggest that chronic granulomatous inflammation and foreign body response at the injection site (SC or IM) occurs due to the drug depot of the product and is independent of glass particulates.

This reviewer agrees that this is a reasonable conclusion.

● Assessment of ISRs from clinical studies of LEN and other ARVs:

According to the applicant, preliminary data from an ongoing Phase 1 Study GS-US-200-5710 (titled, “A Phase 1 Study in Healthy Participant to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous and Intramuscular Lenacapavir”) provides some indication of the extent to which ISRs are independent of glass particulates. In this study, the LEN injection formulations used are not expected to contain any intrinsic glass particles resulting from interaction of LEN injection formulation with borosilicate glass vials because the formulations are pharmacy compounded at the clinical site (b) (4). The applicant notes that participants receiving SC LEN in the study experienced ISRs of similar type, severity, and duration as in Studies GS-US-200-4625 and GS-US-200-4334. The applicant states that these data suggest that the subvisible glass particles are not directly causing nor affecting the ISRs, which are most likely occurring due to the presence of SC LEN depot.

It is noted that other approved ARVs for SC or IM injections have been associated with similar or greater incidence and severity of nodules and induration. Following IM administration of cabotegravir, nodules and indurations were reported in 14% and 12% of patients, respectively. Following SC administration of FUZEON (enfuvirtide), induration and nodules and cysts, were reported in 90% and 80% of patients, respectively.

- Approved labeling **CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)** 1/2021: **Section 6.1 Clinical Trials Experience**
- Approved labeling **FUZEON (enfuvirtide)** 8/2019: **Section 6.1 Clinical Trials Experience**

General Conclusion:

The Applicant states that information submitted (literature and nonclinical and clinical evidence from injectable ARVs) support the position that ISRs, including nodules and induration, most likely result from the presence of the drug depot rather than the potential presence of subvisible glass particulates in the closure system with borosilicate glass vials.

This reviewer agrees that this is a reasonable conclusion.

Appendix F: Table of Injection Site Nodules and Indurations

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration (Days)	Size	Assoc Findings	
1) (b) (6) ✓								
55/M/WH/NH	Nodule #1, L inj site	15	1	16	16-72 (57)	0.1 mm	Visible redness, decrease in size	
	Nodule #2, R inj site	15	1	16	16-72 (57)	0.1 mm	Visible redness, decrease in size	
2) (b) (6)								
66/M/WH/NH	Nodule #1, L upper abd inj site	15	1	15	15 – 381 (367)	1x1.5 cm	Became smaller	
	Nodule #2, R lower abd inj site	15	1	15	15 – 450 (436)	1x1.5 cm	Became smaller	
2nd SC injection	Nodule L lower abd inj site	198	1	198	198 – 562 (365)	?		
	Nodule R upper abd inj site	198	1	198	198 – 562 (365)	?		
3rd SC injection	Nodule L upper abd inj site	381	1	381	381 – ongoing 275			
	Nodule R lower abd inj site	381	1	381	381 – ongoing 275			
3) (b) (6) ✓								
57/M/BL/NH	Nodule #1, LLQ inj site	15	1	16	16 – 85 (70)	0.4 mm	Decreased in size	
	Nodule #2, RUQ inj site	15	1	16	16 – 85 (70)	0.4 mm	Decreased in size	
4) (b) (6)								
52/F/WH/H	Nodules – lower abd quadrant	15	1	16	16 – 268 (253)	1.5 cm	No redness, a little	
	Bilaterally at inj sites	15	1	16	16 – 268 (253)	1.5 cm	Tender on palpation	
	Nodule – Lower abd L quadrant inj site	198	1	199	199 – ongoing 324			
	Nodule – Lower abd L quadrant inj site	198	1	199	199 – ongoing 324			
5) (b) (6)						Week 4	Week 36	
27/F/BL/H	Nodule – R lower quadrant inj site	15	1	43	43 – ongoing 157	2 x 1.7 cm	1.7 x 1	None reported

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration (Days)	Size			Assoc Findings
	Nodule at 1 o'clock position 4 inches to right of 1 st inj site	15	1	43	43 – ongoing 157 269 – ongoing 111	2. x 1.5 cm	1.8 x 0.7		Reported wk 52 analysis also
							? 3 x 2.5		? new nodule; 2 nd injection
						? Week 52			
2 nd SC injection	Nodule – L lower quad abd inj site	197	1	269	269 – ongoing 111	1.7 x 1cm			
	Nodule – L upper outer quad abd inj site	197	1	269	269 – ongoing 111	3 x 2.5 cm			
6) (b) (6)									
67/M/BL/NH	Nodule – R upper quadrant inj site	14	1	14	14 – ongoing 181	0.5 cm			Decreased in size
	Nodule – Lower R quadrant inj site ✓	14	1	14	14 – 54 (41)	0.5 cm			
7) (b) (6)						Day 15	Week 26	Week 52	
63/M/WH/H	Injection site nodule – L	15	1	15	15 – 747 (727)	0.6 x 0.3	1 x 0.4	1.4 x 0.5	none
*photo p 14 IR	Injection site nodule – R	15	1	15	15 – 747 (727)	0.6 x 0.4	1 x 0.3	2.5 x 0.6	none
4 th SC injection	Nodule (no location provided)	561	1	561	561 – ongoing 134				
8) (b) (6)						? Week 26	? Week 52	Week 62	none
62/M/WH/NH	Injection site nodule 1 – R	15	1	15	15 – ongoing 680			2.2 x 1.1	reported
*photo p 15 IR	Injection site nodule 2 – R about 2 cm diagonally inferior to # 1							0.9 x 0.6	
? 5 sites 1 st dose	Injection site nodule 3 – R medial							2.4 x 0.8	
	Injection site nodule 4 – L upper							3.2 x 1.0	
	Injection site nodule 5 – L lower							2.0 x 0.6	
2 nd SC injection	No site specified	197	1	197	197 – ongoing 498				
3 rd SC injection	No site specified	376	1	376	376 – ongoing 319				
9) (b) (6)*						Day 15	Week 26	Week 52	None
53/M/BL/NH	Injection site nodule – R	15	1	15	15 – ongoing 624	1.1 x 0.6	2.2 x 1.3	3.0 x 1.2	reported
* photo p 14 IR	Injection site nodule – L	15	1	15	15 – ongoing 624	1.2 x 1.1	3.0 x 1.2	2.9 x 1.2	

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration (Days)	Size	Assoc Findings
3 rd SC injection	No site specified (nodules)	379	1	379	379 – ongoing 260		
10) (b) (6) ✓							
59/F/BL/NH	Nodule – R lower quadrant inj site	15	1	15	15 – 169 (155)		
	Nodule – R upper quadrant inj site	15	1	15	15 – 169 (155)		
11) (b) (6)							
54/F/WH/NH	Nodule – Lower hemiabdomen inj site	15	1	15	15 – ongoing 529		
2 nd SC injection	2 nodules (R&L) at inj site	197	2	197	197 – 199 (3)		
3 rd SC injection	2 nodules (R&L) at inj site	382	2	382	382 – 384 (3)		
12) (b) (6)							
59/M/WH/H	Nodule – L upper abdomen inj site	15	1	15	15 – 86 (72)		
	Nodule – R lower abdomen inj site	15	1	15	15 – 86 (72)		
2 nd SC injection	Nodule – L lower abdomen inj site	197	1	197	197 – 562 (366)		
	Nodule – R upper abdomen inj site	197	1	197	197 – ongoing 442		
3 rd SC injection	Nodule – L upper inj site	379	1	379	379 – ongoing 260		
	Nodule – R lower abd inj site	379	1	379	379 – ongoing 260		
13) (b) (6)							
48/F/BL/NH	Nodules (bilateral) inj sites	15	1	15	15 – ongoing 554		
14) (b) (6)							
56/F/BL/NH	Nodules – R sided inj site	17	1	18	18 – ongoing 552		
2 nd SC injection	Induration – L abd inj site	197	1	198	198 – 379 (182)		

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration (Days)	Size	Assoc Findings
3 rd SC injection	Nodules – R abd inj site	379	1	380	380 – ongoing 190		
15) (b) (6)							
54/M/WH/H	Induration – inj site (no other info)	15	1	15	15 – ongoing 655		
4 th SC Injection	Induration – inj site (no other info)	561	1	561	561 – ongoing 109		
16) (b) (6)							
27/F/BL/NH							
3 rd SC injection	Mass – (lumps) injection site	386	1	448	448 – 630 (183)		
17) (b) (6)							
52/M/BL/NH							
4 th SC injection	Mass – (bilateral lumps) at injection site	573	1	573	573 – ongoing 59		
18) (b) (6)							
54/M/NP/NP	NP = not permitted						Painless & flexible
2 nd SC injection	Nodule – Upper R abd	193	1	193	193 – 372 (180)		
19) (b) (6)							
27/M/BL/NH	Nodule – abd R lower quadrant inj site	15	1	127	127 – 267 (141)	0.5 cm	
2 nd SC injection	Nodule – abd upper left/umbilicus level inj site	197	1	267	267 – 379 (113)		
	Nodule – lower L abd area	197	1	267	267 – 379 (113)		
20) (b) (6)							
28/M/WH/H	Nodules – lower abdomen	15	1	20	20 – 380 (361)		

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration (Days)	Size	Assoc Findings
21) (b) (6)							
60/M/BL/NH	Induration – (hardness) R injection site	189	1	189	189 – 251 (63)		
22) (b) (6)							
64/M/WH/NH	Induration – (hardness) both sides inj site	15	1	15	15 – 57 (43)		
23) (b) (6)							
39/M/AS/NH	Induration – at both 1 st & 2 nd inj sites	15	1	15	15 – 266 (252)		
2 nd SC injection	Induration – at both 1 st and 2 nd inj sites	204	2	205	205 – 424 (205)		
3 rd SC injection	Induration – at both inj sites	386	1	386	386 – ongoing 108		
24) (b) (6)							
46/M/WH/NH							
3 rd SC injection	Nodule – L & R subcut nod inj site	377	1	377	377 – ongoing 73		
25) (b) (6)							
61/M/WH/NH	Induration – Abd bilateral	16	1	21	21 – 216 (196)		
2 nd SC injection	Induration – Abd bilateral	198	1	199	199 – ongoing 296		
3 rd SC injection	Induration – Abd bilateral	380	1	380	380 – ongoing 115		
26) (b) (6)							
28/M/AS/NH	Induration – at both inj sites	15	1	15	15 -84 (70)		
27) (b) (6)							
35/M/AS/NH	Induration at 1 st inj site	15	2	16	16 – 18 (3)		
2 nd SC injection	Induration at 2 nd inj site	197	1	199	199 – 203 (5)		

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration (Days)	Size	Assoc Findings
28) (b) (6)							
48/F/AS/NH	Induration – L lower quadrant inj site	15	1	16	16 – 170 (155)		
29) (b) (6)							
52/M/AS/NH	Induration – at both inj sites	15	1	16	16 – 30 (15)		
2 nd SC injection	Induration – at both inj sites	196	2	197	197 – 209 (13)		
30) (b) (6)							
57/M/AS/NH	Induration – inj site	197	2	204	204 – ongoing 246		

This table was compiled from the response to IR of 9/8/2021 received 9/23/2021, p. 37 (Appendix Table 2) and from Study GS-US-200-4625 Interim Week 26 Clinical Study Report, Section 16, Listing 16.2.7.8 (pages 1-36).

- This table documents nodules in 18 (25%) and indurations in 11 (15%) of subjects receiving one or greater injections of lenacapavir.

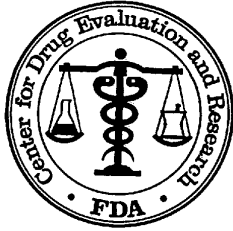
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PATRICIA C BROWN
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 215973
Drug Name:	Sunlenca (Lenacapavir): GS-6207
Indication(s):	Treatment of Treatment of HIV-1 infection in heavily treatment experienced patients with multi-drug resistance. Human immunodeficiency virus infection (disorder)
Studies	A 26-Week Subcutaneous Carcinogenicity Study in Transgenic Mice (001178-T (Hemizygous) RasH2)
Applicant:	Sponsor: Gilead Sciences Inc. 333 Lakeside Dr. Foster City, California 94404, USA
Test facility:	 (b) (6)
Documents Reviewed:	Electronic submission: June 27, 2022, via SN0038
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Pharmacology Toxicology-Infectious Disease
Reviewing Pharmacologist:	Deacquinta L. Diggs, PhD
Project Manager:	Allen, Kevin L
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission, the sponsor included a carcinogenicity study report in mice. This study was intended to assess the carcinogenic potential of Sunlenca (Lenacapavir): GS-6207^{(b) (4)} (Na salt, hereafter referred to as GS-6207) when administered once every 13 weeks by subcutaneous injection (total of 2 doses) to 001178-T (hemizygous) RasH2 mice, with a 13-week observation period following each dose. Results of this review have been discussed with the reviewing pharmacologist Dr. Diggs.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 10 animals. The dose levels for the three treated groups were at 30, 100, or 300 mg/kg/dose, respectively, via SC injection once every 13 weeks (total of 2 doses), for both males and females, as indicated in Table 1. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with one intraperitoneal dose of 75 mg/kg N-methyl-N-nitrosourea on Day 1 of the dosing phase. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received ^{(b) (6)}% w/w polyethylene glycol 300 and ^{(b) (4)}% w/w sterile water for injection and were administered in the same manner as the treated groups.

Table 1: Experimental Design in Mouse Study

Group Name	Group N0.	Target Dose Level (mg/kg/dose)		Number of Animal	
		Male	Female	Males	Females
		Vehicle Control	1	0	0
Low	2	30	30	25	25
Medium	3	100	100	25	25
High	4	300	300	25	25
Positive Control	5	75 MNU	75 MNU	10	10

Animals in group 5 were dosed with one intraperitoneal dose of positive control article on Day 1 of the dosing phase.

Group 1, 2, 3, and 4, were dosed via SC injection once every 13 weeks (total of 2 doses)

During the administration period, all animals were checked for morbidity, mortality, injury, twice daily (a.m. and p.m.), abnormal findings were recorded for toxicity animals as they were observed. Cage side observations were conducted for each carcinogenicity animal once daily during the dosing phase, except on days when detailed observations were conducted. The animals were removed from the cage, and detailed observations were conducted for each animal once during the pre-dose phase, on Day 1, and weekly (based on Day 1) thereafter to Week 26, and on Day 182 of the dosing phase. Detailed observations were also collected for each carcinogenicity animal on the day of scheduled sacrifice (Day 183, only those animals scheduled for sacrifice on that day). Abnormal findings or an indication of normal was recorded. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in

carcinogenicity mice, were recorded, any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Observations included, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights were recorded for carcinogenicity animals once during the predose phase, before dosing on Day 1, and weekly (based on Day 1) thereafter to Week 26 and on Day 182.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, the tests for survival comparisons were performed with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response and for each dosed group against control using Kaplan-Meier product-limit estimates, along with log-rank and Wilcoxon tests. These were performed using LIFETEST procedure in SAS. The time to death or sacrifice (in weeks) was the dependent variable. Treatment group was included as the strata. Animals with a death or sacrifice status recorded as a planned sacrifice (interim or terminal) or an accidental death were censored in the analysis.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 19 (76%), 23 (92%), and 3 (30%) in the vehicle control, low, medium, high, and positive control groups, in male mice, respectively, and 24 (96%), 24 (96%), 21 (84%), 22 (88%), and 4 (40%) in the vehicle control, low, medium, high, and positive control groups, in females, respectively. The sponsor's report concluded that, there were statistically significant higher mortality in the medium dose group, when compared to the vehicle control group in male mice (p -value = 0.0423 for the Log-Rank test and P = 0.0409 for the Wilcoxon test.).

2.1.2. Tumor data analysis

In the sponsor's analysis, tests to compare tumor incidence were performed, with a one-sided risk for increasing or decreasing incidence with dose. Tests were performed for dose response and for each dosed group against the vehicle control group. Occult or non-palpable and fatal tumors were analyzed by the IARC asymptotic fixed interval-based prevalence test and death-rate test (Peto et al., 1980). The cut-off points for the interval-based test were Weeks 1 to 13, 14 to before terminal sacrifice, and the terminal sacrifice. Actual target dose levels were used as the scores for all groups. Fatal and non-fatal tumors were analyzed together, with separate stratum for each. Tumors of uncertain context were included in the analysis as non-fatal. The test was implemented using PROC MULTTEST in the SAS system (SAS, 2008). In the case of sparse tables (<10 total tumor bearing animals across the groups analyzed for the trend or pairwise test), the exact form of the test was used. Otherwise, the asymptotic version of the test was used. For each given tumor type, a statistical analysis was performed if the incidence in at least one dosed group was increased by at least two occurrences over the vehicle control group.

Observable or palpable (superficial as in mammary or skin) tumors were analyzed using the methods previously described for analyzing survival (on-set rate method described in Peto et al., 1980), using the time to death or time of detection of the tumor (in weeks) as a surrogate for the tumor onset time.

Adjustment for the multiplicity:

For multiplicity adjustment testing, the sponsor did not present any adjustment, unadjusted P-values were reported, and statistically significant results are given at the 5% level.

Sponsor's findings:

The sponsor's analysis showed statistically significant increasing dose response relationships at the 5% level, for the incidence of benign papilloma, squamous cell in skin/subcutis in female mice (p-value = 0.0498 for the Log-Rank test and P = 0.0498 for the Wilcoxon test.).

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on June 27, 2022, via SN0038.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female mice separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 19 (76%), 23 (92%), and 3 (30%) in the vehicle control, low, medium, high, and positive control groups, in male mice, respectively, and 24 (96%), 24 (96%), 21 (84%), 22 (88%), and 4 (40%) in the vehicle control, low, medium, high, and positive control groups, in females, respectively. The reviewer's report showed no statistically significant dose response relationship in the mortality of both male and female mice. The pairwise comparisons showed a statistically significant increase in mortality between the medium dose group and the vehicle control group in male mice (p-value = 0.0343).

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of $s_h = 1$. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of

$s_h = \left(\frac{W_h}{W_{\max}} \right)^k < 1$. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score

$s_h = 1$ can be considered as a whole animal, while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat study, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle $W_{\max}$ was considered as 105 for both male and female mice.

For the calculation of p-values, if there were less than 10 tumors bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 30, 100, and 300 for male mice and female mice) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male mice and female mice, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis, for the 26 weeks mouse study this reviewer used significance levels of 0.05 for common and rare tumors, for dose response relationship (trend) tests and for pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Sunlenca (Lenacapavir) dose in both male and female mice. The pairwise comparisons test also showed no statistically significant increases in tumor incidences in any groups, when compared to the vehicle control group in both male and female mice.

The pairwise comparisons showed statistically significant increases in the positive control group for the incidences of malignant lymphoma in hemolymphoid system, benign papilloma, squamous cell in the skin/subcutis, benign papilloma, squamous cell in stomach nonglandular, when compared to the vehicle control group in both male and female mice (p-values <0.0001, =0.0010, =0.0010, for males, and <0.0001, =0.0002, =0.0002, for females, respectively). Also, the pairwise comparisons showed statistically significant increases in the positive control group for the incidences of malignant carcinoma, Squamous Cell in stomach nonglandular in male mice, (p-values =0.0423).

3. Summary

In this submission, the sponsor included a carcinogenicity study report in mice. This study was intended to assess the carcinogenic potential of Sunlenca (Lenacapavir): GS-6207^(b)₍₄₎ (Na salt, hereafter referred to as

GS-6207) when administered once every 13 weeks by subcutaneous injection (total of 2 doses) to 001178-T (hemizygous) RasH2 mice, with a 13-week observation period following each dose.

Mouse Study:

In this study two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 10 animals. The dose levels for the three treated groups were at 30, 100, or 300 mg/kg/dose, respectively, via SC injection once every 13 weeks (total of 2 doses), for both males and females, as indicated in Table 1. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with one intraperitoneal dose of 75 mg/kg N-methyl-N-nitrosourea on Day 1 of the dosing phase. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received (b) (6) % w/w polyethylene glycol 300 and (b) (4) % w/w sterile water for injection, were administered in the same manner as the treated groups.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 19 (76%), 23 (92%), and 3 (30%) in the vehicle control, low, medium, high, and positive control groups, in male mice, respectively, and 24 (96%), 24 (96%), 21 (84%), 22 (88%), and 4 (40%) in the vehicle control, low, medium, high, and positive control groups, in females, respectively. The reviewer's report showed no statistically significant dose response relationship in the mortality of both male and female mice. The pairwise comparisons showed a statistically significant increase in mortality between the medium dose group and the vehicle control group in male mice (p-value = 0.0343).

For tumor data, following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased Sunlenca (Lenacapavir) dose in both male and female mice. The pairwise comparisons test also showed no statistically significant increases in tumor incidences in any groups, when compared to the vehicle control group in both male and female mice.

The pairwise comparisons showed statistically significant increases in the positive control group for the incidences of malignant lymphoma in hematology/lymphoid system, benign papilloma, squamous cell in the skin/subcutis, benign papilloma, squamous cell in stomach nonglandular, when compared to the vehicle control group in both male and female mice (p-values <0.0001, =0.0010, =0.0010, for males, and <0.0001, =0.0002, =0.0002, for females, respectively). Also, the pairwise comparisons showed statistically significant increases in the positive control group for the incidences of malignant carcinoma, Squamous Cell in stomach nonglandular in male mice, (p-values =0.0423).

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI

cc:

Archival NDA 215973- Sunlenca (Lenacapavir)

Dr. Tsong Dr. Rahman

Dr. Lin Dr. Diggs

Allen, Kevin L Dr. Collins

4. Appendix

Table1A: Intercurrent Mortality Rate
Male Mice

Week	0 mg/kg/dose Vehicle Control		30 mg/kg/dose Low		100 mg/kg/dose Med		300 mg/kg/dose High		75 mg MNU Positive	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	2	8.00	.	.	2	20.00
14 - 26	1	4.00	1	4.00	4	24.00	2	8.00	5	70.00
Ter. Sac.	24	96.00	24	96.00	19	76.00	23	92.00	3	30.00
Total	25	100.00	25	100.00	25	100.00	25	100.00	10	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table1B: Intercurrent Mortality Rate
Female Mice

Week	0 mg/kg/dose Vehicle Control		30 mg/kg/dose Low		100 mg/kg/dose Med		300 mg/kg/dose High		75 mg MNU Positive	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	.	.	1	4.00	.	.
14 - 26	1	4.00	1	4.00	4	16.00	2	12.00	6	60.00
Ter. Sac.	24	96.00	24	96.00	21	84.00	22	88.00	4	40.00
Total	25	100.00	25	100.00	25	100.00	25	100.00	10	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 2A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Vehicle Control, Low, Med, high	P-value for Vehicle Control vs Low	P-value for Vehicle Control vs Med	P-value for Vehicle Control vs High	P-value for Vehicle Control vs Positive
Dose-Response (Likelihood Ratio)	0.6981	0.9885	0.0343*	0.5678	<.0001*
Homogeneity (Log-Rank)	0.0398*	0.9885	0.0423*	0.5717	<.0001*

*: Statistically significant at 0.05

Table 2B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Vehicle Control Low, Med, high	P-value for Vehicle Control vs Low	P-value for Vehicle Control vs Med	P-value for Vehicle Control vs High	P-value for Vehicle Control vs Positive
Dose-Response (Likelihood Ratio)	0.2928	0.9885	0.1464	0.2874	0.0004*
Homogeneity (Log-Rank)	0.3583	0.9885	0.1573	0.2974	<.0001*

*: Statistically significant at 0.05

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=25) P - Trend	30 mg Low (N=25) P - VC vs. L	100 mg Med(N=25) P - VC vs. M	300 mg High (N=25) P - VC vs. H	75mg MNU Posi (N=10) P - VC vs. PC
Harderian Gland	B-Adenoma	0/25 (25) 0.6188	1/25 (25) 0.5000	1/25 (22) 0.4681	0/25 (25) NC	0/10 (5) NC
Hematolymphoid System	M-Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (22) NC	0/25 (25) NC	7/10 (9) <0.0001*
	M-Neoplasm, Erythroblastic	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (22) 1.0000	0/25 (25) 1.0000	0/10 (5) 1.0000
Kidney	B-Hemangioma	0/25 (25) 0.7423	1/25 (25) 0.5000	0/25 (22) NC	0/25 (25) NC	0/10 (5) NC
Liver	B-Adenoma, Hepatocellular	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (22) 1.0000	0/25 (25) 1.0000	0/10 (5) 1.0000
Lung	B-Adenoma, Bronchiolo-Alveo*	2/25 (25) 0.5027	2/25 (25) 0.6954	1/25 (22) 0.8582	2/25 (25) 0.6954	0/10 (5) 1.0000
Muscle, Biceps Femoris	M-Hemangiosarcoma	1/25 (25) 1.0000	0/24 (24) 1.0000	0/25 (22) 1.0000	0/24 (24) 1.0000	0/10 (5) 1.0000
Muscle, Skeletal, Other	M-Hemangiosarcoma	0/25 (25) 0.4845	0/25 (25) NC	1/25 (22) 0.4681	0/25 (25) NC	0/10 (5) NC
Preputial Gland	M-Adenocarcinoma	0/25 (25) 0.4898	0/25 (25) NC	1/25 (23) 0.4792	0/25 (25) NC	0/10 (5) NC
Rectum	M-Hemangiosarcoma	0/25 (25) 0.2577	0/25 (25) NC	0/25 (22) NC	1/25 (25) 0.5000	0/10 (5) NC
Skin/Subcutis	B-Papilloma, Squamous Cell	0/25 (25) NC	0/25 (25) NC	0/25 (22) NC	0/25 (25) NC	4/10 (7) 0.0010*
Spleen	B-Hemangioma	1/25 (25) 0.8713	2/25 (25) 0.5000	1/25 (22) 0.7225	0/25 (25) 1.0000	0/10 (5) 1.0000
Stomach, Glandular	B-Adenoma	0/25 (25) 0.2577	0/25 (25) NC	0/25 (22) NC	1/25 (25) 0.5000	0/10 (5) NC
Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (25) 0.4845	0/25 (25) NC	1/25 (22) 0.4681	0/25 (25) NC	4/10 (7) 0.0010*
	M-Carcinoma, Squamous Cell	0/25 (25) 0.7423	1/25 (25) 0.5000	0/25 (22) NC	0/25 (25) NC	2/10 (7) 0.0423*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

NC = not calculable

*: Statistically significant at 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=25) P - Trend	30 mg Low(N=25) P - VC vs. L	100 mg Med(N=25) P - VC vs. M	300 mg High (N=25) P - VC vs. H	75 mg MNU Posi (N=10) P - VC vs. PC
Harderian Gland	B-Adenoma	0/25 (25) 0.7173	2/25 (24) 0.2347	1/25 (23) 0.4792	0/25 (23) NC	0/10 (7) NC
Heart	M-Mesothelioma, Atriocaval	0/25 (25) 0.4896	0/25 (24) NC	1/25 (24) 0.4898	0/25 (23) NC	0/10 (7) NC
Hematolymphoid System	M-Lymphoma	0/25 (25) 0.4842	0/25 (24) NC	1/25 (23) 0.4792	0/25 (23) NC	7/10 (10) <0.0001*
Ileum	M-Hemangiosarcoma	0/25 (25) 0.7368	1/25 (24) 0.4898	0/25 (23) NC	0/25 (23) NC	0/10 (7) NC
Lung	B-Adenoma, Bronchiolo-Alveo*	0/25 (25) 0.4842	0/25 (24) NC	1/25 (23) 0.4792	0/25 (23) NC	0/10 (7) NC
Mammary Gland	M-Hemangiosarcoma	0/24 (24) 0.4947	0/25 (24) NC	1/25 (24) 0.5000	0/25 (23) NC	0/10 (7) NC
Skin/Subcutis	B-Papilloma, Squamous Cell	0/25 (25) 0.2500	0/25 (24) NC	0/25 (23) NC	1/25 (24) 0.4898	5/10 (8) 0.0002*
Spleen	B-Hemangioma	0/25 (25) 0.2421	0/25 (24) NC	0/25 (23) NC	1/25 (23) 0.4792	0/10 (7) NC
	M-Hemangiosarcoma	0/25 (25) 0.0677	0/25 (24) NC	2/25 (24) 0.2347	2/25 (24) 0.2347	0/10 (7) NC
Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (25) 0.4842	0/25 (24) NC	1/25 (23) 0.4792	0/25 (23) NC	5/10 (8) 0.0002*
Thymus	B-Thymoma, Benign	0/25 (25) 0.2421	0/25 (24) NC	0/25 (23) NC	1/25 (23) 0.4792	0/10 (7) NC
Uterus	B-Hemangioma	2/25 (25) 1.0000	0/25 (24) 1.0000	0/24 (22) 1.0000	0/25 (23) 1.0000	0/10 (7) 1.0000
	B-Polyp, Glandular	1/25 (25) 0.9291	2/25 (24) 0.4844	0/24 (22) 1.0000	0/25 (23) 1.0000	0/10 (7) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

NC = not calculable

*: Statistically significant at 0.05 for common and rare tumors, respectively in pairwise comparisons.

Figure 1A: Kaplan-Meier Survival Curves for Male Mice

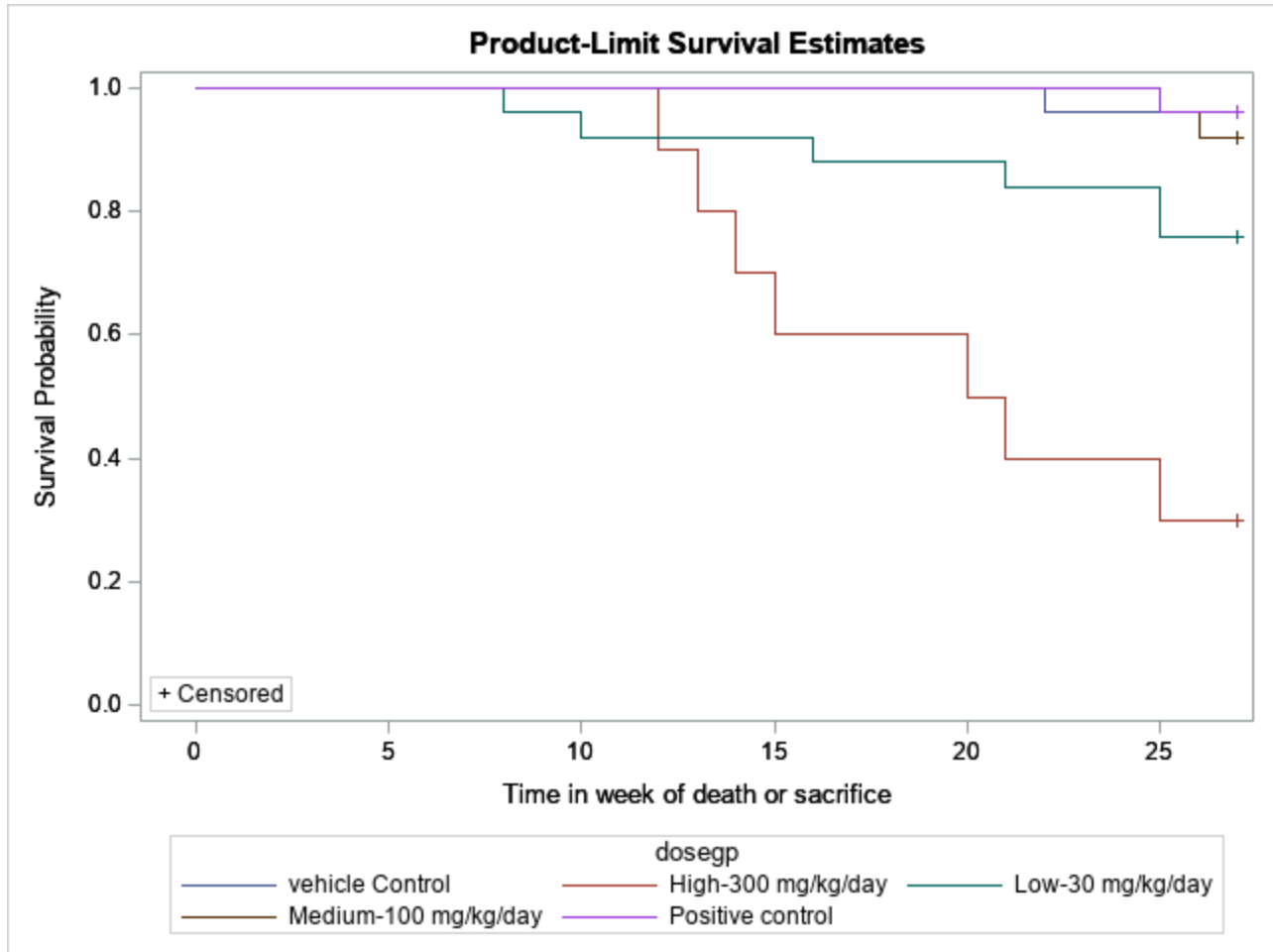
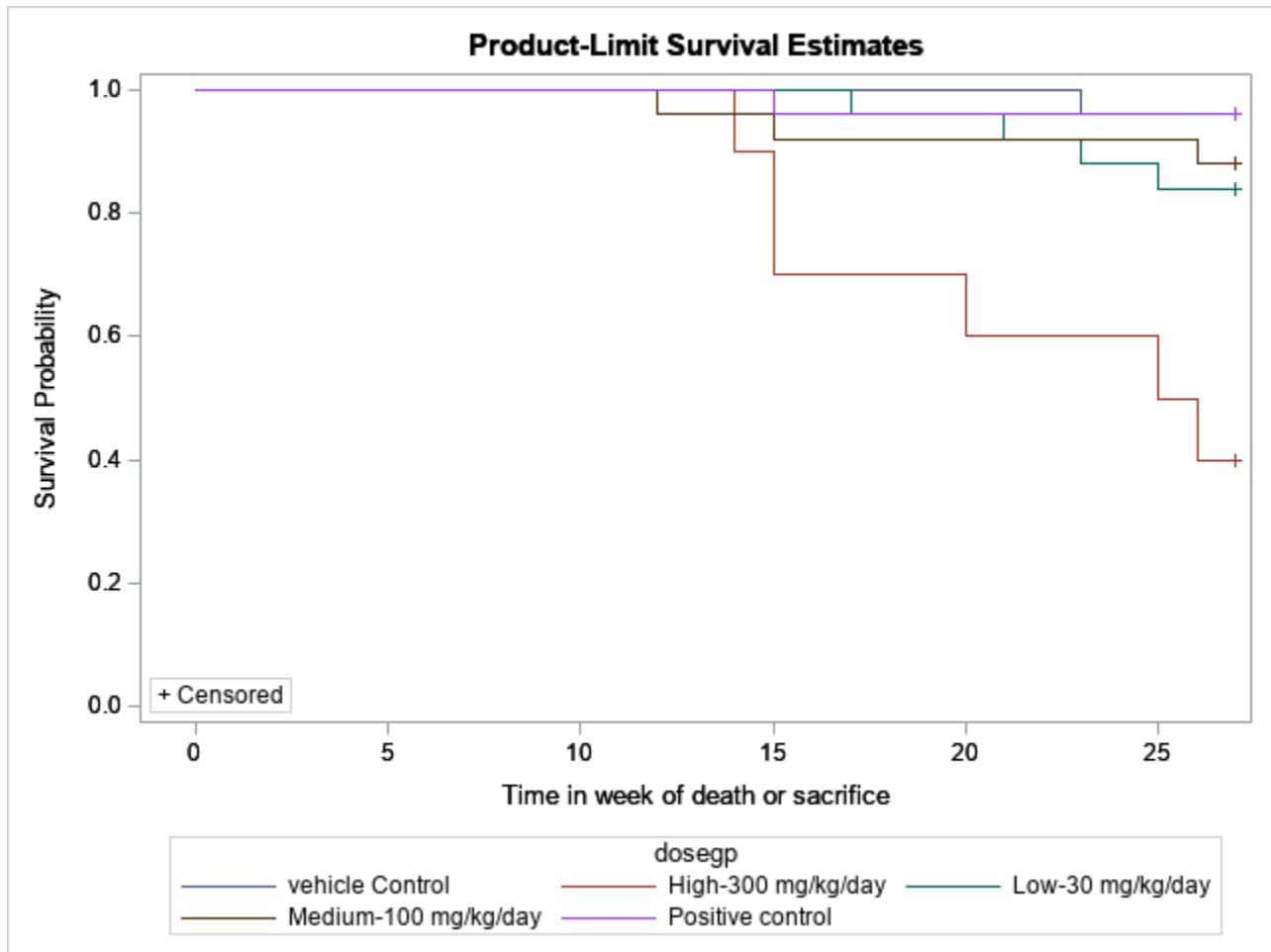


Figure 1B: Kaplan-Meier Survival Curves for Female Mice



5. References:

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9. Tarone RE, "Test for trend in life table analysis", *Biometrika* 1975, 62: 679-82

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/s/

MALICK MBODJ
09/28/2022 11:05:51 AM

KARL K LIN
09/28/2022 02:36:18 PM
Concur with review.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215973
Priority or standard	Priority
Submit date(s)	6/28/2021
Received date(s)	6/28/2021
PDUFA goal date	2/28/2022
Division/office	Division of Antivirals (DAV)
Review completion date	2/25/2022
Established/proper name	Lenacapavir
Proposed proprietary name	Sunlenca
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1) capsid inhibitor
Code name	LEN
Applicant	Gilead
Dosage form(s)/formulation(s)	Injection, for subcutaneous use
Dosing regimen	Initiation: 927 mg by subcutaneous injection (2×1.5 mL injections) and 600 mg orally (2 tablets) on day 1; 600 mg orally (2 tablets) on day 2. Tablets may be taken without regard to food. Maintenance: 927 mg by subcutaneous injection (2×1.5 mL injections) every 6 months (26 weeks) ±2 weeks. Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue, restart initiation from day 1.
Applicant proposed indication(s)/ population(s)	(b) (4)
Proposed SNOMED indication	(b) (4)
Regulatory action	Complete response
Approved dosage (if applicable)	Not applicable
Approved indication(s)/ population(s) (if applicable)	Not applicable
Approved SNOMED term for indication (if applicable)	Not applicable, because the NDA will receive a Complete Response action. If the NDA received an approval action the SNOMED indication would be as follows: 40780007: Human immunodeficiency virus I infection (disorder)

Abbreviations: NDA, new drug application; SNOMED, Systematized Nomenclature for Medicine

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 2. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215974
Priority or standard	Priority
Submit date(s)	6/28/2021
Received date(s)	6/28/2021
PDUFA goal date	2/28/2022
Division/office	Division of Antivirals (DAV)
Review completion date	2/25/2022
Established/proper name	Lenacapavir
Proposed proprietary name	Sunlenca
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1) capsid inhibitor
Code name	LEN
Applicant	Gilead Sciences, Inc.
Dosage form(s)/formulation(s)	Tablets, for oral use
Dosing regimen	Initiation: 927 mg by subcutaneous injection (2×1.5 mL injections) and 600 mg orally (2 tablets) on day 1; 600 mg orally (2 tablets) on day 2. Tablets may be taken without regard to food. Maintenance: 927 mg by subcutaneous injection (2×1.5 mL injections) every 6 months (26 weeks) ±2 weeks. Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue, restart initiation from day 1.
Applicant proposed indication(s)/ population(s)	(b) (4)
Proposed SNOMED indication	(b) (4)
Regulatory action	Complete response
Approved dosage (if applicable)	Not applicable
Approved indication(s)/ population(s) (if applicable)	Not applicable
Approved SNOMED term for indication (if applicable)	Not applicable, because the NDA will receive a Complete Response action. If the NDA received an approval action the SNOMED indication would be as follows: 40780007: [Human immunodeficiency virus I infection (disorder)]

Abbreviations: NDA, new drug application; SNOMED, Systematized Momenclature for Medicine

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Glossary

AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration-time curve
BA	bioavailability
BCRP	breast cancer resistance protein
BIC	bictegravir
BID	twice daily
BMI	body mass index
BPI	boosted protease inhibitor
CA	capsid
CC ₅₀	50% cytotoxic concentration
CCR	C-C chemokine receptor
CD	cluster of differentiation
CDRH	Center for Devices and Radiological Health
CI	confidence interval
CK	creatine kinase
CL	clearance
C _{max}	maximum concentration
COBI	cobicistat
C _{trough}	minimum concentration
CMC	chemistry, manufacturing, and controls
CXCR	C-X-C chemokine receptor
CYP	cytochrome P450
DAV	Division of Antivirals
DDI	drug-drug interaction
DRV	darunavir
DTG	dolutegravir
EC ₅₀	half maximal effective concentration
eGFR	estimated glomerular filtration rate
EFD	embryo-fetal development
ENF	enfurvitide
E-R	exposure-response
ETA	individual random effect
FAS	full analysis set
FDA	Food and Drug Administration
FMP	functional monotherapy period
F _{po}	oral versus intravenous bioavailability
F _{sc}	subcutaneous versus intravenous bioavailability
F/TAF	emtricitabine/tenofovir alafenamide
GD	gestation day

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GCP	good clinical practices
GLP	good laboratory practices
GLSM	geometric least-squares mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HI	hepatic impairment
HIV	human immunodeficiency virus
HTE	heavily treatment experienced
IA	interim analysis
IBL	ibalizumab
IC ₅₀	half maximal inhibitory concentration
IIV	interindividual variability
IND	investigational new drug
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
ISR	injection site reaction
ISS	integrated summary of safety
IV	intravenous
K _{dir}	subcutaneous direct/rapid first-order absorption rate constant
K _{tr}	subcutaneous transit first-order absorption rate constant
LEN	lenacapavir
LTR	long terminal repeat
MATE	multidrug and toxin extrusion protein
MDR	multidrug resistant
MOI	multiplicity of infection
NDA	new drug application
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
OATP	organic anion transporter polypeptide
OBR	optimized background regimen
OCT	organic cation transporter
OFV	objective function value
P	passage
paEC ₉₅	protein-adjusted 95% effective concentration
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic
PEG	polyethylene glycol
PeRC	Pediatric Review Committee
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic
PMR	postmarketing requirement
PO	per oral
PopPK	population pharmacokinetics

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PPND	pre- and postnatal development
PREA	Pediatric Research Equity Act
PLWH	people living with HIV
Q/F	intercompartmental clearance
RAS	resistance-associated substitution
RHD	recommended human dose
RI	renal impairment
RSE	relative standard error
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDM	site-directed mutant
$T_{1/2}$	mean time postinfection to maintain at least half maximal inhibition
TE	treatment experienced
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T_{max}	time to maximum concentration
TN	treatment naïve
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
V_c	volume of distribution in the central compartment
V_p	volume of distribution in the peripheral compartment
VF	virologic failure
VSVG	vesicular stomatitis virus G protein
WT	wild type

I. Executive Summary

1. Summary of Regulatory Action

These new drug applications (NDAs) for both oral (NDA 215974) and injectable formulations (NDA 215973) of lenacapavir (LEN) were submitted by Gilead Sciences. LEN is a first-in-class human immunodeficiency type 1 (HIV-1) capsid inhibitor with Breakthrough Therapy Designation. These NDAs were reviewed by the interdisciplinary review team.

The intended indication for LEN is to be used in combination with other antiretroviral(s) for the treatment of HIV-1 infection in heavily treatment-experienced adult patients with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

The clinical, virology, clinical pharmacology, pharmacology/toxicology, statistics, and regulatory disciplines did not identify issues that preclude approval. Product quality deficiencies were identified which include: (1) product quality information to support the proposed container presentation in borosilicate glass vials was not acceptable for commercial use due to delamination of the vial containers and concern for glass particulate contamination, (2) data supporting aluminosilicate glass vials as an alternative were insufficient for full review. The Product Quality assessment team recommends a complete response based on these deficiencies. I, the signatory authority for these applications, concur with the complete response recommendation and therefore the Agency will issue a complete response for both NDAs because the approval of NDA 215974 is dependent on the approval of NDA 215973. The proposed proprietary name, Sunlenca, was found acceptable only pending approval of the application; therefore, the Applicant will need to resubmit their proposed name when the deficiencies are addressed. Please refer to the Complete Response letter for further details.

The Applicant submitted one adequately designed phase 2/3 trial, Study 4625, that provided substantial evidence of efficacy for the proposed indication. Supportive evidence of efficacy was provided by Study 4334.

The available safety data from the clinical trials demonstrate that LEN is safe for its intended use. I concur that the risks identified in the review of the clinical trials' data can be mitigated through labeling and further evaluated during routine pharmacovigilance.

The long-acting properties of the LEN injectable formulation have potential advantages and disadvantages. The long-acting injectable formulation can be administered every 6 months in combination with other active antiretrovirals. However, because residual concentrations of LEN can remain for prolonged periods, careful selection of patients who agree to the injection dosing schedule is imperative. Nonadherence to the injection dosing schedule can lead to loss of virologic response and development of resistance to this new drug class.

For detailed information supporting the basis for the benefit-risk assessment please refer to the details in this Integrated Assessment document. Please also refer to the Product Quality Reviews for the deficiencies observed resulting in the overall Complete Response action.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Human immunodeficiency virus type 1 (HIV-1) is a transmissible virus that attacks and weakens the immune system. Without effective antiretroviral therapy (ART), HIV-1 infection leads to progressive destruction of the immune system, acquired immunodeficiency syndrome (AIDS)-defining illnesses, and premature death in almost all cases. • The U.S. Centers for Disease Control and Prevention (CDC) estimates that approximately 1.2 million people in the U.S. are living with HIV. In 2019, there were 15,815 deaths among people diagnosed with HIV (CDC 2021). • Maximal and durable suppression of HIV-1 RNA restores and/or preserves the immune system and reduces HIV-associated morbidity and mortality. Most treatment-adherent patients with limited previous HIV treatment experience can maximally and durably suppress HIV-1 RNA using a combination of two or more commercially available drugs from different drug classes. • Treatment failure occurs as a result of drug resistance, drug intolerance, and suboptimal adherence. Resistance-associated substitution(s) selected by one drug often confer(s) resistance to other drugs within that drug class, which further limits treatment options. • Heavily treatment-experienced (HTE) patients have limited remaining options for constructing a fully suppressive antiretroviral (ARV) regimen due to multidrug resistance, intolerance, or safety considerations.	• HTE patients with limited treatment options and evidence of ongoing HIV replication despite ART are at high risk of AIDS-related morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- For patients with multidrug resistant (MDR) HIV-1 infection, providers must individually tailor combination treatment regimens based on previous antiretroviral (ARV) exposure, cumulative viral resistance testing, drug safety and tolerability, and comorbid conditions. - The resulting ARV regimens are often burdensome, less well-tolerated, and associated with inadequate HIV-1 RNA suppression.	HTE patients with limited treatment options need new and effective therapies that lack cross-resistance with commercially available products, have a favorable tolerability profile, and allow for convenient dosing.
Benefit	- Efficacy of lenacapavir (LEN) in HTE patients who were failing treatment due to multidrug resistance, intolerance, or safety considerations was established in Study GS-US-200-4625 (Study 4625), a phase 2/3 trial conducted in two cohorts. - The Study 4625 trial design was consistent with FDA's Guidance for Industry <i>Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment</i> (November 2015). - Cohort 1 of Study 4625 was divided into two periods. During the first period, the Functional Monotherapy Period (FMP), 36 subjects in Study 4625 were randomized 2:1 to receive 14 days of oral LEN or placebo, respectively, in addition to their failing regimen. During the second period, the Maintenance Period, all subjects were unblinded and dosed with LEN (via subcutaneous injection following the 14-day oral lead-in) plus an optimized background regimen (OBR) through at least 52 weeks of follow-up. A second cohort enrolled 36 subjects, all of whom received open-label LEN plus an OBR, in parallel with Cohort 1. - The primary efficacy endpoint for Study 4625 was the proportion of subjects in Cohort 1 achieving a reduction in HIV-1 RNA of $\geq 0.5 \log_{10}$ copies/mL from baseline at the end of the 14-day FMP. The difference in proportions in HIV-1 RNA $\log_{10}$ copies/mL from Day 1 to Day 14 (LEN minus placebo) was -70.8 (95% CI, -34.9, -90.0), demonstrating statistical superiority of LEN compared to placebo. - Early HIV-1 RNA decreases of $> 0.5 \log_{10}$ copies/mL in prior trials have been associated with reduction in clinical disease progression according to the FDA's Guidance for Industry,	- LEN has demonstrated virologic activity in HTE patients with MDR HIV-1 infection who have limited treatment options. - The clinical trial design and endpoints were appropriate for the HTE population with limited treatment options. - Reductions in HIV-1 RNA levels are highly predictive of meaningful clinical benefit, and LEN functional monotherapy was superior to placebo for reducing HIV-1 RNA over 14 days. - Because Study 4625 was uncontrolled during the maintenance period and the interim analysis included follow-up through only Week 26, there is some uncertainty surrounding the contribution of LEN to the durability of virologic response. - Availability of LEN would provide a new and effective first-in-class treatment option for HTE patients with HIV-1 infection and limited alternative options due to multidrug resistance, intolerance or safety considerations. Patients who achieve virologic suppression with LEN plus an OBR would have a reduced risk of HIV/AIDS-related morbidity and mortality. (b) (4)

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NDA 215974 lenacapavir tablets, for oral use

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<i>Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment</i> (November 2015). - The key secondary efficacy endpoints assessed durability of virologic response following the FMP; however, the majority of subjects had not yet completed their Week 52 visits. Based on an interim analysis, 81% of subjects in Cohort 1 maintained HIV-1 RNA <50 copies/mL at the Week 26 visit. - Supplemental efficacy data was provided by a phase 2 trial, Study GS-US-200-4334 (Study 4334). A total of 183 treatment-naïve people living with HIV (PLWH) were randomized to receive one of three regimens containing LEN or an active comparator (bictegravir/emtricitabine/tenofovir alafenamide, [B/F/TAF]). At the Week 28 interim analysis, 94% (147/157) of the subjects who received a regimen containing LEN and 100% (25/25) of the subjects who received B/F/TAF maintained HIV-1 RNA <50 copies/mL.	
Risk and Risk Management	- Study 4625 enrolled 72 subjects from the HTE patient population, and the safety database that included subjects exposed to at least one 927 mg subcutaneous dose of LEN with the same proposed formulation for marketing was 232 subjects. This safety database is smaller than the minimum recommended sample size of 300 to 500, as outlined by FDA's Guidance for Industry <i>Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment</i> (November 2015); however, the overall clinical experience in PLWH and healthy volunteers was 803. - The most common adverse drug reaction during treatment with LEN was injection site reactions (ISRs). Injection site pain, swelling, and erythema were the most common specific ISRs reported, and typically lasted no more than a few days; however, indurations and nodules were reported to have longer durations, and approximately 7-19%, respectively, of cases had not fully resolved following up to 1 year of follow-up.	- Based on the available clinical data, LEN has an acceptable safety profile. Additional information, however, is needed to understand the contributing factors of ISRs with LEN, particularly for subjects with nodules and indurations that have slow or no documented resolution. - LEN resistance emerges readily in virologic failures and thus it is important to use LEN as a component of a complete active ARV regimen. - LEN resistance substitutions do not confer cross-resistance to other currently FDA-approved ARVs. - Longer term data are required to determine durability of LEN and the other ARVs in the OBR. - The product quality information to support the proposed container presentation in borosilicate glass vials was not acceptable for commercial or investigational use due to delamination of the vial containers and concern for glass particulate contamination. The data supporting aluminosilicate glass vials as an alternative was insufficient for full review.

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NDA 215974 lenacapavir tablets, for oral use

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• A review of deaths, serious adverse events (SAEs), and clinically significant laboratory abnormalities did not reveal any patterns to suggest a significant safety risk attributable to LEN; however, all three subjects who prematurely discontinued study drug due to an adverse event were due to injection site nodules or indurations and were considered related to LEN SC injection. • Resistance to LEN occurred frequently in virologic failures. • The LEN resistance substitutions selected in virologic failures did not confer cross-resistance to other current ARVs. • There are not enough data on the durability of LEN as a component of an ARV regimen. Longer-term data from all subjects after Week 26 are needed to determine if resistance to other drugs in the OBR occur. • In the assessment of product quality, the proposed commercial glass vial presentation was found to be incompatible with the drug product solution as glass particles were found in the solution. Combined with concerns for (b) (4) the lack of details provided from container closure integrity testing, lack of intrinsic release controls, and additional information required to determine the acceptability of a proposed alternative aluminosilicate glass vial, the application for LEN for injection was determined to be deficient from the product quality perspective.	

2.2. Conclusions Regarding Benefit-Risk

Infection with HIV-1 continues to be a significant public health concern both domestically and internationally. Although the HIV treatment armamentarium is robust, additional effective ARV treatment options that provide greater flexibility in meeting patients' individual needs and facilitating their tolerance for and adherence to lifelong HIV-1 treatment are needed.

HTE patients infected with MDR HIV-1 represent a rare but important subset of patients living with HIV. Patients with MDR HIV-1 who cannot achieve complete virologic suppression with antiretroviral therapy (ART) are at high risk for AIDS-related morbidity and mortality. This population needs new and effective ARV products that lack cross-resistance with commercially available products, have a favorable tolerability profile, and allow for convenient dosing. LEN, a first-in-class HIV-1 capsid inhibitor with Breakthrough Therapy Drug designation, is one such product. The injectable formulation of LEN provides an option with the advantage of providing a new mechanism of action and maintenance dosing every six months following a lead-in with oral tablets. However, the prolonged residual exposure is an important consideration when LEN is combined with background regimens that have a different dosing schedule and reduced antiviral activity due to resistance or concerns with adherence.

The submitted evidence clearly demonstrates LEN is effective in combination with an OBR in patients with limited options due to multi-drug resistance, intolerance or safety concerns with other ARVs. The pivotal trial, Study 4625 (CAPELLA), demonstrated superiority of LEN compared to placebo, when added to a failing regimen, for the proportion of subjects achieving a reduction in HIV-1 RNA of $\geq 0.5 \log_{10}$ copies/mL after 14 days of treatment. The lack of a control group after Day 14 in Study 4625 limits the ability to precisely quantify the contribution of LEN to long-term virologic suppression. However, the contribution of LEN is reflected by the relatively high rate of virologic suppression achieved with LEN plus an optimized background regimen (OBR) through the Week 26 interim analysis in a population previously unable to achieve virologic suppression. Additional supportive data from the phase 2 study in treatment-naïve PLWH, Study 4334, demonstrated that regimens containing LEN achieved and maintained virologic suppression through the Week 28 interim analysis.

The safety evaluation for LEN was adequate and the demonstrated clinical safety profile of LEN is acceptable for the proposed indication, dose and HTE population. With the exception of local ISRs, treatment-emergent resistance to LEN, and (b) (4), the safety profile of LEN was generally favorable. Injection site indurations and nodules remained persistent in several cases and were a significant cause of study drug discontinuations. The rate of virologic failure reported in Study 4625 reflects the targeted patient population: heavily treatment-experienced patients with advanced HIV/AIDS who are failing current ART and have very few remaining treatment options. Longer-term data will be needed to determine durability of LEN and the other ARVs in the OBR.

With all factors considered, the benefits of LEN when administered with other ARVs clearly outweigh the risks; however, the product quality information to support the proposed container presentation in borosilicate glass vials was not acceptable due to incompatibility of the LEN solution with the vial containers and concern for glass particulate contamination. In addition, there was lack of sufficient data to rule out any contribution of the product quality issues to ISRs.

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Given the safety concerns raised by the product quality issues, the applications for LEN were determined not to be approvable.

II. Interdisciplinary Assessment

3. Introduction

The Applicant has submitted two new drug applications (NDAs) for lenacapavir (LEN) seeking the indication of treatment of HIV-1 infection in combination with other antiretroviral(s) ^(b)₍₄₎

LEN is a first-in-class human immunodeficiency virus type 1 (HIV-1) capsid inhibitor and has been formulated for subcutaneous injection and as a tablet for oral use. The Applicant previously submitted an original investigational new drug (IND) application in 2017 to investigate LEN for injection and in 2018 to investigate LEN for oral use for the treatment of HIV-1 infection. (Refer to Section [III.12](#) for additional regulatory history.) This interdisciplinary assessment combines the review of NDA 215973 for LEN subcutaneous injection and NDA-215974 for LEN oral tablets.

The Applicant conducted two clinical trials in support of the findings of safety and efficacy for LEN, Study GS-US-200-4625 (Study 4625, also referred to as CAPELLA) and Study GS-US-200-4334 (Study 4334, also referred to as CALIBRATE). Study 4625 is an ongoing phase 2/3 trial designed to evaluate the antiviral activity of lenacapavir administered as an add-on to a failing regimen (functional monotherapy) for heavily treatment-experienced (HTE) people living with HIV (PLWH). Study 4334 is a phase 2 trial conducted in a treatment-naïve patient population that serves as supplementary support for the efficacy and safety evaluation of LEN for the indication of treating the HTE HIV-1 population.

Other currently available therapies used as part of the standard of care for the treatment of HIV-1 are discussed in more detail in Section [I.2](#) and are listed in Section [III.12.1](#). When constructing an ARV regimen for heavily-treatment experienced (HTE) PLWH, as noted by the U.S. HIV Treatment Guidelines (NIH 2022), the expected potency and whether a new drug as part of a complete regimen has a new mechanistic action are important considerations. Currently, no other ARV products HIV-1 have been approved in the capsid inhibitor class, nor have any been approved with a dosing interval as long as every 6 months.

3.1. Review Issue List

The review team identified five review issues relevant to the evaluation of benefit (Section [II.6.3](#)) and three review issues relevant to the evaluation of risk (Section [II.7.7](#)).

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Imbalance in Study 4625 Baseline Characteristics

- More subjects in the LEN arm of Cohort 1 in Study 4625 had baseline HIV-1 RNA $\leq 100,000$ copies/mL compared to the placebo arm.
- The mean baseline CD4⁺ cell count and CD4⁺ percentage were higher in the LEN arm than those in the placebo arm.

3.1.1.2. Justification for the Proposed Simplified Dosing Regimen

- The Applicant is proposing a simplified dosing regimen that was not studied during the phase 2/3 LEN clinical development program.
- The Applicant used PK data to support the proposed simplified regimen.

3.1.1.3. Impact of Subjects Not Maintaining Eligibility Criteria: Not Failing on Background Regimen or Nonadherence to Background Regimen

- Several subjects did not meet the established enrollment criteria for Study 4625, including resistance to at least two ARVs from each of at least three of the four main classes or demonstration of virologic failure despite adherence to a failing background regimen.

3.1.1.4. Dosing Interval and Approach to Missed Subcutaneous Maintenance Doses

- The Applicant proposed that during the LEN SC maintenance period, if more than 28 weeks have elapsed since the last LEN SC injection and if it is clinically appropriate to continue LEN treatment, then the indicated dosing regimen should be reinitiated.

3.1.1.5. (b) (4)

- (b) (4)
- (b) (4)

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Resistance Assessments of Virologic Failures

- The assessment of resistance emergence in virologic failures of an LEN-containing ARV regimen is critical to interpreting the overall risk-benefit of LEN and understanding the durability of LEN as a component of an ARV regimen in a heavily treatment-experienced patient population.

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3.1.2.2. Injection Site Reactions

- Injection site reactions were identified as the most common adverse drug reaction among subjects who received subcutaneous injections of lenacapavir; however, long-term experience of subjects after multiple injections was limited in Studies 4625 and 4334.

3.1.2.3. Background Regimens Containing Boosted Protease Inhibitors

- The risk of supratherapeutic LEN exposures when LEN is combined with a background regimen containing boosted protease inhibitors was not prospectively assessed in Study 4625.

3.2. Approach to the Review

[Table 4](#) provides an overview of the clinical trials that substantially contributed to the benefit and risk assessment for LEN. Data from Study GS-US-200-4625 (Study 4625) were the primary clinical trial data submitted in support of efficacy. Study GS-US-200-4334 (Study 4334) provided additional descriptive support for the evaluation of safety and efficacy.

Additional phase 1 studies, such as Study GS-US-200-5709, were used to support a simplified dosing regimen as well as adding supportive safety experience to the overall safety database. Data from the 90-Safety Update Report also provided additional safety data from the ongoing evaluation of subjects enrolled in Studies 4625 and 4334.

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Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Lenacapavir

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
GS-US-200-4625 (CAPELLA) [NCT04150068]	HTE adult and adolescent* people with HIV 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	Control type: Placebo controlled during functional monotherapy period (FMP) only Randomization: Cohort 1: Randomized 2:1 lenacapavir : placebo during FMP Cohort 2: Single-arm, not randomized Blinding: Cohort 1 (FMP only): Blinded Cohort 1 (Maintenance only) and Cohort 2: Open-label Biomarkers: No biomarkers Innovative design features: None	Dosage: <u>Cohort 1:</u> Cohort 1A: (N=24) FMP 1-2 week Oral LEN 600 mg (Day 1 and 2) + 300 mg (Day 8) + Failing Regimen Maintenance: Week 3-54 SC Len (927 mg) + OBR Cohort 1B: (N =12) FMP Weeks 1-2: Pb + Failing Regimen Oral dosing Week 3-4: Oral LEN 600 mg (Days 1 and 2) + 300 mg (Day 8) + OBR Maintenance Week 5-54: SC Len (927 mg) + OBR Number treated: 72 Duration (quantity and units): at least 54 wk	Primary: 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 FMP. Secondary: The proportion of participants in Cohort 1 with plasma HIV-1 RNA <50 copies/mL and <200 copies/mL at Weeks 26 and 52 of treatment based on the FDA-defined snapshot algorithm.	Planned: 100 Actual: 72 Cohort 1: 36 Cohort 1A: 24 Cohort 1B: 12 Cohort 2: 36 (*Note: although eligible, no adolescents actually enrolled)	Centers: 31 Countries: 9

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Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
GS-US-200-4334 (CALIBRATE) [NCT04143594]	Treatment-naive people with HIV ≥18 years of age	Control type: Active control Randomization: Randomized Blinding: Open-label Biomarkers: No biomarkers Innovative design features: None	Dosage: Treatment Group 1 (oral to SC LEN): Induction: oral LEN 600 and 300 mg, SC LEN 927 mg, and oral F/TAF 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 F/TAF 200/25 mg Maintenance: SC LEN 927 mg and oral BIC 75 mg Treatment Group 3 oral LEN 600 and 50 mg and oral F/TAF 200/25 mg Treatment Group 4 Oral B/F/TAF 50/200/25 mg Number treated: 175 Duration (quantity and units): At least 80 wk	Primary: The proportion of participants with HIV-1 RNA <50 copies/mL at Week 54 as determined by the FDA-defined snapshot algorithm Secondary: The proportion of participants with HIV-1 RNA <50 copies/mL at Weeks 28, 38, and 80 as determined by the FDA-defined snapshot algorithm	Planned: 175 Actual: 183 participants; SC LEN + (F/TAF → TAF): 52 participants; SC LEN + (F/TAF → BIC): 53 participants; Oral LEN + F/TAF: 52 participants; B/F/TAF: 25 participants	Centers: 41 Countries: 2

Source: Reviewer summary.

¹ Includes all submitted phase 2/3 clinical trials, except for phase 1 and pharmacokinetic studies.

Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension study; MC, multicenter; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized; SC, subcutaneous; LEN, lenacapavir; FMP, functional monotherapy period; OBR, optimized background regimen; ARV, antiretroviral; F/TAF, emtricitabine/tenofovir alafenamide (co-formulated tablet); TAF, tenofovir alafenamide; BIC, bictegravir; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide (co-formulated tablet)

4. Patient Experience Data

Patient experience data have not yet been submitted. Study GS-US-200-4625 (Study 4625) is ongoing, but the protocol has included collection of patient-reported outcomes. Subjects ≥ 18 years of age will complete the following, if available:

- Symptoms Distress Module, Short Form Health Survey, EQ-5D-5L at Day 1, and at Weeks 4, 16, 26, and 52.
- The Numeric Pain Rating Scale at Day 1 SC, Weeks 26 and 52.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Clinical pharmacology properties of LEN were comprehensively evaluated ([Table 6](#)). The clinical pharmacology review focused on the following review topics:

- Pharmacokinetics (PK) data, modeling, and simulation to support the Applicant’s proposed regimen (Sections [6.1](#) and [6.3.2](#)).
- Strategy for dosing window and missed dose (Section [6.3.4](#)).
- (b) (4) (Section [6.3.1](#)).
- Clinical significance of the effect of intrinsic and extrinsic factors on the PK of LEN (Sections [8.1](#) and [8.2](#)).
- Drug-drug interaction (DDI) potential and labeling recommendations (Section [8.2.2](#))

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics of LEN

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	A human immunodeficiency virus type 1 (HIV-1) capsid inhibitor.
Mechanism of action	Lenacapavir (LEN) is a multistage selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein subunits. LEN inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 linear unintegrated DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).
Antiviral activity	In MT-4 cells, LEN demonstrated antiviral activity with an EC ₅₀ value of 0.19nM and a selectivity index (CC ₅₀ value/EC ₅₀ value) of 140,000. LEN predominately targets at least one essential capsid-mediated step involved in the early stages of HIV replication with an EC ₅₀ value of 0.023nM. LEN also showed an antiviral effect against at least one capsid-mediated process essential for the late stages of HIV replication with a mean late stage EC ₅₀ value of 0.439nM.
Active moieties	LEN
QT prolongation	At LEN concentrations nine-fold higher than the therapeutic concentrations from the Applicant’s proposed dosing regimen, LEN does not prolong the QT interval to any clinically relevant extent.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Characteristic	Drug Information					
	General Information					
Bioanalysis	Liquid chromatography-tandem mass spectrometry methods were validated and used to determine the concentrations of LEN and coadministered drugs in human plasma, urine, and feces (as applicable to individual studies). The analyses were deemed to be acceptable.					
Healthy subjects versus patients	Simulated LEN mean exposures were 25% higher in subjects with HIV-1 infection compared to subjects without HIV-1 infection based on population pharmacokinetic (PK) analysis. This difference is not expected to affect the assessments based on results from healthy volunteers.					
Drug exposure at steady-state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Population PK Parameter Estimates of LEN Following Oral and Subcutaneous Administration of LEN in Heavily Treatment-Experienced Subjects With HIV-1 Infection					
	Parameter Geometric Mean (%CV)	Dosing Regimen in CAPELLA ^a			Applicant's Proposed Dosing Regimen ^b	
		Days 1 and 2: 600 mg (Oral), Day 8: 300 mg (Oral), Day 15: 927 mg (SC)			Day 1: 600 mg (Oral) + 927 mg (SC) Day 2: 600 mg (Oral)	
		Days 1 to 15	Day 15 to End of Week 28 (First SC Dosing Period)	Week 28 to Week 54 (Steady-State Exposure)	Day 1 to End of Week 26	Week 26 to Week 52 (Steady-State Exposure)
	C _{max} (ng/mL)	93.6 (80.7)	69.5 (69.5)	75.2 (69.2)	112 (76.8)	75.2 (69.2)
AUC _{tau} (h·ng/mL)	20,961 (77)	214,911 (68.5)	245,350 (68.1)	230,068 (68.4)	245,349 (68.1)	
C _{trough} (ng/mL)	41.0 (71)	26.0 (70.6)	28.1 (70.4)	26.0 (70.6)	28.1 (70.4)	
Source: Reviewer's analysis.						
^a Post hoc exposures from CAPELLA (N=62) by Population PK analysis.						
^b Simulated exposures by Population PK analysis.						
Range of effective dosage(s) or exposure	Near maximum efficacy is expected at the Applicant's proposed dosing regimen, with the lowest quartile of C _{trough} at least four-fold greater than the in vitro protein-adjusted EC ₉₀ (3.87 ng/mL=IQ1; MT-4 cells), corresponding to an IQ4 of 15.5 ng/mL. No clear relationship was identified between exposure and efficacy endpoints in the phase 2/3 trials with oral loading doses of 600 mg on Day 1 and Day 2 and 300 mg on Day 8 followed by 927 mg SC every 6 months.					
Maximally tolerated dosage or exposure	MTD was not determined. The evaluated dose that achieved the highest exposure in humans was oral 600 mg BID (for up to 11 days).					
Dosage proportionality	Oral: LEN C _{max} and AUC _{inf} increased in a less than dose-proportional manner over single doses of 50 to 1800 mg. SC: LEN C _{max} and AUC _{inf} increased in an approximately dose-proportional manner over single doses of 309 to 927 mg.					
Accumulation	Minimal accumulation is expected based on the ratio of LEN AUC following the second SC dose (AUC _{26 to 52 weeks}) to LEN AUC following the first SC dose (AUC _{0 to 26 weeks}) (mean ratio 1.17).					
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed LEN formulations are 300 mg oral tablets and 309 mg/mL injectable solution for SC administration used in the pivotal Study 4625, phase 2 Study 4334, and phase 1 PK Study 5709.					

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Characteristic		Drug Information		
		Absorption		
Bioavailability	Oral: 6% to 10%; SC: ~100%			
T _{max}	Oral: 4 hours; SC: 77 to 84 days			
Food effect (fed/fasted)	Meal Type	AUC GMR (90% CI)	C_{max} GMR (90% CI)	Median T_{max} (Q1, Q3)
Geometric least square mean and 90% CI	Low-fat meal vs. fasted	0.99 (0.58, 1.67)	1.16 (0.55, 2.42)	5.0 (4.0,6.0) vs. 4.0 (4.0, 6.0)
	High-fat meal vs. fasted	1.15 (0.72, 1.84)	1.45 (0.78, 2.70)	6.0 (4.0, 8.0) vs. 4.0 (4.0, 6.0)
	Formulation: To-be-marketed oral tablet. Low-fat meal is approximately 400 kcal, 25% fat. High-fat meal is approximately 1000 kcal, 50% fat.			
		Distribution		
Mean apparent volume of distribution (central+peripheral)	Oral: 16,411 L at 600 mg and 11,824 L at 300 mg; SC: 902 L			
Plasma protein binding	>98.5%			
Blood: plasma ratio	0.5 to 0.7			
Drug as substrate of transporters	LEN is a substrate of P-gp			
		Elimination		
Mass balance results	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% in feces.			
Mean apparent clearance	Oral: 68 L/h at 600 mg and 49 L/h at 300 mg; SC: 3.7 L/h			
Half-life	Oral: 10 to 12 days; SC: 8 to 12 weeks			
Metabolic pathway(s)	CYP3A5 and UGT1A1			
Primary elimination pathway	Fecal elimination			
		Intrinsic Factors and Specific Populations		
Body weight	Body weight ^{(b) (4)} did not have a clinically meaningful influence on the systemic exposure of LEN.			
Age	Age in the range of 18 years to 78 years did not have a clinically meaningful influence on the systemic exposure of LEN.			
Renal impairment	No dosage adjustment is required for patients with mild, moderate, or severe renal impairment (estimated creatinine clearance ≥15 mL per minute). LEN has not been studied in patients with end-stage renal disease (estimated creatinine clearance <15 mL per minute).			
Hepatic impairment	No dosage adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). LEN has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).			
		Drug Interaction Liability (Drug as Perpetrator)		
Inhibition/induction of metabolism	LEN is a moderate inhibitor of CYP3A			
Inhibition/induction of transporter systems	LEN is an inhibitor of P-glycoprotein and breast cancer resistance protein			

Abbreviations: AUC, area under the concentration-time curve; CC₅₀, 50% cytotoxic concentration; C_{max}, maximum concentration; C_{trough}, trough concentration; CYP, cytochrome P450; %CV, percentage coefficient of variation; EC₅₀, 50% effective dose; GMR, geometric mean ratio; SC, subcutaneous; UGT1A1, uridine diphosphate-glucuronosyltransferase

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Antiviral Activity Against HIV-1 Subtypes

LEN displayed antiviral activity against 23 diverse HIV-1 clinical isolates representing all major subtypes with a median 50% effective concentration (EC₅₀) value of 0.04nM (range 0.02 to 0.16nM) in peripheral blood mononuclear cells (PBMCs) ([Table 124](#)). LEN also showed antiviral activity against two HIV-2 isolates but was 15- to 25-fold less active relative to HIV-1. In a separate study testing the activity of LEN against 40 clinical HIV-1 isolates of diverse subtypes using the PhenoSense Gag-Pro Antiviral Assay, the range of means across subtypes was 0.166 to 0.297nM, with less than two-fold difference in activity across subtypes ([Table 125](#)). The range of means for subtype B isolates was 0.03 to 0.08nM with a median of 0.04nM.

5.1.2. Antiviral Activity of Lenacapavir Against Non-HIV Viruses

LEN was tested against hepatitis B virus (HBV), hepatitis C virus (HCV), human rhinovirus (HRV), and respiratory syncytial virus (RSV) in cell-based assays. LEN did not display selective antiviral activity in cell culture against HCV or HRV up to the highest concentration tested (44 to 50μM) ([Table 129](#)). However, LEN did demonstrate antiviral activity against HBV and RSV at low micromolar concentrations, with EC₅₀ values and corresponding 50% cytotoxic concentration (CC₅₀)/EC₅₀ ratios of 1.5μM and >34, and 8.2μM and >6.1, respectively. These data indicate that LEN is approximately 25,000-fold more active against HIV as compared to HBV. However, a proper clinically active therapy against HBV should be used in HIV/HBV-coinfected patients to maintain the HBV suppression.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. Study 4625 (CAPELLA)

The dose selection for LEN in this study was based on data from nonclinical and clinical studies. Prior to initiation of Study 4625, phase 1 PK and safety data were available in healthy subjects in Studies GS-US-200-4071 and GS-US-200-4538 (Studies 4071 and 4538) where LEN was administered as a single oral dose of up to 1800 mg, a multiple oral daily dose of up to 100 mg, or a single SC dose of up to 927 mg.

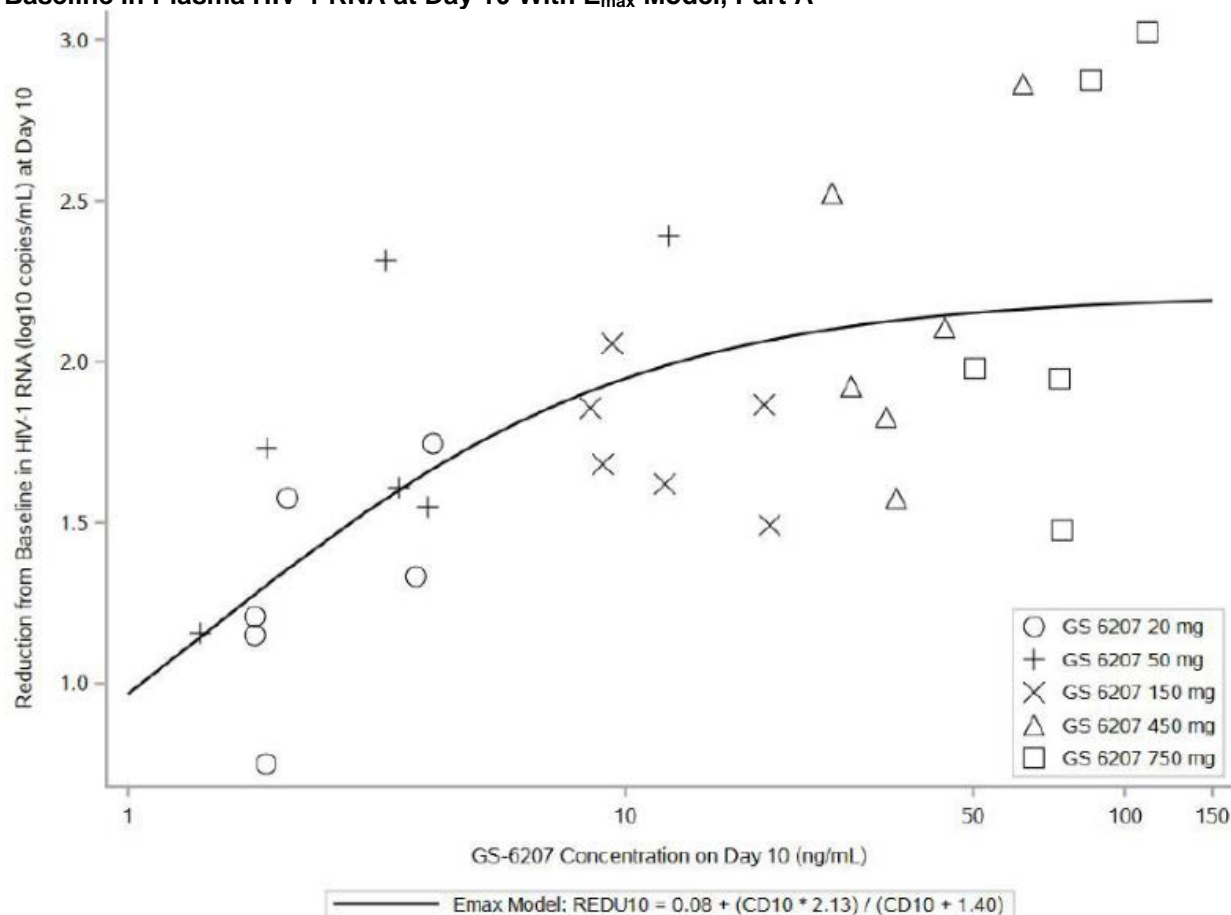
In in vitro studies, LEN was tested at concentrations corresponding to tissue culture equivalent inhibitory quotients (IQs) of 4, 8, 16, and 24, with an IQ of 1 defined as a concentration corresponding to the protein-adjusted 95% effective concentration (paEC₉₅) for wild-type HIV-1 (paEC₉₅ 3.87 ng/mL in MT-4 cells). In Study GS-US-200-4072 (Study 4072), the mean maximum HIV-1 RNA decline over 10 days was 1.8 to 2.2 log₁₀ copies/mL in HIV-1-infected subjects administered LEN monotherapy as a single SC dose of 50 to 450 mg ([Figure 1](#)). All subjects achieved at least 1 log₁₀ copy/mL decline in their HIV-1 RNA at Day 10. Day 10

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antiviral activity was comparable across the 50 to 450 mg dose groups. A target plasma concentration of 15.5 ng/mL (four-fold the IQ or IQ4), which is comparable to the in vivo 90% effective concentration of 12.6 ng/mL in Study 4072, was anticipated to provide antiviral activity in the heavily treatment-experienced (HTE) population.

Figure 1. Study 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



Source: Figure 10 in the Applicant's Clinical Study Report for Study 4072.

Abbreviations: CD10, LEN concentration on day 10 (ng/mL); GS 6207, LEN; HIV, human immunodeficiency virus; REDU10, reduction from baseline in HIV-1 RNA (log₁₀ copies/mL) at day 10. Defined as the difference between the baseline and day 10 HIV-1 RNA values

LEN dosing in pivotal Study 4625 is shown in [Table 7](#). The PK results from this study showed that concentrations of LEN were above IQ4 (15.5 ng/mL) within 2 days of the oral lead-in period and stayed above IQ4 throughout the maintenance period, as shown in [Figure 2](#) and [Figure 3](#).

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Table 7. Description of LEN Treatment in Each Study Period, Study 4625

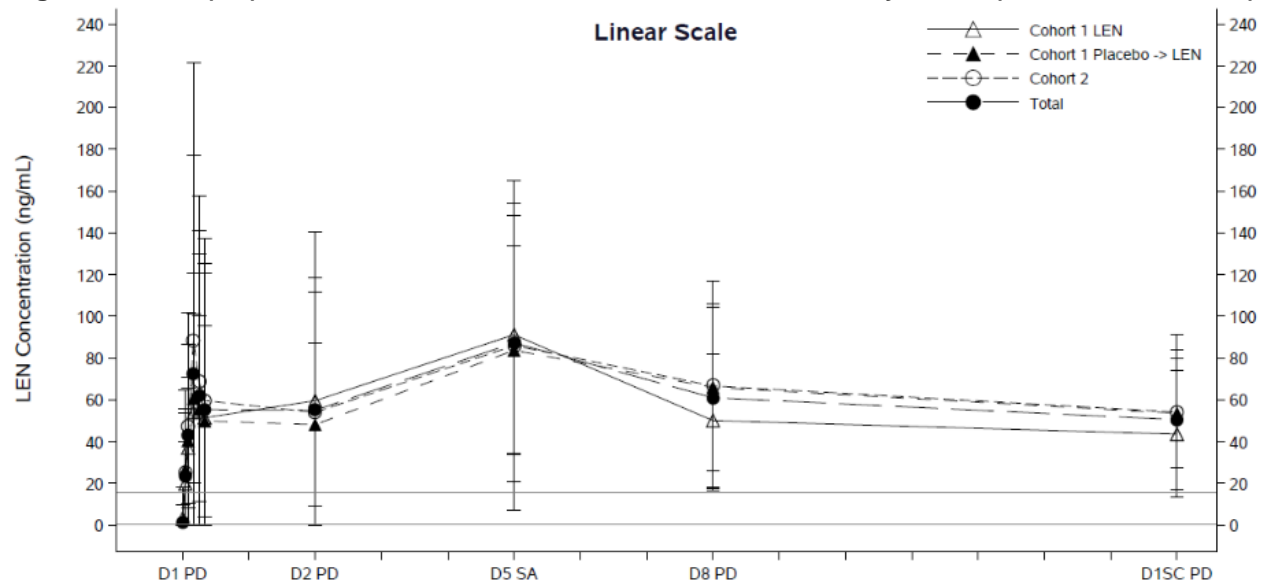
Study Visit	LEN Treatment
Days 1 or 15*	600 mg (2x300 mg)
Days 2 or 16*	600 mg (2x300 mg)
Days 8 or 22*	300 mg (1x300 mg)
Day 1 SC	927 mg (309 mg/mL; 2x1.5 mL)
Week 26	927 mg (309 mg/mL; 2x1.5 mL)
Week 52	927 mg (309 mg/mL; 2x1.5 mL)
Every 6 months (26 weeks) thereafter	927 mg (309 mg/mL; 2x1.5 mL)

Source: Applicant's Clinical Study Report for Study 4625.

* Day 15, 16, and 22 visits were applicable only to subjects who received placebo in the Functional Monotherapy Period at Days 1, 2, and 8.

Abbreviations: LEN, lenacapavir; SC, screening

Figure 2. Mean (SD) Plasma LEN Concentration Versus Time PK Analysis Set (Oral Lead-In Period)

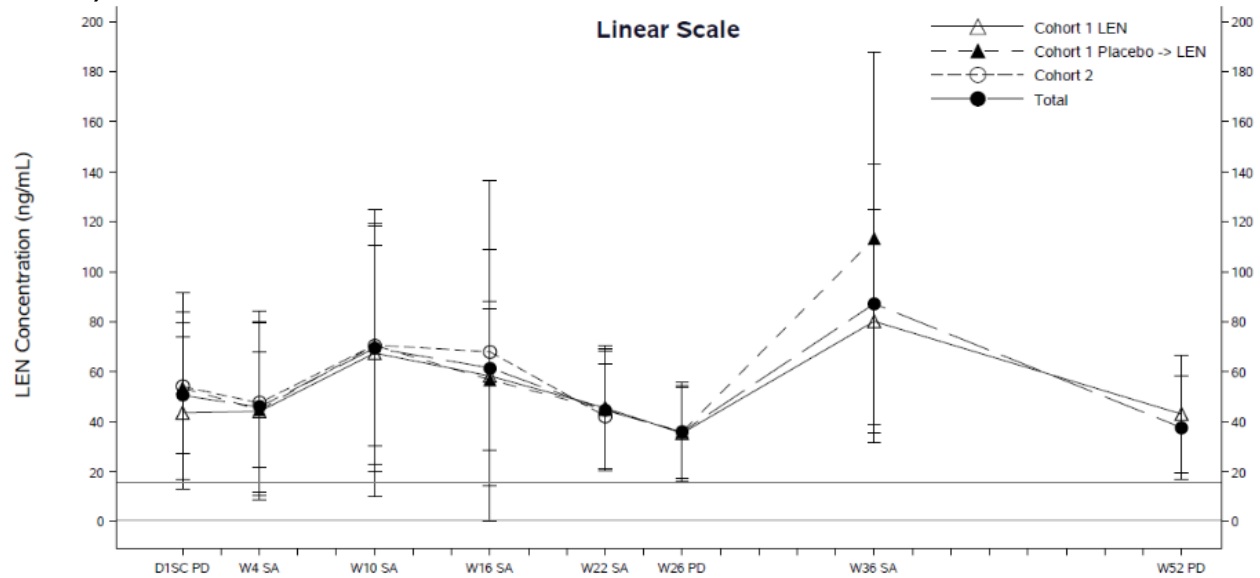


Source: Figure 15.10.1.1.1 in Applicant's Clinical Study Report for Study 4625.

Abbreviations: PD = predose; SA = single anytime; Dx = Day x (relative to first dose of LEN); SC = subcutaneous; C1 = Cohort 1; C2 = Cohort 2; BLQ = below the limit of quantitation; LLOQ = lower limit of quantitation.

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Figure 3. Mean (SD) Plasma LEN Concentration Versus Time PK Analysis Set (SC Maintenance Period)



Source: Figure 15.10.1.1.2 in Applicant's Clinical Study Report for Study 4625.

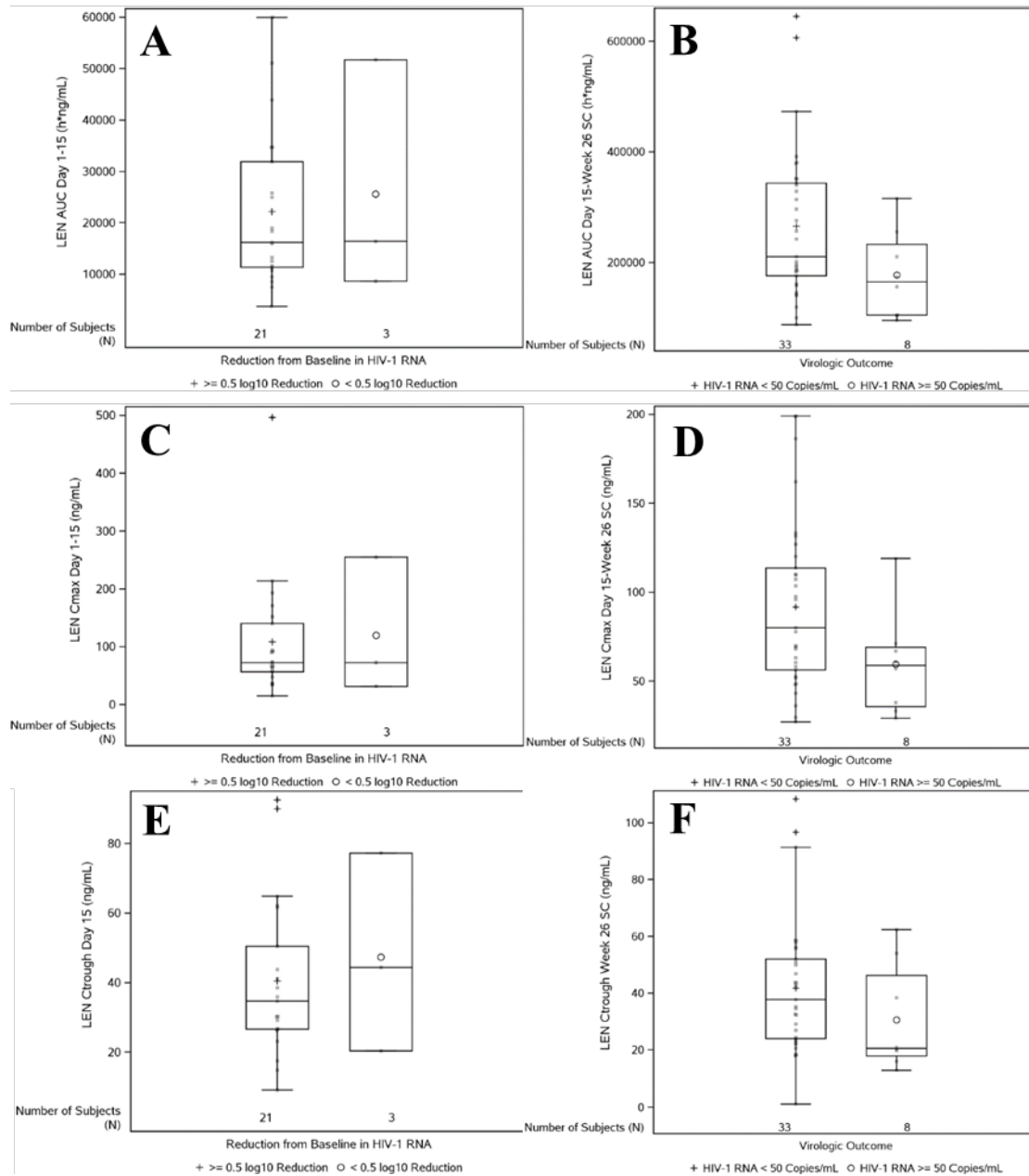
Abbreviations: PD = predose; SA = single anytime; Wx = Week x; SC = subcutaneous; C1 = Cohort 1; C2 = Cohort 2; BLQ = below the limit of quantitation; LLOQ = lower limit of quantitation.

No clear exposure-response (efficacy) could be identified from the pivotal Study 4625. Between subjects who achieved and who did not achieve the primary endpoint (a reduction in HIV-1 RNA of $\geq 0.5 \log_{10}$ copies/mL) at the end of the functional monotherapy period, no statistically significant difference was observed in C_{max} , C_{trough} , or AUC of LEN during the period of days 1 to 15 (Figure 4 A, C, and E) or the period of Day 15 to Week 26 postdose (Figure 4 B, D, and F).

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Figure 4. Box Plot of LEN PK Parameters by Proportion of Subjects Achieving ≥ 0.5 Log₁₀ Reduction From Baseline in HIV-1 RNA: Study 4625 Functional Monotherapy Period Analysis (Cohort 1A) LEN Population PK/PD Analysis Set



Source: Figures 2.1 and 2.2 in Applicant's PK-PD Tables, Figures, Listings.

A, Comparison of LEN AUC Day 1 to 15; B, comparison of LEN AUC Day 15 to Week 26.

C, Comparison of LEN C_{max} Day 1 to 15; D, comparison of LEN C_{max} Day 15 to Week 26.

E, Comparison of LEN C_{trough} at Day 15; F, comparison of LEN C_{trough} at Week 26.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{trough}, minimum concentration; HIV, human immunodeficiency virus; LEN, lenacapavir; PD, pharmacodynamics; PK, pharmacokinetics

6.1.2. Study GS-US-200-5709

Under this NDA, the Applicant proposed a simplified regimen that is different from the regimen studied in Study 4625. This proposed simplified regimen is 927 mg by SC injection and 600 mg orally on Day 1, followed by 600 mg orally on day 2, and 927 mg by SC injection every

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6 months. Because this proposed simplified regimen was not evaluated in Study 4625, there were no clinical efficacy or safety data available for the simplified regimen. Therefore, Study GS-US-200-5709 (Study 5709; which compared the systemic exposures of LEN after the regimens shown in [Table 8](#)) was considered pivotal from a clinical pharmacology standpoint for determining the acceptability of the proposed simplified regimen. An inspection was requested for the clinical and analytical sites for this study. The Division of New Drug Study Integrity within the Office of Study Integrity and Surveillance determined that inspections are not warranted. The Office of Study Integrity and Surveillance inspected the site in August 2018, which falls within the surveillance interval. After reviewing the inspection findings and the written response from the site, the Office of Study Integrity and Surveillance recommended that all study data be accepted for Agency review.

Comparability of LEN exposures between the regimen used in the ongoing phase 2 Study GS-US-200-4334 (Study 4334) and phase 2/3 Study 4625 and the Applicant's proposed simplified regimen is demonstrated based on modeling and simulation and ongoing PK bridging Study 5709 in healthy subjects (Section [6.3.2](#)). The safety and PK of combined oral and SC LEN were evaluated in Study 5709 with the same regimen used in the ongoing phase 2 and phase 2/3 studies (Cohort 1) and the simplified regimen (Cohort 2). Because LEN dosing is the same after month 6 irrespective of the regimen, LEN SC was not administered after Month 6 in Cohort 1 and Cohort 2 in Study 5709.

Table 8. Dose Regimens for Each Study Cohort, Study 5709

Cohort	Cohort 1: Phase 2/Phase 2/3 Regimen	Cohort 2: Simplified Regimen
Dosing regimen	Days 1 and 2: 600 mg oral LEN	Day 1: 927 mg SC LEN + 600 mg oral LEN
	Day 8: 300 mg oral LEN	Day 2: 600 mg oral LEN
	Day 15: 927 mg SC LEN	

Source: Generated by the reviewer based on Applicant's Study Report for Study 5709

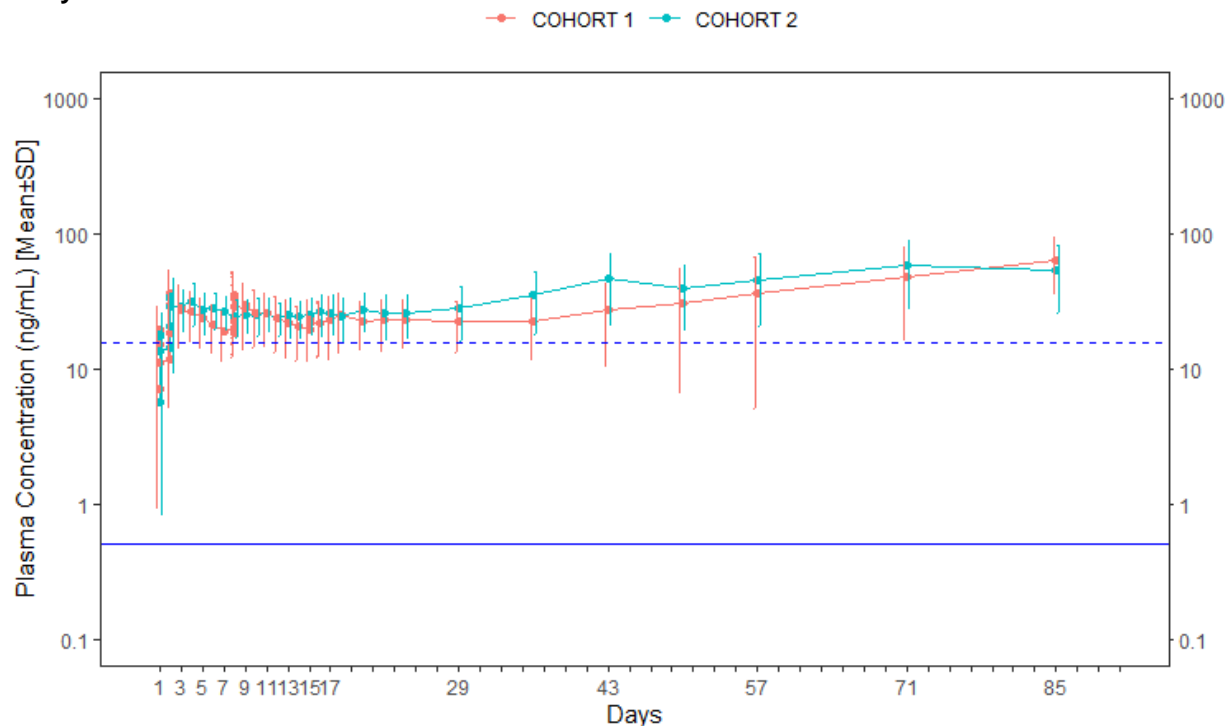
Abbreviation: LEN, lenacapavir; SC, subcutaneous

Comparison of the observed PK profiles to Day 85 indicated the concentrations of LEN after administration of the simplified regimen (Cohort 2) was comparable that of the regimen evaluated in the phase 2/3 study of heavily treatment-experienced people with HIV-1 infection and the phase 2 study of treatment-naïve people with HIV-1 infection (Cohort 1). For both regimens, mean LEN concentrations four-fold higher than the paEC₉₅ (IQ4) were achieved within 2 hours postdose on Day 2 and were maintained to Day 85.

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Figure 5. Mean ($\pm$ SD) Plasma Concentration Versus Time in Cohort 1 and Cohort 2 (to Day 85), Study 5709



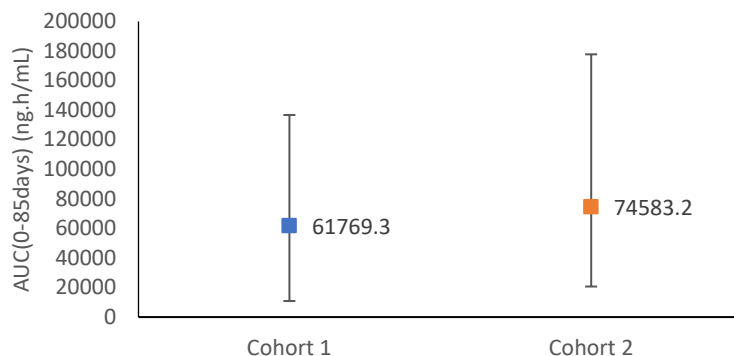
Source: Plotted by the Reviewer using LEN concentration data from Study 5709.

Dotted blue line: IQ4 (15.5 ng/mL); Solid blue line: lower limit of quantitation (LLOQ, 0.5 ng/mL)

Each data point and the associated error bar represents the arithmetic mean LEN concentration and standard deviation (SD), respectively, at each time point.

Abbreviations: IQ4, concentrations that are four-fold greater than the in vitro paEC95 (3.87 ng/mL=IQ1; MT-4 cells); LEN, lenacapavir; LLOQ, lower limit of quantitation

Figure 6. LEN AUC (0 to 85 Days) (Geometric Mean $\pm$ 90%CI) in Cohorts 1 and 2, Study 5709



Source: Plotted by the Reviewer using LEN concentration data from Study 5709.

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; LEN, lenacapavir

In conclusion, observed PK data from Study 5709 demonstrate the similarity of LEN exposure between the proposed simplified regimen and the regimen studied in the pivotal trial. Further discussion of these LEN dosage regimens in the context of labeling is discussed in Section [6.3.2](#).

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Study 4625 (CAPELLA)

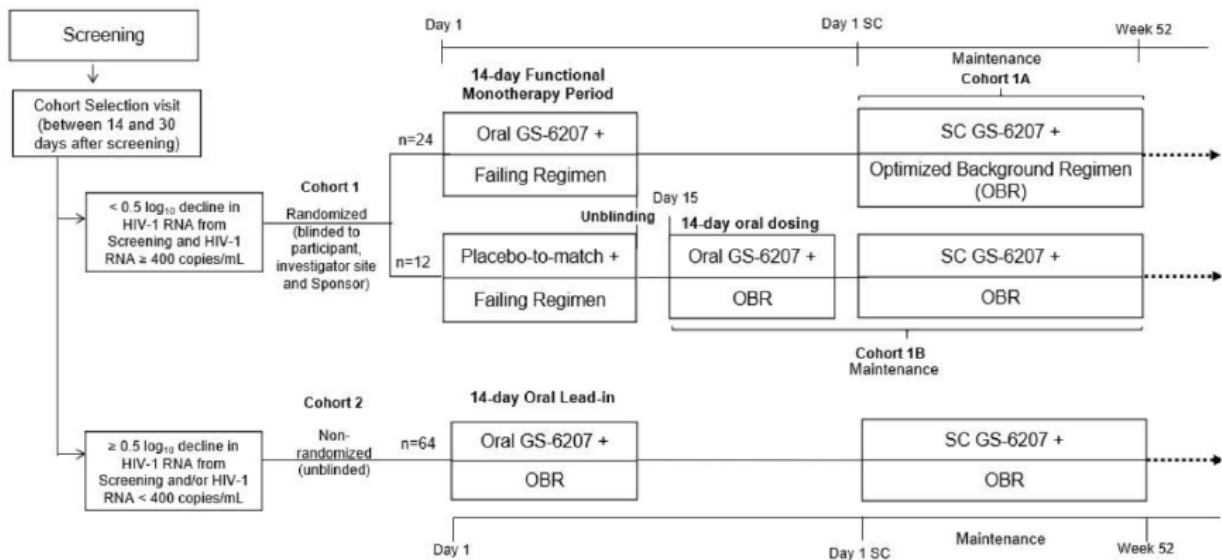
6.2.1.1. Study Design

Results from Study 4625 serve as the basis of the efficacy evaluation. This trial was designed in accordance with the recommendations set forth in FDA’s Guidance for Industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015).

Study 4625 had two cohorts. Eligible subjects who were HTE people living with HIV-1 (PLWH) with multidrug resistance were screened and then had a Cohort Selection visit 14 to 30 days after the Screening visit. During the Cohort Selection visit, if the subject’s HIV-1 RNA was ≥ 400 copies/mL and had $< 0.5 \log_{10}$ decline from Screening, the subject would be enrolled into Cohort 1 for randomization. If Cohort 1 was fully enrolled or the criteria for Cohort 1 were not met, the subject would be enrolled into Cohort 2.

Cohort 1 was a randomized, placebo-controlled, superiority trial in which subjects were randomized to receive 14 days of oral LEN or placebo in addition to their failing ARV regimen (functional monotherapy period [FMP]). At the end of the FMP, subjects who were randomized to receive oral LEN received SC LEN and initiated their optimized background regimen (OBR) on Day 1 SC (defined as 14 days after the first dose of oral LEN). Subjects who were randomized to placebo arm received oral LEN and initiated their OBR on Day 15, and then received SC LEN at Day 1 SC while continuing their OBR. Subjects enrolled in Cohort 2 received oral LEN for 14 days together with an OBR on Day 1. At Day 1 SC, Cohort 2 subjects received SC LEN and continued their OBR (Figure 7).

Figure 7. Study Design Schema, Study 4625



Source: Figure 1 of the Applicant’s Clinical Summary.

Eligible subjects were enrolled into Cohort 2 if Cohort 1 was fully enrolled.

Abbreviations: GS-6207, lenacapavir; HIV, human immunodeficiency virus; OBR, optimized background regimen; SC, subcutaneous

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6.2.1.2. Eligibility Criteria

Key eligibility criteria are summarized in this section, and the full criteria are available in Section [III.15](#).

The study enrolled subjects who met the following inclusion criteria:

- Adults aged ≥ 18 years or adolescents aged ≥ 12 years and weighing ≥ 35 kg, receiving a stable failing ARV regimen for >8 weeks before screening.
- Have HIV-1 RNA ≥ 400 copies/mL at screening.
- HIV resistance reports showing resistance to ≥ 2 antiretroviral medications from each of ≥ 3 of the 4 main classes of antiretroviral medications (integrase strand-transfer inhibitor [INSTI], non-nucleoside reverse transcriptase inhibitor [NNRTI], nucleoside reverse transcriptase inhibitor [NRTI], protease inhibitor [PI]).
- Have ≤ 2 fully active ARV remaining from the 4 main classes that can be effectively combined to form a viable regimen.
- Willing to receive an optimized background regimen together with LEN.

Subjects who met the following exclusion criteria were excluded from the study:

- An opportunistic illness requiring acute therapy within the 30 days prior to screening.
- Active and serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days before screening.
- Acute hepatitis.
- Untreated or newly treated HBV infection.
- HCV infection.
- Clinical decompensated liver cirrhosis.
- Active malignancy requiring acute therapy.
- Current alcohol or substance use.
- Clinically significant abnormal electrocardiogram (ECG).
- Estimated glomerular filtration rate (eGFR) ≤ 50 mL/min.
- Alanine aminotransferase (ALT) $>5\times$ the upper limit of normal (ULN).
- Direct bilirubin $>1.5\times$ ULN.
- Platelets $<50,000/\text{mm}^3$.
- Hemoglobin <8.0 g/dL.
- Use or planned use of exclusionary medications.

6.2.1.3. Statistical Analysis Plan

The Applicant and the review division agreed on the statistical analysis plan prior to trial completion.

The primary efficacy endpoint for Study 4625 was the proportion of subjects in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the FMP. The efficacy analysis population included all subjects who were randomized in the FMP and received at least one dose of blinded study drug (full analysis set [FAS]). Only data collected up to Day 1 SC or Day 15 visit were included in the primary efficacy analysis. For subjects with missing HIV-1 RNA values at the end of the FMP, the value was imputed using the last observation carried forward method. The difference in proportions between two treatment groups were compared using an unconditional exact method with two inverted 1-sided tests at alpha

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level 0.05 to evaluate superiority. The p-value and 95% exact confidence interval (CI) for the point estimate of treatment difference in proportions were provided.

The secondary efficacy endpoints were the proportions of subjects in Cohort 1 with HIV-1 RNA <50 and <200 copies/mL at Weeks 26 and 52 using the U.S. FDA-defined snapshot algorithm. Analyses were based on the all LEN population that was defined as all subjects who were enrolled in the study and received at least one dose of SC LEN. Only results at Week 26 were included as the majority of subjects had not reached Week 52 at the time of NDA submission.

Subgroup analyses were planned for the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 26 as determined by the U.S. FDA-defined snapshot algorithm. Subgroups of interest included age group, sex, race, region, baseline cluster of differentiation (CD)⁴⁺ categories, baseline viral load categories, baseline INSTI resistance categories, genotypic sensitivity score, phenotypic sensitivity score, and overall susceptibility score.

6.2.1.4. Results of Analyses of Clinical Trial Intended to Demonstrate Efficacy, Study 4625 (CAPELLA)

This section summarizes the subject disposition, baseline demographics, clinical characteristics, and primary and key secondary efficacy results to support the efficacy of LEN in HTE subjects with multidrug resistant (MDR) HIV-1 infection. Data from Cohort 1 and Cohort 2 are often shown side-by-side for ease of presentation. However, the two cohorts represent discrete groups with different populations and are not intended to be compared to one another.

6.2.1.4.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Disposition

The study screened a total of 144 subjects. Among them, 72 were enrolled in the study ([Table 9](#)). All of the 72 subjects completed the FMP and received SC LEN injection on Day 1 SC. All of the Cohort 1 subjects also completed the Week 26 assessment. One subject in Cohort 2 prematurely discontinued study drug in the maintenance period due to death.

Baseline Demographics and Clinical Characteristics

The majority of subjects in the trial (Cohort 1 and Cohort 2) were male (75%) and white (40%), the median age was 52 years ranging from 23 to 78 years, and the median body mass index (BMI) was 26 kg/m² ranging from 15 to 43 kg/m² ([Table 10](#)).

For Cohort 1, notably more subjects in the LEN arm had baseline HIV-1 RNA ≤100,000 copies/mL (96%) compared to the placebo arm (50%). The mean baseline CD⁴⁺ cell count and CD⁴⁺ percentage were higher in the LEN arm. The median number of prior ARV medications was nine for both arms. Further discussion of Cohort 1 baseline differences between the LEN and placebo arms is discussed in Section [6.3.1](#).

Compared to Cohort 1, Cohort 2 subjects had more prior antiretroviral (ARV) regimens, higher mean baseline CD⁴⁺ percentage and CD⁴⁺ cell count.

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Table 9. Patient Disposition, Study 4625

Parameter	Cohort 1		Total	Cohort 2
	LEN	Placebo to LEN		
Randomized	24	12	36	36
Functional monotherapy period (Cohort 1)/oral lead-in (Cohort 2)				
Completed study drug	24 (100%)	12 (100%)	36 (100%)	36 (100%)
Prematurely discontinued study drug	0	0	0	0
Maintenance period (to Week 52)				
Completed Week 26	24 (100%)	12 (100%)	36 (100%)	6 (17%)
Continuing study drug	17 (71%)	9 (75%)	26 (72%)	34 (94%)
Completed study drug	7 (29%)	3 (25%)	10 (28%)	1 (3%)
Prematurely discontinued study drug	0	0	0	1 (3%)
Reason: Death	0	0	0	1 (3%)

Source: Statistical reviewer's analysis.

Abbreviations: LEN, lenacapavir

Table 10. Baseline Demographic and Clinical Characteristics, Study 4625

Parameter	Cohort 1			Cohort 2 (N=36)	Overall Total (N=72)
	LEN (N=24)	Placebo (N=12)	Total (N=36)		
Age (years)					
Mean	53.5	49.3	52.1	48.3	50.2
SD	11.31	10.92	11.21	13.67	12.56
Median	55	54	54	48.5	52
Min, max	24.0, 71.0	27.0, 59.0	24.0, 71.0	23.0, 78.0	23.0, 78.0
Sex, n (%)					
Male	17 (70.8)	9 (75.0)	26 (72.2)	28 (77.8)	54 (75.0)
Female	7 (29.2)	3 (25.0)	10 (27.8)	8 (22.2)	18 (25.0)
Race, n (%)					
Black	10 (41.7)	6 (50.0)	16 (44.4)	11 (30.6)	27 (37.5)
White	12 (50.0)	4 (33.3)	16 (44.4)	13 (36.1)	29 (40.3)
Asian	2 (8.3)	1 (8.3)	3 (8.3)	12 (33.3)	15 (20.8)
Not reported	0	1 (8.3)	1 (2.8)	0	1 (1.4)
BMI (kg/m ²)					
Mean	26	24.8	25.6	26.5	26.1
SD	5.38	4.58	5.09	5.76	5.42
Median	24.7	24.3	24.7	25.6	25
Min, max	18.4, 37.1	18.7, 33.5	18.4, 37.1	14.9, 42.6	14.9, 42.6
Baseline HIV-1 RNA copies/mL, n (%)					
≤100k	23 (95.8)	6 (50.0)	29 (80.6)	29 (80.6)	58 (80.6)
>100k	1 (4.2)	6 (50.0)	7 (19.4)	7 (19.4)	14 (19.4)
CD4 ⁺ cells/μL					
Mean	199.3	85.1	161.2	257.9	209.6
SD	166.15	62.89	149.54	273.42	224.17
Median	171.5	84.5	126.5	195	149.5
Min, max	16.0, 827.0	6.0, 237.0	6.0, 827.0	3.0, 1296.0	3.0, 1296.0
Baseline CD4 ⁺ cells/mm ³ , n (%)					
<200	16 (66.7)	11 (91.7)	27 (75.0)	19 (52.8)	46 (63.9)
200 to <350	6 (25.0)	1 (8.3)	7 (19.4)	8 (22.2)	15 (20.8)
350 to <500	1 (4.2)		1 (2.8)	4 (11.1)	5 (6.9)
≥500	1 (4.2)		1 (2.8)	5 (13.9)	6 (8.3)

Parameter	Cohort 1			Cohort 2 (N=36)	Overall Total (N=72)
	LEN (N=24)	Placebo (N=12)	Total (N=36)		
CD4 ⁺ percentage	10.8	5.9	9.2	11.5	10.3
Mean					
SD	7.77	4.12	7.11	8.62	7.93
Median	10.5	4.5	6.9	10.4	8.9
Min, max	1.0, 32.0	1.2, 16.4	1.0, 32.0	0.4, 29.5	0.4, 32.0
Total number of prior ARVs	10.9	10.3	10.7	13.1	11.9
Mean					
SD	6.22	6.05	6.09	5.63	5.95
Median	9	9	9	13	11
Min, max	2.0, 24.0	3.0, 22.0	2.0, 24.0	3.0, 25.0	2.0, 25.0

Source: Statistical reviewer's analysis.

Abbreviations: ARV, antiretroviral; BMI, body mass index; CD, cluster of differentiation; HIV, human immunodeficiency virus; LEN, lenacapavir; SD, standard deviation

6.2.1.4.2. Primary and Key Secondary Efficacy Results

Primary Endpoint

The Applicant's primary efficacy results were confirmed by the statistical review team, and the results demonstrate superiority of LEN compared to placebo for the endpoint of proportion of HIV-1 RNA reduction $\geq 0.5 \log_{10}$ from baseline to the end of the FMP at Day 14. The 95% CI for the difference in the proportions (LEN – placebo) excluded zero and the p-value was statistically significant ($p < 0.0001$), indicating superiority ([Table 11](#)).

Table 11. Primary Efficacy Endpoint of HIV-1 RNA Reduction $\geq 0.5 \log_{10}$ at the End of Functional Monotherapy Period, Study 4625

Parameter	LEN	Placebo	Difference and 95% CI	p-Value
HIV-1 RNA reduction $\geq 0.5 \log_{10}$	21/24 (87.5%)	2/12 (16.7%)	70.8 (34.9, 90.0)	<0.0001

Source: Statistical reviewer's analysis.

The 95% CI of the difference in proportions between groups and the corresponding p value were calculated based on an unconditional exact method using two invert one-sided tests.

Abbreviations: CI, confidence interval; HIV-1, human immunodeficiency virus 1; SD, standard deviation

Secondary Endpoints

Assessing the durability of virologic response in HTE subjects is an important component of understanding the overall efficacy of LEN. At the end of the FMP, all subjects were transitioned from their initial (failing) background regimen to an optimized regimen in combination with open-label LEN. It was planned that the Week 26 and Week 52 HIV-1 RNA would be evaluated as secondary endpoints. The majority of subjects did not complete the Week 52 assessment at the time of NDA submission; thus, only Week 26 data are presented ([Table 12](#)). Approximately 81% subjects in Cohort 1 achieved HIV-1 RNA < 50 copies/mL at Week 26: 66.7% and 87.5% for subjects in the placebo arm who later switched to LEN and the LEN arm, respectively. We did not find imbalances in baseline characteristics that account for the numerical difference between the two groups (see Section [6.3.1](#)). In addition, variations between the two groups could happen due to the small sample size. In Cohort 2 only six subjects completed the Week 26 evaluation, therefore, the review team will revisit this analysis once more data are received.

Table 12. Secondary Endpoints at Week 26, Study 4625

Parameter	Cohort 1			Cohort 2
	LEN	Placebo to LEN	Total	
HIV-1 RNA $\geq$ 50 copies/mL	3/24 (12.5%)	4/12 (33.3%)	7/36 (19.4%)	1/6 (16.7%)
HIV-1 RNA <50 copies/mL	21/24 (87.5%)	8/12 (66.7%)	29/36 (80.6%)	4/6 (66.7%)
No virologic data	0/24 (0.0%)	0/12 (0.0%)	0/36 (0.0%)	1/6 (16.7%)
Discontinued study due to AE/death	0/24 (0.0%)	0/12 (0.0%)	0/36 (0.0%)	1/6 (16.7%)
Discontinued study for other reasons	0/24 (0.0%)	0/12 (0.0%)	0/36 (0.0%)	0/6 (0.0%)
On study but missing data in window	0/24 (0.0%)	0/12 (0.0%)	0/36 (0.0%)	0/6 (0.0%)

Source: Statistical reviewer's analysis.

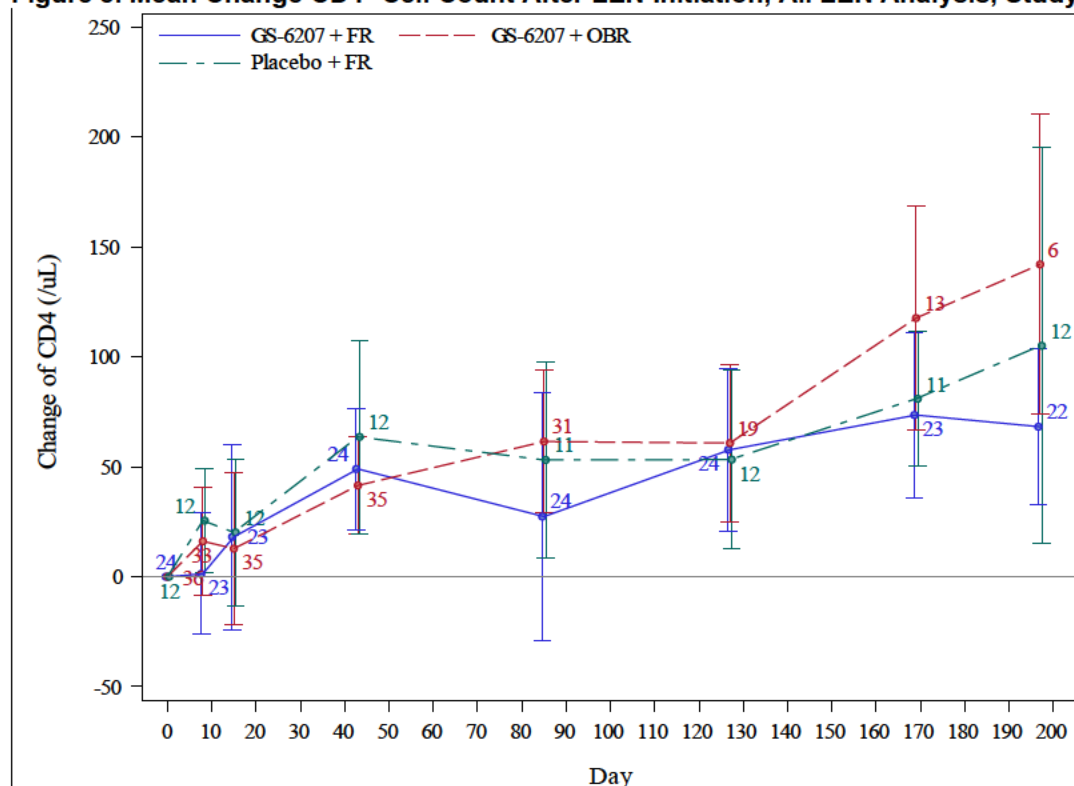
The FDA snapshot algorithm was used. Only six subjects completed 26 weeks of treatment or discontinued the treatment prematurely in Cohort 2.

Abbreviations: AE, adverse event; HIV, human immunodeficiency virus; LEN, lenacapavir

Immunologic Response

To evaluate the restoration of immune function of LEN, change in the CD4⁺ cell count over time for Cohort 1 (presented as two arms) and Cohort 2 subjects are shown in [Figure 8](#). All subjects who were enrolled in the study and received at least one dose of SC LEN were included in the analysis (All LEN analysis). At Week 26, the CD4⁺ cell count increased by a mean (standard deviation [SD]) of 90 cells/ μ L (10² cells/ μ L).

Figure 8. Mean Change CD4⁺ Cell Count After LEN Initiation, All LEN Analysis, Study 4625



Source: Statistical reviewer's analysis.

GS-6207 + FR indicates subjects randomized to the LEN arm in Cohort 1; placebo + FR indicates subjects randomized to the placebo arm in Cohort 1 (Day 0 for this arm was counted on the day before LEN administration); GS-6207 + OBR indicates subjects enrolled in Cohort 2. Numbers indicate the sample size at each timepoint.

Abbreviations: CD, cluster of differentiation; FR, failing regimen; HIV, human immunodeficiency virus; LEN, lenacapavir

6.2.1.4.3. Subgroup Analyses of the Primary Endpoint

Subgroup analyses were conducted to assess the potential for differences in the treatment effect for various demographic and baseline characteristics subgroups (Table 13). Overall, the treatment effect of LEN compared to placebo appeared consistent across subgroups. Of note, the sample sizes for these subgroups were small, which limits the ability to evaluate trends with certainty.

Table 13. Subgroup Analyses for the Primary Endpoint of HIV-1 RNA Reduction $\geq 0.5 \text{ Log}_{10}$ at End of Functional Monotherapy Period, Study 4625

Subgroup		LEN	Placebo
Age group	<50 years	5/6 (83.3%)	0/3 (0%)
	≥ 50 years	16/18 (88.9%)	2/9 (22.2%)
Sex	Female	5/7 (71.4%)	1/3 (33.3%)
	Male	16/17 (94.1%)	1/9 (11.1%)
Race	Black	9/10 (90%)	1/6 (16.7%)
	Other	12/14 (85.7%)	1/6 (16.7%)
CD4 ⁺	<200/ μL	14/16 (87.5%)	1/11 (9.1%)
	$\geq 200/\mu\text{L}$	7/8 (87.5%)	1/1 (100%)
HIV-1 RNA	$\leq 100,000$ copies/mL	20/23 (87%)	1/6 (16.7%)
	>100,000 copies/mL	1/1 (100%)	1/6 (16.7%)

Source: Statistical reviewer's analysis.

Abbreviations: CD, cluster of differentiation; HIV, human immunodeficiency virus; LEN, lenacapavir

6.2.2. Study 4334 (CALIBRATE)

6.2.2.1. Study Design

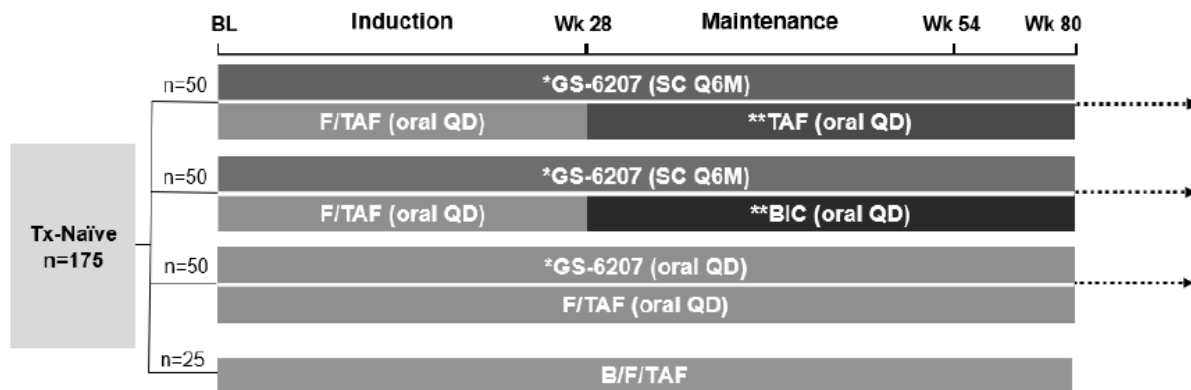
Results from Study 4334 serve as supplementary data for the efficacy and safety evaluation of LEN for the indication of treating the HTE HIV-1 population. This was a phase 2, randomized, open-label, active-controlled study conducted in the treatment-naïve PLWH population. Eligible subjects were randomized in a 2:2:2:1 ratio to SC LEN + (emtricitabine/tenofovir alafenamide [F/TAF] $\rightarrow$ tenofovir alafenamide [TAF]), SC LEN + (F/TAF $\rightarrow$ bicitgravir [BIC]), Oral LEN + F/TAF, or bicitgravir/emtricitabine/tenofovir alafenamide (B/F/TAF) group (Figure 9).

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening.

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NDA 215974 lenacapavir tablets, for oral use

Figure 9. Study Design Schema, Study 4334



*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 $\geq$ 50 copies/mL will discontinue the study at Week 28.

Source: Figure 2 of the Applicant's Clinical Summary.

During the induction period for the first two arms, in addition to the oral daily DVY, subjects also took oral LEN 600 mg on days 1 and 2, then 300 mg on day 8, followed by SC LEN 927 mg on day 15.

Abbreviations: BIC, bicitgravir; BL, baseline; F/TAF, emtricitabine/tenofovir alafenamide; LEN, lenacapavir; QD, once daily; SC, subcutaneous; TAF, tenofovir alafenamide; B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide; Tx, treatment; Wk, week

6.2.2.2. Eligibility Criteria

Key eligibility criteria are summarized in this section and the full criteria are available in Section III.15. Subjects with HIV who met the following criteria were included:

- Aged $\geq$ 18 years.
- ARV naïve (no use of any ARV within 1 month of screening).
- Plasma HIV-1 RNA $\geq$ 200 copies/mL and CD4+ cell count $\geq$ 200 cells/ μ L at screening.

The major exclusion criteria were:

- An opportunistic illness requiring acute therapy.
- Active and serious infections requiring parenteral antibiotic or antifungal therapy.
- HBV.
- HCV.
- Clinical decompensated liver cirrhosis.
- Malignancy requiring acute therapy.
- Alcohol or substance use.
- Significant abnormal ECG.
- eGFR $\leq$ 50 mL/min.
- ALT $>$ 5 $\times$ ULN.
- Direct bilirubin $>$ 1.5 $\times$ ULN.
- Platelets $<$ 50,000/mm³.
- Hemoglobin $<$ 8.0 g/dL.
- Use or planned use of exclusionary medications.

6.2.2.3. Statistical Analysis Plan

The Applicant and the review division agreed on the interim analysis (IA) plan prior to the Week 28 IA.

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The study had four prespecified IAs: Week 28, Week 38, Week 54 (primary analysis), and Week 80. The Week 28 IA was conducted when all subjects completed the Week 28 evaluation. The results of this analysis were used to supplement the efficacy and safety of LEN for the HTE population. There were no multiplicity adjustments planned because this was stated as a phase 2, non-confirmatory study.

The primary endpoint of this study was the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 54 as determined by the U.S. FDA-defined snapshot algorithm. Because the majority of subjects had not yet reached Week 54 at the time of the NDA submission, the primary endpoint was not analyzed.

A secondary endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 28, as determined by the U.S. FDA-defined snapshot algorithm. The FAS was used as the analysis population. Point estimates and 95% CI for the difference in the response rates between each of the LEN-containing regimen groups (Treatment Groups 1 to 3) and the B/F/TAF group (Treatment Group 4) were constructed using stratum-adjusted Mantel-Haenszel proportion as described in Chapter 13 of *Categorical Data Analysis* (Koch et al. 1989), stratified by baseline HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL).

6.2.2.4. Results of Analyses of Clinical Trial Intended to Supplement Efficacy, Study 4334 (CALIBRATE)

6.2.2.4.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Disposition

A total of 183 subjects was randomized into Study 4334. Of these, 182 subjects received at least one dose of study drug and were included in the FAS. All subjects completed Week 28 visit or discontinued the study. All of the 13 subjects who prematurely discontinued the study were from the LEN-containing arms, with the reasons listed as lost to follow up, withdrew consent, investigator's discretion, and lack of efficacy ([Table 14](#)).

Table 14. Patient Disposition, Study 4334

Category	SC LEN + (F/TAF → TAF)	SC LEN + (F/TAF → BIC)	Oral LEN + F/TAF	B/F/TAF
Randomized and received study drug	52	53	52	25
Study drug completion status				
Continuing study drug	47 (90%)	44 (83%)	49 (94%)	25 (100%)
Completed study drug	0	0	0	0
Prematurely discontinued study drug	5 (10%)	9 (17%)	3 (6%)	0
Reason: Lost to follow-up	2 (4%)	1 (2%)	2 (4%)	0
Reason: Subject decision	0	4 (7%)	1 (2%)	0
Reason: Adverse event	0	2 (4%)	0	0
Reason: Investigator's discretion	1 (2%)	1 (2%)	0	0
Reason: Lack of efficacy	2 (4%)	1 (2%)	0	0

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Category	SC LEN + (F/TAF → TAF)	SC LEN + (F/TAF → BIC)	Oral LEN + F/TAF	B/F/TAF
Study completion status				
Completed Week 28 or discontinued	52 (100%)	53 (100%)	52 (100%)	25 (100%)
Continuing study	49 (94%)	46 (89%)	49 (94%)	25 (100%)
Completed study	0	0	0	0
Prematurely discontinued study	3 (6%)	7 (13%)	3 (6%)	0
Reason: Lost to follow-up	2 (4%)	1 (2%)	2 (4%)	0
Reason: Withdrew consent	0	4 (7%)	1 (2%)	0
Reason: Investigator's discretion	1 (2%)	1 (2%)	0	0
Reason: Lack of efficacy	2 (4%)	1 (2%)	0	0

Source: Statistical reviewer's analysis.

Abbreviations: BIC, bicitegravir; F/TAF, emtricitabine/tenofovir alafenamide; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide; LEN, lenacapavir; TAF, tenofovir alafenamide

Baseline Demographics and Clinical Characteristics

Demographic and baseline characteristics were generally similar across the treatment groups. The majority of subjects were male (93%) and Black (52%). The mean age was 32 years, and the mean BMI was 27 kg/m² (Table 15).

The baseline HIV-1 RNA categories, mean CD4⁺ cell count, CD4⁺ categories, and CD4⁺ percentages were comparable across the study groups. A majority of subjects had HIV-1 RNA ≤100,000 copies/mL and were in the CD4⁺ category of ≥200 cells/μL at baseline.

Table 15. Baseline Demographic and Clinical Characteristics, Study 4334

Parameter	Total (N=182)	SC LEN + (F/TAF → TAF) (N=52)	SC LEN + (F/TAF → BIC) (N=53)	Oral LEN + F/TAF (N=52)	B/F/TAF (N=25)
Age (years)					
Mean	31.9	33.1	30.4	31.8	32.8
SD	10.4	9.55	8.85	12.27	11.12
Median	29	31	28	28	29
Min, max	19.0, 72.0	19.0, 61.0	19.0, 56.0	19.0, 72.0	21.0, 61.0
Sex					
Male	170 (93.4)	47 (90.4)	52 (98.1)	46 (88.5)	25 (100.0)
Female	12 (6.6)	5 (9.6)	1 (1.9)	6 (11.5)	
Race, n (%)					
Black	95 (52.2)	24 (46.2)	24 (45.3)	31 (59.6)	16 (64.0)
Other	87 (47.8)	28 (53.8)	29 (54.7)	21 (40.4)	9 (36.0)
BMI (kg/m ²)					
Mean	26.8	27.3	26.2	26.6	27.1
SD	6.43	7.82	5.9	5.67	6.05
Median	25.8	26.4	24.9	26	26.9
Min, max	17.0, 51.1	17.5, 51.1	18.7, 48.9	17.3, 44.3	17.0, 44.1
Baseline HIV-1 RNA (copies/mL), n (%)					
≤100,000	155 (85.2)	47 (90.4)	44 (83.0)	43 (82.7)	21 (84.0)
>100,000	27 (14.8)	5 (9.6)	9 (17.0)	9 (17.3)	4 (16.0)
CD4 ⁺ (cells/μL)					
Mean	495.1	506.1	490.4	470.1	533.9
SD	246.5	297.04	209.92	221.68	260.04
Median	437	403.5	450	409	482
Min, max	175.0, 1846.0	213.0, 1846.0	187.0, 991.0	175.0, 1091.0	232.0, 1443.0

Parameter	Total (N=182)	SC LEN + (F/TAF → TAF) (N=52)	SC LEN + (F/TAF → BIC) (N=53)	Oral LEN + F/TAF (N=52)	B/F/TAF (N=25)
Baseline CD4 ⁺ (cells/mm ³), n (%)					
<350	56 (30.8)	17 (32.7)	16 (30.2)	19 (36.5)	4 (16.0)
350 to <500	58 (31.9)	17 (32.7)	15 (28.3)	15 (28.8)	11 (44.0)
≥500	68 (37.4)	18 (34.6)	22 (41.5)	18 (34.6)	10 (40.0)
CD4 ⁺ percentage					
Mean	24	24.2	24.1	22.7	26.2
SD	8.7	9.92	8.04	8.28	8.18
Median	23.1	22.4	24.6	20.9	26.1
Min, max	8.0, 63.0	8.0, 63.0	8.0, 40.4	8.9, 45.8	12.0, 43.5

Source: Statistical reviewer's analysis.

Abbreviations: BIC, bicitegravir; BMI, body mass index; CD, cluster of differentiation; F/TAF, emtricitabine/tenofovir alafenamide; TAF, tenofovir alafenamide; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide; HIV, human immunodeficiency virus; LEN, lenacapavir; SC, subcutaneous; SD, standard deviation

6.2.2.4.2. Secondary Efficacy Results

The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 28 was 49 of 52 (94.2%), 49 of 53 (92.5%), 49 of 52 (94.2%), and 25 of 25 (100%) for the arms of SC LEN + (F/TAF → TAF), SC LEN + (F/TAF → BIC), oral LEN + F/TAF, and B/F/TAF, respectively. For the combined LEN-containing regimens, 147 of 157 (93.6%) subjects met this criterion (Table 16). Compared to the B/F/TAF arm, the difference of the response rate was -6.3 (LEN combined – B/F/TAF), with a p-value of 0.2. A rapid decrease in HIV-1 RNA after drug initiation was observed, which became stable after Day 30 (Figure 10) in all four arms.

Table 16. Secondary Efficacy Endpoints, Study 4334

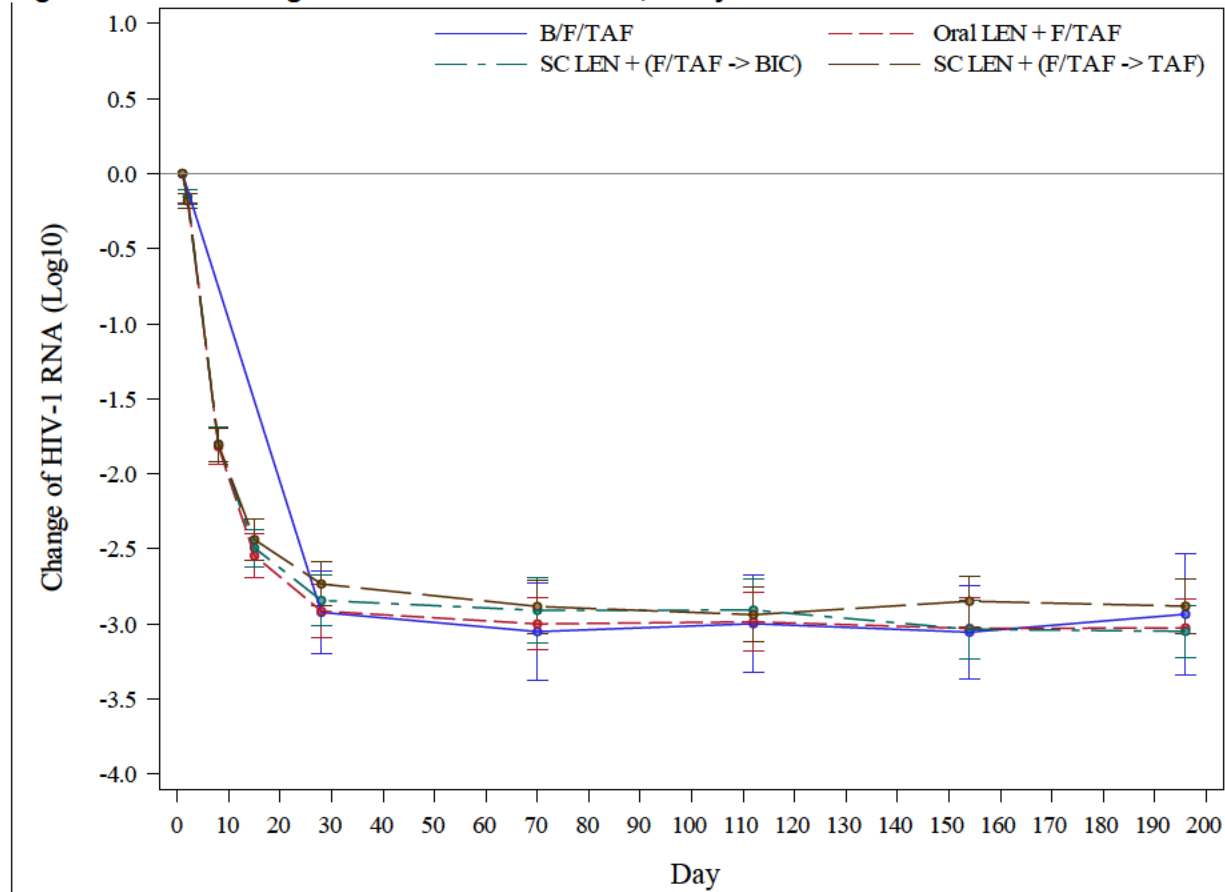
Parameter	LEN Combined	B/F/TAF	Difference and 95% CI
HIV RNA ≥50 copies/mL	2/157 (1.3%)	0/25 (0.0%)	1.3 (-0.5, 3)
HIV RNA <50 copies/mL	147/157 (93.6%)	25/25 (100.0%)	-6.3 (-10.2, -2.5)
No virologic data	8/157 (5.1%)	0/25 (0.0%)	
Discontinued study due to AE or death	1/157 (0.6%)	0/25 (0.0%)	
Discontinued study for other reasons	6/157 (3.8%)	0/25 (0.0%)	
On study but missing data in window	1/157 (0.6%)	0/25 (0.0%)	

Source: Statistical reviewer's analysis.

FDA snapshot algorithm was used. Stratified Cochran–Mantel–Haenszel with baseline HIV-1 RNA level (≤100,000 or >100,000 copies/mL) as the stratification factor was used to calculate risk differences and the associated 95% CI.

Abbreviations: AE, adverse event; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide; CI, confidence interval; HIV, human immunodeficiency virus; LEN, lenacapavir

Figure 10. Mean Change and 95% CI of HIV-1 RNA, Study 4334



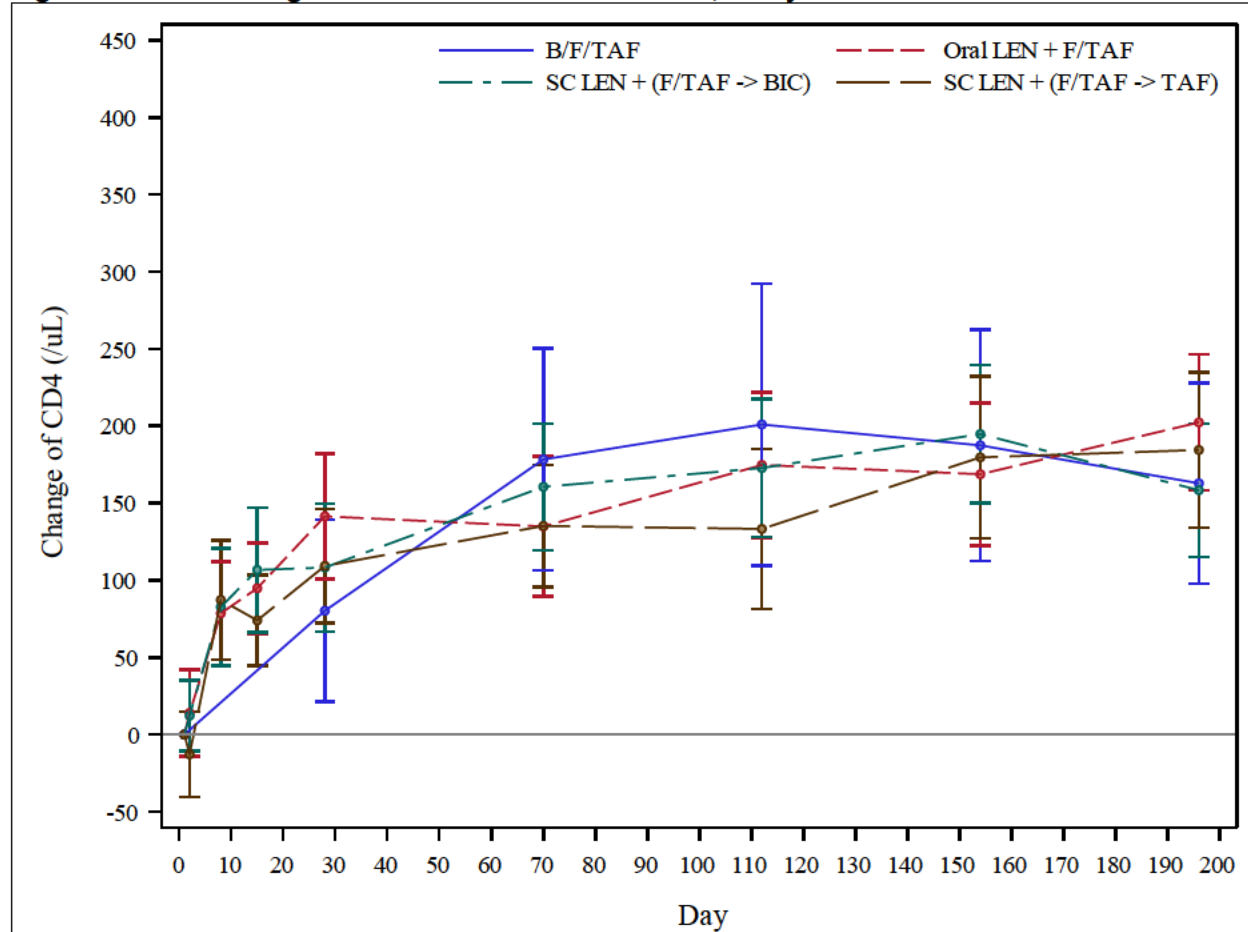
Source: Statistical reviewer's analysis.

Abbreviations: B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide; BIC, bicitgravir; CI, confidence interval; HIV, human immunodeficiency virus; F/TAF, emtricitabine/tenofovir alafenamide; LEN, lenacapavir; SC, subcutaneous; TAF, tenofovir alafenamide

Immunologic Response

The mean changes from the Baseline visit in CD4⁺ cell count over Week 28 were similar across treatment arms ([Figure 11](#)). A more modest immunologic response (increase in CD4⁺ cell count) from Baseline in Study 4625 was consistent with the expected differences in the patient populations (treatment-naïve vs. HTE).

Figure 11. Mean Change and 95% CI of CD4⁺ Cell Count, Study 4334



Source: Statistical reviewer's analysis.

Abbreviations: B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide; BIC, bicitgravir; CI, confidence interval; HIV, human immunodeficiency virus; F/TAF, emtricitabine/tenofovir alafenamide; LEN, lenacapavir; SC, subcutaneous; TAF, tenofovir alafenamide

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Imbalance in Study 4625 Baseline Characteristics

Issue

The baseline imbalance of HIV-1 RNA and CD4⁺ cell count for Cohort 1 between the two randomized arms may impact the interpretability of the primary efficacy results.

Background

In Cohort 1, the mean baseline CD4⁺ cell count and CD4⁺ percentage were higher in the LEN arm than those in the placebo arm (199 versus 85 cells/ μ L CD4⁺ cell counts, and 10.8% versus 5.9% CD4⁺ percentages, respectively).

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In the LEN arm, 46% (11/24) had baseline HIV-1 RNA >20,000 copies/mL with one subject having >100,000 copies/mL. Additionally, seven (29%) LEN-treated subjects had baseline HIV-1 RNA <2000 copies/mL with five (21%) having <1000 copies/mL, and four (17%) subjects did not maintain the eligibility entry criterion of <400 copies/mL through their Baseline visit. In the placebo arm, all 12 subjects (100%) had baseline HIV-1 RNA >20,000 copies/mL with 6 (50%) subjects having >100,000 copies/mL (Table 17).

Table 17. Number of Subjects With High Baseline Viral Loads, Study 4625

Number of Subjects	LEN Cohort 1A	Placebo Cohort 1B
	N=24	N=12
HIV-1 RNA >20,000 copies/mL	11 (46%)	12 (100%)
HIV-1 RNA >100,000 copies/mL	1 (4%)	6 (50%)

Source: FDA Clinical Virology reviewer's analysis.

Abbreviations: HIV, human immunodeficiency virus; LEN, lenacapavir

This finding suggests that subjects in the LEN arm may have had an advantage with regard to their baseline status, and therefore, may have had improved efficacy outcomes compared to subjects in the placebo arm.

Assessment

Post hoc analyses were conducted to explore the association between baseline HIV-1 RNA and CD4⁺ imbalance across Cohort 1 treatment arms and the outcome of HIV-1 RNA reduction of $\geq 0.5 \log_{10}$. The distributions of baseline HIV-1 RNA by arm and by outcome are presented in Table 18. Within each arm, subjects who had reduction $\geq 0.5 \log_{10}$ at the end of the functional monotherapy period generally had higher baseline HIV-1 RNA. Therefore, it appears that the lower baseline HIV-1 RNA level in the LEN arm is not likely associated with more reduction in HIV-1 RNA at the end of the functional monotherapy period. In addition, subgroup analyses (Table 13) showed that the effects of LEN were consistent across the subgroups of HIV-1 RNA $\leq 100,000$ copies/mL and $>100,000$ copies/mL, and the subgroups of CD4⁺ <200 cells/ μ L and ≥ 200 cells/ μ L.

Table 18. Baseline HIV-1 RNA by the Outcome of the Primary Endpoint at the End of Functional Monotherapy Period, Study 4625

HIV-1 RNA Reduction $\geq 0.5 \log_{10}$	Randomized Arm	No. of Subjects	Baseline HIV-1 RNA (copies/mL)			
			Mean	Median	Minimum	Maximum
No	LEN	3	24,097	377	214	71,700
	Placebo	10	99,040	86,500	21,400	212,000
Yes	LEN	21	36,722	16,000	259	252,000
	Placebo	2	121,650	121,650	34,300	209,000

Source: Statistical reviewer's analysis.

Abbreviations: HIV, human immunodeficiency virus; LEN, lenacapavir

Conclusion

The baseline imbalance of HIV-1 RNA and CD4⁺ cell count did not impact the interpretability of the primary efficacy result.

6.3.2. Justification for the Proposed Simplified Dosing Regimen

Issue

The Applicant proposes a simplified dosing regimen that was not studied during the LEN clinical development program.

Background

The LEN dosing regimen evaluated in the phase 2/3 study allowed for a 14-day oral lead-in period, where subjects received oral LEN on Day 1 (600 mg), Day 2 (600 mg), and Day 8 (300 mg) before SC LEN injection on Day 15 (927 mg), then every 26 weeks thereafter. The oral lead-in period enabled an assessment of safety and tolerability of LEN prior to SC LEN administration. Given the established safety profile and lack of exposure-safety relationship from the phase 2 and phase 2/3 trials, the Applicant proposed a simplified dosing regimen as a strategy to potentially improve adherence. The following simplified regimen is proposed: 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 26 weeks thereafter.

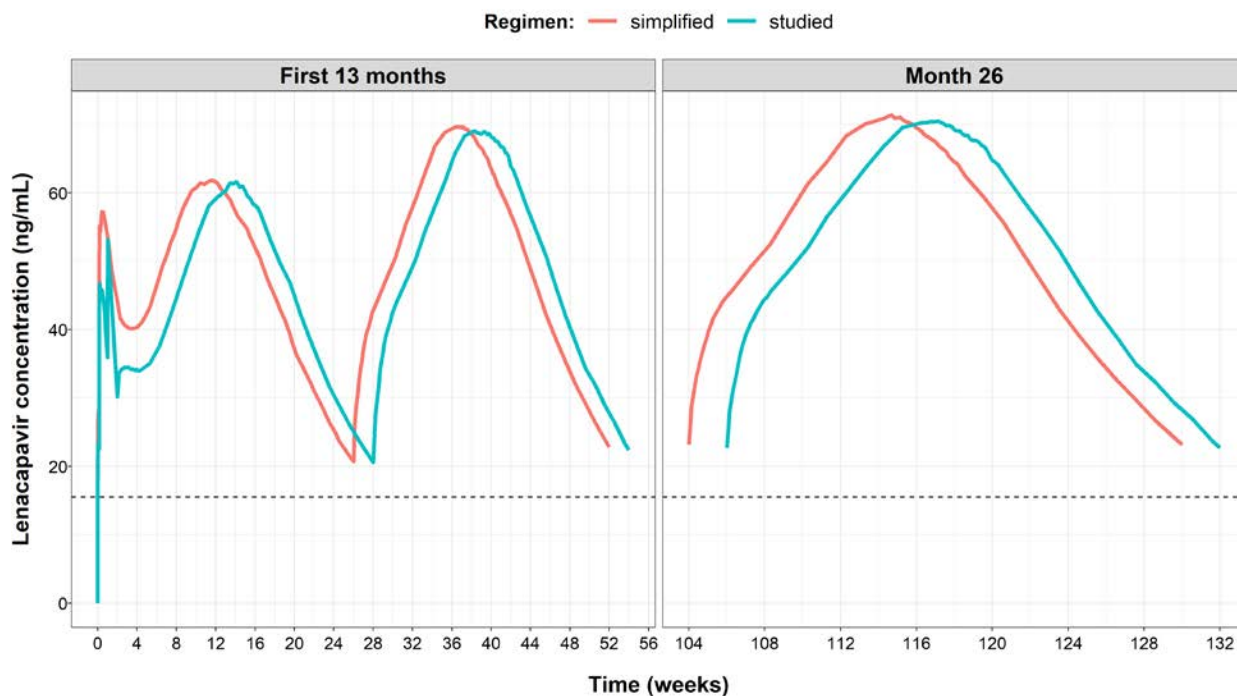
Assessment

The Applicant performed population PK simulations using their final PK model (see Section [III.14.3](#) for further details on the population PK) to compare LEN PK from both the phase 2/3 dosing regimen and the proposed simplified regimen. The simulated LEN concentration-time profiles and the predicted exposure metrics (AUC_{τ} , $C_{\max}$, and C_{trough}) indicated that the simplified regimen has a similar LEN PK profile compared to that evaluated in the phase 2/3 study ([Figure 12](#) and [Table 19](#)). Similar LEN accumulation is expected after the second SC and the seventh SC dose after administration of either regimen ([Figure 12](#)).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Figure 12. Predicted Median LEN PK Profiles in Adult Patients Receiving the Studied Phase 2/3 Regimen or the Simplified Regimen, After the First, Second, and Seventh SC Injections



Source: FDA analysis.

Horizontal dotted line represents the IQ4 threshold of 15.5 ng/mL.

Abbreviations: IQ4, inhibitory quotient 4; LEN, lenacapavir; PK, pharmacokinetic; SC, subcutaneous

Table 19. LEN Exposure After the Phase 2/3 Regimen and Simplified Regimen in Adult Patients With HIV

PK Parameter	Mean (%CV)	
	Phase 2/3 Regimen (N = 62) ^a	Simplified Regimen ^b (Simulated)
AUC _{Day 1-15} (h*ng/mL)	25,962.9 (67.8)	17701.8 (52.9)
C _{max Day 1-15} (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-Week 26} ^c (h*ng/mL)	251,907.2 (48.2)	216,554.8 (68.4)
C _{max Day 15-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-Week 26} (h*ng/mL)	277,902.9 (46.7)	234,294.8 (65.1)
C _{max Day 1-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: Applicant's Summary of Clinical Pharmacology Studies, Table 14, page 80.

Abbreviations: %CV, percentage coefficient of variation; AUC, area under the concentration-time curve, C_{max}, maximum concentration; C_{trough}, minimum concentration

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NDA 215974 lenacapavir tablets, for oral use

Comparison of observed LEN concentration profiles and AUC (to Day 85) of the phase 2/3 regimen (Cohort 1) and the simplified regimen (Cohort 2) of Study 5709 in healthy subjects supported the conclusions from the PK modeling and simulation. The review team considered various options for the recommended dosing to be included in labeling. A summary is provided in [Table 20](#).

Table 20. Summary of Review Considerations for Labeling of Oral Lead-In Options

Category	Simplified Oral Lead-In Only	Oral Only Lead-In Followed by SC Dosing	Both Options Provided in Labeling
Notes	Proposed by the Applicant	Regimen used in Study 4625	Preferred approach by the review team
Initiation	- Day 1: 927 mg SC (2x1.5 mL injections) + 600 mg PO (2 tablets) - Day 2: 600 mg PO (2 tablets)	- Day 1: 600 mg PO (2 tablets) - Day 2: 600 mg PO (2 tablets) - Day 8: 300 mg PO (1 tablet) - Day 15: 927 mg SC (2x1.5 mL injections)	Two options presented in tabular format
Maintenance	927 mg SC (2x1.5 mL injections) q 6 months	927 mg SC (2x1.5 mL injections) q 6 months	927 mg SC (2x1.5 mL injections) q 6 months
Advantages	- Can be initiated same-day by provider - No need for additional office visit	- Regimen supported by clinical trial experience - Allows patient/provider to assess any safety or tolerability concerns before SC dose is administered	Allows provider/patients to decide best option given individual concerns/circumstances
Disadvantages	Relies on PK bridging without support from clinical efficacy data	Requires additional office visit for first SC dose	Complex presentation in label

Source: Reviewer's summary.

Abbreviations: PK, pharmacokinetic; PO, per oral; SC, subcutaneous; q, every

Conclusion

Based on observed and predicted data, the exposures of LEN are anticipated to be similar between the regimen used in Study 4625 and the proposed simplified regimen. The review team agreed that the proposed label should include recommendations for both the simplified regimen and the regimen used in Study 4625.

6.3.3. Impact of Subjects Not Maintaining Eligibility Criteria: Not Failing on Background Regimen or Nonadherence to Background Regimen

Issue

In a clinical trial designed for study in an HTE patient population, it is important to determine if the subjects are truly failing on their pre-trial ARV regimen rather than due to nonadherence to the ARV drugs with no evidence of resistance in their supposed “failing” regimen. If subjects are nonadherent to the regimen and do not have resistance to the “failing” regimen during the LEN functional monotherapy period, it will be difficult to determine the contribution of LEN to efficacy in the background of other active or partially active ARVs.

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Background

The entry eligibility criteria for Study 4625 included:

- Resistance to ≥ 2 ARVs from each of ≥ 3 of the 4 main classes of ARV drugs (INSTI, NNRTI, NRTI, PI), which could include historical reports.
- Plasma HIV-1 RNA ≥ 400 copies/mL at the screening visit while taking a failing background regimen.

Assessment

Eligibility criteria for Cohort 1 included 0.5 log₁₀ HIV-1 RNA decline compared to the Screening visit and HIV-1 RNA ≥ 400 copies/mL at the Cohort Selection visit. There were subjects who did not maintain eligibility criteria for Cohort 1 because of the following reasons:

- There was evidence that a subject was not failing background regimen:
 - Day 1 viral load <400 copies/mL.
 - Decline in viral load from the Screening visit to Baseline.
- There was evidence that a subject was nonadherent to background regimen:
 - <3 class resistance (by genotype, phenotype, or historical)
 - No reported resistance to drugs in failing background regimen

Table 21. Subjects Who Did Not Maintain Eligibility Criteria for Cohort 1 at Baseline, Study 4625

Number of Subjects	LEN Cohort 1A	Placebo Cohort 1B
	N=24	N=12
Not failing on background regimen	5 (21%)	0
HIV-1 RNA <400 copies/mL at Day 1	4 (17%)	0
Not resistant to background regimen at screening (nonadherent)	3 (13%)	3 (25%)

Source: Reviewer's analysis.

Abbreviation: LEN, lenacapavir

Of the 24 subjects in LEN Cohort 1A, 5 subjects (21%) had evidence that they were not failing on their regimen, 4 of whom had <400 copies/mL on Day 1 ([Table 21](#); listed in [Table 22](#). Screening viral loads for these five subjects ranged from 451 to 66,900 copies/mL ([Table 22](#)). Four of these five subjects had active anchor drugs BIC, dolutegravir (DTG), and/or darunavir (DRV) with two of these subjects having no resistance to any of the drugs in their regimen at screening. The fifth subject (Subject ^(b)(6)) had resistance to DTG and DRV at screening, but also had ibalizumab (IBL) as a component of their ARV regimen. No subjects in the placebo Cohort 1B arm had evidence of not failing their regimen.

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Table 22. Subjects Who Were Not Failing on Background Regimen in LEN Cohort 1A (n=5), Study 4625

PID	Failing Background Regimen	SC VL	Day 1 VL	OBT	EFF Y/N	VF WK26	PI RAS at SC	RT RAS at SC	INSTI RAS at SC	Phenotype at SC	Screening ARV-R
(b) (6)	BIC FTC TDF	57,100 33,200	259 (not failing on regimen)	BIC FTC TAF	Y	Y	M46I I47V F53L I54L K55R V82A L90M	M41L D67N L74V K101H/Q Y181C M184V L210W T215Y K219N L228H	L74M T97A Y143R G163R	BIC 0.6 FTC >75 TDF 1.3	NRTI, NNRTI, PI, INSTI (DTG available)
(b) (6)	DTG DRV/C IBL	451 2980	274 (decreased VL at day 1)	FTC TDF IBL	Y	N	L33F M46L I47V T74P V82I I85V L90M	M41L D67N L74I V75T T215C H221C	L74I E138K S147G V151I N155H E157Q G163D	DTG 81 DRV 53	NRTI, PI, INSTI
(b) (6)	DRV/C FTC TAF	66,900 22,600	884 (not failing on regimen)	DRV/c DOR FTC TAF	Y	Y	A71T	M41L D67G T69D V75M L100I K103N M184V L210W T215D K219R	E157Q	DRV 0.81 FTC >79 TDF 0.56	NRTI, NNRTI
(b) (6)	DTG DRV MVC	9810 7730	214 (not failing on regimen)	BIC FTC TAF DRV MVC	N	Y	L33F F53L I54V	M41L E138K Y181C G190E T215C K219R		DTG >0.69 DRV 0.82 MVC susc	NRTI, NNRTI, PI
(b) (6)	DRV/C FTC TDF	866 750	377 (not failing on regimen)	BIC FTC TAF	N	Y	M46I L76V I84I/V	K101K/Q K103E/G/R Y181Y/C T215F/I/S		DRV 1.1 FTC 1.2 TDF 0.73	NNRTI, PI

Source: Reviewer's analysis.

Abbreviations: PID, patient identification number; SC, screening; VL, viral load; OBT, optimized background treatment; BIC, bictegravir; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFF, efficacy; FTC, emtricitabine; IBL, ibalizumab; INSTI, integrase strand transfer inhibitor; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAS, resistance-associated substitution; RT, reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; c/mL, copies/milliliter

Three subjects in each arm (Cohort 1A and 1B) had evidence that they were nonadherent to their “failing” background regimen based on genotypic and phenotypic susceptibility to their background drugs (Table 23). Four of these six had phenotypic susceptibility to all the drugs in their background regimen and the other two had susceptibility to anchor drugs BIC or DRV.

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Table 23. Subjects With Evidence of Nonadherence to Background Regimen (n=6)

PID	ARM	Failing Background Regimen	SC VL	Day 1 VL	OBT	EFF Y/N	VF WK26	PI RAS at SC	RT RAS at SC	INSTI RAS at SC	Pheno SC	Screening ARV-Resistant
(b) (6)	LEN+FR	DTG LPV/r	18,200 180,000	86,600	DTG DRV/c FTC TAF	Y	N		A98S V106I Y188L H221Y	Y143R	DTG 1.7 LPV 1.3	NNRTI
(b) (6)	LEN+FR	BIC ABC FTC TDF ENF FTR IBL	6690 8540	15,100	BIC FTC TAF DOR ENF IBL	Y	N	M46I I47V F53L I54L K55N T74S N88D L90M	M41L D67N K101P V106I V179I T215Y K219Q	V151I	BIC 0.8 FTC 2.6 TDF 1	NRTI, NNRTI, PI
(b) (6)	LEN+FR	DRV/C DOR FTC TAF	50,700 155,000	252,000	DTG DRV/c DOR FTC TAF	Y	N		K103K/N V179V/I M184I/V	L74M V151I N155H	DRV 0.55 DOR 1.1 FTC 1 TDF 0.86	NNRTI
(b) (6)	PLACEBO	DTG DRV/C	73,300 71,000	77,700	DTG DOR	N	N	M46L V82A I84V	D67N T69D K101E/Q Y181C L210W T215D	M154L	DTG 0.67 DRV 0.97	NRTI NNRTI, PI
(b) (6)	PLACEBO	BIC DOR FTC TAF MVC	24,600 17,500	21,900	BIC DOR FTC TAF MVC	N	N	L33F M46I I54I/V K55R G73S L76V V82T I84V L89V L90M	M41L D67N K70R L74I K101E V106I V108I Y181C M184V T215F K219E	K156N	BIC 0.73 DOR 72 FTC >45 TDF 1.3 MVC?	NRTI, NNRTI, PI
(b) (6)	PLACEBO	DRV/C FTC TDF	96,500 135,000	193,000	DTG DRV/c RPV	N	Y	V77I	K65K/R S68G Y181C M184M/V	E92Q	DRV 0.83 FTC >100 TDF 0.58	NRTI

Source: Reviewer's analysis.

Abbreviations: BIC, bicitgravir; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFF, efficacy; FTC, emtricitabine; IBL, ibalizumab; INSTI, integrase strand transfer inhibitor; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background treatment; PI, protease inhibitor; PID, patient identification number; RAS, resistance-associated substitutions; RT, reverse transcriptase inhibitor; SC, screening; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load

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The efficacy (proportion of subjects achieving $\geq 0.5 \log_{10}$ copies/mL reduction from baseline in HIV-1 RNA) of Cohort 1A and 1B was assessed after removing the subjects who had evidence they were not failing their background regimen or were nonadherent to the background regimen. After removing the five subjects who had evidence they were not failing their background regimen, 95% (18/19) of subjects in Cohort 1A (LEN) achieved $\geq 0.5 \log_{10}$ copies/mL reduction in HIV-1 RNA from baseline compared to 17% (2/12) in the placebo Cohort 1B arm (difference of 78%) (Table 24). Removing the six subjects with evidence of nonadherence narrowed the difference between groups (86% [18/21] versus 22% [2/9]; difference of 63.5%) but was still significantly different. Removing both the subjects with evidence of not failing background regimen and subjects with evidence of nonadherence showed efficacy of 94% (15/16) versus 22% (2/9) (difference of 72%) compared to the overall efficacy of 88% (21/24) versus 17% (2/12) (difference of 71.5%). Thus, this supplementary sensitivity analysis confirmed the efficacy of LEN in comparison to placebo and was consistent with the primary endpoint analysis.

Table 24. Supplementary Efficacy Analysis Excluding Subjects Not Failing Background Regimen and/or Had Evidence of Nonadherence: Primary Endpoint of HIV RNA Reduction $\geq 0.5 \log_{10}$, Study 4625

Parameter	LEN	Placebo	Difference and 95% CI	P
Overall	21/24 (88%)	2/12 (17%)	70.8 (34.9, 90.0)	<0.0001
Exclude five subjects not on failing regimen	18/19 (95%)	2/12 (17%)	78.1 (42.6, 94.9)	<0.0001
Exclude six nonadherent subjects	18/21 (86%)	2/9 (22%)	63.5 (21, 87.2)	0.0006
Exclude both nonadherent and not failing	15/16 (94%)	2/9 (22%)	71.5 (29.1, 93.2)	0.0002

Source: Virology reviewer's and Statistical reviewer's analysis.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LEN, lenacapavir

Although the sample size of Cohort 1 was small, and decreased further following sensitivity analysis exclusions, the demonstrated treatment effect for this efficacy analysis remains large. Of note, recent prior studies in the HTE patient population had a similar sample size (e.g., 40 HTE subjects in the phase 3 trial TMB-301 for ibalizumab-uiyk), which may reflect the challenge of enrolling trials in this limited patient population.

Conclusion

Five subjects (21%) in LEN Cohort 1A had evidence that they were not failing on their regimen at study entry, four of whom had < 400 copies/mL on Day 1. Additionally, three subjects in each LEN Cohort 1A and placebo Cohort 1B had evidence that they were nonadherent to their “failing” background regimen based on genotypic and phenotypic susceptibility to their background drugs. Supplementary sensitivity efficacy analyses removing these subjects confirmed the primary endpoint analysis of LEN.

6.3.4. Dosing Interval and Approach to Missed Subcutaneous Maintenance Doses

Issues

- Is administration of SC LEN within the Applicant's proposed dosing window of ± 2 weeks expected to compromise the safety or efficacy of LEN?

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- Is reinitiating therapy with the indicated regimen in patients who did not receive SC LEN up to 28 weeks since the previous SC LEN dose expected to compromise the safety of LEN?

Background

The Applicant has proposed a dosing window of 26 ± 2 weeks (i.e., 24 to 28 weeks) after the previous SC injection. In phase 2 and phase 2/3 studies, SC LEN doses were to be administered within 24 to 28 weeks after the previous SC LEN dose as per protocol.

The Applicant proposes to restart LEN regimen with the oral loading dose, if more than 28 weeks have elapsed since the previous SC LEN injection. For subjects in phase 2 and phase 2/3 studies who were not dosed by Week 28 and continued in the studies, the protocol indicated that the regimen be reinitiated with oral LEN followed by SC LEN administration (oral LEN 600 mg daily for 2 days followed by oral LEN 300 mg on Day 8, with SC LEN injection 927 mg restarting 1 week later) with the intent to rapidly correct LEN concentrations.

Assessment

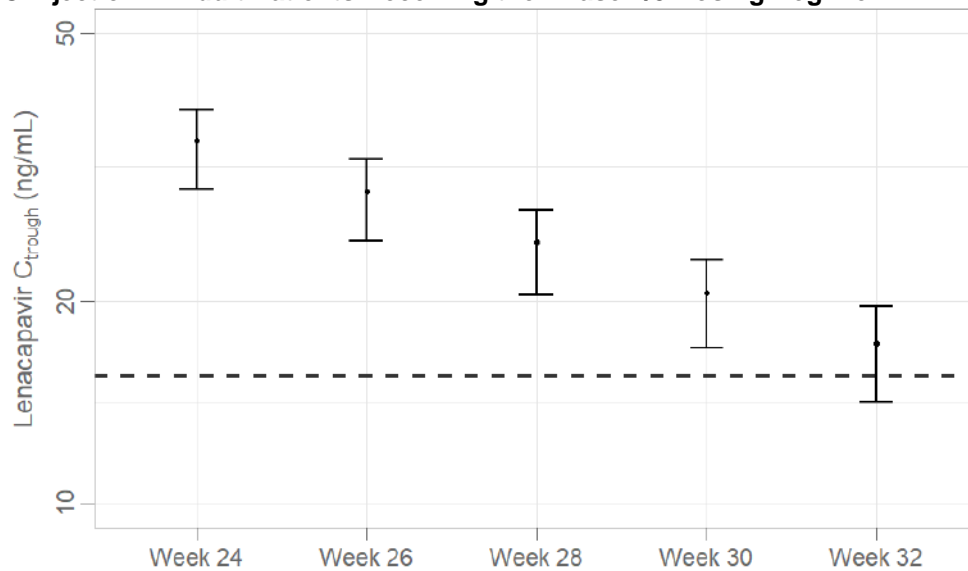
Applicant's Proposed ± 2 -Week Dosing Window

The Applicant predicted the following arithmetic mean C_{trough} (90% CI of mean) in adult patients at Weeks 24, 26, 28, 30 and 32, following the phase 2/3 dosing regimen: 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. According to the analysis conducted by the Applicant ([Figure 13](#)), the lower bound of the 90% CI of the simulated arithmetic mean C_{trough} was consistently above the IQ4 threshold of 15.5 ng/mL, indicating that LEN will maintain efficacious concentrations when dosed within the proposed ± 2 week dosing window.

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Figure 13. Predicted LEN Arithmetic Mean C_{trough} (90% CI of Mean) on Weeks 24 to 32 After the First SC Injection in Adult Patients Receiving 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: Applicant's Summary of Clinical Pharmacology Studies, Figure 13, page 77.

Abbreviations: CI, confidence interval; C_{trough} , minimum concentration; IQ4, inhibitory quotient 4

According to the phase 2 study (4334) and phase 2/3 study (4625) protocols, SC LEN doses were to be administered with a dosing window of 24 to 28 weeks, and the regimen was to be restarted (with oral lead-in) for dosing delays longer than 28 weeks from the last SC injection. However, >75% of the subjects were evaluated for PK or efficacy endpoints 26 weeks after the first SC injection, hence there were insufficient data to assess the appropriateness of the proposed dosing window based on observed LEN PK data.

The review team assessment of the dosing window found that unlike arithmetic mean C_{trough} (as shown in [Figure 14](#)), the geometric mean C_{trough} ([Figure 15](#)) and the median C_{trough} ([Figure 16](#)) showed that at Week 28, after the first SC injection, the average C_{trough} is expected to be around the IQ4 (15.5 ng/mL). Therefore, about 50% of subjects are expected to be below IQ4 at Week 28 ([Figure 16](#), lower panel), which is lower than the predicted average C_{trough} and IQ4 attainment for Week 26 (reference dosing interval, [Figure 15](#) and [Figure 16](#)). The discrepancy between the arithmetic mean C_{trough} (as shown by the Applicant in [Figure 14](#)) and the geometric mean or median C_{trough} ([Figure 15](#) and [Figure 16](#)) is likely, in part, due to the imbalance in LEN exposure between BMI groups in studied patients (4334 and 4625), with underweight patients having higher LEN exposure and overweight/obese patients having lower LEN exposure compared to patients with normal BMI. In addition, as depicted in [Figure 16](#) the difference in the average C_{trough} between Study 4334 (in treatment-naïve patients with HIV) and Study 4625 (in HTE patients with HIV), due to drug-drug interactions (co-medications with cobicistat or ritonavir) in Study 4625, likely contributed to the discrepancy between the overall mean and geometric mean or median C_{trough} (calculated from both studies). The exclusion of subjects with interacting co-medication from Study 4625 decreased the average C_{trough} to levels similar to those observed in Study 4334 (see Section [III.14.3](#) for further details).

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The geometric ($\pm 90\%$ CI) LEN C_{trough} after administration of the LEN second SC dose either 24 or 26 weeks after the first SC dose is expected to be above IQ4 ([Figure 15](#) and [Figure 16](#), middle column of each panel; data not shown for Week 24). By contrast, dosing at 28 weeks ([Figure 15](#) and [Figure 16](#), right column of each panel) is expected to maintain the geometric ($\pm 90\%$ CI) C_{trough} either closer to or at the IQ4 threshold, particularly for overweight and more likely obese patients, as depicted by the lower right panel of [Figure 15](#).

In conclusion, a second injection given 26 weeks instead of 28 weeks after the first injection is more likely to ensure that the geometric mean LEN C_{trough} is well above the IQ4 threshold in all BMI groups. A second injection given 28 weeks after the first injection is expected to maintain the geometric mean C_{trough} either closer to IQ4 or at the IQ4 for a long period of time (due to slower accumulation), particularly in overweight/obese patients. Because most patients in phase 2 and phase 2/3 studies received SC LEN at Week 26, the clinical implications of LEN concentrations falling below IQ4, especially in a subset of overweight/obese patients, at Week 28 are unknown.

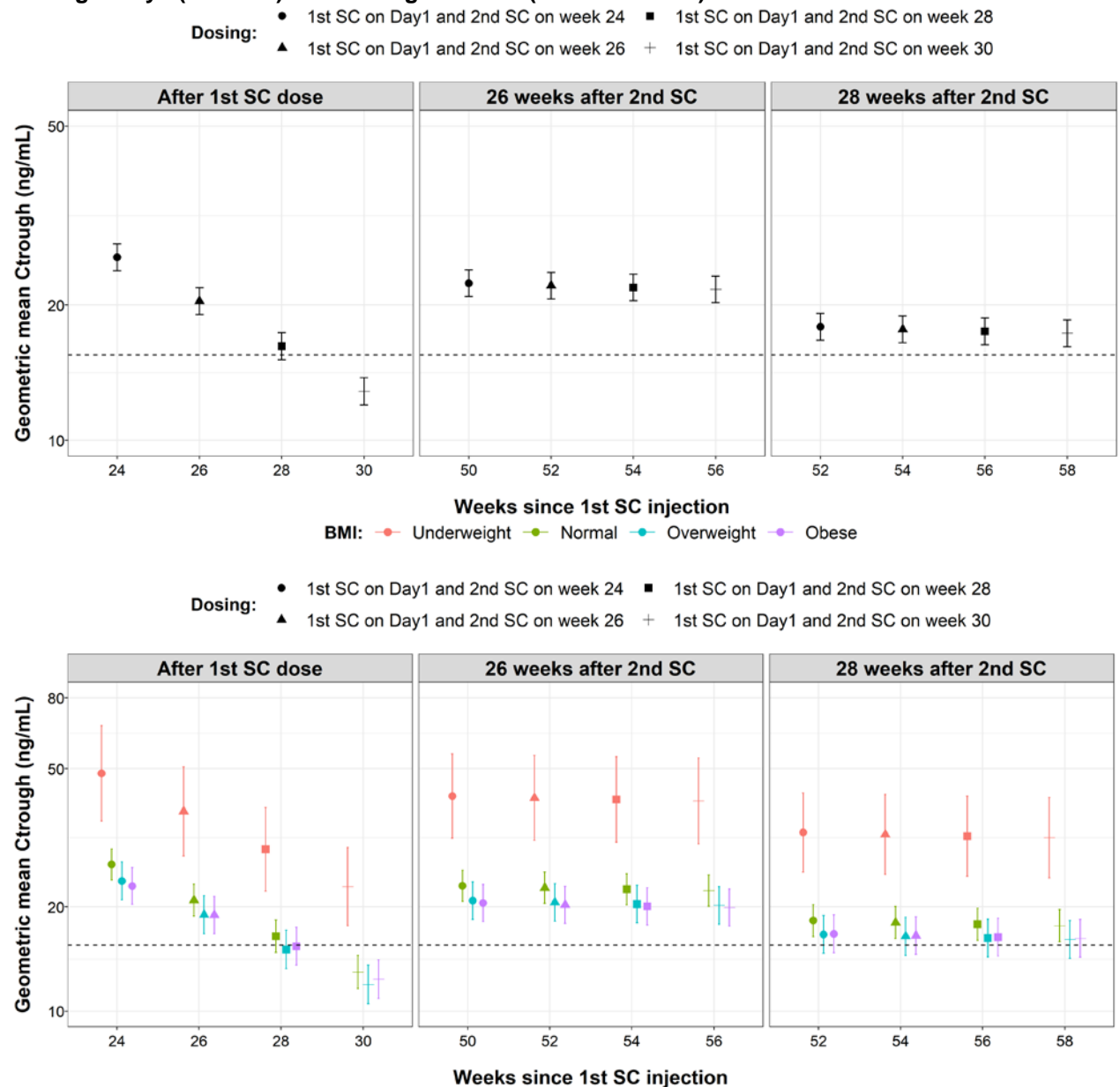
Conclusion

The optimal dosing interval for SC LEN injection is 26 weeks, particularly in overweight and obese patients to maintain LEN geometric mean C_{trough} and its 95% CI well above the IQ4 threshold. However, ± 2 weeks dosing window is acceptable to provide flexibility and facilitate adherence to the SC LEN regimen.

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Figure 14. Predicted Geometric Mean C_{trough} (90% CI), Under the Simplified Dosing, With Various Dosing Delays (First SC) and Dosing Intervals (for Second SC)

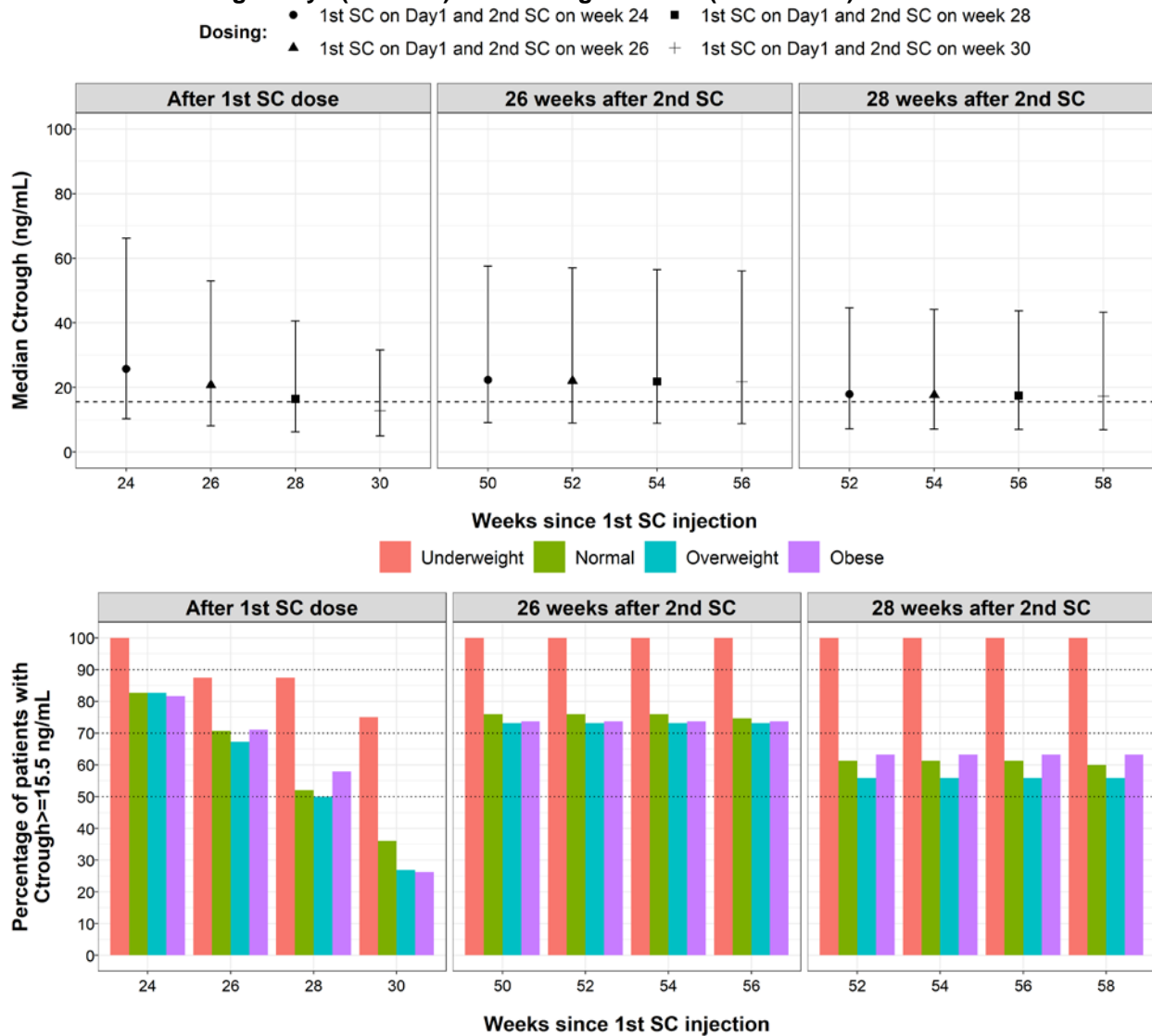


Source: Reviewer's analysis.

Error bars represent the 90% CI of the geometric mean of the predicted C_{trough} from the phase 2 study (4334) and phase 2/3 study (4625). The horizontal dotted line represents the IQ4 at 15.5 ng/mL.

Abbreviations: BMI, body mass index; CI, confidence interval; C_{trough} , minimum concentration; IQ4, inhibitory quotient 4; SC, subcutaneous

Figure 15. Predicted Median C_{trough} and IQ4 Threshold Attainment, Under the Simplified Dosing, With Various Dosing Delays (First SC) and Dosing Intervals (Second SC)



Source: Reviewer's analysis.

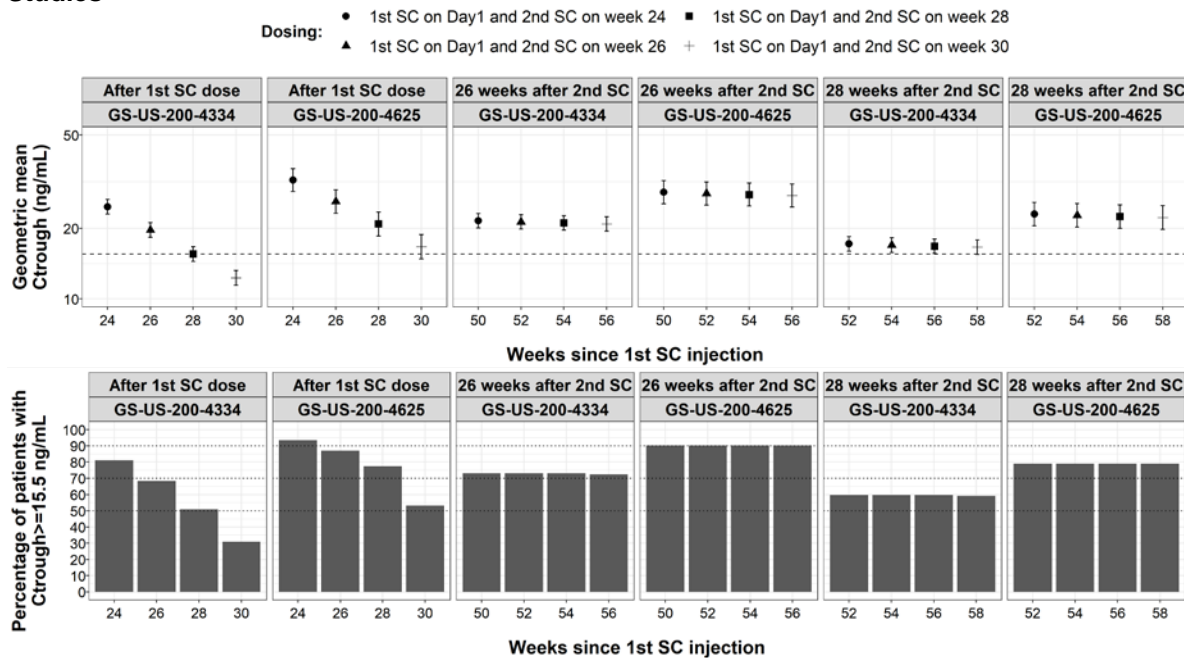
Note: Error bars represent the 5th and 95th percentiles of the predicted C_{trough} from the phase 2 study (4334) and phase 2/3 study (4625), in the absence of booster comedication.

Abbreviations: BMI, body mass index; CI, confidence interval; C_{trough} , minimum concentration; IQ4, inhibitory quotient 4; SC, subcutaneous

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Figure 16. Predicted C_{trough} and IQ4 Threshold Attainment, Under the Simplified Dosing, With Various Dosing Delays (First SC) and Dosing Intervals (Second SC), by Phase 2 and Phase 2/3 Studies



Source: Reviewer's analysis.

Error bars around the geometric mean represent the 90%CI (precision) of the geometric mean. The error bars around the median represent the 5th and 95th percentiles (distribution) of the predicted C_{trough} .

Abbreviations: BMI, body mass index; CI, confidence interval; C_{trough} , minimum concentration; IQ4, inhibitory quotient 4; SC, subcutaneous

Applicant's Proposal of Reinitiating the Indicated Regimen in Patients Who Did Not Receive SC LEN Up To 28 Weeks After the Previous SC LEN Dose

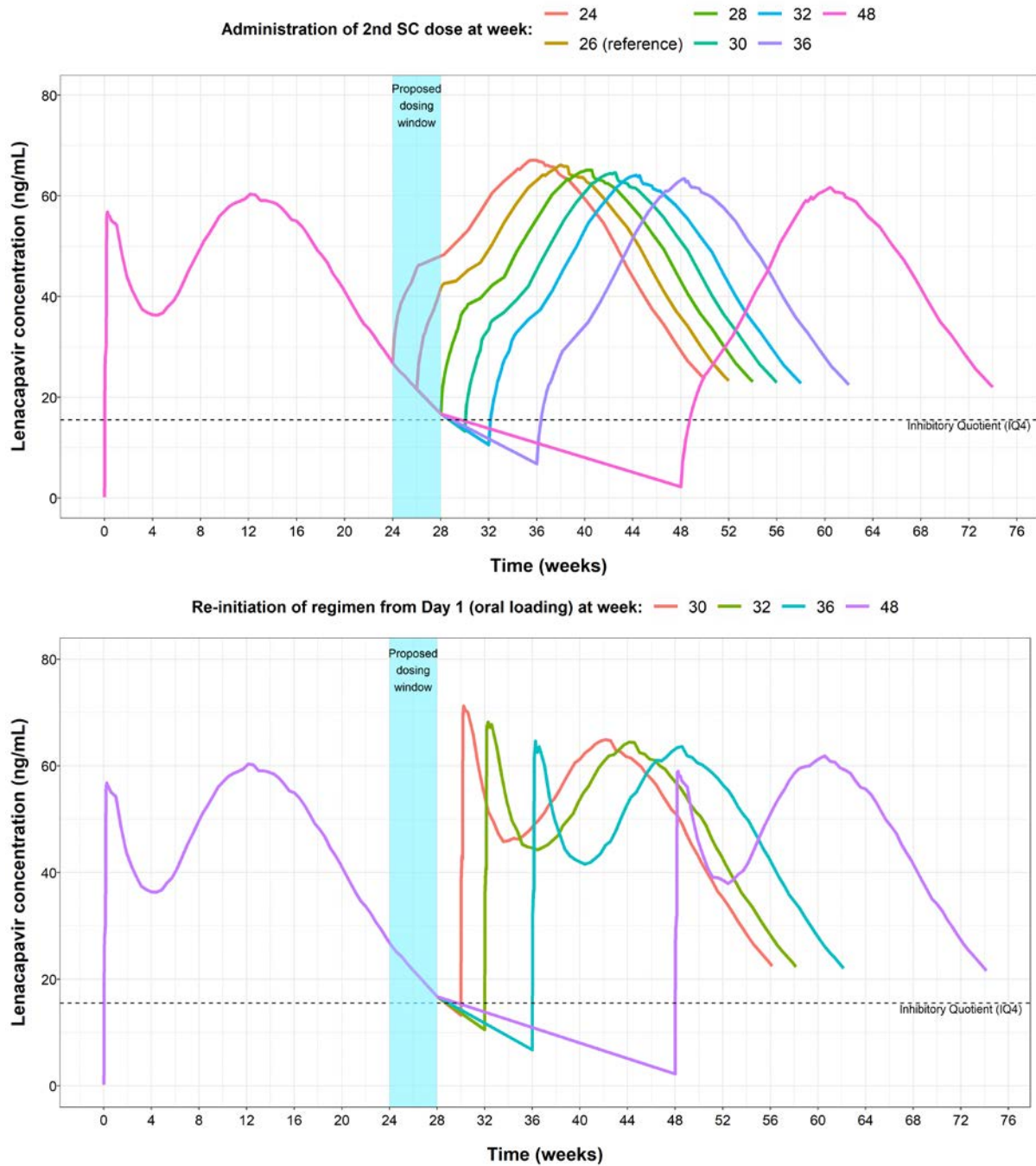
The Applicant proposed that during the LEN SC maintenance period, if more than 28 weeks have elapsed since the last LEN SC injection and if it is clinically appropriate to continue LEN treatment, then reinitiate the indicated dosing regimen.

PK simulations were performed for different dosing delays (Weeks 30 to 48) after the last SC injection followed by either the administration of an SC LEN injection or the reinitiation of the dosing regimen starting with oral loading.

[Figure 17](#) (upper panel) shows that the median LEN concentration from the previous LEN injection stays above IQ4 as long as the next LEN SC injection is administered within the dosing window (± 2 weeks).

The lower panel of [Figure 17](#) shows that reinitiation of the dosing regimen (starting with oral loading) for dosing delays >28 weeks and up to 32 weeks is expected to yield a median C_{trough} and SC C_{max} comparable to the second SC injection from the regular 24 to 28-week dosing window. However, the median C_{max} resulting from the oral loading dose is anticipated to be relatively higher than the median C_{max} observed and predicted with the indicated regimen. Even though the median C_{max} from the loading dose is relatively higher, it remains within acceptable safety ranges and well below the LEN concentrations and C_{max} values observed in the thorough QT study (Study 4332).

Figure 17. Predicted Median LEN PK Profiles Under the Simplified Regimen With Various Dosing Delays and Handling of Dosing Delays



Source: Reviewer's analysis.

Upper panel: dosing delays followed by the administration of a SC LEN injection. Lower panel: dosing delays followed by the re-initiation of the dosing regimen starting by the oral loading. The horizontal dotted line represents the IQ4 threshold at 15.5 ng/mL. Abbreviations: IQ4, inhibitory quotient 4; LEN, lenacapavir; PK, pharmacokinetic; SC, subcutaneous

Conclusion

The Applicant's proposal to reinitiate the indicated dosing regimen if more than 28 weeks have elapsed since the last LEN SC injection, and if it is clinically appropriate to continue LEN treatment, is acceptable.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical studies were conducted using both the oral and subcutaneous routes of exposure to assess both systemic and local toxicity of lenacapavir. Both routes of exposure were used in clinical trials; the oral as a lead-in and the subcutaneous route for maintenance given once every 6 months. Nonclinical safety studies with lenacapavir included good laboratory practice (GLP) single and repeat-dose toxicology studies in rats and dogs; reproductive and developmental toxicology studies in rats and rabbits; and in vitro and in vivo safety pharmacology and genotoxicology studies. Thirteen-week and 2-year carcinogenicity studies in mice and rats, respectively, are currently ongoing and will be part of a future postmarketing requirement (PMR). Overall, the nonclinical safety assessment for lenacapavir was considered acceptable to support marketplace approval from a pharmacology/toxicology perspective. Exposure multiples mentioned in the summary text are based on total lenacapavir concentration. All pertinent studies and findings are summarized in the following section. Full reviews for all studies are located in Section [III.13.2](#).

Safety Pharmacology and Pharmacokinetics

Please see the clinical virology review (Section [III.19](#)) for studies on mechanism of action and antiviral activity.

In safety pharmacology studies, other than a slight decrease in respiration rate at 100 mg/kg, lenacapavir had no adverse effects on other respiratory parameters, neurological functions or changes in electrocardiogram parameters tested in rats and dogs.

The pharmacokinetic profile of lenacapavir (GS-6207) following IV or oral administration was evaluated in portal vein cannulated male Cynomolgus monkeys and Beagle dogs with or without the cytochrome P450 (CYP) inhibitor, aminobenzotriazole, to understand the role of CYP metabolism of lenacapavir. The results from these studies indicated that pretreating dogs and monkeys with aminobenzotriazole did not change lenacapavir oral exposure in dogs or monkeys, but showed the role of intestinal metabolism of lenacapavir.

Lenacapavir was $\geq 98\%$ protein-bound in all animals and humans (unbound fraction was 0.13, 0.83, 1.11, 1.45, and 1.46% in rats, dogs, cynomolgus monkey, Rhesus monkey, and human, respectively) at a concentration of 10mM.

The highest tissue concentration of lenacapavir was detected in the liver up to 42 days followed by kidney cortex, kidneys, pancreas, kidney medulla, brown fat, and thyroid in both intact and bile duct-cannulated nonpigmented male Wister Hanover rats and intact pigmented Long Evans rats. LEN was cleared from all organs by 28 days and from the liver by 56 days.

Several metabolites resulting from glutathione conjugation, pentose conjugation, and glucuronidation were identified in isolated liver microsomes and hepatocytes, plasma, urine,

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feces, bile, and/or liver samples from rats, dogs, monkeys, and humans. Oxidative metabolites were not detected. No new or additional metabolites were observed in human plasma or tissues that were not identified in human isolated microsomes and hepatocytes or in other animal species.

The major routes of elimination in rats and dogs is feces resulting from lenacapavir excretion into the intestines by the p-glycoprotein transporter.

General Toxicology

Repeat-dose toxicology studies were conducted with oral and subcutaneous formulations of lenacapavir to evaluate toxicity from systemic and local toxicity and irritation. The most common toxicity noted among all of the toxicology studies was injection site reactions.

The acute toxicity and tolerability of lenacapavir was evaluated in single dose intravenous studies in both Wistar Hanover rats and Beagle dogs up to 30 mg/kg. Infusion site reactions (cellular inflammation, thrombus, congestion/hemorrhage, edema, and fibrosis) were noted at all doses. Additionally, clinical signs of toxicity in rats included: red urine, ataxia, hypoactivity, vocalization, squinting and/or pale eyes, audible/labored/irregular breathing, and sternal recumbence. Clinical signs of toxicity in dogs included: skin lesions, intermittent tremors, vocalization, and/or discharge of the left eye and front foot.

Pivotal repeat-dose toxicology evaluation for lenacapavir included GLP studies of up to 6-month duration in rats and 9-month duration in dogs via oral or subcutaneous administrations. The skin at the injection site was the target organ of toxicity in both animal species. Additionally, in the 9-month dog study using the clinical formulation, the liver and kidney were also identified as targeted organs of toxicity.

Based on systemic exposure in the repeat-dose studies in rats via subcutaneous administrations, there was no target organ identified at doses up to 100 mg/kg. However, based on local toxicity, the injection site was the target organ identified in the rat studies via subcutaneous administrations in all studies. These injection site reactions were observed after the recovery periods, albeit at a lesser degree of intensity. Toxicities at the injection sites included necrosis, granulomatous inflammation, mixed cell inflammation, and/or macrophage infiltration.

Based on systemic exposure in the repeat-dose studies in dogs via subcutaneous administrations, there was no target organ identified at doses up to 100 mg/kg up to 2 months. However, repeat-dose studies up to 9 months in dogs identified the liver, gall bladder, kidneys, and stomach as targeted organs of toxicity. Liver findings included bile duct degeneration and cell/bile ductule hyperplasia. Gallbladder findings included edema and hyperplasia detected at doses up to 411 mg/kg. Kidney findings included tubule degeneration and dilatation, and findings in the stomach included degeneration/atrophy of mucosa at the highest dose of 411 mg/kg. Additionally, based on local toxicity, the injection site was the target organ identified in all repeat-dose dog studies via subcutaneous administrations up to 411 mg/kg. Toxicities at the injection sites included necrosis, granulomatous inflammation, mixed cell inflammation, and/or macrophage infiltration. These injection site reactions were observed after the recovery periods, albeit at a lesser intensity. Based on systemic exposure, at the no observed adverse effect level (NOAEL), lenacapavir was 32-fold the human exposure at the recommended human dose (RHD) in the 2-month rat study and 6- to 8-fold in the 6-month rat study. Additionally, based on

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systemic exposure, at the NOAEL in the 2- and 9-month dog studies, lenacapavir was 24- and 9-fold the human exposure at the RHD.

In clinical trials, the most notable adverse events (AEs) associated with lenacapavir were nodules that formed at the injection sites, thus reflecting the main toxicities of injection site reactions observed in nonclinical species.

Genotoxicology and Carcinogenicity

Lenacapavir was negative for mutagenesis in the in vitro reverse mutation assay, negative for clastogenicity in the in vitro assay using human peripheral lymphocytes, and negative for genotoxicity in the in vivo micronucleus assay in rats. Additionally, several impurities were identified and tested in a battery of genotoxicology studies for mutagenesis and clastogenicity. Overall, the weight of evidence indicates that lenacapavir does not exhibit genotoxic potential.

The carcinogenicity potential of lenacapavir is being evaluated in a 26-week study (single subcutaneous injection given once every 13 weeks for a total of two doses) in 001178-T (hemizygous) RasH2 mice and a 2-year study (single subcutaneous injection given once every 13 weeks for a total of eight doses) in Wister Hanover rats. These studies are ongoing at the time of NDA submission and will be part of a future PMR.

Reproductive and Developmental Toxicology

No lenacapavir-related effects on male and female fertility parameters occurred with up to 100 mg/kg lenacapavir when administered via a single subcutaneous injection to rats at exposures seven- and five-fold (in males and females, respectively) the RHD. No lenacapavir-related effects on embryo-fetal development (EFD) occurred at doses up to 30 mg/kg lenacapavir when orally administered to rats once daily from gestation day (GD) 6 to 17 at exposures 16-fold the RHD.

In the rabbit EFD study, lower body weight gains at doses up to 20 mg/kg correlated to a dose-dependent decrease in food intake following intravenous administration of lenacapavir. Body weights returned to those of controls levels after 9 days without treatment. No other maternal or fetal toxicity occurred with up to the highest intravenous administration of 20 mg/kg at exposures 39-fold the RHD.

In the pre- and postnatal development (PPND) toxicity study, lenacapavir was administered to pregnant rats via a single subcutaneous injection of doses of 30 and 300 mg/kg on GD 6. There were no maternal toxicities or effects on PPND at doses up to 300 mg/kg at exposures five-fold the RHD. Lactation endpoints were not measured in the PPND study.

Additional Toxicology Studies

Lenacapavir resulted in local toxicity at the injection sites at concentrations up to 500 mg/mL in rabbits. Lenacapavir was not phototoxic, cytotoxic, or considered an eye irritant. Using in vitro skin models, lenacapavir was not considered corrosive but was considered positive in two of three skin sensitization assays. However, in the in vivo assessment, lenacapavir was considered negative for sensitization potential. In the clinical formulation for marketing, the hemolytic potential of lenacapavir is low.

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Exposure Multiples

Exposure multiples ([Table 25](#)) are based on LEN predicted systemic exposure (AUC_{0-24h} 1301) in humans at the recommended dosing regimen.

Table 25. Exposure Margins Based on NOAEL

Study	NOAEL	Adverse Findings	AUC_{0-24hr}^1 (ng·h/mL)	Exposure Multiple ²
Repeat-dose studies (oral)				
4-week rat	30 mg/kg	None	34,500	26
4-week dog	30 mg/kg	None	75,900	58
Repeat-dose studies (subcutaneous)				
43-day rat	ND	Injection site reactions (skin thickening; granulomatous inflammation)	ND	ND
43-day rat	100 mg/kg (systemic effects)	None	583,000 ³	32
92-day rat	ND	Injection site reactions (edema, skin thickening/discoloration, granulomatous inflammation, macrophage infiltrate)	ND	ND
92-day rat	100 mg/kg (systemic effects)	None	307,000 ⁴ 284,000 ⁴ 211,000 ⁴	8 8 6
43-day dog	ND	Injection site reactions (skin discoloration, granulomatous inflammation)	ND	ND
43-day dog	30 mg/kg (systemic effects)	Vocalization, barrel rolling	436,000 ³	24
9-month dog	ND	Injection site reactions (granulomatous inflammation, mixed cell inflammation, macrophage infiltrate, and/or necrosis)	ND	ND
9-month dog	40 mg/kg (systemic effects)	None	352,000 ⁴	9.6
9-month dog	ND	Injection site reactions (granulomatous or mixed cell inflammation, adipose necrosis, fibrosis) Liver (bile duct degeneration, cell/bile duct hyperplasia) Kidney (tubule degeneration and dilatation)	ND	ND
Reproductive toxicology studies				
Fertility and early embryonic development				
Rat (SC)	100 mg/kg	None	270,000 ⁵ 192,000 ⁶	7 5
Embryo-fetal development				
Rat (oral)	30 mg/kg	None	22,000 ⁷	16
Rabbits (IV)	20 mg/kg	Lower body weight gain	204,000 ⁸	39

Study	NOAEL	Adverse Findings	AUC _{0-24hr} ¹ (ng·h/mL)	Exposure Multiple ²
Pre- and postnatal development				
Rat (SC)	300 mg/kg	None	54,800 ⁹	5

Source: Reviewer.

¹ AUC_{0-24h} values for male and female animals combined unless otherwise stated.

² Based on AUC_{tau} values in humans at the proposed dosing regimen: Day 1: 600 mg (oral) + 927 mg (SC); Day 2: 600 mg (oral); maintenance: 927 mg (SC) every 6 months 25 mg (AUC_{tau}=234,294 ng·h/mL) being converted to AUC_{24hr} (234,294/180=1301 ng·h/mL).

³ Based on AUC_{0-336 h}.

⁴ Based on AUC_{0-672 h}.

⁵ Based on AUC_{0-672 h} in males.

⁶ Based on AUC_{0-672 h} in females.

⁷ Females only.

⁸ Based on AUC_{0-96.5 h} in females.

⁹ Based on AUC_{0-192 h} in females.

Abbreviations: AUC, area under the concentration-time curve; IV, intravenous; LEN, lenacapavir; ND, not determined; NOAEL, no observed adverse effect level; SC, subcutaneous

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Lenacapavir is the first in a new class of antiretroviral drugs, so no previously described clinical experience is available to inform any specific safety concern regarding capsid inhibitors.

Immune reconstitution syndrome has been reported with combination antiretroviral therapy, particularly in the initial phase of treatment, in patients whose immune systems develop an inflammatory response to indolent or residual opportunistic infections. This is also often particularly relevant in a heavily treatment-experienced patient population. Loss of virologic response due to drug-drug interactions has been included as a warning in labeling for other ARVs.

For other ARVs that are administered in an injectable form, such as Cabenuva (a long-acting formulation of two drugs, cabotegravir and rilpivirine), injection site reactions are the most common adverse reactions. These were described usually (79%) as localized pain or discomfort. The Cabenuva label notes that “Other manifestations included nodules (14%), induration (12%), swelling (8%), erythema (4%), pruritus (4%), bruising (3%), warmth (2%), and hematoma (2%). Abscess and cellulitis at the injection site were each reported in less than 1% of subjects” (Cabenuva 2021). Serious post-injection reactions were reported in less than 1% of subjects within minutes after the injection of rilpivirine and begin to resolve within a few minutes after the injection. These reactions were characterized by signs and symptoms including dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure.

Additionally, given the long-acting properties of Cabenuva, the label notes that “residual concentrations of both cabotegravir and rilpivirine may remain in the systemic circulation of patients for prolonged periods”; therefore, a warning is included that nonadherence could lead to loss of virologic response and development of resistance.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Lenacapavir has not been approved in any country; therefore, there has been no postmarketing experience with lenacapavir.

7.4. FDA Approach to the Safety Review

Adequacy of Applicant's Clinical Safety Assessments

The review team did not identify any major data quality or integrity issues that preclude performing a safety review. No major issues were identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in Studies 4625 and 4334 were coded according to Version 23.1 and reviewed and were found to be acceptable.

AEs were protocol-defined as: "any untoward medical occurrence in a clinical study participant administered an investigational product, which does not necessarily have a causal relationship with the treatment."

Treatment-emergent adverse events (TEAEs) were defined in the Applicant's analysis, and for the purpose of this review, as any AE that occurred on or after the day of treatment initiation.

Adverse drug reactions were defined for the purpose of this review as any TEAE that was considered by the investigator to be related to the study drug with reasonable possibility.

"Reasonable possibility" is meant to convey that there are facts or evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Serious adverse events (SAEs) were protocol-defined as any untoward medical occurrence that, at any dose, resulted in:

- Death.
- Was life-threatening (note: the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- In-patient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

Severity grades were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017) (NIAID 2017).

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Studies 4625 and 4334 included interim analyses through at least Week 24, and extended observations for repeat SC dosing were ongoing at the time of initial NDA submission for many subjects. As agreed with DAV, the Applicant submitted a 90-Day Safety Update with subsequent safety follow-up. A summary of available study data by date is provided in [Table 26](#).

Table 26. Summary of Ongoing Studies Providing Key Clinical Safety Data for Lenacapavir

Study	Study Start Date (First Subject Screened)	Original NDA Submission Analysis End Date	90-Day Safety Update
GS-US-200-4625	21 November 2019	01 April 2021 (interim Week 24 analysis, last subject last observation)	01 April 2021 to 27 July 2021 ^a
GS-US-200-4334	22 November 2019	26 March 2021 (interim Week 28 analysis, last subject last observation)	26 March 2021 to 25 June 2021
ISS (pooled phase 1)			
GS-US-200-4538 (Cohorts 6, 7, and 10)	30 October 2018	31 August 2020 (final)	
GS-US-200-5709 (Cohorts 1, 2, and 3 ^b)	28 February 2020	31 October 2020	Cohort 1: 31 Oct 2020 to 25 June 2021 Cohort 2: 24 February 2021 to 25 June 2021

Source: Applicant's 90-Day NDA Safety Update.

^a Additional data cut on (b) (6) for one subject.

^b Complete data from Cohort 3 were included in the original NDA submission.

Abbreviations: ISS, integrated summary of safety; NDA, new drug application

Approach to Assessment of Clinical Trial Data

The review approach for assessment of risk consisted of evaluation of the safety data from the phase 2/3 trials separately as well as the pooled safety data from phase 1 studies. These trials were reviewed separately because the studies enrolled different patient populations. Study 4625 included an HTE population, while Study 4334 enrolled a treatment-naïve population, and the phase 1 studies were healthy adults. Results of individual trials are highlighted where important differences may have emerged.

Clinical trial data from Studies 4635 and 4334 were independently analyzed using JMP and JMP Clinical software. Additional analyses were provided by the Clinical Data Scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. Prespecified hypothesis testing was not proposed for safety outcomes in Studies 4625 or 4334. Comparisons are therefore based on descriptive analyses.

Comparisons across arms in Study 4625 were limited because assessment during the randomized portion of the study were limited to the FMP with only the oral administration of LEN. As a general approach, attribution of events due to LEN comparisons across study arms were derived largely from Study 4334 and selected cohorts from phase 1. For relevance to the proposed SC dosing, study arms that included SC LEN were combined and compared to another active control arm randomized to B/F/TAF. Because the pooled phase 1 data were placebo-controlled in healthy volunteers, comparisons across arms were generally more acceptable for the purpose of assessing contribution of LEN; however, the overall sample size achieved in this analysis was small and duration of follow-up was shorter.

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In the Applicant's proposed label, Adverse Reactions (Section 6.1) included only data from Study 4625, as this study included the relevant patient population for the proposed indication, whereas Study 4334 included treatment-naïve subjects that were anticipated to have significant differences in underlying disease severity and comorbid conditions.

7.5. Adequacy of the Clinical Safety Database

Overall, the safety database is adequate to assess the safety of lenacapavir for the proposed indication, dosage regimen, and patient population. See [Table 27](#).

At the time of NDA filing, 803 individuals were enrolled in clinical studies and received at least one dose of LEN, regardless of route (SC, per oral [PO], or intravenous [IV]), formulation, or population (healthy, PLWH). A total of 284 subjects received at least one dose of 927 mg SC LEN (with same proposed SC formulation or equivalent oral dose that is expected to achieve the targeted exposure for at least 6 months). A total of 232 subjects received at least one 927 mg SC dose of LEN with the same proposed formulation for marketing. The total number of PLWH who received SC LEN at the proposed dose/duration (LEN exposures $\geq$ 26 weeks) was 177.

Table 27. Overview of Clinical Safety Data

Study Number	Description of Study	Number of SC LEN Subjects
GS-US-200-4625	Ongoing, phase 2/3, randomized, placebo-controlled, multicenter study in heavily treatment-experienced PLWH	72
GS-US-200-4334	Ongoing, phase 2, randomized, open-label, active-controlled, multicenter study in treatment-naïve PLWH	157*
GS-US-200-4538	Completed, phase 1, randomized, blinded, placebo-controlled, SAD study in healthy subjects	24
GS-US-200-5709	Ongoing, phase 1, open-label, multiple-cohort, multiple-dose study in healthy subjects	31
Total SC LEN safety database		N=232

Source: Reviewer's analysis.

* Fifty-two of these subjects received oral only LEN.

Abbreviations: HTE, heavily treatment-experienced; LEN, lenacapavir; PLWH, people living with HIV; SAD, single ascending dose; SC, subcutaneous

Study 4625 Clinical Safety Experience

In the phase 2/3 study, Study 4625, 72 subjects in Cohorts 1 and 2 received at least one SC dose of LEN. Safety comparisons between randomized subjects, however, were limited to 36 subjects in Cohort 1 during the 14-day FMP, 24 of whom received oral doses of LEN. During the maintenance phase of the study, during which all subjects received SC LEN:

- Thirty-nine subjects received a second dose (Cohort 1: N=36, Cohort 2: N=3).
- Eleven subjects received a third dose (Cohort 1: N=10, Cohort 2: N=1).

A summary of study drug administration in Study 4625 is provided in [Table 28](#).

Table 28. Study Drug Administration, Study 4625

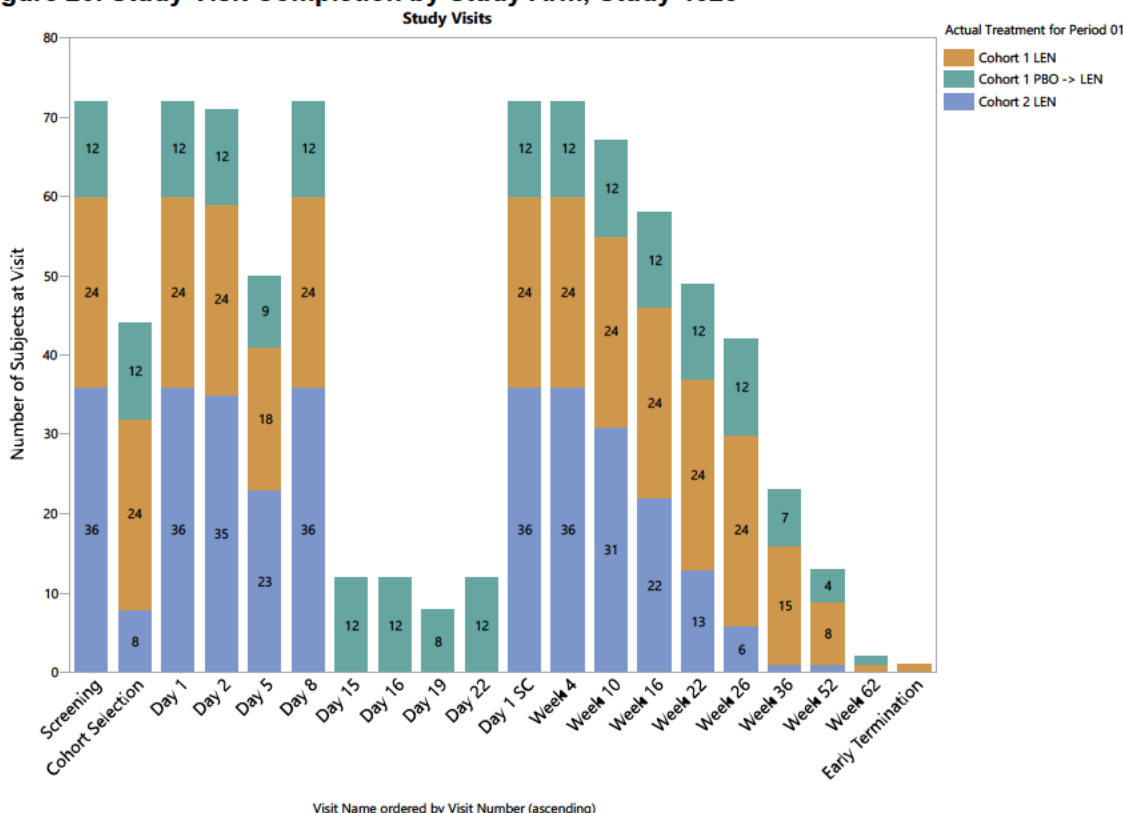
Parameter	Cohort 1			Cohort 2 N=36 n (%)	Total N=72 n (%)
	LEN N=24 n (%)	PBO→LEN N=12 n (%)	All LEN N=36 n (%)		
Oral dose received					
Day 1	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Day 2	24 (100.0%)	12 (100.0%)	36 (100.0%)	35 (97.2%)	71 (98.6%)
Day 8	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Day 15	0	12 (100.0%)	12 (33.3%)	0	12 (16.7%)
Day 16	0	12 (100.0%)	12 (33.3%)	0	12 (16.7%)
Day 22	0	12 (100.0%)	12 (33.3%)	0	12 (16.7%)
Oral reload received prior to Day 1 SC injection	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
Due to missed scheduled oral dosing	0	0	0	0	0
Due to missed scheduled SC dosing	1	0	1	0	1
Day 1 SC injection received	24 (100.0%)	12 (100.0%)		36 (100.0%)	72 (100.0%)
Week 26 SC injection received	24 (100.0%)	12 (100.0%)	36 (100.0%)	3 (8.3%)	39 (54.2%)
Week 52 SC injection received	7 (29.2%)	3 (25.0%)	10 (27.8%)	1 (2.8%)	11 (15.3%)

Source: Study 4625 Interim Week 26 Clinical Study Report, Table 15.11.1.3: Study Drug Administration.

Abbreviations: LEN, lenacapavir; N, number of subjects in the group; n, number of subjects within listed parameter; PBO, placebo; SC, subcutaneous

Study visit completion by study arm and duration of exposure are presented in [Figure 20](#) and [Table 29](#), respectively. Subject ^{(b) (6)} (64-year-old male in Cohort 2/LEN) missed Day 2 visit and Day 2 oral dose. Subject ^{(b) (6)} (47-year-old male in Cohort 1/LEN) achieved $\geq 0.5 \log_{10}$ reduction from baseline in HIV-1 RNA at the end of the FMP, but missed initiation of SC dosing. His VL remained < 20 copies/mL on Day 26 (unscheduled visit), and he restarted oral LEN lead-in followed by SC dosing.

Figure 20. Study Visit Completion by Study Arm, Study 4625



Source: Reviewer's analysis, adsl.xpt and sv.xpt; software, JMP Clinical.
 Abbreviations: LEN, lenacapavir, PBO, placebo

Table 29. Duration of Exposure, Study 4625

Parameter	Cohort 1			Cohort 2 N=36	Total N=72
	LEN N=24	PBO→LEN N=12	All LEN N=36		
Duration of exposure, weeks					
Mean (SD)	48.4 (12)	48.4 (12.2)	48.4 (11.9)	22.2 (9.7)	35.3 (17)
Median (Q1, Q3)	49.4 (36.7, 58.5)	48.8 (36.8, 58.4)	49.4 (36.7, 58.4)	22.2 (15.1, 27.3)	33.1 (22.2, 50.4)
Min, max	30.3, 69.3	32.3, 66.3	30.3, 69.3	2.1, 59.3	2.1, 69.3
Total exposure (person years)	22	11	33	15	49
Patients treated, by duration, n (%)					
<12 weeks	0	0	0	1 (2.8)	1 (1.4)
≥12 to <26 weeks	0	0	0	25 (69.4)	25 (34.7)
≥26 to <50 weeks	13 (54.2)	6 (50.0)	19 (52.8)	9 (25.0)	28 (38.9)
≥50 to <100 weeks	11 (45.8)	6 (50.0)	17 (47.2)	1 (2.8)	18 (25.0)
≥100 weeks	0	0	0	0	0

Source: Clinical data scientist, adsl.xpt; software, R.
 Abbreviations: N, number of subjects in treatment arm; n, number of subjects with a given treatment duration; SD, standard deviation; Q1, first quartile; Q3, third quartile; LEN, lenacapavir, PBO, placebo

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In Study 4625, the following reports were provided regarding status of subject follow-up and study drug exposure as of the 90-Day Safety Update (data cut date of July 27, 2021, except (b) (6) for one subject):

- Sixty-eight subjects were continuing on study drug and 67 subjects (93.1%) had received study drug for ≥ 197 days.
- Forty-five subjects (62.5%) were continuing study drug in the main phase (up to Week 52) after the first SC LEN injection.
- Three additional subjects prematurely discontinued study drug.
- Median duration of follow-up on study across both cohorts was 313 days.
- Sixty-seven subjects (93.1%) had received study drug for ≥ 197 days.

Study 4334 Clinical Safety Experience

A summary of clinical safety experience with SC LEN, as well as with maintenance as oral LEN, in subjects with no prior ARV experience are provided with Study 4334 in [Table 30](#).

Table 30. Duration of Exposure, Study 4334

Parameter	SC LEN + (F/TAF→TAF)	SC LEN + (F/TAF→BIC)	Oral LEN + F/TAF	B/F/TAF	Total SC LEN	Total LEN
	N=52 n (%)	N=53 n (%)	N=52 n (%)			
Duration of exposure, weeks						
Mean (SD)	43.6 (14.8)	43.3 (14.3)	45.2 (13.7)	48.1 (12.1)	43.4 (14.5)	44 (14.2)
Median (Q1, Q3)	39.9 (33.3, 57.3)	42.1 (32.4, 56.3)	44.2 (33.9, 57.7)	52 (35.4, 58.3)	41.4 (33.3, 56.4)	42.3 (33.3, 57)
Min, max	1.1, 69	0.1, 64.4	10.3, 66.1	31.1, 66.4	0.1, 69	0.1, 69
Total exposure (person years)	43	44	45	23	87	132
Patients treated, by duration, n (%)						
<12 wks	2 (3.8)	1 (1.9)	1 (1.9)	0	3 (2.9)	4 (2.5)
≥ 12 to <26 wks	0	3 (5.7)	2 (3.8)	0	3 (2.9)	5 (3.2)
≥ 26 to <50 wks	29 (55.8)	27 (50.9)	26 (50.0)	12 (48.0)	56 (53.3)	82 (52.2)
≥ 50 to <100 wks	21 (40.4)	22 (41.5)	23 (44.2)	13 (52.0)	43 (41.0)	66 (42.0)
≥ 100 wks	0	0	0	0	0	0

Source: Clinical data scientist, adsl.xpt; software, R.

Abbreviations: BIC, B, bicitgravir; BVY, bicitgravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; B ktarvy); DVY, emtricitabine/tenofovir alafenamide; F/TAF, coformulated Descovy; FMP, functional monotherapy period; FR, failing regimen; LEN, lenacapavir; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation; TAF, tenofovir alafenamide

Additional Studies With Clinical Safety Experience

Additional study data contributing to the clinical safety experience with SC LEN that were included the Applicant's pooled analysis of phase 1 studies are listed in [Table 31](#).

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Table 31. Extent of Exposure, Pooled Phase 1, Studies 4538 and 5709

Treatment	Study	Cohort (Dosing)	N	Total N
LEN	GS-US-200-4538	Cohort 6 (927 mg, 309 mg/mL LEN injection 3x1.0 mL)	8	55
		Cohort 7 (927 mg, 309 mg/mL LEN injection 2x1.5 mL)	8	
		Cohort 10 (927 mg, 155 mg/mL LEN injection 3x2 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 2x1.5 mL on day 15)	31	
Placebo	GS-US-200-4538	Two placebo subjects each from 10 cohorts	20	20

Source: Table 1, Applicant's Summary of Clinical Safety (m2.7.4).

Abbreviations: N, number of subjects in group; LEN, lenacapavir

Table 32. Duration of Study, Pooled Phase 1, Studies 4538 and 5709

Parameter	LEN N=50	Placebo N=20	Total N=75
Duration on study (days)			
Mean (SD)	208.8 (178.94)	384.4 (111.09)	255.6 (180.68)
Median	135.0	448.5	225.0
Min, max	27.0, 469	43.0, 465.0	27.0, 469.0
Duration on study, n (%)			
≥7 days	55 (100.0%)	20 (100.0%)	75 (100.0%)
≥28 days	39 (70.9%)	20 (100.0%)	59 (78.7%)
≥42 days	37 (67.3%)	20 (100.0%)	57 (76.0%)
≥72 days	37 (67.3%)	19 (95.0%)	56 (74.7%)
≥162 days	21 (38.2%)	19 (95.0%)	40 (53.3%)
≥252 days	19 (34.5%)	17 (85.0%)	36 (48.0%)
≥372 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%)

Source: Table 4, Applicant's Summary of Clinical Safety (m2.7.4).

Abbreviations: N, number of subjects in group; n, number of subjects with given duration on study; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, Studies 4625 (CAPELLA) and 4334 (CALIBRATE)

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary

An overview of the TEAEs in Studies 4625 and 4334 through at least the Week 26 and Week 28 visit dates, respectively, is shown in [Table 33](#). While the comparisons across the grouped study arms (total LEN in Study 4625 and Study 4334) revealed a trend of higher incidence of AEs as compared with the oral-only regimen of B/F/TAF, there were no serious AEs and very few moderate to severe (Grades 3 to 5) AEs that were considered by the investigator to be study-drug related in any of the studies. Overall, these trends suggest that differences in AEs reported across studies likely reflect underlying differences in patient populations.

Table 33. Overview of Treatment-Emergent Adverse Events, Studies 4625 and 4334

Event	Total LEN Study 4625 N=72 n (%)	Total LEN Study 4334 N=157 n (%)	B/F/TAF Study 4334 N=35 n (%)
	Any treatment-emergent AE ¹	66 (91.7)	136 (86.6)
Study-drug related TEAE ²	45 (62.5)	47 (44.8)	4 (16.0)
Moderate or severe TEAEs (Grade 3-5) ³	13 (18.1)	11 (7.0)	1 (4.0)
Study-drug related TEAE (Grade 3-5) ^{2,3}	4 (0.6)	1 (0.6)	0
Any SAE	4 (5.6)	8 (5.1)	0
SAEs with fatal outcome	1 (1.4)	0	0
Study-drug related SAE ²	0	0	0
AEs leading to discontinuation of study drug	0	2 (1.3)	0
AEs leading to dosage modification of study drug	0	0	0
AEs leading to interruption of study drug	0	0	0
AEs leading to reduction of study drug	0	0	0
AEs leading to dosage delay of study drug	0	0	0

Source: Clinical Data Scientist's and Reviewer's analysis (JMP Clinical 8.1) of the adae.xpt and adsl.xpt datasets.

¹ Includes treatment-emergent AE defined as events that 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.

² Relatedness as determined by the investigator.

³ Severity grades were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 July 2017.

Abbreviations: AE, adverse event; B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths

One subject in Cohort 2 of Study 4625 died on Study Day 90; the cause of death was cancer and was considered by the investigator not to be related to the study drug. Additional details are provided in Section [7.6.3.2](#). There were no deaths reported in Study 4334.

7.6.1.3. Serious Adverse Events

[Table 34](#) summarizes SAEs reported in Studies 4625 and 4334. No SAEs were reported during the FMP in Study 4625.

Table 34. Serious Adverse Events, Studies 4625 and 4334

System Organ Class (SOC) Serious Adverse Event ¹	Total LEN Study 4625 N=72 n (%)	Total SC LEN Study 4334 N=105 n (%)	Total LEN Study 4334 N=157 n (%)	B/F/TAF Study 4334 N=35 n (%)
	Blood and lymphatic system disorders	0	1 (1.0)	1 (1.0)
Lymphadenopathy mediastinal	0	1 (1.0)	1 (1.0)	0
Gastrointestinal disorders	2 (2.8)	1 (1.0)	1 (0.6)	0
Abdominal pain	1 (1.4)	0	0	0
Pancreatic mass	1 (1.4)	0	0	0
Proctalgia	1 (1.4)	0	0	0
Vomiting	0	1 (1.0)	1 (0.6)	0
Infections and infestations	1 (1.4)	4 (3.8)	5 (3.2)	0
<i>Clostridium difficile</i> infection	1 (1.4)	0	0	0
<i>Escherichia</i> infection	0	1 (1.0)	1 (0.6)	0
Perirectal abscess	0	1 (1.0)	1 (0.6)	0
<i>Pneumocystis jirovecii</i> pneumonia	0	0	1 (0.6)	0
Pneumonia	0	1 (1.0)	1 (0.6)	0
Staphylococcal infection	0	1 (1.0)	1 (0.6)	0

System Organ Class (SOC) Serious Adverse Event¹	Total LEN Study 4625 N=72 n (%)	Total SC LEN Study 4334 N=105 n (%)	Total LEN Study 4334 N=157 n (%)	B/F/TAF Study 4334 N=35 n (%)
Injury, poisoning and procedural complications	1 (1.4)	0	1 (0.6)	0
Femoral neck fracture	1 (1.4)	0	0	0
Poisoning	0	0	1 (0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4)	1 (1.0)	1 (0.6)	0
Metastases to central nervous system	0	1 (1.0)	1 (0.6)	0
Neoplasm malignant	1 (1.4)	0	0	0
Non-small cell lung cancer	0	1 (1.0)	1 (0.6)	0
Nervous system disorders	1 (1.4)	0	0	0
Dizziness	1 (1.4)	0	0	0
Psychiatric disorders	0	1 (1.0)	3 (1.9)	0
Bipolar disorder	0	0	1 (0.6)	0
Major depression	0	0	1 (0.6)	0
Psychotic disorder	0	0	1 (0.6)	0
Substance-induced psychotic disorder	0	1 (1.0)	1 (0.6)	0
Respiratory, thoracic, and mediastinal disorders	0	1 (1.0)	2 (1.3)	0
Dyspnea	0	1 (1.0)	1 (0.6)	0
Pleural effusion	0	1 (1.0)	1 (0.6)	0
Pneumothorax	0	0	1 (0.6)	0

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities preferred terms.

Treatment-emergent adverse events (Study 4625) defined as an AE that began on or after the first dose date of blinded study drug. Treatment-emergent events (Study 4334) 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. Duration is 54 weeks for Study 4625 and 80 weeks for Study 4334.

Abbreviations: AE, adverse event; BIC, bictegravir; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; N, number of subjects in treatment arm; n, number of subjects with adverse event; LEN, lenacapavir; SC, subcutaneous; SOC, system organ class.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events

In the original NDA submission, no TEAEs were reported in Study 4625 that led to discontinuation through the follow-up period ending 01 April, 2021. For Study 4334, with follow-up through March 26, 2021 (Week 28 interim analysis), 2 of 105 subjects (1.9%) in the total SC LEN group discontinued study drug prematurely due to AEs of injection site induration. Both occurrences were nonserious and Grade 1 in severity.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 35. Adverse Events Leading to Discontinuation, Studies 4625 and 4334

System Organ Class Preferred Term ¹	Total LEN Study 4625 N=72 n (%)	Total SC LEN Study 4334 N=105 n (%)	Total LEN Study 4334 N=157 n (%)	B/F/TAF Study 4334 N=35 n (%)
	General disorders and administration site conditions	0	2 (1.9)	2 (1.3)
Injection site induration	0	2 (1.9)	2 (1.3)	0

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Coded as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

Treatment-emergent adverse events (Study 4625) defined as an AE that began on or after the first dose date of blinded study drug.

Treatment-emergent events (Study 4334) 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. Duration is 54 weeks for Study 4625 and 80 weeks for Study 4334.

Abbreviations: AE, adverse event; BIC, bicitegravir; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide; N, number of subjects in treatment arm; n, number of subjects with adverse event; LEN, lenacapavir; SC, subcutaneous; SOC, system organ class.

Based on the Applicant's 90-Day Safety Update from the original NDA data cut date through the follow-up period ending July 27, 2021, one subject in Study 4625 prematurely discontinued study drug due to treatment-emergent AEs of injection site nodules, both of which were Grade 1 and were ongoing with follow-up through 25 June, 2021. No new study drug discontinuations due to AEs were reported for Study 4334.

7.6.1.5. Treatment-Emergent Adverse Events

In Study 4625, TEAEs were 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. In Study 4334, 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. [Table 36](#) includes TEAEs occurring at 5% or higher frequency in Study 4625. The most common TEAEs were injection site reactions (ISRs) in the SC LEN arms. The B/F/TAF arm, however, did not include any injectable study drug. Other frequent TEAEs in LEN arms of Studies 4625 and 4334 included nausea, headache, and diarrhea.

Table 36. Treatment-Emergent Adverse Events¹ Occurring at 5% Higher Frequency in Study 4625, Studies 4625 and 4334

Preferred Term ²	Total LEN Study 4625 N=72 n (%)	Total SC LEN Study 4334 N=105 n (%)	Total LEN Study 4334 N=157 n (%)	B/F/TAF Study 4334 N=25 n (%)
	Any TEAE	66 (91.7)	94 (89.5)	136 (86.6)
Injection site swelling	21 (29.2)	24 (22.9)	24 (15.3)	0
Injection site erythema	19 (26.4)	22 (21.0)	22 (14.0)	0
Injection site pain	18 (25.0)	22 (21.0)	22 (14.0)	0
Injection site nodule	14 (19.4)	11 (10.5)	11 (7.0)	0
Injection site induration	9 (12.5)	11 (10.5)	11 (7.0)	0

Preferred Term ²	Total LEN Study 4625 N=72 n (%)	Total SC LEN Study 4334 N=105 n (%)	Total LEN Study 4334 N=157 n (%)	B/F/TAF Study 4334 N=25 n (%)
	Diarrhea	6 (8.3)	6 (5.7)	10 (6.4)
Nausea	6 (8.3)	13 (12.4)	17 (10.8)	1 (4.0)
Cough	5 (6.9)	4 (3.8)	4 (2.5)	1 (4.0)
Headache	5 (6.9)	11 (10.5)	18 (11.5)	2 (8.0)
Pyrexia	5 (6.9)	5 (4.8)	6 (3.8)	1 (4.0)
Urinary tract infection	5 (6.9)	2 (1.9)	6 (3.8)	1 (4.0)
Oral candidiasis	4 (5.6)	3 (2.9)	4 (2.5)	0
Abdominal distention	4 (5.6)	2 (1.9)	2 (1.3)	0
Arthralgia	4 (5.6)	4 (3.8)	6 (3.8)	2 (8.0)
Back pain	4 (5.6)	5 (4.8)	9 (5.7)	2 (8.0)
Constipation	4 (5.6)	0	3 (1.9)	0
Rash	4 (5.6)	1 (1.0)	3 (1.9)	1 (4.0)

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Treatment-emergent adverse event (Study 4625) defined as an adverse event 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. Treatment-emergent events (Study 4334) 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. Duration is 54 weeks for Study 4625 and 80 weeks for Study 4334.

² Coded as MedDRA preferred terms.

Abbreviations: BIC, B, bicitegravir; BVY, bicitegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Bktarvy); DVY, emtricitabine/tenofovir alafenamide; (F/TAF; coformulated; Descovy); MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event; SC, subcutaneous; SOC, system organ class; TEAE, treatment-emergent adverse event

7.6.2. Laboratory Findings

Most laboratory abnormalities in Studies 4625 and 4334 were generally not clinically significant (Grade 1 or 2), and occurred in subjects who had previous underlying conditions such as diabetes.

In Study 4625, Grade 3 laboratory abnormalities were reported in 15 (21%) of 72 subjects. Grade 4 laboratory abnormalities were reported in four (6%) subjects. Grade 3 and 4 abnormalities that occurred in more than two subjects included high creatinine and high fasting glucose. None of the subjects had Grade 3 or higher increase in creatine kinase (CK) or CK-associated AEs such as rhabdomyolysis. Please see additional discussion in Section [7.6.3.6](#).

In Study 4334, Grade 3 laboratory abnormalities were reported in 19 (12%) of the 157 subjects who received LEN (the total LEN group) and 3 (12%) of the 25 subjects in the B/F/TAF group. Grade 4 laboratory abnormalities were reported for seven (5%) subjects in the total LEN group, including three subjects with high CK and one subject each with the following abnormalities: high alanine aminotransferase (ALT), hyperbilirubinemia, fasting triglycerides, high lipase, and nonfasting hyperglycemia. The Grade 4 high ALT was attributed by the investigator to the use of Bactrim for the treatment of *Pneumocystis jirovecii* pneumonia. The Grade 3 and 4 CK elevations were all attributed to strenuous activity, dehydration, or use of creatine, and the levels returned to normal at a later visit. Please see additional discussion in Section [7.6.4.6](#).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 37. Patients Meeting Chemistry Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Studies 4625 and 4334

Laboratory Analysis	Study 4625			Study 4334 ⁴		
	Cohort 1 FMP Only LEN + FR ² N=24 n (%)	Cohort 1 FMP Only PBO + FR ² N=12 n (%)	Total LEN Week 26 ³ N=72 n (%)	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
Sodium, low (mEq/L)						
Any Grade 1 or higher	0	0	13 (18%)	10 (10%)	14 (9%)	1 (4%)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Sodium, high (mEq/L)						
Any Grade 1 or higher	2 (8%)	0	3 (4%)	7 (7%)	10 (6%)	0
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Potassium, low (mEq/L)						
Any Grade 1 or higher	0	1 (8%)	2 (3%)	0	1 (1%)	0
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Potassium, high (mEq/L)						
Any Grade 1 or higher	0	0	3 (4%)	4 (4%)	5 (3%)	0
Grade 2	0	0	1 (1%)	0	0	0
Grade 3	0	0	0	1 (1)	2 (1)	0
Grade 4	0	0	1 (1%)	0	0	0
Bicarbonate, low (mEq/L)						
Any Grade 1 or higher	6 (25%)	2 (17%)	22 (31%)	13 (12%)	18 (12%)	2 (8%)
Grade 2	1 (4%)	1 (8%)	1 (1%)	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Creatinine, high						
Any Grade 1 or higher	2 (8%)	0	17 (23%)	13 (12%)	18 (12%)	9 (36%)
Grade 2	1 (4%)	0	6 (8%)	8 (8%)	12 (8%)	6 (24%)
Grade 3	1 (4%)	0	5 (7%)	3 (3%)	3 (2%)	1 (4%)
Grade 4	0	0	1 (1%)	0	0	0
Creatinine clearance or eGFR, low						
Any Grade 1 or higher	4 (17%)	3 (25%)	31 (43%)	64 (61%)	89 (57%)	19 (76%)
Grade 2	4 (17%)	3 (25%)	24 (33%)	59 (56%)	83 (53%)	17 (68%)
Grade 3	0	0	7 (10%)	5 (5%)	6 (4%)	2 (8%)
Grade 4	0	0	0	0	0	0
Glucose, low (fasting)						
Any Grade 1 or higher	0	0	2 (4%)	6 (6%)	7 (5%)	0
Grade 2	0	0	1 (2%)	3 (3%)	3 (2%)	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Glucose, high (fasting)						
Any Grade 1 or higher	5 (29%)	1 (13%)	17 (31%)	27 (27%)	42 (28%)	6 (29%)
Grade 2	3 (18%)	1 (13%)	8 (15%)	7 (7%)	11 (7%)	1 (5%)
Grade 3	0	0	2 (4%)	3 (2%)	3 (2%)	0
Grade 4	0	0	1 (2%)	0	0	0

Laboratory Analysis	Study 4625			Study 4334 ⁴		
	Cohort 1 FMP Only LEN + FR ² N=24 n (%)	Cohort 1 FMP Only PBO + FR ² N=12 n (%)	Total LEN Week 26 ³ N=72 n (%)	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
	Calcium, low (corrected for albumin)					
Any Grade 1 or higher	0	0	0	3 (3%)	4 (3%)	0
Grade 2	0	0	0	1 (1%)	1 (1%)	0
Grade 3	0	0	0	0	1 (1%)	0
Grade 4	0	0	0	0	0	0
Calcium, high (corrected for albumin)						
Any Grade 1 or higher	0	0	0	2 (2%)	2 (1%)	0
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Magnesium, low (mg/dL)						
Any Grade 1 or higher	0	1 (8%)	3 (4%)	5 (5%)	8 (5%)	2 (8%)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	1 (1%)	2 (1%)	0
Grade 4	0	0	0	0	0	0
Phosphate, low (mg/dL)						
Any Grade 1 or higher	0	1 (8%)	2 (3%)	6 (6%)	10 (6%)	1 (4%)
Grade 2	0	0	1 (1%)	1 (1%)	3 (2%)	1 (4%)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0

Source: Clinical Reviewer summary based on Applicant's Clinical Study Reports for Studies 4625 (Table 15.11.6.4.1.2) and 4334 (Table 15.11.6.4.1).

¹ Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017.

² Cohort 1 Functional Monotherapy Period Analysis only.

³ Cohorts 1 and 2 Week 26 analysis including maintenance.

⁴ Week 24 analysis.

Abbreviations: FMP, functional monotherapy period; FR, failing regimen; PBO, placebo; N, number of subjects; n, number of subjects with abnormality; LEN, lenacapavir; B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide (coformulated; B ktarvy®)

Table 38. Patients Meeting Liver Function Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Studies 4625 and 4334

Laboratory Analysis	Study 4625			Study 4334 ⁴		
	Cohort 1 FMP Only LEN + FR ² N=24 n (%)	Cohort 1 FMP Only PBO + FR ² N=12 n (%)	Total LEN Week 26 ³ N=72 n (%)	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
	Albumin, low (g/dL)					
Any Grade 1 or higher	0	0	2 (3%)	0	1 (1%)	0
Grade 2	0	0	1 (1%)	0	1 (1%)	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Alkaline phosphatase, high						
Any Grade 1 or higher	1 (4%)	0	6 (8%)	1 (1%)	4 (3%)	1 (4%)
Grade 2	0	0	0	0	1 (1%)	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Laboratory Analysis	Study 4625			Study 4334 ⁴		
	Cohort 1 FMP Only LEN + FR ² N=24 n (%)	Cohort 1 FMP Only PBO + FR ² N=12 n (%)	Total LEN Week 26 ³ N=72 n (%)	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
	Laboratory Analysis					
AST (SGOT), high						
Any Grade 1 or higher	0	1	5 (7%)	16 (15%)	24 (15%)	1 (4%)
Grade 2	0	0	1 (1%)	3 (3%)	3 (3%)	0
Grade 3	0	0	0	2 (2%)	4 (3%)	0
Grade 4	0	0	1 (1%)	0	0	0
ALT (SGPT), high						
Any Grade 1 or higher	0	0	8 (11%)	14 (13%)	22 (14%)	1 (4%)
Grade 2	0	0	2 (3%)	3 (3%)	7 (5%)	0
Grade 3	0	0	1 (1%)	0	1 (1%)	0
Grade 4	0	0	0	0	1 (1%)	0
Total bilirubin, high						
Any Grade 1 or higher	0	0	3 (4%)	15 (14%)	25 (16%)	4 (16%)
Grade 2	0	0	0	4 (4%)	4 (3%)	1 (4%)
Grade 3	0	0	0	0	0	1 (4%)
Grade 4	0	0	0	0	1 (1%)	0
Direct bilirubin, high						
Any Grade 1 or higher	0	0	1 (1%)	0	0	0
Grade 2	0	0	0	0	0	0
Grade 3	0	0	1 (1%)	0	0	0
Grade 4	0	0	0	0	0	0
Creatine kinase, high						
Any Grade 1 or higher	0	0	3 (4%)	13 (12%)	21 (13%)	9 (36%)
Grade 2	0	0	0	4 (4%)	7 (5%)	1 (4%)
Grade 3	0	0	0	3 (3%)	4 (3%)	0
Grade 4	0	0	0	2 (2%)	3 (2%)	0
Lipase, high (U/L)						
Any Grade 1 or higher	0	0	7 (10%)	9 (9%)	13 (8%)	0
Grade 2	0	0	3 (4%)	3 (3%)	5 (3%)	0
Grade 3	1 (4%)	0	1 (1%)	2 (2%)	2 (1%)	0
Grade 4	0	0	0	1 (1%)	1 (1%)	0

Source: Clinical Reviewer summary based on Applicant's Clinical Study Reports for Studies 4625 (Table 15.11.6.4.1.2) and 4334 (Table 15.11.6.4.1).

¹ Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.

² Cohort 1 Functional Monotherapy Period analysis only.

³ Cohorts 1 and 2 Week 26 analysis including maintenance.

⁴ Week 24 analysis.

Abbreviations: B/F/TAF, bicitgravir/emtricitabine/tenofovir alafenamide (coformulated; B ktarvy®); FMP, functional monotherapy period; FR, failing regimen; LEN, lenacapavir; N, number of subjects; n, number of subjects with abnormality; PBO, placebo

Table 39. Patients Meeting Hematology Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline, Studies 4625 and 4334

Laboratory Analysis	Study 4625			Study 4334 ⁴		
	Cohort 1 FMP Only LEN + FR ² N=24 n (%)	Cohort 1 FMP Only PBO + FR ² N=12 n (%)	Total LEN Week 26 ³ N=72 n (%)	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
	Hemoglobin, low					
Any Grade 1 or higher	1 (4%)	2 (17%)	6 (8%)	0	2 (1%)	1 (4%)
Grade 2	0	1 (8%)	1 (1%)	0	1 (1%)	0
Grade 3	0	0	1 (1%)	0	0	0
Grade 4	0	0	0	0	0	0
Platelets, decreased						
Any Grade 1 or higher	0	0	3 (4%)	1 (1%)	3 (2%)	0
Grade 2	0	0	1 (1%)	0	1 (1%)	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Absolute neutrophil count (ANC), low						
Any Grade 1 or higher	0	1 (8%)	1 (1%)	4 (4%)	10 (6)	1 (4%)
Grade 2	0	0	0	0	2 (1)	0
Grade 3	0	0	1 (1%)	2 (2%)	2 (1)	0
Grade 4	0	0	0	0	0	0
WBC, decreased						
Any Grade 1 or higher	0	1 (8%)	1 (1%)	3 (3%)	4 (3%)	1 (4%)
Grade 2	0	1 (8%)	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0

Source: Clinical Reviewer summary based on Applicant's Clinical Study Reports for Studies 4625 (Table 15.11.6.4.1.2) and 4334 (Table 15.11.6.4.1).

¹ Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 July 2017.

² Cohort 1 Functional Monotherapy Period analysis only.

³ Cohorts 1 and 2 Week 26 analysis including maintenance.

⁴ Week 24 analysis.

Abbreviations: FMP, functional monotherapy period; FR, failing regimen; PBO, placebo; N, number of subjects; n, number of subjects with abnormality; LEN, lenacapavir; B/F/TAF, bictegavir/emtricitabine/tenofovir alafenamide

Trends in vital signs and body weight in Studies 4625 and 4334 were also reviewed. 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. In Study 4625 at Week 26, the median (Q1, Q3) increase in body weight was 2.0 (−0.9, 5.5) kg. In Study 4334 by Week 28, the median increase in body weight in the Total LEN group was 2.3 (−0.2, 4.8) kg, and the increase in the B/F/TAF group was 2.7 (0, 4.8) kg.

7.6.3. Safety Findings and Concerns, Study 4625 (CAPELLA)

7.6.3.1. Overall Treatment-Emergent Adverse Event Summary

An overview of TEAEs for Study 4625 was previously discussed in Section [7.6.1.1. Table 40](#) lists the TEAEs experienced during the FMP only. One of the limitations of Study 4625 is the lack of a comparator beyond the FMP. Because the two cohorts were not randomized to different regimens during the maintenance period (and all subjects in Cohort 1 received SC LEN

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

following the FMP), comparisons across treatment arms were not expected to provide trends that demonstrate the impact of LEN on safety outcomes (Table 41).

Table 40. Overview of Treatment-Emergent Adverse Events, Functional Monotherapy Period Only, Study 4625, Cohort 1

Event	FMP LEN + FR N=24 n (%)	FMP PBO + FR N=12 n (%)
Any treatment-emergent AE ¹	9 (37.5%)	3 (25.0%)
Moderate or severe AEs (Grade 3-5) ²	0	0
SAEs	0	0
SAEs with fatal outcome	0	0
AEs leading to discontinuation of study drug	0	0
AEs leading to dosage modification of study drug	0	0
AEs leading to interruption of study drug	0	0
AEs leading to reduction of study drug	0	0
AEs leading to dosage delay of study drug	0	0

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Treatment-emergent adverse events 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.

² Coded as MedDRA preferred terms.

Abbreviations: FMP, functional monotherapy period; FR, failing regimen; LEN, lenacapavir; PBO, placebo; AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

Table 41. Overview of Treatment-Emergent Adverse Events, Maintenance Period Only, Study 4625

Event	Cohort 1 N=36 n (%)	Cohort 2 N=36 n (%)	Total LEN N=72 n (%)
Any treatment-emergent AE ¹	33 (91.7%)	33 (91.7%)	66 (91.7%)
Moderate or severe AEs (Grade 3-5) ²	5 (13.9%)	8 (22.2%)	13 (18.1%)
SAEs	2 (5.6%)	2 (5.6%)	4 (5.6%)
SAEs with fatal outcome	0	1 (2.8%)	1 (1.4%)
AEs leading to discontinuation of study drug	0	0	0
AEs leading to dosage modification of study drug	0	0	0
AEs leading to interruption of study drug	0	0	0
AEs leading to reduction of study drug	0	0	0
AEs leading to dosage delay of study drug	0	0	0

Source: CDS review; adae.xpt; software, R.

¹ Treatment-emergent adverse events defined as an AE that began on or after the first dose date of blinded study drug.

² Coded as MedDRA preferred terms.

Abbreviations: LEN, lenacapavir; AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

7.6.3.2. Deaths

One treatment-emergent adverse event resulting in death was reported in Study 4625. This event was not considered related to LEN. No additional deaths were reported with follow-up through July 27, 2021 in the Applicant's 90-Day Safety Report.

Subject (b) (6) was a 61-year-old white male in the United States. At baseline, he had a prior history of non-Hodgkin lymphoma, his HIV-1 RNA was 112,000 copies/mL, and his CD4⁺ cell count was 7/μL (0.8%). His background regimen included ibalizumab, dolutegravir, emtricitabine/tenofovir alafenamide fumarate, and fosamprenavir. On Study Day 15, his HIV-1 RNA was 1250 copies/mL but rebounded to 101,000 copies/mL on Day 50.

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On Day 38 the subject experienced serious dizziness of Grade 3. LEN dose was not changed. The event was considered not related to study drug and resolved on Day 43.

On Day 80 the subject experienced a Grade 5 SAE of “neoplasm malignant”. Due to deteriorating clinical status during hospitalization, the subject was transferred to hospice, where he subsequently died. His cause of death was updated to “metastatic cancer”, and this was a suspected recurrence of his prior non-Hodgkin’s lymphoma. He expired prior to biopsy of the new lesions, no autopsy was performed, nor was any further specific diagnosis on the type of cancer provided by the investigator.

Reviewer comment: Given the prior history and timing of the onset of symptoms, the actual start of the adverse event of “metastatic cancer” was likely prior to the time of study enrollment and was not related to LEN.

7.6.3.3. Serious Adverse Events

No SAEs were reported during the FMP of Study 4625. Serious AEs were reported for 5.6% (4 of 72 subjects); no SAEs were reported in more than one subject. No SAEs were considered related to study drug. As discussed above in Section 7.6.3.2, one SAE (Subject (b) (6)) resulted in death. See [Table 42](#).

Table 42. Serious Adverse Events, Study 4625

Subject ID	Cohort/ Treatment	Age/Sex	Preferred Term ¹	Onset	Related?
(b) (6)	1/LEN	54/Male	Proctalgia	Day 253-260	No
	1/PBO → LEN	54/Male	Pancreatic mass	Day 36-	No
			Abdominal pain	Day 77-115	No
			<i>Clostridium difficile</i> infection	Day 257-262	No
	2/LEN	61/Male	Dizziness	Day 38-43	No
			Neoplasm malignant ²	Day 80-	No
	2/LEN	34/Male	Femoral neck fracture	Day 83-	No

Source: Clinical Reviewer Summary of Applicant’s Narratives of Serious Adverse Events, Deaths, AE Leading to Discontinuation and Snapshot Failures.

¹ Coded as Medical Dictionary for Regulatory Activities preferred terms

² Fatal outcome, as described in Section 7.6.3.2.

Abbreviations: LEN, lenacapavir; AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

Treatment-emergent SAEs were reported in three additional subjects in the Applicant’s 90-Day Safety Update. In total from both cohorts of Study 4625, seven (9.7%) subjects who received LEN experienced an SAE.

- Subject (b) (6) was a 24-year-old male in Cohort 1 who had COVID-19. The event started on Day 266, resolved/recovered on Day 275, and was considered to be unrelated to the study drug.
- Subject (b) (6) was a 50-year-old male in Cohort 1 who had the SAE of pneumonia (reported term: multifocal pneumonia). The event started on Day 465, resolved/recovered on Day 467, and was considered to be unrelated to the study drug.
- Subject (b) (6) was a 51-year-old female in Cohort 2 who had a baseline CD4+ cell count of 14 cells/μL experienced the SAEs of septic shock (Days 177 to 197), and renal impairment and shock (both events, Days 221 to 236). The SAEs of renal impairment and the second event of shock were initially considered related to the study drug by the investigator. Renal function improved promptly while LEN exposure continued, and both

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SAEs resolved in 6 days. The Applicant noted that after the data cut for this NDA Safety Update, based on emerging clinical information regarding these SAEs for this subject, the investigator no longer considered them to be related to study drug.

Additional details of the subjects in the original NDA submission with nonfatal SAEs were provided:

- Subject (b) (6), who had a history of intermittent proctalgia due to prior rectal surgery for squamous cell carcinoma, experienced the unrelated SAE of proctalgia (Days 288 to 289), which was reported in the initial submission, and the additional unrelated SAEs of anal squamous cell carcinoma (Days 257 to 259) and impaired healing (reported term: nonhealing perianal wound; Days 351 to 358) since the NDA submission. In the investigator's opinion, all three SAEs were likely to be related to the subject's underlying conditions.
- In the original NDA submission, subject (b) (6) experienced the SAEs of pancreatic mass (Day 36, ongoing), abdominal pain (Days 77 to 115), and Clostridium difficile colitis (Days 240 to 242). An additional SAE of angina pectoris (Days 367 to 368) was reported and was considered unrelated to the study drug.

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events

No TEAEs were reported in Study 4625 that led to discontinuation through follow-up period ending April 01, 2021. Since the original NDA data cut date through follow-up period ending July 27, 2021, one subject prematurely discontinued study drug due to TEAEs of injection site nodules, both of which were Grade 1 and were ongoing with follow-up through June 25, 2021.

7.6.3.5. Treatment-Emergent Adverse Events

Treatment emergent adverse events reported only during the FMP in subjects of Cohort 1 are presented in [Table 43](#). Nausea was the only AE reported in more than one subject. See [Table 36](#) for a listing of listing of TEAEs from the Week 26 interim analysis of Study 4625, including the Maintenance Period.

Table 43. Treatment-Emergent Adverse Events¹ Occurring During the Functional Monotherapy Period, Study 4625, Cohort 1

Preferred Term²	FMP LEN + FR N=24 n (%)	FMP PBO + FR N=12 n (%)
Any AE	9 (37.5%)	3 (25.0%)
Nausea	3 (12.5%)	0
Diarrhea	1 (4.2%)	1 (8.3%)
Cough	1 (4.2%)	0
Headache	1 (4.2%)	0
Pyrexia	1 (4.2%)	0
Urinary tract infection	1 (4.2%)	0
Arthralgia	1 (4.2%)	0
Rash	1 (4.2%)	0
Fatigue	1 (4.2%)	0
Myalgia	1 (4.2%)	0
Abdominal pain	1 (4.2%)	0
Decreased appetite	1 (4.2%)	0
Hemoptysis	1 (4.2%)	0

Preferred Term ²	FMP LEN + FR	FMP PBO + FR
	N=24 n (%)	N=12 n (%)
Abdominal pain lower	1 (4.2%)	0
Flatulence	1 (4.2%)	0
Photophobia	1 (4.2%)	0
Rhinitis allergic	1 (4.2%)	0
Vessel puncture site hemorrhage	1 (4.2%)	0
Vomiting	0	1 (8.3%)
Neck pain	0	1 (8.3%)
Thrombocytopenia	0	1 (8.3%)
Abscess limb	0	1 (8.3%)

Source: Clinical Data Scientist review; adae.xpt; software, R.

¹ Treatment-emergent adverse event defined as 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. AEs listed without regard to investigator's assessment of relation to study drug.

² Coded as Medical Dictionary for Regulatory Activities preferred terms. Listed in descending order of frequency in the FMP LEN + FR arm.

Abbreviations: FMP, functional monotherapy period; LEN, lenacapavir; FR, failing regimen; PBO, placebo; AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event

7.6.3.6. Laboratory Findings

In both the LEN and placebo groups, 75% of subjects had a postbaseline laboratory abnormality of Grade 1 or higher during the FMP. Grade 3 laboratory abnormalities were reported for 3 subjects (12.5%) in the LEN group (increased creatinine, hyperglycemia [nonfasting], and increased lipase) and no subjects in the placebo group. No subjects experienced any Grade 4 laboratory abnormalities. See [Table 44](#).

Table 44. Subjects Meeting Laboratory Abnormality Criteria, Cumulative Worsened Grade¹ From Baseline During the Functional Monotherapy Period Only, Study 4625, Cohort 1

Subjects With Postbaseline Value	FMP LEN + FR	FMP PBO + FR
	N=24 n (%)	N=12 n (%)
Any Laboratory Grade 1 or higher	18 (75%)	9 (75%)
Grade 1	6 (25%)	4 (33%)
Grade 2	9 (38%)	5 (42%)
Grade 3	3 (13%)	0
Creatinine, high		
Grade 1	0	0
Grade 2	1 (4%)	0
Grade 3	1 (4%)	0
Hyperglycemia, nonfasting		
Grade 1	5 (36%)	0
Grade 2	1 (7%)	0
Grade 3	1 (7%)	0
Lipase, high		
Grade 1	0	0
Grade 2	0	0
Grade 3	1 (4%)	0

Source: Table 15.11.6.4.1.1 in the Applicant's Clinical Study Report for Study 4625.

¹ Severity grades were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017. For each laboratory test, the most severe graded abnormality for that test was counted for a subject.

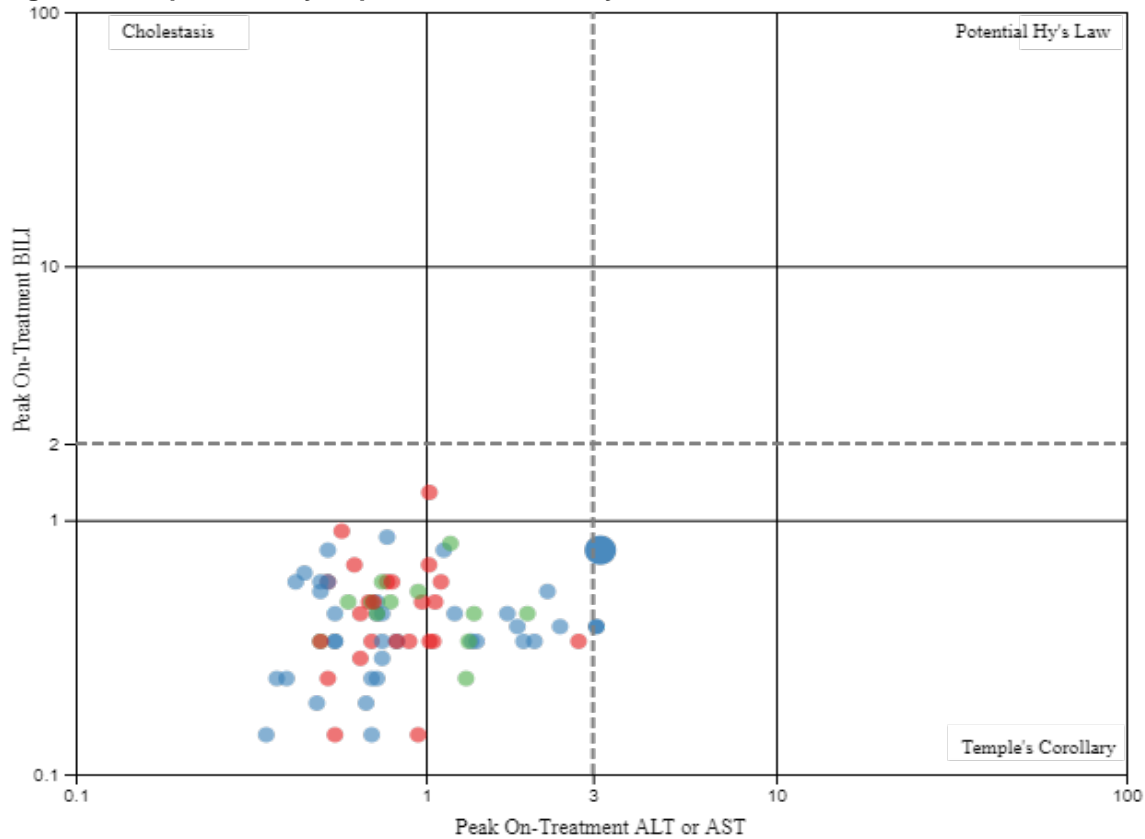
Abbreviations: FMP, functional monotherapy period; LEN, lenacapavir; FR, failing regimen; PBO, placebo; N, number of subjects in group; n, number of subjects with at least one event

In a screening analysis for drug-induced liver injury from all subjects during Study 4625, one subject ((b) (6)) in Cohort 2 (shown as a large blue dot [•] in [Figure 21](#)), who was a 51-

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year-old Asian female, experienced a Grade 3 increase in ALT and a Grade 4 increase in aspartate aminotransferase (AST). These increases were also reported as an AE of immune reconstitution inflammatory syndrome associated with an ongoing medical history of chronic hepatitis B. Laboratory trends are shown below in [Figure 22](#). Given the alternative causes reported, these increases in ALT and AST were not considered related to LEN.

Figure 21. Hepatotoxicity Exploration Plot, Study 4625



Source: Reviewer's analysis, Analysis Studio (adsl.xpt and b.xpt).

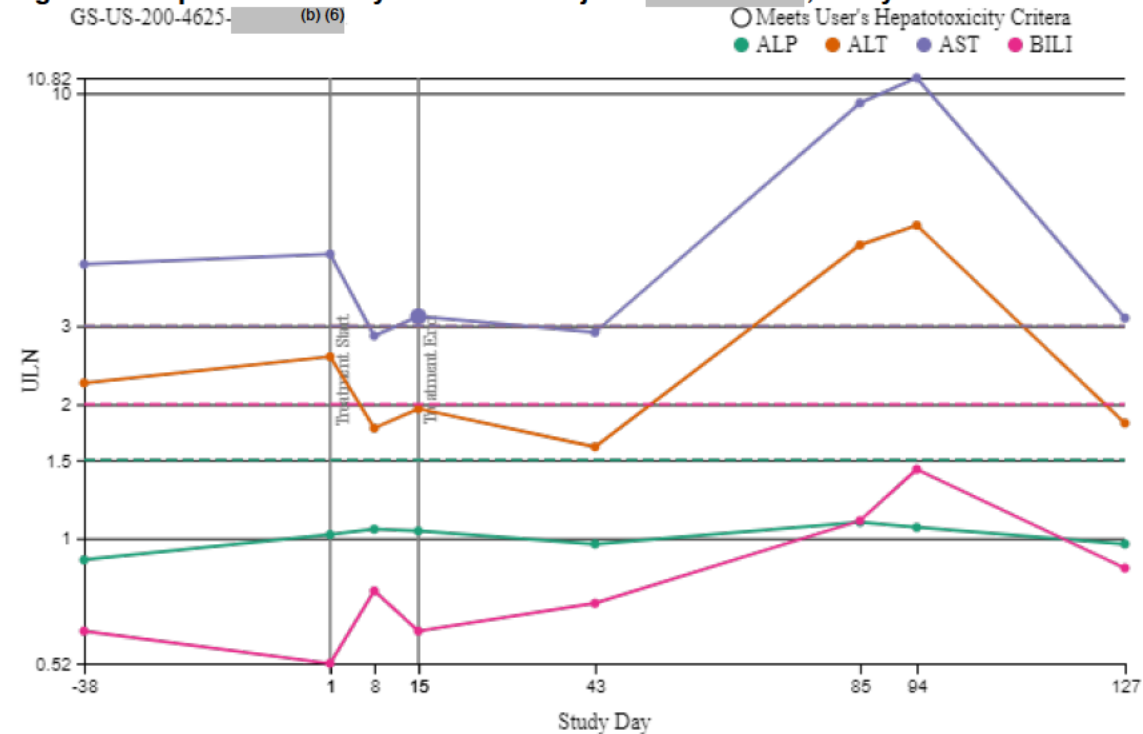
Key: ● Cohort 1 LEN; ● Cohort 1 PBO → LEN; ● Cohort 2 LEN + OBR. Vertical dashed line: ALT or AST cutoff $\geq$ ULN=3; horizontal dashed line: BILI cutoff $\geq$ ULN=2; ALP cutoff ($\geq$ ULN)=1.5.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; LEN, lenacapavir; OBR, optimized background regimen; PBO, placebo; ULN, upper limit of normal

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Figure 22. Hepatic Laboratory Values for Subject # (b) (6), Study 4625



Source: Reviewer's analysis, Analysis Studio (adsl.xpt and b.xpt).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; LEN, lenacapavir; OBR, optimized background regimen; ULN, upper limit of normal

7.6.4. Safety Findings and Concerns, Study 4334 (CALIBRATE)

7.6.4.1. Overall Adverse Event Summary

An overall summary of the TEAEs in Study 4334 through at least the Week 28 analysis date is presented in [Table 45](#). Serious AEs occurred only in the Total LEN total group, eight subjects (5%), four of which were randomized to receive SC LEN. Adverse events related to the study drug occurred at a higher frequency in the SC LEN total group than in the oral LEN or B/F/TAF groups, mainly because of ISRs.

Table 45. Overview of Treatment-Emergent Adverse Events, Study 4334

Event	Total SC LEN N=105 n (%)	Total LEN N=157 n (%)	B/F/TAF N=25 n (%)
Any treatment-emergent AE ¹	94 (90%)	136 (87%)	21 (84%)
Study-drug related TEAE ²	47 (45%)	54 (34%)	4 (16%)
Moderate or severe TEAEs (Grade 3-5) ³	5 (5%)	11 (7%)	1 (4%)
Study-drug related TEAE (Grade 3-5) ^{2,3}	1 (1%)	1 (1%)	0
Any SAE	4 (4%)	8 (5%)	0
SAEs with fatal outcome	0	0	0
Study-drug related SAE ²	0	0	0
AEs leading to discontinuation of study drug	2 (2%)	2 (1%)	0

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Event	Total SC LEN	Total LEN	B/F/TAF
	N=105 n (%)	N=157 n (%)	N=25 n (%)
AEs leading to dosage modification of study drug	0	0	0
AEs leading to interruption of study drug	0	0	0
AEs leading to reduction of study drug	0	0	0
AEs leading to dosage delay of study drug	0	0	0

Source: Clinical Data Scientist's and Reviewer's analysis (JMP Clinical 8.1) of the adae.xpt and adsl.xpt datasets.

¹ Includes treatment-emergent AE defined as an event that 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.

² Relatedness as determined by the investigator.

³ Severity grades were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 July 2017.

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

7.6.4.2. Deaths

No subjects died during Study 4334 through at least the June 25, 2021 data cut provided in the Applicant's 90-Day Safety Update.

7.6.4.3. Serious Adverse Events

Serious AEs were reported for 5% (8 of 157 subjects) in the Total LEN total group. None of the subjects in in the B/F/TAF group experienced any SAEs. A listing of SAEs are provided in [Table 46](#). None of the SAEs were considered by the investigator to be related to the study drug.

Table 46. Serious Adverse Events, Study 4334

Subject ID	Group	Age/Sex	Preferred Term	Onset	Related?
(b) (6)	Oral LEN + F/TAF	46/Male	<i>Pneumocystis jirovecii</i> pneumonia	Day 27-62	No
			Pneumothorax	Day 40-47	No
	Oral LEN + F/TAF	36/Male	Psychotic disorder	Day 43-50	No
	Oral LEN + F/TAF	34/Male	Poisoning	Day 207-211	No
	SC LEN + (F/TAF → BIC)	26/Male	<i>Escherichia</i> infection	Day 41-66	No
			Substance-induced psychotic disorder	Day 89-113	No
	SC LEN + (F/TAF → BIC)	33/Male	Perirectal abscess	Day 32-53	No
	Oral LEN + F/TAF	28/Male	Bipolar disorder	Day 67-77	No
Major depression			Day 67-77	No	
SC LEN + (F/TAF → TAF)	29/Male	Staphylococcal infection	Day 36-52	No	

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Subject ID	Group	Age/Sex	Preferred Term	Onset	Related?
(b) (6)	SC LEN + (F/TAF → TAF)	40/Male	Dyspnea	Day 216-	No
			Lymphadenopathy mediastinal	Day 216-	No
			Pneumonia	Day 216-236	No
			Vomiting	Day 216-	No
			Pleural effusion	Day 217-	No
			Non-small cell lung cancer	Day 219-	No
			Metastases to central nervous system	Day 229-	No

Source: Reviewer's analysis.

¹ Coded as MedDRA preferred terms.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; LEN, lenacapavir; F/TAF, emtricitabine/tenofovir alafenamide; BIC, bictegravir; SC, subcutaneous; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; TAF, tenofovir alafenamide.

Since the original NDA submission, one additional treatment-emergent SAE was reported in the SC LEN + (F/TAF → TAF) group (uterine leiomyoma) and none were reported in the B/F/TAF group. The SAE of uterine leiomyoma (Days 240 to 249) was considered not related to study drug.

7.6.4.4. Dropouts and/or Discontinuations Due to Adverse Events

Two of 105 subjects (2%) in the Total SC LEN group discontinued study drug prematurely due to AEs of injection site induration. Details of the two AEs (Subjects (b) (6) and (b) (6)) are provided in Section 7.7.2. There were no study drug discontinuations in the B/F/TAF arm. No new study drug discontinuations due to AEs were reported for Study 4334 in the Applicant's 90-Day Safety Update.

7.6.4.5. Treatment-Emergent Adverse Events

Excluding injection site reactions (ISRs), the most common (>5%) treatment-emergent adverse events (TEAEs) that were reported more frequently in the Total LEN group than the B/F/TAF group included headache (12%), nausea (11%), lymphadenopathy (8%), diarrhea (6%), depression (6%) and back pain (6%). The most common AEs (≥1%) that were considered by the investigator to be related to study drugs were nausea (5%), diarrhea (3%), fatigue (2%), headache (2%), weight increased (1%), and abdominal pain (1%). No AEs of Grade 3 or higher were reported for more than one subject in any treatment group. In the Total LEN group, 7% (11 of 157 subjects) had AEs of Grade 3 or higher compared to 4% (1 of 25 subjects) in the B/F/TAF group. TEAEs occurring in at least 3% of subjects in the Total LEN group are listed in Table 47.

Table 47. Treatment-Emergent Adverse Events¹ Occurring at 3% in the Total LEN Population, Study 4625

Preferred Term ²	SC LEN + (F/TAF → TAF) (N=52)	SC LEN + (F/TAF → BIC) (N=53)	Oral LEN + F/TAF (N=52)	B/F/TAF (N=25)	Total SC LEN (N=105)	Total LEN (N=157)
Number, n (%), of subjects with any TEAE	50 (96%)	44 (83%)	42 (81%)	21 (84%)	94 (90%)	136 (86.6%)
Injection site swelling	13 (25%)	11 (21%)	0	0	24 (23%)	24 (15%)
Injection site erythema	13 (25%)	9 (17%)	0	0	22 (21%)	22 (14%)
Injection site pain	13 (25%)	9 (17%)	0	0	22 (21%)	22 (14%)
Headache	6 (12%)	5 (9%)	7 (14%)	2 (8%)	11 (11%)	18 (12%)
Nausea	9 (17%)	4 (8%)	4 (8%)	1 (4%)	13 (12%)	17 (11%)
Lymphadenopathy	4 (8%)	4 (8%)	4 (8%)	1 (4%)	8 (8%)	12 (8%)
COVID-19	5 (10%)	3 (6%)	3 (6%)	1 (4%)	8 (8%)	11 (7%)

Preferred Term ²	SC LEN + (F/TAF → TAF) (N=52)	SC LEN + (F/TAF → BIC) (N=53)	Oral LEN + F/TAF (N=52)	B/F/TAF (N=25)	Total SC LEN (N=105)	Total LEN (N=157)
Injection site induration	7 (14%)	4 (8%)	0	0	11 (11%)	11 (7%)
Injection site nodule	6 (12%)	5 (9%)	0	0	11 (11%)	11 (7%)
Diarrhea	2 (4%)	4 (8%)	4 (8%)	1 (4%)	6 (6%)	10 (6%)
Depression	1 (2%)	5 (9%)	3 (6%)	0	6 (6%)	9 (6%)
Back pain	1 (2%)	4 (8%)	4 (8%)	2 (8%)	5 (5%)	9 (6%)
Syphilis	3 (6%)	3 (6%)	2 (4%)	3 (12%)	6 (6%)	8 (5%)
Arthralgia	1 (2%)	3 (6%)	2 (4%)	2 (8%)	4 (4%)	6 (4%)
Anxiety	1 (2%)	2 (4%)	3 (6%)	1 (4%)	3 (3%)	6 (4%)
Dizziness	3 (6%)	1 (2%)	2 (4%)	1 (4%)	4 (4%)	6 (4%)
Fatigue	0	4 (8%)	2 (4%)	1 (4%)	4 (4%)	6 (4%)
Hypertension	3 (6%)	2 (4%)	1 (2%)	1 (4%)	5 (5%)	6 (4%)
Pyrexia	3 (6%)	2 (4%)	1 (2%)	1 (4%)	5 (5%)	6 (4%)
Urinary tract infection	1 (2%)	1 (2%)	4 (8%)	1 (4%)	2 (2%)	6 (4%)
Nasopharyngitis	2 (4%)	2 (4%)	2 (4%)	0	4 (4%)	6 (4%)
Gonorrhea	1 (2%)	2 (4%)	2 (4%)	0	3 (3%)	5 (3%)
Proteinuria	2 (4%)	1 (2%)	2 (4%)	0	3 (3%)	5 (3%)

Source: Applicant's Table 15.11.2.1.3, Study 4334 Interim Week 28 Clinical Study Report.

¹ Treatment-emergent adverse event defined as 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. TEAEs are listed without regard to the investigator's assessment of causality and sorted in descending order of frequency in the Total LEN arm.

² Coded as MedDRA preferred terms.

Abbreviations: N, number of subjects; n, number of subjects with adverse event; MedDRA, Medical Dictionary for Regulatory Activities; LEN, lenacapavir; F/TAF, emtricitabine/tenofovir alafenamide; BIC, bictegravir; SC, subcutaneous; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; TAF, tenofovir alafenamide.

7.6.4.6. Laboratory Findings

Approximately 95% of subjects in any LEN arm (Total LEN group), and 94% of subjects receiving SC LEN, had a postbaseline laboratory abnormality of Grade 1 or higher. All 25 subjects in the comparator arm (B/F/TAF) had a graded abnormality. Please see [Table 37](#), [Table 38](#), and [Table 39](#) in Section [7.6.2](#).

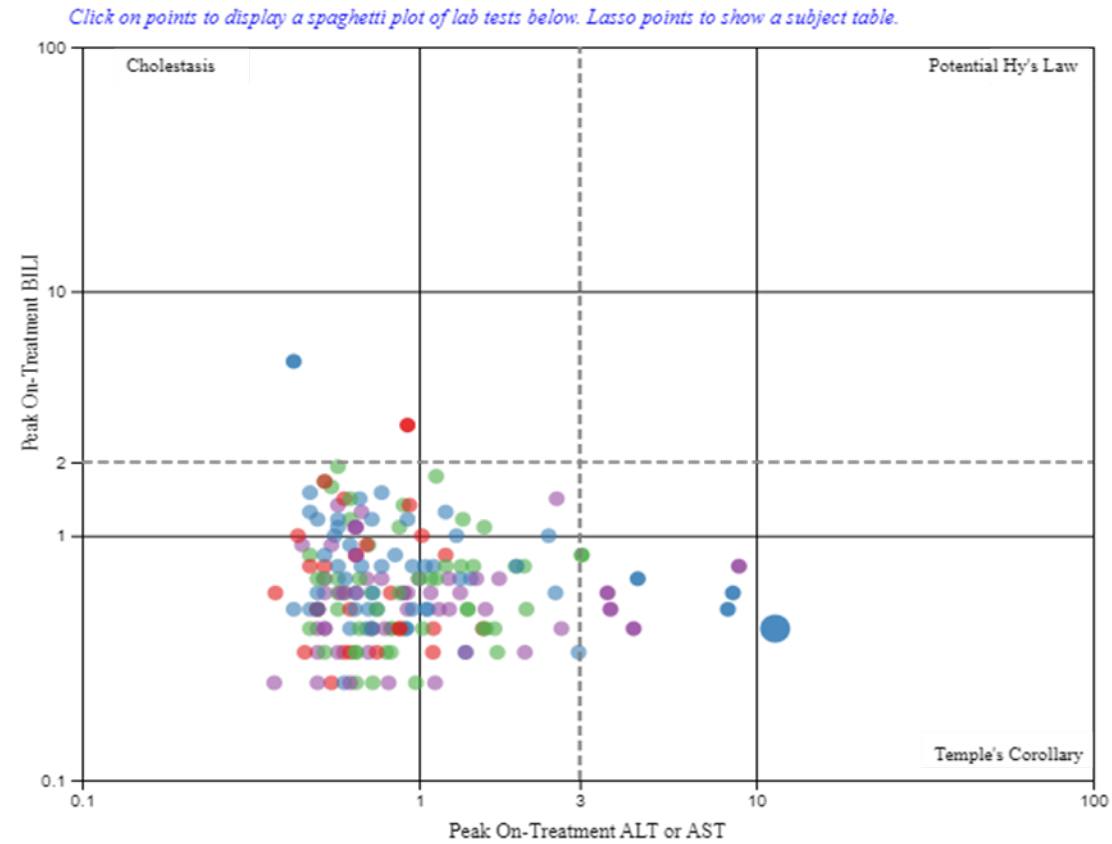
Grade 4 laboratory abnormalities were reported only in the Total LEN group (5% [7 of 157 subjects]) and included high CK (3 subjects), high ALT (1 subject), hyperbilirubinemia (1 subject), fasting triglycerides (1 subject), high lipase (1 subject), and nonfasting hyperglycemia (1 subject).

In a screening analysis for drug-induced liver injury, one subject ((b) (6)) in the Oral LEN + [F/TAF → BIC] arm, shown as a large blue dot [•] in [Figure 23](#) who was a 46-year-old male, who experienced a Grade 4 increase in ALT. These increases were attributed by the investigator to the use of Bactrim for the treatment of *Pneumocystis jirovecii* pneumonia. Laboratory trends are shown in [Figure 24](#).

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Figure 23. Hepatotoxicity Exploration Plot, Study 4334

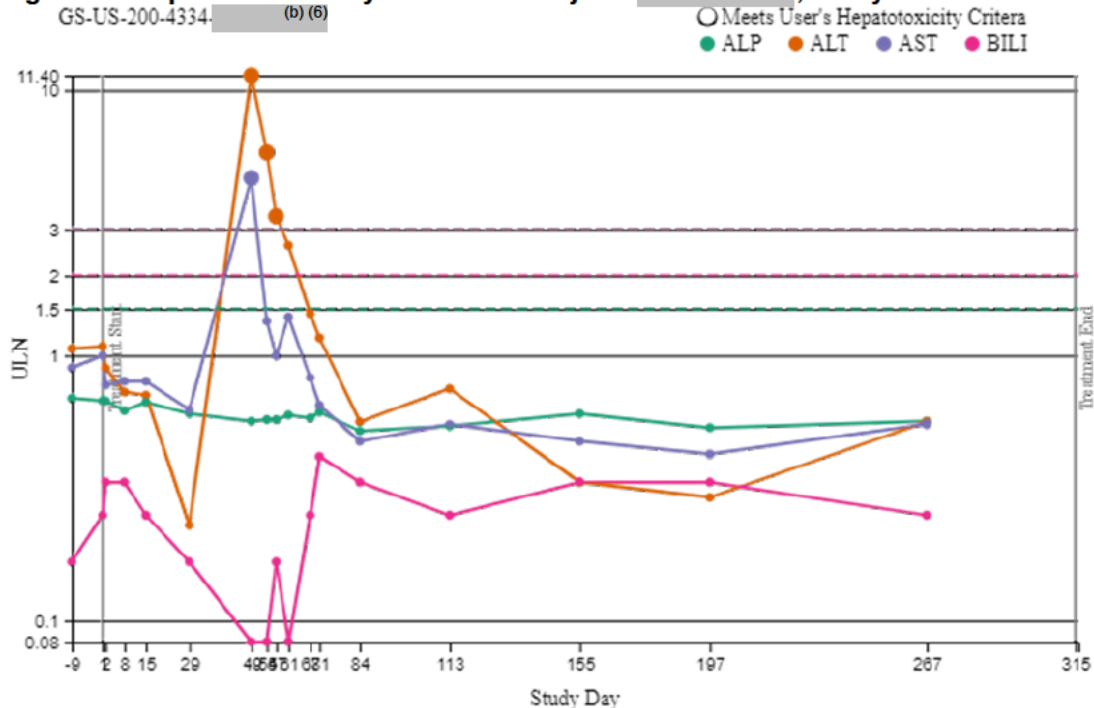


Source: Reviewer's analysis, Analysis Studio (adsl.xpt and b.xpt).

Key: ● B/F/TAF; ● SC LEN + (F/TAF → BIC); ● Oral LEN + (F/TAF → BIC); ● SC LEN + (F/TAF → TAF). Vertical dashed line: ALT or AST cutoff $\geq$ ULN=3; horizontal dashed line: BILI cutoff $\geq$ ULN=2; ALP cutoff ($\geq$ ULN)=1.5.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIC, bicitegravir; BILI, bilirubin; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide; TAF F/TAF, emtricitabine/tenofovir alafenamide; SC, subcutaneous, tenofovir alafenamide LEN, lenacapavir; ULN, upper limit of normal.

Figure 24. Hepatic Laboratory Values for Subject # (b) (6), Study 4334



Source: Reviewer's analysis, Analysis Studio (adsl.xpt and b.xpt). ALT or AST cutoff $\geq$ ULN=10. Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIC, bicitegravir; BILI, bilirubin; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide; F/TAF, emtricitabine/tenofovir alafenamide; SC, subcutaneous; TAF, tenofovir alafenamide; LEN, lenacapavir; ULN, upper limit of normal.

Grade 3 laboratory abnormalities reported for more than two subjects in either the Total LEN or B/F/TAF groups were low creatinine clearance or eGFR (six subjects in the Total LEN group, two subjects in the B/F/TAF arm), high AST (four subjects in the Total LEN group), glycosuria (four subjects in the Total LEN 4 group), high creatine kinase (four subjects in the Total LEN 4 group), high creatinine (three subjects in the Total LEN group, one subject in the B/F/TAF arm), and fasting hyperglycemia (three subjects in the Total LEN group).

There were no clinically relevant changes from baseline for fasting glucose or the fasting lipid parameters of total cholesterol, high-density lipoprotein, and triglycerides by Week 28 in any treatment group.

7.6.5. Safety Findings and Concerns, Pooled Phase 1 Studies

7.6.5.1. Overall Adverse Event Summary

An overview of TEAEs for the pooled phase 1 studies, 4538 and 5709, are provided in [Table 48](#). The majority of AEs were Grade 1 in severity. One subject in the LEN group had an AE of Grade 3 or higher in each of the LEN and placebo groups.

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Table 48. Overview of Treatment-Emergent Adverse Events, Pooled Phase 1 Studies

Event	LEN N=55 n (%)	Placebo N=20 n (%)
Any treatment-emergent AE ¹	51 (93%)	17 (85%)
Any moderate or severe AEs (Grade 3-5) ²	1 (2%)	1 (5%)
Any AE related to study drug	46 (84%)	14 (70%)
SAEs	1 (5%)	1 (5%)
SAEs with fatal outcome	0	0
SAEs related to study drug	0	0
AEs leading to discontinuation of study drug	1 (2%)	0

Source: Applicant's LEN Integrated Summary of Safety, Table 4.

¹ Includes treatment-emergent AEs, defined as events that began on or after the study drug start date, or led to premature study drug discontinuation.

² 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).

Abbreviations: AE, adverse event; LEN, lenacapavir; N, number of subjects in group; n, number of subjects with at least one event SAE, serious adverse event

7.6.5.2. Deaths

There were no subjects in the pooled phase 1 studies that experienced any AE leading to death.

7.6.5.3. Serious Adverse Events

In the pooled analysis, SAEs were reported for one subject (1.8%) in the LEN group (tibia fracture) and one subject (5.0%) in the placebo group (sepsis). Neither of the SAEs were considered related to study drug or led to discontinuation of study drug.

7.6.5.4. Dropouts and/or Discontinuations Due to Adverse Events

For Study 5709, one subject prematurely discontinued study and study drug due to a Grade 1 AE of severe acute respiratory syndrome coronavirus 2. The AE was considered not serious and not related to study drug. No new study drug discontinuations due to AEs were reported in Study 5709 with the 90-Day Safety Update.

7.6.5.5. Treatment-Emergent Adverse Events

In the pooled phase 1 analysis, the four most commonly reported AEs in each treatment group were all ISRs. A listing of TEAEs (reported in >5% of subjects overall) are provided in [Table 49](#).

Table 49. Treatment-Emergent Adverse Events¹ Occurring at 5% in Either Treatment Group, Pooled Phase 1 Studies

Preferred Term²	LEN N=55 n (%)	Placebo N=20 n (%)
Number (%) of subjects with any treatment-emergent AE	51 (93%)	17 (85%)
Injection site induration	40 (73%)	6 (30%)
Injection site pain	31 (56%)	5 (25%)
Injection site erythema	26 (47%)	0
Injection site swelling	13 (24%)	2 (10%)
Headache	11 (20%)	5 (25%)
Injection site nodule	10 (18%)	0
Injection site bruising	7 (13%)	8 (40%)
SARS-CoV-2 test positive	5 (9%)	0
Back pain	3 (6%)	0

	LEN N=55 n (%)	Placebo N=20 n (%)
Preferred Term²		
Hypersensitivity ³	3 (6%)	1 (5%)
Injection site pruritus	3 (6%)	0
Oropharyngeal pain	3 (6%)	1 (5%)
Upper respiratory tract infection	3 (6%)	3 (15%)

Source: Applicant's LEN Integrated Summary of Safety, Table 5.2.

¹ Treatment-emergent adverse event defined as beginning on or after the study drug start date, or led to premature study drug discontinuation. Multiple AEs counted only once per subject for each PT.

² Coded as MedDRA preferred terms.

³ Reported term of environmental allergy.

Abbreviations: AE, adverse event; LEN, lenacapavir; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with adverse event; PT, preferred term; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

7.6.5.6. Laboratory Findings

A summary of laboratory abnormalities worsening to Grade 3 or above from baseline were reported for eight subjects (15%) in the LEN group and four subjects (20%) in the placebo group. Increased creatine phosphokinase of Grade 3 or above occurred in one subject (1.8%) in the LEN group and three subjects (15.0%) in the placebo group. Grade 4 laboratory abnormalities were reported for 2 of 55 subjects (3.6%) who received LEN.

Table 50. Subjects Meeting Laboratory Abnormality Criteria, Worsened to Grade¹ of 3 or Above From Baseline, Pooled Phase 1 Trials

	LEN N=55 n (%)	Placebo N=20 n (%)
Subjects With Postbaseline Value		
Any laboratory Grade 1 or higher	N=55	N=20
Grade 3	8 (15%)	4 (20%)
Grade 4	2 (4%)	1 (5%)
Triglycerides (fasting, increased)	N=55	N=20
Grade 3	3 (6%)	0
Grade 4	2 (4%)	0
LDL (fasting, increased)	N=55	N=20
Grade 3	3 (6%)	1 (5%)
Grade 4	0	0
CPK (increased)	N=55	N=20
Grade 3	1 (2%)	2 (10%)
Grade 4	0	1 (5%)
Serum glucose (fasting, hypoglycemia)	N=55	N=20
Grade 3	1 (2%)	0
Grade 4	0	0
Hemoglobin (decreased)	N=55	N=20
Grade 3	1 (2%)	0
Grade 4	0	0
Creatinine clearance (decreased)	N=55	N=20
Grade 3	0	1 (5%)
Grade 4	0	0
AST (increased)	N=55	N=20
Grade 3	0	1 (5%)
Grade 4	0	0

Subjects With Postbaseline Value	LEN N=55 n (%)	Placebo N=20 n (%)
Lipase (increased)	N=31	N=1
Grade 3	0	0
Grade 4	0	1 (100%)

Source: Applicant's Integrated Summary of Safety, Table 18.

¹ Severity grades were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).

Abbreviations: N, number of subjects; n, number of subjects with abnormality; AST, aspartate aminotransferase; CPK, creatine phosphokinase; LDL, low-density lipoprotein; LEN, lenacapavir

Although not part of the Applicant's Integrated Summary of Safety (ISS) analysis for Studies 4538 and 5709, in Cohort 3 of Study GS-US-200-4329 (Study 4329; a phase 1 study evaluating the safety, tolerability, PK, metabolism, and excretion of LEN following a single IV dose in healthy subjects), one subject 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 serum creatine phosphokinase level elevated to a peak of 380,000 U/L (normal range 0 to 250 U/L), which was accompanied by increased lactate dehydrogenase (585 U/L), but the subject remained asymptomatic. There were no reports of recent strenuous exercise, trauma, illicit substance use, or prior creatine phosphokinase elevations. The time of onset of the rhabdomyolysis (Day 22) for this subject 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, creatine phosphokinase levels for this subject continued to decrease in the presence of ongoing LEN exposure.

Clinical reviewer's comment: Given the lack of presenting symptoms, delayed time of onset, and resolution despite continued LEN exposure, this presentation would be unusual for drug-induced rhabdomyolysis.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Resistance Assessments of Virologic Failures

Issue

The assessment of resistance emergence in virologic failures of an LEN-containing ARV regimen is critical to interpreting the overall risk-benefit of LEN and understanding the durability of LEN as a component of an ARV regimen in an HTE patient population.

Background

Genotypic and phenotypic analyses of the HIV-1 protease, reverse transcriptase (RT), integrase, and capsid (CA) proteins were performed at screening for all subjects enrolled in Study 4625.

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Resistance testing at postscreening timepoints was performed for any subject meeting the criteria of the resistance analysis, which included any subject who received at least one dose of study drug and met one of the following virologic failure (VF) criteria:

- HIV-1 RNA ≥ 50 copies/mL and $< 1 \log_{10}$ HIV-1 RNA reduction from the start of oral LEN at the Week 4 visit, confirmed at a scheduled or unscheduled visit at least 2 weeks following Week 4.
- 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.
- Any study subject with HIV-1 RNA ≥ 50 copies/mL at the study endpoint or study discontinuation who did not meet any of the criteria above.

Monogram Biosciences, Inc. (South San Francisco, CA, USA) was the designated reference laboratory for all resistance analyses at screening and virologic failure. The PhenoSense GT[®] assay (Monogram Biosciences), which determines the genotype for the entire HIV-1 protease and amino acids 1 to 305 of RT and measures the drug susceptibility of all marketed protease and RT inhibitors based on that sequence, was performed for all subjects at screening. The GeneSeq Integrase assay was used to determine the sequence of the entire IN protein, and the PhenoSense Integrase assay measured the drug susceptibility of all marketed INSTIs based on that sequence (Monogram Biosciences). In cases of assay failure, alternative assays such as GeneSeq, GenoSure mg, or GenoSure Integrase (Monogram Biosciences) were used to obtain genotypic information.

HIV-1 CA genotype was determined using the GenoSure Gag-Pro assay, which uses next-generation sequencing (NGS) to detect codon variants present at $> 10\%$ frequency (Monogram Biosciences). The PhenoSense Gag-Pro assay (Monogram Biosciences) was used to assess phenotypic response to LEN.

The phenotypic susceptibility of screening samples from enrolled subjects to entry inhibitors (enfuvirtide, fostemsavir, ibalizumab, maraviroc) was analyzed at the end of the enrollment period. These analyses were conducted using a combination of the Trofile and PhenoSense Entry assays (Monogram Biosciences), which determine the co-receptor tropism and the susceptibility to the inhibitors, respectively, based on the HIV-1 envelope from the subject's sample.

Assessment

Key Capsid Resistance-Associated Substitutions Selected in Cell Culture

LEN-resistant viruses were selected with increasing concentrations of LEN in MT-2 cells following 19 to 103 days in cell culture passage (see Section [III.18](#)).

- At low concentrations, LEN selected for N74D, which conferred 16-fold decreased susceptibility to LEN.
- At higher drug concentrations, LEN selected for Q67H+N74D, which conferred > 2757 -fold decreased susceptibility to LEN.

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- For the LEN selected resistance substitutions, there was no change in susceptibility to any of the tested inhibitors from other antiretroviral classes (atazanavir [PI], dolutegravir [INSTI], efavirenz [NNRTI], and elvitegravir [INSTI]).

LEN-resistant viruses were selected at fixed LEN concentrations in PBMCs over 35 days (See Section III.18).

- Within the projected human plasma exposure range, breakthrough viruses exhibited 5.5- to >200-fold decreases in LEN susceptibility and encoded substitutions N74D (16-fold), L56I (204-fold), Q67H (5-fold), Q67H + N74S (20-fold), or T107N (87-fold).
- At higher concentrations, the treatment-emergent viruses encoded substitutions M66I (>2757-fold), L56I (204-fold), K70N (assay failure), or M66I+Q67H (1594-fold).

Variants containing single or double substitutions conferred reduced susceptibility to LEN (3.8- to >2757-fold) with highest reductions seen with L56I (204-fold), M66I (>2757-fold), M66I + Q67H (1594-fold), Q67H+N74D (>2757-fold), and Q67H+T107N (87-fold) (Table 51 and Section III.18). These mutant viruses were fully susceptible to PIs atazanavir (fold-change range: 0.9- to 1.5) and darunavir (fold-change range: 0.9- to 1.7), indicating the absence of cross-resistance to PIs for these LEN-resistant mutants.

Table 51. Drug Susceptibilities of LEN-Resistance-Associated Substitutions in the PhenoSense Gag-Pro Assay

HIV-1 Capsid Genotype	Replication Capacity (% of WT)	EC ₅₀ Fold-Change Relative to WT Control		
		LEN	ATV	DRV
L56I	3.6%	204	1.5	1.6
M66I	1.5%	>2757	0.9	1.3
Q67H	58%	4.8	1.2	0.9
Q67Y	10%	24	1.4	1.2
K70N	1.2%	AF	AF	AF
N74D	AF	16	0.9	1.1
A105E	32%	4.0	1.1	1.7
T107N	32%	3.8	1.2	1.5
M66I+Q67H	AF	1594	1.2	1.2
Q67H+N74D	AF	>2757	1.0	1.1
Q67H+N74S	15%	20	1.1	1.5
Q67H+T107N	AF	87	1.2	1.2
Median EC₅₀ Fold-Change		24	1.2	1.2

AF = assay failure; ATV = atazanavir; CA = capsid; DRV = darunavir; LEN = lenacapavir; WT = wild-type

Source: Report PC-200-2046, page 7.

Abbreviations: EC₅₀, 50% effective concentration; HIV, human immunodeficiency virus

Screening Resistance in Study 4625

The target population for Study 4625 was HTE HIV-1 subjects with resistance to at least two ARV medications from each of at least three of the four main classes of ARV medications (INSTI, NNRTI, NRTI, PI). In the presence of the RT substitution M184V/I, resistance to lamivudine and emtricitabine did not count towards the total number of drugs with resistance for the NRTI drug class per protocol requirements. Resistance reports were obtained prior to enrollment to confirm that the resistance criteria for enrollment in the study were met. These reports were either generated from the screening visit (Monogram genotypic and phenotypic assays, n=45 of 72) or from historical reports supplied by the investigators (various assays, n=27 of 72). For a subset of subjects, both historical reports and screening reports were used to evaluate the baseline resistance (n=15).

Based on the phenotypic resistance data provided, 78% (28/36) of subjects in Cohort 1 (79% in 1A and 75% in 1B) had greater than three-class resistance (Table 52) with 51% (18/35) showing resistance to the INSTI DTG and 50% (16/32) showing resistance to the PI DRV. Additionally, 84% (27/32) of the subjects in Cohort 1 had C-X-C motif chemokine receptor (CXCR)-4 tropism impacting maraviroc efficacy. Fewer subjects showed resistance to the gp120-directed attachment inhibitor fostemsavir, the CD4⁺-directed post-attachment inhibitor ibalizumab, or the fusion inhibitor enfuvirtide (Table 52).

The presence of resistance substitutions to the four main ARV drug classes was consistent with the high level of resistance observed from phenotypic data. No subject harbored lenacapavir-associated resistance substitutions at study entry.

Table 52. Number of Subjects With Class Phenotypic Resistance at Screening

Class Resistance	LEN Cohort 1A N=24	Placebo Cohort 1B N=12	Nonrandomized Cohort 2
NRTI	20 (83%)	12 (100%)	
NNRTI	21 (88%)	11 (92%)	
PI	17 (71%)	7 (58%)	
INSTI	16 (67%)	5 (42%)	
Three or more class resistant ^a	19 (79%)	9 (75%)	
ENF resistant	2/23 (9%)	3/10 (30%)	0/25 (0%)
IBL resistant	8/23 (35%)	3/10 (30%)	6/25 (24%)
FTR resistant	5/23 (22%)	5/10 (50%)	7/21 (33%)
MVC resistant	19/24 (79%)	8/11 (73%)	14/26 (54%)
DTG resistant	12 (50%)	6/11 (55%)	14/35 (40%)
DRV resistant	14 (58%)	6 (50%)	15/35 (43%)

Source: FDA Analysis

^a Subjects without three-class resistance: (b) (6) (LEN+FR), (b) (6) (LEN+FR), (b) (6) (LEN+FR), (b) (6) (LEN+FR), (b) (6) (LEN+FR), (b) (6) (LEN+FR), (b) (6) (Placebo+FR), (b) (6) (Placebo+FR), (b) (6) (Placebo+FR).

Abbreviations: DRV, darunavir; DTG, dolutegravir; ENF, enfuvirtide; FTR, fostemsavir; IBL, ibalizumab; INSTI, integrase inhibitor; LEN, lenacapavir; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Clinical Resistance Emergence in Virologic Failures of Study 4625

In Cohort 1A, where subjects received LEN + failing regimen for 14 days, 88% (21/24) met the primary endpoint of achieving a reduction in HIV-1 RNA of ≥ 0.5 log₁₀ copies/mL from baseline at the end of the functional monotherapy period (14 days) and of these 21, 3 (14%) were virologic failures at Week 26 (Table 53). The three subjects who did not meet the primary endpoint were also virologic failures at Week 26. In Cohort 1B, where subjects received placebo

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+ failing regimen for 14 days, 17% (2/12) met the primary endpoint and one of these subjects was a virologic failure at Week 26. Of the 10 subjects in the placebo arm who did not meet the primary endpoint, 4 (40%) were virologic failures at Week 26.

Table 53. Clinical Virology Efficacy Overview

Category	LEN + Failing Regimen n=24	Placebo + Failing Regimen n=12
Met primary efficacy endpoint	21/24 (88%)	2/12 (17%)
Virologic failure	3/21 (14%)	1/2 (50%)
Did not meet primary efficacy endpoint	3 (12%)	10/12 (83%)
Virologic failure	3/3 (100%)	4/10 (40%)
Total virologic failures through Week 26	6/24 (25%)	5/12 (42%)

Source: FDA Analysis

Primary endpoint: $\geq 0.5 \log_{10}$ copies/mL from baseline at the end of the functional monotherapy period (14 days).

Abbreviation: LEN, lenacapavir

The total number of virologic failures through Week 26 was 11 (6 in the LEN + failing regimen group and 5 in the placebo + failing regimen group) (Table 54 and Table 55). Seven virologic failures had >50 copies/mL and $<1 \log_{10}$ reduction from start of oral LEN at Week 4, three virologic failures had >50 copies/mL at Week 26, and one had virologic rebound at Week 10.

Of the 11 virologic failures, 3 did not have postbaseline resistance data and 4 had no genotypic or phenotypic evidence of LEN resistance emergence. The other four VFs (one from the LEN functional monotherapy arm [Subject (b) (6)] and three from the placebo functional monotherapy arm [Subjects (b) (6)]) had evidence of genotypic LEN resistance emergence in capsid (Table 54). All four virologic failure isolates had emergent capsid substitution M66I, which was selected by LEN in cell culture selection experiments and conferred >2757 -fold reductions in LEN susceptibility. Other capsid substitutions that emerged with M66I included K70N/R/S, N74D, A78S, A105T and conferred 46- to >1428 -fold reduced susceptibility in the three isolates that had postbaseline phenotypic data (Table 54). We note that S41T in combination with other polymorphisms (S41T+Q50A/S+T107S, S41T+T54M, S41T+H87Q) was associated with virologic failure and emergence of CA resistance substitutions (Subjects (b) (6)) (Table 55) (see Section III.19).

Table 54. Summary of Virologic Failures

Parameter	LEN Functional Monotherapy Cohort 1A n=24	Placebo Functional Monotherapy Cohort 1B n=12
Total virologic failures	6 (25%)	5 (42%)
Virologic failures at week 4	4/24 (17%)	3/12 (25%)
No postbaseline resistance data	3	0
Virologic failure >400 copies/mL	1	4
No LEN resistance emergence	2	2
LEN genotypic resistance emergence	1	3
Emergent CA M66I	1	3
LEN phenotypic resistance emergence (range 12- to 1428-fold)	-	3
Emergent OBR resistance	0/2 (only data from 2 subjects)	0/5
No active drugs in OBR	1	2

Source: FDA Analysis

Abbreviations: LEN, lenacapavir, OBR, optimized background regimen

Table 55. Resistance Emergence in Virologic Failures, Study 4625, Cohort 1A and 1B

PID	ARM	OBT	Timepoint	HIV VL	Emergent Capsid RAS	Phenotypic Resistance
(b) (6)	LEN	DTG DRV/r TDF	WK4	25,200 Suppressed at WK26	S41T T54M M66M/I K70K/N/R/S V191V/I R229R/K	LEN BL 0.91 LEN AF
	Placebo	DTG DRV/C LAM ENF MVC	WK10	5440 Suppressed at WK26	S41A/T H87Q M66I N74D A105T (WK22: Q67Q/H)	DTG >196 DRV 474 LAM >65 ENF-R MVC-R LEN >1428
	Placebo	DTG DRV FTC TAF IBL	WK4	2150	S41T Q50A T107S M66M/I (WK26: A105A/T)	DTG 137 DRV 215 FTC >68 TAF 1.1 IBL-R LEN 46
	Placebo	DTG DRV/C RPV	WK26	561	M66I A78S	DTG >0.51 DRV 0.77 RPV 2.2 LEN 138

Source: FDA Analysis

Bolded: Resistance-associated substitutions, resistant phenotype

All subjects had subtype B except Subject (b) (6), who had subtype AE.

Abbreviations: AF, assay failure; BL, baseline; DRV, darunavir; DRV/C, darunavir; DTG, dolutegravir; ENF, enfurvitide; FTC, emtricitabine; HIV, human immunodeficiency virus; IBL, ibalizumab; MVC, maraviroc; OBT, optimized background treatment; RAS, resistance-associated substitution; RPV, rilpivirine; TAF, tenofovir alafenamide; VL, viral load; WK, week

Next-Generation Sequencing Analysis

An independent assessment was performed by Dr. Eric Donaldson, clinical virology reviewer, using the next-generation sequencing data derived from subjects in clinical Study 4625 who were determined to be treatment failures (Section III.19). The independent analysis compared the capsid gene changes from baseline and postbaseline samples for each virologic failure subject (Table 55). This independent assessment confirmed the emergent substitutions shown in Table 55. Based on the next-generation sequencing analysis, the A78S substitution appears to be polymorphic, because it is present at baseline and later timepoints in several subjects.

Resistance to Drugs in Optimized Background Regimen

Of the subjects who had postbaseline OBR resistance data (two in the LEN arm and five in the placebo arm), none had evidence of resistance emergence to the drugs in the OBR (Table 56). However, three virologic failure subjects (one in the LEN arm [Subject (b) (6)] and two in placebo arm [Subjects (b) (6)]) had no active drugs in their OBR based on baseline and postbaseline genotypic and phenotypic data. We note that two of these subjects (Subjects (b) (6)) also had emergent LEN resistance.

Most of the virologic failures had BIC or DTG (82%; 9/11) or DRV (63%; 7/11) as a component of their OBR with 45% (5/11) using DRV plus BIC or DTG (Table 56). In addition, ibalizumab and maraviroc were each used in two different virologic failures and one virologic failure had both ibalizumab and maraviroc in their OBR. Three of the virologic failures had resistance to

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BIC, DTG and/or DRV with no active drugs in their OBR. However, the other eight had susceptibility to their OBR containing BIC, DTG, or DRV. Of note, five of these eight virologic failures with susceptible OBR drugs had HIV-1 RNA <400 copies/mL at Week 4 (n=4) or Week 26 (n=1). Of the other three virologic failures with active OBR who had HIV-1 RNA >400 copies/mL at Week 4 (n=2) or Week 26 (n=1), two had emergent LEN resistance.

Table 56. ARVs Used in Optimized Background Regimens of Virologic Failures

ARV	LEN Cohort 1A	Placebo Cohort 1B	Total Cohort 1
	N=6	N=5	N=11
Dolutegravir (DTG)	1	4	5 (45%)
Bictegravir (BIC)	4	0	4 (36%)
DTG or BIC	5	4	9 (82%)
Darunavir (DRV)	3	4	7 (63%)
DRV + DTG or BIC	2	3	5 (45%)
Enfuvirtide	0	1	1 (9%)
Fostemsavir	0	0	0 (0%)
Ibalizumab	1	2	3 (33%)
Maraviroc	1	2	3 (33%)

Source: FDA Analysis

Abbreviation: LEN, lenacapavir

Effect of Optimized Background Regimen on Efficacy

Given that OBR was added with LEN at the end of the FMP, the ARVs in the OBR were critical to the durability of the LEN-containing regimen. As shown in [Table 57](#), the INSTIs BIC and DTG were used in the OBR of 69% (25/36) of the subjects and the PI DRV was used in the OBR of 58% (21/36) of the subjects with 36% (13/36) of the subjects having both DRV plus BIC or DTG as components of their OBR. Only 8% (3/36) of subjects in Cohort 1 did not have DTG, BIC, or DRV as a component of their OBR. Additionally, 28% (10/36) were taking IBL, 8% (3/36) were taking FTR, and 3% (3/36) were taking ENF, as a component of their OBR.

The effect of these anchor drugs as components of the OBR on efficacy at Week 26 was assessed. Sixty-four percent (16/25) of subjects with DTG or BIC, 67% (14/21) of subjects with DRV, and 62% (8/13) of subjects with DRV+DTG or BIC in the OBR had HIV-1 RNA <50 copies/mL at Week 26 ([Table 57](#)). Only three subjects did not have BIC, DTG or DRV as components in their OBR and all three had <50 copies/mL at Week 26. One of these subjects (Subject ^{(b) (6)}) had a baseline viral load of only 274 copies/mL, which indicates they were not failing on their background regimen. The other two subjects were resistant to BIC, DTG and ibalizumab, but one was taking fostemsavir (Subject ^{(b) (6)}) and the other was taking maraviroc (Subject ^{(b) (6)}). Longer term data from all subjects after Week 26 is required to determine the durability of LEN as a component of a regimen with other ARVs.

Table 57. ARVs Used in Optimized Background Regimens and Effect on Efficacy Rates

ARV	LEN Cohort 1A N=24	Placebo Cohort 1B N=12	Percentage with Drug in OBT in Cohort 1	Virologic Failure Rate Cohort 1	Efficacy Rate <50 c/mL at Week 26
DTG	10 (42%)	8 (67%)	50% (18/36)	5/18 (28%)	13/18 (72%)
BIC	6 (25%)	1 (8%)	19% (7/36)	4/7 (57%)	3/7 (43%)
DTG or BIC	16 (67%)	9 (75%)	69% (25/36)	9/25 (36%)	16/25 (64%)
DRV	12 (50%)	9 (75%)	58% (21/36)	7/21 (33%)	14/21 (67%)
DRV+DTG/BIC	7 (29%)	6 (50%)	36% (13/36)	5/13 (38%)	8/13 (62%)
Without DTG, BIC, or DRV			8% (3/36)	0/3	3/3*
ENF	1 (4%)	2 (17%)	8% (3/36)	na	na
FTR	3 (13%)	0	8% (3/36)	na	na
IBL	7 (29%)	3 (25%)	28% (10/36)	na	na

Source: FDA Analysis

* (b) (6) (BIC-R, IBL-R, On FTR); (b) (6) (BL VL=274 c/mL); (b) (6) (DTG-R, IBL-R, on MVC and IBL).

Abbreviations: BIC, bicitegravir; c/mL, copies per milliliter; DRV, darunavir; DTG, dolutegravir; ENF, enfurvitide; FTR, fostemsavir; IBL, balizumab; LEN, lenacapavir; na, not assessed

Cross-Resistance

Lenacapavir demonstrated antiviral activity in cell culture against a broad spectrum of HIV-1 site-directed mutants and patient-derived HIV-1 isolates with resistance to the four main classes of antiretroviral agents (INSTIs, NNRTIs, NRTIs, and PIs; n=58), and to viruses resistant to fostemsavir (gp120-directed attachment inhibitor), ibalizumab (CD4-directed postattachment inhibitor), maraviroc (C-C chemokine receptor [CCR5] coreceptor inhibitor), and enfuvirtide (gp41 fusion inhibitor) (n=42) (Section III.18). In addition, the antiviral activity of LEN in patient isolates was unaffected by the presence of naturally occurring Gag polymorphisms at gag cleavage sites with or without PI resistance.

PIs (atazanavir, darunavir, nelfinavir, and saquinavir) showed wildtype antiviral activity against LEN site-directed mutants with capsid substitutions Q67H or Y, Q67H+N74D, Q67H+N74S, and Q67H+T107N, N74D, and T107N indicating a lack of cross-resistance with PIs.

Conclusion

HIV-1 variants with reduced susceptibility to lenacapavir have been selected in cell culture. Resistance selections with lenacapavir identified seven substitutions in capsid: L56I, M66I, Q67H, K70N, N74D/S, and T107N singly or in dual combination. Phenotypic susceptibility to lenacapavir was reduced 4- to >3,226-fold, relative to wild-type virus.

In the randomized Cohort 1 of CAPELLA, 31% (11/36; six in LEN Cohort 1A and five in placebo Cohort 1B) of heavily treatment-experienced subjects were virologic failures at Week 26 (confirmed HIV-1 RNA $\geq$ 50 copies/mL). Lenacapavir resistance-associated capsid substitutions were found in 36% (n=4) of the 11 virologic failure subjects with the M66I CA substitution emerging in all 4 virologic failures, alone or in combination with other lenacapavir resistance-associated capsid substitutions including Q67Q/H, K70K/N/R/S, N74D, and A105T. These treatment-emergent capsid resistance substitutions were confirmed by FDA independent analyses. The virologic failure isolates with emergent capsid resistance-associated substitutions had reduced lenacapavir susceptibility ranging from 46- to >1428-fold. There were no treatment-emergent resistance substitutions to components of the optimized background regimen in the

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virologic failures, but based on genotypic and phenotypic data, three virologic failures had no active drugs in their OBR.

- LEN resistance emerges readily in virologic failures and thus it is important to use LEN as a component of a complete active ARV regimen.
- LEN resistance substitutions do not confer cross-resistance to other ARVs.
- Longer term data from all subjects after Week 26 is required to determine durability of LEN and the other ARVs in the OBR.

7.7.2. Injection Site Reactions

Issue

Injection site reactions were identified as the most common adverse drug reaction among subjects who received subcutaneous injections of lenacapavir; however, long-term experience of subjects after multiple injections was limited in Studies 4625 and 4334.

Background

Other prior experience with long-acting subcutaneously injectable antiretrovirals that have a similar dosing regimen includes Cabenuva (cabotegravir and rilpivirine). Injection site reactions were the most common adverse reactions reported with Cabenuva and were described usually (79%) as localized pain or discomfort (Cabenuva 2021). Fuzeon (enfuvirtide) is another injectable antiretroviral drug with 98% of subjects experiencing at least one injection site reaction (described as pain, discomfort, erythema, nodules and cysts, and ecchymosis) (Fuzeon 2019); however, this product is indicated to be administered twice daily.

Injection site nodules have been reported with a number of other drug classes, including glucagon-like peptide 1 (GLP-1) receptor agonists used for treatment of patients with type 2 diabetes. General injection-site reactions (e.g., erythema, pain, or rash) have been reported with all of the commercially available GLP-1 receptor agonists (i.e., exenatide, lixisenatide, liraglutide, dulaglutide, and semaglutide (Hearn and Sherman 2021). Injection site nodules have rarely been described with other long-acting or extended-release drug products, such as exenatide. Although the mechanism for development of such nodules is not entirely clear, available histopathology data reveal the presence of eosinophils and granuloma at these sites, and therefore, hypersensitivity to the formulation may be one plausible mechanism (Jones et al. 2015). Surgical excision or some other medical intervention, such as serial intralesional corticosteroid injections, may be required for treatment of persistent lesions.

Lenacapavir is a capsid inhibitor with not only a new mechanism of action, but also unique, albeit not fully understood, physical properties when injected that provide its sustained exposure.

Assessment

Injection site reactions were the most common adverse reaction reported with LEN SC injection. Preferred terms related to injection site in Studies 4625 or 4334 were further explored in the following table ([Table 58](#)). Injection site swelling, erythema, pain, nodule, and induration were the specific MedDRA preferred terms that were most frequently (>10%) reported. None of the ISRs were considered serious.

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In Study 4625, 61.1% of subjects reported any ISR (54.2% considered related to study drug), and most ISRs were Grade 1 or 2 severity. Two subjects (2.8%) reported Grade 3 ISRs (Subjects (b) (6), and (b) (6)) that were considered by the investigator to be related to LEN. Subject (b) (6) had “bilateral swelling at injection site max diameter cm 10” reported on Day 16 and ending on Day 19. Subject (b) (6) experienced “pain at injection site (1st)” on Day 16 and ending on Day 19.

In Study 4334, 43.8% of subjects who received SC LEN reported any ISR (39.0% considered related to study drug). All ISRs were Grade 1 or 2, except one Grade 3 injection site nodule (Subject (b) (6) in the SC LEN + (F/TAF → BIC) group). Two subjects in Study 4334, both in the SC LEN + (F/TAF → BIC) group, reported injection site induration that led to study drug discontinuation. Subject (b) (6) experienced injection site induration, which was considered Grade 1 in severity, on Day 15 (same day as the first SC injection). The subject discontinued treatment due to the ISR on Day 211. The following description by the investigator for was provided:

Early termination at Week 28. The nodules are nontender and not visible, but one has increased, rather than decreased, in size over time. The nodules are palpable and affect the participant’s self-esteem. “Constant reminder” of HIV infection. Smaller and less bothersome at the last visit.

Subject (b) (6) experienced injection site induration, which was considered Grade 1 in severity, on Day 15 (same day as the first SC injection). The subject discontinued treatment due to the ISR on Day 156. The following description was provided:

The investigator reported the subject stated the SC injection was very uncomfortable and left nodules in the abdomen that are still present.

Table 58. Injection Site Reactions, Safety Population, Studies 4625 and 4334

Preferred Term ¹	Study 4625	Study 4334
	Total LEN N=72 n (%)	Total SC LEN N=105 n (%)
Any injection site reaction	44 (61.1%)	46 (43.8%)
Injection site swelling	21 (29.2%)	24 (22.9%)
Injection site erythema	19 (26.4%)	22 (21.0%)
Injection site pain	18 (25.0%)	22 (21.0%)
Injection site nodule	14 (19.4%)	11 (10.5%)
Injection site induration	9 (12.5%)	11 (10.5%)
Injection site edema	3 (4.2%)	0
Injection site pruritus	3 (4.2%)	0
Injection site discomfort	1 (1.4%)	0
Injection site extravasation	1 (1.4%)	0
Injection site granuloma	1 (1.4%)	0
Injection site hematoma	1 (1.4%)	1 (1.0%)
Injection site reaction	1 (1.4%)	0
Injection site ulcer	1 (1.4%)	0
Injection site bruising	0	1 (1.0%)
Injection site cellulitis	0	1 (1.0%)

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	Study 4625	Study 4334
	Total LEN N=72 n (%)	Total SC LEN N=105 n (%)
Preferred Term¹		
Injection site mass	0	3 (2.9%)
Injection site paresthesia	0	1 (1.0%)
Injection site warmth	0	1 (1.0%)

Source: Reviewer's analysis, JMP Clinical v. 8.1.

¹ Includes treatment-emergent adverse events irrespective of assessment of causality.

Abbreviations: LEN, lenacapavir; SC, subcutaneous

The durations of ISRs by specific preferred terms in Studies 4625 and 4334 are summarized in the following table (Table 59). The duration of induration and nodules were much longer (approximately 6 to 12 months) than other injection site reactions (e.g., erythema, pain and swelling, lasting approximately 1 to 3 weeks).

Table 59. Injection Site Reaction Duration, Safety Population, Studies 4625 and 4334

	Study 4625	Study 4334
Preferred Term	Total LEN Median Duration (Q1, Q3)	Total SC LEN Median Duration (Q1, Q3)
Injection site swelling	11 days (5, 20)	10 days (5, 14)
Injection site erythema	6 days (3, 8)	5 days (2, 11)
Injection site pain	3 days (2, 6)	4 days (1, 10)
Injection site nodule	153 days (72, 232)	189 days (123, 338)
Injection site induration	71 days (29, 171)	143 days (74, 213)

Source: Adapted from the Applicant's Study 4625 Clinical Study Report, Section 11.2.4 and Study 4334 CSR, Section 11.2.4.

Abbreviations: LEN, lenacapavir; Q1, first quartile; Q2, second quartile; SC, subcutaneous

Data provided in the original NDA submission lacked an analysis of duration that accounted for subjects who had an injection site nodule or induration that had not resolved by the interim data cut. In their 90-Day Safety Update, data for the following table (Table 60) were provided. After approximately one year of median follow-up after the first dose of LEN, 7% to 10% of subjects had a study drug-related injection site induration that was unresolved, and approximately 11% to 19% had an unresolved nodule.

Table 60. Study Drug-Related Injection Site Nodules and Induration, Safety Population, Studies 4625 and 4334

	Study 4625	Study 4334
Parameter	Total LEN	Total SC LEN
Subjects who received at least one injection	72	103
Total number of SC LEN doses administered	166	243
Median duration of follow-up, days (min, max) ^a	313 (90, 583)	368 (59, 555)
Induration (% of subjects w/ ≥1 injection)	11 (15.3%)	13 (12.6%)
Mean duration (SD) of resolved (days)	101 (95)	133 (85)
Min, max; resolved (days)	3, 252	4, 213
Any ongoing	5 (6.9%)	10 (9.7%)
Nodule (% of subjects w/ ≥1 injection)	17 (23.6%)	14 (13.6%)
Mean duration (SD) of resolved (days)	156 (129)	227 (122)
Min, max; resolved (days)	41, 436	26, 424
Any ongoing	14 (19.4%)	11 (10.7%)

Source: Applicant's 90-Day Safety Update, supplemental tables and figures.

Study drug-related AE is defined as an adverse event marked as "Related" on the adverse event eCRF. Study 4625: Table Req13210.1; Table Req13210.3 Included CRF data collected up to July 27, 2021 (except for one subject with (b) (6)).

Study 4334: Table Req13210.4; Table Req13210.6 Included CRF data collected up to June 25, 2021.

^a Duration of follow-up is duration on study for 4625 and duration of study drug exposure for 4334, and was calculated from the first dose of LEN (including oral LEN).

Abbreviations: CRF, case report form; LEN, lenacapavir; SC, subcutaneous; SD, standard deviation

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Investigators described most induration and nodules similarly as palpable with elongated shape, not visible, not painful, and not associated with any redness. The maximum size for the majority of injection site nodules and indurations was approximately 1 to 4 cm. Anecdotally, indurations and nodules were more visible in participants who were leaner with little fat tissue in the abdomen. For instance, in Study 4334: Subject (b) (6) had nodules reported as Grade 3 “injection site nodule” starting on Day 194, and was ongoing at the 90-Day safety data cut. The investigator noted that he tried pinching and angling the injection to try and keep it in the subcutaneous space and avoid muscle tissue. The lesions were further described as “visible, golf ball size nodules” at the two injection sites with intense pain (9 on the pain scale). The pictures shown below in [Figure 25](#) were taken after the second LEN injection at Week 28. The subject discontinued study drug.

Figure 25. Photographs of Injection Site Nodules in Subject (b) (6) at Week 28, Study 4334

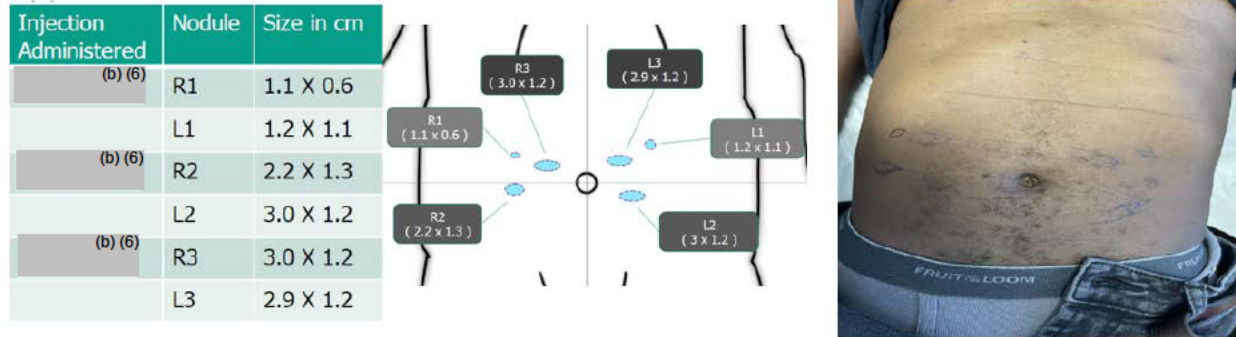


Source: Figure 9 in the Applicant's Response to FDA's September 8, 2021 Information Request, m1.11.3 submitted September 23, 2021.

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Subject (b) (6) (Figure 26) had six ongoing palpable nodules (note: circumscribed blue markings made by the investigator). This was a 53-year-old male who experienced Grade 1 injection site nodules, initially reported on Day 15 (same day as the first dose of SC LEN). The AE was considered related to the study drug by the investigator and was associated with injection site pain. Although the pain resolved after Day 15, the nodules were ongoing through the Week 52 visit.

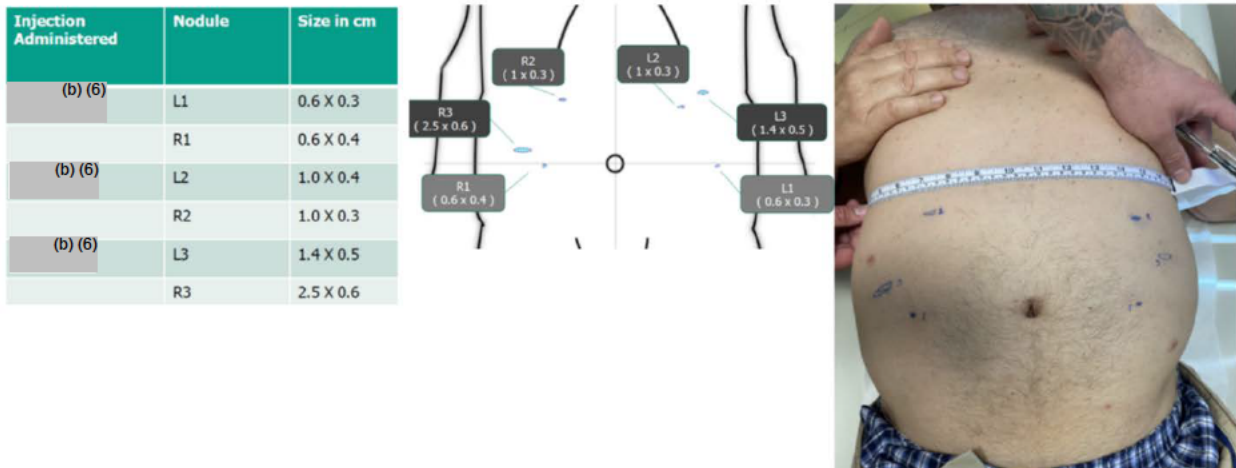
Figure 26. Photograph of Injection Site Nodules, Subject (b) (6) at Week 52, Study 4265



Source: Figure 3 in the Applicant's Response to FDA's September 8, 2021 Information Request, m1.11.3 submitted September 23, 2021.

Subject (b) (6) (Figure 27) had ongoing injection site nodules since the first LEN SC dose. Nodules were palpable 14 months later (note: circumscribed blue markings made by the investigator). This was a 63-year-old male who experienced Grade 1 injection site nodules, initially reported on Day 15 (same day as the first dose of SC LEN). The AE was considered related to the study drug by the investigator and was associated with injection site erythema, which resolved on Day 17, and injection site swelling, which resolved on Day 34.

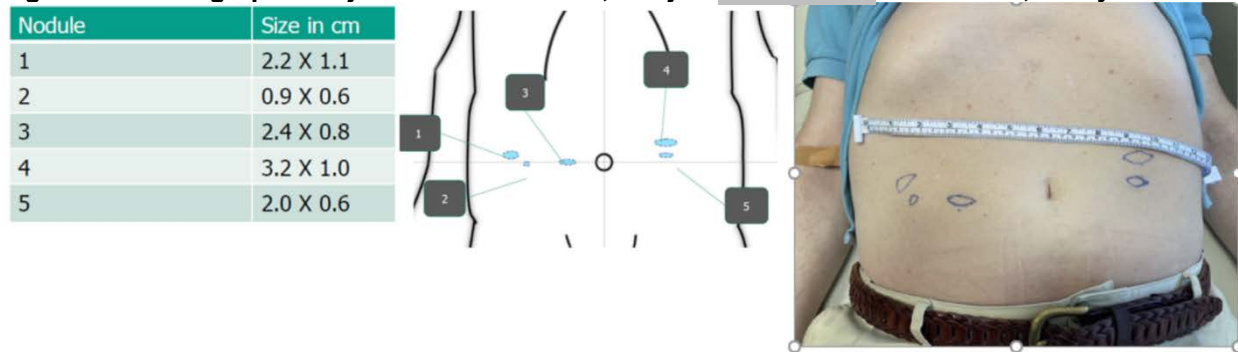
Figure 27. Photograph of Injection Site Nodules, Subject (b) (6) at Week 62, Study 4265



Source: Figure 4 in the Applicant's Response to FDA's September 8, 2021 Information Request, m1.11.3 submitted September 23, 2022.

Subject (b) (6) (Figure 28) had ongoing injection site nodules since the first LEN SC dose (note: circumscribed blue markings made by the investigator). This was a 62-year-old male who experienced Grade 1 injection site nodules, initially reported on Day 15 (same day as the first dose of SC LEN).

Figure 28. Photograph of Injection Site Nodules, Subject (b) (6) at Week 62, Study 4265



Source: Figure 5 in the Applicant's Response to FDA's September 8, 2021 Information Request, m1.11.3 submitted September 23, 2022.

Subject (b) (6) was a 54-year-old male with a history of anal cancer and colorectal surgery who had ongoing injection site induration following the first SC LEN dose. The area of induration was about 2×2 cm at both abdominal sites of the first SC injections and did not have any erythema or warmth. The photograph (Figure 29) was taken after the Week 62 visit (induration circumscribed by black marks on the photos). The induration decreased in size but did not resolve completely.

Figure 29. Photographs of Injection Site Induration, Subject (b) (6) at Week 62, Study 4265



Source: Figure 6 in the Applicant's Response to FDA's September 8, 2021 Information Request, m1.11.3 submitted September 23, 2022.

Subject (b) (6) (Figure 30) had injection site induration after the first SC LEN dose. This was a 52-year-old male who reported moderate pain and mild erythema 1 day following the first SC injection. The AEs of injection pain and erythema resolved after Day 2, while induration resolved after about 2 weeks.

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Figure 30. Photographs of Injection Site Induration, Subject (b) (6), Study 4265



Source: Figure 7 in the Applicant's Response to FDA's September 8, 2021 Information Request, m1.11.3 submitted September 23, 2022.

Subject (b) (6) (Figure 31) reported injection site induration after the first and second SC LEN doses at the Week 36 visit. The initial injections were associated with pain that resolved after 2 days and edema, which resolved after 3 days. The first injection site induration was resolved at Day 216. The second is still ongoing. The indurated areas were not visible, with no edema or redness, and had decreased since onset.

Figure 31. Photograph of Injection Site Induration, Subject (b) (6) at Week 36, Study 4265



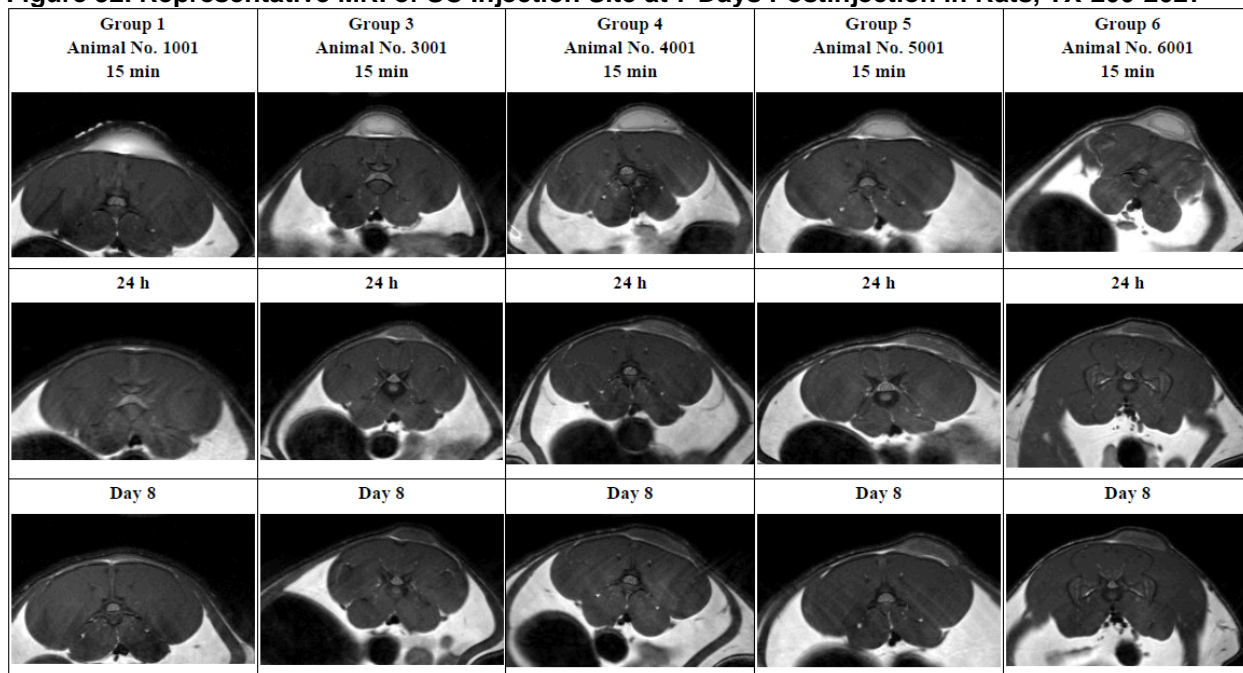
Source: Figure 7 in the Applicant's Response to FDA's September 8, 2021 Information Request, m1.11.3 submitted September 23, 2022.

No biopsies or histopathologic examinations were obtained from any clinical study subjects experiencing injection site nodules or indurations; however, nonclinical studies of rats (TX-200-2014), rabbits (TX-200-2033) and dogs (TX-200-2047) demonstrated “granulomatous inflammation” (please see Section [III.13.2.3](#) for additional discussion). “Inflammation and foreign body response” to the LEN SC depot was considered an expected host response similar to observations with SC and intramuscular implantation of bioactive material, including those for HIV treatment. Of note, however, these nonclinical studies were not likely to have used the same drug products as presented in borosilicate glass vials that were used in the clinical studies.

An *in vivo* study (TX-200-2027) in rats using magnetic resonance imaging also demonstrated findings at the injection site formed after LEN injection up to 7 days following SC injection. [Figure 32](#) shows a magnetic resonance image demonstrating that a drug (b) (4) (called “depot” by the Applicant) is formed at the site of injection after SC LEN injection in the rat. It is

unclear, however, precisely how the depot is formed at the SC injection site (b) (4)

Figure 32. Representative MRI of SC Injection Site at 7 Days Postinjection in Rats, TX-200-2027



Source: Appendix 2 of Appendix 6, Study TX-200-2027, 4.2.3.7.7 Toxicity Studies.

Abbreviations: MRI, magnetic resonance image; SC, subcutaneous

A consultation request was submitted to the Division of Dermatology and Dentistry in the Office of New Drugs that requested any recommendations for additional clinical safety information to be submitted regarding these reactions and recommendations for communication of injection site reactions in labeling. The Division of Dermatology and Dentistry recommended that in ongoing trials, where possible, injection site nodules be followed to resolution or stabilization. Human histopathology should be obtained to rule out the presence of findings such as necrosis, hypersensitivity, granulomas, foreign bodies, and fibrous tissue. In addition, the Division of Dermatology and Dentistry agreed with the expanded characterization of injection site reactions in Section 6 (Adverse Reactions) of the label, and that elevation to Section 5 (Warnings and Precautions) was not necessary at this time given there were no reports to date of AEs that were considered serious or life-threatening.

As discussed in further detail in the Integrated Quality Review, the LEN injectable drug substance has a high pH (>9) and no intrinsic release controls. Additionally, the proposed vial containers (borosilicate), which were also used in clinical trials, demonstrated incompatibility with the drug product, degradation of the vial surface, and glass particles found in the solution.

Conclusion

Injection site reactions can be characterized as having a short-term phase lasting a few days (e.g., pain, swelling, and erythema) or a long-term phase (e.g., indurations and nodules), some of which were still resolving over a period of weeks to months. Indurations and nodules were generally described as palpable with an elongated shape (up to 1 to 4 cm), not visible, not painful, and not associated with any erythema. Nodules were more visible in subjects who were

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leaner with little fat tissue in the abdomen. Several subjects in Study 4625 had indurations or nodules that had not fully resolved at the time of the last safety update. Due to the lack of understanding of the histopathology at the injection sites in patients who experienced longer times to resolution of indurations and nodules, and the relationship with the unique properties of the drug product solution, it is unclear whether these subjects may have experienced permanent tissue damage. Additionally, given the concern about the incompatibility of the drug substance with borosilicate glass and resulting delamination of the vial containers (please refer to the chemistry, manufacturing, and controls review), contribution of glass particulate contamination cannot be ruled out.

During the initial exchange of updates to the draft labeling for LEN, the Division of Antivirals (DAV) requested additional description of injection site reactions similar to the presentation in the Cabenuva label, with additional description of nodules and induration and details of time to resolution provided as a separate subsection entitled “Injection-Associated Adverse Reactions” in Section 6 (Adverse Reactions) of the proposed label.

From a clinical safety perspective, additional information is needed to understand the contributing factors of injection site reactions with LEN, particularly for subjects who have prolonged resolution with nodules and indurations. Where clinically indicated, at the discretion of an independent dermatologist, DAV requested that the Applicant obtain human histopathology (e.g., punch biopsy), and specimens should be examined by an independent dermatopathologist.

From a product quality perspective, several deficiencies, including (b) (4), and glass particle contamination, were the basis for the recommendation of nonapproval. Additional concerns included (b) (4) and the atypical mechanism of release following injection of the drug product. Although the Applicant has withdrawn the proposal for the borosilicate glass vial presentation, the proposal for aluminosilicate glass vials lacked a comprehensive and validated study to support this alternative presentation through the drug product expiry period. Of note, on 20 December, 2021, a supporting investigational new drug (IND) application for these NDAs (IND 136260), as well as IND (b) (4) (with ongoing clinical studies for pre-exposure prophylaxis of HIV-1), were placed on Full Clinical Hold due to the lack of information needed to assess risks of lenacapavir injection and the extent to which glass particulate contamination, including subvisible particles, may be associated with injection site nodules, indurations, or other clinical effects.

7.7.3. Background Regimens Containing Boosted Protease Inhibitors

Issue

The risk of suprathreshold LEN exposures when LEN is combined with a background regimen containing boosted protease inhibitors was not prospectively assessed in Study 4625.

Background

Most regimens containing boosted protease inhibitors (BPIs) are typically used as second-line options, or when INSTIs are not available. The HTE patient population by definition has limited alternative options to construct a complete regimen; therefore, BPIs may be an important component of an optimized background regimen.

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Based on in vitro data, LEN was found to be a substrate of cytochrome P450 (CYP)3A and uridine diphosphate glucuronosyltransferase (UGT)1A1 enzymes and p-glycoprotein (P-gp) transporters. In the dedicated DDI study, Study GS-US-200-4333 (Study 4333), an approximate two-fold increase in LEN exposures was observed with mixed CYP3A/P-gp inhibition associated with cobicistat, and an approximate four- to six-fold increase LEN exposure was observed with mixed CYP3A/P-gp/ UGT inhibition associated with atazanavir/cobicistat; therefore, given the potential for clinically significant drug-drug interactions with LEN due to the combined strong inhibition of CYP3A, P-gp, and UGT1A1 together, Study 4625 did not allow concomitant use of atazanavir (ATV, an inhibitor of CYP3A and UGT1A1) when boosted with either cobicistat (COBI) or ritonavir (RTV). The results from Study 4333 also showed an 84% decrease in LEN AUC when LEN was coadministered with rifampin, a strong CYP3A inducer; and 56% decrease in LEN AUC when LEN was coadministered with efavirenz, a moderate CYP3A inducer. CYP3A inducers (e.g., rifampin, efavirenz, tipranavir) were disallowed in Study 4625. Background regimens with other BPIs were allowed. Please refer to Section [8.2.2](#) for additional discussion of drug interactions.

Assessment

Clinical Safety Experience With Supratherapeutic Doses of LEN

Clinical safety experience was reviewed from two clinical studies where doses of LEN were predicted to provide higher exposures than what was studied in Study 4625. Study 4332 was a phase 1 QT study, which evaluated a 600 mg dose of LEN (2×300 mg tablets) taken orally twice-daily for 8 days to achieve supratherapeutic exposure. Study 5709 was a phase 1 PK study, and Cohort 3 evaluated a 600 mg dose of LEN (2×300 mg tablets) taken orally twice daily for 10 days. Although direct comparisons between these studies are limited (because they are in different patient populations: healthy volunteers versus treatment-naïve and heavily treatment-experienced subjects), the clinical safety experience from this analysis may be informative regarding potential exposure-related effects attributable to LEN.

Table 61. Systemic Exposures of LEN Across Clinical Studies Where Supratherapeutic Exposures Were Achieved or Observed Relative to Study 4625, Study 4332 and Cohort 3 of Study 5709

Parameter	Supratherapeutic Exposure		Therapeutic Exposure	
	Study 4332	Study 5709 Cohort 3	Study 4625	
LEN dosing	Oral 600 mg BID for 8 days	Oral 600 mg BID for 10 days, followed by QD for 1 day	Oral lead-in (Days 1 to 15)	SC 827 mg (Day 15 to end of Month 6)
C _{max} (ng/mL)	1070.4	1012.1	124.4	87.3
Fold-difference (versus Study 4625 oral lead-in)	8.6	8.1	N/A	N/A

Source: Applicant's September 22, 2022 Response to FDA Request for Information, Table 3.

Abbreviations: BID, twice daily; C_{max}, maximum concentration; LEN, lenacapavir; N/A, not applicable; QD, every day

In Studies 4332 or 5709 Cohort 3, no deaths, treatment-emergent serious AEs, TEAEs of Grade 3 or higher related study drug, or TEAEs leading to premature discontinuation of study drug were reported in subjects with supratherapeutic exposures of LEN.

With a focus on hepatotoxicity, an exploration into the potential for laboratory abnormalities was reviewed in the setting of supratherapeutic doses of LEN. None of the subjects in Study 4332

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had any signs or symptoms or AEs suggestive of hepatotoxicity (e.g., concurrent elevation in direct bilirubin and transaminases).

Post Hoc Analysis of Study 4625: Safety of LEN in Combination With Background Regimens Containing BPIs Versus Non-BPI Regimens

In Study 4625, 18 (29%) subjects received LEN with COBI, 19 (30.6%) subjects received RTV, and 19 (30.6%) received DRV. A summary of adverse events comparing subjects on an OBR containing a BPI versus subjects without a BPI is shown in [Table 62](#).

Table 62. Summary of Safety of LEN in Subjects on OBR Containing BPI Versus Subjects Without BPI in the OBR, Study 4625

Parameter	Subjects With BPI in OBR (n=42)	Subjects Without BPI in OBR (n=30)
Any TEAE	40 (95.2%)	26 (86.7%)
TEAE with Grade 3 or higher	9 (21.4%)	4 (13.3%)
TEAE with Grade 2 or higher	24 (57.1%)	15 (50.0%)
TEAE related to study drug	26 (61.9%)	19 (63.3%)
TEAE related to study drug with Grade 3 or higher	3 (7.1%)	1 (3.3%)
TEAE related to study drug with Grade 2 or higher	12 (28.6%)	7 (23.3%)
TE Serious AE	1 (2.4%)	3 (10.0%)
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 drug	0	1 (3.3%)
Death	0	1 (3.3%)

Source: Applicant's September 22, 2022 response to an FDA Request for Information, Table 4.

Abbreviations: AE, adverse event; BPI, boosted protease inhibitor; FDA, Food and Drug Administration; OBR, optimized background regimen; TEAE, treatment-emergent adverse event

A summary of TEAEs by preferred terms comparing subjects on LEN when combined with an OBR containing a BPI versus subjects without a BPI is shown in [Table 63](#).

Table 63. TEAEs With LEN in Subjects on OBR Containing BPI Versus Subjects Without BPI in the OBR, Study 4625

Preferred Term	Subjects With BPI in OBR (n=42)	Subjects Without BPI in OBR (n=30)
Constipation	4 (9.5%)	0
Cough	4 (9.5%)	1 (3.3%)
Diarrhea	4 (9.5%)	2 (6.7%)
Nausea	4 (9.5%)	2 (6.7%)
Abdominal distension	3 (7.1%)	1 (3.3%)
Arthralgia	3 (7.1%)	1 (3.3%)
Dyspnea	3 (7.1%)	0
Headache	3 (7.1%)	2 (6.7%)
Myalgia	3 (7.1%)	0

Source: Applicant's September 22, 2022 Response to an FDA Request for Information, Table 4.

Abbreviations: BPI, boosted protease inhibitor; FDA, Food and Drug Administration; LEN, lenacapavir; OBR, optimized background regimen; TEAE, treatment-emergent adverse event

A summary of laboratory abnormalities comparing subjects on LEN when combined with an OBR containing a BPI versus subjects without a BPI is shown in [Table 64](#).

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Table 64. Laboratory Abnormalities With LEN in Subjects on OBR Containing BPI Versus Subjects Without BPI in the OBR, Study 4625

Parameter	Subjects With BPI in OBR (n=42)	Subjects Without BPI in OBR (n=30)
Any Grade 1 or higher	37 (88.1%)	29 (96.7%)
Any Grade 3 or 4	12 (28.6%)	7 (23.3%)
Creatinine clearance or eGFR, low	6 (14.3%)	1 (3.3%)
Creatinine, high	4 (9.5%)	2 (6.7%)
Hyperglycemia, nonfasting	2 ^a (7.1%)	1 ^c (4.5%)
Hyperglycemia, fasting	2 ^b (5.9%)	1 ^d (4.8%)
Glycosuria (dipstick)	2 (4.8%)	2 (6.7%)
Proteinuria (dipstick)	2 (4.8%)	0
ALT, high	1 (2.4%)	0
AST, high	1 (2.4%)	0
Direct bilirubin (increased)	1 (2.4%)	0
Hyperkalemia	1 (2.4%)	0

Source: Applicant's September 22, 2022 Response to an FDA Request for Information, Table 4.

^a Denominator is 28.

^b Denominator is 34.

^c Denominator is 22.

^d Denominator is 21.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPI, boosted protease inhibitor; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; OBR, optimized background regimen

Conclusion

Analysis of safety experience with LEN and regimens containing BPIs revealed adverse event and laboratory profiles previously anticipated with BPIs. With the exception of regimens containing ATV/COBI or ATV/RTV, no additional significant safety concerns were revealed with dose exploration studies and similar suprathreshold exposures of LEN (up to approximately two-fold higher) that would be expected when combined with BPIs.

Labeling for LEN should include the recommendation against concomitant administration with ATV/COBI or ATV/RTV, but no clinically significant drug interactions have been observed with DRV/COBI.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Renal Impairment

Results from Study 4329 (mass balance study) showed that renal excretion is a minor excretion pathway of LEN, representing 0.237% of total dose. However, severe renal impairment (RI) may affect uptake and efflux transporters and metabolic enzymes in the liver and gastrointestinal tract. Increases in exposure in subjects with severe RI for drugs that are not renally excreted may be due to the effects of uremic toxin on either intestinal or hepatic cell transporters, metabolizing enzymes, or both. This phenomenon has been observed for other drugs, such as raloxifene and revefenacin, which show significantly higher exposures in subjects with severe RI despite not being primarily eliminated renally.

In the RI Study 4330, subjects with severe RI (estimated creatinine clearance ≥ 15 mL/min) were administered 300 mg single oral dose of LEN. LEN geometric least-squares mean (GLSM) AUC

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and C_{max} were 162% and 84% higher, respectively, in subjects with severe renal impairment compared to subjects with normal renal function. As LEN has linear PK, these results can be extrapolated to the recommended dosing regimen. Based on cross-study PK comparisons, even larger exposure increases were observed without safety concerns in other studies. As shown in [Table 65](#), in Studies 4332 and 5709, the magnitude of increase in LEN C_{max} and AUC following 600 mg BID relative to the therapeutic exposure was higher compared with the magnitude of increase in LEN C_{max} and AUC in Study 4330. Therefore, the impact of RI on LEN PK is not considered clinically significant.

Table 65. Cross-Study Comparison of Impact of RI, HI, and Regimen on LEN PK

PK	Study 4330 Severe RI vs. Healthy Control	Study 4331 Moderate HI vs. Healthy Control	Study 4332 600 mg BID for 8 Days (at Day 12) vs. Therapeutic Exposure	Study 5709, Cohort 3 600 mg BID for 11 Days (at Day 11) vs. Therapeutic Exposure
C_{max}	↑ 162%	↑ 161%	↑ 784%	↑ 794%
AUC	↑ 84% (AUC _{inf})	↑ 47% (AUC _{inf})	↑ 1401% (AUC _{0-12h})	↑ 1369% (AUC _{0-12h})

Source: PK analyses for the RI and HI studies from the Applicant's study reports. Other calculated percentage changes are from the reviewer's analyses based on the GLSM ratios of the PK parameters in the Applicant's study reports.

Note: The GLSM of PK parameters for the Therapeutic Exposure were based on population PK estimates from the phase 2/3 Study 4625.

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum concentration; GLSM, geometric least-squares mean; HI, hepatic impairment; PK, pharmacokinetic; RI, renal impairment

The review team agrees with the Applicant's proposed labeling that no dose adjustment of LEN is required in patients with mild, moderate, or severe RI, and that LEN has not been studied in patients with end-stage renal disease (estimated creatinine clearance <15 mL/min) (Section [III.13.2](#)).

8.1.2. Hepatic Impairment

In vitro studies indicated that LEN is a substrate of enzymes CYP3A5 and UGT1A1. In addition, metabolism of LEN was also observed in the clinical Study 4329. Therefore, hepatic impairment (HI) is expected to have an impact on LEN PK.

In HI Study 4331, subjects with moderate HI (Child-Pugh Class B) were administered a 300 mg single oral dose of LEN. GLSM LEN AUC and C_{max} were 47% and 161% higher, respectively, in subjects with moderate HI compared to subjects with normal hepatic function. As shown in [Table 65](#), in Studies 4332 and 5709, the magnitude of increase in GLSM mean C_{max} and AUC following 600 mg BID relative to the therapeutic exposure was higher compared with the magnitude of increase in C_{max} and AUC in Studies 4331. Therefore, the impact of moderate HI on LEN PK is not considered clinically significant.

The review team agrees with the Applicant's proposed labeling that no dose adjustment of LEN is required in patients with mild or moderate HI (Child-Pugh Class A or B), and that LEN has not been studied in patients with severe hepatic impairment (Child-Pugh C) (Section [III.13.2](#)).

8.1.3. Other Intrinsic Factors

Population PK analyses indicate that sex, race, age (18 to 78 years), and body weight do not have a clinically significant effect on LEN PK. No subjects >78 years old were enrolled in the clinical studies (see Section [III.14.3](#)).

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8.2. Extrinsic Factors

8.2.1. Food Effect

Study GS-US-200-4071 evaluated the impact of a standard light meal (400 kcal and 25% fat) and the impact of a high-fat meal (1000 kcal and 50% fat) on LEN PK. Two LEN solution-in-capsule formulations and the to-be-marketed oral tablet formulation were used in the study.

Regardless of the calorie and fat content of the meal, food had no significant effect on plasma LEN PK. LEN was given without regard to food in the Phase 3 trials CAPELLA and CALIBRATE. The review team agrees with the Applicant's proposed labeling that LEN can be administered with or without food (see Section [III.14.2](#)).

8.2.2. Drug-Drug Interactions

Effects of Other Drugs on LEN

In vitro studies (see Section [III.13.1](#) for details) indicate that LEN is a substrate of CYP3A, P-gp and UGT1A1, but not a substrate of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, breast cancer resistance protein, or organic anion transporter polypeptide (OATP)1B1 and OATP1B3. In vitro studies to evaluate if LEN is a substrate of renal transporters were not conducted because the absorption, distribution, metabolism, excretion data suggest that active renal secretion is not expected to be significant.

Drug-drug interaction Study 4333 (see Section [III.14.2](#) for details) was conducted in healthy volunteers to evaluate the effect of CYP3A, P-gp, and UGT1A1 modulators as well as the effect of an acid-reducing agent on the PK of LEN.

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Table 66. Effects of Other Drugs on LEN, Study 4333

Coadministered Drug	Characteristics of Coadministered Drug for DDI	Mean Ratio of LEN Pharmacokinetic Parameters (90% CI); No Effect=1.00		Clinical Implication
		C _{max}	AUC	
Cobicistat	Strong CYP3A inhibitor and P-gp inhibitor	2.10 (1.62, 2.72)	2.28 (1.75, 2.96)	
Darunavir/cobicistat	Strong CYP3A inhibitor and P-gp inducer/inhibitor	2.30 (1.79, 2.95)	1.94 (1.50, 2.52)	LEN can be coadministered with CYP3A and/or P-gp inhibitors
Voriconazole	Strong CYP3A inhibitor	1.09 (0.81, 1.47)	1.41 (1.10, 1.81)	
Atazanavir/cobicistat	Strong CYP3A inhibitor and P-gp/UGT1A1 inhibitor	6.60 (4.99, 8.73)	4.21 (3.19, 5.57)	Coadministration of LEN and atazanavir/cobicistat or atazanavir/ritonavir is not recommended
Rifampin	Strong CYP3A inducer and P-gp/UGT inducer	0.45 (0.34, 0.60)	0.16 (0.12, 0.20)	Coadministration of LEN and strong CYP3A inducers is contraindicated
Efavirenz	Moderate CYP3A inducer and P-gp inducer	0.64 (0.45, 0.92)	0.44 (0.32, 0.59)	Coadministration of LEN and moderate CYP3A inducers is not recommended
Famotidine (2 hours before)	H2-blocker	1.01 (0.75, 1.34)	1.28 (1.00, 1.63)	LEN can be coadministered with acid-reducing agents

Source:

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; CYP, cytochrome P450; LEN, lenacapavir; P-gp, p-glycoprotein; UGT, uridine diphosphate glucosyltransferase

Coadministration With Inhibitors of CYP3A, P-gp, and/or UGT1A1

Coadministration of drugs that are inhibitors of CYP3A (strong), P-gp, and UGT1A1 together (i.e., atazanavir [ATV]/COBI or ATV/RTV) with LEN during treatment is not recommended. Of note, use of ATV was not allowed in Studies 4625 and 4334. Clinical DDI results confirmed the in vitro findings and showed that an inhibitor of CYP3A (strong), P-gp, and UGT1A1 together (ATV/COBI) increased LEN concentrations to a larger degree than coadministration with an inhibitor of CYP3A (strong) and P-gp (COBI and DRV/COBI) or a strong CYP3A inhibitor alone (voriconazole) (Table 67).

Coadministration of LEN with a strong inhibitor of CYP3A and P-gp (e.g., DRV/RTV, DRV/COBI) together, a strong CYP3A inhibitor alone, or a P-gp inhibitor alone is not expected to result in a clinically significant effect on LEN concentrations. In Study 4625, 18 (29%) subjects coadministered LEN with COBI, 19 (30.6%) subjects with RTV, and 19 (30.6%) with DRV. In addition, the increase of LEN C_{max} (<3-fold) due to coadministration with a strong inhibitor of CYP3A and P-gp together, a strong CYP3A inhibitor alone, or a P-gp inhibitor alone is much less than the 9-fold higher C_{max} observed following oral LEN 600 mg BID (Studies 5709 and 4332, up to 11 days) versus the C_{max} observed with the regimen studied in the pivotal trial without safety concerns. Safety data from Cohort 3 of Study 4334 (LEN oral 600 mg on day 1 and day 2, and oral 50 mg once daily starting day 3), which provided comparable C_{max} and C_{trough} but about 2-fold higher $AUC_{0-6month}$ as compared to the proposed regimen, also supports coadministration of LEN with a strong inhibitor of CYP3A and P-gp together, a strong CYP3A inhibitor alone, or a P-gp inhibitor alone.

Coadministration With Inducers of CYP3A

Coadministration of strong inducers of CYP3A during treatment with LEN is contraindicated and coadministration of moderate inducers of CYP3A during treatment with LEN is not recommended. Drugs that are strong inducers of CYP3A (e.g., rifampin), or that are moderate inducers of CYP3A (e.g., efavirenz), may significantly decrease plasma concentrations of LEN, which may result in loss of therapeutic effect of LEN and development of resistance. A strong inducer of CYP3A is expected to be an inducer of P-gp and UGT1A1 with lower potency because CYP3A, P-gp, and UGTs are all regulated by the pregnane X receptor. Therefore, other strong inducers of CYP3A are expected to decrease LEN concentrations by a similar magnitude as rifampin. Although exposure-response (E-R) relationship analyses for Study 4625 indicated that there was no clear E-R relationship identified for efficacy or safety (see Section 6.1), strong or moderate CYP3A inducers were not allowed in pivotal trials. In addition, although based on the exploratory E-R relationship analysis (Study 4072), near maximum efficacy is expected in the lowest quartile of C_{trough} (see Section III.25). A decrease in LEN exposures by strong or moderate CYP3A inducers will most likely result in LEN exposures in the range for which the current E-R relationships may not be applicable.

Coadministration With Acid-Reducing Agents

LEN is practically insoluble in aqueous media, gastric fluid, or intestinal fluid and exhibits higher solubility at $pH \geq 6$. The effect of famotidine LEN exposures was assessed. Administration of a single dose of LEN 2 hours after famotidine did not result in clinically

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significant changes in LEN PK (28% increase in mean LEN AUC_{inf}). Accordingly, there are no restrictions for use of LEN with acid-reducing agents.

Effect of LEN on Other Drugs

Considering the results of both in vitro and in vivo DDI studies, LEN is a moderate inhibitor of CYP3A and is an inhibitor of P-gp.

The DDI potential evaluation was based on FDA Guidance for Industry: *In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020). In vitro studies indicate that LEN is an inhibitor of both gut and hepatic CYP3A, mainly due to time-dependent or mechanism-based inhibition. Using static mechanistic models, the ratio of LEN AUC (AUC_r) of oral LEN coadministered with a CYP3A inhibitor to oral LEN alone is predicted to be approximately 5-fold, with about 1.7-fold due to gut CYP3A inhibition and 2.9-fold due to hepatic CYP3A inhibition. The predicted AUC_r is about 2.8-fold following coadministration of a CYP3A inhibitor with SC LEN compared to SC LEN alone. In vitro studies also indicate that LEN is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT 1A1. LEN is an inhibitor of OATP1B1 or OATP1B3, but is not likely to inhibit P-gp, breast cancer resistance protein (BCRP), OAT1, OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion protein (MATE)1, or MATE2K. In vitro studies indicate LEN is not expected to be an inducer of CYP enzymes.

As shown in [Table 67](#), DDI Study 4333 showed that LEN is a moderate inhibitor of CYP3A (as observed by coadministration of LEN with midazolam [MDZ] resulting in a 259% increase in mean AUC_{inf}). MDZ administered 1 day after LEN resulted in a similar magnitude of effect on MDZ concentrations, indicating that the effect of LEN on MDZ concentrations is mainly through hepatic CYP3A inhibition.

Concomitant use of LEN with CYP3A substrates can increase the exposures and risk of adverse reactions of these substrates. Avoid coadministration of LEN with CYP3A substrates where minimal concentration changes may lead to serious toxicities.

Study 4333 also showed that LEN appeared to inhibit P-gp transporter (as observed by coadministration of LEN with TAF resulting in a 32% increase in AUC_{inf}) and BCRP transporter (as observed by coadministration of LEN with rosuvastatin resulting in a 31% increase in AUC_{inf}). Although in vitro data suggested that LEN is a weak inhibitor of OATP1B1, LEN does not inhibit OATP transporters in vivo (based on no significant changes in PIT exposures). Therefore, substrates of BCRP and OATP can be coadministered with LEN while therapeutic monitoring of digoxin (a P-gp substrate) concentrations is recommended when LEN is coadministered with digoxin.

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Table 67. Effect of LEN on Other Drugs, Study 4333

Coadministered Drug	DDI Pathway	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect=1.00		Clinical Implication
		C _{max}	AUC	
Tenofovir alafenamide	P-gp	1.24 (0.98, 1.58)	1.32 (1.09, 1.59)	For P-gp-sensitive substrates with narrow therapeutic index (e.g., digoxin): Use with caution and monitor digoxin therapeutic concentration
Tenofovir		1.23 (1.05, 1.44)	1.47 (1.27, 1.71)	
Pitavastatin (simultaneous administration)	OATP	1.00 (0.84, 1.19)	1.11 (1.00, 1.25)	No restriction with OATP substrates
Pitavastatin (3 days after LEN)		0.85 (0.69, 1.05)	0.96 (0.87, 1.07)	
Rosuvastatin	BCRP	1.57 (1.38, 1.80)	1.31 (1.19, 1.43)	No restriction with BCRP substrates
Midazolam (simultaneous administration)	CYP3A	1.94 (1.81, 2.08)	3.59 (3.30, 3.91)	LEN is a moderate inhibitor of CYP3A. Concomitant use of lenacapavir increases the C _{max} and AUC of CYP3A substrates, which may increase the risk of adverse reactions of these substrates
Midazolam (1 day after lenacapavir)		2.16 (2.02, 2.30)	4.08 (3.77, 4.41)	

Source:

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; CI, confidence interval; C_{max}, maximum concentration; CYP, cytochrome P450; LEN, lenacapavir; OATP, organic anion transporting polypeptide; P-gp, p-glycoprotein

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If LEN is discontinued, residual concentrations of LEN may remain in the systemic circulation of patients for prolonged periods. These concentrations may affect the exposures of other drugs (i.e., sensitive CYP3A substrates) that are initiated within 9 months after the last subcutaneous dose of LEN. Using a static mechanistic model, the Applicant concluded that inhibition of CYP3A is possible only at LEN concentrations above 14.9 ng/mL and LEN concentrations are predicted to decline below this value by approximately 8.3 months after the last LEN SC injection, thereby suggesting a low likelihood of LEN to be a significant perpetrator of DDIs 9 months after the last LEN SC dose.

8.3. Plans for Pediatric Drug Development

- The NDAs for lenacapavir trigger PREA as a new active ingredient.
- In their Agreed Amended initial Pediatric Study Plan, the Applicant requested a partial waiver for pediatric HTE patients from birth to <12 years, because studies in this patient population are impossible or highly impracticable.
-  (b) (4)
- There are no nonclinical or clinical safety issues that indicate a concern for continuing the study of LEN specifically in adolescents, but the lack of enrollment in Study 4625 likely reflects the lack of a sufficient number of adolescents to target this patient population (i.e., heavily treatment experienced with multidrug resistance) for further clinical study.
-  (b) (6)
- The next studies anticipated to enroll adolescents  (b) (4)) are ongoing studies for pre-exposure prophylaxis.
- DAV met with the PeRC on 16 November, 2021. The PeRC agreed with the plan to request partial waiver of pediatric patients from birth to <12 years of age studies because necessary studies are impossible or highly impracticable.
- The PeRC also agreed to grant deferred studies for pediatrics 12 to 18 years of age who weigh at least 35 kg.
- Similar to the approach taken with Rukobia (fostemsavir), DAV proposed considering the following Pediatric Research Equity Act PMR language: “Conduct a clinical study to evaluate week 24 safety of lenacapavir in adolescents from 12 years to less than 18 years of age who weigh at least 35 kg.” The PeRC agreed with this plan.

8.4. Pregnancy and Lactation

The reproductive and development toxicology studies with lenacapavir are summarized in Section [6.1](#). In the fertility study, lenacapavir was administered to male and female rats via a single subcutaneous injection of 20 or 100 mg/kg at 4 and 6 weeks prior to pairing to male and female rats, respectively. LEN had no effect on male or female fertility in rats, at doses up to

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100 mg/kg, at exposures 7- and 5-fold (in males and females, respectively) those observed at the RHD.

No significant toxicological effects on embryo-fetal growth or development were observed in rats when lenacapavir was administered at oral doses up to 30 mg/kg from GD 6 to 17, at exposures 16-fold the RHD.

Lower body weight gains that correlated with a decrease in food intake was observed in rabbits when lenacapavir was administered intravenously at doses up to 20 mg/kg from GD 7 to 19, at exposures 39-fold the RHD.

In the PPND toxicity study, lenacapavir was administered to pregnant rats via a single subcutaneous injection on GD 6. Lactation was not measured in the PPND study. There were no maternal toxicities or effects on PPND that occurred up to 300 mg/kg at exposures 5-fold the RHD.

9. Product Quality

The Quality Assessment team completed an integrated assessment from the drug substance, drug product, manufacturing, microbiology, biopharmaceutics and environmental disciplines. The team determined that NDA 215794, for oral LEN tablet, was approvable from the product quality perspective; however, NDA 215793, for LEN injection, was found to be deficient from a product quality perspective. One of the proposed commercial vial containers (borosilicate) was not compatible with the drug product solution. Degradation of the vial surface was evident from microscopic imaging, and glass particles were found in the solution. Considering (b) (4) and concern for glass particle contamination, approval of the proposed alternative aluminosilicate glass vial will require a comprehensive validated study. Further, data supporting the container closure integrity testing remained outstanding despite numerous information requests to the Applicant. The Quality Assessment team also notified the OND review team about the atypical nature of this product, including the lack of intrinsic release controls and the concern about a subcutaneous product with a pH >9. Please refer to the integrated reviews for both NDAs, 215973 and 215974, completed January 12, 2022, for additional details.

Although each discipline recommended approval for NDA 215794, both NDA 215793 and NDA 215794 will receive a Complete Response action. As stated above, deficiencies were identified in the product quality information for the LEN injection NDA. The approval of the oral LEN NDA is contingent on the approval of the LEN injection NDA; therefore, the LEN injection NDA deficiencies must be adequately addressed before the oral LEN NDA can be approved.

9.1. Device or Combination Product Considerations

As the proposed kit of lenacapavir injection includes drug delivery devices, a Center for Devices and Radiological Health (CDRH) consult was initiated. All the components (devices) of the proposed kit, including vial access devices, disposable syringes and injection safety needles, are 510k cleared, thus the CDRH review team determined that no additional review was needed. The Applicant also submitted device validation studies, thus the Division of Medication Error

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Prevention and Analysis (DMEPA) team was also consulted. The DMEPA team determined that a Human Factors study and results were not required for NDA submission.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Study 4625 was the pivotal study supporting the finding of efficacy for the NDAs 215973 and 215974. Clinical sites that were chosen for inspection primarily were based on numbers of enrolled subjects, site efficacy, and prior inspectional history. Please refer to Section [III.21](#) for a summary of findings from clinical site inspections.

Table 68. Study Sites Requested for Inspection, Study 4625

Site ID	Name	Location	Notes
00698	Edwin DeJesus, MD	Orlando, FL	Five subjects were screened and enrolled
00407	Peter J. Ruane, MD	Los Angeles, CA	Ten subjects were screened, three were enrolled

Source: FDA analysis.

11. Advisory Committee Summary

This application was not taken to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and there were no controversial issues that would benefit from discussion by an advisory committee.

III. Appendices

12. Summary of Regulatory History

Lenacapavir (LEN), formerly known as GS-6207, is a human immunodeficiency virus (HIV)-1 capsid inhibitor that is being developed as a solution for subcutaneous injection under investigational new drug (IND) 136260 and as a tablet for oral use under IND 138311. The dosage forms were intended to be used in conjunction for the treatment of HIV-1 infection.

On 30 August, 2017, Gilead Sciences submitted a meeting request under Pre-IND 136260 for LEN, injection. Pre-IND guidance on the nonclinical studies needed to support the alternative injectable formulations of LEN that Gilead planned to use in their clinical trials was provided to Gilead on 25 October, 2017 via a Written Response correspondence.

IND 136260 was submitted 21 December, 2017 and the Agency deemed it safe-to-proceed on 20 January, 2018. Fast Track Designation was granted on 23 March, 2018 for the treatment of HIV-1 infection on the basis that the submitted information was sufficiently likely to support use of LEN as (b) (4) parenteral formulation with a new mechanism of action, and therefore, LEN demonstrated the potential to address an unmet medical need.

On 20 March, 2018, Gilead submitted a new IND 138311 for lenacapavir tablets, for the treatment of HIV-1 infection and the Agency deemed the IND safe to proceed on 19 April, 2018. Fast Track Designation was granted on 19 September, 2018 for the treatment of HIV-1 infection.

On 30 May, 2019, the development program for LEN (IND 136260) for the treatment of HIV-1 infection in heavily treatment-experienced (HTE) patients with multidrug resistant (MDR) virus was granted Breakthrough Therapy Designation. The decision was based upon the need for an antiretroviral agent with a new mechanism of action and no overlapping resistance with any approved agent that could potentially meet the high unmet medical need in HTE patients with limited treatment options. A Type B, Initial Breakthrough Therapy meeting was held on 6 August, 2019 during which the phase 2/3 development program and proposed registration plan to support an indication for treatment of HIV-1 infection in HTE patients with MDR HIV-1 was discussed. The Agency generally agreed with the proposed phase 2/3 Study 4625 to support the submission of a new drug application (NDA). The clinical trial would investigate the use of a 14-day lenacapavir oral lead-in dosing, followed by LEN, subcutaneous injections on Day 15 and every 6 months.

On 19 March, 2020, a rat carcinogenicity Special Protocol Assessment was submitted to IND 136260; and on 26 June, 2020, a mouse carcinogenicity Special Protocol Assessment was submitted. The Executive Carcinogenicity Assessment Committee agreed with the Special Protocol Assessments, but they provided recommendations on the design of the studies.

An Agreed initial Pediatric Study Plan was issued by the Agency on 27 May, 2020. The agreed initial Pediatric Study Plan covered (b) (4), HTE adolescents ≥ 35 kg with MDR HIV would be enrolled in Study 4625. However, difficulties in enrollment of this population were anticipated, (b) (4)

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(b) (4). A plan to seek a waiver for HTE children <12 years of age was included.

On September 6, 2020, Meeting Preliminary Comments were issued for a Type C Chemistry, Manufacturing, and Controls (CMC) meeting requested to discuss the proposed excess volume for LEN 300 mg/mL and the design validation strategy for the lenacapavir vial kit. The meeting was canceled by the firm following receipt of preliminary comments.

On January 13, 2021, the Agency issued Preliminary Comments for a Type B Pre-NDA meeting requested under INDs 136260 and 138311, the purpose of which was to discuss the strategy for submission of NDAs for lenacapavir, key aspects related to content and format of the NDAs, to obtain feedback on the proposed content of the NDA Safety Update, and to seek feedback and agreement on the revisions to the dosing regimen used in the Phase 3 clinical trial. In the Preliminary Comments, the Agency agreed that clinical studies 4625 (primary registrational study in intended population), 4334 (supportive efficacy and safety study), and 4538 and 5709 (supportive safety studies) were appropriate to submit in the initial NDAs. Regarding the proposal to submit a simplified regimen that would include oral loading dose on Day 1 and Day 2 with the injection administered on Day 1, the Agency stated that the acceptability of the dosing regimen is contingent upon availability of adequate pharmacokinetic (PK), safety and efficacy data and would be a review issue. The Agency further agreed that having a single U.S. Prescribing Information for both injection and tablet dosage forms is appropriate. Regarding a transgenic mouse study draft report and SEND databases, the Agency requested that these be submitted either with the NDA or after approval. Following receipt of the Preliminary Comments the meeting was canceled.

On 11 February, 2021, the Agency provided the firm with Human Factors Validation Study Protocol Advice containing recommended protocol revisions in response to a Human Factors Validation Protocol submitted 11 December, 2020, regarding a co-package kit containing injection vials, syringes, vial access devices, and injection needles.

On 31 March, 2021, a Proprietary Name Request Unacceptable letter was issued by the Agency, detailing that the proposed proprietary name, SUNLENCA, could result in medication errors due to confusion with another product currently under review. Ultimate acceptability of the proposed name would be dependent upon which underlying application is approved first.

On 25 May, 2021, a Final Written Response was issued by the Agency in response to a type B, meeting, the purpose of which was to discuss phase 2/3 clinical data from Studies 4625 and 4334 in advance of NDA filing. The Agency agreed that the preliminary data from these studies were appropriate to support the firm's proposed initial NDAs.

12.1. Antiretroviral Drugs Approved for the Treatment of HIV-1

Table 69. Single-Entity Antiretroviral Drugs Approved for the Treatment of HIV-1

Drug Class (Abbreviation) [Number Currently Available in Class]	Full Drug Name (Abbreviation)
Nucleos(t)ide reverse transcriptase inhibitor (NRTI) [8]	Abacavir (ABC)
	Didanosine (ddI)
	Emtricitabine (FTC)
	Lamivudine (3TC)
	Stavudine (d4T)
	Tenofovir alafenamide (TAF)
	Tenofovir disoproxil fumarate (TDF)
	Zalcitabine (ddC) ^a
Non-nucleoside transcriptase inhibitor (NNRTI) [5]	Zidovudine (AZT)
	Delavirdine (DLV) ^a
	Doravirine (DOR)
	Efavirenz (EFV)
	Etravirine (ETR)
	Nevirapine (NVP)
Protease inhibitor (PI) [9]	Rilpivirine (RPV)
	Amprenavir (APV) ^a
	Atazanvir (ATV)
	Darunavir (DRV)
	Fosamprenavir (FPV)
	Indinavir (IDV)
	(b) (4)
	Nelfinavir (NFV)
	Ritonavir (RTV) ^b
Integrase strand transfer inhibitor (INSTI) [4]	Saquinavir (SQV)
	Tipranavir (TPV)
	(b) (4)
	Dolutegravir (DTG)
CCR5 co-receptor antagonist [1]	Elvitegravir (EVG)
HIV-1 gp41-directed fusion inhibitor [1]	Raltegravir (RAL)
CD4-directed post-attachment inhibitor [1]	Cabotegravir (CAB)
CYP3A Inhibitor [2]	Maraviroc (MVC)
	Enfuvirtide (T20)
HIV-1 gp120-directed attachment inhibitor [1]	Ibalizumab (IBA) ^d
	Cobicistat (COBI)
	Ritonavir (RTV) ^c
	Fostemsavir (FTR) ^d

Source: Reviewer's analysis.

^a Marketing discontinued by the manufacturer.

^b Drugs that inhibit metabolic enzymes and enhance the exposure of ARVs.

^c Although RTV is approved as a single-entity antiretroviral, it is most commonly used adjunctively as a CYP3A inhibitor.

^d Approved for treatment of heavily treatment-experienced adults with multidrug-resistant HIV-1.

Abbreviations: CCR, C-C chemokine receptor; CD, cluster of differentiation; gp, glycoprotein; HIV, human immunodeficiency virus

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 70. Coformulated Regimens

Trade Name (Abbreviations)	ARV Drugs Included in the STR	Dosing Recommendation^a	Approved Indications
INSTI plus Two NRTIs			
Biktarvy (BIC/TAF/FTC)	BIC 50 mg / TAF 25 mg / FTC 200 mg	One tablet once daily	Treatment-naïve Switch/maintenance
Genvoya (EVG/COBI/TAF/FTC)	EVG 150 mg / COBI 150 mg / TAF 10 mg/ FTC 200 mg	One tablet once daily with food	Treatment-naïve Switch/maintenance
Stribild (EVG/COBI/TDF/FTC)	EVF 150 mg / COBI 150 mg / TDF 300 mg/ FTC 200 mg	One tablet once daily with food	Treatment-naïve Switch/maintenance
Triumeq (DTG/ABC/3TC)	DTG 50 mg / ABC 600 mg / 3TC 300 mg	One tablet once daily	Limitation of use: no INSTI resistance
INSTI plus One NRTI			
Dovato (DTG/3TC)	DTG 50 mg / 3TC 300 mg	One tablet once daily	Treatment-naïve Switch/maintenance
PI plus Two NRTIs			
Symtuza (DRV/COBI/TAF/FTC)	DRV 800 mg / COBI 150 mg / TAF 10 mg / FTC 200 mg	One tablet once daily with food	Treatment-naïve Switch/maintenance
NNRTI plus Two NRTIs			
Atripla (EFV/TDF/FTC)	EFV 600 mg / TDF 300 mg / FTC 200 mg	One tablet once daily on an empty stomach, preferably at bedtime	Indicated as a “complete regimen or in combination” Treatment-naïve Switch/maintenance
Complera (RPV/TDF/FTC)	RPV 25 mg / TDF 300 mg / FTC 200 mg	One tablet once daily with a meal	Limitation: HIV-1 RNA ≤100,000 copies/mL
Delstrigo (DOR/TDF/3TC)	DOR 100 mg / TDF 300 mg / 3TC 300 mg	One tablet once daily	Treatment-naïve Switch/maintenance
Odefsey (RPV/TAF/FTC)	RPV 25 mg / TAF 25 mg / FTC 200 mg	One tablet once daily with a meal	Treatment-naïve Switch/maintenance Limitation: HIV-1 RNA ≤100,000 copies/mL
Symfi (EFV/TDF/3TC)	EFV 600 mg / TDF 300 mg / 3TC 300 mg	One tablet once daily on an empty stomach, preferably at bedtime	Indicated as a “complete regimen”
Symfi Lo (EFV/TDF/3TC)	EFV 400 mg / TDF 300 mg / 3TC 300 mg	One tablet once daily on an empty stomach, preferably at bedtime	Indicated as a “complete regimen”
INSTI plus One NNRTI			
Cabenuva (CAB/RPV)	CAB 600 mg / RPV 900 mg and CAB 400 mg / RPV 600 mg	IM injection monthly or every 2 months	Switch/maintenance only
Juluca (DTG/RPV)	DTG 50 mg / RPV 25 mg	One tablet once daily with a meal	Switch/maintenance only

Source: Adapted from the Department of Health and Human Services Guidelines (HHS 2019)

^a For dose adjustments in patients with renal or hepatic insufficiency, see individual drug labels. When no food restriction is listed, the STR can be taken with or without food.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; BIC, bictegravir; CAB, cabotegravir; COBI, cobicistat; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; STR, single-tablet regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

Selected nonclinical studies were originally submitted and reviewed under INDs 136260 and 138311. All nonclinical safety studies conducted in support of LEN were also submitted to the present NDA and are reviewed in the following sections.

13.2. Individual Reviews of Studies Submitted to the NDA

The nonclinical studies were originally submitted under IND 138311 for the oral route of administration and under IND 136260 for the subcutaneous route. Both routes of exposure were used in clinical trials; the oral as a lead-in and the subcutaneous route for maintenance, given once every 6 months. All selected nonclinical safety studies conducted in support of LEN (also referred to as GS-6207 in nonclinical study reports) were also submitted to NDA 215973 and are reviewed in the following sections.

13.2.1. Individual Reviews of Studies Submitted to the NDA

13.2.1.1. Secondary Pharmacology

At 10 μ M, LEN showed no response (inhibition or induction >50%) against a panel of 87 receptors, ion channels, and transporters.

13.2.1.2. Safety Pharmacology

Table 71. Safety Pharmacology Studies

Study Title/Study No.	Findings
Cardiovascular function via SC injection (TX-200-2006) Beagle dogs (6/sex/dose) 0, 10, 30, and 100 mg/kg/dose Once every 2 weeks for four total doses	(b) (4) administration did not produce any significant effects on electrocardiography parameters at doses up to 100 mg/kg, the highest dose tested.
Central nervous system function via SC injection (TX-200-2005) Wister Han rats (20/sex/group) 0, 10, 30, and 100 mg/kg/dose One dose given every other week for four total doses	(b) (4) had no significant effects on the functional observational battery of tests.

Study Title/Study No.	Findings
Respiratory system function via SC injection (PC-200-2014) Wister Han rats, males 0, 10, 30, and 100 mg/kg Single dose	LEN administration resulted in a 5% increase in tidal volume at 30 mg/kg and a 11% increase in the 100 mg/kg compared to controls that lasted up to 72 hours postdose. There was no effect on respiration rate at 10 or 30 mg/kg compared to controls but there was a 6% decrease at 100 mg/kg. Although GS-6207 related differences in mean tidal volume and respiration rate were noted in the high dose groups, these differences were not statistically significant. The NOAEL for respiration is 30 mg/kg based on the GS-6207 related decrease in respiration rate at 100 mg/kg.

Source: Reviewer.

Abbreviations: LEN, lenacapavir; NOAEL, no observable adverse effect level; SC, subcutaneous

13.2.2. Absorption, Distribution, Metabolism, Excretion/PK

Absorption

In Vitro

- The bidirectional permeability of GS-6207 was investigated using monolayers of the human colon carcinoma cell line (Caco-2). Refer to Section [14.1.1](#) for more information.

In Vivo

Oral single dose absorption studies were conducted in Sprague Dawley rats (5 mg/kg), Beagle dogs (4 mg/kg), and Cynomolgus and Rhesus monkeys (4 mg/kg) following oral administration of GS-6207.

- The time to maximum concentration (T_{max}) ranged from 8.7 to 18.7 across species.
- An exposure (area under the concentration-time curve [AUC_{INF}]) was not determined for Cynomolgus monkeys. However the exposure in Rhesus monkeys was 1133nM•h. In rats and dogs, the exposure was 25,200 and 16,533nM•h, respectively. In addition, the C_{max} was 336, 471, 17.7, and 29.4nM in rats, dogs, Cynomolgus and Rhesus monkeys, respectively.

The pharmacokinetic profile of GS-6207 in various formulations was conducted in multiple studies in rats, dogs, and monkeys. The oral routes in these studies were administered formulations for liquid capsules, liquid-filled capsules, and tablets. The subcutaneous routes of administration were different formulations (b) (4)

(b) (4), and GS-6207 as a (b) (4) or sodium salt. Selected studies to support the final oral and subcutaneous formulations are presented below.

The PK profile of various GS-6207 formulations was evaluated in Beagle dogs. The pharmacokinetic parameters for the different formulations are presented in [Table 72](#); GS-6207 in various liquid capsule formulation is presented in [Table 73](#); and GS-6207 formulated as tablets (40, 80, or 300 mg) or liquid-filled capsules (40 mg) is presented in [Table 74](#).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 72. Pharmacokinetic Parameters of Various Formulations of GS-6207 Following a Single Oral Administration in Male Beagle Dogs

Group ID / Formulation	Dose (mg/kg)	Number of Animals	AUC _{last} (μM•h)	AUC _{inf} (μM•h)	C _{max} (μM)	T _{max} (h)
1/A	30	3	59.7 ± 82.4	60.9 ± 84.3	2.967 ± 4.189	3.3 ± 1.2
2/B	30	3	69.6 ± 58.6	70.6 ± 58.5	2.472 ± 1.957	16.7 ± 12.7
3/C	30	6	92.9 ± 33.6	93.1 ± 33.5	3.225 ± 1.614	10.0 ± 8.0
4/B	100	6	148 ± 37	148 ± 37	4.253 ± 0.732	12.0 ± 0.0
5/C	100	6	120 ± 52	121 ± 53	2.890 ± 0.860	15.7 ± 9.7

Formulation A: (b) (4)

(b) (4)

Formulation B: (b) (4)

Formulation C:

Source: Pharmacokinetic study report AD-200-2019.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; ID, identity; T_{max}, time to maximum concentration

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 73. Pharmacokinetic Parameters of GS-6207 in Liquid Capsules Following a Single Oral Administration in Male Beagle Dogs

Group ID / Formulation	GS-6207 Dose Concentration (mg/mL)	Fasted or Fed	Pretreatment	AUC _{0-72h} (nM•h) ^a	AUC _{inf} (nM•h) ^a	C _{max} (nM) ^a	T _{max} (h) ^a	F% ^{a,b}
1 / A	10	Fasted	None	2447 ± 1124	2591 ± 1196	147 ± 29	7.3 ± 8.2	25 ± 12
2 / B	10	Fasted	None	2539 ± 1128	2700 ± 1222	118 ± 43	11.0 ± 10.1	26 ± 13
3 / B	10	Fasted	Pentagastrin	2792 ± 703	3339 ± 864	114 ± 45	4.7 ± 1.6	35 ± 8
4 / B	50	Fasted	Pentagastrin	1993 ± 767	2256 ± 987	64.8 ± 12.5	4.8 ± 1.8	26 ± 11
5 / B	50	Fed	None	1778 ± 856	2155 ± 1126	70.3 ± 19.6	4.7 ± 1.6	21 ± 9
6 / B	100	Fasted	Pentagastrin	1197 ± 465	1791 ± 1334	51.4 ± 16.6	5.3 ± 2.1	15 ± 7
7 / A	100	Fasted	Pentagastrin	1346 ± 390	1953 ± 823	59.7 ± 20.2	5.3 ± 2.1	17 ± 5
8 / C	100	Fasted	Pentagastrin	1181 ± 575	1303 ± 634	53.2 ± 16.7	7.7 ± 8.0	11 ± 4
9 / D	100	Fasted	Pentagastrin	1667 ± 1045	1867 ± 1188	71.2 ± 25.8	5.0 ± 1.1	16 ± 9
10 / D	50	Fasted	Pentagastrin	2178 ± 1243	2329 ± 1348	82.7 ± 32.1	4.0 ± 0.0	22 ± 10

^a Values are the mean ± standard deviation from 6 animals.

^b %F calculated based on AUC_{0-72h} with average IV AUC_{0-72h} = 13,467 nM•h at 1 mg/kg from report AD-200-2011.

See footnotes for formulation content, fasting condition and pretreatment in Table 1.

Formulation A: liquid filled capsule (LFC) (b) (4); Formulation B: LFC (b) (4), (b) (4); Formulation C: LFC (b) (4); Formulation D: LFC (b) (4)

Under fasted condition, animals were fasted at least 12 hours prior to dosing and fed 4 hours post dose. Under fed condition, animals were fed 2 hours prior to dosing.

For the pentagastrin-pretreated dog model, pentagastrin (6 µg/kg) was administered intramuscularly ~ 30 minutes prior to dosing to ensure an acidic pH in the gastrointestinal tract.

Source: Pharmacokinetic study report AD-200-2036.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; F, bioavailability; ID, identity; IV, intravenous; T_{max}, time to maximum concentration

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 74. Pharmacokinetic Parameters of GS-6207 Following a Single Oral Administration in Male Beagle Dogs

Group ID	GS-6207 Dose (mg fixed)	Fasted ^a or Fed	AUC _{0-72h} (nM•h)	AUC _{inf} (nM•h)	C _{max} (nM)	F%
1	40	Fasted	4495 ± 3408	5030 ± 3783	166 ± 64	8.5 ± 6.3
2	40	Fasted	3376 ± 2945	4440 ± 3527	151 ± 79	7.7 ± 6.4
3	40	Fed	4573 ± 3348	5548 ± 4149	162 ± 93	9.4 ± 7.6
4	80	Fasted	6945 ± 1652	7704 ± 1791	437 ± 108	6.9 ± 1.9
5	300	Fasted	15841 ± 10000	18554 ± 11070	718 ± 409	4.3 ± 2.9

a Animals in the fasted group were pre-treated with pentagastrin (6 µg/kg intramuscular injection) to ensure an acidic pH in the gastrointestinal tract

Source: Pharmacokinetic study report AD-200-2042.

Group 1: Liquid filled capsule per dog (b) (4)

Group 2: One tablet per dog in (b) (4)

Groups 3 to 5: One tablet per dog in (b) (4)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; F, bioavailability; ID, identity; IV, intravenous; T_{max}, time to maximum concentration

LEN as a free acid or sodium salt in aqueous solution was administered to male Beagle dogs via a single subcutaneous injection. The pharmacokinetic profile of LEN free acid or sodium salt is presented in [Table 75](#).

Table 75. Pharmacokinetic Parameters of LEN Sodium Salt in Beagle Dogs Following Subcutaneous Administration

LEN Ionization State	Group ID	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	AUC _{0-72h} (µM•h)	AUC _{last} (µM•h)	AUC _{inf} (µM•h)	C _{max} (µM)	T _{max} (h)
Free Acid	1	6 ^a	200	0.03	0.98 ± 0.16	72.7 ± 20.8	88.9 ± 28.0	0.063 ± 0.019	392 ± 97
	2	12 ^b	200	0.06	2.24 ± 0.36	124 ± 24	138 ± 19	0.144 ± 0.034	448 ± 97
	3	12 ^b	300	0.04	1.09 ± 0.51	126 ± 72	NC	0.143 ± 0.082	392 ± 97
	4	12 ^b	400	0.03	0.83 ± 0.36	111 ± 14	NC	0.107 ± 0.013	336 ± 0
Sodium Salt	5	6 ^c	100	0.06	9.90 ± 6.06	91.7 ± 4.1	91.9 ± 4.1	0.259 ± 0.069	240 ± 166
	6	6 ^c	200	0.03	4.92 ± 0.58	83.6 ± 18.0	84.4 ± 18.0	0.392 ± 0.097	392 ± 97
	7	6 ^c	300	0.02	2.98 ± 1.91	43.2 ± 50.8	44.6 ± 50.2	0.122 ± 0.154	144 ± 166

Source: Pharmacokinetic study report AD-200-2039.

^a Formulated as solution in (b) (4) water.

^b Formulated as solution in (b) (4) water.

^c Formulated as solution in (b) (4) water.

Values are means ± standard deviation from n=3 dogs.

Abbreviations: AUC, area under the concentration-time curve; C, concentration; LEN, lenacapavir; NC, not calculated due to insufficient data; PEG, polyethylene glycol; T, time of concentration observed; T_{1/2}, half-life; T_{max}, time to maximum concentration

The PK profile of a single subcutaneous injection of 12 mg/kg GS-6207 formulated in polyethylene glycol 300 aqueous solution was evaluated in male Beagle dogs. The PK parameters are presented in [Table 76](#).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 76. Pharmacokinetic Parameters of GS-6207 (12 mg/kg) Following a Single SC Administration in Male Beagle Dogs (Mean±SD, n=3)

AUC _{last} (μM•h)	C _{max} (μM)	T _{max} (h)
139 ± 8	0.133 ± 0.010	336 ± 0

Source: Pharmacokinetic study report AD-200-2051.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; SC, subcutaneous; SD, standard deviation; T_{max}, time to maximum concentration

The PK profile of GS-6207 following intravenous (IV) or oral administration was evaluated in portal vein cannulated male Cynomolgus monkeys and Beagle dogs with or without the cytochrome P450 (CYP) inhibitor, aminobenzotriazole, to understand the role of CYP metabolism of GS-6207. The results from these studies indicated that pretreating dogs and monkeys with aminobenzotriazole did not change GS-6207 oral exposure in dogs or monkeys, suggesting role of intestinal metabolism of GS-6207.

Distribution

In Vitro

- Protein binding was evaluated in plasma from CD-1 mice. GS-6207 was 99.8% protein-bound (unbound fraction was 0.18%) at a concentration of 2μM.
- The distribution between the cellular and soluble fractions of blood was evaluated in whole blood from Sprague Dawley rats, Beagle dogs, Cynomolgus and Rhesus monkeys, and humans. At an initial concentration of 0.5μM, GS-6207 was nearly excluded from the blood cellular fraction with the blood:plasma concentration ratios in animals being 0.59 to 0.67 and 0.64 in human.
- Protein binding was evaluated in plasma from Sprague Dawley rats, Beagle dogs, Cynomolgus and Rhesus monkeys, and humans. GS-6207 was ≥98% protein-bound in all animals and human (unbound fraction was 0.13, 0.83, 1.11, 1.45, and 1.46% in rat, dogs, Cynomolgus monkey, Rhesus monkey, and human, respectively) at 10mM.

In Vivo

- The absorption, tissue distribution and excretion of [¹⁴C]GS-6207 was evaluated following a single IV (3 mg/kg-IV; n=3 to 26) dose of GS-6207 in both intact and bile duct-cannulated nonpigmented male Wistar Hanover and intact pigmented Long Evans rats. The highest concentration was in the liver in both species of rats up to 1008 hours (42 days) followed by kidney cortex, kidneys, pancreas, kidney medulla, brown fat, and thyroid. GS-6207 was cleared from all organs by 672 hours and in the liver by 1344 hours (56 days).

Metabolism

In Vitro

- The metabolic profile of GS-6207 was evaluated in Wistar Han rat, Beagle dog, cynomolgus and Rhesus monkey, and human microsomes and hepatocytes in vitro.
 - In all animal species and human microsomes, 90 to 94% of radioactivity detected was from unchanged [¹⁴C]GS-6207. In microsomes, [¹⁴C]GS-6207 metabolism occurred via oxidation, reduction, defluorination, and glutathione conjugation.

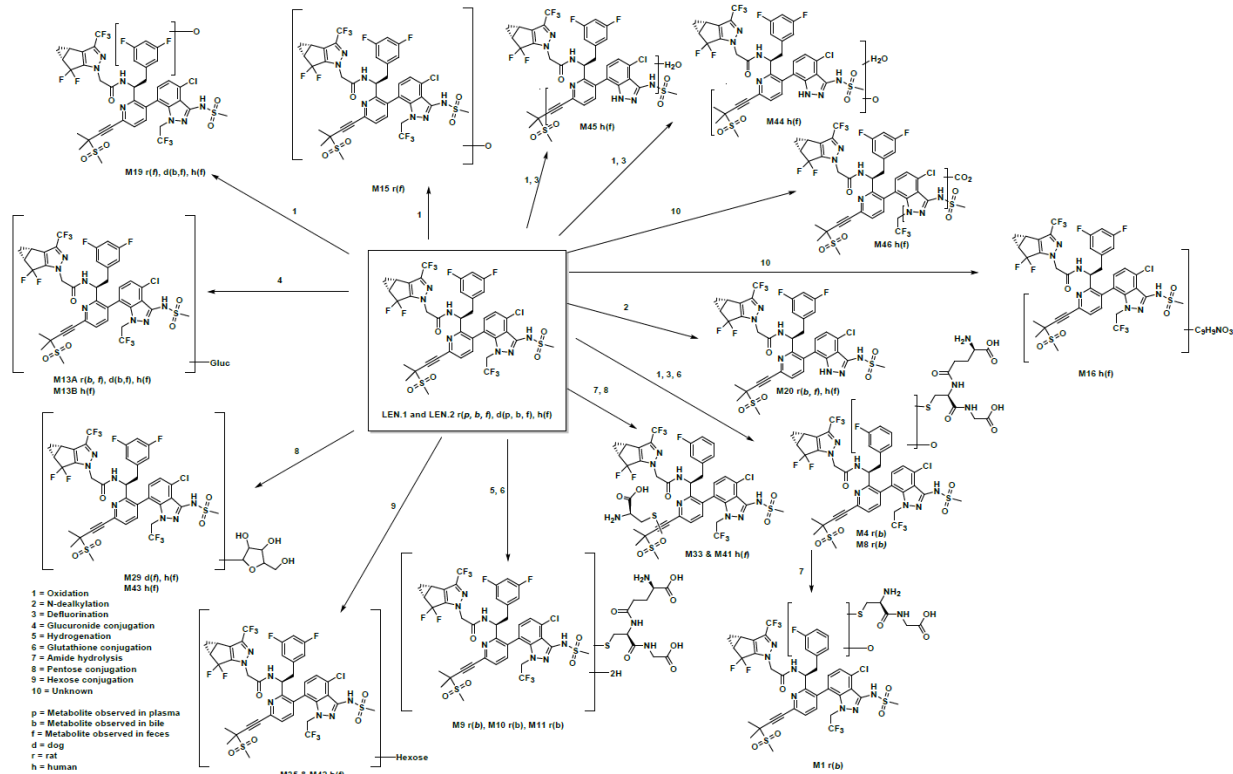
NDA 215973 lenacapavir injection, for subcutaneous use
 NDA 215974 lenacapavir tablets, for oral use

- Metabolism in hepatocytes occurred via glutathione conjugation, pentose conjugation, and glucuronidation. Oxidative metabolites were not detected.
- There were no unique human metabolites.

In Vivo

- The metabolism of [14C]GS-6207 was evaluated in plasma, urine, bile, and feces from intact and bile duct-cannulated Sprague Dawley rats and Beagle dogs.
- The proposed metabolic pathways in the rat, dog and human are presented in [Figure 33](#).

Figure 33. Proposed Biotransformation Pathways of LEN in Sprague-Dawley Rats, Beagle Dogs, and Humans



Source: Pharmacokinetic written summary.
 Abbreviation: LEN, lenacapavir

Excretion

- The excretion of GS-6207 was evaluated following a single 30-minute IV infusion (1 mg/kg; n=3) in male bile-duct cannulated male Sprague Dawley rats. The results indicate that GS-6207 is excreted into the intestines by the P-glycoprotein (P-gp) transporter and excreted in rat feces.
- The absorption and excretion of [14C]GS-6207 was evaluated following a single 1 mg/kg IV dose in intact and bile-duct cannulated Beagle Dogs and a 2 mg/kg oral dose in intact dogs. The results indicated that GS-6207 was primarily excreted in the feces.

13.2.3. General Toxicology

13.2.3.1. Single-Dose Toxicology/Toxicokinetics

A single dose subcutaneous (SC) dose range-finding toxicology study was conducted to determine the doses to use in future carcinogenic studies to characterize the potential long-term carcinogenic effects of GS-6207. The study was evaluated in rasH2 Transgenic mice (0, 30, 99, or 300 mg/kg) with a 13-week recovery period.

- The skin at the injection site and the liver appeared to be the targeted organs of toxicity.
- The liver weight was increased at 99 and 300 mg/kg and was correlated with slight centrilobular hepatocyte vacuolation, an increased incidence of minimal hepatocyte degeneration/necrosis, and an increase in alanine aminotransferase (ALT) at 300 mg/kg.
- Injection site reactions were observed in various animals at each dose in females and at 300 mg/kg in males; a palpable mass was detected at 300 mg/kg.
- Hematology findings (increases in white blood cells, lymphocytes, and eosinophils in males and leukocytes) were detected sporadically in males and females at each dose.
- The no observable adverse effect level (NOAEL) was 300 mg/kg in males and 99 mg/kg in females due to clinical observations and gross and histopathology findings at the injection site and histopathology findings in the liver at 300 mg/kg.

A single dose intravenous toxicology study to characterize potential systemic effects of GS-6207 was evaluated via a 30-minute IV infusion to Wistar Han rats (0, 3, 10, or 30 mg/kg) with a 15-day recovery period.

- Several rats dosed with GS-6207 or control had to be euthanized early because of declining health due to the infusion procedure.
- Clinical observations were noted in various rats at each dose (red urine, ataxia, hypoactivity, vocalization, squinting and/or pale eyes, audible/labored/irregular breathing, and sternal recumbence).
- Decrease in body weight gain was observed in male rats at 30 mg/kg.
- Increases in neutrophil counts, ALT, creatine kinase (CK), positive blood urine, and liver weights were observed at 10 and/or 30 mg/kg.
- Hemorrhage of valve leaflets, mixed cell inflammation, and myocardial degeneration/necrosis was found in dosed and control animals.
- Infusion site reactions (cellular inflammation, thrombus, congestion/hemorrhage, edema, and fibrosis) were noted at all doses.

To characterize potential systemic effects, GS-6207 was evaluated via a single 30-minute IV infusion to Beagle dogs (0, 3, 10, or 30 mg/kg) with a 15-day recovery period.

- Clinical observations (skin lesions, intermittent tremors, vocalization, and/or discharge of the left eye and front foot) were observed at all doses and in controls. These observations were unlikely related to GS-6207 and IV dosing procedure because they were noted in controls.
- A GS-6207-related decrease in body weight gain was observed in all dogs at doses ≥ 3 mg/kg that only correlated with a decrease in food consumption in female dogs. The decrease in weight in dogs lasted throughout recovery.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

- Hematology findings (red blood cell count, hemoglobin, and hematocrit), prothrombin time or activated partial thromboplastin time prolongation, and an increase in hepatic enzymes were noted at 30 mg/kg.
- Histopathology findings in the liver included hepatocyte degeneration (at ≥ 3 mg/kg in males and ≥ 10 mg/kg in females), individual necrosis (30 mg/kg in two males and at 10 mg/kg in one female), mixed cell infiltrate (at ≥ 10 mg/kg in males and females), and hemorrhage (one male and three females and 30 mg/kg and one female at ≥ 3 mg/kg). The GS-6207-related liver findings at Day 2 were not detected at Day 15.

Table 77. Toxicokinetics Parameters for Single Intravenous Doses of LEN in Rats and Dogs

Species	N/Sex	Route	Dose (mg/kg)	T _{max} (Hours)		C _{max} (ng/mL)		AUC _{0-inf} (ng•hr/mL)	
				M	F	M	F	M	F
WH rats	9M 9F	IV	3	1.5	0.58	1,340	1,240	35,900	35,200
			10	0.75	0.58	4,830	4,590	103,000	107,000
			30	0.75	0.58	14,100	12,300	239,000	223,000
Beagle dogs	2 to 5M 2 to 5F	IV	3	0.58	0.58	5,140	5,140	39,200	31,500
			10	0.58	0.58	15,600	15,400	265,000	124,000
			30	0.58	0.58	32,700	45,200	463,000	1,070,000

Source: Study reports TX-200-2029 and TX-200-2030.

Abbreviations: AUC, area under the concentration-time curve; C, concentration; C_{max}, maximum concentration; F, female; IV, intravenous; M, male; T, time of concentration observed; T_{max}, time to maximum concentration; WH, Wister Han

13.2.3.2. Repeat-Dose Toxicology/Toxicokinetics

A 4-Week Oral Gavage Toxicity and Toxicokinetic Study of GS-6207 in Wister Han Rats (TX-200-2011)

Key Study Findings

- No target organ of toxicity was identified.
- Longer clotting time (activated partial thromboplastin time) in males was noted at all doses and an increase in cholesterol was noted in females at all doses. These findings were not considered adverse and the significance of these findings is unclear as there was no other data to correlate with the findings.
- The NOAEL was 30 mg/kg.
 - The Day 28 AUC_{0-24hr} (male and female combined) was 34,500 ng•h/mL.
- The exposure margin was 26× based on predicted human exposures based on the recommended human dose (RHD).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 78. Four-Week Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 3, 10, and 30 mg/kg/day; given once daily for 4 weeks.
Route of administration	Oral gavage
Formulation/vehicle	(b) (4)
Species/strain	Rat/Wistar Hanover
Number/sex/group	10/sex/group (toxicity) 3/sex/control (TK) 9/sex/group (TK)
Age	7 weeks
Conducting laboratory	(b) (4)
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer.

Abbreviations: GLP, good laboratory practices; TK, toxicokinetic; (b) (4)

Table 79. Four-Week Rat Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily for mortality, abnormalities, and signs of pain and distress. No treatment-related deaths.
Clinical signs	Clinical signs were monitored at least once daily. No treatment-related findings.
Body weights	Body weights were recorded weekly. No treatment-related findings.
Ophthalmoscopy	Ophthalmic exams were conducted once at predose and on dose day 25 for the control and dosed groups. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals on dose days 7 and 28. No treatment-related findings.
Clinical chemistry	Blood samples were collected from fasted animals on dose days 7 and 28. Clotting time (APTT) was 5% longer in males at doses ≥ 10 when compared with controls. Cholesterol was increased (21 to 36%) in a non-dose dependent manner in all dosed females when compared with the controls on days 7 and 29 of dosing. Although the significance of this finding is unclear it appears to be test-article related but not a toxicity concern because there were no other pathology changes to correlate with this effect. There were no test-article related effects on coagulation noted in males.
Urinalysis	Urine was collected on during the overnight period before days 7 and 28. No treatment-related findings.
Gross pathology	Animals were sacrificed on day 29. No treatment-related findings.
Organ weights	No treatment-related findings.
Histopathology	No treatment-related findings.
Adequate battery:	Yes
Special evaluation: Hepatic enzymes	A 2.7-fold increase in CYP3A activity was observed in female animals dosed with 30 mg/kg compared with controls. There were no effects in males.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Parameter	Major Findings					
Toxicokinetics Sample collection times: days 1 and 28 predose and 1, 3, 8, and 12 hours postdose.	Four-Week Toxicokinetic Parameters in Rat With Oral Administration					
	GS-6207 (mg/kg/dose)	Sex	AUC ₀₋₂₄ (ng•h/mL)		C _{max} (ng/mL)	
			Day 1	Day 28	Day 1	Day 28
	3	Male	2890	16400	178	829
		Female	2700	14200	149	658
		MF Combined	2790	15300	144	712
	10	Male	12000	27800	727	1500
		Female	8560	27800	439	1460
		MF Combined	10300	27800	583	1480
	30	Male	16200	33700	792	1650
Female		14700	35400	889	2110	
MF Combined		15400	34500	790	1700	
Source: TX-200-2011 Male (M); female (F) Source: Table 4 from the Applicant's toxicology written summary.						

Source: Reviewer.

Abbreviations: APTT, activated partial thromboplastin time; AUC, area under the concentration-time curve; C, concentration; C_{max}, maximum concentration; CYP, cytochrome P450; F, female; M, male

A 4-Week Oral Gavage Toxicity and Toxicokinetic Study of GS-6207 in Dogs (TX-200-2012)

Key Study Findings

- A nonadverse increase in liver enzymes in one male and one female at 30 mg/kg that correlated with slight biliary duct hyperplasia in the female.
- Dose dependent increase in male liver weights without correlative gross pathology or histopathology was not considered adverse.
- The NOAEL was 30 mg/kg.
 - Exposure on Day 28: AUC_{0-24h} (male and female combined) was 75,900 ng•h/mL and maximum concentration (C_{max}) was 2790 ng/mL.
- The exposure margin was 58× based on predicted human exposures based in the RHD.

Table 80. Four-Week Dog Oral Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 1, 5, and 30 mg/kg/day; once daily for 4 weeks.
Route of administration	Oral gavage
Formulation/vehicle	(b) (4)
Species/strain	Dog/Beagle
Number/sex/group	4/sex/group
Age	9 to 10 months old
Conducting laboratory	(b) (4)
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer.

Abbreviations: GLP, good laboratory practices; (b) (4)

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 81. Four-Week Dog Oral Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily. One male animal dosed with 30 mg/kg was necropsied on day 19 due to oral gavage error.
Clinical signs	Clinical signs were monitored twice daily. Struggling during dosing occurred in dosed males and females in more animals and at greater incidence at 30 mg/kg groups. The significance of the finding is unclear.
Body weights	Body weights were recorded weekly. No treatment-related findings.
Ophthalmoscopy	Ophthalmic exams were conducted on the control and dosed groups prior to treatment and at dose day 25. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals on day 7 and 29. No treatment-related findings.
Clinical chemistry	Blood samples were collected from fasted animals on day 7 and 29. There was an increase in ALT in 1 male (111%; 2-fold) and one female (459%; 5.5-fold) at 30 mg/kg when compared with the controls. However, this female (#D0704) also had an increase in AST (137.5%; 2-fold), ALP (158%; 2.6-fold), and GGT (100%; 2-fold). The findings in this female correlated with slight bile duct hyperplasia. These findings indicate a potentially small test-article related effect on the liver.
Urinalysis	Urine was collected during the overnight period prior to days 7 and 29. No treatment-related findings.
Gross pathology	Animals were sacrificed on day 29. No treatment-related findings.
Organ weights	Although not statistically significant, there was a test-article related increase in relative (to body weight) liver weights in males by 8, 10, and 29% in the 1, 5, and 30 mg/kg groups, respectively. There were gross pathology and histopathology findings to correlate with the increased weights.
Histopathology	Bile duct: One female animal dosed with 30 mg/kg had slight bile duct hyperplasia that correlated with an increase AST, ALT, and GGT.
Adequate battery: Yes	
Special evaluation: Hepatic enzymes	In females there was an increase (≥ 2 -fold) in CYP1A and CYP2B activities at 1 and 30 mg/kg, respectively.

Toxicokinetics

Sample collection times: days 1 and 28 predose and 1, 3, 8, and 12 hours postdose.

Four-Week Toxicokinetic Parameters in Rat With Oral Administration

GS-6207 (mg/kg/dose)	Sex	AUC ₀₋₂₄ (ng•h/mL)		C _{max} (ng/mL)	
		Study Day 1	Study Day 28	Study Day 1	Study Day 28
1	Male	1920	4610	129	263
	Female	1400	2270	92.7	146
	MF Combined	1660	3440	111	204
5	Male	9510	20400	721	1310
	Female	6500	18200	467	1160
	MF Combined	8010	19300	594	1230
30	Male	54700	82900	3110	4520
	Female	45700	70600	2470	4290
	MF Combined	50200	75900	2790	4390

Source: TX-200-2012

Source: Table 14 from the Applicant's toxicology written summary.

Source: FDA reviewer.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; C, concentration; CYP, cytochrome P450; F, female; GGT, gamma-glutamyl transferase; M, male

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

A Four-Dose (Twice Monthly) Subcutaneous Injection Toxicity and Toxicokinetic Study of GS-6207 in Wister Han Rats (TX-200-2005)

Key Study Findings

- Injection site reactions, in all dosed rats, and thickening of the skin were observed during gross pathology analysis and was correlated with granulomatous inflammation observed during histopathology.
- Systemic toxicity was not observed. The NOAEL, based on injection site reactions, could not be determined due to injection site reactions at all doses.
- The NOAEL based on systemic effects was 100 mg/kg.
 - Exposure on study Day 43 (male and female combined): AUC_{0-336h} was 583,000 ng·h/mL and C_{max} was 2080 ng/mL.
- The exposure margin, based on the lack of systemic effects, was 32× based on predicted human exposures based in the RHD.

Table 82. Four-Dose Rat SC Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 10, 30, and 100 mg/kg/dose; one dose given every other week (four doses total)
Route of administration	Oral gavage
Formulation/vehicle	(b) (4) sterile water for injection, USP
Species/strain	Rat/Wistar Hanover
Number/sex/group	20/sex/group (toxicity) 3/sex/control (TK) 12/sex/group (TK)
Age	6 to 7 weeks
Conducting laboratory	(b) (4)
Deviation from study protocol affecting interpretation of results	None

Source: FDA reviewer.

Abbreviations: GLP, good laboratory practices; TK, toxicokinetic; USP, United States Pharmacopeia

Table 83. Four-Dose Rat SC Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily for mortality, abnormalities, and signs of pain or distress. One control male was found dead on day 21 soon after shaving. One female dosed with 10 mg/kg was found dead on day 15 (TK assigned animal). The death of the male was procedure related. Since there were no changes in weight or abnormal clinical findings in the female animal, the death of this animal is unknown, but it is not likely related to GS-6207 since there were no deaths at higher doses.
Clinical signs	Clinical signs were monitored at least once daily. No treatment-related findings.
Body weights	Body weights were recorded weekly. The week following the first dose there was a statistically significant decrease in body weight gain by 14 and 17% in males at 10 and ≥ 30 mg/kg/dose, respectively. Additional in males, the week following the third dose, there was a statistically significant decrease in body weight gain by 16% at 100 mg/kg. In females, the week following the first dose there was a statistically significant decrease in body weight gain by 21 and 17% at 30 and 100 mg/kg/dose, respectively.
Feed consumption	Food intake was measured weekly. No treatment-related findings.
Ophthalmoscopy	Ophthalmic exams were conducted on the control and dosed groups prior to treatment and at week 12. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals at terminal sacrifice 1 (Day 57) and terminal sacrifice 2 (Day 85). No treatment-related findings.
Clinical chemistry	Blood samples were collected from fasted animals at terminal sacrifice 1 (Day 57) and terminal sacrifice 2 (Day 85). On Day 57, there was a 29.7 and 32.8% increase in cholesterol in males and females, respectively, at 100 mg/kg/dose. On Day 85 (end of recovery period; 6 weeks after the last dose) the cholesterol remained increased in males only (by 18%) at 100 mg/kg/dose.
Urinalysis	Urine was collected during the overnight period prior to terminal sacrifice 1 (Day 57) and terminal sacrifice 2 (Day 85). No treatment-related findings.
Gross pathology	Thickening of the skin was observed at the SC injection sites at all doses in males; at doses ≥ 30 mg/kg/dose in females at the end of dosing period and in all dosed groups at the end of the recovery period.
Organ weights	At the end of the dosing period there was an 8 and 11% increase in relative (to body and brain weights, respectively) liver weight at 100 mg/kg/dose in males. In females, there was a 7.6 and 11% increase in relative (to body and brain weights, respectively) liver weight at 100 mg/kg/dose. Although this increase appears to be test-article related there were no increases in hepatic enzymes or effects on liver histopathology to correlate with these effects. There were no effects on liver weights at the end of the recovery period.
Histopathology Adequate battery: Yes	<u>Injection sites</u> : Test-article related effects at the injection sites observed during gross pathology correlated with granulomatous inflammation observed during histopathology analysis in all doses at terminal necropsy 1 and terminal necropsy 2. Moderate inflammation occurred mostly at doses ≥ 30 mg/kg/dose and marked inflammation was only observed at 100 mg/kg/dose.
Special evaluation: Hepatic enzymes	In females at 100 mg/kg/dose, there was a 2.3-fold increase in CYP3A.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Parameter	Major Findings					
Toxicokinetics Sample collection times: days 1 and 43 predose and 8, 24, 48, 72, 96, 168, 336, 672 (Day 43 only), 1008 (Day 43 only), 1344 (Day 43 only), and 1680 (Day 43 only) hours postdose.	Week-2 Toxicokinetic Parameters for the Rat With Oral Administration					
	Dose (mg/kg/dose)	Sex	AUC _{0-336h} (ng·h/mL)		C _{max} (ng/mL)	
			Day 1	Day 43	Day 1	Day 43
	10	Male	64,100	134,000	241	410
		Female	55,700	106,000	215	451
		MF Combined	59,900	120,000	203	419
	30	Male	146,000	314,000	586	1060
		Female	124,000	244,000	445	843
		MF Combined	135,000	279,000	516	945
	100	Male	338,000	608,000	1230	2500
Female		338,000	559,000	1290	2130	
MF Combined		338,000	583,000	1260	2080	

Source: Table 4 from the Applicant's toxicology written summary.

Source: FDA reviewer.

Abbreviations: AUC, area under the concentration-time curve; C, concentration; C_{max}, maximum concentration; CYP, cytochrome P450; F, female; M, male; SC, subcutaneous; T, time of concentration observed; TK, toxicokinetic

A Single- and Two-Dose Subcutaneous Injection Toxicity and Toxicokinetic Study With Three Formulations of GS-6207 in Wister Han Rats With a 13-Week Observation Period After Each Dose (TX-200-2014)

Key Study Findings

- GS-6207-related edema, skin thickening and/or discoloration, granulomatous inflammation, and macrophage infiltrate were present at the injection site in all formulations. The incidence and severity were highest with the 400 mg/mL without (b) (4) formulation and lowest with the 200 mg/mL without (b) (4). Findings of granulomatous inflammation were still present at the end of the recovery periods but showed signs of recovery.
- In general, exposure, AUC and C_{max} (male and female combined), were similar for all three formulations and there was no difference in exposure between sexes.
 - Day 92 exposure profiles:
 - C_{max} and AUC₀₋₆₇₂ values were 742 ng/mL and 307,000 ng·h/mL, respectively, in animals dosed with 200 mg/mL GS-6207 without (b) (4).
 - C_{max} and AUC₀₋₆₇₂ values were 780 ng/mL and 284,000 ng·h/mL, respectively, in animals dosed with 200 mg/mL GS-6207 with (b) (4).
 - C_{max} and AUC₀₋₆₇₂ values were 451 ng/mL and 211,000 ng·h/mL, respectively, in animals dosed with 400 mg/mL GS-6207 without (b) (4).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 84. One- or Two-Dose Rat SC Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0 and 100 mg/kg/dose in three formulations
Route of administration	SC injection
Formulation/vehicle	(b) (4) Water
Species/strain	Rat/Wistar Hanover
Number/sex/group	10/sex/group (toxicity) 3 to 4/sex/group (TK)
Age	6 to 8 weeks
Conducting laboratory	(b) (4)
Deviation from study protocol affecting interpretation of results	None. The Applicant considered this their 6-month rat study. All animals in groups 1 to 8 were dosed on day 1 and observed for 13 weeks. Groups 1 to 4 were necropsied after the 13-week observation period whereas groups 5 to 8 received a second dose (Day 92) and observed for 13 weeks. Following this 13-week observation period, groups 5 to 8 were necropsied.

Source: FDA reviewer.

Abbreviations: GLP, good laboratory practices; SC, subcutaneous; PEG, polyethylene glycol; TK, toxicokinetic

Table 85. One- or Two-Dose Rat SC Toxicity Study Findings

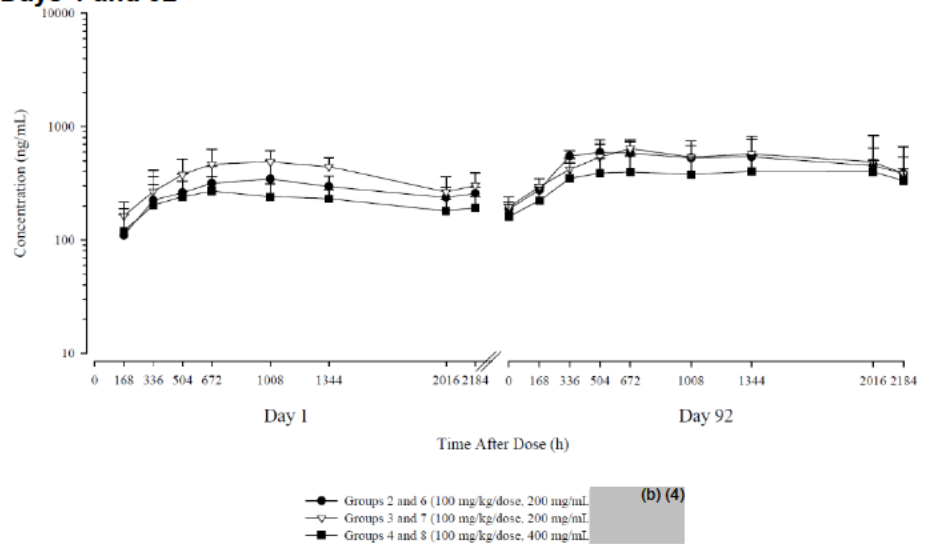
Parameter	Major Findings
Mortality	Animals were examined twice daily. No treatment-related findings.
Clinical signs	Clinical signs were monitored at least once daily. Dermal observations considered GS-6207 related included slight to moderate edema was observed in formulations with or without (b) (4). These observations were observed beginning 24 hours after the dose was administered on days 1 and/or 92. GS-6207 related edema was still observed through the recovery period (13 or 26 weeks) but showed signs of recovery by days 92 (for those given a single dose on day 1) and 176 (for those given a dose on days 1 and 92). The incidence of edema was highest in animals dosed with 200 mg/mL with (b) (4) or 400 mg/mL without (b) (4).
Body weights	Body weights were recorded weekly. No treatment related effects.
Feed consumption	Food intake was measured weekly. No treatment related effects.
Ophthalmoscopy	Ophthalmic exams were conducted on the control and dosed groups prior to treatment, at Week 13, and once during Week 26. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals on sacrifice days 92 and 183. No treatment-related findings.
Clinical chemistry	Blood samples were collected from fasted animals on sacrifice days 92 and 183. No treatment-related findings.
Urinalysis	Urine was collected during the overnight period prior to days 92 and 183. No treatment-related findings.
Gross pathology	Animals were sacrificed on days 92 and 183. Thickening of the skin and/or discoloration was observed at the at the SC injection sites at the end of the first dose (Day 2) and end of the observation period after the second dose (Day 183).
Organ weights	No treatment-related effects.

Parameter	Major Findings
Histopathology Adequate battery: Yes	Injection sites: GS-6207 related findings of minimal to moderate granulomatous inflammation observed during histopathology for necropsy 1 (Day 92). GS-6207 related findings observed at injection site A (dosed on Day 1) and B (dosed on Day 92) include minimal to moderate granulomatous inflammation and slight necrosis in 1 of 10 males. Animals dosed with 100 mg/kg GS-6207 in 400 mg/mL without (b) (4) had the highest incidence and severity of findings and those dosed with the 200 mg/mL without (b) (4) formulation had the lowest.

Dose (mg/kg/dose) (formulation)	Sex	AUC _{0-672h} (ng•h/mL)		C _{max} (ng/mL)	
		After 1 injection	After 2 injections	After 1 injection	After 2 injections
100 (200 mg/mL, (b) (4))	Male	155,000	338,000	427	846
	Female	98,500	276,000	331	637
	MF Combined	127,000	307,000	379	742
100 (200 mg/mL, (b) (4))	Male	184,000	276,000	544	856
	Female	166,000	293,000	539	703
	MF Combined	175,000	284,000	542	780
100 (400 mg/mL, (b) (4))	Male	133,000	265,000	318	570
	Female	102,000	156,000	254	332
	MF Combined	117,000	211,000	286	451

Source: Table 5 from the Applicant's toxicology written summary.

Combined Concentration of GS-6207 in Male and Female Rat Plasma on Days 1 and 92



Source: Figure B.1 from the Applicant's toxicology report TX-200-2014.

Source: FDA reviewer.

Abbreviations: AUC, area under the concentration-time curve; curve; C, concentration; C_{max}, maximum concentration; F, female; M, male; SC, subcutaneous; T, time of concentration observed

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

A Four-Dose (Twice Monthly) Subcutaneous Toxicity and Toxicokinetic Study of GS-6207 in Beagle Dogs (TX-200-2006)

Key Study Findings

- A NOAEL based on injection site reactions could not be established due to macroscopic findings of raised skin at all doses that correlated with granulomatous inflammation that was unable to fully recover. Vocalization and struggling occurred after the first dose leading to the remaining dosing time points being done under anesthesia.
- A NOAEL based on an absence of systemic effects was determined to be 30 mg/kg.
 - Exposure on Study Day 43 (male and female combined): AUC_{0-336h} was 436,000 ng·h/mL and C_{max} was 2,230 ng/mL.
- The exposure margin, based on the lack of systemic effects, was 24× based on predicted human exposures based on the RHD

Table 86. Four-Dose (Twice Monthly) Dog SC Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 10, 30 and 100 mg/kg/dose (dosed once every 2 weeks for a total of 4 doses)
Route of administration	SC injection
Formulation/vehicle	(b) (4) sterile water for injection, USP
Species/strain	Dog/Beagle
Number/sex/group	6/sex/group
Age	9 to 10 months
Conducting laboratory	(b) (4)
Deviation from study protocol affecting interpretation of results	None. 3/sex/group monitored for 6 weeks after dosing (recovery group).

Source: Reviewer.

Abbreviations: GLP, good laboratory practices; SC, subcutaneous; USP, United States Pharmacopeia

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 87. Four-Dose (Twice Monthly) Dog SC Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily. In the 100 mg/kg group all male animals and 2 of 6 females were sacrificed early on Days 15 and 22, respectively, due to vocalization during and after dosing or barrel rolling. The remaining 4 females dosed at 100 mg/kg did not continue in the study. All other animals survived until the end of the study and were dosed while under anesthesia.
Clinical signs	Clinical signs were monitored at least once daily. Clinical observations of vocalization and struggling during dosing and barrel rolling were observed sporadically all doses. Skin discoloration at the injection site was observed in females at 30 or 100 mg/kg. Raised skin was observed at the injection site in males at 100 mg/kg. At 30 and 100 mg/kg, the skin on the left dorsal side was raised in both males and females.
Body weights	Body weights were recorded weekly. No treatment related effects.
Feed consumption	Food intake was measured weekly. No treatment related effects.
Ophthalmoscopy	Ophthalmic exams were conducted on the control and dosed groups prior to treatment, at Week 8, and 2 weeks after the last dose. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals twice during the predose period and on sacrifice Day 57. No treatment-related findings.
Clinical chemistry	Blood samples were collected from fasted animals twice during the predose period and on sacrifice Day 57. No treatment-related findings.
Urinalysis	Urine was collected during the overnight period prior to Day 57. No treatment-related findings.
Gross pathology	Animals were sacrificed on day 57. Injection site: raised areas were observed across all doses at terminal necropsy 1 (Day 57) and at all doses in males and at 30 mg/kg in females at terminal necropsy 2 (Day 85). The animals dosed at 100 mg/kg that were sacrificed early had scabbing and thickening of the skin at injection sites A and B.
Organ weights	No treatment-related effects.
Histopathology Adequate battery: Yes	<u>Injection sites:</u> At terminal necropsy #1 (Day 57) minimal to marked granulomatous inflammation was observed at all doses in males and females at all four injection sites. At terminal necropsy #2 (Day 85), although not fully resolved, there was a slight decrease in the incidence of granulomatous inflammation at all four injection sites.
Special evaluation: Hepatic enzymes	There were no GS-6207 related effects on total microsomal protein yield, total cytochrome P450 (CYP) content, CYP1A, CYP2B, CYP3A, CYP2E, CYP4A, or uridine 5'-diphospho-glucuronosyltransferase.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Parameter	Major Findings					
Toxicokinetics	Toxicokinetic Parameters for GS-6207 in Dogs Following SC Injection					
	Dose (mg/kg/dose)	Sex	AUC _{0-336h} (ng·h/mL)		C _{max} (ng/mL)	
Study Day 1			Study Day 43	Study Day 1	Study Day 43	
Sample collection times: days 1 and 43 predose and every 7, 24, 48, 72, 96, 168, 336 (Day 43 only), 672 (Day 43 only), and 1008 (Day 43 only) hours postdose.	10	Male	112,000	127,000	632	634
		Female	79,900	110,000	507	648
		MF Combined	96,100	118,000	570	641
	30	Male	311,000	391,000	1730	2210
		Female	339,000	481,000	2040	2240
		MF Combined	325,000	436,000	1890	2230
	100	Male	925,000	NA ^b	4260	NA ^b
		Female	1,350,000 ^a	NA ^b	6020	NA ^b
		MF Combined	1,030,000 ^a	-	4700	-

Source: Table 7 from the Applicant's toxicology written summary.

^a Females were euthanized on day 15; therefore, the 336-hour samples are from the unscheduled collection (approximately 333 hours).

^b All males and two of six females in Group 4 (100 mg/kg, the only group 4 females that were dosed) underwent early sacrifice on day 22.

Source: Reviewer.

Abbreviations: AUC, area under the concentration-time curve; C, concentration; C_{max}, maximum concentration; F, female; M, male; NA, not applicable; SC, subcutaneous

A 9-Month (Once Monthly) Subcutaneous Injection Toxicity and Toxicokinetic Study With Three Formulations of GS-6207 in Beagle Dogs (TX-200-2017)

Key Study Findings

- There was no systemic toxicity observed.
- Injection site reactions were observed at all doses with or without the (b) (4) formulation. During histopathology analysis, GS-6207 related findings of granulomatous inflammation, mixed cell inflammation, macrophage infiltration, and/or necrosis were observed at the injection sites during each necropsy.
- A NOAEL based on injection site reactions could not be established.
- A NOAEL based on an absence of systemic effects was determined to be 40 mg/kg (400 mg/mL GS-6207 without (b) (4)).
 - Exposure on Study Day 225 (male and female combined): AUC₀₋₆₇₂ was 352,000 ng·h/mL and C_{max} was 658 ng/mL.
- The exposure margin, based on the lack of systemic effects, was 9.6× based on predicted human exposures based on the RHD.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 88. Nine-Month (Once Monthly) Dog Subcutaneous Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 20 mg/kg (200 mg/mL with or without (b) (4)), 40 mg/kg (400 mg/mL without (b) (4)); dosed once monthly for 9 months
Route of administration	SC injection
Formulation/vehicle	(b) (4) (sterile water for injection)
Species/strain	Dog/Beagle
Number/sex/group	9/sex/group
Age	9 to 11 months
Conducting laboratory	(b) (4)
Deviation from study protocol	None.
affecting interpretation of results	There was no recovery group in this study.

Source: Reviewer.

Table 89. Nine-Month (Once Monthly Dosing) Dog SC Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily. There were no treatment related findings.
Clinical signs	Clinical signs were monitored at least once daily. Vocalization; struggling during dosing; barrel rolling; walking in circles; and/or licking, scratching, and snapping/biting at the dose site occurred (typically lasting 5 minutes or less) in control and GS-6207 dosed dogs immediately postdosing after each monthly dose. These observations did decrease in recurrence at later doses. One female dosed with 20 mg/kg (with (b) (4)) was hypoactive, had oral discharge, slowed heart rate, and labored breathing postdose on Day 29. The veterinarian treated the animal for anaphylactoid reaction with diphenhydramine and epinephrine. Later the same day, the animal appeared normal. GS-6207 related raised area of the skin at the dosing site occurred in controls and dosed animals. GS-6207 related slight to severe edema and erythema were observed in dosed animals beginning 24 hours postdose at the injection sites and noted at all schedule necropsies. Edema persisted longer in animals dosed with 40 mg/kg than those with 20 mg/kg.
Body weights	Body weights were recorded weekly. No treatment related effects.
Feed consumption	Food intake was measured weekly. No treatment related effects.
Ophthalmoscopy	Ophthalmic exams were conducted on the control and dosed groups prior to treatment, at Week 8, and 2 weeks after the last dose. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals twice during predose and within 2 days of scheduled sacrifices. No treatment-related findings.
Clinical chemistry	Blood samples were collected from fasted animals twice during predose and within 2 days of scheduled sacrifices. No treatment-related findings.
Urinalysis	Urine was collected overnight prior to scheduled sacrifices. No treatment-related findings.
Gross pathology	GS-6207 related injection site reactions of thickening, discoloration, and/or scabbing of the skin were observed at all doses and injection sites at each necropsy.
Organ weights	No treatment-related effects.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Parameter	Major Findings					
Histopathology Adequate battery: Yes	Animals were sacrificed on day 88 (necropsy 1), day 172 (interim necropsy), or day 256 (terminal necropsy). The major finding during histopathology analysis were injection site reactions. GS-6207 related macrophage infiltration, granulomatous inflammation, mixed cell inflammation, and/or necrosis was noted at the injection sites in dosed animals. The incidences and severity appeared to be dose dependent. Although still present at necropsy day 256, there was a dose-dependent decrease in the incidence and severity of injection site reactions.					
Special evaluation: Hepatic enzymes	There were no GS-6207 related effects on total microsomal protein yield, total cytochrome P450 (CYP) content, CYP1A, CYP2B, CYP3A, CYP2E, CYP4A, or uridine 5'-diphospho-glucuronosyltransferase.					
Toxicokinetics	Toxicokinetic Parameters for GS-6207 in Dogs Following SC Injection					
Sample collection times: Day 1 predose and 24, 72, 168, 336 (on day 15) hours postdose; on days 29, 58, 85, 141, 169, and 197 predose and a72 and 336 hours postdose; on days 113 and 225 predose and 72, 168, 336, and 504 hours postdose and on day 253 predose and 72 hours postdose.	Dose (mg/kg/dose) (formulation)	Sex	AUC_{0-672h} (ng•h/mL)		C_{max} (ng/mL)	
	20 (200 mg/mL, (b) (4))	Male	Study Day 197	Study Day 225	Study Day 197	Study Day 225
		Female	311,000	312,000	511	571
		MF Combined	167,000	221,000	294	416
	20 (200 mg/mL, (b) (4))	Male	239,000	267,000	402	494
		Female	276,000	301,000	472	580
		MF Combined	309,000	254,000	625	530
	40 (400 mg/mL, (b) (4))	Male	292,000	277,000	549	555
		Female	355,000	363,000	612	723
		MF Combined	335,000	340,000	589	592

Source: Applicant's study report TX-200-2017.

Source: Reviewer.

Abbreviations: AUC, area under the concentration-time curve; C, concentration; C_{max}, maximum concentration; F, female; M, male; NA, not applicable; SC, subcutaneous

A 9-Month (Once Monthly) Subcutaneous Injection Toxicity and Toxicokinetic Study of GS-6207 in Beagle Dogs With a 2- and 13-Week Observation (Recovery) Period (TX-200-2047)

Key Study Findings

- Injection site reactions were detected at all tested doses.
 - Injection site reactions were observed at the end of the observation period but to a lesser degree and incidence.
- Histopathology findings:
 - Liver (bile duct degeneration, cell/bile ductule hyperplasia) and gallbladder (edema, hyperplasia) findings were detected at all tested doses.
 - Findings were observed at a lower severity and incidence at the end of the recovery period.

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- Kidney (tubule degeneration and dilatation, pigment) and stomach (degeneration/atrophy of mucosa) findings were detected at 411 mg/kg at interim necropsy 1 (Day 73)
 - Findings were not detected at terminal necropsy 1 (Day 143)
- A NOAEL was not determined due to injection site reaction, and liver and kidney findings still detectable after the 13-week observation period at all doses.

Table 90. Once-Monthly (9 Months) Dog SC Toxicity Study Design

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 130, and 411 mg/kg/dose (dosed once every 4 weeks)
Route of administration	SC injection
Formulation/vehicle	(b) (4) polyethylene glycol 300 (PEG300), (b) (4) % w/w sterile water for injection
Species/strain	Dog/Beagle
Number/sex/group	4 to 6/sex/group
Age	9 to 10 months
Conducting laboratory	(b) (4)
Deviation from study protocol affecting interpretation of results	None.
Unique design	Animals were dosed once every 4 weeks for up to 37 weeks then sacrificed after a 2- or 13-week recovery period. The dosing site locations were as follows: A: Upper left dorsal region B: Upper right dorsal region C: Upper middle left dorsal region D: Upper middle right dorsal region E: Middle left dorsal region F: Middle right dorsal region G: Lower middle left dorsal region H: Lower middle right dorsal region I: Lower left dorsal region J: Lower right dorsal region

Source: Reviewer.

Abbreviation: SC, subcutaneous

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Table 91. Once-Weekly Dosing for 9 Months Dog SC Toxicity Study Findings

Parameter	Major Findings
Mortality	Animals were examined twice daily. In the 411 mg/kg group, dosing did not proceed past Day 57 due to a decline in health due to treatment. One male and two females were euthanized early on Days 51, 71, and 82, respectively. (unscheduled interval). An interim necropsy of 411 mg/kg dosed animals (three males and two females) occurred on Day 73 and the terminal necropsy for the remaining animals in this dose group occurred on Day 143. All vehicle and 130 mg/kg animals survived until their scheduled interim (Day 143) or terminal (Day 268) necropsy.
Clinical signs	Clinical signs were monitored at least once daily. Clinical observations of vocalization, circling, excessive biting and aggression towards handler were noted in dosed and control animals on Days 1 and 29. Beginning on day 32 animals were anesthetized prior to dosing. GS-6207-related injection site reactions included swollen area at the sites, palpable mass, edema, and erythema were noted at 130 and 411 mg/kg.
Body weights	Body weights were recorded weekly. GS-6207 related decrease in body weight up to 19% was noted in animals dosed at 411 mg/kg that were euthanized early.
Feed consumption	Food intake was measured weekly. No treatment related effects.
Ophthalmoscopy	Ophthalmic examinations were conducted prior to treatment, and on Days 72, 138, and 262. No treatment-related findings.
Hematology	Blood samples were collected from fasted animals twice during predose and on Days 87, 115, 143, 171, 199, 227, 225, and 268. GS-6207 related effects on remaining animals dosed with 411 mg/kg were similar to those from the animals that were necropsied early and included increased white blood cells and/or neutrophile counts and fibrinogen concentrations noted at necropsy 1 (Day 73) but not present at terminal necropsy (Day 143) suggesting reversibility of these effects. GS-6207 related effects on animals dosed with 130 mg/kg included increased fibrinogen concentrations on Days 87 and 115 which correlated with inflammation at the injection sites noted during terminal necropsy (Day 268).

Clinical chemistry Blood samples were collected from fasted animals twice predose and on Days 87, 115, 143, 171, 199, 227, 225, and 268.

Unscheduled necropsy animals (400 mg/kg; n=3)

The three animals dosed with 411 mg/kg that were euthanized early (Days 51, 71, or 82) had GS-6207–related increases in total bilirubin, ALP, GGT, ALT, AST, and bile acid concentrations (see table below). These effects correlate with histopathology findings in the liver.

Various decreases in sodium, chloride, and potassium. Increase in cholesterol in males only on Days 70 and 73 and in various other animals on Days 87 and 115 but normal levels on Day 143 (indicative of reversibility).

GS-6207–Related Effects in Animals Dosed With 411 mg/kg at Unscheduled Necropsy

Sex	GS-6207		
	411 mg/kg/dose		
	Male	Female	
Animal Identification	D0201	D0502	D0504
Day of Dosing Phase	51	71	82
Total bilirubin concentration			
Predose Day 16	0.1	<0.1	<0.1
Day of Moribund Necropsy	6.3	6.2	2.8
% Difference	+6200%	+6100%	+2700%
ALP activity			
Predose Day 16	71	83	92
Day of Moribund Necropsy	886	1229	992
% Difference	+1147.9%	1380.7%	+978.3%
GGT activity			
Predose Day 16	<3.0	<3.0	<3.0
Day of Moribund Necropsy	34	34	29
% Difference	+1033.3%	+1033.3%	+866.7%
ALT activity			
Predose Day 16	34	36	27
Day of Moribund Necropsy	586	316	203
% Difference	+1623.5%	+777.8%	+651.9%
AST activity			
Predose Day 16	29	28	20
Day of Moribund Necropsy	153	86	47
% Difference	+427.6%	—	—
Total Bile Acid concentration			
Mean control Day 60	<1	<1	<1
Day of Moribund Necropsy	56	>196	176
% Difference	+5500%	+19500%	+17500%
Albumin concentration			
Predose Day 16	3.4	3.9	3.5
Day of Moribund Necropsy	2.0	3.3	2.1
% Difference	-41.2%	—	-40.0%
Total protein concentration			
Predose Day 16	6.1	6.0	5.6
Day of Moribund Necropsy	4.2	5.2	3.8
% Difference	-31.1%	—	-32.1%
Fibrinogen concentration			
Predose Day 16	292	161	209
Day of Moribund Necropsy	276	364	387
% Difference	—	+126%	+85.2%
Reticulocyte count			
Predose Day 16	33.9	27.7	11.5
Day of Moribund Necropsy	19.2	10.0	18.4
% Difference	-43.4%	-63.9%	—
Lymphocyte count			
Predose Day 16	4.42	2.32	2.62
Day of Moribund Necropsy	3.23	1.58	3.73
% Difference	—	-31.9%	—

Source: Applicant's study report TX-200-2047.

-, no effect observed; ±, increase/decrease

Parameter	Major Findings
	GS-6207-related effects on remaining animals dosed with 411 mg/kg were similar to those from the animals that were necropsied early and included increases in bilirubin and bile acid (starting on Day 60) and increases in GGT, ALP, and ALT suggesting cholestasis and were noted at interim necropsy 1 (Day 73) and in individual animals on Days 87 and 115. In males on terminal necropsy Day 143, the increases in the aforementioned endpoints were not observed indicating reversibility. There were increases in cholesterol levels in males only on Days 60, 73, 87, and 115. However, there were the increase was not detected on terminal necropsy Day 143. In the animals that were necropsied early and dosed with 411 mg/kg, there were GS-6207 related decreases in albumin and total protein with a decrease in the A:G ratio. There effects were not observed at terminal necropsy (Day 143). GS-6207-related effects in animals dosed with 130 mg/kg were similar do those at the 411 mg/kg, but at a lesser degree, and included an increase in ALT, GGT, and/or ALP and bile acid starting on Day 87 and at various time points up to terminal necropsy (Day 268). These effects correlated to histopathology findings in the liver and bile duct.
Urinalysis	Urine was collected during the overnight period prior to Days 87, 115, 143, 171, 199, 227, 225, and 268. Two males dosed with 411 mg/kg had GS-6207 related orange discoloration and/or positive bilirubin reaction on Day 60, indicative of bilirubin in the urine.
Gross pathology	Animals were sacrificed on Days 73, 143, and 268. <u>Unscheduled Necropsy Animals (411 mg/kg; n=3)</u> In one animal necropsied early there was a finding of bilateral yellow eye sclera and in another was discoloration noted in the aorta, kidney, liver, and oral mucosa and a thickened gall bladder. In animals dosed at ≥ 130 mg/kg, there was thickening and/or discoloration at the injection sites.
Organ weights	No treatment-related effects detected at terminal necropsy Day 1 (Day 143 in animals dosed with 411 mg/kg) or terminal necropsy Day 2 (Day 268 in animals dosed with control and 130 mg/kg).

Parameter	Major Findings
Histopathology	<u>Unscheduled Necropsy Animals (Days 51 to 82) and Interim Necropsy 1 (Day 73); 411 mg/kg Group</u>
Adequate battery: Yes	GS-6207-related findings included the following: • <u>Liver</u>: slight vacuolar hepatocyte; minimal bile duct epithelium degeneration; minimal to slight bile pigment, and/or minimal to moderate oval cell/bile duct hyperplasia. • <u>Gall bladder</u>: Minimal to slight epithelial hyperplasia; minimal edema. • <u>Kidney</u>: Minimal tubule degeneration and dilatation; and minimal pigment. • <u>Stomach</u>: minimal to marked degeneration/atrophy of the mucosa. • Injection sites A, B, and/or C: minimal to marked adipose tissue necrosis, granulomatous or mix cell inflammation, and/or fibrosis. <u>Interim Necropsy 2/Terminal Necropsy 1 (Day 143)</u> • Findings previously noted at 411 mg/kg during necropsy 1 in the stomach and kidney were not detected, indicating reversal. • <u>Liver</u>: Previous findings were reverse except oval cell/bile ductule hyperplasia. These findings were detected at a lower incidence, indicating partial reversal. • <u>Gall bladder</u>: Mucosal edema was fully reversed. All previous findings detected during the previous necropsy were detected at a lesser degree, indicating partial reversibility. • <u>Injection sites A, B, and/or C</u>: All previous findings at injection site A were still detected but at a lesser incidence, indicating partial reversibility. However, adipose tissue necrosis in females was fully reversed. All findings previously noted at injection site B were no longer detected, indicating full reversibility. All previous findings at injection site C were still detecting but at a lesser degree and/or severity indicating partial reversibility. However, adipose tissue necrosis was no longer detected in females indicating full reversibility. <u>Terminal Necropsy 2 (Day 269)</u> The only animals remaining at this time point were those dosed with 130 mg/kg. • <u>Liver</u>: Minimal to slight oval cell/bile ductule hyperplasia; minimal periductular fibrosis (males only); and a minimal increase in pigmented macrophages. • <u>Gall bladder</u>: Minimal epithelium hyperplasia, minimal to slight increase secretion in the lumen; and minimal to slight pigment in the lumen. • <u>Injection sites A to J</u>: In general, the following was noted in most, but not all, injection sites: minimal to moderate granulomatous inflammation, adipose tissue necrosis, fibrosis, and pseudocyst.

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Parameter	Major Findings							
Toxicokinetics	Toxicokinetic Parameters for GS-6207 in Dogs Following SC Injection: Days 85, 113, 141, 169, 197, 225, and 253							
Sample collection times: Predose and every 24, 72 and 168 hours postdose on days 1 and 15; 72 and 336 hours postdose on days 29, 32, 57, 85, 141, 169, and 197; 72, 168, 336, and 504 hours postdose on days 113 and 225; and 72 hours postdose on day 253. During weeks 11 and 21 of 411 mg/kg interim and terminal necropsies, respectively.	Dose Level (mg/kg/dose)	Day	Sex	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (h*ng/mL)	AUC _{0-336h} (h*ng/mL)	AUC _{0-672h} (h*ng/mL)
	130	85	M	3460	372	1940000	951000	1940000
			F	4900	204	2910000	1480000	2910000
			MF	4180	288	2430000	1220000	2430000
		113	M	4040	138	2300000	1140000	2300000
			F	4610	330	2650000	1280000	2650000
			MF	4320	234	2470000	1210000	2470000
		141	M	4180	522	2370000	1170000	2370000
			F	5340	672	3010000	1420000	3010000
			MF	4760	597	2690000	1300000	2690000
		169	M	4540	222	2480000	1320000	2480000
			F	5430	222	2990000	1590000	2990000
			MF	4980	222	2730000	1450000	2730000
		197	M	4300	204	2640000	1310000	2640000
			F	6220	354	3650000	1740000	3650000
			MF	5260	279	3150000	1520000	3150000
		225	M	4640	504	2850000	1360000	2850000
			F	6320	288	3540000	1720000	3540000
			MF	5480	396	3200000	1540000	3200000
		253	M	4520	72.0	NA	NA	NA
			F	5210	72.0	NA	NA	NA
			MF	4860	72.0	NA	NA	NA

NA = Not applicable.

Note: AUC_{0-336h} and AUC_{0-672h} were not able to be calculated on Day 253, as samples were only collected to 72 hours postdose.

Source: Applicant's study report TX-200-2047.

Source: Reviewer.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; C_{max}, maximum concentration; GGT, gamma glutamyl transferase; SC, subcutaneous; T_{max}, time to maximum concentration

13.2.3.3. General Toxicology; Additional Studies (Nonpivotal)

A 7-Day Once-Daily Oral Gavage Tolerability and Toxicokinetic Study of GS-6207 in Female Nonpregnant New Zealand White Rabbits (TX-200-2035)

In a 7-day, non-GLP-compliant study, GS-6207 formulated in (b) (4) was administered to nonpregnant female new Zealand white rabbits (3/group) at doses of 0 (control), 100, 300, and 1000 mg/kg with dose volumes of 1.3, 0.2, 0.6, and 2 mL/kg, respectively. On Day 4, one female was found dead and on Day 5 another had to be euthanized in extremis in the 1000 mg/kg dose group. The mortality and extremis condition were due to intubation errors at dosing. There were no test article related findings in this study. The NOAEL was 1000 mg/kg.

Assessment of Subcutaneous Depot Following a Single Subcutaneous Infusion of GS-6207 in Wister Han Rat (TX-200-2027)

In a single-dose, nonGLP-compliant abbreviated study, GS-6207 formulated in vehicle 1 (PEG300 (b) (4); water; (b) (4)) or vehicle 2 (PEG300:water (b) (4)) was administered to male Wister Han rats (3/group) at a dose concentration of 300 mg/mL in a volume of 0.25 mL. A 21-gauge needle was used in all groups, except that in the GS-6207 in vehicle 1 group a 25-gauge needle was used. Both control groups and all GS-6207 groups had similar depot volume following dosing 24 hours and 7 days postdose. There was a decrease in volume in all groups. The controls groups had a higher rate of decrease in volume. The infusion rate and needle gauge

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did not significantly affect depot size or heterogeneity. All groups presented similar heterogeneity of the depot over the time course of the study.

A 7-Day Subcutaneous and Intramuscular Dose Range-Finding Toxicity Study of GS-714207 in Male Wister Han Rats (TX-200-2002)

In a 7-day, non-GLP-compliant exploratory study, GS-6207 formulated in (b) (4) % sterile water for injection was administered to male Wister Han rats (5 males/group) at doses of 0 (control), 5, 30, and 100 mg/kg at a dose volume of 1 mL/kg via subcutaneous or intramuscular injection. Changes in hematology (increases in neutrophil, lymphocytes, and monocytes), coagulation (increase in fibrinogen), and serum chemistry (increase globulin and decrease in albumin) were observed in animals dosed ≥ 30 mg/kg via SC administration, indicating an inflammatory response. Thickening of the injection site was noted in animals dosed ≥ 30 mg/kg via SC administration, and discoloration was noted at the injection site in two animals dosed with 5 mg/kg via intramuscular administration. There was minimal to marked necrosis at the injection site at all doses via SC administration. The NOAEL for SC administration, based on injection site reactions, could not be determined due to necrotic tissue at injection sites. The NOAEL for SC administration based on systemic effects was 100 mg/kg. The NOAEL for intramuscular administration based on no injection site reactions or systemic effects observed was 5 mg/kg.

A 7-Day Subcutaneous Injection Dose Range-Finding Toxicity Study of GS-714207 in Male Beagle Dog (TX-200-2004)

In a 7-day, non-GLP-compliant exploratory study, GS-6207 formulated in (b) (4) % sterile water for injection was administered to male beagle dogs (3 males/group) at doses of 0 (control), 3, 10, and 30 mg/kg at a dose volume of 0.75 mL/kg via subcutaneous injection. Changes in hematology (increases in neutrophil, monocytes, and white blood cells; decrease in reticulocytes), coagulation (increase in fibrinogen), and serum chemistry (increase in ALP; increase globulin and cholesterol; and decrease in the albumin globulin ratio) were observed at 10 and/or 30 mg/kg. A decrease in thymus weight that correlated with a decrease in thymus cellularity was observed during histopathology analysis. Injection site reactions included thickening at the site and a mass noted during gross pathology. Cellular inflammation, hemorrhage, and fibrin were detected at each dose. An abscess formation was observed at doses ≥ 10 mg/kg and vascular inflammation in some animals was observed at 3 and 10 mg/kg. The NOAEL for SC administration, based on injection site reactions and abscess formation at doses ≥ 10 mg/kg, was 3 mg/kg. The NOAEL for SC administration based on systemic effects was 30 mg/kg.

13.2.4. Genetic Toxicology

Table 92. Genetic Toxicology

Study Title/Study No.	Key Study Findings
In Vitro Reverse Mutation Assay in Bacterial Cells (TX-200-2007) GLP compliance: Yes Study is valid: Yes	• TA98, TA100, TA1535, TA1537 and WP2uvrA strains were incubated with up to 5000 $\mu\text{g}/\text{plate}$ GS-6207 with and without S9 metabolic activation. • No dose-related, two-fold increase in the number of revertant colonies was observed for the five tester strains. • GS-6207 was not mutagenic under the experimental conditions.

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Study Title/Study No.	Key Study Findings
Assay for Chromosomal Aberrations In Vitro in Culture Human Peripheral Lymphocytes (TX-200-2008) GLP compliance: Yes Study is valid: Yes	• Cultured human peripheral lymphocytes were exposed with up to 500 µg/mL for 3 or 24 hours without S9 metabolic activation and for 3 hours with up to 500 µg/mL with S9 metabolic activation. • GS-6207 was considered negative for inducing chromosomal aberrations in in vitro human peripheral blood lymphocytes. • GS-6207 was negative for clastogenicity under the experimental conditions.
Assay for Micronucleus Induction in Rat Bone Marrow (TX-200-2005) GLP compliance: Yes Study is valid: Yes	• Wister Hanover male rats received multiple SC doses at 0, 10, 30, and 100 mg/kg given once every other week (four total doses) prior to assessing bone marrow for micronucleated polychromatic erythrocytes at scheduled sacrifices. • GS-6207 was not genotoxic under the experimental conditions.

Other genetic toxicology studies

Multiple process impurities were tested in a battery of genetic toxicology assays. Overall, the weight of evidence of these tests does not suggest a cause for concern. The details for these tests are below.

In Vitro Bacterial Reverse Mutation Assay for Impurities (b) (4)

- (b) (4) was the highest impurity ((b) (4) % in a total of (b) (4) % impurities) identified in the drug product batch, GS-6207, used for the toxicology studies.
 - (b) (4) did not cause an increase in revertant colonies when compared with the control.
 - (b) (4) tested negative in the Ames assay.
 - (b) (4)
 - It was not present in the drug product (GS-6207) used in the toxicology studies.
 - Toxicity was observed at $\geq$ (b) (4) $\mu\text{g}/\text{plate}$ in strain TA1535 in the presence of S9. (b) (4) caused an increase in revertant colonies that were ≥ 2 -fold (strains TA98, TA100, and WP2 uvrA in the presence of S9) or ≥ 3 -fold (strains TA1537 in the presence of S9) when compared with the control.
 - In conclusion, (b) (4) tested positive in the Ames assay in three *Salmonella typhimurium* strains (TA98, TA100, and TA 1537) and one strain of *Escherichia coli* (WP2 uvrA).
 - (b) (4), it was not present in the drug product used in the toxicology studies.
 - In experiment 1, toxicity was not clearly observed. (b) (4) caused a reduction in induced revertant numbers at (b) (4) $\mu\text{g}/\text{plate}$ in strains TA100, TA1535, and TA1537 in the presence and absence of S9.
 - In experiment 2, toxicity (a reduction in revertant numbers) was observed at (b) (4) $\mu\text{g}/\text{plate}$ in strain TA1537 in the absence of S9. To determine mutagenic activity of (b) (4), in experiment 1, strain TA100 in the absence and presence of S9, had an increase in revertant numbers (≥ 2 -fold) at (b) (4) $\mu\text{g}/\text{plate}$. However, in experiment 2 the strain TA100 the increase in revertant number was observed at $\geq$ (b) (4) $\mu\text{g}/\text{plate}$ in the presence of S9.
 - In conclusion, it appears that (b) (4) has mutagenic activity in strain TA100 with S9 activation.
 - (b) (4) It was not present in the drug product (GS-6207) used in the toxicology studies.
 - A precipitate was observed at $\geq$ (b) (4) $\mu\text{g}/\text{plate}$ in the absence and presence of S9.
 - No toxicity was observed. (b) (4) did not cause an increase in revertant colonies when compared with the control.
 - In conclusion, (b) (4) tested negative in the Ames assay.
- In Vitro Mammalian Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes for (b) (4) and (b) (4)
- (b) (4) It was not present in the drug product (GS-6207) used in the toxicology studies.

Study Title/Study No.	Key Study Findings
	- Cytotoxicity was observed with and without S9 metabolic activation at doses $\geq$ (b) (4) $\mu\text{g/mL}$. - There were no increases chromosomal aberrations with or without S9 metabolic activation.
	• (b) (4). - Cytotoxicity was not observed in this assay with or without S9 metabolic activation in any of the treatment groups. - There were no increases in chromosomal aberrations with or without S9 metabolic activation.

Source: Reviewer.

Abbreviation: GLP, good laboratory practices

13.2.5. Carcinogenicity

The carcinogenicity potential of LEN is ongoing in a 26-week study (single subcutaneous injection given once every 13 weeks for a total of two doses) in 001178-T (hemizygous) RasH2 mice and a 2-year study (single subcutaneous injection given once every 13 weeks for a total of eight doses) in Wister Hanover rats. These studies are ongoing at the time of NDA submission and will be part of a postmarketing requirement (PMR).

13.2.6. Reproductive and Developmental Toxicology

13.2.6.1. Fertility and Early Embryonic Development

A Subcutaneous Injection Study of the Effects of GS-6207 on Fertility and Early Embryonic Development to Implantation in Sprague Dawley Rats (TX-200-2043)

Key Study Findings

- There were no test article-related effects on male and female fertility or early embryonic development when GS-6207 was administered once via the subcutaneous route.
 - The NOAEL was 100 mg/kg which corresponded to a C_{max} of 577 ng/mL and $AUC_{0-1008\text{h}}$ of 441,000 ng·h/mL in males and a C_{max} of 597 ng/mL and $AUC_{0-672\text{h}}$ of 192,000 ng·h/mL in females.
- The exposure margin was 7 $\times$ and 5 $\times$ for males and females, respectively, based on predicted human exposures based on the RHD

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

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Table 93. Methods of Subcutaneous Fertility and Embryo-Fetal Development Study in Female and Male Rats

Parameter	Method Details
Dose and frequency of dosing:	0 (vehicle), 20 or 100 mg/kg One single injection
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) % (w/w) sterile water for injection (with (b) (4) for GS-6207 groups only)
Species/strain:	Rat, Sprague-Dawley
Number/sex/group:	25/sex/group (main) 3/sex/control and 6/sex/treated group (TK)
Satellite groups:	Toxicokinetic (TK) group
Study design:	The animals were given a single subcutaneous dose. Females: 4 weeks prior to mating. Males: 6 weeks prior to mating.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer.

Table 94. Observations and Results, Study TX-200-2043

Parameter	Major Findings
Mortality	No treatment-related findings.
Clinical signs	No treatment-related findings.
Food consumption	No treatment-related findings.
Body weights	No treatment-related findings.
Sperm count	No treatment-related findings.
Sperm velocity	No treatment-related findings.
Necropsy findings	No treatment-related findings.

Toxicokinetics **Toxicokinetic Parameters for GS-6207 in Rat Fertility and Embryo-Fetal Development Study**

Blood samples were collected predose and 24, 72, 168, 336, 672, and 1008 (males only at this time point) hours postdose.

Dose (mg/kg)	Sex	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (ng•h/mL)	AUC _{0-672h} (ng•h/mL)	AUC _{0-1008h} (ng•h/mL)	C _{last} (ng/mL)	T _{last} (h)
20	M	188	672	161,000	103,000	161,000	157	1008
	F	153	336	91,100	91,100	NC	123	672
	MF	168	336	150,000	97,200	N/A	157	1008
100	M	577	672	441,000	270,000	441,000	439	1008
	F	597	24.0	192,000	192,000	NC	290	672
	MF	493	24.0	378,000	231,000	N/A	439	1008

N/A Not applicable.

NC Not calculated as samples were only collected to 672 hours.

Note: MF data are based on the analysis of the combined concentration data for both males and females, where applicable.

Additionally, only male samples were collected out to 1008 hours because this includes the 6 weeks prior to mating; female sample collections ended at 672 hours because this includes the 4 weeks prior to mating.

Source: Table 15 of the Toxicology Written Summary.

Source: Reviewer.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{last}, last measured concentration; F, female; M, male; T_{last}, time at the last measured concentration

13.2.6.2. Embryo-Fetal Development

An Oral (Gavage) Dose Range-Finding Study of the Effects of GS-6207 on Embryo-Fetal Development in Sprague-Dawley Rats (TX-200-2031)

GS-6207 was administered to Sprague-Dawley rats (3 rats/control and 6 rats/dose group) from gestation day (GD) 6 to 17 at doses of 0 ([REDACTED] (b) (4)), 3, 30, and 300 mg/kg with a dose volume of 2 mL/kg via oral gavage once daily. There were no test article-related deaths or effects on the endpoints evaluated (mortality, clinical observations, body weights, body weight gains, gravid uterine weights, food consumption, gross necropsy findings, intrauterine growth and survival, and fetal external and visceral morphology). The NOAEL for maternal and embryo-fetal development was 300 mg/kg. The Day 17 AUC_{0-24h} at the NOAEL was 26,300 ng·h/mL.

An Oral (Gavage) Study of the Effects of GS-6207 on Embryo-Fetal Development in Sprague Dawley Rats (TX-200-2036)

Key Study Findings

- There were no test article-related effects on embryo-fetal development.
 - The NOAEL for maternal and embryo-fetal development was 30 mg/kg which corresponded to an AUC_{0-24h} of 22,000 ng·h/mL for gestation day (GD) 17.
- The exposure margin was 16× based on predicted human exposures based on the RHD.

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance: Yes

Table 95. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 3, 10, or 30 mg/kg/day Once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	[REDACTED] (b) (4)
Species/strain:	Rats, Sprague-Dawley
Number/sex/group:	25 females/group (main)
Satellite groups:	An additional 3/females/control and 6/females/dosed were used for toxicokinetic analysis
Study design:	Dosing GD 6 to GD 17
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer.

Abbreviations: GD, gestation day; [REDACTED] (b) (4)

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NDA 215974 lenacapavir tablets, for oral use

Table 96. Observations and Results, Study TX-200-2031

Parameter	Major Findings			
Mortality	One female dosed at 3 mg/kg was found dead on GD 18. This death was attributed to gavage errors.			
Clinical signs	No treatment-related findings.			
Body weights	No treatment-related findings.			
Necropsy findings Cesarean section data	No treatment-related findings.			
Necropsy findings Offspring	No treatment-related findings.			
Toxicokinetics	TK Parameters for GS-6207 in Rat EFD Study; GD 6 and 17			
Blood samples were collected on GD 6 and 17 at 0, 1, 3, 8, 12, and 24 hours postdose.	GD	Dose (mg/kg/day)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
	6	3	209	4410
		10	529	10,700
		30	692	13,300
	17	3	435	9200
		10	1050	17,800
		30	1210	22,000

Source: Table 16 of the Toxicology Written Summary.

Source: FDA reviewer.

Abbreviations: AUC, area under the concentration-time curve; EFD, embryofetal development; C_{max}, maximum concentration; GD, gestation day; TK, toxicokinetic

A 30-Minute IV Infusion Dose Range-Finding Study of the Effect of GS-6207 on Embryo-Fetal Development in New Zealand White Rabbits (TX-200-2032)

GS-6207 was administered to New Zealand White rabbits (6 presumed pregnant/group) once daily from GD 7 to 19 at doses of 0 (), 5, 10, or 20 mg/kg at a dose volume of 0.667 mL/kg via intravenous infusion over a 30-minute period. One female in the 10 mg/kg group was euthanized in extremis on GD 13. This animal had a reduction in body weight when compared to the controls and a decrease in food intake. Other clinical observations noted in this animal included a decrease in fecal output, soft or mucoid feces, and brown staining on the tail and hindlimbs. There were no test article-related deaths or effects on the endpoints evaluated (clinical signs, body weights, body weight gains, gravid uterine weights, food consumption, toxicokinetic parameters, gross necropsy findings, intrauterine growth and survival, and fetal morphology). The NOAEL for maternal and embryo-fetal development was 20 mg/kg. The day 19 AUC_{0-24h} at the NOAEL was 178,000 ng·h/mL.

A 30-Minute IV Infusion Study of the Effect of GS-6207 on Embryo-Fetal Development in New Zealand White Rabbits (TX-200-2037)

Key Study Findings

- Lower body weight gains across all doses correlated to a dose-dependent decrease in food intake.
 - Body weights returned to those of controls levels after 9 days without treatment, as measured before necropsy.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

- There were no test article-related findings on pregnant dam health or embryo-fetal development.
 - The NOAEL for maternal and embryo-fetal development was 20 mg/kg, which corresponded to an AUC_{0-96.5h} of 204,000 ng·h/mL for GD 19.
- The exposure margin was 39× based on predicted human exposures based on the RHD.

Table 97. Methods of IV Embryo-Fetal Developmental Study in Rabbit

Parameter	Method Details
Dose and frequency of dosing:	0, 5, 10, or 20 mg/kg/day; once daily
Route of administration:	Intravenous
Formulation/vehicle:	(b) (4)
Species/strain:	Rabbits, New Zealand White
Number/sex/group:	22 females/group
Satellite groups:	None
Study design:	Dosing GD 7 to GD 19. The post-treatment period was from GD 20 to 29 and animals were euthanized on GD 29.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer.

Abbreviations: GD, gestation day; IV, intravenous; USP, United States Pharmacopeia

Table 98. Observations and Results

Parameter	Major Findings																																		
Mortality	One female dosed with 20 mg/kg was found dead on GD 19. This death was attributed to gavage and/or restraint errors.																																		
Clinical signs	Skin discoloration, bruising, and scabbing was noted in all dose groups at the injection sites.																																		
Body weights	There was a 33% (1.5-fold), 55% (2.2-fold), and 68% (3-fold) lower mean body weight gains at 5, 10, and 20 mg/kg, respectively, when compared with the controls.																																		
Necropsy findings Cesarean section data	No treatment-related findings.																																		
Necropsy findings Offspring	No treatment-related findings.																																		
Toxicokinetics Blood samples were collected on GD 7 0.48 h post start of infusion and 3, 6, 12, and 24 h post the end of infusion; and on GD 19 at predose, 0.48 h post start of infusion and 3, 6, 12, 24, 48, 72, and 96 h post the end of infusion.	Toxicokinetic Parameters for GS-6207 in Rat EFD Study; GD 6 and 19 (From a Dose-Range Finding Study) <table border="1"> <thead> <tr> <th rowspan="2">Dose</th> <th colspan="2">AUC_(0-24.5h) (ng·hr/mL)</th> <th colspan="2">AUC_(0-96.5h) (ng·hr/mL)</th> <th colspan="2">C_{max} (ng/mL)</th> </tr> <tr> <th>GD 7</th> <th>GD 19</th> <th>GD 7</th> <th>GD 19</th> <th>GD 7</th> <th>GD 19</th> </tr> </thead> <tbody> <tr> <td>5 mg/kg/day</td> <td>13,700</td> <td>26,600</td> <td>NA</td> <td>31,200</td> <td>4330</td> <td>7120</td> </tr> <tr> <td>10 mg/kg/day</td> <td>44,200</td> <td>89,500</td> <td>NA</td> <td>101,000</td> <td>15,100</td> <td>22,300</td> </tr> <tr> <td>20 mg/kg/day</td> <td>134,000</td> <td>178,000</td> <td>NA</td> <td>204,000</td> <td>46,700</td> <td>45,700</td> </tr> </tbody> </table> NA = Not applicable. Source: Table 18 of the Toxicology Written Summary.	Dose	AUC _(0-24.5h) (ng·hr/mL)		AUC _(0-96.5h) (ng·hr/mL)		C _{max} (ng/mL)		GD 7	GD 19	GD 7	GD 19	GD 7	GD 19	5 mg/kg/day	13,700	26,600	NA	31,200	4330	7120	10 mg/kg/day	44,200	89,500	NA	101,000	15,100	22,300	20 mg/kg/day	134,000	178,000	NA	204,000	46,700	45,700
Dose	AUC _(0-24.5h) (ng·hr/mL)		AUC _(0-96.5h) (ng·hr/mL)		C _{max} (ng/mL)																														
	GD 7	GD 19	GD 7	GD 19	GD 7	GD 19																													
5 mg/kg/day	13,700	26,600	NA	31,200	4330	7120																													
10 mg/kg/day	44,200	89,500	NA	101,000	15,100	22,300																													
20 mg/kg/day	134,000	178,000	NA	204,000	46,700	45,700																													

Source: Reviewer.

Abbreviations: EFD, embryofetal development; GD, gestation day

13.2.6.3. Pre- and Postnatal Development

A Subcutaneous Injection Study of the Effect of GS-6207 on Pre- and Postnatal Development, Including Maternal Function in Sprague-Dawley Rats (TX-200-2049)

Key Study Findings

- Thickening at the injection site was noted in animals dosed with 30 and 300 mg/kg.
- No major effects were observed in pups or dams at the highest dose tested.
- The NOAEL for maternal health (F0 generation) and fetal toxicity (F1 generation) was 300 mg/kg which corresponded to an AUC_{0-τ} and AUC_{0-192h} of 54,800 ng·h/mL and C_{max} of 412 ng/mL for GD 6.
- The exposure margin, based on the lack of systemic effects and the predicted human exposures based on the RHD, was 5×

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Table 99. Methods of SC Injection Pre- and Postnatal Developmental Toxicity Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 30, 300 mg/kg Single injection
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) PEG 300 and (b) (4) % sterile water for injection
Species/strain:	Rat/ Sprague Dawley
Number/sex/group:	24 females per group
Satellite groups:	Toxicokinetics
Study design:	Because GS-6207 is (b) (4) drug, animals were given a single subcutaneous injection on GD 6. A satellite group of animals (3 female controls and 6 females in the 30 and 300 mg/kg groups) was included to evaluate the toxicokinetic profile. F1 pups were mated after weaning and the following endpoints were assessed: reproductive performance, maternal macroscopic finding, and embryonic (corpora lutea, implantation sites, viable embryos, dead embryos, early and late resorptions, total resorptions, and pre-and post-implantation loss) finds at necropsy were noted.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer.

Abbreviations: GD, gestation day; SC, subcutaneous

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 100. Observations and Results

Generation	Major Findings																					
F0 dams	• There was 1 female at 300 mg/kg who was not pregnant (nongravid). • A swollen dorsal trunk at the injection site was noted in females at 300 mg/kg. • Scabbing on the dorsal trunk was also observed in 5 females at 300 mg/kg. • Thickening of the dorsal scapula occurred in dosed animals at a higher incidence in animals dosed with 300 mg/kg.																					
F1 generation	There were 8 (6), 3 (3), and 9 (4) pups (total litters) in the control, 30, and 300 mg/kg groups, respectively, that were found dead or euthanized due to being in an extremis condition. One (1), four (3), and three (2) pups (litters) were missing or possibly cannibalized.																					
F2 generation	No assessment conducted																					
Toxicokinetics	TK Parameters for GS-6207 in Pregnant Rats PPND Study; GD 6																					
Blood samples collected on GD 6 predose and 72, 96, 168, and 192 h postdose and once on LD 10.	<table border="1"><thead><tr><th>Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>T_{max} (h)</th><th>AUC₀₋₁ (ng•h/mL)</th><th>AUC_{0-192h} (ng•h/mL)</th><th>C_{last} (ng/mL)</th><th>T_{last} (h)</th></tr></thead><tbody><tr><td>30</td><td>87.6</td><td>96.0</td><td>10.900</td><td>10.900</td><td>78.5</td><td>192</td></tr><tr><td>300</td><td>412</td><td>72.0</td><td>54,800</td><td>54,800</td><td>395</td><td>192</td></tr></tbody></table>	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₁ (ng•h/mL)	AUC _{0-192h} (ng•h/mL)	C _{last} (ng/mL)	T _{last} (h)	30	87.6	96.0	10.900	10.900	78.5	192	300	412	72.0	54,800	54,800	395	192
Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₁ (ng•h/mL)	AUC _{0-192h} (ng•h/mL)	C _{last} (ng/mL)	T _{last} (h)																
30	87.6	96.0	10.900	10.900	78.5	192																
300	412	72.0	54,800	54,800	395	192																

Source: Table 19 of the Toxicology Written Summary.

Source: Reviewer.

Abbreviations: GD, gestation day; LD, lactation day; PPND, pre- and postnatal development; TK, toxicokinetic

13.2.7. Other Toxicology Studies

Table 101. Additional Toxicology Studies

Local Tolerance / TX-200-2010 New Zealand White Rabbits 0 [REDACTED] (b) (4) [REDACTED] 50 and 100 mg (in vehicle 1) 50 and 100 mg (in vehicle 2) via a single subcutaneous injection N=6 males/group	Dermal findings (very slight edema; slight to well-defined erythema; and desquamation) observed starting on Day 4 had resolved by the end of the study (Day 28) were due to the test article in vehicle 1 and/or vehicle 2 at dose site A (left dorsal region).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Local Tolerance / TX-200-2019 New Zealand White Rabbits Three formulations (200 mg/mL with or without (b) (4), or 400 mg/mL without (b) (4), or 0 (b) (4) (b) (4) 100, 200, or 400 mg/kg via a single subcutaneous injection. N=12 males/group	At all four necropsy timepoints (days 4, 92, 183 and 274) the skin of the animals was thick at the injection sites at all doses. Histopathology findings of mix cell inflammation, necrosis, and/or granulomatous inflammation were noted at each necropsy. The incidences and severity of the injection site reactions did not appear to be dose dependent. There was a decrease in the severity of injection site reactions over time.
Local Tolerance / TX-200-2033 New Zealand White Rabbits Two formulations (300 mg/mL with or without (b) (4)) 0 (b) (4) w/w polyethylene glycol 300 (PEG):water 150 or 300 mg via a single subcutaneous injection N=6 males/group	Slight to severe edema was noted in animals dosed with 300 mg (without (b) (4)) and 150 or 300 mg (with (b) (4)) from 72 hours postdose through Day 29. Thickening of the skin was noted in all GS-6207 dosed animals. The findings detected during necropsy 1 (Day 4) or necropsy 2 (Day 29) included mixed cell or granulomatous inflammation, necrosis, and/or mononuclear cell infiltrates at the injection sites in GS-6207 dosed animals. The incidences and severity of the injection site reactions did not appear to be dose dependent nor did they decrease over time.
Local Tolerance / TX-200-2038 New Zealand White Rabbits 0 (b) (4) polyethylene glycol 300, (b) (4) water for injection) 300 mg/mL via a single subcutaneous injection N=9 females/group	GS-6207-related injection site reactions were noted at each necropsy. Marked necrosis and minimal cell inflammation was observed at necropsy 1 (Day 4). At necropsy 2 (Day 29), marked to severe granulomatous inflammation were detected. At the final necropsy (Day 92) slight to moderate granulomatous inflammation were detected.
Local Tolerance / TX-200-2048 New Zealand White Rabbits 0 (b) (4) polyethylene glycol, (b) (4) water for injection) 500 mg/mL via a single subcutaneous injection N=6 males/group	GS-6207-related injection site reactions were noted at each necropsy. During necropsy 1 (72 hours postdose) granulomatous inflammation in the subcutis and dermis correlated with ulcer/necrosis and acanthosis in the epidermis, and foreign body material in the subcutis and dermis were detected. At the final necropsy (Day 29) granulomatous inflammation in the subcutis and dermis correlated with acanthosis in the epidermis, and foreign body material and mixed cell infiltrates in the dermis were detected.
Phototoxicity / TX-200-2013 1.78, 3.16, 5.62, 10, 17.8, 31.6, 56.2, and 100 µg/mL	GS-6207 was not phototoxic in a neutral red uptake study in BALB/c3T3 mouse fibroblasts. Half maximal inhibitory concentrations values (-UVR or +UVR) could not be calculated indicating that GS-6207 did not show cytotoxicity or phototoxicity in this assay.
Hemolytic Potential / TX-200-2034 0 (vehicle 1: (b) (4)) 0 (vehicle 2: (b) (4)) 0.2, 2, and 3 mg/mL in vehicle 1 30 mg/mL in vehicle 2	GS-6207 in both vehicle resulted in minimal to moderate hemolysis of rat, dog, and human whole blood. Whereas, GS-6207 in vehicle 2 resulted in minimal to moderate hemolysis of dog blood but little to no hemolysis in human blood.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Ocular Toxicity / TX-200-2051 750 mg applied to each of the 3 corneas of bovine	GS-6207 was not considered an ocular irritant at 750 mg in bovine.
Dermal Toxicity / TX-200-2053 In vitro skin model EpiDerm • Purified water (negative control) • 8N potassium hydroxide (positive control) • GS-6207	GS-6207 was not considered a corrosive agent in the in vitro skin model EpiDerm test.
Local Lymph Node Assay / TX-200-2053 CBA/CaCrI mice 10, 25, and 50% w/v in dimethylformamide via topical application the auditory pinnae once daily on days 1, 2, and 3. N=5 females/group	GS-6207 was not considered a skin sensitizer under the conditions of this assay.
In Chemico Skin Sensitization Assay / TX-200-2071 (Direct Peptide Reactivity Assay) 100mM GS-6207 in 1:1 mixture of water:acetonitrile	GS-6207 resulted in a cysteine depletion of 0%, lysine depletion of 33.31%, and the mean cysteine and lysine depletion was 16.65%. GS-6207 tested positive with low reactivity in this assay.
In Vitro Skin Sensitization / TX-200-2072 (ARE-Nrf2 Luciferase Test Method) Concentration ranging from 0.98 to 2000µM (in dimethyl sulfoxide)	GS-6207 was not considered a skin sensitizer under the conditions of this assay.
In Vitro Skin Sensitization / TX-200-2073 (human cell line activation test) Human monocytic leukemia cells line (THP-1) were treated with GS-6207 concentrations ranging from 17.53 to 62.80 µg/mL	GS-6207 treatment resulted in a relative fluorescence intensity (RFI) of ≥150% for the cell surface marker CD86 in 7 of 8 concentrations and the RFI for CD54 was ≤200%. The results of the CD86 test indicate that GS-6207 is positive in the human cell line activation test for skin sensitizers.

Source: Reviewer.

Abbreviation: CD, cluster of differentiation; UVR, ultraviolet radiation

Impurity Studies

A Single-Dose Subcutaneous Injection Impurity Qualification Study With GS-6207 in Wister Han Rats With a 4-Week Observation (Recovery) Period (TX-200-2042; GLP)

In single dose impurity study, GS-6207 (pure), GS-6207-A (with impurities), or GS-6207-B (with impurities) formulated in PEG-300/sterile water for injection/ (b) (4) was administered to male and female Wister Han rats (3/sex/control and 3/sex/dose group) at a dose of 0 (control) or 100 mg/kg (GS-6207-treated groups) with a dose volume of 1.34 mL/kg via subcutaneous injection. GS-6207-related changes in serum chemistry detected 5 days postdose (increases in globulin; decrease in albumin:globulin ratio; and a decrease in albumin [males only]) suggested inflammation. At the end of the recovery period, these findings were not detected. Injection site reactions were detected in all GS-6207-treated animals and included minimal to marked granulomatous inflammation. The inclusion of the impurities did not affect the injection site reactions detected.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

A Single Dose Subcutaneous Injection Impurity Qualification Toxicity And Toxicokinetic Study of GS-6207 in Wister Han Rats With a 13-Week Observation (Recovery) Period (TX-200-2050; GLP)

In single dose impurity study, GS-6207 (pure, sodium salt form), GS-6207-A (with impurities, free acid form), or GS-6207-B (with impurities, sodium salt form) formulated in PEG-300/sterile water for injection/ (b) (4) was administered to male and female Wister Han rats (3/sex/control and 3/sex/dose group) at a dose of 0 (control) or 100 mg/kg (GS-6207 treated groups) with a dose volume of 1.34 mL/kg via subcutaneous injection. Injections site reactions were detected in all GS-6207, GS-6207-A, and GS-6207-B-dosed animals. Minimal to slight, focal or multifocal, infiltrates of macrophages were detected in at all doses in males and in GS-6207 or GS-6207-B females. The increase in incidence and severity of the macrophage finding was highest in males dosed with GS-6207-A and females dosed with GS-6207-B. Minimal granulomatous inflammation at the injection site was detected in a single female dosed with GS-6207. Dosing animals with GS-6207, GS-6207-A, and GS-6207-B did not induce micronuclei in the peripheral blood reticulocytes.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

14.1.1. Absorption

Bidirectional permeability of LEN through Caco-2 cell monolayers was evaluated in Study AD-200-2009. Low forward permeability through monolayers of Caco-2 cells and evidence for efflux transport were observed for LEN.

14.1.2. Distribution

Protein binding of LEN was evaluated in Studies AD-200-2020, AD-200-2021, AD-200-2032, and AD-200-2048. The binding of LEN to human plasma proteins, human hepatic microsomes, human serum albumin, or purified α 1-acid glycoprotein was high, with mean fraction bound of 98.5%, 89.2%, >99.9%, and 93%, respectively. The binding of LEN to human plasma proteins, human hepatic microsomes, human serum albumin, or purified α 1-acid glycoprotein was high, with a mean fraction bound of 98.5%, 89.2%, >99.9%, and 93%, respectively. The human blood-plasma ratio was 0.64, showing minimal binding to blood cells.

14.1.3. Metabolism

LEN stability was evaluated in phosphate buffered saline, plasma, hepatic microsomes, hepatocytes, and Hurel® hepatic co-cultures in Studies AD-200-2047, AD-200-2022, AD-200-2008, and AD-200-2037. The studies showed that LEN exists in two (b) (4) forms, (b) (4). The LEN (b) (4) pattern was stable over time and is not influenced by binding proteins or enzymes in plasma. LEN showed high metabolic stability across all species in both hepatic microsomes, hepatocytes, and Hurel® hepatocyte co-cultures. LEN was predicted to have a low hepatic metabolic clearance in human.

14.1.4. Drug-Drug Interaction Potential—LEN as a Victim

LEN was evaluated as a substrate of cytochrome P450 (CYP) enzymes, UDP glucuronosyl transferase (UGT) enzymes, P-gp, BCRP, organic anion transporter peptide (OATP)1B1, and OATP1B3 in Studies AD-200-2030, AD-200-2054, AD-200-2033, AD-200-2005, AD-200-2025, and AD-200-2027. Very slow metabolism of LEN by CYP3A5 or UGT1A1 was observed in in vitro phenotyping studies, indicating LEN is a substrate for CYP3A5 and UGT1A1. LEN is also a substrate for P-gp. LEN is not a substrate for other CYP or UGT isozymes, nor a substrate for breast-cancer resistance protein (BCRP) or hepatic uptake transporters.

14.1.5. Drug-Drug Interaction Potential—LEN as a Perpetrator

The potential of LEN as an inhibitor for CYP enzymes, UGT1A1, P-gp (MDR1), BCRP, OATP1B1, OATP1B3, OAT1, OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion protein (MATE)1, MATE2K, and bile salt export pump was evaluated in Studies AD-200-2028, AD-200-2050, AD-200-2031, AD-200-2026, AD-200-2035. The results showed that LEN is a moderate CYP3A inhibitor, mainly through mechanism-based inhibition. The potential of LEN as an inhibitor was evaluated using static mechanistic models (Report AD-200-2055), described in the FDA Guidance for Industry: *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020). Based on the criteria defined in the guidance, LEN is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT1A1. LEN is an inhibitor of OATP1B1 or OATP1B3, but is not likely to inhibit P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K. LEN is expected to increase the concentrations of CYP3A substrates by about five- and two-fold with LEN oral and SC injection, respectively.

The induction potential of LEN on the aryl hydrocarbon receptor, constitutive androstane receptor, and pregnane X receptor was evaluated in Study AD-200-2029. In vitro characterization of LEN for CYP induction potential was conducted using Sandwich Cultured Transporter-Certified™ hepatocytes in Study AD-200-2049. The data suggested no potential for activation of genes regulated by the aryl hydrocarbon receptor or constitutive androstane receptor. LEN activated pregnane X receptor, exceeding two-fold activation at concentrations of $LEN \geq 2.5 \mu M$. In Study AD-200-2049, CYP3A4 mRNA was unchanged in two of the three donors; the mRNA fold over control increased more than two-fold in the third donor and reached a maximum of 23% of the positive control at $3 \mu M$ LEN (a cytopathic dose). Thus, while this effect was only seen in one donor it suggests that induction of CYP3A4 and pregnane X receptor-regulated gene products by LEN cannot be ruled out completely. The potential of LEN as an inducer was evaluated using static mechanistic models. Based on the FDA in vitro drug-drug interaction (DDI) guidance, LEN would not be classified as an inducer following either SC or oral administration (Report AD-200-2055).

14.2. In Vivo Studies

Table 102. Study GS-US-200-4333

Location	GS-US-200-4333 Final CSR
Title	A Phase 1 Study to Evaluate Transporter and Cytochrome (CYP) 450-Mediated Drug-Drug Interactions Between GS-6207 (LEN) and Probe Drugs
Trial design	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. Cohort 1: LEN (reference treatment for Cohorts 2 and 3) Treatment A: Single dose of oral LEN 300 mg (6x50 mg capsules, (b) (4)) administered in the morning under <u>fed</u> conditions 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 to 90. On Day 11, 300 mg LEN (6x50 mg capsules, (b) (4)) was coadministered with COBI. 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 to 90. On Day 11, 300 mg LEN (6x50 mg capsules, (b) (4)) was coadministered with COBI. Cohort 4: LEN (reference treatment for Cohorts 5, 8, 9, and 10) Treatment D: Single dose of oral LEN 300 mg (1x300 mg tablet, sodium) administered in the morning under <u>fasted</u> conditions 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 to 24, administered under <u>fasted</u> 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. LEN 300 mg (1x300 mg tablet, sodium) was coadministered with VORI on Day 2. Cohort 6: LEN (reference for Cohort 7) Treatment F: Single dose of oral LEN 300 mg (1x300 mg tablet, sodium) administered in the morning under <u>fed</u> conditions Cohort 7: Atazanavir/Cobicistat (ATV/COBI; mixed Pgp/CYP3A/UGT1A1 inhibitor) and LEN Treatment G: ATV/COBI (300/150 mg) once daily in the morning under <u>fed</u> conditions on Days 1 to 60. On Day 10, LEN 300 mg (1x300 mg tablet, sodium) was coadministered with ATV/COBI 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 <u>fasted</u> conditions on Days 1 to 25. On the day of discharge (Day 26), no dose was administered. On Day 14, LEN 300 mg (1x300 mg tablet, sodium) was administered in the morning followed by RIF dosing in the afternoon. Cohort 9: Efavirenz (EFV; moderate CYP3A and P-gp inducer) and LEN Treatment I: EFV (600 mg) administered once daily in the evening under <u>fasted</u> conditions on Days 1 to 25. On the day of discharge (Day 26), no dose was administered. On Day 14, LEN 300 mg (1x300 mg tablet, sodium) was administered in the morning followed by EFV dosing in the afternoon. Cohort 10: Famotidine (FAM; H2RA) and LEN Treatment J: FAM (40 mg) administered in the morning then LEN 300 mg (1x300 mg tablet, sodium) 2 hours after FAM dosing under <u>fasted</u> conditions on Day 1 Cohort 11: Pitavastatin (PIT; <u>OATP substrate</u>), rosuvastatin (ROS; <u>BCRP substrate</u>), tenofovir alafenamide (TAF; <u>P-gp substrate</u>), midazolam (MDZ; <u>CYP3A substrate</u>), and LEN

	Period 1	Period 2	Period 3	Period 4
Cohort 11	Day 1 PIT (2 mg)	Day 4 ROS (5 mg)	Day 7 TAF (25 mg)	Day 10 MDZ (2.5 mg)
	Period 5	Period 6	Period 7	Period 8
Cohort 11	Days 11-12 LEN (600 mg) ^a BID	Day 15 LEN (600 mg) + PIT (2 mg)	Day 18 LEN (600 mg) ^{a+} ROS (5 mg)	Day 21 LEN (600 mg) ^a + TAF (25 mg)
	Period 9	Period 10	Period 11	
Cohort 11	Day 24 LEN (600 mg) + MDZ (2.5 mg)	Day 25 MDZ (2.5 mg)	Day 27 PIT (2 mg)	

^a LEN 600 mg (2x300 mg tablets, sodium)

PK Sample collection time points Plasma PK Sampling

Intensive PK samples were collected for LEN at:

- Cohort 1: Predose and up to 64 days postdose following LEN administration on Day 1
- Cohorts 2 and 3: Predose and up to 80 days postdose following LEN administration on Day 11
- Cohorts 4 and 10: Predose and up to 24 days postdose following LEN administration on Day 1
- Cohort 5: Predose and up to 24 days postdose following LEN administration on Day 2
- Cohort 6: Predose and up to 51 days postdose following LEN administration on Day 1
- Cohort 7: Predose and up to 51 days postdose following LEN administration on Day 10
- Cohorts 8 and 9: Predose and up to 13 days postdose following LEN administration on Day 14
- Cohort 11 (LEN PK):
 - Day 11: 0 (predose, ≤5 minutes before LEN dose), 12 hours postdose.
 - Day 12: 0 (predose, ≤5 minutes before LEN dose), 12 hours postdose.
 - Days 15, 18, and 21: 0 (predose, ≤5 minutes before LEN dose) and up to 48 hours postdose.
 - Day 24: 0 (predose, ≤5 minutes before LEN dose), and up to 120 hours postdose.
- Intensive PK samples were collected for PIT, ROS, TAF, and MDZ (Cohort 11) at:
 - PIT (Days 1, 15, and 27): predose and up to 48 hours postdose.
 - ROS (Days 4 and 18): predose, and up to 72 hours postdose.
 - TAF (Days 7 and 21): predose and up to 8 hours postdose.
 - TFV (Days 7 and 21): predose and up to 96 hours postdose.
 - MDZ (and 1-OH-MIDZ) (Days 10, 24, 25): predose and up to 24 hours postdose.

Results

Study 4333: Statistical Comparisons of PIT PK Parameters Following Administration Alone, PIT Administered Simultaneous With LEN, and PIT Administered Staggered From LEN Under Fed Conditions in Cohort 11 (PIT PK Analysis Set)PIT 2 mg Administered Simultaneously With LEN 600 mg day 15 vs. PIT day 1

PK Parameter	GLSM		
	PIT 2 mg + LEN 600 mg (Simultaneous Administration) (Test, N = 30)	PIT 2 mg (Reference, N = 31)	%GLSM Ratio (90% CI) Test/Reference
AUC _{inf} (h·ng/mL)	92.70	83.19 ^a	111.44 (99.63, 124.65)
AUC _{last} (h·ng/mL)	85.31	74.80	114.05 (101.05, 128.72)
C _{max} (ng/mL)	27.69	27.72	99.88 (83.57, 119.38)

PIT 2 mg Administered Staggered From LEN 600 mg Day 27 vs. PIT Day 1

PK Parameter	GLSM		
	PIT 2 mg + LEN 600 mg (Staggered Administration) (Test, N = 28)	PIT 2 mg (Reference, N = 31)	%GLSM Ratio (90% CI) Test/Reference
AUC _{inf} (h·ng/mL)	80.19 ^b	83.19 ^a	96.40 (87.06, 106.74)
AUC _{last} (h·ng/mL)	67.05	74.80	89.64 (76.95, 104.43)
C _{max} (ng/mL)	23.60	27.72	85.13 (68.72, 105.47)

PIT was staggered 3 days after the last dose of LEN.

N, number of participants in the PK Analysis Set.

ANOVA model includes treatment as a fixed effect and participant as a random effect.

^a N=30^b N=26**Study 4333: Statistical Comparisons of ROS PK Parameters Following Administration of ROS Alone or With LEN Under Fed Conditions in Cohort 11 (ROS PK Analysis Set)**

PK Parameter	GLSM		
	ROS 5 mg + LEN 600 mg (Test, N = 30)	ROS 5 mg (Reference, N = 30)	%GLSM Ratio (90% CI) Test/Reference
AUC _{inf} (h·ng/mL)	15.17 ^a	11.60 ^b	130.72 (119.20, 143.35)
AUC _{last} (h·ng/mL)	11.36	9.01	126.06 (112.50, 141.25)
C _{max} (ng/mL)	1.52	0.97	157.48 (138.08, 179.62)

N, number of participants in the PK Analysis Set.

ANOVA model includes treatment as a fixed effect and participant as a random effect.

^a N=29^b N=28

Study 4333: Statistical Comparisons of TAF PK Parameters Following Administration of TAF Alone or With LEN Under Fed Conditions in Cohort 11 (TAF PK Analysis Set)

PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	TAF 25 mg + LEN 600 mg (Test, N = 28)	TAF 25 mg (Reference, N = 30)	
AUC _{last} (h·ng/mL)	304.40	230.90	131.83 (109.22, 159.13)
C _{max} (ng/mL)	275.63	221.45	124.46 (98.34, 157.53)

N, number of participants in the PK Analysis Set.

ANOVA model includes treatment as a fixed effect and participant as a random effect.

Study 4333: Statistical Comparisons of TFV PK Parameters Following Administration of TAF Alone or With LEN Under Fed Conditions in Cohort 11 (TFV PK Analysis Set)

PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	TAF 25 mg + LEN 600 mg (Test, N = 28)	TAF 25 mg (Reference, N = 30)	
AUC _{inf} (h·ng/mL)	295.07	200.20	147.39 (126.95, 171.11)
AUC _{last} (h·ng/mL)	229.29	165.46	138.58 (115.14, 166.78)
C _{max} (ng/mL)	7.40	6.02	123.08 (105.25, 143.93)

N, number of participants in the PK Analysis Set.

ANOVA model includes treatment as a fixed effect and participant as a random effect.

Study 4333: Statistical Comparisons of MDZ and 1-OH-MDZ PK Parameters Following Administration of MDZ Alone, MDZ Administered Simultaneous With LEN, and MDZ Administered Staggered From LEN Under Fed Conditions in Cohort 11 (MDZ and 1-OH-MDZ PK Analysis Sets)

PK Parameter	MDZ			1-OH-MDZ		
	GLSM		%GLSM Ratio (90% CI) Test/Reference	GLSM		%GLSM Ratio (90% CI) Test/Reference
	MDZ 2.5 mg + LEN 600 mg (Test, N = 28)	MDZ 2.5 mg (Reference, N = 30)		MDZ 2.5 mg + LEN 600 mg (Test, N = 28)	MDZ 2.5 mg (Reference, N = 30)	
AUC _{inf} (h·ng/mL)	178.78	49.80	358.99 (329.52, 391.10)	9.99	13.20	75.71 (71.63, 80.02)
AUC _{last} (h·ng/mL)	148.22	47.66	311.00 (287.17, 336.81)	8.46	12.35	68.49 (64.47, 72.75)
C _{max} (ng/mL)	17.55	9.06	193.64 (180.63, 207.59)	1.32	2.44	54.07 (49.67, 58.86)

PK Parameter	MDZ			1-OH-MDZ		
	GLSM		%GLSM Ratio (90% CI) Test/Reference	GLSM		%GLSM Ratio (90% CI) Test/Reference
	MDZ 2.5 mg + Not Coadminis- tered LEN 600 mg (Test, N = 28)	MDZ 2.5 mg (Reference, N = 30)		MDZ 2.5 mg + Not Coadminis- tered LEN 600 mg (Test, N = 28)	MDZ 2.5 mg (Reference, N = 30)	
AUC _{inf} (h·ng/mL)	202.98	49.80	407.58 (377.09, 440.54)	11.04	13.20	83.65 (79.78, 87.71)
AUC _{last} (h·ng/mL)	168.97	47.66	354.56 (331.85, 378.81)	9.32	12.35	75.52 (71.70, 79.54)
C _{max} (ng/mL)	19.55	9.06	215.69 (201.84, 230.49)	1.27	2.44	52.01 (47.59, 56.83)

MDZ was staggered 1 day after the last dose of LEN.

N, number of participants in the PK Analysis Set.

Analysis of variance model includes treatment as a fixed effect and participant as a random effect.

Study 4333: Statistical Comparisons of LEN PK Parameters Following Administration of LEN Alone, LEN With COBI, and LEN With DRV/COBI Under Fed Conditions in Cohorts 1, 2, and 3 (LEN PK Analysis Set)

PK Parameter	COBI+LEN vs LEN			DRV/COBI+LEN vs LEN		
	GLSM		%GLSM Ratio (90% CI) Test/Reference	GLSM		%GLSM Ratio (90% CI) Test/Reference
	COBI 150 mg + LEN 300 mg (Test, N = 29)	LEN 300 mg (Reference, N = 30)		DRV/COBI 800/150 mg + LEN 300 mg (Test, N = 29)	LEN 300 mg (Reference, N = 30)	
AUC _{inf} (h*ng/mL)	19403.00	8524.31	227.62 (174.98, 296.09)	16550.97	8524.31	194.16 (149.59, 252.01)
AUC _{last} (h*ng/mL)	14050.50	8213.44	171.07 (132.27, 221.25)	12639.23	8213.44	153.88 (118.45, 199.92)
C _{max} (ng/mL)	51.14	24.38	209.74 (161.98, 271.60)	56.00	24.38	229.65 (178.75, 295.05)

N, number of participants in the PK Analysis Set.

Analysis of variance model includes treatment as a fixed effect.

Study 4333: Statistical Comparisons of LEN PK Parameters Following Administration of LEN Alone or LEN With VORI Under Fasting Conditions in Cohorts 4 and 5 (LEN PK Analysis Set)

PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	VORI 200 mg + LEN 300 mg (Test, N = 25)	LEN 300 mg (Reference, N = 27)	
AUC _{inf} (h*ng/mL)	6439.01	4560.48	141.19 (109.89, 181.40)
AUC _{last} (h*ng/mL)	4314.57	2924.94	147.51 (108.81, 199.98)
C _{max} (ng/mL)	17.16	15.67	109.49 (81.30, 147.45)

N, number of participants in the PK Analysis Set.

Analysis of variance model includes treatment as a fixed effect.

Study 4333: Statistical Comparisons of LEN PK Parameters Following Administration of LEN Alone and LEN With ATV/COBI Under Fed Conditions in Cohorts 6 and 7 (LEN PK Analysis Set)

PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	ATV/COBI 300/150 mg + LEN 300 mg (Test, N = 21)	LEN 300 mg (Reference, N = 25)	
AUC _{inf} (h*ng/mL)	20181.07	4788.62	421.44 (319.01, 556.75)
AUC _{last} (h*ng/mL)	17128.86	4297.38	398.59 (294.69, 539.12)
C _{max} (ng/mL)	102.44	15.52	659.99 (498.87, 873.14)

N, number of participants in the PK Analysis Set.

Analysis of variance model includes treatment as a fixed effect.

Study 4333: Statistical Comparisons of LEN PK Parameters Following Administration of LEN Alone, LEN With RIF, and LEN With EFV Under Fasted Conditions in Cohorts 4, 8, and 9 (LEN PK Analysis Set)

PK Parameter	RIF+LEN vs LEN			EFV+LEN vs LEN		
	GLSM		%GLSM Ratio (90% CI) Test/Reference	GLSM		%GLSM Ratio (90% CI) Test/Reference
	RIF 600 mg + LEN 300 mg (Test, N = 25)	LEN 300 mg (Reference, N = 27)		EFV 600 mg + LEN 300 mg (Test, N = 18)	LEN 300 mg (Reference, N = 27)	
AUC _{inf} (h*ng/mL)	706.82 ^a	4560.48	15.50 (12.16, 19.75)	1989.76	4560.48	43.63 (32.12, 59.27)
AUC _{last} (h*ng/mL)	626.69	2924.94	21.43 (15.84, 28.97)	1363.39	2924.94	46.61 (32.68, 66.49)
C _{max} (ng/mL)	7.01	15.67	44.72 (33.56, 59.58)	10.05	15.67	64.14 (44.52, 92.41)

N, number of participants in the PK Analysis Set.

Analysis of variance model includes treatment as a fixed effect.

^a N=24

Study 4333: Statistical Comparisons of LEN PK Parameters Following Administration of LEN Alone or LEN With FAM Under Fasting Conditions in Cohorts 4 and 10 (LEN PK Analysis Set)

PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	FAM 40 mg + LEN 300 mg (Test, N = 25)	LEN 300 mg (Reference, N = 27)	
AUC _{inf} (h·ng/mL)	5825.60	4560.48	127.74 (100.17, 162.89)
AUC _{last} (h·ng/mL)	4018.50	2924.94	137.39 (102.53, 184.09)
C _{max} (ng/mL)	15.76	15.67	100.57 (75.22, 134.45)

N, number of participants in the PK Analysis Set.

Analysis of variance model includes treatment as a fixed effect.

Source:

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; BID, twice daily; CI, confidence interval; C_{max}, maximum concentration; DDI, drug-drug interaction; GLSM, geometric least-squares mean; LEN, lenacapavir; OATP, organic anion transporting polypeptide; P-gp, p-glycoprotein; PK, pharmacokinetic; UGT, uridine galactosyltransferase

Table 103. Study GS-US-200-5709

Location	GS-US-200-5709 Interim CSR; GS-US-200-5709 Day 85 Addendum
Title	A Phase 1 Study in Healthy Participants to Evaluate the Safety, Tolerability and Pharmacokinetics of Lenacapavir (LEN)
Trial design	<u>Cohort 1:</u> Participants received oral LEN 600 mg (2x300 mg tablets, sodium) on Days 1 and 2, 300 mg (1x300 mg tablet, sodium) on Day 8, and SC LEN 927 mg (2x1.5 mL 309 mg/mL sodium salt [NaS]) on Day 15. <u>Cohort 2:</u> Participants received SC LEN 927 mg (2x1.5 mL 309 mg/mL NaS) and oral LEN 600 mg (2x300 mg tablets, sodium) on Days 1 and 2. <u>Cohort 3:</u> Participants received oral LEN 600 mg (2x300 mg tablets, sodium) twice daily on Days 1 to 10 and oral LEN 600 mg (2x300 mg tablets, sodium) once on Day 11.
PK Sample collection time points	<u>Plasma PK sampling</u> Intensive plasma PK sampling occurred relative to the morning dose of LEN at the following time points for each cohort: • Cohort 1: – Day 1: predose and up to 12 hours postdose. – Day 2: predose and up to 120 hours postdose. – Day 8: predose and up to 144 hours postdose. – Day 15: predose, up to 449 days postdose and at early termination. • Cohort 2: – Day 1: predose and up to 12 hours postdose. – Day 2: predose, up to 742 days postdose and at early termination. • Cohort 3: – Days 1 and 2: predose and up to 12 hours postdose (prior to second dose). – Days 3, 4, 8, 9, and 10: predose and 12 hours postdose (prior to PM dose). – Day 11: predose and up to 12 hours postdose. – A single PK sample was collected at the ET visit, if applicable.

Results

Study 5709: Summary Statistics of Plasma Pharmacokinetic Parameters (Cohort 1) (LEN PK Analysis Set) (Study 5709 Day 85 Addendum)

PK Parameter Mean (%CV)	LEN			
	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 = 30)
C _{max} (ng/mL)	22.0 (45.5)	40.4 (43.4)	39.3 (44.7)	58.7 (58.1)
T _{max} (h) ^a [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]	2028.04 (1682.45, 2688.23) [84.5]
C _{last} (ng/mL)	11.2 (60.8)	19.2 (40.8)	20.6 (43.1)	25.0 (81.7)
T _{last} (h) ^a [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]	5037.95 (4032.00, 5042.33) [209.9]

%CV = percentage coefficient of variation; BLQ = below the limit of quantitation; LEN = lenacapavir; LLOQ = lower limit of quantitation; NaS = sodium salt; 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 was defined as 0.5 ng/mL for LEN.

Study 5709: Summary Statistics of Plasma Pharmacokinetic Parameters (Cohort 2) (LEN PK Analysis Set) (Study 5709 Day 85 Addendum)

PK Parameter Mean (%CV)	LEN	
	Day 1 927 mg SC LEN (2 × 1.5 mL 309 mg/mL NaS) 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)	64.7 (45.0)
T _{max} (h) ^a [days]	6.00 (4.00, 8.00) [0.25]	1653.74 (12.00, 1653.98) [68.9]
C _{last} (ng/mL)	13.6 (36.5)	53.8 (54.2)
T _{last} (h) ^a [days]	12.0 (12.0, 12.0) [0.50]	1991.16 (1990.70, 1991.18) [83.0]

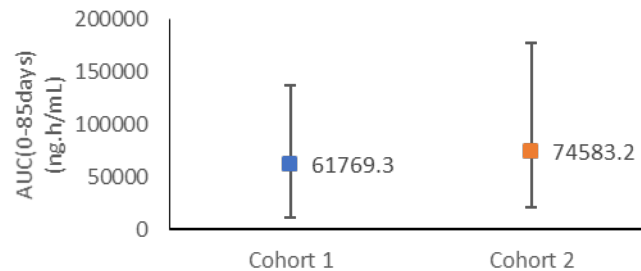
%CV = percentage coefficient of variation; BLQ = below the limit of quantitation; LEN = lenacapavir; LLOQ = lower limit of quantitation; NaS = sodium salt; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous

^a Median (Q1, Q3)

Values BLQ were treated as 0 for predose and one-half of the LLOQ for postdose summaries.

LLOQ was defined as 0.5 ng/mL for LEN.

GS US 200 5709: LEN AUC (0-85 Days) (Geometric Mean±90% CI) Comparison of Cohort 1 and Cohort 2



Study 5709: Summary Statistics of Plasma Pharmacokinetic Parameters (Cohort 3) (LEN PK Analysis Set) (Study 5709 Interim CSR)

PK Parameter Mean (%CV)	LEN							
	600 mg oral LEN (2 × 300 mg tablets; AM dose) and 600 mg oral LEN (2 × 300 mg tablets; PM dose)							600 mg oral LEN (2 × 300 mg tablets; AM dose)
	Day 1 (N = 15)	Day 2 (N = 15)	Day 3 (N = 15)	Day 4 (N = 15)	Day 8 (N = 15)	Day 9 (N = 15)	Day 10 (N = 15)	Day 11 (N = 15)
AUC _{0-12h} (hng/mL)	135.4 (30.7)	894.4 (47.2)	NC	NC	NC	NC	NC	9706.9 (28.2)
C _{max} (ng/mL)	19.0 (24.0)	96.4 (49.5)	NC	NC	NC	NC	NC	1012.1 (26.2)
T _{max} (h) ^a	5.00 (4.00, 5.00)	8.00 (5.00, 11.97)	NC	NC	NC	NC	NC	4.00 (4.00, 5.00)
C _{last} (ng/mL)	11.1 (39.9)	88.4 (45.2)	241.6 (41.2)	376.9 (31.7)	604.8 (32.6)	680.5 (28.2)	751.9 (25.7)	787.7 (31.3)
T _{last} (h) ^a	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)
C ₀ (ng/mL)	BLQ (BLQ)	42.0 (47.2)	152.6 (49.7)	342.4 (39.6)	558.5 (36.8)	699.9 (33.2)	693.1 (35.0)	788.8 (32.1)

^a Median (Q1, Q3)C₀, concentration at time 0 hours.

Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.

LLOQ was defined as 0.5 ng/mL for LEN.

Source:

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{last}, last observed concentration; C_{max}, maximum concentration; CSR, clinical study report; LLOQ, lower limit of quantitation; PK, pharmacokinetic; T_{last}, time at C_{last}; T_{max}, time to C_{max}.

Table 104. Study GS-US-200-4072

Location	GS-US-200-4072 Final CSR
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
Trial design	This was a randomized, double-blinded, placebo-controlled, multicenter, multicohort study of LEN (Part A) and TAF (Part B) monotherapy in people with HIV. Results from Part B of the study are not discussed here. 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 to 5 were determined based on cumulative safety data (to at least Day 14) and available PK and antiviral activity data from previous cohorts, as well as available safety data (to 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. <i>The formulation of LEN used was LEN 100 mg/mL suspension, free acid.</i> All participants initiated once-daily bicitegravir/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.
PK Sample collection time points	<u>Plasma PK Sampling</u> Intensive plasma PK sampling occurred relative to study drug dosing time at the following time points for each study part. Study Part A (Cohorts 1 to 5): Day 1: 0 (predose), and up to 225 days postdose.

Results

Study 4072: LEN Plasma Pharmacokinetic Parameters Following Single-Dose Administration of LEN—Part A (LEN PK Analysis Set)

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)

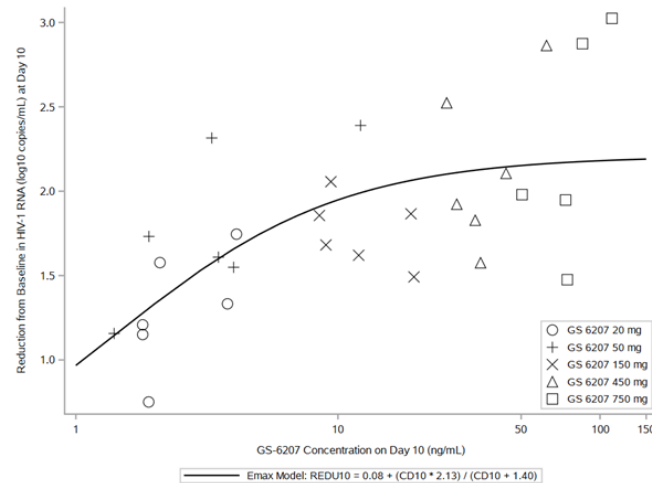
Data are means (%CV), except for T_{max}, T_{last}, and t_{1/2}, which are medians (Q1, Q3) hours [median days].

Pharmacokinetics/Pharmacodynamics

Plasma concentrations of LEN were fit to an E_{max} model to evaluate the concentration-response relationship between LEN concentration at Day 10 and the reduction from baseline in HIV-1 RNA at Day 10. Due to the limited amount of data at low concentration values and reduction in HIV-1 RNA in the placebo group, the E_{max} model was not forced through the origin (0,0).

Following single-dose SC administration of LEN, the E_{max} was predicted to be a 2.13 log₁₀ copies/mL decline in HIV-1 RNA at Day 10. The in vivo 90% effective concentration (EC₉₀) of LEN on Day 10 demonstrated by the E_{max} model was 12.6 ng/mL. Based on this analysis, mean LEN concentrations ≥12.6 ng/mL are predicted to provide near maximal (94%) antiviral activity.

Study 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)



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).
 CD10, LEN concentration on Day 10 (ng/mL)

Source:

Abbreviations: %CV, percentage coefficient of variation; E_{max}, maximum effect; HIV, human immunodeficiency virus; LEN, lenacapavir; PD, pharmacodynamic; PK, pharmacokinetic; Q1, first quartile; Q3, third quartile; SC, subcutaneous; TAF, tenofovir alafenamide

Table 105. Study GS-US-200-4330

Study number	GS-US-200-4330
Report location	GS-US-200-4330 Final CSR
Study 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
Description of trial design	<u>Inclusion Criteria</u> Male and nonpregnant/nonlactating female subjects, ages 18 to 79 years with severe renal impairment or normal renal function (creatinine clearance [CL_{cr}] ≥90 mL/min), were eligible. Subjects must have had 12-lead electrocardiogram (ECG) without clinically significant abnormalities, with either severe renal impairment or normal renal function (CL_{cr} ≥90 mL/min using the Cockcroft Gault equation). Subjects with renal impairment must have had a severe renal impairment classification (15 ≤ CL_{cr} ≤29 mL/min using the Cockcroft Gault equation) at screening that was unchanged during the 3 months prior to study drug dosing. Subjects with severe renal impairment requiring or anticipated to require dialysis within 90 days of study entry were not eligible. <u>Treatment</u> Subjects with renal impairment received a single dose of lenacapavir (LEN) (1×300 mg tablet) administered orally on Day 1. Dosing in matched healthy controls with normal renal function began after a matched subject with renal impairment had completed pharmacokinetic (PK) assessments through Day 4. Matched healthy controls received a single dose of LEN (1×300 mg tablet). Duration of dosing was 1 day. The study duration (not including screening) was approximately 60 days (±1 day) including follow-up.
PK Sampling scheme	<u>Plasma PK Collection</u> Intensive PK sampling occurred relative to the morning dose of LEN at the following time points for each cohort: Day 1: 0 (predose, ≤5 minutes before dose), 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose.

Days 4, 6, 8, 15, 22, 29, 36, 43, and 50: A single anytime PK sample was collected.

Additional plasma samples were collected for plasma protein binding evaluation on Day 1 at 2, 4, 6, 8, 12, 24, and 48 hours postdose. In addition, a plasma sample was collected on Days 15 and 50 and were utilized for plasma protein binding evaluation.

Urine PK Sampling

All urine samples were collected predose (void; within a 12-hour period prior to Day 1 dose), and over the following collection intervals after Day 1: 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours postdose.

Results

The plasma PK parameters of LEN (by renal group) are presented below. C_{max} and AUC were 2.6- and 1.9-fold higher, respectively, in subjects with severe renal impairment compared to subjects with normal renal function. However, larger increases in exposures were observed in other clinical studies. In Study 4332, the C_{max} and AUC_{tau} to Day 12 were 1070 ng/mL and 10,641 h·ng/mL, respectively, more than 7- and 12-fold higher, respectively, than the therapeutic exposure in the CAPELLA study. Similar results were observed in Study 5709. There are no safety concerns for both studies. Therefore, the observed exposure elevation in subjects with severe renal impairment is not clinically significant.

Study 4330: Summary Statistics and Statistical Comparison of Plasma PK Parameters (LEN PK Analysis Set)

PK Parameter	Mean ^a (%CV)		Severe Renal Impairment/Matched Healthy Control %Geometric Least-Squares Mean Ratio (90% CI)
	Severe Renal Impairment (N=10)	Matched Healthy Control (N=10)	
C_{max} (ng/mL)	118 (129)	22.1 (43.6)	262 (112, 614)
AUC _{last} (h·ng/mL)	18,335 (101)	6844 (48.8)	189 (95.2, 377)
AUC _{inf} (h·ng/mL)	18,997 (98.3)	7401 (47.6)	184 (93.6, 360)
CL/F (mL/h)	44,063 (138.3)	51,822 (56.3)	-
T_{max} (h) ^b	8.00 (6.00, 24.0)	6.00 (6.00, 8.00)	-
$t_{1/2}$ (h) ^b	234 (178, 354)	318 (270, 357)	-

^a Data are means (%CV).

^b $t_{1/2}$ and T_{max} are presented as medians (Q1, Q3).

No pharmacodynamic analyses were performed for this study.

Source: Applicant's study report for Study 4330.

Abbreviations: %CV, percentage coefficient of variation; AUC, area under the concentration-time curve; C_{max} , maximum concentration; LEN, lenacapavir; PK, pharmacokinetic; Q1, first quartile; Q3, third quartile

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 106. Study GS-US-200-4331

Study number	GS-US-200-4331			
Report location	GS-US-200-4331 Final CSR			
Study 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			
Description of trial design	Inclusion Criteria			
	Eligible subjects were male or nonpregnant, nonlactating female subjects, aged 18 to 75 years (inclusive) with normal or moderately impaired hepatic function based on the Current Procedural Terminology (CPT) classification system (CPT Class B). Subjects 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.			
PK Sampling scheme	Treatment			
	Each subject received a single dose of LEN 300 mg (batch number: GJ1901D1) on Day 1. Participants received study drug for 1 day. Study duration was up to 121 days (not including screening window).			
Results	Plasma PK Collection			
	Intensive PK sampling occurred relative to dosing of LEN at the following time points: Day 1: 0 (predose, ≤5 minutes before dose), 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose. A single anytime PK sample was collected on days 4, 6, 8, 15, 22, 29, 36, 43, 50, 64, 78, 92, and 120, as applicable. Additional plasma samples were collected for plasma protein binding evaluation on Day 1 at 2, 4, 6, 8, 12, 24, and 48 hours postdose.			
Results	The plasma PK parameters for LEN and statistical comparisons are presented in the table below. C _{max} and AUC were 2.6- and 1.6-fold higher, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. These exposure increases are not clinically significant (see conclusion for Study 4330).			
	Study 4331: Summary Statistics and Statistical Comparisons of LEN Plasma PK Parameters (LEN PK Analysis Set)			
		Mean^a (%CV)		
		Moderate Hepatic Impairment (N=10)	Normal Hepatic Function (N=10)	Moderate Hepatic Impairment/Normal Hepatic Function %GLSM Ratio (90% CI)
	PK Parameter			
	AUC _{inf} (h·ng/mL)	14,183.9 (62.6)	9216.1 (53.2)	146.59 (94.70, 226.91)
	AUC _{last} (h·ng/mL)	14,045.2 (62.6)	8614.9 (57.6)	156.57 (100.98, 242.76)
	C _{max} (ng/mL)	82.7 (82.1)	26.8 (55.1)	261.23 (151.03, 451.85)
	T _{max} (h) ^a	2137.73 (1849.42, 2185.33)	1969.21 (1847.53, 2160.20)	-
	CL/F (L/h)	29.1 (55.0)	41.4 (55.0)	-
	t _{1/2} (h) ^a	303.07 (250.79, 365.80)	314.13 (284.11, 361.88)	-
^a Median (Q1, Q3). N, number of subjects in the PK Analysis Set. Means are unadjusted arithmetic means.				

Source: Applicant's study report for Study 4331.

Abbreviations: CV, coefficient of variation; AUC, area under the concentration-time curve; CL/F, oral clearance; C_{max}, maximum concentration; GLSM, geometric least-squares mean; PK, pharmacokinetics; Q1, first quartile; Q3, second quartile; t_{1/2}, half-life

Table 107. Study GS-US-200-4329

Study number	GS-US-200-4329

Report location	GS-US-200-4329 Final CSR																																						
Study title	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Metabolism and Excretion of IV GS-6207 in Healthy Subjects																																						
Description of trial design	<u>Inclusion Criteria (Clinical Pharmacology Related)</u> Eligible subjects were aged 18 to 55 years, inclusive (male only for Study Part B), with a creatinine clearance (CLcr) $\geq$90 mL/min, and with a normal liver function at screening. <u>Treatment</u> <i>Study Part A:</i> On the morning of Day 1, each subject received a single dose of LEN 10 mg or placebo, administered as a 1-hour IV infusion, without regard to food. <i>Study Part B:</i> On the morning of Day 1, each subject received a single dose of LEN 20 mg, containing a mixture of both unlabeled LEN and [^{14}C]LEN (equivalent to approximately 200 μCi), administered as a 1-hour IV infusion, without regard to food.																																						
PK Sampling scheme	<u>Plasma PK Collection (Study Part A)</u> Plasma samples for intensive PK analysis were collected at the following time points relative to the start time of infusion on Day 1: (predose [$\leq$30 minutes before dose]), 1, 2, 4, 6, 8, 12, 24, and 48 hours after the start of the infusion. A single anytime PK sample was collected on Days 4, 6, 8, 10, 12, 15, 22, 29, 36, 43, 57, 64, 71, 78, 85, and early termination (if applicable). <u>Study Part B (Plasma and Urine PK Collection)</u> Blood samples for plasma PK analysis of unlabeled LEN (and metabolites, if appropriate) were collected at the following time points relative to the start time of infusion on Day 1: 0 (predose [$\leq$30 minutes before dose]), 1, 2, 4, 6, 8, 12, 24, and 48 hours after the start of the infusion. A single anytime PK sample was collected on Days 4, 6, 8, 10, 12, 15, 22, 29, 36, 43, 50, and early termination (if applicable). Subjects who participated in the extended confinement period had a single anytime PK sample collected on Days 57, 64, 71, 78, 85, 99, 113, 127, and 141, as applicable.																																						
Results	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. Statistical comparisons of dose-normalized primary LEN PK parameters after single dose of LEN 10 mg and 20 mg in Cohort 1 and 3, respectively, are summarized in the table below. Study 4329: Statistical Comparisons of Dose-Normalized Plasma PK Parameters for LEN (PK Analysis Set) <table border="1"> <thead> <tr> <th rowspan="3">Parameter</th> <th colspan="4">Group</th> <th colspan="2">Statistical Comparison</th> </tr> <tr> <th colspan="2">Test (20 mg)</th> <th colspan="2">Reference (10 mg)</th> <th rowspan="2">%GLSM Ratio (90% CI)</th> <th rowspan="2">Model rMSE</th> </tr> <tr> <th>n</th> <th>GLSM</th> <th>n</th> <th>GLSM</th> </tr> </thead> <tbody> <tr> <td>AUC_{inf} Norm by dose (h·ng/mL/mg)</td> <td>10</td> <td>2114.25</td> <td>8</td> <td>2301.19</td> <td>91.88 (75.10, 112.40)</td> <td>0.243</td> </tr> <tr> <td>AUC_{last} Norm by dose (h·ng/mL/mg)</td> <td>10</td> <td>1901.73</td> <td>8</td> <td>2241.29</td> <td>84.85 (67.41, 106.81)</td> <td>0.278</td> </tr> <tr> <td>C_{max} Norm by dose (ng/mL/mg)</td> <td>10</td> <td>101.18</td> <td>8</td> <td>159.59</td> <td>63.40 (53.02, 75.82)</td> <td>0.216</td> </tr> </tbody> </table>	Parameter	Group				Statistical Comparison		Test (20 mg)		Reference (10 mg)		%GLSM Ratio (90% CI)	Model rMSE	n	GLSM	n	GLSM	AUC _{inf} Norm by dose (h·ng/mL/mg)	10	2114.25	8	2301.19	91.88 (75.10, 112.40)	0.243	AUC _{last} Norm by dose (h·ng/mL/mg)	10	1901.73	8	2241.29	84.85 (67.41, 106.81)	0.278	C _{max} Norm by dose (ng/mL/mg)	10	101.18	8	159.59	63.40 (53.02, 75.82)	0.216
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Analysis of Plasma Samples for [¹⁴C]LEN and [¹⁴C]Metabolites

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%.

Analysis of Fecal Samples for [¹⁴C]LEN and [¹⁴C]Metabolites

Unchanged LEN was the most abundant component recovered in feces and accounted for a mean abundance of 43.4% of the total fecal radioactivity. 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 two 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 ¹⁴C dose, respectively. Each of the other metabolites identified in feces accounted for <2% of the dose.

Summary of Mass Balance

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).

Source: Applicant's study report for Study 4329.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; GLSM, geometric least-squares mean; IV, intravenous; PK, pharmacokinetic rMSE, root mean square error

Table 108. Study GS-US-200-4071

Study number	GS-US-200-4071
Report location	GS-US-200-4071 Final CSR
Study 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
Description of trial design	This study proceeded in four parts, as follows: 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 ((b) (4) , 50 mg/mL) Part B (Cohorts 3 to 6): Randomized, blinded, placebo-controlled, single dose study with staggered dose escalations, oral solution in capsule ((b) (4) 50 or 100 mg/mL) Part C (Cohorts 7 to 11): Randomized, blinded, placebo-controlled, single-dose study with staggered dose escalations, oral tablets (50 mg or 300 mg) Part D (Cohorts 12 to 17): Open-label, parallel-group, single-dose food effect study, oral tablets (300 mg) Note: this review only includes discussion of Part C and Part D of Study 4071, because Part A and Part B used LEN oral solution in capsule formulations that are not to-be-market formulations. <u>Inclusion Criteria:</u> Eligible volunteers were an approximately even distribution of healthy male and healthy nonpregnant, nonlactating female volunteers, with body mass index of ≥19.0 and ≤30.0 kg/m², normal 12-lead electrocardiogram (ECG) or an ECG with abnormalities deemed clinically insignificant by the investigator, normal renal function (creatinine clearance ≥90 mL/min). <u>Treatment:</u> Volunteers received study drug for ≤11 days. Study duration was up to 87 days (not including screening window).

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

PK Sampling scheme	Plasma concentrations of LEN were determined, and PK parameters were estimated. Intensive plasma PK sampling occurred relative to the morning dose of LEN at the following time points: Day 1: 0 (predose [≤ 5 minutes before dose]), 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose. A single anytime PK sample was collected on Days 4, 6, 8, 15, 22, 29, 36, 43, 50, 57, and 64.

Results
Food Effect
PK parameters after administration of single doses of LEN oral tablets administered with a high-fat or light (low-fat meal), as well as comparison with fasted condition, are presented in the table below.

Study 4071: Plasma PK Parameters of LEN Following Single-Dose Administration of LEN 300 mg Tablets Under Fasted Conditions, With a High-Fat/High-Calorie Meal, or With a Light Meal (PK Analysis Set)

PK Parameter Mean (%CV)	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)	7692.1 (57.8)	8056.5 (39.8)	7293.4 (49.6)	115.22 (71.97, 184.48)	98.63 (58.17, 167.21)
C _{max} (ng/mL)	33.7 (96.3)	35.0 (33.0)	32.6 (62.4)	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)	Not calculated	Not calculated
t _{1/2} (h) ^a	242.64 (204.37, 281.36)	267.11 (243.70, 357.17)	287.46 (255.37, 321.85)	Not calculated	Not calculated

^a Median (Q1, Q3).

Source: Applicant's study report for Study 4071.

Abbreviations: %CV, percentage coefficient of variation; AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; GLSM, geometric least-squares mean; LEN, lenacapavir; PK, pharmacokinetic; t_{1/2}, half-life; T_{max}, time to maximum concentration

Table 109. Study GS-US-200-4538

Study number	GS-US-200-4538
Report location	GS-US-200-4538 Final CSR
Study 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
Description of trial design	<u>Inclusion Criteria:</u> Healthy male and healthy nonpregnant, nonlactating female subjects, aged 18 through 45 years, inclusive, with body mass index (BMI) of ≥ 19 and ≤ 30 kg/m ² , normal electrocardiogram (ECG), and normal renal function with creatinine clearance (CL _{cr}) ≥ 90 mL/min. <u>Treatment:</u> Study subjects received single dose (Day 1) of lenacapavir (LEN) with follow up for up to 450 days (not including screening window). The batch number for Formulation 2 (309 mg/mL, NaS) is GB1803A1. All study drugs were administered in the morning without regard to fasting status. The treatment for Part B is listed below: Cohort 5: LEN 309 mg SC Formulation 2 (309 mg/mL, NaS) (1x1 mL injection) Cohort 6: LEN 927 mg SC Formulation 2 (309 mg/mL, NaS) (3x1 mL injections) Cohort 7: LEN 927 mg SC Formulation 2 (309 mg/mL, NaS) (2x1.5 mL injections) Cohort 8: Not initiated.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

PK Sampling scheme	Blood samples for plasma PK were collected at the following time points relative to the time of dosing: Day 1: 0 (predose; ≤5 minutes before dose), 2, 4, 8, and 12 hours postdose Day 2: 24 and 36 hours postdose Days 3, 4, 6, 8, 10, 15, 22, 29, 36, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 393, 421, 449: a single anytime PK sample was collected.

Results Administration of 927 mg of 309 mg/mL NaS formulation of LEN 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. A volume of 1.0 mL versus 1.5 mL per injection did not affect LEN PK (Cohort 6 versus Cohort 7). The PK parameters after the administration 309 mg/mL NaS formulation of LEN are listed in the table below.

Study 4538: Summary Statistics of Plasma PK Parameters, LEN 309 mg/mL NaS (LEN PK Analysis Set)

PK Parameter Mean (% CV)	Cohort 5 (309 mg, 309 mg/mL 1×1 mL)	Cohort 6 (927 mg, 309 mg/mL 3×1 mL)	Cohort 7 (927 mg, 309 mg/mL 2×1.5 mL)
AUC _{6month} (h·ng/mL)	44,083.9 (33.2)	183,820.6 (39.3)	165,735.5 (27.6)
AUC _{last} (h·ng/mL)	63,414.1 (28.6)	186,428.8 (52.9)	196,592.6 (49.2)
AUC _{inf} (h·ng/mL)	66,173.0 (27.6)	226,534.1 (32)	232,382.4 (28.7)
C _{max} (ng/mL)	17.7 (50.3)	67.0 (54.8)	61.2 (43.5)
T _{max} (h) ^a	2352.22 (1405.14, 3336.09)	1848.00 (1680.00, 2016.00)	2016.94 (1680.00, 2629.08)
t _{1/2} (h) ^a	1859.94 (1665.30, 2386.67)	1277.39 (1184.33, 1334.53)	1939.25 (1486.68, 2354.08)

^a median (Q1, Q3).

Source: Applicant's study report for Study 4538.

Abbreviations: %CV, percentage coefficient of variation; AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; LEN, lenacapavir; PK, pharmacokinetic; SC, subcutaneous; t_{1/2}, half-life; T_{max}, time to maximum concentration

Table 110. Study GS-US-200-4334

Study number	GS-US-200-4334
Report location	GS-US-200-4334 Final CSR
Study 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

Description of trial design	<u>Inclusion criteria</u>	
	People with HIV who met the following criteria were included: age ≥18 years, antiretroviral (ARV) naïve (no use of any ARV within 1 month of screening); furthermore, at screening, subjects had plasma HIV-1 RNA ≥200 copies/mL and CD4 ⁺ cell count ≥200 cells/μL.	
	<u>Treatment</u>	
	Subjects were treated for at least 80 weeks.	
	Study 4334: Treatments for Study Groups	
	Treatment	
	Group	Time Period
		Study Treatments
	1	Induction (Day 1 to Week 27) • Oral LEN 600 mg (2×300 mg tablet) on days 1 and 2; 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 927 mg (309 mg/mL; 2×1.5 mL) on day 15
		Maintenance (Week 28 to Week 80) • SC LEN 927 mg (309 mg/mL; 2×1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily TAF (25 mg)
	2	Induction (Day 1 to Week 27) • Oral LEN 600 mg (2×300 mg tablets) on days 1 and 2; 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^b • SC LEN 927 mg (309 mg/mL; 2×1.5 mL) on day 15
		Maintenance (Week 28 to Week 80) • SC LEN 927 mg (309 mg/mL; 2×1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily BIC (75 mg)
	3	Day 1 to Week 80 • Oral LEN 600 mg (2×300 mg tablet) on days 1 and 2; 50 mg (1×50 mg tablet) daily from day 3 onwards • Oral daily DVY (F/TAF 200/25 mg)
	4	Day 1 to Week 80 • Oral daily BVY (B/F/TAF 50/200/25 mg)
	^a Treatment Group 1 participants with <50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped DVY at Week 28 and initiated oral daily TAF.	
	^b Treatment Group 2 participants with <50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped DVY at Week 28 and initiated oral daily BIC.	
	All study drugs were administered without regard to food.	
PK Sampling scheme	<u>For Treatment Groups 1 and 2</u>	
	Plasma PK sampling occurred relative to dosing of LEN at the following time points for all subjects:	
	Days 1, 2, and 8: Predose (within 30 minutes of dosing); a single timed PK sample between 1 and 6 hours postdose.	
	Day 5 (if visit is completed): a single anytime PK sample.	
	At day 15 and at all visits with LEN SC injections: a single predose PK sample.	
	Starting at Week 4 visit, at all visits without LEN SC injections: a single anytime PK sample.	

PK substudy (at least 10 subjects in Treatment Group 1 and at least 10 subjects in Treatment Group 2):

Day 1 and Week 38: Predose (within 30 minutes of dosing), 0.5, 1, 2, 3, 4, 5, 6, and 8 hours postdose

PBMC substudy (approximately 15 [total] subjects from Treatment Groups 1 and 2):

PBMC PK samples were taken at one of the following visits: Week 4, 10, 16, or 22: Predose (within 30 minutes of dosing), 1, 2, and 6 hours postdose; 12 hours postdose sample was collected if possible.

For Treatment Group 3

Starting at Day 1 visit, a single anytime PK sample at all study visits.

PK substudy (at least 15 subjects from Treatment Group 3):

PK samples were taken at one of the following visits: Week 16, 22, or 28:

Predose (within 30 minutes of dosing), 0.5, 1, 2, 3, 4, 5, 6, and 8 hours postdose

For Treatment Group 4

Starting at Day 1 visit, a single anytime PK sample at all study visits.

Results

For both SC LEN (SC LEN + [DVY → TAF] and SC LEN + [DVY → BIC] treatment groups) and oral LEN 50 mg once daily (oral LEN + DVY treatment group), mean LEN concentrations above IQ4 (15.5 ng/mL) were achieved by Day 2 and were maintained throughout the duration of follow-up for this interim analysis.

PK Results

A summary of the LEN plasma exposures estimated based on the final population PK model is provided in the table below.

Summary of Mean (%CV) PK Exposure for Lenacapavir in Participants Who Received LEN in Study 4334

PK Parameter Mean (CV%)	Cohorts 1 and 2 (N=98)	Cohort 3 (N=51)
AUC _{tau} days 1-15 (h·ng/mL)	13,809.3 (56.4)	-
C _{max} days 1-15 (ng/mL)	61.0 (67.1)	-
C _{trough} day 15 (ng/mL)	28.8 (38.5)	-
AUC _{tau} day 15-Week 26 (h·ng/mL)	204,805.4 (49.4)	-
C _{max} day 15-Week 26 (ng/mL)	81.0 (70.4)	-
C _{trough} Week 26 (ng/mL)	22.5 (63.4)	-
AUC _{tau} day 1-Week 26 (h·ng/mL)	218,711.9 (47.8)	-
C _{max} day 1-Week 26 (ng/mL)	93.1 (61.9)	-
AUC _{tau} (h·ng/mL)	-	2759.1 (60.8)
C _{max} (ng/mL)	-	116.3 (60.4)
C _{trough} (ng/mL)	-	112.9 (61.2)

Source: Applicant's population PK report.

Abbreviations: %CV, percentage coefficient of variation; AUC, area under the concentration-time curve; BIC, B, bicitgravir; BVY, bicitgravir/emtricitabine/tenofovir alafenamide (B/F/TAF, coformulated; Biktarvy); CD, cluster of differentiation; C_{max}, maximum concentration; C_{trough}, minimum concentration; DVY, DVY, emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); F, emtricitabine; HIV, human immunodeficiency virus; IQ4, inhibitory quotient 4; LEN, lenacapavir; PK, pharmacokinetic; SC, subcutaneous; TAF, tenofovir alafenamide

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 111. Study GS-US-200-4625

Study number	GS-US-200-4625																				
Report location	GS-US-200-4625 Final CSR																				
Study 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																				
Description of trial design	<u>Inclusion Criteria</u> Heavily treatment-experienced (HTE) adults ≥ 18 years (at all sites) or adolescents aged ≥ 12 years and weighing ≥ 35 kg (at sites in North America and Dominican Republic); were receiving a stable failing regimen for > 8 weeks before screening and were willing to continue that regimen until day 1. <u>Treatment</u> Subjects were treated for at least 54 weeks. The table below summarizes the treatment for each period during the study. Study 4265: Treatment Description for Each Study Period <table border="1"> <thead> <tr> <th>Study Visit</th> <th>Treatment</th> </tr> </thead> <tbody> <tr> <td>Day 1 or 15^a</td> <td>600 mg (2x300 mg)</td> </tr> <tr> <td>Day 2 or 16^a</td> <td>600 mg (2x300 mg)</td> </tr> <tr> <td>Day 8 or 22^a</td> <td>300 mg (1x300 mg)</td> </tr> <tr> <td>Day 1 SC</td> <td>927 mg (309 mg/mL; 2x1.5 mL)</td> </tr> <tr> <td>Week 26</td> <td>927 mg (309 mg/mL; 2x1.5 mL)</td> </tr> <tr> <td>Week 52</td> <td>927 mg (309 mg/mL; 2x1.5 mL)</td> </tr> <tr> <td>Every 6 months (26 weeks) thereafter</td> <td>927 mg (309 mg/mL; 2x1.5 mL)</td> </tr> </tbody> </table> ^a Days 15, 16, and 22 visits were applicable only to participants who received placebo in the Functional Monotherapy Period at days 1, 2, and 8.	Study Visit	Treatment	Day 1 or 15 ^a	600 mg (2x300 mg)	Day 2 or 16 ^a	600 mg (2x300 mg)	Day 8 or 22 ^a	300 mg (1x300 mg)	Day 1 SC	927 mg (309 mg/mL; 2x1.5 mL)	Week 26	927 mg (309 mg/mL; 2x1.5 mL)	Week 52	927 mg (309 mg/mL; 2x1.5 mL)	Every 6 months (26 weeks) thereafter	927 mg (309 mg/mL; 2x1.5 mL)				
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Week 52	927 mg (309 mg/mL; 2x1.5 mL)																				
Every 6 months (26 weeks) thereafter	927 mg (309 mg/mL; 2x1.5 mL)																				
PK Sampling scheme	Plasma PK sampling occurred relative to dosing of LEN at the following time points for all subjects: Day 1 (for all subjects) and Day 15 (for Cohort 1B subjects only): 0 (predose, ≤ 30 minutes before dose), 1, 2, 4, 6, and 8 hours postdose. Days 2, 8, 16, and 22: a predose sample (within 30 minutes of dosing) and a single timed PK sample between 1 and 6 hours postdose days 5 and 19 (if the visits are completed): a single anytime PK sample. During the Maintenance Period, at all visits without SC LEN injections: A single anytime PK sample was collected. During the Maintenance Period, at all visits with SC LEN injections: A single predose (within 30 minutes of dosing) PK sample was collected (while subjects continued to receive study drug).																				
Results	A summary of the LEN plasma exposures estimated based on the final population PK model is provided in the table below. Summary of Mean (%CV) PK Exposure for LEN in Participants Who Received LEN in Study 4625 <table border="1"> <thead> <tr> <th>PK Parameter</th> <th>Cohorts 1 and 2 (N=62)</th> </tr> </thead> <tbody> <tr> <td>Mean (CV%)</td> <td></td> </tr> <tr> <td>AUC_{tau} days 1-15 (h·ng/mL)</td> <td>25,962.9 (67.8)</td> </tr> <tr> <td>C_{max} days 1-15 (ng/mL)</td> <td>124.4 (85.1)</td> </tr> <tr> <td>C_{trough} day 15 (ng/mL)</td> <td>48.6 (52.1)</td> </tr> <tr> <td>AUC_{tau} day 15-Week 26 (h·ng/mL)</td> <td>251,907.2 (48.2)</td> </tr> <tr> <td>C_{max} day 15-Week 26 (ng/mL)</td> <td>87.3 (49.4)</td> </tr> <tr> <td>C_{trough} Week 26 (ng/mL)</td> <td>35.1 (59.2)</td> </tr> <tr> <td>AUC_{tau} day 1-Week 26 (h·ng/mL)</td> <td>277,902.9 (46.7)</td> </tr> <tr> <td>C_{max} day 1-Week 26 (ng/mL)</td> <td>136.2 (75.2)</td> </tr> </tbody> </table>	PK Parameter	Cohorts 1 and 2 (N=62)	Mean (CV%)		AUC _{tau} days 1-15 (h·ng/mL)	25,962.9 (67.8)	C _{max} days 1-15 (ng/mL)	124.4 (85.1)	C _{trough} day 15 (ng/mL)	48.6 (52.1)	AUC _{tau} day 15-Week 26 (h·ng/mL)	251,907.2 (48.2)	C _{max} day 15-Week 26 (ng/mL)	87.3 (49.4)	C _{trough} Week 26 (ng/mL)	35.1 (59.2)	AUC _{tau} day 1-Week 26 (h·ng/mL)	277,902.9 (46.7)	C _{max} day 1-Week 26 (ng/mL)	136.2 (75.2)
PK Parameter	Cohorts 1 and 2 (N=62)																				
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C _{max} day 1-Week 26 (ng/mL)	136.2 (75.2)																				

Source: Applicant's population PK report.

Abbreviations: %CV, percentage coefficient of variation; LEN, lenacapavir; AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{trough}, minimum concentration; PK, pharmacokinetic; SC, subcutaneous

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 112. Study GS-US-200-4332

Study number	GS-US-200-4332					
Report location	GS-US-200-4332 Final CSR					
Study 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					
Description of trial design	<u>Inclusion Criteria</u>					
	Healthy male and nonpregnant, nonlactating female subjects aged 18 to 45 years (inclusive) were enrolled in the study.					
Description of trial design	<u>Treatment</u>					
	Following completion of screening and Day -2 assessments, eligible subjects were randomized in a 2:1:1 manner within each group to Treatment Sequences 1, 2, and 3, respectively.					
Study 4332: Treatment Description for Each Study Period						
	Treatment Sequence	Period 1	Period 2	Period 3		
		Day -1	Day 1	Day 2-4	Days 5-12	
					Day 13	
	1 (n=48)	Baseline	B PTM MOXI	WO	C LEN 600 mg BID	B PTM MOXI
	2 (n=24)	Baseline	A MOXI 400 mg	WO	D PTM LEN BID	B PTM MOXI
	3 (n=24)	Baseline	B PTM MOXI	WO	D PTM LEN BID	A MOXI 400 mg
Treatment A: Single oral dose of 400 mg MOXI (1x400 mg tablet), under fed conditions, in the morning.						
Treatment B: Single oral dose of PTM MOXI (1 tablet), under fed conditions, in the morning.						
Treatment C: Administration of twice-daily LEN 600 mg (2x300 mg tablet) 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: Administration of twice-daily PTM LEN (2 tablets) 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).						
PK Sampling scheme	Intensive PK sampling occurred relative to the morning administration of study drug at the following time points: Days -1, 1, 6, 12, and 13: 0 (predose, ≤5 minutes before dose), 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours postdose. PK samples collected on Day -1 were time-matched to the planned time points on Days 1, 6, 12, and 13. On Day 6, the 12-hour PK sample was collected prior to the administration of the PM dose. A single PK sample was collected at the early termination visit, if appropriate.					
PD Sampling scheme	Digital ECGs were captured and transferred to the designated core cardiology laboratory for ECG analysis. Three 12-lead ECGs (downloaded from the Mortara digital recorder within a 5-minute interval) were extracted for each predetermined time point below relative to AM dosing on that day, on the study days indicated: Days -1, 1, 6, 12, and 13: 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours after AM dose. ECG on the baseline day -1 were time-matched to the planned time points on Days 1, 6, 12, and 13. On Day 6, the 12-hour ECG was collected prior to the administration of the PM dose. When ECGs and PK samples were collected at the same time point, the ECG collection time was adjusted such that it occurred prior to the PK sample collection.					

Results LEN plasma PK parameters on Study Days 6 and 12 following twice-daily oral administration of LEN 600 mg for up to 8 days are summarized in the table below.

Study 4332: Summary of LEN Pharmacokinetic 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)	10,640.6 (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) [#]	5.00 (5.00, 11.97)	4.00 (0.00, 5.00)	-
C _{last} (ng/mL)	258.6 (56.4)	771.7 (37.7)	-

[#] Data are medians (Q1, Q3).

Participant (b) (6) early terminated due to an adverse event on Day 5 and is excluded from analysis.

PK/PD Results

The results of the Applicant's and reviewer's separate analyses suggest an absence of significant QTc prolongation at the proposed therapeutic dose. The peak concentration observed with highest dose studied (i.e., 600 mg twice daily; Day 12 of study) is expected to offer approximately 8.8-fold margin over the therapeutic exposures associated with the maximum proposed dose at the steady-state (Phase 2/3 Study 4625 in HTE PLWH). At LEN concentrations approximately 9-fold the therapeutic concentrations from the recommended dosing regimen, lenacapavir does not prolong the QT interval to any clinically relevant extent.

Source: Applicant's study report for Study 4332.

Abbreviations: %CV, percentage coefficient of variation; AUC, area under the concentration-time curve; BID, twice daily; CI, confidence interval; C_{last}, last measured concentration; C_{max}, maximum concentration; ECG, electrocardiogram; GLSM, geometric least-squares mean; HTE, heavily treatment-experienced; LEN, lenacapavir; MOXI, moxifloxacin; PD, pharmacodynamic; PK, pharmacokinetic; PTM, placebo-to-match; PLWH, people living with human immunodeficiency virus; Q1, first quartile; Q3, third quartile; QTc, corrected QT interval; T_{max}, time to maximum concentration; WO, washout

14.3. Pharmacometrics Review

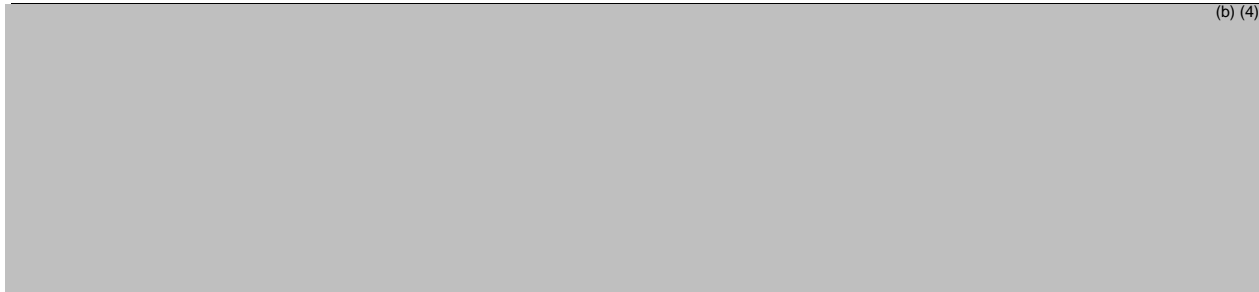
The Applicant's population PK analysis is considered acceptable in describing the observed LEN concentrations in healthy subjects and patients. The PK model was used to support the current submission as outlined below:

Table 113. Utility of the Population PK Model

Utility of the Final Model	Reviewer's Comments
Predict exposures at alternative dosing regimen and derive exposure metrics for exposure-response analyses	- The PK model was used to predict AUC, C_{max}, and C_{trough} under the studied and proposed simplified dosing regimen. - The PK model was used to justify the selection of the dosing interval (26±2 weeks). - The PK model was used to justify the proposed handling of dosing delay, with the recommendation to restart treatment with PO loading, if more than 28 weeks elapsed since the last SC injection.
	- The Applicant's initial final model is acceptable for generating exposure metrics and predicting the exposure under alternative dosing regimen (see Section II.6.3.2). - The reviewer's evaluation of the PK model identified that underweight subjects are expected to have a 66% higher LEN SC bioavailability and obese subjects to have 23% lower F_{sc}, compared to normal and overweight subjects. The BMI effect on F_{sc}, particularly in obese subject, is not expected to impact the target of having the mean C_{trough} (and 90% CI of the mean) above the IQ4 of 15.5 (Section II.6.3.4).

Utility of the Final Model	Reviewer's Comments
	The 26-week dosing interval instead of 28-week dosing interval is more likely to insure that the average LEN C_{trough} is above the IQ4 threshold in all BMI groups and in the absence of drug interactions that increase exposure (e.g. antiretrovirals containing pharmacoenhancers). See Section II.6.3.4.

(b) (4)



Source:

Abbreviations: AUC, area under the concentration-time curve; BMI, body mass index; CI, confidence interval; C_{max} , maximum concentration; C_{trough} , minimum concentration; F_{sc} , subcutaneous bioavailability; IQ4, inhibitory quotient 4; LEN, lenacapavir; PK, pharmacokinetic; SC, subcutaneous

14.3.1. Applicant's Population PK Analysis

The population PK (popPK) analysis was based on PK data from seven studies ([Table 114](#)): five phase 1 studies in healthy subjects (4071, 4329, 4333, 4538, and 5709), one phase 2 study in treatment-naïve patients with HIV (Study 4334), and one phase 2/3 study in HTE patients (Study 4625). In phase 1 studies, LEN was administered as either an oral dose, a 1-hour IV infusion, an SC injection, or a combination of oral loading and SC injection. In phase 2 and phase 2/3 studies, LEN was administered as an oral lead-in followed by SC administration.

The analysis dataset comprised 7053 PK observations from 384 subjects, including 198 below limit of quantification concentrations. The limit of quantification was 0.5 ng/mL for Studies 4071, 4334, 4538, 4625 and 5709, and 0.1 ng/mL for Studies 4329 and 4333. below limit of quantification samples represented about 2.8% of the PK data, and therefore were excluded from the analysis.

The summary statistics for the continuous and categorical covariates are presented by study in [Table 115](#). The analysis population was primarily male (77.6%) white (56.8%) subjects, with a median (range) age of 34 years (18 to 78 years), weight of 75.9 kg (41.4 to 164 kg), body mass index (BMI) of 26.1 kg/m² (14.9 to 51.1 kg/m²), and 54.9% of subjects were patients with HIV.

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Table 114. LEN Clinical Studies Used for the Population Pharmacokinetic Analysis

Study	Study Design/Population	N/Treatment
GS-US-200-4071	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	8 subjects planned on active treatment per cohort Cohort (included in this analysis): Treatment 7: 300 mg (1 × 300 mg tablet) GS-6207 or placebo 8: 900 mg (3 × 300 mg tablets) GS-6207 or placebo 9: Up to 1800 mg GS-6207 or placebo 10: 50 mg GS-6207 or placebo 12: 300 mg GS-6207 (tablet), high fat, high calorie meal 13: 300 mg GS-6207 (tablet), light meal
GS-US-200-4329	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Metabolism, and Excretion of IV GS-6207 in Healthy Volunteers	8 subjects planned on active treatment for Cohort 1 and 10 subjects planned on active treatment for Cohort 3 Cohort (included in this analysis): Treatment 1: 10 mg IV GS-6207 as an 1-hour infusion 3: 20 mg IV GS-6207 as an 1-hour infusion
GS-US-200-4333	A Phase 1 Study to Evaluate Transporter and Cytochrome 450-Mediated Drug-Drug Interactions Between GS-6207 and Probe Drugs	25 subjects planned on active treatment for Cohort 4 and Cohort 6 Cohort (included in this analysis): Treatment 4: Single dose of oral GS-6207 300 mg (1 × 300-mg tablet) administered under fasted conditions 6: Single dose of oral GS-6207 300 mg (1 × 300-mg tablet) administered under fed conditions
GS-US-200-4334	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	50 subjects planned on active treatment for each of Cohorts 1, 2, and 3 Cohort (included in this analysis): Treatment 1: Induction: GS-6207 600 mg PO on Day 1 and Day 2, GS-6207, then 300 mg PO on Day 8, then subcutaneous GS-6207 927 mg on Day 15 + PO daily F/TAF (200/25 mg) from Day 1 onward, for a total of 28 weeks Maintenance: SC GS-6207 927 mg on Week 28 and every 26 weeks + PO daily TAF (25 mg) 2: Induction: GS-6207 600 mg PO on Day 1 and Day 2, GS-6207, then 300 mg PO on Day 8, then SC GS-6207 927 mg on Day 15 + PO daily F/TAF (200/25 mg) from Day 1 onward, for a total of 28 weeks Maintenance: SC GS-6207 927 mg on Week 28 and every 26 weeks + PO daily bictegravir (BIC) (75 mg) from Week 28 onward 3: GS-6207 600 mg PO on Day 1 and Day 2 then PO daily GS-6207 then 50 mg + PO daily F/TAF (200/25 mg) from Day 1 onward
GS-US-200-4538	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 Volunteers	8 subjects planned on active treatment for each of Cohorts 6, 7, and 10 Cohort (included in this analysis): Treatment 6: 900 mg SC with 300 mg/mL, sodium salt formulation 7: 900 mg SC with 300 mg/mL, sodium salt formulation 10: 900 mg SC with 150 mg/mL, sodium salt formulation
GS-US-200-4625	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	24 subjects planned on active treatment for Cohort 1A, and 12 placebo to lenacapavir crossover subjects for Cohort 1B, and 64 subjects planned on active treatment for Cohort 2 Cohort (included in this analysis): Treatment 1A: Day 1 and 2 600 mg GS-6207 oral tablets Day 8 300 mg GS-6207 oral tablet Day 15 927 mg GS-6207 SC (every 26 weeks thereafter) 1B: Day 1-15 Placebo oral tablet Days 15 and 16: 600 mg GS-6207 oral tablets Day 22: 300 mg GS-6207 oral tablet Day 30: 927 mg GS-6207 SC (every 26 weeks thereafter) 2: Days 1 and 2: 600 mg GS-6207 oral tablets Day 8: 300 mg GS-6207 oral tablet Day 15: 927 mg GS-6207 SC (every 26 weeks thereafter)
GS-US-200-5709	A Phase 1 Study in Healthy Volunteers to Evaluate the Safety, Tolerability, and Pharmacokinetics of lenacapavir (LEN)	30 subjects planned on active treatment for Cohort 1 Cohort (included in this analysis): Treatment 1: Days 1 and 2: 600 mg GS-6207 oral tablets Day 8: 300 mg GS-6207 oral tablet Day 15: 927 mg GS-6207 SC

F = emtricitabine; IV = intravenous; PO = oral; SC = subcutaneous; TAF = tenofovir alafenamide

Source: Applicant's Population PK Report, Appendix 7.2, pages 95-96.

Abbreviation: HIV, human immunodeficiency virus

NDA 215973 lenacapavir injection, for subcutaneous use
 NDA 215974 lenacapavir tablets, for oral use

Table 115. Summary of Demographic Characteristics

Covariate	Statistics	GS-US-200-4071 (N = 48)	GS-US-200-4329 (N = 18)	GS-US-200-4333 (N = 52)	GS-US-200-4334 (N = 149)	GS-US-200-4538 (N = 24)	GS-US-200-4625 (N = 62)	GS-US-200-5709 (N = 31)	Total (N = 384)
Age (years)	Mean (SD)	32.9 (8.03)	33.6 (7.51)	34.3 (7.82)	31.6 (9.61)	34.8 (7.58)	51.1 (11.5)	32.1 (5.91)	35.6 (11.4)
	Median (CV%)	35.0 (24.4)	30.5 (22.4)	34.0 (22.8)	29.0 (30.4)	36.0 (21.8)	52.5 (22.4)	32.0 (18.4)	34.0 (31.9)
	[Min, Max]	[19.0, 45.0]	[22.0, 48.0]	[18.0, 45.0]	[19.0, 62.0]	[21.0, 45.0]	[24.0, 78.0]	[22.0, 43.0]	[18.0, 78.0]
WT (kg)	Mean (SD)	74.3 (11.8)	79.8 (9.13)	74.9 (10.6)	80.8 (20.9)	72.9 (9.85)	75.4 (19.5)	79.1 (9.87)	77.6 (16.9)
	Median (CV%)	74.9 (15.8)	81.7 (11.4)	73.6 (14.1)	77.1 (25.9)	72.7 (13.5)	70.0 (25.9)	78.6 (12.5)	75.9 (21.8)
	[Min, Max]	[55.2, 101]	[59.5, 89.5]	[52.5, 97.0]	[47.6, 164]	[56.4, 91.0]	[41.4, 127]	[54.3, 95.6]	[41.4, 164]
BMI (kg/m ²)	Mean (SD)	25.7 (3.29)	26.7 (2.15)	26.2 (2.33)	26.6 (6.59)	25.4 (2.51)	25.9 (5.48)	26.7 (2.50)	26.3 (4.99)
	Median (CV%)	26.3 (12.8)	26.5 (8.1)	26.2 (8.9)	25.7 (24.8)	25.3 (9.9)	24.7 (21.1)	26.8 (9.3)	26.1 (19.0)
	[Min, Max]	[19.1, 30.3]	[23.1, 29.7]	[20.9, 29.9]	[17.3, 51.1]	[20.7, 29.3]	[14.9, 42.9]	[21.9, 30.3]	[14.9, 51.1]
BSA (m ²)	Mean (SD)	1.87 (0.177)	1.95 (0.147)	1.85 (0.160)	1.96 (0.265)	1.85 (0.169)	1.87 (0.277)	1.94 (0.154)	1.91 (0.231)
	Median (CV%)	1.85 (9.5)	1.99 (7.5)	1.83 (8.6)	1.92 (13.5)	1.87 (9.1)	1.84 (14.8)	1.94 (8.0)	1.90 (12.1)
	[Min, Max]	[1.56, 2.29]	[1.60, 2.13]	[1.52, 2.18]	[1.42, 2.85]	[1.56, 2.13]	[1.31, 2.46]	[1.54, 2.20]	[1.31, 2.85]
CL _{cr} (mL/min)	Mean (SD)	129 (30.8)	116 (14.0)	116 (20.4)	134 (38.9)	123 (14.5)	93.0 (25.6)	128 (19.0)	122 (33.4)
	Median (CV%)	122 (23.9)	112 (12.1)	113 (17.6)	130 (29.1)	122 (11.8)	91.1 (27.5)	129 (14.8)	117 (27.3)
	[Min, Max]	[93.7, 238]	[98.5, 142]	[82.2, 179]	[68.6, 330]	[92.4, 153]	[46.8, 178]	[86.9, 164]	[46.8, 330]
eGFR MDRD175 (mL/min/1.73 m ²)	Mean (SD)	104 (21.4)	94.1 (15.5)	92.3 (14.9)	109 (25.1)	101 (13.5)	85.2 (18.4)	99.0 (18.2)	100 (22.6)
	Median (CV%)	102 (20.6)	96.3 (16.5)	91.7 (16.1)	106 (22.9)	103 (13.3)	84.5 (21.6)	101 (18.4)	96.6 (22.5)
	[Min, Max]	[66.7, 148]	[70.6, 128]	[63.2, 129]	[58.8, 218]	[66.2, 127]	[44.3, 127]	[66.4, 143]	[44.3, 218]

BMI = body mass index; BSA = body surface area; CL_{cr} = creatinine clearance; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; N = number of participants; SD = standard deviation; WT = body weight

NDA 215973 lenacapavir injection, for subcutaneous use
NDA 215974 lenacapavir tablets, for oral use

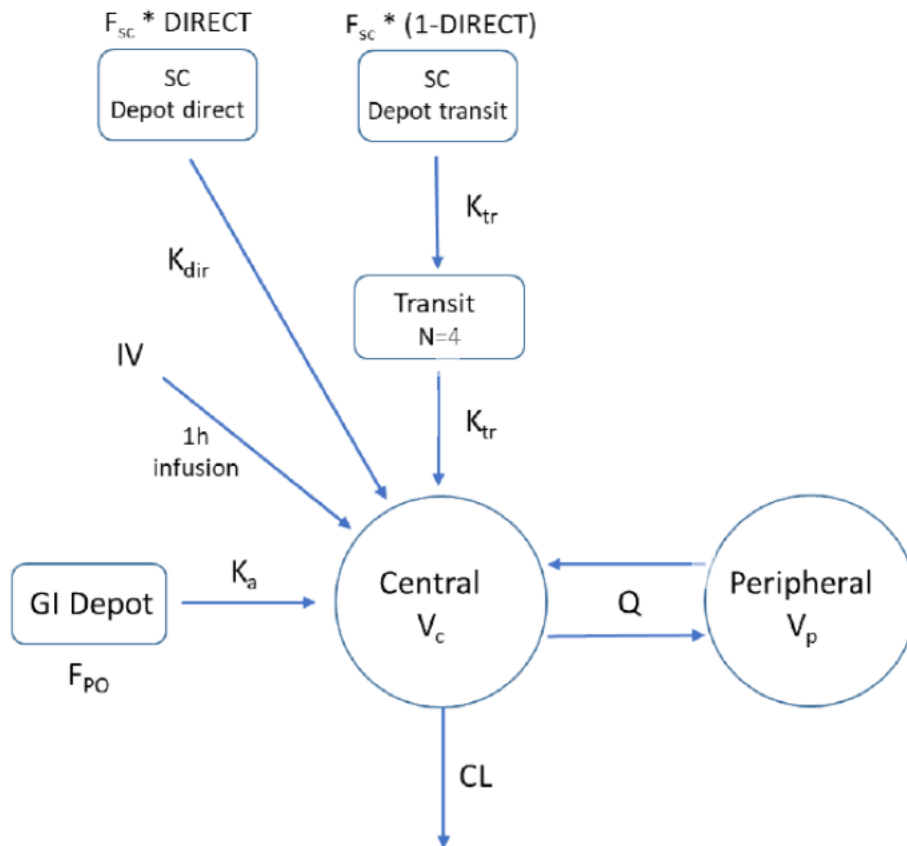
Covariate	Category	GS-US-200-4071 N (%)	GS-US-200-4329 N (%)	GS-US-200-4333 N (%)	GS-US-200-4334 N (%)	GS-US-200-4538 N (%)	GS-US-200-4625 N (%)	GS-US-200-5709 N (%)	Total N (%)
Sex	Male	30 (62.5%)	14 (77.8%)	36 (69.2%)	137 (91.9%)	16 (66.7%)	46 (74.2%)	19 (61.3%)	298 (77.6%)
	Female	18 (37.5%)	4 (22.2%)	16 (30.8%)	12 (8.1%)	8 (33.3%)	16 (25.8%)	12 (38.7%)	86 (22.4%)
Race	White	39 (81.2%)	7 (38.9%)	44 (84.6%)	62 (41.6%)	20 (83.3%)	26 (41.9%)	20 (64.5%)	218 (56.8%)
	Black	9 (18.8%)	11 (61.1%)	8 (15.4%)	80 (53.7%)	4 (16.7%)	23 (37.1%)	11 (35.5%)	146 (38.0%)
	Asian	0 (0%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	12 (19.4%)	0 (0%)	14 (3.6%)
	Other	0 (0%)	0 (0%)	0 (0%)	5 (3.4%)	0 (0%)	1 (1.6%)	0 (0%)	6 (1.6%)
Ethnicity	Not Hispanic or Latino	46 (95.8%)	0 (0%)	52 (100%)	68 (45.6%)	24 (100%)	13 (21.0%)	31 (100%)	234 (60.9%)
	Hispanic or Latino	2 (4.2%)	18 (100%)	0 (0%)	81 (54.4%)	0 (0%)	48 (77.4%)	0 (0%)	149 (38.8%)
	Not reported	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	1 (0.3%)
Background therapy	F/TAF	0 (0%)	0 (0%)	0 (0%)	99 (66.4%)	0 (0%)	0 (0%)	0 (0%)	99 (25.8%)
	B/F/TAF	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (4.8%)	0 (0%)	3 (0.8%)
	TAF + F/TAF	0 (0%)	0 (0%)	0 (0%)	25 (16.8%)	0 (0%)	0 (0%)	0 (0%)	25 (6.5%)
	F/TAF + Bictegravir	0 (0%)	0 (0%)	0 (0%)	25 (16.8%)	0 (0%)	0 (0%)	0 (0%)	25 (6.5%)
	Contains COBI but not RTV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	18 (29.0%)	0 (0%)	18 (4.7%)
	Contains RTV but not COBI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (30.6%)	0 (0%)	19 (4.9%)
	Contains DRV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (30.6%)	0 (0%)	19 (4.9%)
	All Other ARVs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.2%)	0 (0%)	2 (0.5%)
	Missing	48 (100%)	18 (100%)	52 (100%)	0 (0%)	24 (100%)	1 (1.6%)	31 (100%)	174 (45.3%)
Health Status	HV	48 (100%)	18 (100%)	52 (100%)	0 (0%)	24 (100%)	0 (0%)	31 (100%)	173 (45.1%)
	HIV	0 (0%)	0 (0%)	0 (0%)	149 (100%)	0 (0%)	62 (100%)	0 (0%)	211 (54.9%)

ARV = antiretroviral; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; COBI = cobicistat (Tybost®); DRV = darunavir; HV = healthy volunteer; F/TAF = emtricitabine/tenofovir alafenamide; N = number of participants; RTV = ritonavir; TAF = tenofovir alafenamide.
Source: Applicant's Population PK Report, Table 3-4, pages 29-30.

Base PK Model

The PK of LEN was best described by a two-compartment distribution model with linear elimination from the central compartment. The oral LEN absorption was best characterized by a first-order absorption process, and the SC absorption was best characterized by a parallel direct first-order absorption and a delayed absorption process with four transit compartments. The PK model was parameterized in terms of clearance (CL), central and peripheral volumes of distribution (V_c and V_p , respectively), intercompartmental clearance (Q/F), oral (PO) absorption rate constant (K_a), PO bioavailability relative to IV (F_{po}), SC direct/rapid first-order absorption rate constant (K_{dir}), SC transit first-order absorption rate constant (K_{tr}), fraction of the SC dose absorbed through the rapid/direct process, and the SC bioavailability relative to IV (F_{sc}). Between-subject variability or inter-individual variability (IIV) was estimated on CL, V_p , dissociation rate constant (K_a), K_{tr} , and F_{sc} . The residual error model consisted of a combined additive and proportional error model. The final structural model for lenacapavir is presented in [Figure 34](#).

Figure 34. Schematic of the Structural PK Model for LEN



DIRECT = fraction of SC dose absorbed through direct first-order absorption; GI = gastrointestinal; IV = intravenous;
 PK = pharmacokinetic; SC = subcutaneous

Source: *Applicant's Population PK Report, Figure 2, page 32.*

Abbreviations: F_{po}, PO bioavailability relative to IV; F_{sc}, SC bioavailability relative to IV; K_{dir}, direct/rapid first-order absorption rate constant; K_a, dissociation constant; K_{dir}, direct/rapid first-order absorption rate constant; K_{tr}, transit first-order absorption rate constant; Q, intercompartmental clearance; V_c, central volume of distribution; V_p, peripheral volume of distribution

Covariates Analysis

The following continuous covariates were evaluated during covariate model selection: Age, weight, PO dose, food, and estimated glomerular filtration rate (eGFR using the Modification of Diet in Renal Disease formula). The evaluated categorical covariates were: sex (male as reference), race (white as reference), ethnicity (non-Hispanic as reference), formulation (tablet, sodium salt solution [300 mg/mL], sodium salt solution [150 mg/mL], and IV solution), antiretroviral background therapies (none as reference see [Table 115](#)), and health status (patient with HIV as reference).

The following covariates were included in the final model:

- weight on ^{(b) (4)} Q, V_c and V_p (using allometric scaling standardized to 70 kg).
- ^{(b) (4)}
- Dose on ^{(b) (4)} F_{po} (using a power model standardized to a 600 mg dose).
- Health status (healthy) on CL and V_p (using a proportional linear model).
- ^{(b) (4)} (using a proportional linear model).
- Formulation (sodium salt solution [155 mg/mL] versus [309 mg/mL]) on K_{tr} and V_p (using a proportional linear model).
- Antiretroviral background therapy (contains cobicistat [COBI] or ritonavir [RTV] as a booster versus all others) as a time-varying covariate on F_{po} (using a proportional linear model).

Final Model

The parameter estimates from the final popPK model for LEN are listed in [Table 116](#). According to the Applicant's popPK model, for an average 70 kg, 34-year-old male patient with HIV, receiving 600 mg (PO or SC) LEN with no interacting antiretroviral therapy, the population estimates for LEN CL, V_c, Q, V_p, PO K_a, F_{po}, SC K_{dir}, SC K_{tr}, F_{sc}, and SC fraction for direct absorption are 4.05 L/h, 68 L, 41.2 L/h, 908 L, 0.0287 h⁻¹, 6.24%, 0.000376 h⁻¹, 0.00201 h⁻¹, 103%, and 42%, respectively.

The estimated IIV expressed as the coefficient of variation (%CV) was 44%, 85%, 78%, 32%, and 39% for CL, V_p, K_a, K_{tr}, and F_{sc} respectively. The interindividual random effect (ETA) shrinkage from the final PopPK model was 9.9%, 5.4%, 10.1%, 41.9%, and 41.5% for CL, V_p, K_a, K_{tr}, and F_{sc}, respectively. Inclusion of IIV on additional parameters ^{(b) (4)} resulted in model instability, as indicated by large relative standard errors (RSEs) or high condition numbers.

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Table 116. Parameter Estimates From the Final Population PK Model

Parameter	Final PopPK Model Estimate [RSE] ^a	Bootstrap Final Model Median Estimate [2.5th; 97.5th Percentiles]
(b) (4)		

According to the Applicant’s model, weight was found to be a statistically significant covariate on CL, V_c , Q, and V_p , where weight was included using fixed allometric exponents of 0.75 and 1 for clearances and volume of distributions, respectively. However, the predicted effect of weight on exposure metrics was not considered clinically relevant, with an estimated percent change in

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steady-state AUC_{τ} , $C_{\max}$, and C_{trough} values (τ : Day 1 to Day 15 for PO loading and Day 15 to Week 26 for SC) ranging between -32% and 24% for patients weighing 109 kg and 55 kg (i.e., 95th and 5th weight percentile), respectively, compared to a typical patient (70 kg, 34-year-old male, unboosted).

Boosters (COBI or RTV) were found to affect PO bioavailability but not SC bioavailability, with a 58.7% increase in F_{po} , and thus, in PO exposures.

Healthy volunteers were estimated to have higher CL (30.4% increase) and V_p (133% increase) compared to patients with HIV. The predicted percentage decrease in steady-state AUC_{τ} , $C_{\max}$, and C_{trough} values were 43%, 32%, and 39% for the PO loading phase (τ : Day 1 to Day 15) and 38%, 50%, and 30% for the SC administration phase (τ : Day 15 to Week 26) compared to a typical patient.

Dose was found to affect PO bioavailability, with an estimated average F_{po} of 6.24% for the 600 mg PO dose and 8.3% for the lower 300 mg PO dose, indicating a less than dose-proportional increase in exposure with increased PO dose. In addition to the effect of PO dose on F_{po} , the Applicant model included an effect of (b) (4)

(b) (4) The estimated effect of (b) (4) was small (at clinically relevant doses of 300 to 927 mg) and not precise (RSE of (b) (4) %). Besides, the physiological and mechanistic rationale of including this covariate (b) (4) was questioned by the review team.

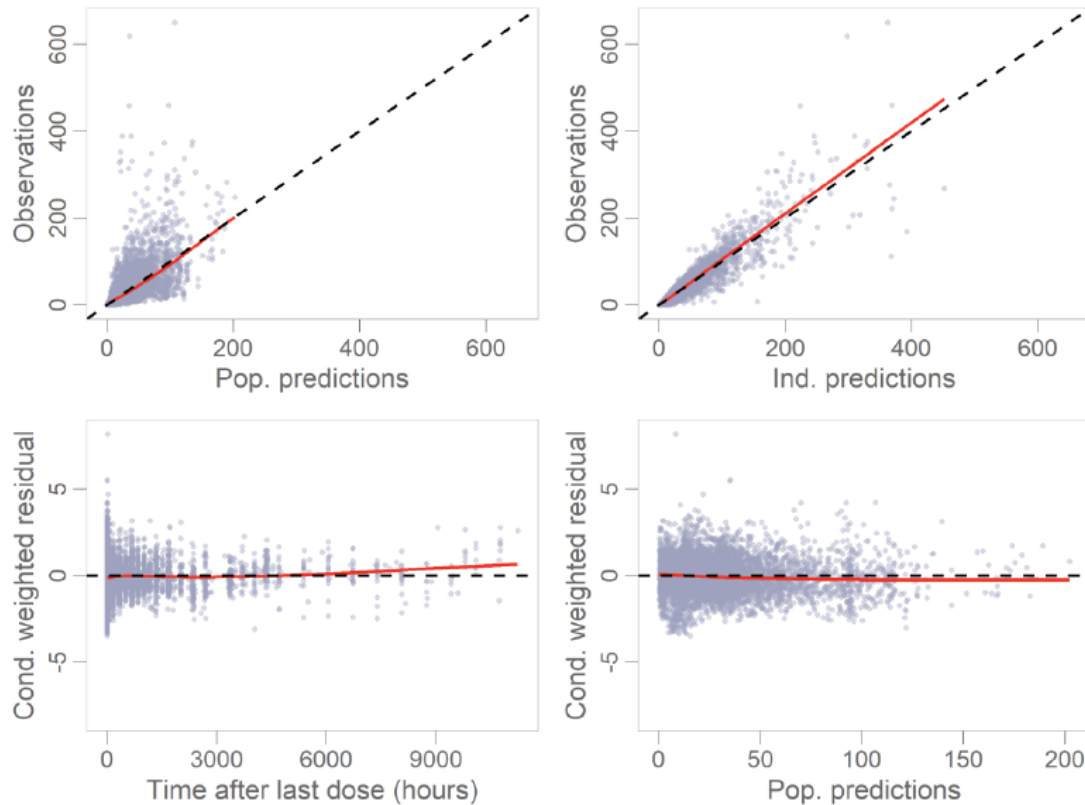
(b) (4)

Finally, the lower SC formulation strength (155 mg/mL versus 309 mg/mL) was found to have an effect on V_p and K_{tr} , with an estimated 79% lower V_p , and a more rapid SC absorption with a 34.5% higher K_{tr} for the 155 mg/mL SC salt solution. Accounting for the differences between the 2 SC formulation strength improved the PK model fit and the visual predictive checks. Only the 309 mg/mL SC formulation strength will be used for the commercial product.

The goodness-of-fit plots from the final popPK model, are shown in [Figure 35](#). The plots of the observed concentrations versus population as well as the individual predicted concentrations show random normal scatter around the identity lines, indicating absence of systematic bias and show good agreement between the individual predicted and observed concentrations. The conditional weighted residuals versus time after last dose or versus population predicted concentrations also show random normal scatter around zero with no specific trend, indicating no major model misspecifications.

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Figure 35. Goodness-of-Fit Plots From the Final PK Model



Ind. = individual; Pop. = population; PopPK = population pharmacokinetic

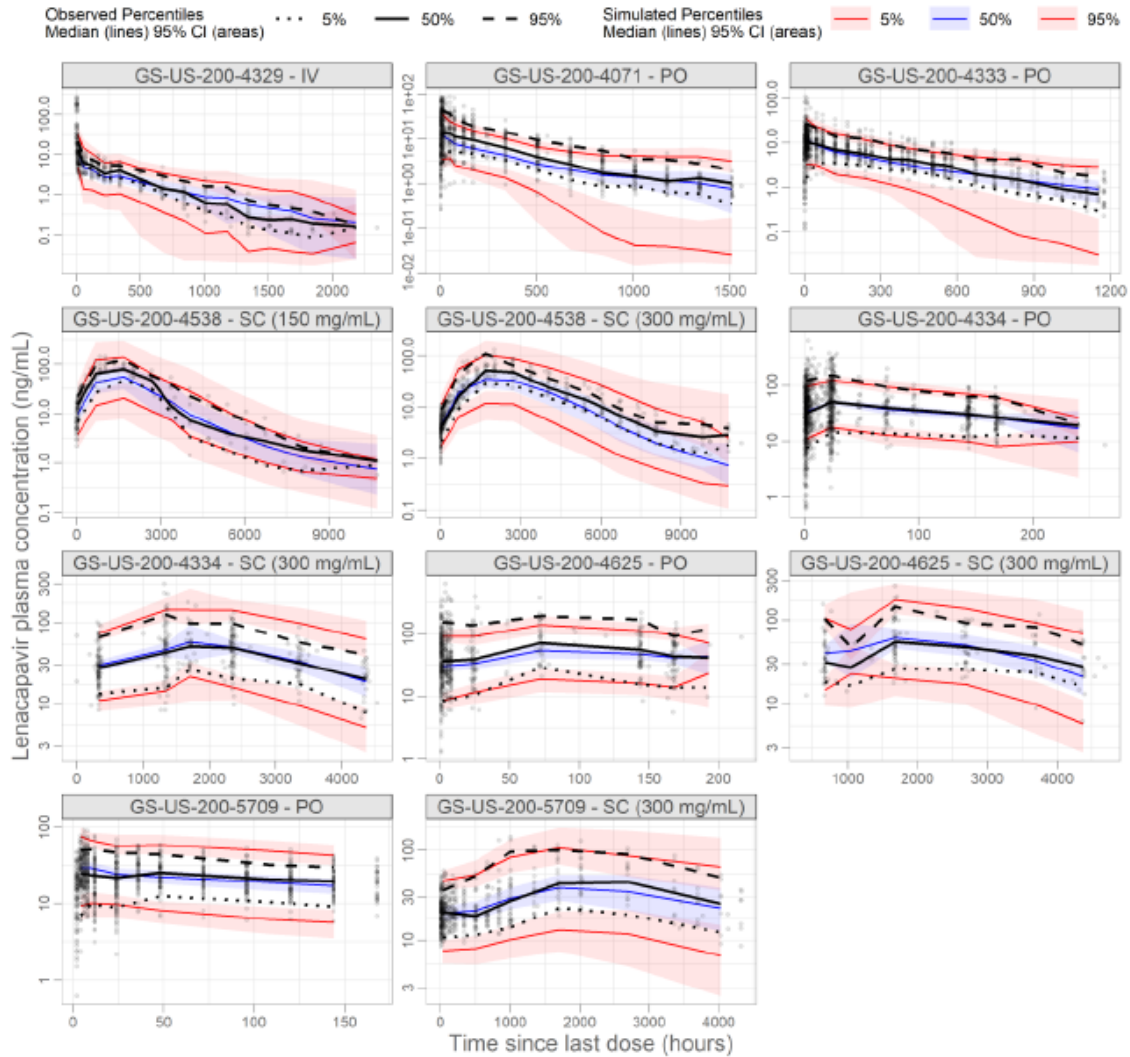
The circles represent individual data points, the red lines represent loess smooth curves, and the dashed lines represent either the line of unity ($y = x$) or the unity line at 0 ($y = 0$).

Source: Applicant's Population PK Report, Figure 6, page 41.

The prediction-corrected visual predictive checks plots ([Figure 36](#)) of concentrations versus time after last dose showed a reasonable agreement between the observed and simulated data. The central tendency and variability of the LEN concentrations across analyzed patients populations and different formulations was adequately captured. The IIV is slightly overpredicted in healthy volunteers studies only, irrespective of the formulation used (i.e., higher 5th percentiles from Studies 4329, 4071, 4333, and 4538). However the median and 95% percentiles of the observed concentration are well captured.

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Figure 36. Prediction-Corrected Visual Predictive Check From Final PK Model Stratified by Study and Formulation



CI = confidence interval; IV = intravenous; pcVPC = prediction-corrected visual predictive check; PopPK = population pharmacokinetic; PO = oral; SC = subcutaneous
 The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentiles, dotted and dashed black lines, respectively) of the observed data in all participants. The blue area is the 95% CI of the simulated median, and the red area is the 95% CI of the simulated 5th and 95th percentiles. The black circles are the individual observed data corrected by model predictions.

Source: Applicant's Population PK Report, Figure 7, page 43.

14.3.2. Reviewer's Comments on the Applicant's Population PK Analysis

Assessment of the Covariate Analysis

- The Applicant's PK model reasonably describes the observed concentrations from LEN clinical studies.

- The PK parameters from the final model were estimated with acceptable precision, with a %RSE ranging between 4% and 32%, except for the covariate effect of (b) (4).
- Among the PK parameters that are affected by the identified covariates, the ETA shrinkage was acceptable with a relatively higher shrinkage for K_{tr} (41.9%) and F_{sc} (41.5%), which makes the graphical assessment of covariates on these parameters less reliable.

- (b) (4)

- The Applicant's popPK model included dose effect as a continuous variable on both F_{po} (b) (4). As the less than dose proportional increase in AUC_{inf} and C_{max} from the PO formulation is likely due to saturable PO absorption, only the inclusion of dose effect on F_{po} is needed. In addition, the effect of dose (b) (4) was not precisely estimated (%RSE of (b) (4)) and most importantly, the range of doses included in the relationship was not limited to the PO doses but also included the SC dose.

The review team evaluation, in addition to the Applicant reassessment, found that (b) (4) was not a statistically significant covariate (b) (4) with an increase in OFV by less than 9 points (for 1 degree of freedom) after removal of the covariate. Therefore, as physiologically and mechanistically expected, only the effect of dose on F_{po} is clinically relevant and kept in the updated PK model. The removal of (b) (4) from the PK model did not alter the initial PK parameters and their variability estimates.

- The Applicant classified background antiretroviral (ARV) therapies, potentially known to interact with the PO exposure of LEN, as ARV containing COBI (n=18), ARV containing ritonavir (RTV, n=19), ARV containing darunavir (DRV, n=19) with unreported booster (pharmcoenhancer) used, and other ARVs in 2 patients on multiple background regimens including DRV (fostemsavir, dolutegravir, ibalizumab, F/TAF and darunavir). All patients on comedications with known interactions were HTE patients belonging to Study 4625. In their initial assessment of the DDI effect on F_{po} , the Applicant grouped together patients receiving ARV containing COBI or RTV (n=37), and estimated a combined effect of 58.7% increase in F_{po} . The Applicant did not evaluate the effect of COBI- and RTV-containing ARVs separately. In addition, in the PK model, the Applicant evaluated the effect on F_{po} in patients either receiving DRV with unknown/unreported booster (n=19) or receiving multiple background regimens including DRV (n=2). After an information request to the Applicant, recommending separate evaluation of boosted ARV drugs, the Applicant estimated a separate effect on F_{po} for COBI- and RTV-containing ARVs, with an

estimated 28.6% increase for COBI-containing ARVs and 110% increase for RTV-containing ARVs. The Applicant did not address the investigation of DRV effect used either alone (with unknown/unreported booster) or as part of a multiple background regimen. The remaining PK parameters from the updated PK model were comparable to the initial final model PK parameters and their variability estimates.

The review team evaluation of ARVs DDI on F_{po} , estimated a 28% increase for COBI-containing ARVs, a 95% increase for RTV-containing ARVs, a 52% increase in HTE patients receiving DRV (with unspecified booster), with a high variability in the estimated mean effect (%RSE from 41.4% to 47.5%). In two HTE patients who received DRV at some point as part of a varying multiple background regimen, the estimated increase in F_{po} was about 37.4% compared to patients without a known DDI, and the estimated effect was not statistically significant and did not worsen the OFV. The PK model estimated effect of COBI-containing ARVs and DRV (with unspecified booster) on F_{po} was lower than the observed effect of COBI alone or DRV/COBI combination on LEN AUC_{inf} in the dedicated DDI Study 4333 (not included in the popPK dataset/analysis). In the dedicated study in healthy participants, COBI alone and the DRV/COBI combination increased AUC_{inf} by 128% and 94%, respectively. However, the head-to-head comparison of results from Study 4333 and the PK model estimated effect from Study 4625 is challenging. In fact, the PK data from Study 4333 were not included in the PK modeling and the estimated effects from the PK model were in HTE patients from Study 4625 with varying baseline ARVs backgrounds. In addition, the COBI-containing ARVs likely contained drugs/protease inhibitors other than DRV.

- The review team evaluation of the covariate plots for F_{sc} found that formulation strength had an effect on the SC bioavailability of LEN, with an estimated 71% higher F_{sc} for the lower SC formulation strength of 155 mg/mL compared to the 309 mg/mL SC formulation. However, the estimated effect was not found to be statistically significant (at a significance level of 0.001), with a decrease in OFV by 10.1 points (for 1 degree of freedom). The estimated effect of SC formulation strength on V_3 and K_{tr} , as determined by the Applicant, remained unchanged. Although not statistically significant, the effect of SC formulation strength on F_{sc} was kept in the revised PK model, given the 71% effect and the 10 point drop in OFV.
- Finally, the review team evaluation of the covariate plots for F_{sc} and (b) (4) (SC slow absorption), as well as the PK profiles, identified that BMI affected the LEN exposure, with trends of higher exposures in underweight subjects and lower exposures in obese patients. After an information request to the Applicant, recommending the evaluation of BMI (either continuous or categorical) as a covariate on (b) (4) and F_{sc} , the Applicant reported that the inclusion of BMI (as a continuous variable) on (b) (4) and F_{sc} resulted in a decrease in OFV of (b) (4) and 10.2 points, respectively. Of the two, only the BMI effect on (b) (4) was retained by the Applicant (b) (4), and the trends observed for the final model between weight and (b) (4) or F_{sc} were both addressed after inclusion of the BMI- (b) (4) relationship. The Applicant's updated PK model included BMI as a continuous variable using a power model standardized to a median BMI of 26.1 kg/m², with an estimated power exponent of -0.55. The remaining PK parameters from the updated PK model were comparable to the initial final model PK parameters and their variability estimates.

The review team evaluation on BMI either as a continuous or categorical variable (using the same PK dataset) found that the BMI effect on F_{sc} was more pronounced than the effect on $(b)_{(4)}$ when the covariate was included on both F_{sc} and $(b)_{(4)}$. The ETA covariate plots, across different studies and SC formulation strength, showed higher F_{sc} and $(b)_{(4)}$ for underweight subjects ($n=5$, receiving SC), lower F_{sc} and $(b)_{(4)}$ for obese subjects ($n=35$), and comparable F_{sc} and $(b)_{(4)}$ for normal ($n=90$) and overweight subjects ($n=75$). The review team PK modeling using BMI as a categorical variable on $(b)_{(4)r}$ and F_{sc} resulted in a drop in OFV by $(b)_{(4)}$ and 16 points (for 2 degrees of freedom), respectively. The concomitant inclusion of BMI on both F_{sc} and $(b)_{(4)r}$ in the PK model estimated a $(b)_{(4)}\%$ higher and $(b)_{(4)}\%$ lower $(b)_{(4)}$ in underweight and obese subjects, and a 66% higher and 23% lower F_{sc} in underweight and obese subjects, respectively, compared to normal and overweight subjects. The mean effect of underweight BMI on F_{sc} (of 66%) was not precisely estimated (with a %RSE of 73.4%), likely due to the small number of underweight subjects ($n=5$) in the PK dataset and studies, as well as the high variability in PK profile observed in few of these subjects. The backward elimination of BMI on $(b)_{(4)}$ did not significantly change the OFV ($(b)_{(4)}$ increase in OFV). In agreement with the observed effect of BMI groups on the PK profiles (flatter PK profiles for obese and higher PK profiles in underweight subjects) and the absence of obvious faster or delayed absorption amongst the BMI groups, the inclusion and retention of the BMI effect on F_{sc} only instead of $(b)_{(4)}$ was considered more relevant.

In conclusion, the Applicant's reassessment of the covariate analysis and the review team's separate evaluation of the Applicant's updated PK model found that according to the PK modeling:

- $(b)_{(4)}$ were not significant or relevant covariates $(b)_{(4)}$. Both covariates effect $(b)_{(4)}$ was removed from the PK model.
- The inclusion of $(b)_{(4)}$ in addition to F_{po} , was not mechanistically justified and was not relevant. The effect of $(b)_{(4)}$ was removed from the model.
- Cobicistat-containing ARVs had a 28% increase in F_{po} . RTV-containing ARVs had a 95% increase in F_{po} . HTE patients receiving DRV (with unspecified booster) had a 52% increase in F_{po} .
- Underweight subjects were estimated to have a 66% higher LEN SC bioavailability and obese subjects to have 23% lower F_{sc} , compared to normal and overweight subjects. The BMI effect on F_{sc} , particularly in obese subjects, is not expected to impact the target of having the mean C_{trough} (and 90% CI of the mean) above the inhibitory quotient 4 (IQ4) of 15.5 ng/mL for a 26-week dosing window ([Figure 14](#) and [Figure 16](#), Section [II.6.3.4](#)).

[Table 117](#) summarizes the parameter estimates from the reviewer's updated PK model.

Table 117. Parameter Estimates From the Reviewer's Updated Population PK Model

Parameter	Estimate (%RSE)	Bootstrap Estimate ^a (95% CI)
Clearance, CL (L/h)	3.29 (8.7)	3.31 (2.72-4.16)
Central volume, V _c (L)	68.3 (6.1)	68 (62.1-75.2)
Peripheral volume, V _p (L)	726 (9.8)	741 (571-953)
Intercompartmental clearance, Q (L/h)	40.9 (5.5)	41 (37.4-44.5)
PO absorption rate constant, k _a (1/h)	0.0352 (9.7)	0.0347 (0.0286-0.043)
SC transit absorption rate constant, k _{tr} (1/h)	0.00205 (3.2)	0.00199 (0.00189-0.00212)
SC direct absorption rate constant, k _{dir} (1/h)	0.00037 (7.8)	0.000368 (0.000294-0.000445)
SC fraction for direct absorption	0.423 (5.1)	0.423 (0.379-0.471)
PO bioavailability relative to IV, F _{po}	0.0484 (9.9)	0.0496 (0.0395-0.0607)
SC bioavailability relative to IV, F _{sc}	0.881 (9.4)	0.923 (0.723-1.1)
Dose effect on F _{po}	-0.473 (7.9)	-0.465 (-0.546--0.374)
COBI-containing ARV effect on F _{po}	0.284 (47.5)	0.262 (0.059-0.511)
RTV-containing ARV effect on F _{po}	0.949 (46.6)	0.953 (0.343-2.35)
DRV-containing ARV effect on F _{po}	0.519 (41.4)	0.477 (0.0915-1)
Healthy volunteer effect on CL	0.231 (20.5)	0.241 (0.122-0.375)
Healthy volunteer effect on V _p	1.46 (14.1)	1.45 (1.06-1.82)
Weight effect on CL and Q	0.75 (fixed)	-
Weight effect on V _c and V _p	1 (fixed)	-
SC 150 mg/mL effect on V _p	-0.831 (4.5)	-0.828 (-0.9--0.752)
SC 150 mg/mL effect on k _{tr}	0.437 (46.9)	0.453 (0.254-0.677)
SC 150 mg/mL effect on F _{sc}	0.707 (29.1)	0.662 (0.372-0.967)
Underweight BMI on F _{sc}	0.664 (73.4)	0.743 (0.0963-1.59)
Obese BMI on F _{sc}	-0.232 (22.9)	0.267 (0.148-0.372)
IIV on CL (%CV)	45 (9.4) [shrinkage: 5.5%]	47.6 (42.9-51.6)
IIV on V _p (%CV)	81 (11.9) [shrinkage: 4.3%]	93.8 (81.7-110)
IIV on k _{tr} (%CV)	31 (19.4) [shrinkage: 41.8%]	32.6 (24.6-39.5)
IIV on k _a (%CV)	78 (9.1) [shrinkage: 10.2%]	91 (82.3-102)
IIV on F _{sc} (%CV)	39 (19.8) [shrinkage: 40.4%]	38.9 (31.7-45.3)
Correlation between CL and V _p variances (%)	64%	0.651 (0.549-0.752)
Residual proportional variability (%CV)	27.3% (4) [shrinkage: 8%]	27.8 (26.9-28.6)
Residual additive (ng/mL)	0.0025 (fixed)	-

Source: Reviewer's analysis.

^a The bootstrap estimates and 95% CI are reported as median and (2.5th to 97.5th percentiles) of the parameter estimates. A total of 148 of the 200 bootstrap replicates converged and were used for the bootstrap results.Abbreviations: %CV, percentage coefficient of variation; BMI, body mass index; CI, confidence interval; COBI, cobicistat; DRV, darunavir; F_{po}, PO bioavailability relative to IV; F_{sc}, SC bioavailability relative to IV; IIV, interindividual variation; IV, intravenous; K_{dir}, direct/rapid first-order absorption rate constant; K_a, dissociation constant; K_{dir}, direct/rapid first-order absorption rate constant; K_{tr}, transit first-order absorption rate constant; PO, per oral; Q, intercompartmental clearance; RSE, relative standard error; RTV, ritonavir; SC, subcutaneous; V_c, central volume of distribution; V_p, peripheral volume of distribution

14.4. Summary of Bioanalytical Method Validation and Performance

The review team reviewed the bioanalytical method validation reports and sample analysis reports for the quantitation of LEN in human plasma. Method validation and sample analysis

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were acceptable. The validated bioanalytical method GS07HPP supported Studies 4625 and 5709. Validation results for bioanalytical methods are listed in [Table 118](#).

Table 118. Summary of Validation and Performance of Bioanalytical Method Used to Quantify LEN in Plasma for Studies 4625 and 5709

Links to bioanalytical method validation report and summary of biopharmaceutical studies	\\cdsesub1\evsprod\NDA215973\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ (b) (4) -8359841\method-val- (b) (4) -8359841-amend2.pdf \\cdsesub1\evsprod\NDA215973\0001\m2\27-clin-sum\summary-biopharm.pdf
Study number	8359841
Bioanalytical method ID	GS07HPP
Method description	LC-MS/MS
Analytical matrix	K ₂ EDTA human plasma
Storage conditions	-10 to -30°C and -60 to -80°C
Stability in matrix	24 hours at room temperature Five freeze-thaw cycles at -10 to -30°C and -60 to -80°C 748 days at -10 to -30°C 748 days at -60 to -80°C
Stability in blood	2 hours at room temperature and wet ice conditions
Processed extract stability	96 hours at 2 to 8°C
LLOQ to ULOQ	0.5 ng/mL to 500 ng/mL
Validated range	0.500 to 500 ng/mL
Accumulated accuracy (%RE) from LLOQ to ULOQ:	-6.2 to 3.3%
Cumulative precision (%CV) from LLOQ to ULOQ	≤8.3%
Within-run %CV	2.0 to 10.3%
Within-run % RE range	-8.5 to 14.2%
Between-run %CV	4.5 to 8.7%
Between-run %RE range	-4.8 to 4.6%
Experimental start date	30 March 2017
Experimental completion date	04 April 2018

Source: Reviewer's summary of the Applicant's bioanalytical and validation reports.

Abbreviations: %CV, percentage coefficient of variation; %RE, percent relative error; ID, identity; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantitation; ULOQ, upper limit of quantitation

15. Trial Design: Additional Information and Assessment

15.1. Study 4625 (CAPELLA)

Table 119 Study 4625 (CAPELLA)

(b) (4)	



Amendment 1:	This is a summary of the major changes made to the original protocol dated 25 September 2019 and reflected in Amendment #1 dated 18 December 2019. Added Clinical Trials.gov Identifier (04150068). Added Nonclinical Pharmacology and Toxicology Studies information to the Introduction of the protocol. Clarified that PROs will be completed if available. Changed the name of (b) (4) to Symptom Distress Module. Specified that the PROs must be completed prior to other study procedures. Removed language associated with (b) (4). Specified the disallowed medications and contraceptive methods that are not approved in Japan. Revised Study Procedures Table, Appendix 2 and the associated footnote in reference to the above noted PRO changes. Updated text given non-clinical reproductive toxicity and in vitro induction data.
Amendment 2:	This is a summary of the major changes made to Amendment #1 dated 18 December 2019 and reflected in Amendment #2 dated 01 September 2020. Corrected concentration of GS-6207 injection from 300 mg/mL to 309 mg/mL to accurately reflect the label claim of the finished product based on improved accuracy on measurement of the product density since Amendment 1. No changes to the actual product concentration have been made. Corrected SC dose from 300 mg to 309 mg and 900 mg to 927 mg. Changed SC product name from GS-6207 sodium injection, 300 mg/mL to GS-6207 injection, 309 mg/mL. Added GS-6207 drug product's International Non-proprietary Name Lenacapavir, LEN. Added phase 1 study (GS-US-200-4333) data. Clarified language in the biomarker testing section. Added requirement for the collection of participant's meal time in the dosage and drug administration section. Updated prior and concomitant medication section. Revised inclusion criterion 9. Added guidance for rescreening of participants. Corrected suboptimal virologic response criteria. Updated Follow-up visits requirement. Revised G3/G4 retest requirements. Gilead's Pharmacovigilance and Epidemiology group has been renamed to Gilead Global Patient Safety (GLPS). Name change has been made throughout the protocol.

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	Broadened the second Full Analysis Set (FAS) definition to include all participants who receive at least one dose of GS-6207. The secondary analyses windows at Week 26 and Week 52 have been updated to begin from the start of GS-6207 therapy (oral) instead of the start of GS-6207 SC therapy. Updated contraceptive requirements and revised the duration for pregnancy/pregnancy outcome reporting requirements. Added risks and mitigation strategies associated with an ongoing pandemic (such as coronavirus disease 2019).

Source: Applicant's protocol synopsis

Abbreviations: λ_z , terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug; ALT, alanine aminotransferase; ARV, antiretroviral; AUC, area under the concentration-time curve; CD, cluster of differentiation; C_{D14} , concentration on day 14; C_{last} , last measured concentration; C_{max} , maximum concentration; C_t , concentration at time t; ECG, electrocardiogram; FDA, Food and Drug Administration; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; IND, investigational new drug; LEN, lenacapavir; LLOQ, lower limit of quantification; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RT, reverse transcriptase; SC, subcutaneous; T_{last} , time at last measured concentration; T_{max} , time to maximum concentration; V_2/F , volume of the peripheral compartment after oral administration

15.2. Study 4334 (CALIBRATE)

Table 120 Study 4334 (CALIBRATE)

(b) (4)





Amendment 1:	This is a summary of the major changes made to the original protocol dated 02 October 2019 and reflected in Amendment #1 dated 05 November 2019. Added ClinicalTrials.gov identifier (NCT04143594). Clarified that Patient Reported Outcomes (PROs) will be completed, if available. Removed (b) (4). Revised timepoints for completion of HIVTSQ12. It will be completed at Day 15 instead of (b) (4). Specified that HIVTSQ12, HIVDQoL, and EQ-ED-5L must be completed prior to other study procedures. Specified that Injection Acceptability Scale and Numeric Pain Rating Scale must be completed after SC GS-6207 administration and completion of other study procedures. Added Injection Site Reaction Assessment Worksheet to Study Procedures table.
Amendment 2:	This is a summary of the major changes made to Amendment #1 dated 05 November 2019 and reflected in Amendment #2 dated 24 January 2020. Updated eligibility criteria. Added Nonclinical Pharmacology and Toxicology Studies information to the Introduction of the protocol. Updated text giving nonclinical reproductive toxicity and in vitro induction data. Clarified that medications for malignancy may be disallowed and are not listed in the table of disallowed medications.

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	Clarified that bottles may be kept on site until completion of Day 2 visits. Shortened the screening window to 30 days. Added the collection of demographic information, including gender at birth, sexual orientation, and gender identity to Screening visit. Added lipid panel to be collected at all visits except Day 5 visit.
Amendment 3:	A summary of the major changes made to Amendment #2 dated 24 January 2020, reflected in Amendment #3 dated 01 September 2020. Corrected concentration of GS-6207 injection from 300 mg/mL to 309 mg/mL to accurately reflect the strength of the finished product based on improved accuracy on measurement of the product density since Amendment 2. No changes to the actual product label claim have been made. Corrected SC dose from 300 mg to 309 mg and due to the corrected SC dose concentration updated from 900 mg to 927 mg. Changed SC product name from GS-6207 sodium injection, 300 mg/mL to GS-6207 injection, 309 mg/mL. Added GS-6207 drug product's International Non-proprietary name Lenacapavir, LEN. Added phase 1 study (GS-US-200-4333) data. Clarified language in the biomarker testing section. Added requirement for the collection of participant's meal time in the dosage and drug administration section. Updated prior and concomitant medication section. Revised inclusion criterion 7. Added guidance for rescreening of participants. Updated Follow-up visits requirement. Revised G3/G4 retest requirements. Gilead's Pharmacovigilance and Epidemiology group has been renamed to Gilead Global Patient Safety (GLPS). Name change has been made throughout the protocol. Updated DMC analysis section to allow data from the planned analyses to be used for GS-6207 regulatory filing or to support other studies. Updated statistical method used. Updated contraceptive requirements and revised the duration for pregnancy/pregnancy outcome reporting requirements. Added information on risks on study management due to pandemic (such as coronavirus disease 2019) and risk mitigation strategy.

Source: Applicant's synopsis.

Abbreviations: λ_z , terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug; ALT, alanine aminotransferase; ARV, antiretroviral; AUC, area under the concentration-time curve; CD, cluster of differentiation; C_{D14} , concentration on day 14; C_{last} , last measured concentration; C_{max} , maximum concentration; C_t , concentration at time t; C_{tau} , concentration at end of dosing interval; ECG, electrocardiogram; FDA, Food and Drug Administration; FTC, emtricitabine; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; IMP, investigational medicinal product; IND, investigational new drug; LEN, lenacapavir; LLOQ, lower limit of quantification; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RT, reverse transcriptase; SC, subcutaneous; TFV, tenofovir; T_{last} , time at last measured concentration; T_{max} , time to maximum concentration; V2/F, volume of the peripheral compartment after oral administration

16. Efficacy: Additional Information and Assessment

Study 4625

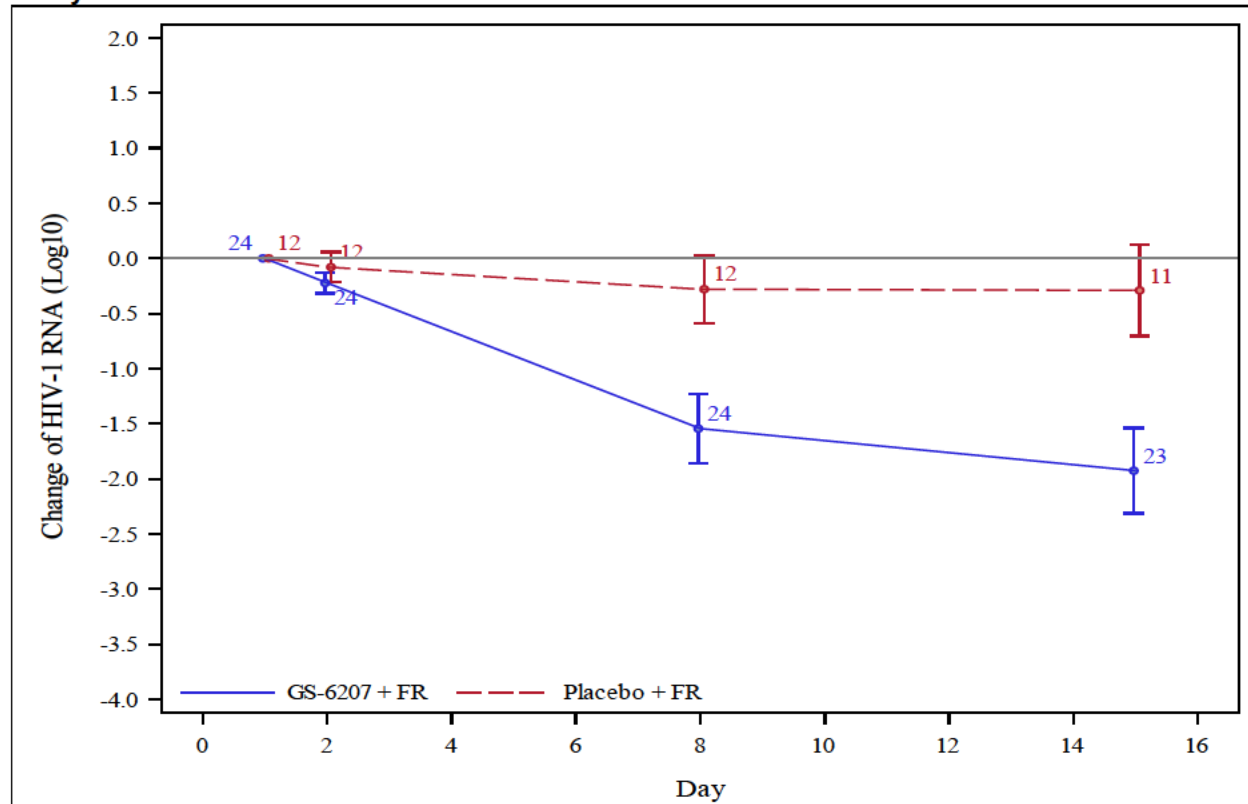
Supplementary Analyses for the Primary Endpoint

The review team identified subjects who were not on failing regimen (five subjects) or who were nonadherent (six subjects) and were randomized to Cohort 1 (details of the subjects can be found in Section II.6.3.2). Supplementary analyses were conducted to exclude those subjects to determine the impact on the primary efficacy results. For the following analyses, the five subjects who were not on failing regimen, or the six nonadherent subjects, or both groups were excluded from the analysis so that the robustness of the primary endpoint could be evaluated. The results were consistent (Table 24).

HIV-1 RNA Change Over Time

The mean change and 95% CI of HIV-1 RNA over time for the functional monotherapy period for Cohort 1 and the all LEN analysis for both Cohort 1 and Cohort 2 are presented in Figure 37 and Figure 38. A rapid decline of HIV-1 RNA was observed right after the drug's initiation and the trend of declination slowed down after Day 15.

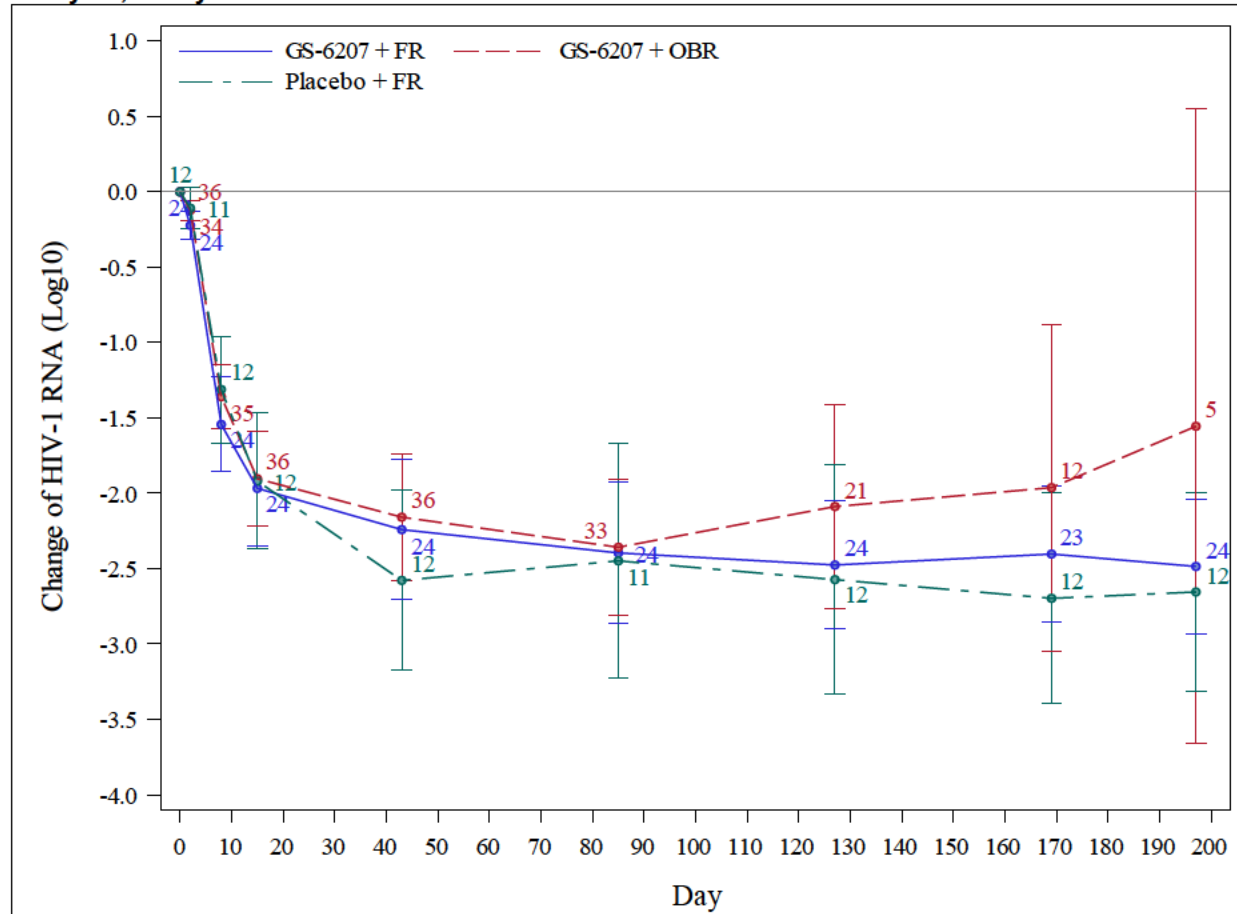
Figure 37. Mean Change and 95% CI of HIV-1 RNA Over Time, Functional Monotherapy Period, Study 4625



Source: Statistical reviewer's analysis.

Abbreviations: CI, confidence interval; FR, failing regimen; HIV, human immunodeficiency virus

Figure 38. Mean Change and 95% CI of HIV-1 RNA Over Time After LEN Administration, All LEN Analysis, Study 4625



Source: Statistical reviewer's analysis.

GS-6207 + FR indicates subjects randomized to the LEN arm in Cohort 1; placebo + FR indicates subjects randomized to the placebo arm in Cohort 1 (Day 0 for this arm was counted on the day immediately before LEN administration); GS-6207 + OBR indicates subjects enrolled in Cohort 2. Numbers indicate sample sizes.

Abbreviations: CI, confidence interval; FR, failing regimen; HIV, human immunodeficiency virus; LEN, lenacapavir

Subgroup Analyses for the Endpoint of HIV-1 RNA <50 Copies/mL at Week 26

The protocol preplanned subgroup analyses were at Week 26. At this timepoint, the proportion of subjects with HIV-1 RNA <50 copies/mL was numerically higher in the subgroup of age <50 years, female, baseline CD4⁺ cell count ≥200 cells/μL, and baseline HIV-1 RNA level ≤100,000 copies/mL (Table 121).

Table 121. Subgroup Analyses for the Endpoint of HIV-1 RNA <50 Copies/mL at Week 26

Subgroup	LEN	Placebo	Overall
Age group	<50 years	6/6 (100%)	100% (9/9)
	≥50 years	15/18 (83.3%)	74% (20/27)
Sex	Female	6/7 (85.7%)	90% (9/10)
	Male	15/17 (88.2%)	77% (20/26)
Race	Black	9/10 (90%)	81% (13/16)
	Other	12/14 (85.7%)	80% (16/20)
HIV-1 RNA	≤100,000 copies/mL	20/23 (87%)	86% (25/29)
	>100,000 copies/mL	1/1 (100%)	57% (4/7)

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Subgroup		LEN	Placebo	Overall
CD4+ cell count	<200/ μ L	14/16 (87.5%)	7/11 (63.6%)	78% (21/27)
	$\geq$ 200/ μ L	7/8 (87.5%)	1/1 (100%)	89% (8/9)
Number of fully active ARV agents in the OBR	0	3/4 (75%)	1/2 (50%)	67% (4/6)
	1	6/7 (85.7%)	6/7 (85.7%)	86% (12/14)
	$\geq$ 2	12/13 (92.3%)	1/3 (33.3%)	81% (13/16)
Use of DTG and/or DRV in the OBR	With DTG and DRV	6/6 (100%)	4/6 (66.7%)	83% (10/12)
	With DTG, without DRV	4/4 (100%)	1/2 (50%)	83% (5/6)
	Without DTG, with DRV	5/6 (83.3%)	2/3 (66.7%)	78% (7/9)
	Without DTG or DRV	6/8 (75%)	1/1 (100%)	78% (7/9)
Baseline INSTI resistance profile	With INSTI resistance	19/20 (95%)	4/7 (57.1%)	85% (23/27)
	Without INSTI resistance	2/4 (50%)	3/4 (75%)	63% (5/8)

Source: Statistical reviewer's analysis.

An FDA-defined snapshot algorithm was used.

Abbreviations: ARV, antiretroviral; CD, cluster of differentiation; DTG, dolutegravir; DRV, darunavir; HIV, human immunodeficiency virus; INSTI, integrase inhibitor; LEN, lenacapavir; OBR, optimized background regimen

17. Clinical Safety: Additional Information and Assessment

No additional clinical safety assessments were conducted. Analysis of clinical safety outcomes by demographic subgroups were specifically not included here because of the small sample sizes anticipated with Studies 4625 and 4334, which would limit meaningful interpretation of the analyses.

18. Mechanism of Action/Drug Resistance

Mechanism of Action

Co-Crystal Structure of Lenacapavir Bound to Cross-Linked Capsid Hexamer (Report No. PC-200-2022)

A 2.0-Angstrom protein X-ray crystal structure was determined for the cross-linked capsid hexamer in complex with LEN to characterize the interaction of LEN with the HIV-1 capsid. LEN binds directly at the interface formed by two adjacent capsid monomers, such that up to six molecules of LEN can bind to each capsid hexamer. LEN forms extensive interactions with the binding pocket (Figure 39). The central amide and pyridine ring of LEN form hydrogen bonds with Asn57 within the N-terminal domain of one monomer, whereas the indazole and sulfonamide groups of LEN make hydrogen bonds with Gln179 and Asn183 within the C-terminal domain of the neighboring monomer. Thus, LEN binds at the intermolecular interface between the N-terminal domain of one subunit and the C-terminal domain of the neighboring subunit within the same capsid hexamer. Additionally, the LEN binding site is shared by capsid-binding host nuclear import factors (Price et al. 2012; Matreyek et al. 2013; Bhattacharya et al. 2014). This observation supports that LEN may compete with nuclear import machinery for binding to capsid and thereby interfere with nuclear transport.

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Figure 39. Co-Crystal Structure of LEN Bound to Cross-Linked HIV-1 CA Hexamer

(b) (4)

Abbreviations: Asn, asparagine; CA, capsid; CTD, C-terminal domain; Gln, glycine; HIV, human immunodeficiency virus; LEN, lenacapavir; Lys, lysine; NTD, N-terminal domain

LEN Binding to Recombinant Capsid Proteins (Report No. PC-200-2022)

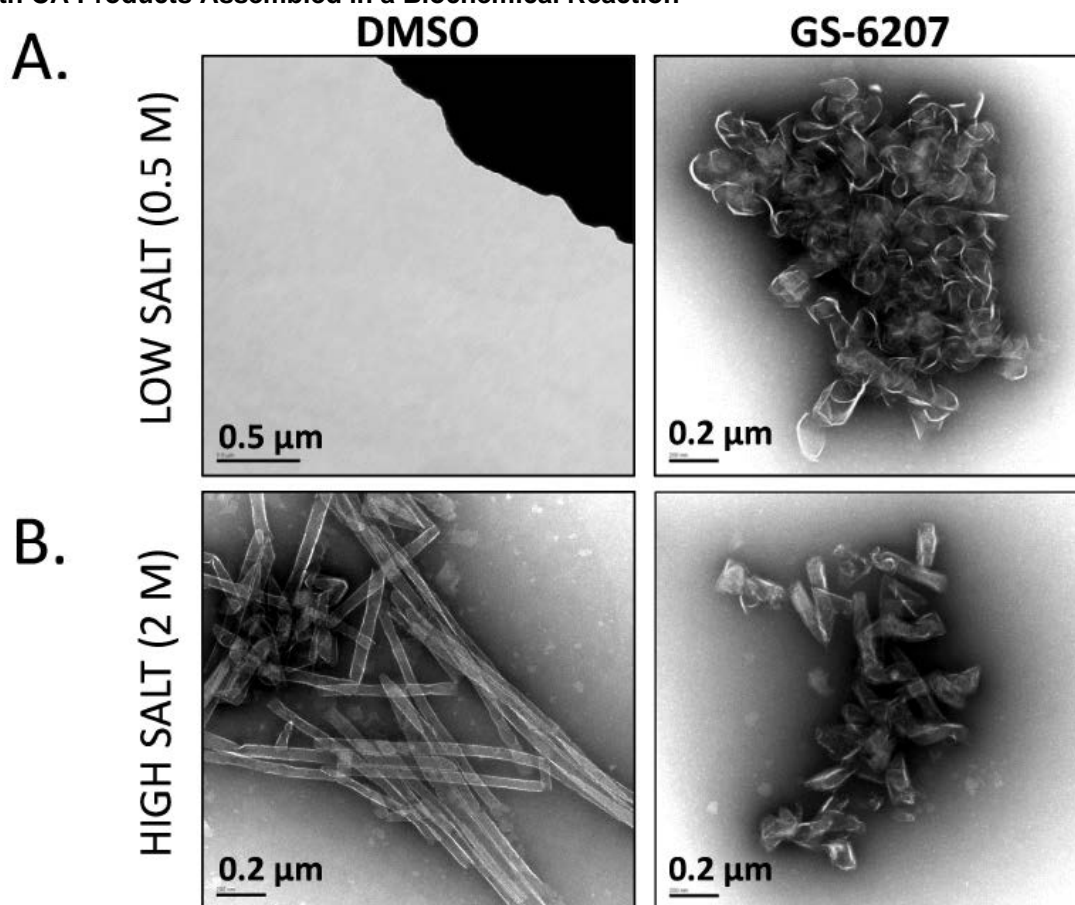
The binding affinities of LEN to wild-type capsid hexamers and hexamers containing the M66I substitution (identified in resistance selection studies) (Report PC-200-2025) were evaluated by surface plasmon resonance. Surface plasmon resonance sensorgrams showed dose-dependent and saturable binding of LEN to cross-linked wild-type capsid hexamer with an equilibrium binding constant of 1.4nM. LEN binding to cross-linked M66I mutant hexamers was 80-fold weaker, with an equilibrium binding constant of 110nM.

Effect on Capsid Assembly in a Biochemical Assay (Report No. PC-200-2022)

Capsid protein can spontaneously oligomerize under high ionic strength conditions to form open-ended, tube-like structures comprised of repeating capsid hexamers. The assembly kinetics of full-length capsid were measured under high ionic strength condition (2M NaCl) in the presence and absence of LEN using an assembly assay based on monitoring the change in sample absorbance at 350 nm. LEN showed a dose-dependent increase in the rate and extent of capsid assembly with a mean concentration yielding 50% activation of 0.32μM (mean of six independent determinations).

Additionally, assembly products formed under both low ionic strength (0.5M NaCl) and high ionic strength (2M NaCl) conditions were visualized by negative staining and transmission electron microscopy. Under low ionic strength (0.5M NaCl) conditions, full-length capsid did not undergo self-assembly, but in the presence of 40 μ M LEN, formed large numbers of capsid polymers that were shorter and generally more disordered (Figure 40A) relative to the long capsid tube-like structures universally observed in the absence of the compound in the high ionic strength buffer, a condition that is permissive for capsid protein assembly in the absence of LEN (Figure 40A). At a higher NaCl concentration (2M) with LEN, capsid polymers were also shorter and malformed (disordered and closed) relative to the uniform tubular polymers formed by full-length capsid in the absence of this compound (Figure 40B). LEN induced the production of poorly organized multimeric capsid polymers.

Figure 40. Electron Micrographs Showing the Effect of LEN (GS-6207) on the Morphology of HIV-1 Full Length CA Products Assembled in a Biochemical Reaction



In vitro assembly of 40 μ M FL CA was performed in the absence (1% DMSO) and presence of equimolar concentration of GS-6207 in buffer containing (A) low salt (0.5 M NaCl) or (B) high salt (2 M NaCl) concentrations. The black bar on micrographs represents scale in micrometers.

Source: Report No. PC-200-2022, page 15.

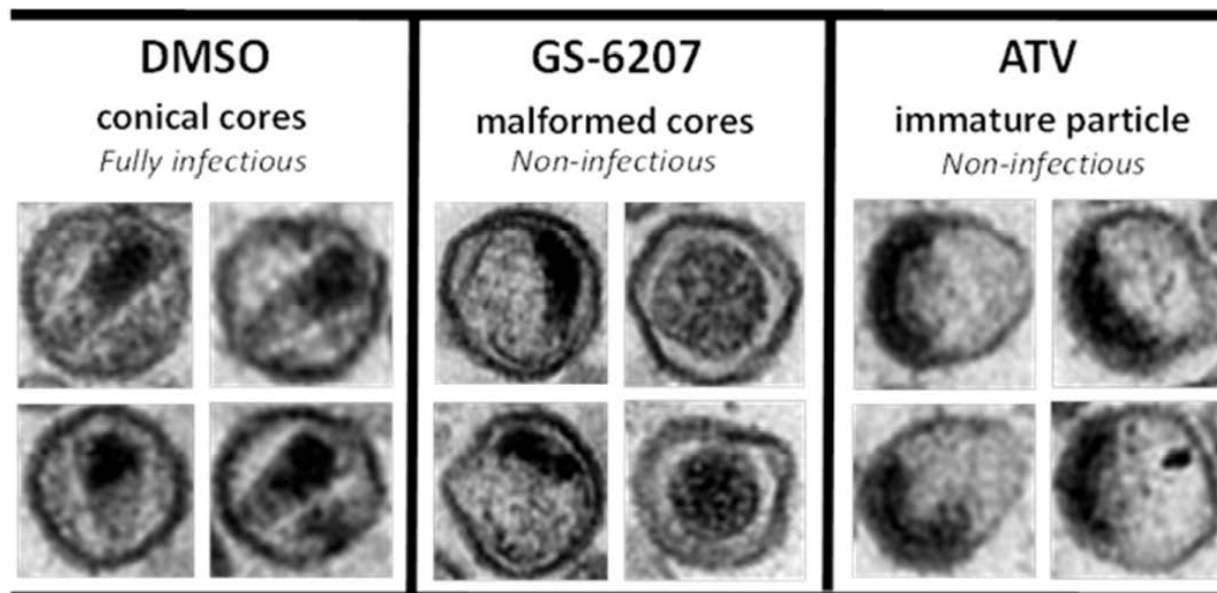
Abbreviations: CA, capsid; DMSO, dimethyl sulfoxide; FL, full length; HIV, human immunodeficiency virus; LEN, lenacapavir

Effects on Capsid Morphology (Report PC-200-2023)

The morphology of capsid structures was examined in ultrathin-sectioned virions produced in the presence and absence of LEN by transmission electron microscopy (Figure 41). The vehicle

(dimethyl sulfoxide)-treated controls showed the expected conical capsids with an encased dark signal at the wide end of the cone consistent with negative staining of viral nucleic acids. In contrast, virions produced in the presence of LEN contained predominantly malformed capsid cores in which the nucleic acids were either regionally or diffusely confined within the irregularly shaped capsid core. This altered capsid morphology is consistent with the finding that LEN accelerates the assembly of recombinant capsid protein into poorly organized capsid polymers. The morphology of HIV-1 particles produced in the presence of LEN was distinct from virions produced in the presence of the protease inhibitor atazanavir, which uniformly contained an immature, discontinuous Gag/Gag-Pol polyprotein lattice. Virions produced in the presence of LEN or atazanavir were noninfectious when serially diluted well below the EC_{50} concentration of each compound and used to infect CEM-NKR CCR5⁺Luc⁺ indicator cells.

Figure 41. Electron Micrographs Showing Capsid Morphology of HIV-1IIB Strain Produced in the Presence and Absence of Lenacapavir (GS-6207) or Atazanavir (ATV)



MT-2 cells chronically infected with HIV-1 IIB strain (MT-2/IIB) were incubated in the presence of 0.25% DMSO, 50 nM GS-6207 or 1 μ M ATV for 4 days. Cell culture supernatants were serially diluted and tested for infectivity on CEM-NK^R CCR5⁺Luc⁺ cells. The virus associated with the cell samples was pelleted by centrifugation, fixed, ultrathin sectioned, counter stained and examined on an electron microscope.

Source: Report PC-200-2023, page 9.

Abbreviations: CCR, C-C chemokine receptor; HIV, human immunodeficiency virus

Inhibition of Production of Mature HIV-1 Virions by Capsid Binding

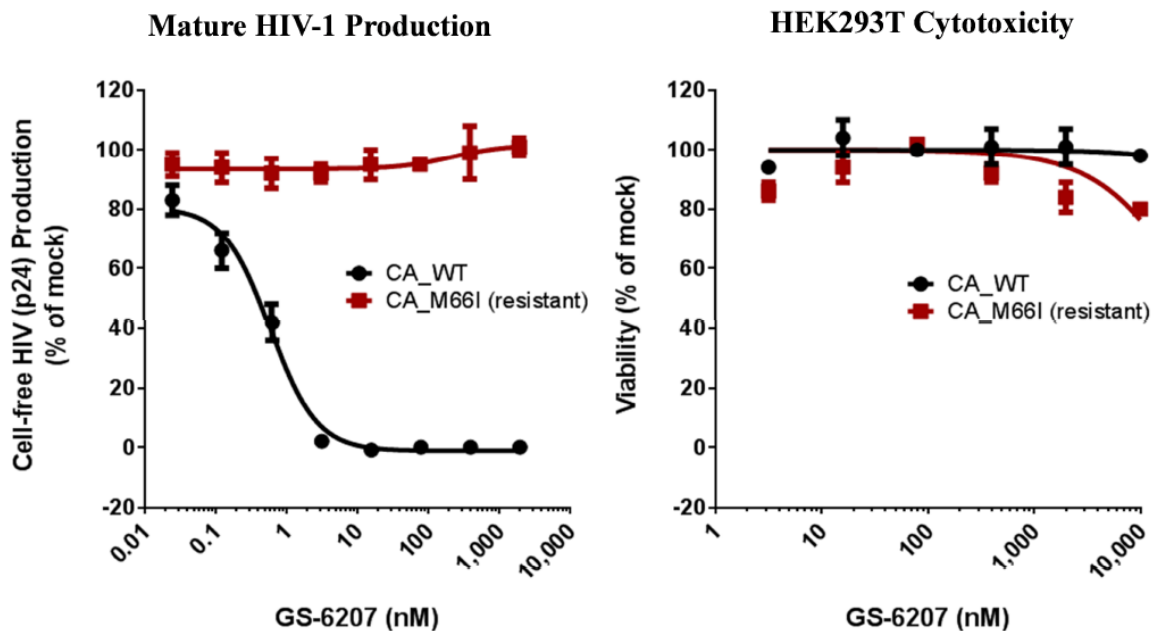
The effects of LEN on virus production and cell viability was assessed in HEK293T cells following transient transfection with plasmids encoding the vesicular stomatitis virus envelope and a single-cycle HIV-1 reporter virus. LEN showed a dose-dependent reduction in the amount of mature wild-type HIV-1 released into cell culture supernatants, with a mean 50% effective concentration (EC_{50}) value of 0.305nM as determined by p24 (capsid) enzyme-linked immunosorbent assay (Figure 42). The effect on the production of mature extracellular virions occurred at concentrations of LEN within the range of its late-stage antiviral EC_{50} value of 0.44nM, which suggests that this effect may represent the major mechanism by which LEN mediates its late-stage antiviral activity. The effect of LEN on virus production required the wild-type capsid domain since this effect was not observed with the M66I capsid mutant (mean

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$EC_{50} > 2\mu\text{M}$). In addition, the compound effect is virus-specific since LEN showed no cytotoxicity in HEK293T cells up to the highest concentration tested ($10\mu\text{M}$) ([Figure 42](#)).

Figure 42. Effect of LEN (GS-6207) on the Production of Mature Extracellular WT and the M66I Capsid Mutant in HEK293T Cells



Source: Report PC-200-2023, page 11.

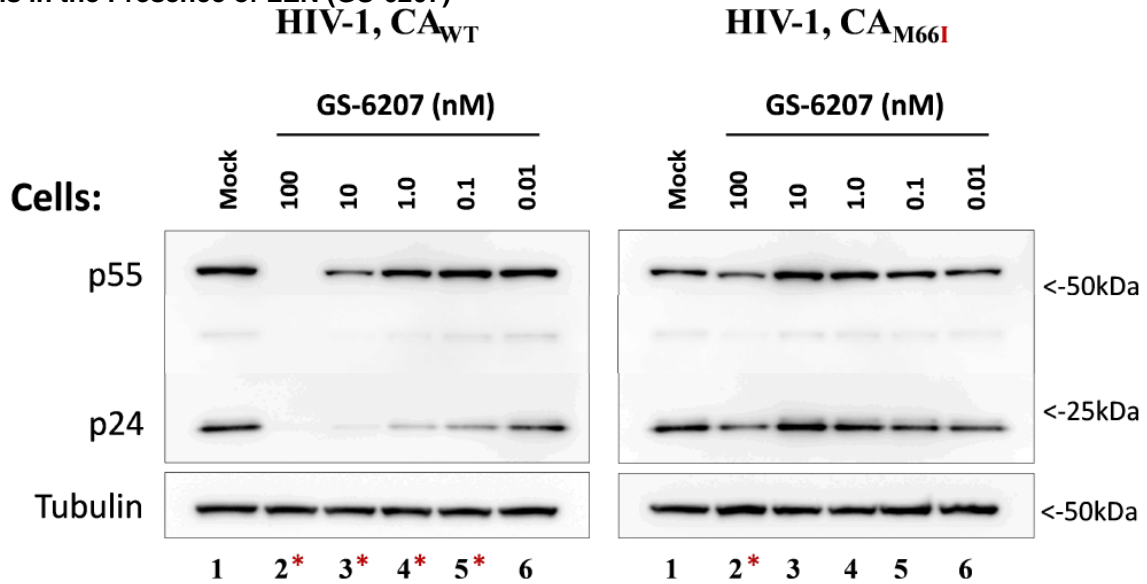
Abbreviations: LEN, lenacapavir; HEK, human embryonic kidney; HIV, human immunodeficiency virus; WT, wild type

Dose-Dependent Reduction in Intracellular HIV-1 Gag/p24 Levels by a Mechanism That Requires Capsid Domain Binding

The effect of LEN on HIV-1 Gag polyprotein expression and maturation was assessed by anti-p24 western blot analyses using cell lysates from HEK293T cells producing infectious virus ([Figure 43](#)). Cells producing wild-type HIV-1 in the presence of 10 to 100nM LEN (23- to 227-fold its late-stage EC_{50} value) showed reduced intracellular levels of capsid (p24) and Gag (p55) proteins relative to the vehicle-treated (mock) control sample. At lower concentrations of LEN (0.1 to 1nM), Gag levels remained unaffected by the presence of the compound whereas capsid levels were reduced relative to the mock control. The Applicant states LEN is unlikely to act by inhibiting Gag/Gag-Pol polyprotein cleavage since reduced capsid levels were not associated with a concomitant increase in Gag levels, as would be expected, and because malformed capsid cores were readily observed in virus particles produced in the presence of LEN. The intracellular downregulation of these viral proteins is dependent on a specific interaction between LEN and the capsid domain of mature (p24) and immature (Gag/Gag-Pol) capsid proteins, because these proteins were not reduced by LEN when using the M66I capsid HIV-1 mutant ([Figure 43](#)). These data suggest that the reduced production of virus particles observed with LEN is likely due to an increased rate of Gag/p24 intracellular turnover following specific binding of LEN to the capsid domain of intracellular Gag/Gag-Pol precursor polyproteins by a mechanism that is not yet determined.

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Figure 43. Dose-Dependent, Capsid-Binding Dependent Reduction in Intracellular Gag/p24 Proteins in the Presence of LEN (GS-6207)



HEK293T cells were co-transfected with plasmids encoding the VSVG envelope and a single-cycle HIV-1 reporter construct encoding WT or the M66I capsid mutant resistant to GS-6207 and then incubated in the presence and absence of GS-6207 for 2 days. Cell lysates from these virus-producing cells were then prepared, separated by SDS-PAGE, transferred to nitrocellulose and analyzed by anti-p24 (capsid) and anti-tubulin (loading control) Western blotting. Asterisks denote concentrations of GS-6207 that reduce intracellular levels of immature Gag (p55) precursor protein, mature capsid (p24) protein, or both in cells producing WT HIV-1 or the GS-6207 resistant HIV-1 variant encoding the capsid M66I mutation.

Source: Report PC-200-2023, page 12.

Abbreviations: HIV, human immunodeficiency virus; LEN, lenacapavir; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; VSVG, vesicular stomatitis virus G protein; WT, wild type

Effect of LEN on the Early Stages of HIV-1 Replication (Report PC-200-2024)

LEN retains full antiviral efficacy when the presence of the compound is selectively restricted to the target cell infection phase (i.e., the early stage of the replication cycle), with a mean early stage EC₅₀ value of 0.023nM. The antiviral activity of LEN was assessed in CEM-NKr CCR5⁺Luc⁺ T cells infected with pseudotyped HIV-1 expressing one of four different viral envelope proteins. These viral envelope glycoproteins were selected because their surface expression confers either broad host cell tropism (VSVG) or restricted HIV-1 entry into CD4⁺ cells expressing the C-X-C chemokine receptor (CXCR)4 coreceptor (NL4-3), the C-C chemokine receptor (CCR)5 coreceptor (JRFL), or other chemokine coreceptor (HT593.1). LEN displayed similar antiviral activity against all pseudotyped HIV-1 viruses tested with a range of EC₅₀ values between 0.046 and 0.106nM (Table 122). These data indicate that LEN functions independently of the viral envelope protein.

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Table 122. Effect of Virus Envelope Glycoprotein on LEN Antiviral Activity in MT-2 Cells

Envelope Glycoprotein Co-Expressed With HIV-1(Δ Env)	Pseudovirus Tropism	GS-6207 Single-Cycle EC_{50} (nM) ^a
NL4-3	CXCR4	0.106 ± 0.041
JRFL	CCR5	0.046 ± 0.012
92HT593.1	CXCR4 / CCR5 (Dual tropic)	0.077 ± 0.008
VSV(G)	Broad	0.041 ± 0.007

^a EC_{50} values (mean ± SD) obtained from 4 independent experiments performed in triplicate

Source: Report PC-200-2024, page 12.

Abbreviations: CCR, C-C chemokine receptor; CXCR, C-X-C motif chemokine receptor; EC_{50} , 50% effective dose; HIV, human immunodeficiency virus; LEN, lenacapavir; SD, standard deviation; VSVG, vesicular stomatitis virus G protein

The BlaM-Vpr reporter assay was used to quantify HIV entry into peripheral blood mononuclear cells (PBMCs) treated with LEN. This assay uses HIV-1 variant containing copackaged β -lactamase enzyme which, when transferred to the target cell's cytosol following virus-host cell membrane fusion, can be detected and quantified through enzymatic cleavage of the fluorescent substrate CCF2. The PBMCs from three donors were independently infected with BlaM/HIV-1 (NL4-3 strain) in the presence of LEN or control compounds, loaded with CCF2 substrate dye, and $CD3^+ CD4^+ CD8^-$ cells containing virus entry were enumerated by flow cytometry to detect the cleaved CCF2 dye after 16 hours of incubation. Whereas only a low proportion of blue $CD3^+ CD4^+ CD8^-$ cells were detected in PBMC cultures following a mock-infection (mean 0.6%), mean infection rates with BlaM/HIV were 17% in the presence of dimethyl sulfoxide (DMSO; vehicle control). As expected, treatment with the CXCR4 small-molecule control inhibitor AMD3100 (1 μ M) greatly reduced virus entry to near background levels (mean 0.8%). In contrast, treatment with 1 μ M of either LEN or the INSTI dolutegravir did not reduce HIV entry into PBMCs (mean 18 to 21%). These data indicate that LEN induces a post-entry block in HIV replication.

A time-of-drug-addition assay was used to determine how long after initiating a synchronized HIV-1 infection LEN could be added to the culture before a 50% decline in its maximal antiviral efficacy was observed. MT-2 cells were infected with VSVG-HIV-LUC reporter virus, washed to remove unabsorbed virus, and then compounds were added to the culture either immediately postinfection (time 0) or at 4-hour intervals (+4, +8, +12, +16, +20, +24, +28, and +32 hours) postinfection. Compounds were added at a fixed drug concentration conferring maximal viral suppression, equivalent to 10- or 100-fold their respective EC_{50} value. The mean time postinfection to maintain at least half maximal inhibition ($T_{1/2}$) for LEN was ~ 15.3 hours. The $T_{1/2}$ observed with the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine were 10.2 and 11.3 hours, respectively, whereas the $T_{1/2}$ for each of two integrase strand-transfer inhibitors (INSTIs) (raltegravir, DTG) was 16.6 hours. These data indicate that LEN inhibits HIV infection sometime after reverse transcription but before HIV integration.

The effect of LEN on the accumulation of early HIV-1 replication products in acutely infected MT-2 cells was assessed by quantitative PCR. Cells were infected with single-cycle VSVG-HIV-LUC virus and then treated with DMSO (vehicle control), LEN, efavirenz, dolutegravir, or atazanavir. Total DNA was harvested 12, 24, and 48 hours postinfection. The amounts of reverse transcribed strong-stop and second-strand transfer DNA products (early and late reverse transcription, respectively) and abortive 2-long terminal repeat (2-LTR) circles produced only in

the nucleus were quantified by quantitative PCR at 12 and 24 hours postinfection, respectively, whereas the amounts of integration products (Alu-LTR) were quantified by digital-droplet PCR at 48 hours postinfection. All measured quantities were normalized against the corresponding CCR5 gene copies in the same sample and expressed as a fold-change value relative to the DMSO-treated infected control (set to 100%) for each target amplicon measured (Table 123). As expected, treatment with the late-acting PI atazanavir had no effect on the accumulation of any of the four replication products analyzed in this single-cycle infection study. In contrast, the NNRTI efavirenz significantly reduced the accumulation of all four replication products as expected. Treatment with the INSTI dolutegravir specifically reduced integration products, and thus, increased integration failures, leading to a three-fold increase in the accumulation of abortive 2-LTR circles in the nucleus. Although high concentrations of LEN (244-fold its EC₅₀ value) produced an HIV replication product profile similar to efavirenz, indicating LEN can inhibit reverse transcription under conditions of extremely high drug exposure, this was not the case at lower and still fully suppressive LEN concentrations. For instance, MT-2 cells treated with 0.25 to 2.5nM LEN (6.1- to 61-fold its EC₅₀ value) showed a unique impact on HIV infection product profile relative to the control inhibitors, with no effect on the accumulation of reverse transcription products, but profoundly reduced levels of integration products and abortive 2-LTR circles. Thus, LEN primarily inhibits HIV replication at a step after reverse transcription, but before integration. Two-LTR circles did not accumulate in the presence of LEN as observed with dolutegravir, but instead were reduced, suggesting that the compound likely prevents integration by inhibiting the translocation of viral preintegration complexes into the nucleus.

Table 123. Effect of LEN (GS-6207) Versus Control Inhibitors on the Accumulation of Products of Reverse Transcription, HIV Integration, and Integration Failure

Compound	Concentration Used (nM) ^a	Fold EC ₅₀	Direct Effect on Reverse Transcription (RT)		Integration Failure	Direct Effect on Integration
			Early-RT (fold-change) ^a	Late-RT (fold-change) ^a	2-LTR Circles (fold-change) ^a	Alu-LTR (fold-change) ^a
DMSO	-	-	1.0	1.0	1.0	1.0
GS-6207	0.05	1.2	1.1	1.0	1.0	0.6
	0.25	6.1	1.0	0.8	0.4	0.06
	1.25	31	0.9	1.0	0.3	0.02
	2.5	61	0.6	0.7	0.3	0.01
	10	244	0.3	0.2	0.1	0.01
EFV	500	250	0.4	0.2	0.1	0.03
DTG	500	94	1.2	1.0	3.0	0.02
ATV	500	27	1.1	1.1	0.7	0.8

^a Copy numbers for each HIV target amplicon were normalized against the corresponding copy numbers for the endogenous CCR5 gene from the same sample and expressed as a fold-change (FC) value relative to the DMSO-treated infected control (set to 100%) for each target amplicon measured. Values represent the mean of three replicates from a single experiment. Fold-change in target product accumulation is colored green for FC ≥ 1.5, orange for FC > 0.1 to ≤ 0.5, and red for FC ≤ 0.1.

Source: Report PC-200-2024, page 15.

Abbreviations: ATV, atazanavir; CCR, C-C chemokine receptor; DMSO, dimethyl sulfoxide; EC₅₀, 50% effective concentration; EFV, efavirenz; DTG, dolutegravir; HIV, human immunodeficiency virus; LEN, lenacapavir; LTR, long terminal repeat

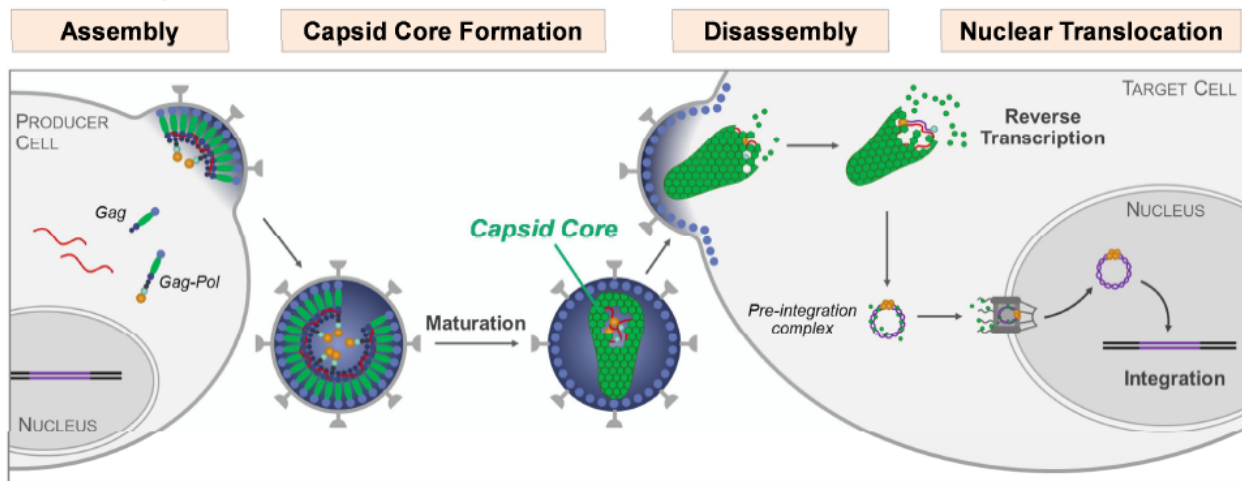
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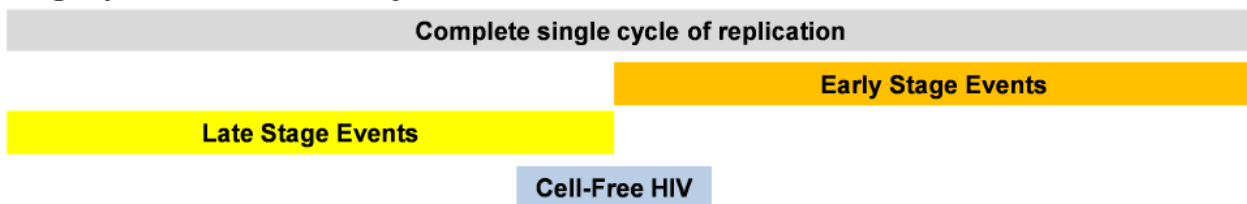
In summary, there is evidence that LEN acts through mechanisms both at early and late stages of HIV-1 replication and is a multistage inhibitor (Figure 44). LEN binds directly to the interface between capsid protein subunits. Lenacapavir inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).

Figure 44. LEN Inhibition of Early and Late Stages of HIV-1 Replication

Essential Capsid-mediated Processes:



Drug Exposure in Antiviral Assays:



Source: Report PC-200-2021, page 10.

Abbreviations: HIV, human immunodeficiency virus; LEN, lenacapavir

Antiviral Activity

The antiviral activity of a novel HIV-1 capsid inhibitor LEN was evaluated using a 5-day cytopathic assay in the MT-4 T-lymphoblastoid cell line acutely infected with HIV-1_{IIIB} (Report PC-200-2018). In parallel, the cytotoxicity of LEN was assessed in corresponding uninfected MT-4 cells. LEN had an EC₅₀ value of 0.19nM in MT-4 cells and a selectivity index (50% cytotoxic concentration [CC₅₀]/EC₅₀) of 140,000. In addition, the EC₉₅ value of LEN in MT-4 cells was calculated as 0.23nM from the EC₅₀ value and Hill slope values that were accurately determined from a 40-point dose response curve. Taking into account the human serum shift determined by equilibrium dialysis (AD-200-2020), LEN exhibited a plasma protein binding-adjusted EC₉₅ (paEC₉₅) value of 4nM.

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The antiviral activity of LEN was evaluated in acutely infected human CD4⁺ T-lymphocytes and monocyte-derived macrophages from three independent donors using 7- and 12-day virus production assays, respectively (Report PC-200-2019). In parallel, the cytotoxicity of LEN was determined in these cells. In CD4⁺ T lymphocytes, LEN had a mean EC₅₀ and CC₅₀ values of 0.06 nM and >50μM, respectively, with a selectivity index of >833,330. LEN had mean EC₅₀ and CC₅₀ values of 0.03nM and >50μM, respectively, in monocyte-derived macrophages with a selectivity index of >1,670,000. In comparison, the EC₅₀ values of LEN in primary CD4⁺ T cells and macrophages were lower compared to control INSTI dolutegravir and PI atazanavir.

When LEN was tested against HIV-1_{NL4-3} in CEM-NKR CCR5⁺Luc⁺ T-lymphoblastoid cells infected with a wide range of multiplicities of infection (MOIs; 0.01 to 1.25), there was antiviral activity at all tested MOIs (Report PC-200-2031). EC₅₀ values increased as MOI increased, with EC₅₀ values ranging from 0.028 to 0.455nM (16-fold increase) across the 125-fold range.

Antiviral Activity Against Clinical Isolates

The antiretroviral activity of LEN was tested against 23 clinical isolates of HIV-1 and two isolates of HIV-2 in freshly isolated human PBMCs (Report PC-200-2020). LEN showed antiviral activity against all tested HIV-1 clinical isolates representing all major subtypes with mean and median EC₅₀ values of 0.05 and 0.04nM, respectively, and a range of EC₅₀ values between 0.02 and 0.16nM ([Table 124](#)). The range of means for subtype B isolates was 0.03 to 0.08nM and median was 0.04nM. LEN had lower activity against the two tested isolates of HIV-2 with EC₅₀ values of 0.57 and 1.02nM, which is 4- to 50-fold.

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Table 124. Antiviral Activity of LEN (GS-6207) Against HIV Clinical Isolates

Virus Isolate	HIV-1 Subtype	EC ₅₀ (nM)		
		GS-6207	DTG	AZT
HIV-1 92UG031	A	0.04	0.63	51.6
HIV-1 92UG037	A	0.07	0.47	21.7
HIV-1 89BZ_167	B	0.08	1.18	10.1
HIV-1 90US_873	B	0.04	0.82	13.2
HIV-1 91US001	B	0.03	0.53	20.3
HIV-1 91US004	B	0.04	0.40	19.7
HIV-1 96TH_NP1538	B	0.05	0.40	4.10
HIV-1 BaL	B	0.04	0.40	43.2
HIV-1 JR-CSF	B	0.04	0.41	4.53
HIV-1 YU-2	B	0.04	ND	1.32
HIV-1 92BR025	C	0.05	0.91	16.9
HIV-1 98US_MSC5016	C	0.10	0.77	37.8
HIV-1 92UG001	D	0.02	1.09	7.29
HIV-1 98UG_57128	D	0.03	0.70	6.61
HIV-1 CMU02	E	0.05	0.81	8.31
HIV-1 CMU08	E	0.05	0.96	34.1
HIV-1 93BR020	F	0.05	0.38	25.1
HIV-1 JV1083	G	0.16	0.93	20.5
HIV-1 YBF30	Group N	0.02	0.54	8.96
HIV-1 BCF01	Group O	0.04	0.64	10.5
HIV-1 90TH_CM235	CRF01_AE	0.04	1.02	10.7
HIV-1 01CM008BBY	CRF02_AG	0.05	1.04	8.21
HIV-1 91DJ263	CRF02_AG	0.04	0.45	34.9
HIV-2 CBL-20	N/A	0.57	0.36	14.3
HIV-2 CDC310319	N/A	1.02	1.81	28.8

a EC₅₀ values represent the mean of triplicate runs; ND = not determined

Source: Report PC-200-2020, page 10.

Abbreviations: AZT, zidovudine; DTG, dolutegravir; EC₅₀, 50% effective concentration; HIV, human immunodeficiency virus; LEN, lenacapavir; N/A, not applicable

In a separate study testing the activity of LEN against 40 clinical HIV-1 isolates of diverse subtypes using the PhenoSense Gag-Pro Antiviral Assay, there were no notable differences observed in the mean LEN EC₅₀ values for any of the HIV-1 subtypes evaluated (Report PC-200-2041). The range of means across subtypes was 0.166 to 0.297nM, with less than two-fold difference in activity across subtypes (Table 125). The study above employed a different test system and assay endpoint (PBMCs infected by primary isolates with RT endpoint) from the one utilized in this study. Thus, the Applicant states that direct comparisons of antiviral activity values cannot be made between the studies. However, in both studies, LEN demonstrated antiviral activity within a narrow range of EC₅₀ values across the HIV-1 subtypes tested.

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Table 125. LEN Antiviral Activity Across HIV-1 Subtypes

HIV-1 Subtype	A	A1	AE	AG	B	BF	C	D	G	H
Geometric Mean IC ₅₀ , nM ^a	0.252	0.266	0.234	0.274	0.228	0.194	0.273	0.166	0.297	0.201
n	2	2	6	3	12	1	5	4	3	2

a Geometric mean IC₅₀ values include wild-type and drug-resistant clinical isolates

Source: Report PC-200-2041, page 8.

Abbreviations: HIV, human immunodeficiency virus; IC₅₀, 50% inhibitory concentration; LEN, lenacapavir

Activity of LEN Against HIV Capsid Protein Polymorphisms (Report PC-200-2032)

A publicly available source of 10,512 capsid population sequences representing eight major HIV-1 subtypes was used to evaluate the conservation of the capsid protein and the LEN binding site ([Table 126](#)). Capsid consensus sequences across the eight subtypes were found to have >91% sequence identity across the whole protein sequence. Of the 24 amino acid residues within the LEN binding site defined by x-ray crystallography, 20 residues (83%) had a sequence conservation between 94% and 100% across all 8 subtypes, including all 7 capsid amino acid positions associated with cell culture resistance to LEN (L56 [100%], M66 [100%], Q67 [99% for CRF01_AE, 100% for other subtypes], K70 [100%], N74 [100%], A105 [100%], and T107 [94-99%]). The CRF01_AE subtype contained a 1% prevalence of the Q67H substitution that confers ~6-fold resistance to LEN. None of the T107 substitutions identified was the T107N variant that is associated with reduced susceptibility to LEN. The T107N substitution conferring 4-fold resistance to LEN was identified in a single patient and was the only established LEN resistance-associated substitution detected in capsid by deep sequencing among the analyzed patient isolates.

The remaining four binding site residues (S41, T54, Y169, and Q179) were mutated in >5% of patient isolates (n=104) and three of them (S41, T54, and Y169) were variable in >25% of patient isolates in at least one major HIV-1 subtype. The impact of these identified substitutions on the susceptibility of isolates to LEN is assessed below.

Collectively, these data indicate a high degree of sequence conservation within the LEN binding site in HIV-1 capsid, which suggests a low-risk of capsid binding site polymorphisms having an impact on LEN antiviral efficacy.

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Table 126. LEN (GS-6207) Binding Site Residue Conservation in HIV-1 Capsid by Population Sequencing

Location in Capsid Hexamer ^a	Condon Position ^a	GS-6207 Binding Site Residue Conservation (%) ^b							
		B	AI	C	D	F1	G	01_AE	02_AG
Monomer 1, NTD	50	Q(96) H(1) S/T(1,1)	Q(92) G(3) H/S(2,2) Y(1)	Q(90) S/T(4,2) G/E(1,1) A/H(1,1)	Q(88) S/G(5,3) A/T(1,1)	Q(99) T(1)	Q(95) S(2) G/H(1,1)	Q	Q(96) G/T(1,1)
	53	N	N	N	N	N	N	N	N
	54	T(99)	T(7) M(88) V(3) L/S(1,1)	T(94) S(5)	T(92) S(4) L/V(2,1)	T(98) S/P(1,1)	T(97) L(2) S/V(1,1)	T(1) M(98) S(1)	T(0) M(100)
	56	L	L	L	L	L	L	L	L
	57	N	N	N	N(98) H(1)	N	N	N	N
	63	Q	Q	Q	Q	Q	Q	Q	Q
	66	M	M	M	M	M	M	M	M
	67	Q	Q	Q	Q	Q	Q	Q(99) H(1)	Q
	69	L	L	L	L	L	L	L	L
	70	K	K	K	K	K	K	K	K
	73	I	I	I	I	I	I	I	I
	74	N	N	N	N	N	N	N	N
	105	A	A	A	A	A	A	A	A
	106	G	G	G	G	G	G	G	G
	107	T(99) S(1)	T(99) A(1)	T(98) S(1)	T(99)	T(96) S/A(3,1)	T(94) S/A(3,3)	T(99) S(1)	T(98) V(2)
	130	Y	Y	Y	Y	Y	Y	Y	Y
Monomer 2, NTD	37	I	I	I	I	I	I	I	I
	38	P	P	P	P	P	P	P	P
	41	S(74) T(21) A(5)	S(92) T(7) L(1)	S(4) T(95)	S(68) T(28) A/I(2,1)	S(94) T(3) A/V(2,1)	S(53) T(46) V(1)	S(98) T(2)	S(63) T(37)
Monomer 2, CTD	169	Y(99) F(1)	Y(1) F(99)	Y(0) F(100)	Y	Y(1) F(99)	Y(0) F(100)	Y(98) F(2)	Y(0) F(100)
	172	L	L	L	L	L(99) V(1)	L	L	L
	173	R	R	R	R	R	R	R	R
	179	Q	Q	Q	Q(98) T(1)	Q	Q(99) T(1)	Q	Q
	182	K	K	K	K(99)	K	K	K(99)	K

^a Capsid residues within proximity of GS-6207 molecule based on co-crystal x-ray structure of GS-6207 bound to capsid cross-linked hexamer (PC-200-2022). Capsid codon positions are colored red if a substitution is associated with >3-fold resistance to GS-6207 (PC-200-2026). NTD-1, NTD-2, and CTD-2 refer to domains from 2 adjacent capsid monomers.

^b Capsid amino acid positions are colored green if conservation > 95%, yellow if conservation > 75% to ≤ 95%, and orange if conservation ≤ 75%. Residues without a percent conservation noted indicate complete conservation. Percentages do not always add up to 100% due to low level variants with <1% prevalence. GS-6207 resistant Q67H variant is colored red.

Source: Report PC-200-2032, page 10.

Abbreviations: CTD, C-terminal domain; HIV, human immunodeficiency virus; LEN, lenacapavir; NTD, N-terminal domain

The antiviral activity of LEN was measured against a panel of 36 site-directed HIV-1_{NL4.3} capsid mutants in MT-4 T-cells (Table 127). These capsid variants were comprised predominantly of LEN binding site polymorphisms (n=30) previously identified by population-level and higher

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resolution next generation sequence analyses above. The 30 capsid polymorphisms spanned eight codons (S41, Q50, T54, N57, T107, Y169, L172, and N183) located within the LEN binding site as defined by x-ray cocrystallography, with asparagine 57 and, to a lesser extent, asparagine 183 providing important hydrogen bond interactions with LEN.

Ninety-three percent of the capsid polymorphisms (28/30) remained fully susceptible to LEN antiviral activity (0.7- to 2.4-fold change in susceptibility) (Report PC-200-2038). The remaining two capsid polymorphisms, Q50E and N57H, conferred low-level (3-fold) and high-level (>5,000-fold) resistance, respectively, to LEN relative to wild-type virus while remaining fully susceptible to efavirenz and bictegravir. The Q50E and N57H variants, neither of which is selected for in cell culture with LEN, showed reduced infectivity in MT-4 cells (20% and 30% of wild-type, respectively) and were detected in HIV-1 at only 1% prevalence exclusively in either subtype C (Q50E) or subtype D (N57H) isolates.

Additionally, LEN was tested against six resistance-associated substitutions (S41A, K70R, H87P, L111I, V165I, and L172I) previously identified by cell culture selection with the Pfizer capsid inhibitor PF74 or its close analogue PF-3759857. These capsid inhibitors bind a site on capsid that partially overlaps with that of LEN. LEN retained full activity against five of the PF74-related resistance substitutions with susceptibility ranging from 1.1- to 1.6-fold. One substitution (V165I) could not be evaluated for potential LEN resistance due to a significant loss of HIV-1 infectivity (0.2% of wild-type).

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Table 127. Antiviral Susceptibility of Capsid Site-Directed HIV-1 Mutants and Polymorphisms to LEN in Cell Culture

HIV-1 Capsid Genotype	Infectivity (% of WT) ^a	Single-Cycle Antiviral Activity in MT-4 Cells					
		EFV		BIC		GS-6207	
		EC ₅₀ (nM) ^b	Fold-Change ^c	EC ₅₀ (nM) ^b	Fold-Change ^c	EC ₅₀ (nM) ^b	Fold-Change ^c
WT	100	0.69 ± 0.14	1.0	1.3 ± 0.1	1.1	0.05 ± 0.01	1.0
S41A ^d	90 ± 4	0.68 ± 0.19	0.9	1.3 ± 0.1	1.1	0.06 ± 0.01	1.2
S41I	41 ± 1	0.65 ± 0.12	0.9	1.5 ± 0.2	1.3	0.07 ± 0.01	1.3
S41L	32 ± 1	0.70 ± 0.19	1.0	1.5 ± 0.1	1.3	0.08 ± 0.01	1.5
S41T	54 ± 3	0.85 ± 0.23	1.2	1.5 ± 0.1	1.3	0.08 ± 0.01	1.5
S41V	84 ± 7	0.65 ± 0.16	0.9	1.3 ± 0.2	1.1	0.06 ± 0.01	1.1
Q50A	95 ± 5	0.70 ± 0.14	1.0	1.3 ± 0.1	1.1	0.07 ± 0.01	1.4
Q50E	20 ± 1	0.57 ± 0.05	0.8	1.8 ± 0.1	1.5	0.16 ± 0.01	3.0
Q50G	72 ± 6	0.65 ± 0.07	0.9	1.1 ± 0.1	0.9	0.06 ± 0.01	1.2
Q50H	54 ± 3	0.58 ± 0.11	0.8	0.6 ± 0.0	0.6	0.05 ± 0.01	1.0
Q50S	240 ± 23	0.65 ± 0.11	0.9	1.1 ± 0.1	0.9	0.06 ± 0.01	1.1
Q50T	206 ± 9	0.67 ± 0.13	0.9	1.2 ± 0.2	1.1	0.05 ± 0.01	1.0
Q50Y	7 ± 1	0.49 ± 0.11	0.7	0.6 ± 0.0	0.5	0.12 ± 0.01	2.3
T54L	19 ± 1	0.80 ± 0.13	1.1	1.3 ± 0.1	1.1	0.05 ± 0.01	1.1
T54M	50 ± 1	0.68 ± 0.12	0.9	1.6 ± 0.1	1.4	0.07 ± 0.01	1.3
T54S	9 ± 1	1.04 ± 0.15	1.4	1.1 ± 0.1	0.9	0.13 ± 0.02	2.4
T54V	51 ± 2	0.79 ± 0.17	1.1	1.2 ± 0.2	1.0	0.07 ± 0.01	1.4
N57H	30 ± 1	1.00 ± 0.16	1.4	1.0 ± 0.2	0.8	>250	>5,000
K70R ^e	12 ± 1	0.72 ± 0.09	1.0	1.0 ± 0.0	0.8	0.07 ± 0.01	1.4
H87P ^e	243 ± 17	0.80 ± 0.08	1.1	1.1 ± 0.0	1.0	0.05 ± 0.01	1.1
T107A	287 ± 9	0.80 ± 0.04	1.1	1.1 ± 0.0	1.0	0.04 ± 0.01	0.7
T107S	281 ± 19	0.79 ± 0.13	1.1	1.1 ± 0.1	1.0	0.07 ± 0.01	1.3
T107V	67 ± 6	0.85 ± 0.06	1.2	1.1 ± 0.1	1.0	0.05 ± 0.01	1.0
L111I ^e	29 ± 1	0.59 ± 0.04	0.8	1.4 ± 0.1	1.2	0.08 ± 0.01	1.5
V165I ^d	0.2 ± 0.1	ND ^f	ND ^f	ND ^f	ND ^f	ND ^f	ND ^f
Y169F	69 ± 6	1.20 ± 0.14	1.7	0.9 ± 0.0	0.8	0.04 ± 0.01	0.7
L172I ^d	206 ± 15	0.67 ± 0.06	0.9	1.1 ± 0.1	0.9	0.08 ± 0.01	1.6
L172V	8 ± 1	0.70 ± 0.04	1.0	1.1 ± 0.1	1.0	0.11 ± 0.01	2.2
Q179T	87 ± 5	0.69 ± 0.06	1.0	1.1 ± 0.1	1.0	0.05 ± 0.01	0.9

HIV-1 Capsid Genotype	Infectivity (% of WT) ^a	Single-Cycle Antiviral Activity in MT-4 Cells					
		EFV		BIC		GS-6207	
		EC ₅₀ (nM) ^b	Fold- Change ^c	EC ₅₀ (nM) ^b	Fold- Change ^c	EC ₅₀ (nM) ^b	Fold- Change ^c
K182R	43 ± 4	0.54 ± 0.06	0.8	0.9 ± 0.0	0.8	0.08 ± 0.01	1.5
N183A	173 ± 10	0.76 ± 0.09	1.1	1.1 ± 0.2	0.9	0.04 ± 0.01	0.8
N183G	160 ± 7	0.75 ± 0.07	1.0	1.1 ± 0.1	1.0	0.06 ± 0.01	1.2
N183H	194 ± 7	0.67 ± 0.05	0.9	1.2 ± 0.1	1.0	0.04 ± 0.01	0.8
N183Q	159 ± 1	0.70 ± 0.01	1.0	1.0 ± 0.0	0.9	0.03 ± 0.01	0.6
N183S	94 ± 6	0.76 ± 0.03	1.0	1.1 ± 0.1	1.0	0.04 ± 0.01	0.7
N183T	79 ± 2	0.71 ± 0.01	1.0	1.0 ± 0.0	0.9	0.03 ± 0.01	0.7
N183V	15 ± 3	0.58 ± 0.06	0.8	0.9 ± 0.1	0.8	0.04 ± 0.01	0.7

a Infectivity values (mean ± SD) were obtained from a single experiment performed in duplicate.

b EC₅₀ values (mean ± SD) were obtained from 3 independent experiments performed in triplicate.

c Fold-Change, ratio of mutant HIV EC₅₀/ WT HIV EC₅₀.

d The S41A, V165I and L172I mutations are derived from a four capsid mutant variant (4Mut) previously identified by *in vitro* selection with the capsid inhibitor PF74 (Zhou 2015). The 4th mutation not shown here (Q67H) is a major GS-6207 RAM and confers low-level (6.3-fold) resistance to GS-6207 (PC-200-2026).

e The K70R, H87P and L111I mutants are derived from a five capsid mutant variant (5Mut) previously identified by *in vitro* selection with the PF74-related capsid compound PF-3759857 (Blair 2010), (Shi 2015). The remaining two observed mutations were Q67H and T107N, the latter of which alone is also a major GS-6207 RAM and alone confers low-level (4.0-fold) resistance to GS-6207 and high-level (62-fold) resistance to GS-6207 in combination with Q67H (PC-200-2026).

e ND, not determined due to poor infectivity of the V165I capsid HIV-1 mutant.

Source: Report PC-200-2038, pages 9 and 10.

Abbreviations: BIC, bictegravir; EC₅₀, 50% effective concentration; EFV, efavirenz; HIV, human immunodeficiency virus; LEN, lenacapavir; ND, not determined; RAM, resistance-associated mutation; SD, standard deviation; WT, wild type

Inhibition of Early and Late HIV-1 Replication (Report PC-200-2021)

The antiviral activity of LEN was evaluated in the MT-2 T-lymphoblastoid cell line using a single-cycle reporter assay. These assays were set up such that the compound was present selectively at the early stage, late stage, or during the full course of a single round of HIV infection. LEN had a mean EC₅₀ value of 0.025nM against a single round infection of MT-2 cells with wild-type HIV-1 reporter virus (Table 128). In contrast, LEN had decreased antiviral activity against the capsid M66I resistant HIV-1 variant during a single round infection with an EC₅₀ value >50nM. LEN retained full antiviral efficacy when the presence of the compound was selectively restricted to the target cell infection phase with a mean early stage EC₅₀ value of 0.023nM, indicating LEN predominately targets at least one essential capsid-mediated step involved in the early stages of HIV replication. However, even when restricted to the late stage in virus producer cells, LEN had a mean late stage EC₅₀ value of 0.439nM with no cytotoxicity in the HEK293T producer cells up to the highest concentration tested (CC₅₀ value >50nM). Thus, LEN also targets with ~18-fold reduced activity late-stage capsid-mediated HIV replication functions. As controls, the INSTI raltegravir and the PI atazanavir showed a much more restricted antiviral effect specific only to the early and late stages of HIV replication, respectively. Finally, LEN was capable of irreversibly inactivating fully infectious cell-free HIV-1 with a mean EC₅₀ value of 25nM. Collectively, these data show that LEN has antiviral activity against both early- and late-stage essential processes in the HIV-1 replication cycle.

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Table 128. Antiviral Activity of LEN (GS-6207) at Distinct Stages of HIV-1 Replication Cycle in MT-2 Cells

Compound	EC ₅₀ (nM) ^{a,b}					CC ₅₀ (nM) ^{a,b}
	Complete Replication Cycle (Wild-type)	Target Cell Infection (Early)	Virus Production & Maturation (Late)	Complete Replication Cycle (CA_M66I)	Inactivation of Cell-Free HIV-1 (Virucidal) ^c	Cytotoxicity in HEK293T Producer Cells
GS-6207	0.025 ± 0.003	0.023 ± 0.008	0.439 ± 0.181	> 50	24.6	> 50
RAL	1.7 ± 0.1	1.9 ± 0.8	> 1,000	1.8 ± 0.4	> 5,000	> 1,000
ATV	2.0 ± 1.0	> 1,000	2.3 ± 0.9	4.1 ± 0.8	NT	> 1,000
PD-404,182	NT	NT	NT	NT	< 5,000	NT
NVP	NT	NT	NT	NT	> 5,000	NT

a EC₅₀ and CC₅₀ values represent mean ± SD obtained from 3 independent experiments performed in triplicate.

b NT, not tested

c Virucidal EC₅₀ values represent mean obtained from 2 independent experiments performed in triplicate. Assay positive (PD-404,182) and negative (NVP, RAL) control compounds were each tested at 5 μM and showed an average infectivity of 0.7%, 95% and 87% relative to the mock-treated controls after removing compound by a 20,000-fold sample dilution prior to MT-2 cell infection.

Source: Report PC-200-2021, page 10.

Abbreviations: ATV, atazanavir; CC₅₀, 50% cytotoxic concentration; EC₅₀, 50% effective concentration; HEK, human embryonic kidney; HIV, human immunodeficiency virus; LEN, lenacapavir; NVP, nevirapine; RAL, raltegravir; SD, standard deviation

Antiviral Activity of LEN Against Non-HIV Viruses

LEN was tested against hepatitis B virus (HBV), hepatitis C virus, human rhinovirus, and respiratory syncytial virus in cell-based assays. LEN did not display selectivity in cell culture antiviral activity against HCV or HRV up to the highest concentration tested (44 to 50 μM) (Table 129). LEN did demonstrate antiviral activity against HBV and respiratory syncytial virus at low micromolar concentrations, with EC₅₀ values and corresponding CC₅₀/EC₅₀ ratios of 1.5 μM and >34, and 8.2 μM and >6.1, respectively. These data indicate that LEN is approximately 25,000-fold more active against HIV as compared to HBV. However, a proper clinically active therapy against HBV should be used in HIV/HBV coinfecting patients to maintain the HBV suppression.

Table 129. Antiviral Activity Against a Panel of Non-HIV Viruses

Virus	Positive Control ^a		GS-6207 ^a		Puromycin ^a
	Compound	EC ₅₀ (nM)	EC ₅₀ (nM)	CC ₅₀ (nM)	CC ₅₀ (nM)
HCV 1b replicon	ITMN-191	1.0 ± 0.5	> 29,000	> 44,400	0.43 ± 0.10
HCV 2a replicon	ITMN-191	20.9 ± 3.1	> 31,600	> 44,400	0.56 ± 0.11
HBV	Lamivudine	34.9 ± 18.7	1,462 ± 256	> 50,000	> 4,360
HRV-16	Rupintrivir	68.1 ± 22.4	> 50,000	> 50,000	0.94 ± 0.09
RSV A2	YM-53403	250 ± 24	8,199 ± 3,313	> 50,000	0.44 ± 0.02

a EC₅₀ and CC₅₀ values (mean ± SD) obtained from at least 3 independent experiments performed in quadruplicate.

Source: Report PC-200-2029, page 11.

Abbreviations: CC₅₀, 50% cytotoxic concentration; EC₅₀, 50% effective concentration; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus

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Cytotoxicity

The cytotoxicity of LEN was assessed in parallel uninfected MT-4 cultures. LEN showed low cytotoxicity in MT-4 cells with CC_{50} values of 26,600nM, yielding a selectivity index of 140,000 (Report PC-200-2018).

LEN showed mean CC_{50} values of $>50\mu\text{M}$ in both human $CD4^+$ T-lymphocytes and monocyte-derived macrophages giving selectivity indices of $>833,330$ (Report PC-200-2019). LEN cytotoxicity was measured in normal resting and activated human PBMCs, demonstrating a lack of cytotoxicity, with CC_{50} values of >44 and $>50\mu\text{M}$, respectively.

LEN was tested for cytotoxicity in a panel of four human cell lines nonpermissive to HIV-1 infection, including two hepatoma cell lines (Huh7 and HepG2), a prostate carcinoma cell line (PC-3) and a normal embryonic lung fibroblast line (MRC-5) (Report PC-200-2028). The HepG2 and PC-3 cells used in this study were galactose-adapted for enhanced sensitivity to mitochondria toxicity (Marroquin et al. 2007). LEN did not display any significant cytotoxicity against the four tested cell lines. CC_{50} values for LEN in the tested cell types were $>44\mu\text{M}$. Relative to its EC_{50} value for anti-HIV-1 activity in primary human $CD4^+$ T-lymphocytes (EC_{50} 0.06nM), a selectivity index of $>730,000$ was achieved for LEN in all cell types tested. Puromycin was used as a positive control and showed CC_{50} values of 0.3 to $1.0\mu\text{M}$.

In addition to these cell lines, the cytotoxicity of LEN was tested in primary human hepatocytes from three independent donors. LEN yielded CC_{50} values $>50\mu\text{M}$ in primary hepatocytes following a 5-day incubation with the tested compounds, while CC_{50} values for the positive control puromycin ranged from 0.93 to $2.10\mu\text{M}$ in these cells.

Antiviral Combination Activity in Cell Culture

The anti-HIV-1 activity of LEN was examined in combination with representative inhibitors from four major classes of antiretrovirals comprising the INSTI dolutegravir, the NNRTI efavirenz, the nucleoside reverse transcriptase inhibitor (NRTI) tenofovir alafenamide, and the HIV protease inhibitor (PI) darunavir. Pair-wise combinations of LEN with dolutegravir, efavirenz, tenofovir alafenamide, or darunavir showed synergistic anti-HIV activity when tested using HIV-1_{IIIIB}-infected MT-2 cells ([Table 130](#)). No antagonistic antiviral interaction was observed between LEN and any of the clinically approved anti-HIV drugs tested.

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Table 130. Anti-HIV-1 Cell Culture Activity of LEN in Combination With Selected Antiretrovirals

Drug Combination ^a	Synergy/Antagonism Volume ($\mu\text{M}^2\%$) ^b		Combination Effect
	Type	Mean $\pm$ SD	
GS-6207 + TAF	Synergy	87 $\pm$ 32	Moderately Synergistic
	Antagonism	-8 $\pm$ 7	
GS-6207 + EFV	Synergy	101 $\pm$ 40	Highly Synergistic
	Antagonism	-8 $\pm$ 8	
GS-6207 + DTG	Synergy	116 $\pm$ 13	Highly Synergistic
	Antagonism	-8 $\pm$ 7	
GS-6207 + DRV	Synergy	119 $\pm$ 39	Highly Synergistic
	Antagonism	-3 $\pm$ 3	
GS-6207 + GS-6207	Synergy	18 $\pm$ 8	Additive
	Antagonism	-16 $\pm$ 6	
TAF + EVG	Synergy	164 $\pm$ 24	Highly Synergistic
	Antagonism	-3 $\pm$ 3	
RBV + d4T	Synergy	0 $\pm$ 0	Highly Antagonistic
	Antagonism	-398 $\pm$ 23	

a TAF = tenofovir alafenamide, EFV = efavirenz, DTG = dolutegravir, DRV = darunavir, EVG = elvitegravir, RBV = ribavirin, d4T = stavudine

b The synergy/antagonism volumes represent the mean ($\pm$ SD) of 3 independent experiments performed in triplicate

Source: Report PC-200-2030, page 8.

Abbreviations: HIV, human immunodeficiency virus; LEN, lenacapavir; SD, standard deviation

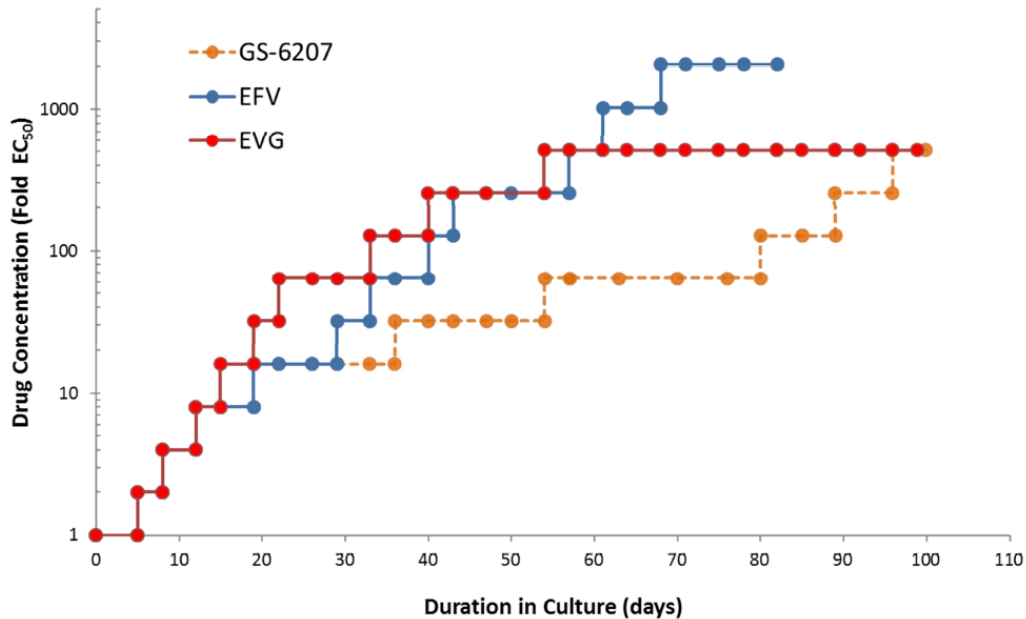
Resistance Selection

Selection for HIV-1 variants resistant to LEN was performed in cell culture using two approaches (Report PC-200-2025). In the first approach, resistance selection using an increasing concentration method was performed with LEN in MT-2 cells infected with clonal HIV-1_{HXB2D}. Parallel resistance selections were performed in the presence of efavirenz and elvitegravir as comparative controls and in the absence of drug. The kinetics of resistance emergence was similar among all three compounds early in the selection, but then LEN progressed more slowly relative to efavirenz and elvitegravir as drug concentrations were increased ([Figure 45](#)).

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Figure 45. Dose Escalation Resistance Selections With LEN, Efavirenz (EFV), and Elvitegravir (EVG) in MT-2 Cells



Resistance selections were initiated at a drug concentration equal to 1x the EC₅₀ determined for each drug (i.e., EC₅₀ = 0.070 nM, 0.9 nM and 1.0 nM for GS-6207, EFV and EVG, respectively). Whenever extensive CPE was observed in the cell culture, the viral supernatant was harvested and a 100 µL aliquot was used to infect fresh MT-2 cells in the presence of 1x and 2x the previously tested drug concentration.

Source: Report PC-200-2025, page 13.

Abbreviations: CPE, cytopathic effect; EC₅₀, 50% effective concentration; LEN, lenacapavir

At lower LEN drug pressure (8- to 16-fold the EC₅₀), LEN selected for virus encoding the capsid substitution N74D ([Table 131](#)). At higher drug concentrations, LEN selected for virus encoding the dual capsid mutant N74D+T107N (passage 6), which was immediately replaced in the next passage by another dual capsid variant Q67H+N74D, which persisted to the end of selection after 103 days in culture at LEN concentrations 512-fold the EC₅₀. These substitutions are located in the LEN binding site defined by X-ray crystallography. Clonal sequencing results confirmed that the Q67H and T107N substitutions were each individually linked to the N74D substitution on the same viral genome. Additional sequencing of the matrix and SP1 regions adjacent to the capsid gene, as well as the viral protease, reverse transcriptase, and integrase coding regions, showed no additional genotypic changes relative to the HXB2D parental sequence.

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Table 131. Genotypic Profile of LEN Resistant Selected Passages

Selected Virus ^a	Drug Concentration (Fold EC ₅₀)	Mutation(s) ^b
No Drug P8	-	None
GS-6207 P3	4	None
GS-6207 P4	8	N74D
GS-6207 P5	16	N74D
GS-6207 P6	32	N74D, T107N/T
GS-6207 P7	64	Q67H, N74D
GS-6207 P8	128	Q67H, N74D
GS-6207 P9	256	Q67H, N74D
GS-6207 P10	512	Q67H, N74D

Source: Report PC-200-2025, page 15.

^a Viral passage numbers are indicated as: P1, P2, P3...etc.

^b Relative to the HIV-1 HXB2D consensus sequence.

Abbreviations: EC₅₀, 50% effective concentration; HIV, human immunodeficiency virus; LEN, lenacapavir

The passage 4 (P4) virus selected with 0.56nM LEN (8× EC₅₀) and encoding the capsid N74D substitution showed 5.5-fold reduction in susceptibility to LEN with no change in susceptibility to EFV, dolutegravir, EVG, or atazanavir. Passage (P) 6 virus grown in the presence of 2.24nM LEN (32× EC₅₀) and encoding the capsid N74D+T107N variant had an EC₅₀ 1.79nM at P7 versus EC₅₀ 1.42nM at P4 and showed no cross resistance. Passage 7 virus selected in the presence of 4.48nM LEN (64× EC₅₀) and encoding the capsid N74D+Q67H variant showed 43-fold resistance to LEN. A peak LEN resistance of >150-fold was observed with P9 and P10 virus isolates.

In the second approach, resistance selection was conducted in MT-2 cells infected with HIV-1_{HXB2D} using a 10-fold higher MOI and several fixed concentrations of LEN (0.92, 1.9, 3.7, 5.5, and 9.2nM) over a 32-day selection. These test concentrations correspond to tissue culture equivalent (IQs of 4, 8, 16, 24, and 40, respectively, with an IQ of 1 defined as a concentration corresponding to the EC₉₅ for LEN (0.23nM). The rate and frequency of viral breakthrough for fixed LEN concentrations was compared to that of emtricitabine, efavirenz, rilpivirine, and atazanavir, with each used at a fixed drug concentration equal to their respective tissue culture equivalent (i.e. adjusted for protein binding) of the clinical plasma trough concentration (C_{min}). At a fixed concentration of 0.92nM LEN (IQ of 4), a replicating virus emerged in three of eight independent infected samples tested and each isolate encoded the capsid N74D substitution identified at low LEN concentrations. No breakthrough virus emerged at any of the higher concentrations of LEN tested here. In comparison, parallel selections with emtricitabine and rilpivirine resulted in rapid emergence of the M184I/V variants in seven of eight samples and a breakthrough of the Y181I RT variant in one of eight infected samples tested, respectively, while selections with efavirenz, atazanavir and dolutegravir each did not lead to any breakthrough of drug-resistant HIV-1 variants.

Viral breakthrough selections were also conducted over a period of 35 days using a similar set of LEN and control test concentrations in human PBMCs infected separately with six different patient-derived isolates of HIV-1. Four weeks into these selections, an aliquot (1/10th) of the cell-free culture supernatants was transferred onto fresh target cells and cultured for another

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7 days to enrich for HIV-1 breakthrough variants that retained significant infectivity and replication capacity in the presence of each tested drug. Day 35 cell-free culture supernatants were harvested and analyzed for the presence of breakthrough virus by measuring the presence of virus by p24 enzyme-linked immunosorbent assay and virus infectivity on CEM-NKr CCR5⁺Luc⁺ indicator cells.

Among the six analyzed HIV-1 isolates, dolutegravir was the only compound to completely suppress viral breakthrough. Emtricitabine, rilpivirine and efavirenz each showed some frequency of viral breakthrough in PBMCs against the six tested isolates, with clinically relevant mutant HIV-1 variants emerging. At an IQ of 4, LEN showed a breakthrough better than emtricitabine and comparable to rilpivirine. Within its projected human plasma exposure range (IQ 4 to 8), LEN breakthrough viruses encoded the capsid substitutions L56I, or Q67H±N74S, N74D, or T107N. At IQ 16 and IQ 24 equivalent LEN concentrations, N74D and Q67H single capsid substitutions were less frequently observed and instead, the emergent viruses encoded capsid substitutions L56I, M66I, K70N or M66I+Q67H.

Assessment of Site-Directed Resistance Mutants

The antiviral activity of LEN was tested against 11 site-directed HIV-1 mutants encoding the major p24 domain substitutions identified in the drug selection studies including both single and double capsid mutants (L56I, M66I, Q67H, K70N, N74D, T107N, M66I/Q67H, Q67H/N74D, Q67H/N74S, Q67H/T107N, and N74D/T107N) (Report PC-200-2026). Antiviral activity was tested using both single-cycle and multi-round infection assays performed in the MT-2 and CEM-NKR CCR5⁺Luc⁺ T cell lines, respectively. In the single-cycle infection assay, mutant viruses, Q67H and T107N, conferred 4- to 6.3-fold decreased susceptibility to LEN relative to the wild-type virus; K70N, N74D and Q67H/N74S conferred 22- to 32-fold decreased LEN susceptibility; and L56I and M66I, as well as each of the remaining four double mutant viruses, all conferred 58- to >3,226-fold decreased LEN susceptibility ([Table 132](#)). LEN showed 8.8-fold and 21-fold reduced activity, respectively, against the Q67Y and A105E substitutions previously identified upon drug selection with structurally similar analogs of LEN but not with LEN itself.

In addition to these drug resistant variants, HIV-1 containing the capsid P90A site-directed substitution conferring loss of host cyclophilin A binding to capsid was also studied. This P90A variant remained fully susceptible to inhibition by LEN in MT-2 cells indicating LEN inhibits HIV replication independent of cyclophilin A binding to capsid. The replication kinetics of the major drug resistant capsid variants was investigated in parallel with wild-type virus over a period of 19 days in primary human CD4⁺ T cells and in monocyte-derived macrophages. With the exception of the Q67H substitution, each capsid mutant that was tested displayed severely diminished replication capacity relative to the wild-type virus in both cell types. Moreover, the replicative fitness of these mutants was not significantly improved in the presence of LEN in either cell type.

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Table 132. LEN Antiviral Susceptibility of HIV-1 Capsid SDMs: Single-Cycle Infectivity Assay in MT-2 Cells

HIV-1 Capsid Genotype	Rationale for Each SDM ^a	Single-Cycle Infectivity (% of WT) ^b	Single-Cycle Antiviral Activity in MT-2 Cells ^b			
			GS-6207		EFV	
			EC ₅₀ (nM)	Fold-resistance	EC ₅₀ (nM)	Fold-resistance
WT	-	100	0.031 ± 0.003	-	0.866 ± 0.089	-
L56I	A	8 ± 1	7.40 ± 0.67	239	1.67 ± 0.18	1.9
M66I	A	4 ± 2	> 100	> 3,226	1.36 ± 0.32	1.6
Q67H	A	121 ± 16	0.196 ± 0.028	6.3	0.958 ± 0.019	1.1
Q67Y	C	39 ± 5	0.635 ± 0.040	21	1.03 ± 0.11	1.2
K70N	A	7 ± 1	0.741 ± 0.214	24	1.24 ± 0.07	1.4
N74D	A	50 ± 11	0.682 ± 0.106	22	0.501 ± 0.011	0.6
P90A	B	13 ± 3	0.037 ± 0.001	1.2	0.842 ± 0.015	1.0
A105E	C	9 ± 3	0.272 ± 0.044	8.8	0.639 ± 0.105	0.7
T107N	A	44 ± 4	0.124 ± 0.006	4.0	0.708 ± 0.054	0.8
M66I + Q67H	A	8 ± 2	> 100	> 3,226	1.41 ± 0.06	1.6
Q67H + N74D	A	29 ± 6	34.1 ± 2.6	1,099	0.634 ± 0.134	0.7
Q67H + N74S	A	33 ± 5	0.996 ± 0.176	32	1.36 ± 0.10	1.6
Q67H + T107N	A	41 ± 7	1.91 ± 0.12	62	0.733 ± 0.095	0.9

a A = mutation isolated during *in vitro* selection with GS-6207 (PC-200-2025); B = mutation conferring loss of CypA binding; C = mutation isolated during *in vitro* selection with close analogues of GS-6207 but not with GS-6207 itself.

b Infectivity and EC₅₀ values (mean ± SD) were each measured 3 days post-infection and were obtained from 3 independent experiments performed in triplicate.

Source: PC-200-2026, page 13.

Abbreviations: EC₅₀, 50% effective concentration; EFV, efavirenz; HIV, human immunodeficiency virus; SD, standard deviation; SDM, site-directed mutation; WT, wild type

Phenotypic resistance to the mutant variants was similar between the single-cycle and multi-round replication assays except the magnitude of fold-resistance to LEN appeared to be ~3-fold lower in the multi-round assays relative to the single-cycle assays.

The effect of the major LEN-resistant substitutions on HIV-1 replication capacity was investigated in parallel with WT HIV-1 over a period of 19 days in primary human CD4⁺ T cells and in monocyte-derived macrophages. The Q67H variant displayed 87 to 100% replicative capacity in CD4⁺ T lymphocytes and ~60% in monocyte-derived macrophages through 19 days. The L56I mutant had low replication fitness (3 to 14%) in T lymphocytes but 44 to 57% in macrophages. The other capsid mutants tested displayed diminished replication capacity in one or both of the primary target cells tested, with the N74D and Q67H/N74D showing the most diminished replication fitness (<5%). In general, these mutants were less fit in primary CD4⁺ T cells (0.03 to 28%) than in monocyte-derived macrophages (1.9 to 72%) over the 19 days in culture. The degree of replicative rescue observed in the presence of the LEN compound in both cell types was marginal for all tested mutants.

The antiviral activity of LEN was tested against a panel of HIV-1 capsid variants encoding LEN (or structural analogues of LEN)-associated resistance substitutions using the PhenoSense Gag-

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Pro assay from Monogram Biosciences. Assessment of virus encoding the K70N substitution resulted in assay failure, and drug susceptibility could not be determined. Relative to WT virus, variants containing single or double substitutions conferred reduced susceptibility to LEN (3.8- to >2757-fold and 20- to >2757-fold, respectively) (Table 132). In comparison, mutant viruses were fully susceptible to the PIs atazanavir (fold-change range: 0.9- to 1.5) and darunavir (fold-change range: 0.9- to 1.7), indicating the absence of cross-resistance to PIs in these LEN-resistant mutants. The fold-change values determined in the Gag-Pro assay showed good correlation ($r^2=0.97$) with prior data established for 11 of the SDMs in a single-cycle viral replication assay in the MT-2 cell line above (PC-200-2026).

Cross-Resistance

Against the Four Main ARV Classes

The antiviral activity of LEN was tested in MT-2 cells against a panel of drug-resistant HIV-1 mutant variants. The panel included HIV-1 mutants resistant to INSTIs, NNRTIs, NRTIs, or PIs. (n=18) (Report PC-200-2027). LEN remained fully active against all tested HIV-1 mutant variants (Table 133).

Table 133. Activity of LEN Against INSTI-, NNRTI-, NRTI-, and PI-Resistant HIV-1 Mutants

Antiretroviral Inhibitor Class	Drug-Resistant HIV-1 Mutant ¹	LEN	Positive Control	
		Fold-resistance ²	Compound ³	Fold-resistance ²
NRTI	K65R	0.6	FTC	12.8
	M184V	0.5		>42
	6TAMs	0.4		4.1
NNRTI	K103N	0.3	EFV	14.4
	Y181C	1.7		3.3
	Y188L	0.5		>23
	L100I/K103N	0.5		>23
	K103N/Y181C	0.5		>23
INSTI	Y143R	0.5	RAL	10.2
	E138K/Q148K	0.8	EVG	>53
	G140S/Q148R	0.9		>53
	E92Q/N155H	0.9		>53
	N155H/Q148R	1.3		>53
	M50I/R263K	0.9		5.1
PI	I50V	0.6	DRV	31.8
	I84V/L90M	0.3	ATV	32.9
	I54V/V82S	0.4		32.4
	G48V/V82A/L90M	0.4		15.2

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¹ The antiviral activity of WT HIV-1 and HIV-1 encoding RT mutations (NRTI/NNRTIs), IN mutations (INSTIs), or PR mutations (PIs) was measured. 6TAMs: M41L, D67N, K70R, L210W, T215F, K219Q.

² Mean fold-resistance values (mutant EC₅₀/WT EC₅₀) obtained from 3 independent experiments (Data from m2.6.3, Section 1, PC-200-2027).

■ > 2-fold, ■ > 10-fold, ■ > 50-fold

³ ATV = atazanavir; DRV = darunavir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RAL = raltegravir

Source: 2.6.2 Pharmacology Written Summary, page 19.

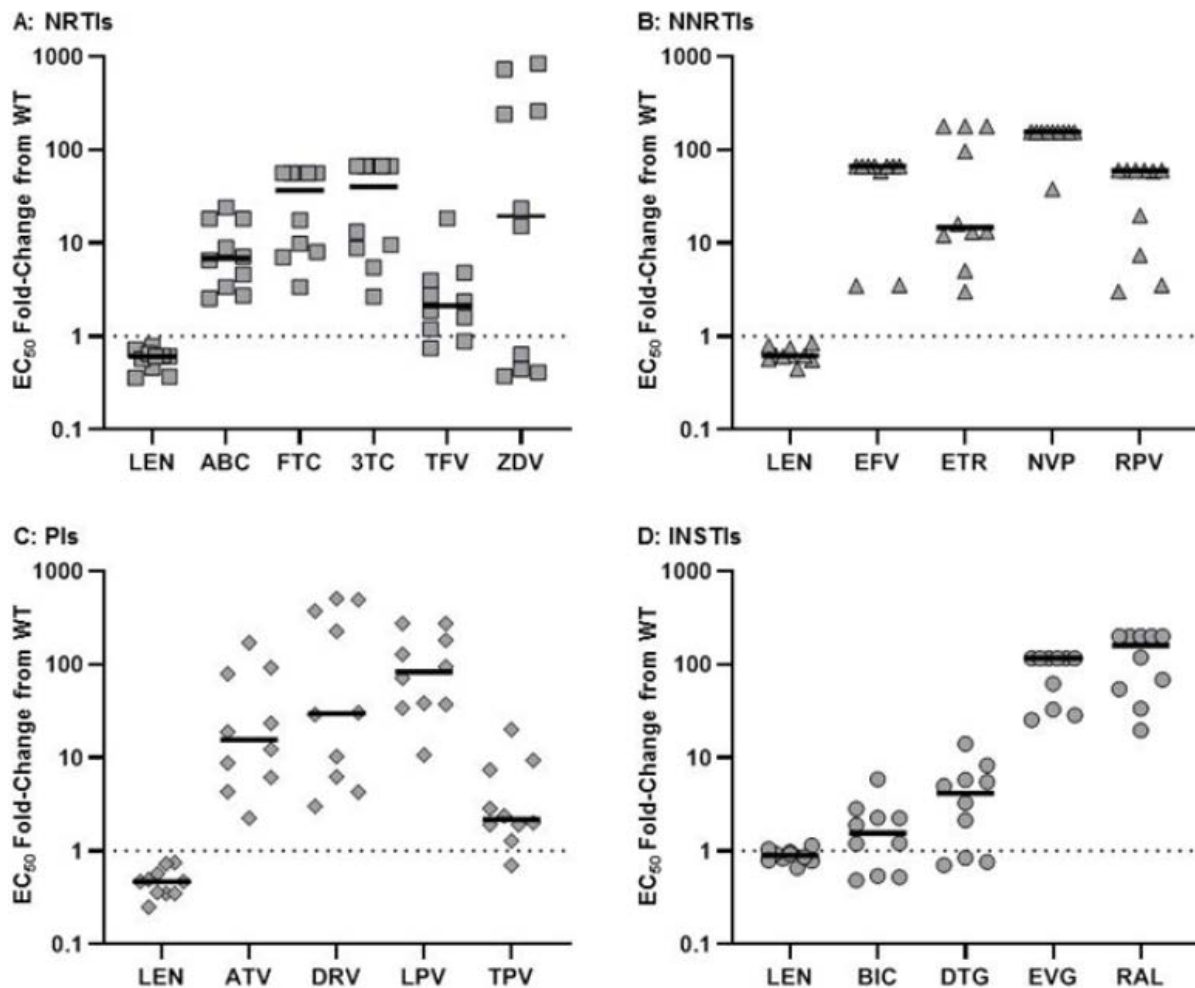
Abbreviations: EC₅₀, 50% effective concentration; HIV, human immunodeficiency virus; INSTI, integrase inhibitor; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RT, reverse transcriptase; TAM, treatment-associated mutation; WT, wild type

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In addition, the antiviral activity of LEN was tested against a panel of 40 patient isolates resistant to at least one of the four main ARV classes (INSTIs, NNRTIs, NRTIs, and PIs) using the PhenoSense GT single-cycle assay or the PhenoSense Integrase single-cycle assay (Monogram Biosciences) (10 in each category) (Report PC-200-2044) (Figure 46). LEN displayed wild-type-like activity against all these patient isolates with a median EC_{50} fold-change of 0.62 (range 0.25 to 1.1), indicating a lack of cross-resistance.

Figure 46. Drug Susceptibilities in HIV-1 Isolates With Resistance Substitutions to the Four Main ARV Drug Classes



Source: Report PC-200-2044, page 7.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; BIC, bictegravir; DRV, darunavir; DTG, dolutegravir; EC_{50} , 50% effective concentration; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FTC, emtricitabine; HIV, human immunodeficiency virus; INSTI, integrase inhibitor; LEN, lenacapavir; LPV, lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; TFV, tenofovir; TPV, tipranavir; ZDV, zidovudine; WT, wild type

Antiviral Activity Against PI-Resistant Clinical Isolates

The antiretroviral activity of the novel HIV capsid inhibitor lenacapavir (LEN; GS-6207) was tested against 40 clinical HIV-1 isolates of diverse subtypes including isolates harboring HIV PI resistance substitutions (Report PC-200-2041). LEN EC_{50} values against tested wild-type isolates ranged from 0.15 to 0.36nM, with a geometric mean of 0.24nM. In comparison, the geometric

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mean EC₅₀ values for the HIV PIs atazanavir, darunavir, and lopinavir against the same tested isolates were 7.9nM (range 2.47 to 15), 0.95nM (range 0.21 to 2.7nM), and 11nM (range 2.60 to 35nM), respectively. Additionally, three PI-resistant isolates were analyzed (Isolate 20-141494: L10V, I15V, K20R, M36I, R41R/K, M46I, I54V, K55K/R, R57K, I62V, L63P, A71V, L76V, V82I/T, I93L; Isolate 20-141498: L10I, T12N, K14R, L24I, M46I, I54V, L63P, I64V, V82A; Isolate 20-141517: L10I, V11V/I, I13V, I15V, K20R, V32I, L33F, E35D, M36I, N37D, F53L, D60E, L63P, H69Q, A71V, V82A, I84V, L89F, L90M, I93L). There was no change in susceptibility to LEN for the three PI-resistant isolates compared to wild-type isolates. However, PIs atazanavir, darunavir, and LPV exhibited 3.4- to 16.8-fold reduced susceptibility for viruses containing PI resistance substitutions relative to wild-type, as expected.

Antiviral Activity Against Treatment-Experienced and -Naïve Patient Isolates

The antiviral activity of LEN was tested against a panel of treatment-experienced and treatment-naïve HIV-1 patient isolates that contained naturally occurring gag polymorphisms. Fifty-one patient-derived isolates comprising 36 treatment-experienced (TE) and 15 treatment-naïve (TN) were cloned into pXXLAI, and their drug susceptibilities to capsid inhibitor (LEN), protease inhibitors (atazanavir, darunavir), and investigational protease cleavage site inhibitors (bevrimat, GSK-3532795) were measured in the multicycle HIV-1 assay in MT-2 cells.

The cloned Gag and protease fragment sequence of the isolates were assessed for the presence of resistance-associated substitutions of PIs, capsid inhibitors (CAI), and protease cleavage site inhibitors (Report PC-200-2036). None of the TE or TN isolates contained CAI resistance substitutions. A majority of the TE isolates (94%) harbored primary PI resistance substitutions while none were found in the TN isolates. Most TE (81%) and TN (93%) isolates contained naturally occurring gag polymorphisms associated with protease cleavage site inhibitor resistance (V362I, Q369H, V370A/M/I, T371Q/Del/S). In both TN and TE isolates, LEN exhibited average EC₅₀ values of 88 and 89pM, respectively, with minimal variability across all isolates. In contrast, the investigational protease cleavage site inhibitors bevrimat and GSK-3532795, showed 40- to 94-fold reduced activity in both TN and TE isolates, reflecting the occurrence of naturally existing gag polymorphisms associated with resistance to the cleavage site inhibitor class ([Table 134](#)). Resistance to the PIs atazanavir and darunavir was higher in TE isolates as expected in the presence of PI resistance substitutions, with mean fold-change EC₅₀ above wild-type of 21 and 34, respectively, compared to fold-change of 1.0 for both drugs in TN isolates ([Table 134](#)). The NRTI control compound showed wild-type susceptibility across all isolates, reflective of the wild-type reverse transcriptase sequence.

LEN displayed wild-type-WT-like activity against the panel of patient isolates, regardless of the level of previous exposure to antiretroviral therapy in these patients. The antiviral activity of LEN was not affected by the presence of naturally occurring Gag polymorphisms and prior treatment experience with PI resistance did not alter the antiviral activity of LEN.

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Table 134. Drug Susceptibility of a Panel of Treatment-Experienced and Treatment-Naïve HIV-1 Patient Isolates With Naturally Occurring Gag Polymorphisms

Isolate Type	Mean Drug Susceptibilities (EC ₅₀ Fold-Change from Wild-Type, range)					
	GS-6207 (CAI)	DRV (PI)	ATV (PI)	BVM (MI)	GSK-795* (MI)	TAF (NRTI)
TE (n=36)	0.9 0.4 – 1.8	21 0.5 – >112	35 0.5 – >66	40 0.5 – >64	94 0.5 – >333	0.8 0.3 – 1.4
TN (n=15)	0.9 0.6 – 1.6	1.0 0.5 – 1.8	1.0 0.5 – 1.9	42 1.7 – >64	72 1.1 – >333	0.9 0.5 – 1.5

CAI: capsid inhibitor; MI: maturation inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; TE: treatment-experienced isolates; TN: treatment-naïve isolates.

Source: Report PC-200-2036, page 9.

Abbreviations: ATV, atazanavir; BVM, bevirimat; DRV, darunavir; EC₅₀, 50% effective concentration; HIV, human immunodeficiency virus; TAF, tenofovir alafenamide

Of the 36 TE patient isolates, 24 had Gag cleavage-site substitutions (V362I, Q369H, V370A/M/I, T371Q/Del/S). LEN displayed an average EC₅₀ value of 89pM with minimal variability (range 0.4 to 1.8pM) regardless of the presence or absence of Gag cleavage site substitutions (Report PC-200-2037).

Antiviral Activity of LEN Against HIV Gag Cleavage Site Polymorphisms

The antiviral activity of LEN was tested against a panel of site-directed mutant viruses (n=19) and HIV-1 isolates from TE people living with HIV (PLWH) (TE; n=24) containing Gag cleavage site polymorphism substitutions with or without protease inhibitor resistance (Report PC-200-2037). Substitutions at the capsid/SP1 cleavage site (L363F/M, A364V) have been associated with resistance to investigational protease cleavage site inhibitors, such as bevirimat. Substitutions at the NC/SP2 (Q430R, A431V, K436E/S, I437T/V) and SP2/p6 (L449H/V/F, P453L) cleavage sites are associated with resistance to PIs.

Drug susceptibilities of the capsid inhibitor (LEN), protease cleavage site inhibitors (bevirimat, GSK-3532795), and PIs (atazanavir, darunavir) were assessed in the multicycle HIV-1 assay in MT-2 cells. LEN showed wild-type activity with an average EC₅₀ value of 102pM across all 19 mutants, with fold-changes from wild-type ranging from 0.7 to 1.9. Reduced susceptibility (>5-fold) to bevirimat and GSK-3532795, was seen with substitutions at positions 363 and 364, as expected.

Susceptibility of LEN Site-Directed Mutants to PIs and Protease Cleavage Site Inhibitors

The antiviral activity of LEN, PIs, and protease cleavage site inhibitors was tested in a multicycle HIV-1 antiviral assay in MT-2 cells against a panel of twelve site-directed mutants (SDM) viruses containing LEN resistance substitutions selected in cell culture resistance experiments (Table 135). The antiviral activity of LEN, PIs, and protease cleavage site inhibitors was tested in a multicycle HIV-1 antiviral assay in MT-2 cells against a panel of twelve site-directed mutants viruses containing LEN resistance substitutions selected in cell culture resistance experiments (Table 135). Data were obtained for only seven of twelve site-directed mutants, and showed that relative susceptibility to LEN ranged from 4.1- to 306-fold change (mean 52.3-fold) in these mutants compared to the wild type virus in the multicycle assay, which correlated well with LEN phenotypic data obtained for these mutants in a single-cycle assay.

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Drug susceptibility for the remaining five site-directed mutants could not be evaluated, as the mutants did not show adequate infectivity in this multicycle HIV-1 antiviral assay, consistent with the reduced replication capacity previously observed for these mutants in single cycle HIV-1 antiviral experiments. Susceptibility of site-directed mutants to the PIs atazanavir, darunavir, nelfinavir, and saquinavir was similar to the wild-type control (mean FC of 1.2, 1.2, 1.0, and 1.2, respectively), indicating a lack of cross-resistance to PIs in these LEN-resistant mutants. Susceptibility of site-directed mutants to the protease cleavage site inhibitors was similar to that of the wild-type virus, indicating the absence of cross-resistance.

Table 135. Phenotypic Assessment of Site-Directed Mutants With Capsid Substitutions

Average EC ₅₀ Fold Change Compared to WT Control ^a									
Mutant ID	CA Mutations	CAI	PI				MI		NRTI Control
		LEN	DRV	ATV	NFV	SQV	BVM	GSK-795 ^b	TAF
114	Q67H	5.7**	1.4**	1.7**	1.2	1.3	1.1	1.2	1.5
115	Q67Y	10.3**	1.1	1.4	0.9	1.6	0.7	0.9	1.5
117	N74D	14.3**	1.1	0.8	0.4	0.8	0.7	0.9	1.6
120	T107N	4.1**	1.1	1.0	0.7	0.8	1.3	1.1	0.9
122	Q67H+N74D	306**	1.1	0.9	0.9	1.3	0.6	1.1	1.2
123	Q67H+N74S	8.4**	2.1**	1.9*	1.9*	1.7*	1.0	1.6	1.3
124	Q67H+T107N	18.2**	1.2	0.8	0.7	0.9	0.5	0.8	0.7
Mean Fold Change		52.4	1.2	1.2	1.0	1.2	0.8	1.1	1.2

a Average of at least 3 independent experiments; statistical significance (unpaired student T-test), *: p<0.05; **: p<0.01

b GSK-795: GSK-3532795/BMS-955176

ATV: atazanavir; BVM: bevirimat; CA: capsid; CAI: capsid inhibitor; DRV: darunavir; MI: maturation inhibitor; NFV: nelfinavir; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; SQV: saquinavir; WT: wild-type

Source: Report PC-200-2045, page 8.

Abbreviations: EC₅₀, 50% effective concentration; ID, identity; LEN, lenacapavir; TAF, tenofovir alafenamide

19. Clinical Virology

A listing of the virologic failures from Study 4625 with their failing regimen, OBR, resistance at screening, primary efficacy endpoint, genotypic data for capsid PI, reverse transcriptase, and INSTI and phenotypic data at Day 1 and failure timepoints are shown in [Table 136](#).

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Table 136. Listing of Virologic Failures (N=6 LEN Cohort 1A; N=5 Placebo Cohort 1B; N=6 Cohort 2)

PID	Arm	Failing BGRD Regimen	OBR	Timepoint	Resistance	HIV VL	1° EFF Y/N	Capsid	PI Resistance	RT Resistance	INSTI Resistance	Phenotypic Resistance
(b) (6)	LEN+FR	BIC FTC TAF		Day 1	NRTI NNRTI PI INSTI (DTG available)	259 not failing on regimen	Y	L172L/I	M46I I47V F53L I54L K55R V82A L90M	M41L D67N L74V K101H/Q Y181C M184V L210W T215Y K219N L228H	L74M T97A Y143R G163R	BIC 0.6 FTC >75 TDF 1.3 LEN 1.0
			BIC FTC TAF	WK26		150			ND	ND	ND	AF
(b) (6)	LEN+FR	BIC FTC TDF DOR IBL		Day 1	NRTI NNRTI PI INSTI	75200	Y		L33F M46I I54L G73S L76V I84V L90M	D67N K70R A98S V106M V108I Y181V M184V T215F K219E	L74I/M Q95Q/K E138E/K S147S/G N155H E157E/Q	BIC 52 FTC >80 TDF 1.5 DOR >85 IBL-R LEN 0.76 ND
			BIC FTC TDF DOR IBL	WK26		342		ND	ND	ND	ND	ND
(b) (6)	LEN+FR	DRV/C FTC TDF		Day 1	NRTI NNRTI	884 not failing on regimen	Y	H87Q	A71T	M41L D67G T69D V75M L100I K103N M184V L210W T215D K219R	E157Q	DRV 0.81 FTC >79 TDF 0.56 LEN 0.93
			DRV/c FTC TDF DOR	WK4		155		H87Q	ND	ND	ND	ND

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PID	Arm	Failing BGRD Regimen	OBR	Timepoint	Resistance	HIV VL	1° EFF Y/N	Capsid	PI Resistance	RT Resistance	INSTI Resistance	Phenotypic Resistance
(b) (6)	LEN+FR	DTG DRV MVC		Day 1	NRTI NNRTI PI	214 not failing on regimen 186	N		L33F F53L I54V	M41L E138K Y181C G190E T215C K219R		DTG >0.69 DRV 0.82 LEN 0.87
			BIC FTC TAF DRV MVC	WK4				NONE	Y181C T215C	I161T		DTG 0.56 DRV 0.9
(b) (6)	LEN+FR	LAM		Day 1	NRTI PI INSTI (DRV DTG available)	71,700	N	S41T T54M	M46I I54V V82A L89M	D67N K70R M184V T215F/I K219E	G140A Q148R	LAM >89 (DRV DTG available) LEN 0.91
			DTG DRV/r TDF	WK4		25,200		S41T T54M M66M/I K70K/N/R/S V191V/I R229R/K	ND	ND	ND	LEN AF
			DTG DRV/r TDF	WK26		34						
(b) (6)	LEN+FR	DRV/C FTC TDF		Day 1	NNRTI PI	377 not failing on regimen 137	N	S41T V191V/I	M46I L76V I84I/V	K101K/Q K103E/G/R Y181Y/C T215F/I/S		DRV 1.1 FTC 1.2 TDF 0.73 LEN AF LEN AF
			BIC FTC TAF	WK4				S41T N139N/D V191I	N88N/K	NONE	V113I K136K/E G140D NA	LEN AF
				WK26		164						LEN AF

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PID	Arm	Failing BGRD Regimen	OBR	Timepoint	Resistance	HIV VL	1° EFF	Capsid	PI Resistance	RT Resistance	INSTI Resistance	Phenotypic Resistance				
							Y/N									
(b) (6)	Placebo	DTG DRV/C LAM ENF MVC		Day 1	NRTI NNRTI PI INSTI	102,000	N	S41T H87Q	V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41M/L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	DTG >89 DRV 386 LAM >89 ENF-R MVC-R LEN 0.85				
				DTG DRV/C LAM ENF MVC	WK10	5440	S41A/T H87Q M66I N74D A105T	V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	DTG >196 DRV 474 LAM >65 ENF-R MVC-R LEN >1428					
					WK22	206	S41A/T H87Q Q67Q/H S41A M66I N74D A105T	V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	ND					
					WK26	19		V32I L33F I54M A71T G73S V77I I84V L89V L90M	M41L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N						
				(b) (6)	Placebo	DTG ABC LAM		Day 1	NRTI NNRTI INSTI	52,400 (Day 2)	Y	S41A	T74T/A	M41M/L K101Q K103R Y181Y/C M184M/V L210L/W T215C	T97T/A E138E/K S147S/G N155N/H K156N	DTG 1.4 ABC 2.8 LAM >91 LEN 1.04

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PID	Arm	Failing BGRD Regimen	OBR	Timepoint	Resistance	HIV VL	1° EFF Y/N	Capsid	PI Resistance	RT Resistance	INSTI Resistance	Phenotypic Resistance
			DRV/C FTC TAF	WK4		6380		S41A I115I/V	H69H/Q	M41M/L K43K/T K101Q K103R Y181Y/C M184M/V L210L/W T215C	ND	DRV 0.73 FTC 3.9 TAF 0.96 LEN 0.71
(b) (6)	PLACEBO	FTC TDF IBL		DAY 1	NRTI NNRTI PI INSTI	62,100	N	S41T Q50A/S T107S	M46I I47V I50V K55R A71V G73E L76V V82T L89V	M41L D67N L74I A98A/G L100I K103N V108V/I M184V L210W T215Y K219N L228H	T97A E138K G140S Q148H G163S	FTC >83 TDF 1.8 IBL-R LEN 1.33
			DTG DRV FTC TAF IBL	WK4		2150		S41T Q50A T107S M66M/I	M36M/I M46I I47V I50V K55R A71V G73E L76V V82T L89V	M41L D67N L74I L100I K103N K104K/R V108I M184V L210W T215Y K219N L228H	T97A E138K G140S Q148H G163S A175A/T	DTG 137 DRV 215 FTC >68 TAF 1.1 IBL-R

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PID	Arm	Failing BGRD Regimen	OBR	Timepoint	Resistance	HIV VL	1° EFF Y/N	Capsid	PI Resistance	RT Resistance	INSTI Resistance	Phenotypic Resistance
				WK26		2420		S41T Q50A T107S A105A/T	M36M/I M46I I47V I50V K55R A71V G73E L76V V82T L89V	M41L D67N L74I L100I K103N K104K/R V108I M184V L210W T215Y K219N L228H	ND	TAF 1.4 LEN 46
(b) (6)	PLACEBO	DRV/C FTC TDF		DAY 1	NRTI (PI, NNRTI and INSTI available) nonadherent	193,000	N		V77I	K65K/R S68S/G Y181C M184M/V	E92Q	DRV 0.83 FTC >100 TDF 0.58 LEN 0.9
				WK26		561		M66I A78S	V77I	K65R S68N Y181C		DTG >0.51 DRV 0.77 RPV 2.2 LEN 138
				WK52		11,400						

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PID	Arm	Failing BGRD Regimen	OBR	Timepoint	Resistance	HIV VL	1° EFF Y/N	Capsid	PI Resistance	RT Resistance	INSTI Resistance	Phenotypic Resistance
(b) (6)	PLACEBO	DRV FTC		DAY 1	NRTI NNRTI PI	175,000	N		V32I L33M M46L I54L K55K/R G73S T74P I84V I85V L89V L90M	A62V D67E T69G/S A98G V106I Y181F M184V Y188L L210W T215Y		DRV >568 FTC >68 LEN 0.89 DTG 0.61
			DTG LAM IBL MVC	WK4		260			V32I L33M M46L I54L G73S T74P I84V I85V L89V L90M	A62V D67E T69G A98G V106I Y181F M184V Y188L L210W T215Y	E96E/G	DTG - LAM >49 IBL MVC LEN ND

Source: FDA Review team analysis.

Bolded: Resistance-associated substitutions and resistant phenotype.

Abbreviations: ABC, abacavir; AF, assay failure; BGRD, background; BIC, bictegravir; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFF, efficacy; ENF, enfuvirtide; FTC, emtricitabine; HIV, human immunodeficiency virus; IBL, ibalizumab; INSTI, integrase inhibitor; LAM, lamivudine; LEN, lenacapavir; MVC, maraviroc; N, no; ND, not determined; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; PI, protease inhibitor; PID patient identity; RPV, rilpivirine; RT, reverse transcriptase; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; WK, week; Y, yes

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Table 137. Study 4625: Randomized Arms LEN and Placebo Cohorts 1A and 1B: Screening Results

PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen	Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
(b) (6)	LEN+FR	ABC RAL	NRTI NNRTI INSTI	Y	2140	DRV/C FTC TAF IBL	Y	N	M46I T74P I84V L90M	D67N K70R L100I K103N T215Y K219H P225H	E138K G140S Q148H	ABC 1.8 RAL >176
(b) (6)	LEN+FR	BIC FTC TDF	NRTI NNRTI INSTI	Y	28,600	DRV/C FTC TAF	Y	N	L33F T74A	T69S K101P K103N M184V L210F/S T215F	T97A E138K G140S Q148H	FTC >90 TDF 1.8 BIC 113
(b) (6)	LEN+FR	RAL TDF	NNRTI PI INSTI (DTG available)	Y	35,300	BIC FTC TAF IBL	Y	N	L33F I54M K55R T74S I84V L90M	K101K/E V108V/I H221Y P225H	E138D V151I N155H E157Q G163K	TDF 0.5 RAL 75
(b) (6)	LEN+FR	BIC FTC TDF	NRTI NNRTI PI INSTI (DTG available)	N	259 not failing on regimen	BIC FTC TAF	Y	Y	M46I I47V F53L I54L K55R V82A L90M	M41L D67N L74V K101H/Q Y181C M184V L210W T215Y K219N L228H	L74M T97A Y143R G163R	BIC 0.6 FTC >75 TDF 1.3

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PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen	Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
(b) (6)	LEN+FR	DTG LPV/r	NNRTI	N nonadherent	86,600	DTG DRV/C FTC TAF	Y	N		A98S V106I Y188L H221Y	Y143R	DTG 1.7 LPV 1.3
(b) (6)	LEN+FR	BIC ABC FTC TAF ENF FTR IBL	NRTI NNRTI PI	N nonadherent	15,100	BIC FTC TAF DOR ENF IBL	Y	N	M46I I47V F53L I54L K55N T74S N88D L90M	M41L D67N K101P V106I V179I T215Y K219Q	V151I	BIC 0.8 FTC 2.6 TDF 1 ENF (susc) FTR-R IBL-R
(b) (6)	LEN+FR	BIC FTC TAF DOR IBL	NRTI NNRTI PI INSTI	Y	75,200	BIC FTC TAF DOR IBL	Y	Y	L33F M46I I54L G73S L76V I84V L90M	D67N K70R A98S V106M V108I Y181V M184V T215F K219E	L74I/M Q95Q/K E138E/K S147S/G N155H E157E/Q	BIC 52 FTC >80 TDF 1.5 DOR >85 IBL -
(b) (6)	LEN+FR	DRV/C FTC TDF	NRTI PI	N (INSTI and NNRTI available)	1320	DTG DOR	Y	N	L33F M46I I54L L76V	M41L M184V L210W T215Y	T97T/A G193G/R	DRV - FTC - TDF -
(b) (6)	LEN+FR	BIC FTC TDF DRV/C DOR	NRTI NNRTI PI INSTI	Y	28,700	DTG FTC TAF FTR	Y	N	L33M M46I I47A I85V	M41L L74I A98S K103S V106V/A V108V/I M184V L210W T215Y K219N P225H	L74M E138K G140S Q148H	BIC 122 FTC >57 TDF 1.4 DRV 403 DOR >77

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PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen		Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
				Y	N								
(b) (6)	LEN+FR	DTG DRV FTC TDF	NRTI NNRTI PI INSTI	Y		14,000	DTG DRV FTC TDF	Y	N	L33I M46L I54L T74S I84V I85V	M41L D67N T69D K70K/R A98G K101H Y181C M184V G190A T215F K219Q	L74I E138K G140A S147G Q148R E157Q	DTG - DRV - FTC - TDF -
(b) (6)	LEN+FR	BIC DRV/C FTC TDF	NRTI NNRTI PI INSTI (DTG available)	Y		16,000	DTG FTC TAF	Y	N	L33F M46I I47V I54L I84V	M41L D67S K70R/T L74I V75L A98G V106 V108A Y181C M184V G190A T215F K219E H221Y	L74I Y143C F181L	BIC 1.5 DRV 18 FTC >36 TDF 2.5
(b) (6)	LEN+FR	BIC FTC TDF IBL TPV	NRTI NNRTI PI INSTI	Y		36,400	FTR FTC TAF	Y	N	L33F M46I A71V T74P V77I V82T L89M L90M	M41L S68G L74I L100I K103N Y115F V179I M184V Y188L L210W T215Y	L74M T97A G140S Q148H G163Q	BIC 127 FTC >94 TDF 1.7 TPV >33 IBL-R
(b) (6)	LEN+FR	DTG DRV/C IBL	NRTI PI INSTI	Y		274 (decreased VL at day1)	IBL FTC TDF	Y	N	L33F M46L I47V T74P V82I I85V L90M	M41L D67N L74I V75T T215C H221C	L74I E138K S147G V151I N155H E157Q G163D	DTG 81 DRV 53 IBL-R

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PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen		Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
(b) (6)	LEN+FR	DRV/C FTC TDF	NRTI NNRTI	N		884 (not failing on regimen)	DRV/C FTC TAF DOR	Y	Y	A71T	M41L D67G T69D V75M L100I K103N M184V L210W T215D K219R	E157Q	DRV 0.81 FTC >79 TDF 0.56
(b) (6)	LEN+FR	IBL	NRTI NNRTI PI	Y		78,500	DTG IBL ABC LAM	Y	N	M46I I54M I84V L89V	D67N T69N K70R K101E V106I Y181C T215I K219E		IBL-R
(b) (6)	LEN+FR	DTG DRV MVC	NRTI NNRTI PI	N (not failing on regimen)		214 (not failing on regimen)	BIC FTC TAF DRV MVC	N	Y	L33F F53L I54V	M41L E138K Y181C G190E T215C K219R		DTG >0.69 DRV 0.82 MVC (SUSC)
(b) (6)	LEN+FR	DOR LAM TDF IBL	NRTI NNRTI INSTI	Y		35,200	DRV/C FTC TDF ABC	Y	N	V82L L90M	K65K/R K70G/R A98S L100I K103N V106 Y115F V179 Y181Y/C L210W T215C K219Q H221Y	T97A E138K G140S Q148H K156N	DOR 40 LAM 13 TDF 0.99 IBL-R

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PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen	Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
(b) (6)	LEN+FR	DTG DRV DOR FTC TDF IBL	NRTI NNRTI PI INSTI	Y	14,500	IBL MVC RPV LAM	Y	N	L33M M46I I47V F53L I54L K55R G73S I84V L89V	M41L D67N T69D L74I/V V75M L100I/V M184V G190Q L210W T215Y K219R H221L	T97A E138K G140S Q148H	DTG >89 DRV 430 DOR >78 FTC >100 TDF 1.12 IBL-R
(b) (6)	LEN+FR	LAM	NRTI PI INSTI	Y (DRV DTG available)	71,700	DTG DRV TDF	N	Y	M46I I54V V82A L89M	D67N K70R M184V T215F/I K219E	G140A Q148R	LAM >89 (DRV DTG available)
(b) (6)	LEN+FR	DTG DRV FTC TAF IBL	NRTI NNRTI PI INSTI	Y	37,800	DTG DRV FTC TAF ABC IBL	Y	N	M46I I47V I54M K55R G73S V82I L90M	D67G S68G K70R L74I V75L A98G L100I V108I Y181I M184V T215F K219E	T97A E138K G140S Q148H M154I	DTG 297 DRV 124 FTC >56 TDF 0.56 IBL-R
(b) (6)	LEN+FR	DTG DRV FTC TDF FTR IBL	NRTI NNRTI PI INSTI	Y	1900	DTG DRV FTC TAF FTR IBL	Y	N	L33F M46L I54L G73T T74P V82T I84V L89V L90M	D67S K70G L100I K103S Y115F M184V K219Q H221Y	L74M T97A Y143C I147G N155H E157Q	DTG 96 DRV 539 FTC >57 TDF 2.7 FTR-R IBL-R
(b) (6)	LEN+FR	DTG RPV	NRTI NNRTI INSTI	Y	10,500	DRV/C FTC TAF	Y	N	M46I F53L	M41L V75I V106A V108I E138A V179I T215C	E138K G140S Q148H N155H E157Q	RPV 26 DTG >89

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PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen		Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
(b) (6)	LEN+FR	DRV/C DOR FTC TDF	NNRTI	N nonadherent		252,000	DTG DRV/C FTC TAF DOR	Y	N		K103K/N V179V/I M184I/V	L74M V151I N155H	DRV 0.55 DOR 1.1 FTC 1 TDF 0.86
(b) (6)	LEN+FR	DRV/C FTC TDF	NNRTI PI	N		377 (not failing on regimen)	BIC FTC TAF	N	Y	M46I L76V I84I/V	K101K/Q K103E/G/R Y181Y/C T215F/I/S		DRV 1.1 FTC 1.2 TDF 0.73
(b) (6)	PLACEBO	DTG DRV/C	NRTI NNRTI PI	N nonadherent		77,700	DTG DOR	N	N	M46L V82A I84V	D67N T69D K101E/Q Y181C L210W T215D	M154L	DTG 0.67 DRV 0.97
(b) (6)	PLACEBO	DTG DRV FTC TDF ETR	NRTI NNRTI PI INSTI	Y		24,000	DTG DRV FTC TAF	N	N	L33F I47V I50V K55N G73S V82A L89V L90M	D67N T69D K70R A98S K101P E138E/A V179L M184V T215V K219Q	T97A E138T G140S Q148H K156N	DTG >89 DRV >617 ETR >223 FTC >90 TDF 1.1
(b) (6)	PLACEBO	DTG ABC LAM	NRTI NNRTI INSTI	Y		34,300	DRV LAM TDF AZT	Y	N		T69N L74V K103N Y115F M184V	E138K G140A S147G Q148K	DTG 77 ABC 13 LAM >98
(b) (6)	PLACEBO	BIC FTC TDF	NRTI NNRTI	N (INSTI and PI available)		21,400	DRV/C DOR	N	N	M36M/I R57K A71T	A62V V75I L100I K103N M184V	N/A No data provided but Applicant says INSTI-R	BIC -- FTC 0.87 TDF 0.75

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PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen	Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
(b) (6)	PLACEBO	DTG DRV FTC TAF IBL MVC	NRTI NNRTI PI	Y	108,000	DTG DRV FTC TAF ENF IBL MVC	N	N	L33F M46I I47V F53F/L I54M K55R V82A I84V L89I L90M	D67G K70R A98S V106I M184V Y188L L210W T215Y K219E	na	DTG -- DRV 366 FTC >54 TDF 1.24 IBL-R MVC-R
(b) (6)	PLACEBO	BIC DOR FTC TAF MVC	NRTI NNRTI PI	Y (BIC available; nonadherent?)	21,900	BIC FTC TAF DOR MVC	N	N	L33F M46I I54I/V K55R G73S L76V V82T I84V L89V L90M	M41L D67N K70R L74I K101E V106I V108I Y181C M184V T215F K219E	K156N	BIC 0.73 DOR 72 FTC >45 TDF 1.3 MVC N/A
(b) (6)	PLACEBO	DTG DRV/C LAM ENF MVC	NRTI NNRTI PI INSTI	Y	102,000	DTG DRV/C LAM ENF MVC	N	Y	I54M G73S I84V L89V L90M	M41L D67G T69D Y181I M184V Y188L T215F	T97A E138K G140S Q148H K156N	DTG >89 DRV 386 LAM >89 ENF-R MVC-R
(b) (6)	PLACEBO	DTG ABC LAM	NRTI NNRTI INSTI	Y (DTG available)	52,400 (Day 2)	DRV/C FTC TAF	Y	Y	T74T/A	M41L K101Q K103R Y181C M184M/V L210L/W T215C	T97T/A E138E/K S147S/G N155N/H K156N	DTG 1.4 ABC 2.8 LAM >91
(b) (6)	PLACEBO	RPV FTC TDF	NRTI NNRTI	N (PI and INSTI available)	212,000	DTG DRV TDF	N	N	M36I L89M	K70E V75S K101E V108I Q151M Y181C M184V G190A H221H/Y		RPV 32 FTC >72 TDF 1.5

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PID	Arm	Failing BGRD Regimen	Screening Resistance	Resistant to 3 Classes & Failing on Regimen	Day 1 VL	OBT	EFF Y/N	VF WK26	PI Resistance at SC	RT Resistance at SC	INSTI Resistance at SC	Phenotypic SC Resistance
(b) (6)	PLACEBO	FTC TDF IBL	NRTI NNRTI PI INSTI	Y	62,100	DTG DRV FTC TAF IBL	N	Y	M46I I47V I50V K55R G73E L76V V82T L89V	M41L D67N L74I A98A/G L100I K103N V108V/I M184V L210W T215Y K219N L228H	T97A E138K G140S Q148H G163S	FTC >83 TDF 1.8 IBL-R
(b) (6)	PLACEBO	DRV/C FTC TDF	NRTI	N (PI, NNRTI and INSTI available) nonadherent	193,000	DTG DRV/C RPV	N	Y	V77I	K65K/R S68G Y181C M184M/V	E92Q	DRV 0.83 FTC >100 TDF 0.58
(b) (6)	PLACEBO	DRV FTC	NRTI NNRTI PI	Y (DTG available)	175,000	DTG LAM IBL MVC	N	Y	L33M M46L I54L K55R G73S T74P I84V I85V L89V L90M	A62V D67E T69S A98G V106I Y181F M184V Y188L L210W T215Y		DRV >568 FTC >68

Source: FDA Review team analysis.

Bolded: Resistant phenotype.

Abbreviations: ABC, abacavir; AF, assay failure; BGRD, background; BIC, bictegravir; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFF, efficacy; ENF, enfuvirtide; FTC, emtricitabine; HIV, human immunodeficiency virus; IBL, ibalizumab; INSTI, integrase inhibitor; LAM, lamivudine; LEN, lenacapavir; MVC, maraviroc; N, no; N/A, not applicable; ND, not determined; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background treatment; PI, protease inhibitor; PID, patient identity; RPV, rilpivirine; RT, reverse transcriptase; SC, screening; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VF, virologic failure; VL, viral load; WK, week; Y, yes

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Table 138. Overall Susceptibility Scores of Eleven Subjects Who Did Not Appear to Meet Resistance Entry Criteria

Participant ID	Baseline Resistance Data Source ^a	Overall Susceptibility Score (OSS) ^a																							Number Class with R ^b								
		INSTI					NNRTI							NRTI					PI														
		BIC	DTG	EVG	RAL	Total with R ^b	DLV	DOR	EFV	ETR	NVP	RPV	Total with R ^b	ABC	AZT	d4T	d4I	FTC	3TC	TFV	Total with R ^b	ATV	DRV	FPV		IDV	LPV	MPV	RTV	SQV	TPV	Total with R ^b	
(b) (6)	Historical	1	1	0.5	0	2	ND	ND	0	0	0	0	4	0	0	0	0	0	0	0	0.5	5 ^c	1	1	1	1	1	0.5	0.5	0.5	1	3	4
	Screening	1	1	1	1	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0	0	5 ^c	0	0	0	0	0	0	0	0	0	9	3
	Historical	0.5	0.5	0	0	4	ND	ND	0	1	0	1	2	0.5	1	1	0.5	0	0	1	2 ^c	0.5	1	0.5	0.5	0.5	0.5	ND	0.5	1	6	4	
	Historical	1	1	1	1	0	0	ND	0	0	0	0	5	0.5	0	0	0.5	1	1	0	5	0	0	0	0	0	0	0	0	0	9	3	
	Historical and Screening ^d	1	1	0	0	2	0	1	1	0	0	1	3	0	1	1	0	0	0	0.5	3 ^c	1	1	1	1	1	1	1	1	1	0	5	
	Historical	0	0	0	0	4	ND	0.5	0	0	0	0	5	0	0	0	0	0	0	0	5 ^c	1	1	1	1	1	1	1	1	1	0	3	
	Historical	1	1	1	1	0	ND	0	0	0	0	0	5	0	0	0	0	0.5	0.5	0.5	7	0	0	0	0	0	0	ND	0	0.5	8	3	
	Screening	1	1	0.5	0.5	2	1	1	1	1	1	1	0	0	0	0	0	0	0	0	5 ^c	1	0	0	1	0	0	0	0	1	1	5	3
	Historical and Screening ^d	1	1	1	1	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0.5	5 ^c	0.5	0.5	0	0.5	0.5	0.5	ND	0.5	0.5	8	3	
	Historical	1	1	0.5	0.5	2	0	ND	0	0.5	0	ND	4	0	0	0	0	0	0	0.5	5 ^c	1	1	1	1	1	1	1	1	1	0	3	
	Historical	1	1	1	1	0	ND	ND	1	1	0.5	0.5	2	0.5	0.5	0.5	1	1	1	0.5	4	0.5	1	0.5	1	0.5	0.5	0.5	0.5	0.5	7	3	

Abbreviations: 3TC = Lamivudine; ABC = Abacavir; ATV = Atazanavir; AZT = Zidovudine; BIC = Bictegravir; d4T = Stavudine; d4I = Didanosine; DLV = Delamanvir; DOR = Doravirine; DRV = Darunavir; DTG = Dolutegravir; EFV = Efavirenz; ETR = Etravirine; EVG = Etravirine; FPV = Fosamprenavir; FTC = Emtricitabine; IDV = Indinavir; INSTI = integrase strand-transfer inhibitor; LPV = Lopinavir; ND = not determined; NVP = Nevirapine; NNRTI = non-nucleoside RT inhibitor; NRTI = nucleoside RT inhibitor; NVP = Nevirapine; OSS = overall susceptibility score; PI = protease inhibitor; R = resistance; RAL = Raltegravir; RPV = Rilpivirine; RT = reverse transcriptase; RTV = Raltegravir; SQV = Saquinavir; TPV = Tenofovir; TPV = Tenofovir

a Overall susceptibility score for each drug was determined from the resistance analysis at screening (Monogram Biosciences) or from historical resistance records (supplied by Investigators). OSS values of 1, 0.5, and 0 correspond to sensitive, partially resistant, and resistant, respectively.

b Count of drugs with resistance in class (OSS = 0 or 0.5, corresponding to resistance or partial resistance, respectively).

c INSTI resistance data were from historical record while PI and RTI resistance data were from the screening analysis for this participant.

d PI resistance data were from historical record while INSTI and RTI resistance data were from the screening analysis for this participant.

e Resistance to FTC and 3TC did not count towards the total number of NNRTI drugs with resistance due to the presence of the RT mutation M184V/I per protocol requirements.

Source: GS-US-200-4625 Week 26 Interim Virology Study Report, PC-200-2043: Virology Listings 2, Listing 3, and Listing 8

Source: Applicant's analysis.

Table 139. Resistance Emergence in Virologic Failures, Study 4625 Cohort 2

PID	Arm	OBT	Timepoint	HIV VL	Emergent Capsid RAS	Phenotypic Resistance
(b) (6)	LEN+OBT	BIC FTC TAF DRV DTG	WK4	75,500	Q67H K70R T107S	TDF LEN 14.8
	LEN+OBT	DTG FTC TAF FOS IBL	WK10	68,100	M66M/I Q67Q/H/K K70K/R T107T/S A124I/V	DTG 126 FTC >55 TAF 0.7 FOS >122 IBL-R LEN 12.2
	LEN+OBT	DOR FOS IBL	WK4	11,000	M66I T107A H120S	DOR >95 FOS >206 IBL-R LEN 239
	LEN+OBT	DTG DRV	WK10	10,500	K70H A105A/S/T T107T/N	DTG 0.99 DRV 1.7 LEN 265

Source: FDA analysis.

Bolded: Resistance-associated substitutions and resistant phenotype.

Abbreviations: BIC, bictegravir; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; FOS, fosamprenavir; FTC, emtricitabine; HIV, human immunodeficiency virus; IBL, ibalizumab; LEN, lenacapavir; OBT, optimized background treatment; PID, patient identity; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; WK, week

Next-Generation Sequencing Analysis

An independent assessment was performed by Dr. Eric Donaldson, clinical virology reviewer, using the next-generation sequencing data derived from subjects in clinical Study 4625 who were determined to be treatment failures (note: this analysis included eight subjects from Cohort 2).

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The independent analysis compared the capsid gene changes from baseline and postbaseline samples for each virologic failure subject to determine if treatment-emergent substitutions could be detected. Different capsid sequences were used as references for the mapping of capsid genes from different HIV-1 genotypes and subgroups, including 1) AE (n=2), HIV-1 isolate M114 subtype CRF01_AE from Thailand (DQ354117.1); 2) B (n=16), HIV-1 isolate JRFL from USA (U63632.1); and 3) BF (n=1), HIV-1 isolate CH80 subtype BF from Chile (FJ358521.1).

Fastq files for all samples from virologic failures in clinical Study 4625 were mapped to reference sequences using the CLC Genomics Workbench. Variants were detected using the Low Frequency Variant Caller. Substitutions associated with treatment were detected by comparing baseline samples to post-baseline samples and identifying substitutions that were not detected at baseline (frequency <3%) but were detected at later timepoints in multiple subjects and at frequencies $\geq 5\%$.

Table 140. Resistance Analysis of Treatment Failures From Clinical Study 4625 (DAV Analysis)

GTSG	AAPOS	No. of Subjects	RESIST CAT	Explanation
	V11I	1	P-RAS	(b) (6) TE, 5% W4; 12% W10
	N21S	2	P-RAS	(b) (6) TE, 3% W10; 9% W22 and (b) (6): TE, 2% W10
	Q63H	1	P-RAS	(b) (6): TE, 6% W4
	M66I	5	RAS	TE >20% in 5 TF subjects: (b) (6)
	Q67H	3	RAS	TE >20% in 3 TF subjects: (b) (6)
	K70R	3	RAS	(b) (6). Q67K also emerged at 10% in (b) (6)
				TE >25% in two TF ((b) (6)) and 2% in (b) (6)
B	N74D	1	P-RAS	(b) (6) TE >90% W10 and W22
	E79K	1	P-RAS	(b) (6) TE 6% W4
	A105T	3	RAS	TE >35% in (b) (6) (W10 and W22) and (b) (6) (W26) and 5% in (b) (6) (W26)
	V134I	1	P-RAS	(b) (6) TE, 8% W4
	N139D	1	P-RAS	(b) (6) TE, 24% W4. N139S detected at 2% in (W4) and (b) (6) (W10)
	I153V	1	BL P-RAS	>90% at BL
	P160S	1	BL P-RAS	>90% at BL
	R162K	1	BL P-RAS	9% at BL
	L172I	1	BL P-RAS	>75% at BL

GTSG	AAPOS	No. of Subjects	RESIST CAT	Explanation
	S41T	1	BL-PRAS	(b) (6) >99% at BL
	V59M	1	PRAS	(b) (6) TE, 4% W4
	M66I	1	RAS	(b) (6) TE, >80%, W4; also observed in subgroup B
AE	K70S/Q/N	1	P-RAS	(b) (6) 15%, 9%, 5% W4; also observed in subgroup B
	E71D	1	PRAS	(b) (6) 99% at BL
	A105T	1	RAS	(b) (6) TE, 3% W4; also observed in subgroup B
	S149G	1	BL-PRAS	(b) (6) >99% at BL
	R229K	1	PRAS	(b) (6) TE, >10% W4
BF	K70N/Q	1	RAS	(b) (6) increases of 34% for both substitutions by W10

Source: FDA Analysis

Abbreviations: AAPOS, amino acid position; Action, action to take for follow-up if not already completed; BL, baseline substitution that may have impacted antiviral activity; DAV, Division of Antivirals; Explain, explanation of RESIST CAT; GTSG, HIV-1 genotype and subgroup; P-RAS, potential RAS but does not fully meet the RAS criteria; RESIST CAT, resistance category; RAS, resistance-associated substitution (not present at baseline, >20% TE, in more than one subject who failed); TE, treatment emergent; TF, treatment failure; W, week

Among subjects treated with LEN who were infected with subtype B HIV-1, treatment-emergent substitutions in the capsid occurred in two or more subjects at five positions, including substitutions N21S (n=2, low frequency), M66I (n=5, treatment-emergent at >20% in all subjects), Q67H (n=3, treatment-emergent at >20% in all subjects), K70R (n=3, treatment-emergent at >25% in two subjects), and A105T (n=3, treatment-emergent at >35% in two subjects).

Exploratory Analysis of Other Capsid Substitutions

The subjects in Cohort 1 of Study 4625 were analyzed for presence at screening and postbaseline of LEN capsid binding site variants including polymorphisms (S41, Q50, T54, N57, T107, Y169, L172, and N183) and six resistance-associated substitutions (S41A, K70R, H87P, L111I, V165I, and L172I) previously identified by cell culture selection with the Pfizer capsid inhibitor PF74 or its close analogue PF-3759857 ([Table 141](#)). No subjects in Cohort 1 had substitutions at N57, K70, L111, V165, Y169, or Q179 at screening.

- Of the 10 subjects with substitution S41T or A at screening in the phase 1A and 1B cohorts of the trial, 6 (60%) were virologic failures. Phenotypic data for a site-directed mutant with S41T showed a 1.5-fold change ([Table 141](#)).
- Only one subject had the Q50A/S substitution at screening and this subject in the placebo cohort was a virologic failure at Week 26. Site-directed mutant variant Q50E conferred low-level (3-fold) decreased susceptibility to LEN.
- Two subjects had T54M at screening, one in the placebo cohort was a success and the other in the LEN cohort was a virologic failure at Week 4. Phenotypic data for site-directed mutant with T54M showed a 1.3-fold change ([Table 141](#)).
- Six subjects had H87Q, 1 of 3 in placebo arm was a virologic failure and 1 of 3 in the LEN cohort was a virologic failure. Phenotypic data for a site-directed mutant with H87P showed a 1.1-fold change ([Table 141](#)).
- Four subjects had T107S at screening, (2 placebo and 2 LEN) and only one in the placebo cohort was a virologic failure. Phenotypic data for site-directed mutant with T107S showed a 1.3-fold change ([Table 141](#)).

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- Only one subject had L172L/I (LEN cohort) and this subject was a virologic failure. Phenotypic data for site-directed mutant with T107S showed a 1.6-fold change ([Table 141](#)).

These results are summarized in [Table 141](#). The data are too limited to make definitive conclusions and no action is indicated regarding these substitutions in the package insert at this point. However, we note that S41T in combination with other polymorphisms (S41T+Q50A/S+T107S, S41T+T54M, S41T +H87Q) was associated with virologic failure and emergence of capsid resistance substitutions (Subjects (b) (6)).

Table 141. Exploratory Analysis of CA Polymorphisms and Other CA Substitutions

Substitution	Arm	PID	Timepoint Present	Endpoint
S41T	Placebo	GS-US-200-4625- (b) (6)	SC	Success
S41T	Placebo	GS-US-200-4625- (b) (6)	SC	Primary endpoint failure but WK26 success
S41S/T	LEN	GS-US-200-4625- (b) (6)	SC	Success
S41T	LEN	GS-US-200-4625- (b) (6)	SC	Success
S41A/T	Placebo	GS-US-200-4625- (b) (6)	SC (S41T) and postbaseline (S41A/T)	Primary endpoint failure and WK10 and 22 failure
S41T	LEN	GS-US-200-4625- (b) (6)	SC	Success
S41A	Placebo	GS-US-200-4625- (b) (6)	SC and postbaseline	WK4 and 22 failure
S41T	LEN	GS-US-200-4625- (b) (6)	SC and postbaseline	Primary endpoint failure and WK4 failure
S41T	Placebo	GS-US-200-4625- (b) (6)	SC and postbaseline	Primary endpoint failure and WK4 and 26 failure
S41T	LEN	GS-US-200-4625- (b) (6)	SC and postbaseline	Primary endpoint failure and WK4 failure
Q50A/S	Placebo	(b) (6)	SC and postbaseline	WK26 failure
T54M	Placebo	(b) (6)	SC	Success
	LEN	(b) (6)	SC and postbaseline	Primary endpoint failure and WK4 failure
H87Q	Placebo	(b) (6)	SC	Success
	LEN	(b) (6)	SC	Success
	Placebo	(b) (6)	SC and postbaseline	Primary endpoint failure and WK16 failure
	LEN	(b) (6)	SC and WK 4	Primary success and WK4 failure; WK26 success
	Placebo	(b) (6)	SC	Success
	LEN	(b) (6)	SC	Success

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Substitution	Arm	PID	Timepoint Present	Endpoint
T107S	LEN	(b) (6)	SC	Success
	Placebo		SC	Success
	Placebo		SC and postbaseline	Primary endpoint failure and WK4 and WK26 failure
	LEN		SC	Success
L172L/I	LEN		SC only	Primary endpoint success and WK26 failure

Source: FDA Analysis

No subject had a substitution at N57, K70, L111, V165, Y169, or Q179 at screening.

Capsid variants, Q50E and N57H, conferred low-level (3-fold) and high-level (>5,000-fold) resistance, respectively, to LEN, whereas the others remained fully susceptible to LEN with 0.7- to 2.4-fold changes in LEN susceptibility (Report PC-200-2038).

Abbreviations: CA, capsid; LEN, lenacapavir; PID, patient identity; SC, subcutaneous; WK, week

20. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

21. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Routine PDUFA inspections were completed by the Office of Scientific Investigations. The data from Studies 4625 and 4334 submitted to the Agency in support of NDAs 215973 and 215974, appear reliable based on available information. Please also refer to Section [II.10](#) for a list of clinical sites.

Clinical site inspections were conducted for two clinical investigators, Drs. DeJesus and Ruane. The inspections covered one clinical trial, Protocol GS-US-200-4625. Overall, the study appears to have been conducted adequately, and the data generated by these two sites appear acceptable in support of the respective indication.

During the inspections, the primary efficacy endpoint source data (i.e., the HIV-1 RNA test results at baseline [Day 1] and at the end of the functional monotherapy period [Day 15]) were verified against the Applicant's data line listings for all subjects randomized at the two sites selected for inspection. No discrepancies were noted.

Important enrollment and other protocol deviations were noted for three of the five subjects enrolled at Dr. DeJesus' site (Site 00698). These protocol deviations are not likely to have an impact on the overall study results.

22. Labeling Summary of Considerations and Key Additional Information

Initial comments on the Applicant's proposed labeling were conveyed on 23 November, 2021 and the Applicant responded on 3 December, 2021. The Applicant's 3 December, 2021 draft

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labeling has was not substantively reviewed in this cycle. Additional labeling negotiations will be needed upon receipt of the Applicant's response to the Complete Response action.

23. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) were considered:

- Pediatric Research Equity Act PMR-1: Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of lenacapavir in treatment-experienced children living with HIV-1 infection who are less than 18 years of age and weighing at least 35 kg. The safety and antiviral activity of lenacapavir in pediatric subjects must be evaluated for a minimum of 24 weeks.
- Injection site reactions PMR-2: Submit final study reports from Studies 4625 and 4334. Assessments of adverse events related to injection site reactions must be followed until resolution or until study completion.
- Carcinogenicity PMR-3: Submit final study report from a 2-year rat carcinogenicity study.
- Carcinogenicity PMR-4: Submit final study report from the 13-week mouse carcinogenicity study.

PMRs are not applicable for these applications, however, because the recommended approval action is a complete response.

24. Financial Disclosure

Table 142. Covered Clinical Studies: GS-US-200-4625 (Study 4625) and GS-US-200-4334 (Study 4334)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 349		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 4 Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

25. References

Literature

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26. Review Team

Table 143. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Kevin Allen, MS
Nonclinical Reviewer	Deacqunita Diggs, PhD
Nonclinical Team Leader	Laine Peyton Myers, PhD
Office of Clinical Pharmacology Reviewer(s)	Jenny Zheng, PhD Xing Jing, PhD Elyes Dahmane, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Mario Sampson, PharmD Justin Earp, Ph.D.
Clinical Reviewer	Benjamin Lorenz, MD
Clinical Team Leader	Sarah Connelly, MD
Statistical Reviewer	Hengrui Sun, PhD
Statistical Team Leader	Thamban Valappil, PhD
Clinical Virology Reviewers	Lisa Naeger, PhD Eric Donaldson, PhD
Clinical Virology Team Leader	Jules O'Rear, PhD
Cross-Disciplinary Team Leader	Sarah Connelly, MD
Division Director (pharm/tox)	Hanan Ghantous, PhD
Associate Director for Therapeutic Review (OCP/DIDP)	Vikram Arya, Ph.D., FCP
Division Director (OB)	Dionne Price, PhD
Division Director (clinical)	Debra Birnkrant, MD
Office Director (or designated signatory authority)	Adam Sherwat, MD

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 144. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	
CMC ATL	David Claffey, PhD
Drug Product	Shalini Anand, PhD David Claffey, PhD
Drug Substance	Karina Zuck, PhD Paresma Patel, PhD
Biopharmaceutics	Qi Zhang, PhD Elsbeth Chikhale, PhD
Process/Facility (NDA 215973)	David Acevedo, PhD Steve Rhieu, PhD
Process/Facility (NDA 215974)	Abdollah Koolivand, PhD Hang Guo, PhD
Microbiology	Jonathan Burgos, PhD Paul Dexter, PhD
RBPM	Shamika Brooks Erica Keafer
OPDP	Wendy Lubarsky, PharmD
OSI	Cheryl Grandinetti Phillip Kronstein

NDA 215973 lenacapavir injection, for subcutaneous use

NDA 215974 lenacapavir tablets, for oral use

Office or Discipline	Name(s)
OSE/DEPI	Natasha Pratt Mingfeng Zhang
OSE/DMEPA	Sevan Koejian Melina Fanari
OSE/DRM	Laura Zendel Theresa Ng
Other	

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

Table 145 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Deacquinta Diggs, PhD	OND/OID/DPTID	7.1, 8.4, 13 ☒ Authored ☐ Approved
Reviewer	Signature: Deacquinta L. Diggs -S Digitally signed by Deacquinta L. Diggs -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002226049, cn=Deacquinta L. Diggs -S Date: 2022.02.14 16:05:29 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Laine Peyton Myers, PhD, DABT	OND/OID/DPTID	7.1, 8.4, 13 ☐ Authored ☒ Approved
Team Leader	Signature: Laine P. Myers -S Digitally signed by Laine P. Myers -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laine P. Myers -S, 0.9.2342.19200300.100.1.1=1300389063 Date: 2022.02.14 16:22:29 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Hanan Ghantous, PhD, DABT	OND/OID/DPTID	7.1, 8.4, 13 ☐ Authored ☒ Approved
Division Director	Signature: Hanan N. Ghantous -S Digitally signed by Hanan N. Ghantous -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300169484, cn=Hanan N. Ghantous -S Date: 2022.02.14 16:41:43 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Virology	Lisa Naeger, PhD	OND/OID/DAV	5, 5.1, 6.6.1, 6.6.3, 7.7.1, 18, 19 ☒ Authored ☐ Approved
Reviewer	Signature: Lisa K. Naeger -S Digitally signed by Lisa K. Naeger -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lisa K. Naeger -S, 0.9.2342.19200300.100.1.1=1300191458 Date: 2022.02.14 10:50:26 -05'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
 Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Virology	Eric Donaldson, PhD	OND/OID/DAV	7.7.1, 18 ☐ Authored ☒ Approved
Secondary Reviewer	Signature: Eric F. Donaldson - S Digitally signed by Eric F. Donaldson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000981636, cn=Eric F. Donaldson -S Date: 2022.02.14 10:16:36 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Virology	Jules O'Rear, PhD	OND/OID/DAV	5, 5.1, 6.6.1, 6.6.3, 7.7.1, 18, 19 ☐ Authored ☒ Approved
Team Leader	Signature: Julian J. O'rear -S Digitally signed by Julian J. O'rear -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150659, cn=Julian J. O'rear -S Date: 2022.02.15 09:15:52 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Jenny Zheng, PhD	OTS/OCP/DIDP	5, 6.1.2, 8.1, 8.2, 14.1, 14.2 ☒ Authored ☐ Approved
Reviewer	Signature: Huimin Zheng -S Digitally signed by Huimin Zheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Huimin Zheng - S, 0.9.2342.19200300.100.1.1=1300152484 Date: 2022.02.14 14:47:09 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Xing Jing, PhD	OTS/OCP/DIDP	5, 6.1.1, 8.1, 14.2, 14.4 ☒ Authored ☐ Approved
Reviewer	Signature: Xing Jing -S (Affiliate) Digitally signed by Xing Jing -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001331871, cn=Xing Jing -S (Affiliate) Date: 2022.02.14 12:24:33 -05'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Mario Sampson, PhD	OTS/OCP/DIDP	5, 6.1, 6.3.2, 6.3.4, 6.3.5, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Team Leader	Digitally signed by Mario Sampson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mario Sampson -S, 0.9.2342.19200300.100.1.1=2001365806 Date: 2022.02.15 12:10:29 -06'00'		
	Signature: Mario Sampson -S		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology/Pharmacometrics	Eyes Dahmane, PhD	OTS/OCP/DPM	5, 6.3.2, 6.3.4, 6.3.5, 14.3 ☒ Authored ☐ Approved
Reviewer	Digitally signed by Eyes Dahmane -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Eyes Dahmane -S, 0.9.2342.19200300.100.1.1=2003183231 Date: 2022.02.14 15:22:11 -05'00'		
	Signature: Eyes Dahmane -S		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology/Pharmacometrics	Justin Earp, PhD	OTS/OCP/DPM	5, 6.3.2, 6.3.4, 6.3.5, 14.3 ☐ Authored ☒ Approved
Team Leader	Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2022.02.15 15:24:11 -05'00'		
	Signature: Justin C. Earp -S		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Vikram Arya, PhD	OTS/OCP/DIDP	5, 6.1, 6.3.2, 6.3.4, 6.3.5, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Tertiary Reviewer	Digitally signed by Vikram Arya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vikram Arya -S, 0.9.2342.19200300.100.1.1=1300221914 Date: 2022.02.15 11:42:44 -05'00'		
	Signature: Vikram Arya -S		

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 Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Biometrics	Hengrui Sun, PhD	OTS/OB/DBIV	6.2, 6.3, 6.4, 6.5, 6.6.1, 16 ☒ Authored ☐ Approved
Reviewer	Signature: Hengrui Sun -S Digitally signed by Hengrui Sun -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hengrui Sun -S, 0.9.2342.19200300.100.1.1=2002024499 Date: 2022.02.14 16:36:41 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Biometrics	Thamban Valappil, PhD	OND/OB/DBIV	6.2, 6.3, 6.4, 6.5, 6.6.1, 16 ☐ Authored ☒ Approved
Team Leader	Signature: Thamban I. Valappil -S Digitally signed by Thamban I. Valappil -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151694, cn=Thamban I. Valappil -S Date: 2022.02.15 21:07:33 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Cross-Disciplinary	Kevin Allen	OND/ORO/DROID	12 ☒ Authored ☐ Approved
Project Manager	Signature: Kevin L. Allen -S Digitally signed by Kevin L. Allen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kevin L. Allen -S, 0.9.2342.19200300.100.1.1=2002905679 Date: 2022.02.14 09:29:55 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Benjamin Lorenz, MD	OND/OID/DAV	I, II, 12, 15, 16, 17, 20, 21, 22, 23, 24 ☒ Authored ☒ Approved
Primary Reviewer	Signature: Benjamin D. Lorenz -S Digitally signed by Benjamin D. Lorenz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000287409, cn=Benjamin D. Lorenz -S Date: 2022.02.16 12:02:32 -05'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Sarah Connelly, MD	OND/OID/DAV	Section I ☒ Authored ☒ Approved
Cross-Disciplinary Team Lead	Signature: Sarah M. Connelly -S Digitally signed by Sarah M. Connelly -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300383550, cn=Sarah M. Connelly -S Date: 2022.02.24 16:09:12 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Debra Birnkrant, MD	OND/OID/DAV	☐ Authored ☒ Approved
Division Director	Signature: Debra B. Birnkrant -S Digitally signed by Debra B. Birnkrant -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300049410, cn=Debra B. Birnkrant -S Date: 2022.02.25 08:01:59 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Cross-Disciplinary	Adam Sherwat, MD	OND/OID	☐ Authored ☒ Approved
Signatory Authority	See DARRTS signature below		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

KEVIN L ALLEN
02/28/2022 10:07:56 AM

ADAM I SHERWAT
02/28/2022 10:20:11 AM



Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel 301-769-2110
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MEMORANDUM

Date: December 16, 2021

From: Patricia Brown, MD, Medical Officer, Division of Dermatology and Dentistry (DDD)

Through: Gordana Diglisic, MD, Clinical Team Leader, DDD
Kendall Marcus, MD, Division Director, DDD

To: Dr. Ben Lorenz, MD, OID/DAV (Division of Antivirals)
Kevin Allen, CSO, OID/DAV

CC: Margaret Kober, CPMS

Re: DDD Consult #2116: Lenacapavir (NDA 215973, NDA 215974)

Lenacapavir (LEN) is currently under review as an NME under two NDAs, 215973 [injectable (SC) (b) (4)] and 215974 (tablets). The proposed indication by the Applicant is (b) (4)

(b) (4).” Injection site reactions (ISRs) were the most common adverse reaction with lenacapavir subcutaneous injection. Based on preclinical histology in rats, rabbits and dogs these reactions were observed to be inflammatory granulomas. DAV is requesting DDD advice regarding the need for additional safety data regarding these reactions and any recommendations for communication of ISRs in labeling.

Materials Reviewed:

- NDA 215973 (Supporting Document# 1: 06/28/2021):
 - Section 2.5: Clinical Overview
 - Section 5.3.5.1:
 - Study GS-US-200-4625 Interim Week 26 Clinical Study Report
 - Narratives – Interim Week 26
 - Amendment: 90-Day Safety Update Report (SD# 11 received 9/24/2021)
- Responses to Information Requests:
 - Response (9/23/2021- SD# 9) to Information Request submitted (9/8/2021)

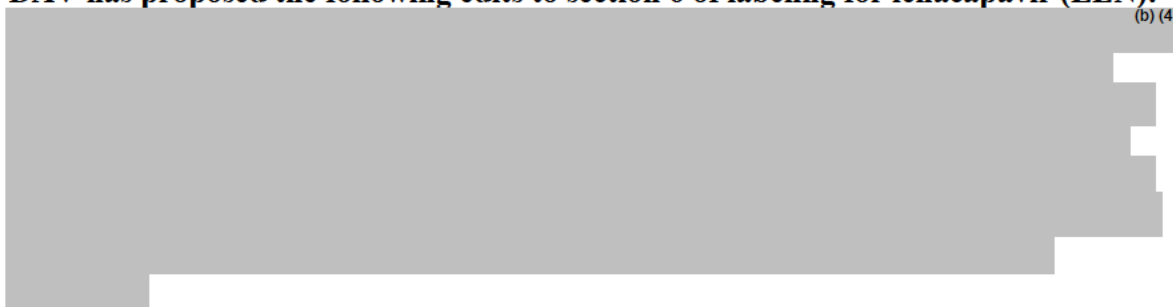
- Response (10/26/2021- SD# 16) to Information Request submitted (10/12/2021)
- FDA product labeling:
 - BYDUREON BCISE® (exenatide extended-release) injectable suspension, for subcutaneous use. Initial U.S. Approval: 2005
 - CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension, co-packaged for intramuscular use. Initial U.S. Approval: 2021
 - DEPO-SUBQ PROVERA 104 (medroxyprogesterone acetate) injectable suspension, for subcutaneous use. Initial U.S. Approval: 1959
 - FIRMAGON® (degarelix for injection) for subcutaneous use. Initial U.S. Approval: 2008
 - FUZEON® (enfuvirtide) for Injection. Initial U.S. Approval: 2003
 - HUMULIN R (insulin human injection), for subcutaneous or intravenous use. Initial U.S. Approval: 1982
 - Lovenox (enoxaparin sodium injection), for subcutaneous and intravenous use. Initial U.S. Approval: 1993
 - QWO™ (collagenase clostridium histolyticum-aes) for injection, for subcutaneous use. Initial U.S. Approval: 2020
 - STRENSIQ® (asfotase alfa) injection, for subcutaneous use. Initial U.S. Approval: 2015
 - SUSTOL® (granisetron) extended-release injection, for subcutaneous use. Initial U.S. Approval: 1993
- Literature references (see Appendix B)

Question for DDD

- “Considering the length of time for resolution of injection site nodules and indurations with SC LEN injections, and with particular concern for individuals with low body fat percentage, does DDD recommend that additional clinical safety information be submitted regarding these reactions? In addition, we request any recommendations for communication of ISRs in labeling.”

DDD Response:

- **DAV has proposed the following edits to section 6 of labeling for lenacapavir (LEN):**



DDD agrees with DAV proposed edits to labeling for LEN in Section 6. DDD also agrees that inclusion of the adverse reaction of injection site nodules in the Warnings and Precautions section of labeling is not required at this time. In addition, a Med Guide is not needed at this time (see discussion below).

- DDD recommends that in ongoing trials, where possible, injection site nodules be followed to resolution or stabilization. In addition, DDD recommends that human histopathology be obtained (e.g., punch biopsy in a few subjects). The presence of findings such as necrosis, hypersensitivity, granulomas, foreign bodies, fibrous tissue, etc. can aid in understanding

the pathophysiology of nodule formation. This in turn can increase understanding of which treatments are most likely to be useful.

Background:

From Consult Request:

Background: “Lenacapavir (LEN) is currently under review as an NME under two NDAs. NDA-215973 (b)(4), and documentation for LEN tablets is included in NDA-215974 with cross-reference to NDA 215973). The proposed indication is for treatment of heavily treatment experienced patients with HIV-1 infection. The proposed regimen is 927 mg by subcutaneous injection (2 x 1.5 mL injections) with an oral lead-in, followed by maintenance with 927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months (26 weeks).

Injection site reactions were the most common adverse reaction with lenacapavir subcutaneous injection. Based on preclinical histology in rats, rabbits and dogs these reactions were observed to be inflammatory granulomas. Our concern is that injection site nodules and indurations were not all completely resolved by the primary data safety cut with at least 26 weeks interim follow-up in Study GS-US-200-4625, and among the resolved reports, were approximately 1-4 cm at maximum size and lasting several weeks/months.

The sponsor has provided additional safety data in response to our information requests based on data from Study GS-US-200-4625 and a supportive study, Study GS-US-200-4334. Anecdotally, in lower body fat individuals, investigators had more difficulty finding adequate injection sites and nodules were more pronounced (see photographs provided in response to our Question 4 in their response: [SDN 9, m1.11.3](#)).

Several formulations were evaluated (e.g., in Study GS-US-200-4538, with free acid, sodium salt, (b)(4)), and the sponsor chose a sodium salt solution (solvent: PEG 300) with a high pH ((b)(4)) as the final proposed drug product. The kits include 22G ½ inch needles provided for the injections.”

Review:

Histopathology:

Clinical Histopathology:

There is no human histopathology included in the pivotal Phase 2/3 trial (GS-US-200-4625) to support NDA 215973.

Nonclinical Histopathology:

The Applicant notes that nonclinical studies of rats (TX-200-2014), rabbits (TX-200-2033) and dogs (TX-200-2047) showed microscopic findings of granulomatous inflammation at subcutaneous (SC) injection sites. The Applicant notes further that granulomatous inflammation has been observed after SC and intramuscular implantation of bioactive material, including those for HIV treatment and concludes that inflammation and foreign body response to the lenacapavir (LEN) SC depot is an expected host response. (IR response received 9/23/2021, p. 12)

Discussion of Injection Site Reactions/Nodules:

Injection site reactions are a local phenomenon defined as a constellation of symptoms, that can include swelling, erythema, pruritus, and pain around the site of injection. Injection site reactions

can be divided into two groups according to their mechanism of action: irritative reactions (immediate) and allergic reactions (immediate or delayed) to the excipient or to the drug itself.¹ Allergic or hypersensitivity reactions are induced by IgE, IgG/IgM, complement or T cells and can be categorized into Types I-IV.

There was no standardized definition of nodule or induration provided to Investigators for the pivotal clinical trial, GS-US-200-4625 or for the supportive trial, GS-US-200-4334.

The Applicant, however, has included the following definitions of induration and nodule in Injection site manuals for the Phase 1 trials: GS-US-4070, GS-US-200-4538. (IR response received 10/26/2021, pp. 41/65 and 49/65)

Induration: (Palpable thickening, firmness, or hardening of soft tissue). Usually well demarcated with palpable borders, can be visible (raised or sunken compared to surrounding skin), is often ‘woody’ to touch and has a flat shape (versus the rounder shape of a nodule); it can best be described by palpation.²

Nodule: Discrete or well-demarcated soft tissue mass or lump that is firm.³

Specifically, regarding injection site nodules:

In the literature injection site nodules have been reported with a number of drug products.

One class of drug products includes glucagon-like peptide 1 (GLP-1) receptor agonists used for treatment of patients with type 2 diabetes. General injection-site reactions (e.g., erythema, pain, or rash) have been reported with all of the commercially available GLP-1 receptor agonists (i.e., exenatide, lixisenatide, liraglutide, dulaglutide, and semaglutide).⁴

Though not common, a number of cases of injection site nodules have been reported with use of exenatide extended-release. Jones et al (2015) reviewed FAERS reports of injection site nodules associated with use of exenatide-extended release and reviewed published cases. They found that exenatide extended-release-associated injection-site reactions may induce large nodule formation and, in isolated cases, may require hospitalization, surgical excision, or some other medical

¹ Thomaidou E, Ramot Y. Injection site reactions with the use of biological agents. *Dermatol Ther.* 2019 Mar;32(2):e12817. doi: 10.1111/dth.12817. Epub 2019 Jan 29. PMID: 30637967.

² Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, Heath P, Hennig R, Rothstein E, Schuind A, Varricchio F; Brighton Collaboration Local Reactions Working Group for Induration at or near Injection Site. Induration at or near injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine.* 2007 Aug 1;25(31):5839-57. doi: 10.1016/j.vaccine.2007.04.062. Epub 2007 May 8. PMID: 17553602.

³ Rothstein E, Kohl KS, Ball L, Halperin SA, Halsey N, Hammer SJ, Heath PT, Hennig R, Kleppinger C, Labadie J, Varricchio F, Vermeer P, Walop W; Brighton Collaboration Local Reaction Working Group. Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine.* 2004 Jan 26;22(5-6):575-85. doi: 10.1016/j.vaccine.2003.09.005. PMID: 14741147.

⁴ Hearn EB, Sherman JJ. Injection-Site Nodules Associated With Once-Weekly Subcutaneous Administration of Semaglutide. *Diabetes Spectr.* 2021 Jan;34(1):73-75. doi: 10.2337/ds20-0033. PMID: 33627997; PMCID: PMC7887535.

intervention to mitigate. ¹ Riswold and Flynn (2018)² reported the case of a 60-year-old man who presented with 6 large, persistent nodules of the abdomen and left thigh, occurring after each of his exenatide extended-release weekly injections. A nodule that was treated with serial intralesional triamcinolone injections showed significant improvement obviating the need for multiple surgical procedures.

The specific mechanism by which exenatide extended-release can cause serious injection-site nodules is not entirely clear. The clinical description of some cases is consistent with a hypersensitivity reaction (e.g., local induration, warmth, and pruritus). Available histopathology data reveal the presence of eosinophils and granuloma in these sites, and therefore hypersensitivity to the formulation may be one plausible mechanism.³

Hearn and Sherman (2021)⁴ report a case of injection-site nodules associated with semaglutide injected subcutaneously once-weekly. The patient did not experience nodules until reaching the appropriately titrated maximum dose 6 weeks after therapy initiation. The authors state that this delay in adverse reaction supports the hypotheses of antibody or eosinophilic response. Such responses occur most commonly after multiple exposures over time. The nodules were reported to be quarter-sized, hard, erythematous, pruritic, and raised, appearing within minutes of injection and typically disappearing within 2 to 4 days. The case report did not include histopathology.

Ko et al (2020)⁵ report a case of eosinophilic panniculitis by histopathology in a patient developing a nodule on the thigh over the period of a week after exenatide extended-release injection. The nodule was described as “tender.”

Subcutaneous nodules at the injection site may occur following use of a wide range of vaccines.

Miliauskas and Mukherjee (1993)⁶ reported on four patients having a single subcutaneous nodule at the site of a previous vaccine injection. Three nodules occurred after injection of diphtheria, tetanus, and pertussis vaccination and one after tetanus toxoid vaccination. Presentation was with a mass 4-22 months after vaccination at the site of injection. Histologically, three patients had a necrotizing granulomatous reaction with a surrounding infiltrate of lymphocytes, plasma cells, histiocytes, and associated fibrosis. The fourth patient demonstrated a lymphohistiocytic reaction with a predominance of histiocytic cells as well as associated plasma cells, fibroblasts, and fibrosis. The lymphoid infiltration in these reactions showed a predominance of T-lymphocytes versus B-lymphocytes. Aluminum was demonstrated in necrotic foci, inflammatory stroma, and the granular

¹ Jones SC, Ryan DL, Pratt VS, Niak A, Brinker AD. Injection-Site Nodules Associated With the Use of Exenatide Extended-Release Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *Diabetes Spectr.* 2015 Nov;28(4):283-8. doi: 10.2337/diaspect.28.4.283. PMID: 26597395; PMCID: PMC4647172.

² Riswold K, Flynn V. Persistent injection site nodules from exenatide: Successful treatment with intralesional triamcinolone. *JAAD Case Rep.* 2018 Sep 18;4(8):830-832. doi: 10.1016/j.jcdr.2018.06.009. PMID: 30238049; PMCID: PMC6143713.

³ Jones SC, Ryan DL, Pratt VS, Brinker AD, op. cit.

⁴ Hearn EB, Sherman JJ. Injection-Site Nodules Associated With Once-Weekly Subcutaneous Administration of Semaglutide. *Diabetes Spectr.* 2021 Jan;34(1):73-75. doi: 10.2337/ds20-0033. PMID: 33627997; PMCID: PMC7887535.

⁵ Ko JW, Park KD, Lee Y, Lee JH, Hong DK. Eosinophilic Panniculitis Following the Subcutaneous Injection of Exenatide Extended-Release. *Ann Dermatol.* 2020 Jun;32(3):230-232. doi: 10.5021/ad.2020.32.3.230. Epub 2020 Apr 24. PMID: 33911742; PMCID: PMC7992610.

⁶ Miliauskas JR, Mukherjee T, Dixon B. Postimmunization (vaccination) injection-site reactions. A report of four cases and review of the literature. *Am J Surg Pathol.* 1993 May;17(5):516-24. PMID: 8470766.

cytoplasm of histiocytes. The reactions are thought to be immunologic or hypersensitivity reactions associated with the aluminum contents of the preparation.

Silcock et al (2020)¹ studied subcutaneous nodules following immunization in children in Victoria Australia. They found that nodules were associated with immunizations containing aluminum (74%, 36/49 nodules), no aluminum (8%, 4 nodules) and unknown (18%, 9 nodules). Most cases developed symptoms within 3 days postimmunization (59%, 24 cases). Pruritus was associated in 41% (17 cases). Around 1/3 (34%) of nodules resolved 6 months post immunization, 2/3 (68%) by 12 months, however 1/4 (24%) remained persistent for >24 months. Five cases had prior nodules and 1 case had recurrence with subsequent immunization. Eighty-three % (34 cases) were fully immunized for age at follow-up.

In a discussion of literature, the authors note that the injection method likely contributes to nodule development in immunization, with inadvertent subcutaneous injection associated with high rates of nodules. The subcutaneous injection is associated with greater local inflammatory reaction compared to intramuscular (IM) delivery. This is supported by evidence that longer needle length reduces immunization reactogenicity, to ensure vaccine delivery to an intramuscular location despite variations in individual delivery technique.

Other drug classes reported to be associated with injection site nodules include low-molecular weight heparin and gonadotropin releasing hormone (GnRH) agonists used to treat prostate cancer.

Val and Val-Bernal (2014)² reported on a subcutaneous infiltrative nodule occurring at the injection site of low-molecular weight heparin (LMWH). They describe a 23-year-old woman having a 3.8-cm solitary, fibrofatty, poorly demarcated nodule involving the subcutaneous tissue of the infraumbilical abdominal wall. The nodule appeared 4 years after repeated local administration of LMWH. Microscopically, the nodule showed atypical cells, with bizarre nuclei in the septa of cellular fibrous tissue dissecting the adipose lobules, in the absence of any other malignant changes. The authors speculate that the lesion may result from the combination of an idiosyncratic reaction to the LMWH with local trauma being a probable promoting factor. Alternatively, they state that the reactive proliferation may be entirely due to the trauma represented by repeated injections.

Shiota et al. (2007)³ described injection-site granulomas resulting from the administration of both leuprorelin acetate (Leuprolide acetate Eligard) and goserelin acetate (Zoladex) for the treatment of prostatic cancer. The authors noted that injection-site granulomas caused by leuprorelin acetate had been previously reported. They present the case of an 81-year-old man having subcutaneous nodules of the abdominal wall and upper arm, where 11.25 mg of leuprorelin acetate had been injected for the treatment of prostate cancer. Because of these nodules, treatment was changed to goserelin acetate. Nevertheless, the patient developed another subcutaneous nodule at the injection

¹Silcock R, Crawford NW, Selvaraj G, McMinn A, Danchin M, Lazzaro T, Perrett KP. Subcutaneous nodules following immunization in children; in Victoria, Australia from 2007 to 2016. *Vaccine*. 2020 Mar 30;38(15):3169-3177. doi: 10.1016/j.vaccine.2019.12.066. Epub 2020 Mar 5. PMID: 32147295.

² Val D, Val-Bernal J. Subcutaneous infiltrative nodule at the injection site of low-molecular weight heparin simulating malignancy. *Am J Dermatopathol*. 2014 May;36(5):397-401. doi: 10.1097/DAD.0b013e31829ff8f5. PMID: 24067804.

³ Shiota M, Tokuda N, Kanou T, Yamasaki H. Injection-site granulomas resulting from the administration of both leuprorelin acetate and goserelin acetate for the treatment of prostatic cancer. *J Nippon Med Sch*. 2007 Aug;74(4):306-8. doi: 10.1272/jnms.74.306. PMID: 17878701.

site. Histological examination showed that these nodules consisted of CD3- positive T lymphocytes and CD68-positive histiocytes associated with granulomatous changes. The authors state that the granulomas had likely been caused by delayed-type hypersensitivity to leuporelin acetate injection. They state further that the granuloma that formed after goserelin acetate injection might have developed owing to the immunogenicity of the previous leuporelin acetate injections.

FDA Approved Drug Product Labeling:

Approved FDA labeling for a number of drug products includes the adverse reaction of injection site nodules. For some products information regarding injection site nodules is present in Warnings and Precautions. Among the most extensive descriptions of injection site nodules occurs in approved FDA labeling for exenatide injection, suspension, extended-release product **BYDUREON BCISE®** (see Appendix B).

Regarding the current NDAs under review: 215973, 215974

The primary study that supports the safety and efficacy of LEN is the Phase 2/3 study in HTE (heavily treatment experienced) PWH (Study GS-US-200-4625), which is further supported by a Phase 2 study of LEN in treatment-naive PWH (Study GS-US-200-4334).

Supportive safety data are also provided from 2 Phase 1 studies in healthy participants (Studies GS-US-200-4538 and GS-US-200-5709); these Phase 1 studies also contributed to the characterization of the pharmacokinetic (PK) profiles of LEN and its metabolites, supporting the clinical pharmacology of LEN and the dosing interval.

The primary data (for establishing safety and efficacy) is based on 26-week data from **GS-US-200-4625** (CAPELLA), described by the Applicant as a “partially randomized, placebo-controlled, double-blind multicenter trial.” The proposed indication, as of the time of this consult (11/30/21 – labeling sent to applicant 11/23/2021), is “the treatment of (HIV-1) infection in heavily treatment experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.”

Trial **GS-US-200-4625** was conducted 31 sites in 9 countries (US, Thailand, Italy, Dominican Republic, Spain, France, Canada, Taiwan, and South Africa).

The trial was composed of two cohorts. Subjects were enrolled into the randomized cohort (Cohort 1) if they had a $< 0.5 \log_{10}$ HIV-1 RNA decline compared to the screening visit. Subjects were enrolled into the non-randomized cohort (Cohort 2) if they had a $\geq 0.5 \log_{10}$ HIV-1 RNA decline compared to the screening visit or after Cohort 1 reached its planned sample size.

Cohort 1 (N=36, randomized): In the 14-day functional monotherapy period, subjects in Cohort 1 were randomized in a 2:1 ratio in a blinded fashion to receive either drug product or placebo, while continuing their failing regimen. This period was to establish the virologic activity of the drug product. After the functional monotherapy period, subjects who had received drug product continued on drug product along with an optimized background regimen (OBR); subjects who had received placebo during this period were to initiate drug product along with an OBR (A regimen, at the discretion of the investigator, that has at least one fully active drug in addition to LEN).

Cohort 2 (N=36, non-randomized): Subjects in cohort 2 initiated drug product and an OBR on Day 1.

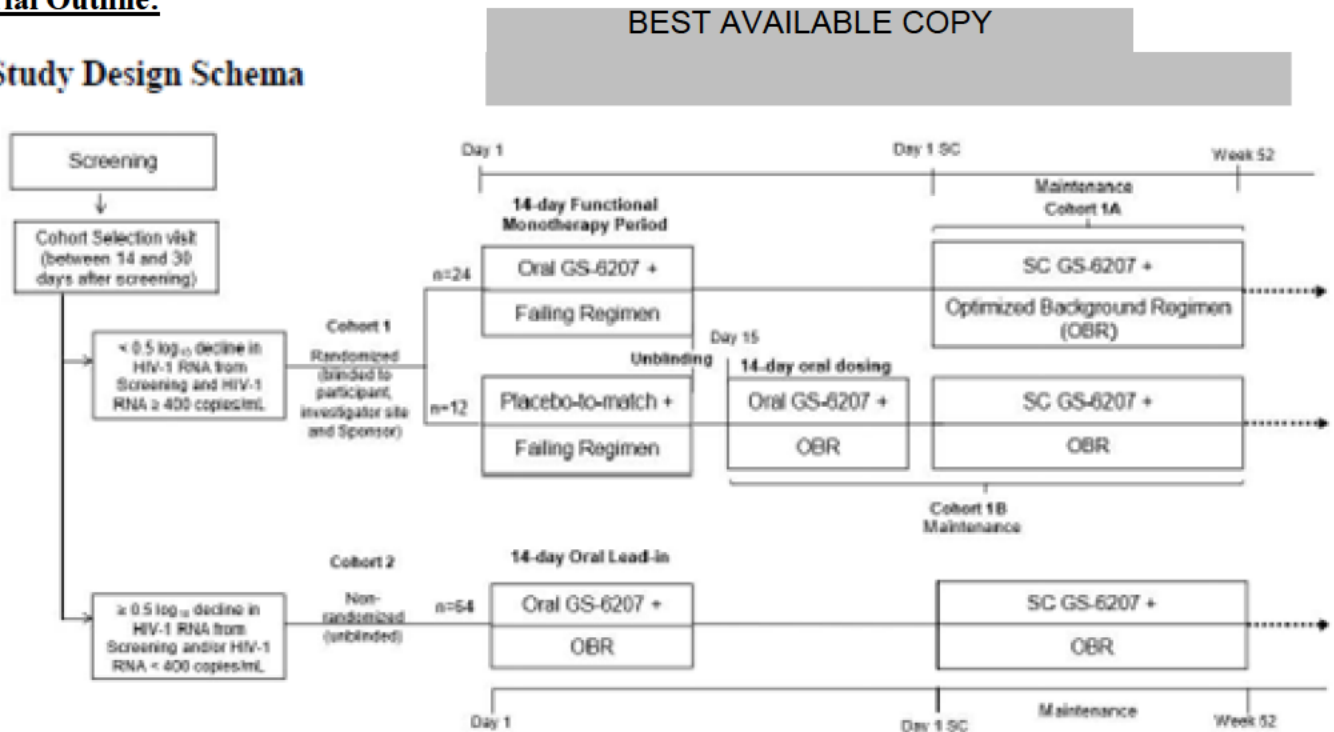
Study Endpoints:

The primary efficacy endpoint was the proportion of subjects in Cohort 1 achieving $\geq 0.5 \log_{10}$ copies/mL reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period.

The secondary efficacy endpoint was the proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 of treatment based on the US Food and Drug Administration (FDA)-defined snapshot algorithm

Trial Outline:

Study Design Schema



This trial design shows that there is no arm where active injected drug is compared with placebo injected drug. There are two enrolled cohorts: Cohort 1, if subjects had a $< 0.5 \log_{10}$ HIV-1 RNA decline compared to the screening visit and Cohort 2, if subjects had a $\geq 0.5 \log_{10}$ HIV-1 RNA decline compared to the screening visit or after Cohort 1 reached its planned sample size. Regarding Cohort 1, in the 14-day functional monotherapy period, subjects in Cohort 1 were randomized in a 2:1 ratio in a blinded fashion to receive either drug product or placebo, while continuing their failing regimen.

- **Cohort 1A** subjects received subcutaneous (SC) LEN on day 1 SC (14 days after 1st dose of oral LEN) and once every 6 months (26 weeks). Also initiate their OBR
- **Cohort 1B** subjects received placebo for 14 days, then oral LEN for and initiate their OBR on Day 15, then SC LEN at Day 1 SC (14 days after 1st dose of oral LEN and 28 days into trial) and once every 6 months (26 weeks).
- **Cohort 2:** received oral LEN for 14 days, then SC LEN at Day 1 SC (14 days after 1st dose of oral LEN) and once every 6 months (26 weeks).

For trial GS-US-200-4675: No specific instructions were given to the various trial sites on how to report injection site reactions. The adverse event (AE) toxicity scale used was DAIDS (Division of AIDS) version 2.1 (see Appendix A). See following table for summary information on study design for trials GS-US-200-5709, GS-US-200-4625 (primary trial) and GS-US-200-4334.

Table 8. GS-US-200-5709, -4625, and -4334: Differences in Study design and Other Relevant Factors between Studies

	Study 5709	Study 4625	Study 4334
Objectives	Phase 1 to evaluate PK in healthy participants	Phase 2/3 to evaluate efficacy and safety in heavily treatment experienced PWH	Phase 2 to evaluate efficacy and safety in treatment naïve PWH
Number of investigators	1	42	41
Number of sites	1	31	41
Countries	US	9 countries (US, Thailand, Italy, Dominican Republic, Spain, France, Canada, Taiwan, and South Africa)	2 countries (US and Dominican Republic),
Specific instructions describing the SC injection technique given to sites	No (However, similar Phase 1 studies were being conducted at the same time under the same investigator, for which pharmacy manual was given out)	Yes (Pharmacy manual - Appendix 4)	Yes (Pharmacy manual - Appendix 3)

	Study 5709	Study 4625	Study 4334
Specific instructions on how to report injection site reactions given to sites	No (However, similar Phase 1 studies were being conducted at the same time under the same investigator, for which ISR manual was given out)	No	No
Confinement required per protocol	(For intensive PK sample collection) Cohort 1: 17 days Cohort 2: 15 Days	None	None
Complete or symptom-driven physical examination post SC LEN per protocol	Cohort 1: Days 1-17 (daily), 18, 20, 22, 24, 29, 36, 43, 50, 57, 71, 85, 99, 127, 155, 169, 183, 197, 211, 225, 239, 267, 295, 323, 351, 379, 407, 435, and 463; Cohort 2: Days 1-15 (daily), 16, 17, 18, 20, 22, 24, 29, 36, 43, 50, 57, 71, 85, 99, 127, 155, 169, 183, 197, 211, 225, 239, 267, 295, 323, 351, 379, 407, 435, 463, 519, 575, 631, 687, and 743	Weeks 4, 10, 16, 22, 26, 36 and 52	Weeks 4, 10, 16, 22, 28, 38, 54, 64 and 80
AE toxicity scale	DAIDS version 2.1	DAIDS version 2.1	DAIDS version 2.1

AE = adverse events; DAIDS = Division of AIDS; ISR(s) = injection site reaction(s); LEN = lenacapavir; PK = pharmacokinetics; PWH = people with HIV; SC = subcutaneous; US = United States

Response to IR of 10/12/2021 received 10/26/2021, p.15

For Trial GS-US-200-4625:

Lenacapavir 927 mg injection (309 mg/mL) was administered in the abdomen via SC route on Day 1 SC, Weeks 26, 52, and every 6 months (26 weeks) thereafter (Week 26 Clinical Study for trial GS-US-200-4625 Report, p. 32).

Note: Each SC dose consists of 2 SC injections into the abdomen (Week 26 Clinical Study Report for trial GS-US-200-4625, p. 349). See also below:

4.0 LEN Subcutaneous Injection

All participants will receive 2 x 1.5 mL LEN Injections (927 mg) at their Day 1 SC visit i.e. 14 days after their first dose of oral LEN (14 days after Day 15 visits for participants in Cohort 1 who received PTM for the first 14 days). They will continue to receive LEN injections every 6 months during their participation in the study.

Two vials will be dispensed by the IWRS system to prepare and administer two injections (1.5 mL each). Injections should be administered at different abdominal sites, no more than 15 minutes apart. Injections should be prepared and administered according to the instructions below.

Note: Study drug preparation and administration should be completed by appropriately trained and delegated site staff.

1.5 mL Injection Preparation and Administration Instructions:

13. With one hand, pinch a fold of skin where the injection is to be given. The initial injection should be given in the right lower quadrant of the abdomen. If a subject has a tattoo or scar in the right lower quadrant, another quadrant may be used. For the second injection, rotate injection site clockwise, ensuring the subsequent injection is at least 4 inches away from the previous injection site. For additional injections, rotate injection sites clockwise, ensuring subsequent injections are at least 4 inches away from the other injection site(s). The injection site location(s) should be noted in the source documents.

From Pharmacy Manual (p. 4/5) for Trial GS-US-200-4625: Response to IR of 10/12/2021 received 10/26/2021.

There was no standardized definition of nodule or induration provided to Investigators for the pivotal clinical trial, GS-US-200-4625 or for the supportive trial, GS-US-200-4334.

The Applicant, however, included the following definitions of induration and nodule in Injection site manuals for the Phase 1 trials: GS-US-4070, GS-US-200-4538. (IR response received 10/25/2021, pp. 41/65 and 49/65)

Induration: (Palpable thickening, firmness, or hardening of soft tissue). Usually well demarcated with palpable borders, can be visible (raised or sunken compared to surrounding skin), is often ‘woody’ to touch and has a flat shape (versus the rounder shape of a nodule); it can best be described by palpation.¹

Nodule: Discrete or well-demarcated soft tissue mass or lump that is firm.²

A total of 72 participants were enrolled, 36 into Cohort 1 and 36 into Cohort 2.

Premature Study Drug Withdrawal: Prior to April 1, 2021, the original NDA data cut-off date, no study subjects had discontinued study drug due to an AE. However, since that date, one participant (██████████^{(b) (6)}) in Study GS-US-200-4625 prematurely discontinued study drug (day

¹ Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, Heath P, Hennig R, Rothstein E, Schuind A, Varricchio F; Brighton Collaboration Local Reactions Working Group for Induration at or near Injection Site. Induration at or near injection site: case definition and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007 Aug 1;25(31):5839-57. doi: 10.1016/j.vaccine.2007.04.062. Epub 2007 May 8. PMID: 17553602.

² Rothstein E, Kohl KS, Ball L, Halperin SA, Halsey N, Hammer SJ, Heath PT, Hennig R, Kleppinger C, Labadie J, Varricchio F, Vermeer P, Walop W; Brighton Collaboration Local Reaction Working Group. Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine*. 2004 Jan 26;22(5-6):575-85. doi: 10.1016/j.vaccine.2003.09.005. PMID: 14741147.

379) due to treatment-emergent AEs of injection site nodules. The subject was a 56-year-old black female in the USA. The subject experienced an injection site nodule on Day 18 and on Day 380. Both nodules were Grade 1 (defined as 2.5 to < 5 cm in diameter OR 6.25 to < 25 cm² surface area AND symptoms causing no or minimal interference with usual social and functional activities see also DAIDS Table in Appendix) and were ongoing (GS-US-200-4625, 90-Day Safety Update, Listing 4). The investigator reported that “the nodules were uncomfortable, and the subject did not want the nodules to return.”

**GS-US-200-4625: Study Drug Related Injection Site Reactions:
All LEN Analysis (Safety Analysis Set)**

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)		
Number of Participants Who Received At Least 1 Injection	24	12	36	36	72
Injection site nodule	8 (33.3%)	3 (25.0%)	11 (30.6%)	2 (5.6%)	13 (18.1%)

Study GS-US-200-4625 Interim Week 26 Clinical Study Report, adapted from Table 22, p. 90/628

Following the Day 1 SC dose of LEN in a total of 72 subjects the 4th most frequently reported ISR (reported in ≥ 10% of subjects overall) was injection site nodules. Of 72 subjects receiving one injection, 13 or 18.1 % were noted to have injection site nodules after one injection at the NDA data cut off (for trial GS-US-200-4625) date of April 1, 2021.

- The median time of onset was the same day as injection.
- The median duration (Q1,Q3) as reported by the Applicant was 156 days (71, 279) (Interim Week 26 Clinical Study Report, p. 89/628).
- The median duration of those that resolved was 70 days.
- As of 150 days after injection 16 nodules in 9 (12.5%) subjects were ongoing. Of subjects having nodules 9 of 13 (69%) were ongoing 150 days after injection.
- As of 221 days after injection 10 nodules in 6 (8.3%) subjects were ongoing. Of subjects having nodules 6 of 13 (46 %) were ongoing 221 days after injection.

Note: The Applicant provided information in the IR of September 8, 2021, received September 21, 2021 to indicate that after a median follow up of 225 days, 69% of subjects with nodules and 62% of subjects with indurations had not resolved following the first study drug injections. In this case duration of follow-up is duration on study for GS-US-200-4625.

A total of 16 (22.2%) subjects were noted to have nodules after the 90-Day Update Data Cut off date of July 27, 2021 (additional data cutoff date of (b) (6) for one participant).

See Table next page regarding injection site nodules in subjects receiving one dose of study drug.

Percentage of Ongoing and Resolved Induration and Nodules in Study GS-US-200-4625 at the Time of the 90-Day Safety Update Data Cut

	GS-US-200-4625	
	NDA Data Cut	90-Day Safety Update Data Cut
Number of Participants Received at Least One Injection	72	72
Median Duration of follow-up, Days (Min, Max) ^a	225 (90, 485)	313 (90, 583)
Participant-level Analysis		
Number of Participants with Injection Site Nodule after the 1 st LEN dose	13	16
Resolved	4 (30.8%)	6 (37.5%)
Ongoing	9 (69.2%)	10 (62.5%)
Number of Participants with Any Injection Site Induration after the 1 st LEN dose	8	8
Resolved	3 (37.5%)	6 (75.0%)
Ongoing	5 (62.5%)	2 (25.0%)

^a Duration of follow-up is duration on study for GS-US-200-4625 and was calculated from the first dose of LEN (including oral LEN)

Response to IR of 9/8/2021 received 9/23/2021, p 19

Following the Week 26 SC dose of LEN in a total of **39** participants (second dose), the 4th most frequently reported ISR (reported in $\geq 5\%$ of participants overall) was injection site nodules. Of 39 subjects receiving a second LEN injection **2** or 5.1% were noted to have injection site nodules at the NDA data cut off (for trial GS-US-200-4625) date of April 1, 2021.

- The median time of onset was the same day as injection.
- The median duration (Q1,Q3) as reported by the Applicant was 142 days (134, 150) (Interim Week 26 Clinical Study Report, p. 89/628). Nodules in both subjects (2 sets of two) were ongoing at 134 and 150 days.

Response to IR of 9/8/2021 received 9/23/2021:

Per Investigators (trials GS-US-200-4625 and GS-US-200-4334):

- Nodules reported as palpable with elongated shape, not visible, not painful, and not associated with any redness.
- The maximum size for the majority of injection site nodules and indurations were approximately 1 to 4 cm
- Some investigators anecdotally noted that the induration/nodules were more visible in participants who were leaner with little fat tissue in the abdomen.

In trial GS-US-2004625, photographic documentation of the injection site was provided for 6 participants ((b) (6) -nodules, (b) (6) -nodules, (b) (6) -nodules, (b) (6) -

induration, (b) (6)-induration, and (b) (6)-induration). Response to IR 9/8/2021 received 9/21/2021, p. 13

Descriptions of nodules for 9 subjects and induration for 6 subjects were provided from 15 subjects who participated in Trial GS-US-200-4625. In general, associated symptoms were not significant. Size, where available, was reported to decrease in 4 subjects and to increase in 2 subjects.

Representative Measurements and Descriptions for Subjects in Trial GS-US-200-4625

Participant number	TEAE	Grade	Duration	Size in cm	Description by the investigator
(b) (6)	Injection site nodule #1, #2	1	16 -72 both	0.1 mm	The participant noticed the nodules first, visible, redness, very shallow, decreased in size
	Injection site nodule #1, #2	1	15 - ongoing both	1.0 x 1.5	Minimally apparent on visual exam, firm, moveable in the subcutaneous tissue, no redness or tenderness, not inflamed, become smaller
	Injection site nodule #1, #2	1	16 -85 both	0.4 mm	The participant noticed the nodules first, minor in size, palpable, very shallow, decreased in size
	Injection site nodule	1	16 - ongoing	1.5	The participant noted it first when they bend over or feel for them in the abdomen, pea-sized, not visible, no redness, a little tender when palpated. About 1.0 cm depth.
	Injection site nodule #1, #2	1	43 - ongoing	Week 4: 2.5 x 1.7 , 2.5 x 1.5; Week 36: 1.7 x 1, 1.8 x 0.7 , 3 x 2.5	Not painful, or discomfort. The participant is concerned the same will occur with subsequent injections; requesting the injections be administered in a another area besides the abdomen: thighs or arms.
	Injection site nodule #1, #2	1	14 - ongoing (#1); 14 - 54 (#2)	0.5	The participant noticed the nodules first only when touches his abdomen, not painful at 1 month, decreased in size. Depth is 5 mm
	Injection site nodule	1	15 - ongoing	Day 15: 0.6 x 0.3 (L), 0.6 x 0.4 (R); Week 26: 1 x 0.4 (L), 1 X 0.3 (R); Week 52: 1.4 x 0.5 (L), 2.5 x 0.6 (R)	Nodule were palpable 14 months later despite intervening adnominal obesity
	Injection site nodule	1	15 - ongoing	Week 62: 2.2 x 1.1, 0.9 x 0.6, 2.4 x 0.8, 3.2 x 1.0, 2.0 x 0.6	

Participant number	TEAE	Grade	Duration	Size in cm	Description by the investigator
(b) (6)	Injection site nodule	1	15 - ongoing	Day 15: 1.1 x 0.6 (R), 1.2 X 1.1 (L); Week 26: 2.2 x 1.3 (R), 3.0 x 1.2 (L); Week 52: 3.0 x 1.2 (R), 2.9 x 1.2 (L)	6 nodules easily palpable in this slim individual. Participant not perturbed
	Injection site induration	1	15 - ongoing	2 x 2	The participant has non-tender indurated area about 2 x 2 cm on both sides. No erythema, no warmth, reduced in size, but haven't disappeared at Week 62 with no erythema or swelling. The nodules are not visible unless palpating them and don't cause discomfort to the participant.
	Injection site induration #1, #2	1	21 – 216 (#1) 199 – ongoing (#2)	Similar r size for both: 1 - 1.5 x 2 – 2.5	Ongoing injection site induration after the 2 nd LEN dose. The participant feels it upon touch. Tender, not visible, no edema or erythema. Decreased in size
	Injection site induration (both sites)	1	16- 30		Painless subcutaneous nodule after the 1 st LEN dose. The participant reported that the nodule disappeared after Day 9
	Injection site induration (both sites)	1	15 - 43		No association with tenderness or redness, visible to the participant, decreased since onset
	Injection site induration	1	16 - 18	10 cm (noted by the participant)	Noted by the participant: both injection site similar, 10 cm on Day 1 SC, visible to the participant, associated with redness, decreased since onset.
	Injection site induration	1	15 - ongoing	1	Week 4: 1 cm, redness. Week 10: hardness without redness, no measurements.

Response to IR 9/8/2021 received 9/23/2021, p. 37, Appendix Table 2.

See also Reviewer’s Table (Appendix C) of injection site nodules for more information.

Regarding possible correlation between viral load and development of nodules (e.g., number, onset, duration, resolution, associated symptoms) we note that data is provided regarding the association of nodules/indurations with CD4 count:

Response to IR of 10/12/2021 received 10/26/2021, p 13:

The odds ratio of the participants experiencing the AEs of injection site induration or nodule (as compared to not experiencing) for low/normal CD4 count (vs high) was 1.18 (95% CI: 0.42 to 3.30) for Study GS-US-200-4334 and 0.54 (95% CI: 0.20 to 1.47) for Study GS-US-200-4625; the 95% CI in both studies contained 1, indicating no statistical significance. Although the sample sizes are small for robust analyses, these data suggest that there is no association between low/normal CD4 count and AEs of injection site induration or nodule.

Table 7. GS-US-200-4334 and GS-US-200-4625: Association of injection site induration or nodule following the 1st LEN injection with CD4 count using the 90-Day Safety update data cut

Study	Lower Baseline CD4	Higher Baseline CD4	Odds Ratio
GS-US-200-4334 (n=103)	7/33 (21.2%)	13/70 (18.6%)	1.18 (0.42 to 3.30)
GS-US-200-4625 (n=72)	13/46 (28.3%)	11/26 (42.3%)	0.54 (0.20 to 1.47)

For trial GS-US-200-4625, 200 cells/ μ L was used as cutoff for low/normal CD4 count. For trial GS-US-200-4334, 350 cells/ μ L was used as cutoff for low/normal CD4 count (due to small size of < 200 cells/ μ L in the study, per Applicant).

Applicant's assessment of injection site reactions: Response to IR of 10/12/2021 received 10/23/202, pp. 11, 12

“To summarize, we have conducted a comprehensive assessment of injection site reactions (ISRs) across the LEN program, including detailed review of individual cases with the investigators. Our overall assessment is as follows. In Studies GS-US-200-4625 and GS-US-200-4334, approximately half or fewer of the participants (55.6% and 38.8%, respectively) experienced at least 1 AEs of LEN-related ISRs, which were mostly non-serous, Grade 1 or 2, and rarely led to study drug discontinuation. Most AEs of ISRs resolved within days, but those of induration and nodules lasted longer (as described in Gilead's previous response, Seq 0008). These AEs of induration or nodules were generally small (less than a few centimeters), not visible to the participant or the investigator, not causing persistent discomfort to participants, and only detectable upon deep palpation. There were rarely any gross inflammatory components, such as tenderness or erythema, to these AEs of induration or nodules, and when there was coincident pain or erythema, they resolved quickly. There were no reports of tissue destruction (e.g. necrosis), or, upon careful review, suggestion of other more serious reactions such as sterile abscess or persistent tissue damage. No participants appeared to have any safety signal suggesting that LEN was being administered into a deeper tissue than the intended subcutaneous space (e.g. muscle). In written, verbal, and video communication with investigators who took care of participants with AEs of persistent induration or nodule, none were concerned with any potential long term permanent adverse effect, none felt the AEs required additional consultation (e.g. with a dermatologist), and all agreed that those AEs were resolving slowly over time. In general investigators commented on the benign nature of nodules, with some noting that nodules might be more visible in a person who is lean and self-conscious of body image.”

Nodules:

“Based on the totality of Gilead's nonclinical assessment, the induration or nodules after SC LEN injection appears to be a normal and expected tissue body response, manifesting as chronic granulomatous inflammation histologically, to a foreign body (i.e. a drug depot) without permanent adverse effect. We have not found evidence of injection site nodules or induration being reflective of more serious complications, or resulting from aberrant injections, nor have we found evidence that nodules are related to body habitus or immunologic status The presence of injection site nodule or induration appears not to in any way diminish the efficacy of LEN. That assessment is also supported by the findings from the popPK modeling where LEN exposures were similar between participants with and without

injection site induration/nodules, indicating the lack of impact of induration/nodules on LEN release profile.... In summary, our assessment is that nodules that rise to the level of AE reporting occur in a subset of individuals receiving LEN, represent subcutaneous deposition of the drug itself and expected tissue reaction, and are not associated with adverse clinical or pharmacologic consequences.”

Question for DDD

- Considering the length of time for resolution of injection site nodules and indurations with SC LEN injections, and with particular concern for individuals with low body fat percentage, does DDD recommend that additional clinical safety information be submitted regarding these reactions? In addition, we request any recommendations for communication of ISRs in labeling.

Response:

- At this time no additional information requests are needed.

(To better understand the phenomenon of injection site nodules DDD recommended that additional information would be useful. Therefore, an email was sent to the DAV reviewer November 15, 2021, pertaining to subjects who received one or two injections and requesting information about items such as number of subjects, median time to onset of nodules, median duration, size over time, median time to resolution, associated symptoms, etc. The DAV reviewer responded with the suggestion that the IR of September 8, 2021 and the safety update of September 21, 2021 might contain much of this information.

Much of the desired information was found using listing 16.2.7.8 from the original NDA, the safety update of 9/21/2021, and Appendix Table 2: IR of 9/8/2021 response received 9/23/2021.)

- Regarding labeling:
On November 23, 2021, DAV submitted labeling to the Applicant on with a comment under section **6.1 Clinical Trials Experience** as follows:

Commented [FDA11]: Note to Applicant from FDA: Include detailed information regarding ISRs, similar to the Cabenuva label. This section should include the following information:

- Noting ISRs as most frequent ADR
- Frequencies by grade and type (e.g., swelling, erythema, pruritus).
- Prominently describe induration and nodules: maximum size, median/max duration, and % subjects who have not reported resolution

On December 3, 2021, the Applicant provided Draft labeling as follows:

(b) (4)

Applicant response to FDA comment:

Proposed detailed ISR data have been included. As ISR size data were collected post-hoc, and given that “nodule” has a commonly understood clinical definition with size range*, Gilead proposes to [REDACTED] (b) (4)

The Applicant cited the following source: NDA 215973, m2.7.4, Section 2.1.7.1; m5.3.5.1, GS-US-200-4625, Section 15.1, Table 15.11.2.4.1 and Table 15.11.2.4.2; Section 16.2.7, Listing 16.2.7.8 **“Nodule: A larger (0.5- to 5.0-cm), firm lesion raised above the surface of the surrounding skin. This differs from a papule only in size (e.g., a large dermal nevomelanocytic nevus)” Alterations in the Skin. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 20e. McGraw Hill; 2018. Accessed November 30, 2021. <https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=159213808>*

DAV has proposed the following edits to the Applicant Response:

To Applicant (from DAV reviewer): Thank you for amending this section. Added maximum size and % subjects who have not reported resolution as previously requested because this is essential information for patients and prescribers to consider. Nodule size is not routinely known or standardized. Completed information added here as referenced from your response to Comment 4a in the 22 Sept 2021 Information Amendment.

Regarding edits to labeling, DDD agrees with the review division.

Location in labeling:

It is noted that adverse reactions of injection site nodules were included in section 6.1 Clinical trials Experience and not in Warnings and Precautions. DDD agrees with the review division based on the following:

Nodules were all considered grade 1, and information on associated symptoms, where available, indicated that they were not serious. It is noted that one subject ((b) (6)) in Study GS-US-200-4625 prematurely discontinued study drug (day 379) due to treatment-emergent AEs of injection site nodules. The subject was a 56-year-old black female in the USA. The subject experienced an injection site nodule on Day 18 and on Day 380. Both nodules were Grade 1 (2.5 to < 5 cm in diameter OR 6.25 to < 25 cm² surface area AND symptoms causing no or minimal interference with usual social and functional activities) and were ongoing (GS-US-200-4625, 90-Day Safety Update, Listing 4). The investigator reported that “the nodules were uncomfortable, and the subject did not want the nodules to return.” Although the subject withdrew due to injection site nodules available information does not indicate that the event was serious.

(Relevant criteria for Warnings and Precautions (per October 2011 Guidance for Industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*) include the following: Serious AEs: Death, Life-threatening AE, hospitalization, significant disruption of ability to conduct normal life functions, congenital anomaly; medical judgement may jeopardize patient. Indication; relative seriousness of condition, Incidence high absolute risk of AE; AE that could lead to serious outcome unless dosage changed, Preventable by patient selection to avoid potentially serious outcome, AE significantly affecting compliance.)

Medication Guide:

The DAV reviewer does not recommend inclusion of a Medication Guide since nodules, as a safety issue, did not satisfy criteria that would necessitate a Medication Guide. DDD agrees with the review division.

Per the Guidance of November 2011, Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS):

Section 208.1(c) authorizes FDA to require a Medication Guide if FDA determines one or more of the following circumstances exist: (1) The drug product is one for which patient labeling could help prevent serious adverse effects. (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients’ decision to use, or continue to use, the product. (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug’s effectiveness.

Additional DDD Recommendations for Ongoing or Future Trials:

DDD recommends that for ongoing trials where possible that nodules be followed to resolution or stabilization. In addition, DDD recommends that human histopathology be obtained (e.g., punch biopsy in a few subjects). The presence of findings such as necrosis, hypersensitivity, granulomas, foreign bodies, fibrous tissue, etc. can aid in understanding the pathophysiology of nodule formation. This in turn can increase understanding of which treatments are most likely to be useful.

Patricia C. Brown, MD
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Appendix A: DAIDS (Division of AIDS) Version 2.1:

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Injection Site Pain or Tenderness <i>Report only one</i>	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function <u>OR</u> Hospitalization indicated
Injection Site Erythema or Redness¹² <i>Report only one</i> <i>> 15 years of age</i>	2.5 to < 5 cm in diameter <u>OR</u> 6.25 to < 25 cm ² surface area <u>AND</u> Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter <u>OR</u> ≥ 25 to < 100 cm ² surface area <u>OR</u> Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter <u>OR</u> ≥ 100 cm ² surface area <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage <u>OR</u> Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
<i>≤ 15 years of age</i>	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) <u>OR</u> Ulceration <u>OR</u> Secondary infection <u>OR</u> Phlebitis <u>OR</u> Sterile abscess <u>OR</u> Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling <i>Report only one</i> <i>> 15 years of age</i>	Same as for Injection Site Erythema or Redness , > 15 years of age	Same as for Injection Site Erythema or Redness , > 15 years of age	Same as for Injection Site Erythema or Redness , > 15 years of age	Same as for Injection Site Erythema or Redness , > 15 years of age
<i>≤ 15 years of age</i>	Same as for Injection Site Erythema or Redness , ≤ 15 years of age	Same as for Injection Site Erythema or Redness , ≤ 15 years of age	Same as for Injection Site Erythema or Redness , ≤ 15 years of age	Same as for Injection Site Erythema or Redness , ≤ 15 years of age
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized <u>OR</u> Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

¹² Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Appendix B: Examples of Labeling Related to Injection Site Nodules

BYDUREON BCISE® (exenatide extended-release) injectable suspension, for subcutaneous use. Initial U.S. Approval: 2005

5.9 Injection-Site Reactions There have been postmarketing reports of serious injection-site reactions (e.g., abscess, cellulitis, and necrosis), with or without subcutaneous nodules, with the use of BYDUREON [see Adverse Reactions (6.3)]. Isolated cases required surgical intervention.

6.1 Clinical Trial Experience

Table 1 summarizes the adverse reactions with an incidence $\geq 5\%$ occurring in BYDUREON BCISE-treated adult patients in the pooled data from the controlled and extension phases, including 10 weeks of follow-up, of the two comparator-controlled 28-week clinical trials. Adverse reactions were identified based on known adverse reactions associated with BYDUREON.

Table 1: Adverse Reactions Reported in $\geq 5\%$ of BYDUREON BCISE-Treated Patients from Pooled Clinical Trial Data in Patients with Type 2 Diabetes Mellitus

	BYDUREON BCISE 2 mg N = 526 %
Injection site nodule	10.5
Nausea	8.2

Note: Percentages are based on the number of patients who were randomized and received at least one dose of BYDUREON BCISE.

Adverse Reactions Leading to Discontinuation of Therapy

The incidence of discontinuation of therapy due to adverse reactions was 3.9% for BYDUREON BCISE-treated patients in the two comparator-controlled 28-week trials in adults. The most common classes of adverse reactions leading to discontinuation of therapy for BYDUREON BCISE-treated patients were Gastrointestinal Disorders 2.0% and General Disorders and Administration Site Conditions 1.2%. For BYDUREON BCISE-treated patients, the most frequent adverse reactions leading to discontinuation of therapy within each of these respective classes were diarrhea (0.7%), nausea (0.7%), vomiting (0.5%) and injection-site nodule (0.5%).

Injection-Site Adverse Reactions In the two comparator-controlled 28-week trials in adults, injection site reactions (including injection site nodule, injection site pruritus, injection site bruising) were observed in 23.9% of patients treated with BYDUREON BCISE. The formation of subcutaneous nodules is consistent with the properties of the microspheres used in BYDUREON BCISE.

Other drug products having labeling describing injection site nodules in **Section 5: Warnings and Precautions** include; granisetron (SUSTOL), enfuvirtide (FUZEON), and medroxyprogesterone acetate (DEPO-SUBQ-PROVERA).

- Drug products having labeling describing injection site nodules in **Section 6: Adverse Reactions** include; cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension (CABENUVA), enoxaparin sodium injection (LOVENOX), insulin human injection

(HUMULIN R), asfotase alfa (STRENSIQ), collagenase clostridium histolyticum-aaes (QWO), degarelix (FIRMAGON), among others.

An example follows:

**CABENUVA (cabotegravir extended-release injectable; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use
Initial U.S. Approval: 2021**

Section 6.1 Clinical Trials Experience

Injection-Associated Adverse Reactions

Local Injection Site Reactions (ISRs): The most frequent adverse reactions associated with the intramuscular administration of CABENUVA were ISRs. After 14,682 injections, 3,663 ISRs were reported. One percent (1%) of subjects discontinued treatment with CABENUVA because of ISRs. Most ISRs were mild (Grade 1, 75%) or moderate (Grade 2, 36%). Four percent (4%) of subjects experienced severe (Grade 3) ISRs, and no subjects experienced Grade 4 ISRs. The most commonly reported ISR was localized pain/discomfort (79%) regardless of severity or relatedness. Other manifestations of ISRs reported in more than 1% of subjects over the duration of the analysis period included **nodules (14%)***, induration (12%), swelling (8%), erythema (4%), pruritus (4%), bruising (3%), warmth (2%), and hematoma (2%). Abscess and cellulitis at the injection site were each reported in less than 1% of subjects. The median duration of ISR events was 3 days.

*Bolted by reviewer for emphasis

Appendix C: Literature References

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Appendix D: Table of Injection Site Nodules

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration Days	Size		Assoc Findings
1) (b) (6)								
55/M/WH/NH	Nodule #1, L inj site	15	1	16	16-72 (57)	0.1 mm		Visible redness, decrease in size
	Nodule #2, R inj site	15	1	16	16-72 (57)	0.1 mm		Visible redness, decrease in size
2) (b) (6)								
66/M/WH/NH	Nodule #1, L upper abd inj site	15	1	15	15 – ongoing 333	1x1.5 cm		Became smaller
	Nodule #2, R lower abd inj site	15	1	15	15 – ongoing 333	1x1.5 cm		Became smaller
2nd SC injection	Nodule L lower abd inj site	198	1	198	198 – ongoing 150	?		
	Nodule R upper abd inj site	198	1	198	198 – ongoing 150	?		
3) (b) (6)								
57/M/BL/NH	Nodule #1, LLQ inj site	15	1	16	16 – 85 (70)	0.4 mm		Decreased in size
	Nodule #2, RUQ inj site	15	1	16	16 – 85 (70)	0.4 mm		Decreased in size
4) (b) (6)								
52/F/WH/H	Nodules – lower abd quadrant	15	1	16	16 – ongoing 199	1.5 cm		No redness, a little tender on palpation
	Bilaterally at inj sites	15	1	16	16 – ongoing 199	1.5 cm		
5) (b) (6)						Week 4	Week 36	
27/F/BL/H	Nodule – R lower quadrant inj site	15	1	43	43 – ongoing 157	2 x 1.7 cm	1.7 x 1	None reported
	Nodule at 1 o'clock position 4 inches to right of 1 st inj site	15	1	43	43 – ongoing 157	2. x 1.5 cm	1.8 x 0.7	
							? 3 x 2.5	? new nodule; 2 nd injection
6) (b) (6)								
67/M/BL/NH	Nodule – R upper quadrant inj site	14	1	14	14 – ongoing 100	0.5 cm		Decreased in size
	Nodule – Lower R quadrant inj site	14	1	14	14 – 54 (41)	0.5 cm		

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration Days	Size			Assoc Findings
7) (b) (6)						Day 15	Week 26	Week 52	
63/M/WH/H	Injection site nodule - L	15	1	15	15 – ongoing 372	0.6 x 0.3	1 x 0.4	1.4 x 0.5	none
*photo p 14 IR	Injection site nodule - R	15	1	15	15 – ongoing 372	0.6 x 0.4	1 x 0.3	2.5 x 0.6	none
8) (b) (6)						? Week 26	? Week 52	Week 62	none
62/M/WH/NH	Injection site nodule 1 – R	15	1	15	15 – ongoing 372			2.2 x 1.1	reported
*photo p 15 IR	Injection site nodule 2 – R about 2 cm diagonally inferior to # 1							0.9 x 0.6	
? 5 sites 1 st dose	Injection site nodule 3 – R medial							2.4 x 0.8	
	Injection site nodule 4 – L upper							3.2 x 1.0	
	Injection site nodule 5 – L lower							2.0 x 0.6	
9) (b) (6) *						Day 15	Week 26	Week 52	None
53/M/BL/NH	Injection site nodule - R	15	1	15	15 – ongoing 316	1.1 x 0.6	2.2 x 1.3	3.0 x 1.2	reported
* photo p 14 IR	Injection site nodule - L	15	1	15	15 – ongoing 316	1.2 x 1.1	3.0 x 1.2	2.9 x 1.2	
10) (b) (6)									
59/F/BL/NH	Nodule - R lower quadrant inj site	15	1	15	15 – 169 (155)				
	Nodule – R upper quadrant inj site	15	1	15	15 – 169 (155)				
11) (b) (6)									
54/F/WH/NH	Nodule – Lower hemiabdomen inj site	15	1	15	15 – ongoing (221)				
12) (b) (6)									
59/M/WH/H	Nodule – L upper abdomen inj site	15	1	15	15 – 86 (72)				
	Nodule – R lower abdomen inj site	15	1	15	15 – 86 (72)				
2nd SC injection	Nodule – L lower abdomen inj site	197	1	197	197 – ongoing (134)				
	Nodule – R upper abdomen inj site	197	1	197	197 – ongoing (134)				

Subj ID	TEAE	Inj Day	Grade	Onset Day	Duration Days	Size	Assoc Findings
13) (b) (6)							
48/F/BL/NH	Nodules (bilateral) inj sites	15	1	15	15 – ongoing (242)		

This table was compiled from the response to IR of 9/8/2021 received 9/23/2021, p. 37 (Appendix Table 2) and from Study GS-US-200-4625 Interim Week 26 Clinical Study Report, Section 16, Listing 16.2.7.8 (pages 1-36).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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