SECTION 2.5—CLINICAL OVERVIEW

LENACAPAVIR

Gilead Sciences

[redacted] 20[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A	alemtuzumab
ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARAs	acid reducing agents
ART	ARV therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BCRP	breast cancer resistance protein
BIC	bictegravir
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CCR5	chemokine receptor 5
CD4	clusters of differentiation 4
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
COBI	cobicistat
CPK	creatinine phosphokinase
CSR	clinical study report
C_{trough}	concentration at the end of the dosing interval
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
DRV	darunavir
DTG	dolutegravir
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EMA	European Medicines Agency

ETV	etravirine
EU	European Union
F	bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
Gilead	Gilead Sciences
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HTE	heavily treatment-experienced
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IND	investigational new drug
INSTIs	integrase strand-transfer inhibitors
IQ	inhibitory quotient
ISR	injection site reaction
IV	intravenous
LEN	lenacapavir
LSM	least-squares mean
MDR	multidrug resistant
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NRTIs	nucleoside reverse transcriptase inhibitors
NNRTIs	nonnucleoside reverse transcriptase inhibitors
OBR	optimized background regimen
OSS	overall susceptibility score
$paEC_{95}$	protein adjusted 95% effective concentration
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic
PP	per protocol
PWH	people with HIV
Q1	first quartile
Q3	third quartile
QT (interval)	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
ΔΔQTc	time-matched, baseline-adjusted, placebo-corrected QTc
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RIF	rifampin

RNA	ribonucleic acid
SAEs	serious AEs
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
T_{max}	time (observed time point) of C_{max}
TQT	thorough QT
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
US	United States

1. PRODUCT DEVELOPMENT RATIONALE

Gilead Sciences (Gilead) is submitting this dossier in support of a new marketing application for tablet and subcutaneous (SC) formulations of lenacapavir (LEN; GS-6207). Lenacapavir is proposed for the treatment of heavily treatment-experienced (HTE) people with HIV (PWH) who are multidrug resistant (MDR).

This overview presents the clinical rationale for the development of LEN and reviews the information that is relevant to the benefit/risk assessment for the use of LEN in HTE PWH. This overview includes biopharmaceutic, clinical pharmacology, efficacy, and safety data that support the proposed labeling and patient information.

1.1. Scientific Background

1.1.1. HIV-Infection and Current Treatment Options

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38 million people infected worldwide and approximately 26 million on antiretroviral (ARV) treatment {UNAIDS 2020}. Advances in combination ARV therapy (ART) for HIV-1 have led to durable suppression of viral replication, allowing for preservation and reconstitution of immunologic function and averting disease progression to AIDS, ultimately delivering a normal quality of life and life expectancy. For the vast majority of PWH, these are possible with a well-tolerated once-daily therapy. While combination ART for the treatment of HIV-1 infection has largely reduced the morbidity and mortality previously associated with HIV-1 disease, a subset of PWH continue to experience virologic and immunologic failure.

People with HIV have a high risk of morbidity related to HIV-1 disease progression, opportunistic infections, comorbidities, and HIV/AIDS-related death. There remains a high unmet medical need for new well-tolerated therapies for individuals failing currently available therapies as a result of multidrug resistance, who have limited treatment options due to medication intolerance or safety considerations. Options that address ARV resistance are needed, particularly ones taking into account the desires of PWH for simpler, longer-acting therapies.

The HTE PWH with multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV-1 viral suppression {Department of Health and Human Services (DHHS) 2013, Thompson 2010, U. S. Department of Health and Human Services 2015, Williams 2014}. The current therapies available for HTE PWH are described in Section 6.1.1.1. Treatment challenges faced by adult HTE PWH are also relevant for treatment-experienced adolescents, including those who acquired HIV-1 infection via perinatal transmission. These adolescents often have an extensive history of treatment with suboptimal and potentially toxic agents (eg, zidovudine) due to lack of pediatric formulations of more effective and less toxic agents.

1.1.2. Rationale for LEN Development

Developing safe and effective therapies for PWH with MDR HIV-1 remains a priority. Newer treatments that are not impacted by resistance to existing ARV classes are needed to control viral replication, preserve immune function, and prevent clinical progression. Moreover, even without a complete virologic suppression, a sustained reduction in HIV-1 RNA (≥ 0.5 $\log_{10}$ copies/mL) can be of clinical importance even if viral suppression is not achieved.

Lenacapavir is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function targeted for the treatment of HIV-1 infection. Lenacapavir has potent antiviral activity, with no overlapping resistance with any approved products. It has a low human clearance and is being developed as a long-acting ARV for treatment and prevention. Lenacapavir has the potential to meet the high unmet medical need in PWH with MDR with limited treatment options.

Two dosage forms of LEN are currently in development, a solution for SC injection, which is administered once every 6 months, and a film-coated tablet formulation for initial loading.

Lenacapavir has demonstrated efficacy in the treatment of HIV-1 infection in adults with MDR HIV-1 infection failing their current ARV regimen when administered in combination with other ARTs.

As described herein, clinical data demonstrate the following:

- Lenacapavir led to a rapid and clinically relevant decline in viral load when added to a failing regimen in HTE PWH.
- Lenacapavir in combination with an optimized background regimen (OBR) led to high rates of virologic suppression at Week 26.
- Clinically meaningful increases in CD4 cell counts were observed over 26 weeks following LEN administration together with OBR.
- Lenacapavir was generally safe and well tolerated in HTE participants.

1.2. Overview of the Clinical Development Program

The primary study that supports the safety and efficacy of LEN is the Phase 2/3 study in HTE 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) (Table 1).

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.

Table 1. Overview of Key Studies Included in This Overview

Study Number	Description of Study	Data Cross Reference	Module 2 Cross−Reference
Study in HTE PWH			
GS-US-200-4625	Ongoing, Phase 2/3, randomized, placebo–controlled, multicenter study	GS-US-200-4625 Interim Week 26 CSR	m2.7.3, Section 2.1
Study in Treatment-Naive PWH			
GS-US-200-4334	Ongoing, Phase 2, randomized, open–label, active–controlled, multicenter study	GS-US-200-4334 Interim Week 28 CSR	m2.7.3, Section 2.2
Studies in Healthy Participants			
GS-US-200-4538	Completed, Phase 1, randomized, blinded, placebo–controlled, SAD study	GS-US-200-4538 Final CSR	m2.7.1, Section 2.1.2
GS-US-200-5709	Ongoing, Phase 1, open–label, multiple–cohort, multiple–dose study	GS-US-200-5709 Interim CSR	m2.7.2, Section 2.2.3

CSR = clinical study report; HTE = heavily treatment-experienced; PWH = people with HIV; SAD = single ascending dose

In these studies, 284 participants received at least 1 dose of LEN with comparable exposure to LEN as the planned regimen for commercialization (PWH, n = 229; healthy participants, n = 55), including 177 PWH (HTE, n = 72; treatment naive, n = 105) who received SC LEN, following an oral lead-in.

1.2.1. Regulatory Guidelines and Advice

All studies conducted in the LEN development program met the requirement for International Council for Harmonisation (ICH) guidelines. Therefore, data should be interchangeable across regions. For studies and sites conducted under a United States (US) investigational new drug (IND) application, investigators were required to ensure that the basic principles of "Good Clinical Practice" (GCP) were adhered to, as outlined in 21 CFR 312, subpart D. These standards are consistent with the requirements of the European Community Directive 2001/20/EC. All study designs were reviewed and approved by the regulatory agencies of the countries in which the studies were conducted.

The unmet needs for treatment options in HTE PWH are recognized by LEN as described above.

The overall clinical development plan for LEN for the treatment of HIV in HTE PWH was discussed at the Breakthrough Therapy Designation meeting on [redacted] 20[redacted]. At the meeting and during subsequent communications, the US Food and Drug Administration (FDA) provided feedback on the proposed Phase 2/3 study design and provided general endorsement that the proposed study would support submission of a new drug application (NDA) for LEN for the treatment of HIV-1 in HTE PWH.

The size and composition of the safety database have been discussed and it was agreed with regulatory agencies including the US FDA and the European Medicines Agency (EMA) Rapporteurs to include PWH from Studies GS-US-200-4625 and GS-US-200-4334, as well as safety data from healthy participants with similar LEN exposure to the proposed dose for commercialization (Studies GS-US-200-5709 and GS-US-200-4538). It was also agreed with the US FDA and EMA that, given the target mechanism of action of LEN, provision of carcinogenicity study reports could be provided after the initial marketing application (see m2.4, Section 4.5).

Based upon the clinical evidence provided in this dossier, Gilead is seeking registration of LEN in combination with other ARVs for the treatment of HIV-1 in MDR PWH who are failing their current ARV regimen due to resistance, intolerance, or safety considerations.

2. OVERVIEW OF BIOPHARMACEUTICS

Biopharmaceutical studies of LEN are summarized in detail in m2.7.1.

2.1. Formulation

Both an oral and SC formulation of LEN are part of the commercial regimen.

Lenacapavir tablets, 300 mg, are capsule-shaped, film-coated beige tablets, debossed with "GSI" on one side of the tablet and "62L" on the other side of the tablet. Each tablet core contains the equivalent of 300 mg LEN free acid in the form of LEN sodium salt. In addition to the active ingredient, LEN tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, mannitol, poloxamer 407, copovidone, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, iron oxide red, iron oxide black, and iron oxide yellow. Lenacapavir tablet was the oral formulation used in the ongoing Phase 2 and 2/3 studies.

Lenacapavir injection, 309 mg/mL, is a clear, yellow-to-brown solution for SC injection. In addition to the active ingredient (LEN sodium), LEN injection, 309 mg/mL, contains the following inactive ingredients: polyethylene glycol 300 and water for injection. Lenacapavir SC formulation was the one used in the ongoing Phase 2 and 2/3 studies.

2.2. Dissolution Profile

The dissolution profile for the proposed commercial LEN 300 mg tablet formulation showed that dissolution data are comparable between the tablet lots and consistent with the dissolution profile expected for an immediate-release formulation with not less than 80% of LEN dissolved by 30 minutes (m2.7.1, Section 1.2).

2.3. Bioavailability

The %F of LEN following oral administration was estimated based on the observed exposure to LEN following intravenous (IV) 10 or 20 mg LEN and oral 300 mg LEN tablet administration to healthy participants (Studies GS-US-200-4329 [m2.7.2, Section 2.2.1] and GS-US-200-4071 [m2.7.1, Section 2.2.1]). Comparison of LEN AUC following IV and oral administration, and when correcting for dose, indicates that absolute bioavailability (%F) following administration of LEN 300 mg tablet is low (%F of approximately 10%). Based on population PK modeling, the estimated %F for LEN 600 mg is approximately 6.24% in PWH (CTRA-2021-1054 LEN PopPK, m2.7.2, Section 3.1.5).

The absolute bioavailability of LEN following SC administration was estimated based on the observed exposure to LEN following IV and SC administration to healthy participants (Studies GS-US-200-4329 [m2.7.2, Section 2.2.1] and GS-US-200-4538 [m2.7.1, Section 2.1.2], respectively). Comparison of LEN AUC following IV LEN 10 or 20 mg and SC LEN 927 mg administration, and when correcting for dose, indicates that LEN is completely absorbed following SC administration of the 927-mg dose.

Further details are provided in m2.7.1, Section 3.2.

2.4. Food Effect on Exposure

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

Administration of LEN tablets with either a high-fat, high-calorie meal (approximately 1000 kcal and 50% fat) or a light meal (approximately 400 kcal and 25% fat) resulted in comparable AUC or C_{max}, relative to fasted conditions. As a result, food is not expected to have a clinically relevant effect on the PK of LEN oral tablets. Lenacapavir was administered without regard to food in the ongoing Phase 2 and 2/3 studies (GS-US-200-4334 and GS-US-200-4625). Based on population PK analysis, food status was not identified as a statistically significant covariate on LEN PK (CTRA-2021-1054 LEN PopPK, m2.7.2, Section 3.1.7.1). These data support dosing of LEN tablets without regard to food.

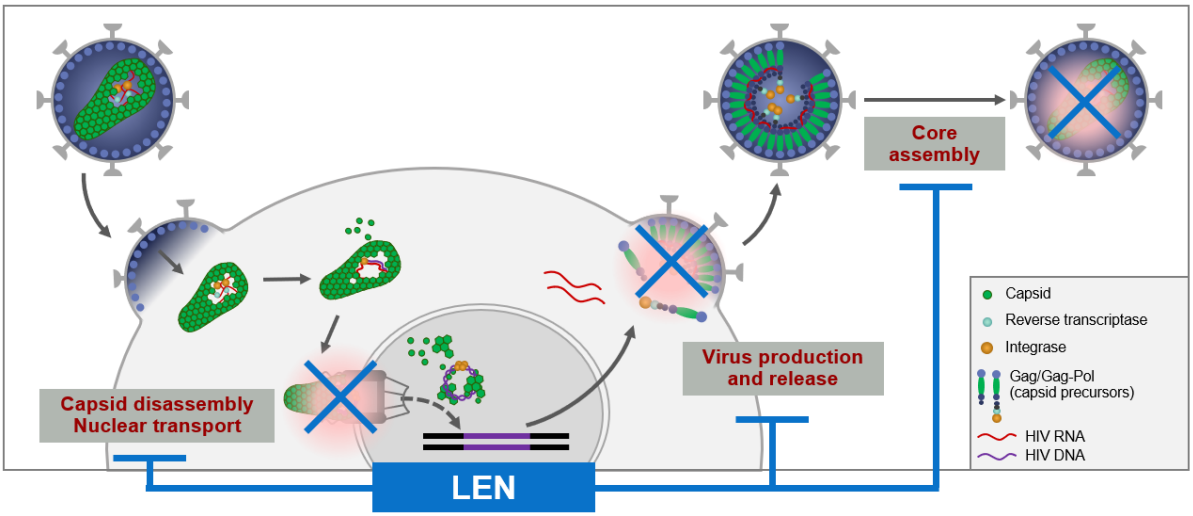
For the SC formulation, the effect of food was not evaluated.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

3.1. Pharmacology

Lenacapavir is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function. Lenacapavir inhibits HIV-1 at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Virus produced in the presence of LEN displays improperly shaped capsids. These malformed virus particles can still infect a new target cell but cannot replicate as they are unable to support reverse transcription without a properly formed capsid core (Figure 1).

Figure 1. Lenacapavir Mode of Action



LEN = lenacapavir

Lenacapavir is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and low aqueous solubility. These combined characteristics allow LEN to be well suited for a long-acting parenteral formulation that can potentially be used as a novel long-acting ARV for treatment of or prevention for HIV-1 infection administered monthly or less frequently.

Lenacapavir is anticipated to be active against all major types of HIV-1, including those that have developed resistance to existing classes of ARVs (eg, nucleoside reverse transcriptase inhibitors [NRTIs], nonnucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], and integrase strand-transfer inhibitors [INSTIs]).

3.2. Virology

A comprehensive program of nonclinical and clinical studies has characterized the antiviral activity of LEN. Nonclinical virology studies were performed to evaluate the activity of LEN in biochemical and cell-based in vitro systems.

In the HTE population in Study GS-US-200-4625, resistance development to LEN was observed in 11.1% (8 of 72) of participants through Week 26, reflecting the limited treatment options available for this population. The virologic profiles for the 8 participants with emergent capsid resistance suggest that LEN may have been the sole ARV in these participants at the time of virologic failure. The most prevalent mutation observed, M66I, alone or combination with other known LEN-associated capsid mutations, was associated with a mean decrease in LEN susceptibility of 234-fold, when compared with wild type.

In the treatment-naive population in Study GS-US-200-4334, emergence of resistance mutations through Week 28 was rare (Q67H + K70R; 0.6% [1 of 157] of participants who received oral or SC LEN). In the predominantly treatment-naive population in Study GS-US-200-4072, emergence of resistance (Q67H) was noted in 2 participants receiving subtherapeutic doses of LEN.

Further details on the nonclinical and clinical virology analyses for LEN are provided in m2.7.2, Sections 4.1 and 4.2, respectively.

3.3. Clinical Pharmacokinetics

A comprehensive clinical pharmacology program was conducted with LEN in Phase 1, 2, and 2/3 studies to support the use of LEN for the treatment of PWH (m2.7.2, Sections 1.2 and 1.3). Phase 1 clinical studies evaluated the PK of single-dose escalations for both the LEN tablet and SC formulations in healthy participants and in PWH, absorption, distribution, metabolism, and elimination (ADME), a thorough QT (TQT) study, the potential for LEN to affect other drugs, and the potential of food, organ impairment, or other demographic factors to affect LEN. The PK of LEN was also evaluated in PWH in Phase 2 and 2/3 clinical studies. Population PK analyses evaluated intrinsic and extrinsic factors affecting the PK of LEN in PWH, and potential relationships were evaluated between LEN exposure and efficacy and safety outcomes. The PK and PK/pharmacodynamic (PD) conclusions based on these data are summarized in the following sections.

3.3.1. Absorption, Distribution, Metabolism, and Excretion

Detailed summaries of clinical and nonclinical studies investigating the ADME of LEN are provided in m2.7.2, Section 3.1.

3.3.1.1. Absorption

The absorption of LEN is discussed in detail in m2.7.2, Section 3.1.1.

Oral Administration

Lenacapavir is absorbed following oral administration with peak plasma concentrations occurring 4 to 8 hours after administration of LEN. Absolute bioavailability following oral lenacapavir administration is low (approximately 6.2% to 10%). Lenacapavir is a substrate of P-glycoprotein (P-gp).

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

Subcutaneous Administration

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

3.3.1.2. Distribution

The distribution of LEN is discussed in detail in m2.7.2, Section 3.1.2.

The apparent volume of distribution was 19,240 L after oral administration and ranged from 9500 to 11,700 L after SC administration.

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

3.3.1.3. Metabolism and Elimination

The metabolism and elimination of LEN is discussed in detail in m2.7.2, Section 3.1.3.

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

Lenacapavir is cleared by metabolism, excretion into bile, and intestinal secretion by P-gp. Metabolism plays a minor role in LEN elimination. Lenacapavir was metabolized via oxidation, N-dealkylation, hydrogenation, amid hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation, primarily via cytochrome P450 (CYP)3A4 and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). No single metabolite contributed > 10% of total radioactive exposure.

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

3.3.2. Effect of Intrinsic Factors

The effect of intrinsic factors is discussed in detail in m2.7.2, Section 3.1.6.

Population analyses using data from adult trials did not identify any clinically relevant differences due to age, gender, race/ethnicity, or weight on the PK of LEN. No dose adjustment of LEN is required for participants > 65 years of age. Health status (PWH vs healthy) was identified as a statistically significant covariate. Lenacapavir exposures were approximately 30% to 50% lower in healthy participants as compared with HTE PWH (ie, LEN exposures in HTE PWH were 43% to 100% higher as compared with healthy participants).

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

Renal Impairment

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

Hepatic Impairment

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

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

3.3.3. Effect of Extrinsic Factors

The effect of extrinsic factors is discussed in detail in m2.7.2, Section 3.1.7.

The impact of extrinsic factors on the PK of LEN was evaluated in Phase 1 studies and drug-drug interaction (DDI) studies, and as part of population PK analyses.

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

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

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

LEN appears to weakly inhibit breast cancer resistance protein (BCRP) and P-gp, and moderately inhibits CYP3A. Therefore, caution is advised if LEN is coadministered with sensitive CYP3A substrates with narrow therapeutic index, but not with P-gp, BCRP, or organic anion transporting polypeptide.

3.3.4. Clinical Pharmacokinetics/Pharmacodynamics

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

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

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

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

3.4. Rationale for Proposed LEN Dosing Regimen

In the Phase 2 and 2/3 studies, the selected LEN dosing regimen consisted of a 14-day oral lead-in period (oral LEN 600 mg on Day 1 and 2, oral LEN 300 mg on Day 8), followed by SC LEN injection 927 mg on Day 15 and every 6 months (26 weeks) thereafter. This 14-day oral lead-in enabled the following: oral loading (from a PK standpoint); an assessment of the contribution of LEN to the efficacy of an otherwise failing regimen (during the Functional Monotherapy Period of Study GS-US-200-4625); and an assessment of safety and tolerability of LEN prior to administration of SC LEN injection. However, this entire 14-day oral lead-in is not considered necessary for early establishment of efficacious exposure and can be simplified to improve adherence without compromising efficacy. As such, in the proposed LEN dosing regimen, oral loading is administered over 2 days at the time of administration of SC LEN injection.

Given the established safety profile and lack of exposure-safety relationships for LEN in Studies GS-US-200-4625 and GS-US-200-4334, the following simplified LEN dosing regimen is proposed for the treatment of HTE PWH: oral LEN 600 mg and SC LEN injection 927 mg on Day 1, oral LEN 600 mg on Day 2, followed by SC LEN injection 927 mg every 6 months (26 weeks) thereafter. Simulations using a population PK model indicate that this simplified regimen will yield a comparable LEN PK profile to that of the Phase 2 and 2/3 dosing regimen and should be considered the preferred LEN dosing regimen (m2.7.2, Section 3.2.1.3).

A 4-week dosing window around the every-6 month (26 ± 2 weeks since the last dose) dosing regimen for SC LEN injection is predicted to maintain safe and efficacious LEN exposures based on modeling and simulation results of the Phase 2 and 2/3 dosing regimen (m2.7.2, Section 3.2.1.2). The observed LEN concentration profiles of the simplified regimen and the Phase 2/3 regimen from Study GS-US-200-5709 supported the conclusions from PK modeling and simulation.

4. OVERVIEW OF EFFICACY

The primary study supporting the clinical efficacy up to Week 26 in HTE PWH is the Phase 2/3 Study GS-US-200-4625. This initial application includes efficacy data when all participants in Cohort 1 had completed the Week 26 SC visit (ie, 26 weeks after the first dose of SC LEN) or prematurely discontinued the study drug. As of [redacted] 20[redacted], 33 of 36 participants in Cohort 2 have yet to reach Week 26 (with 1 of whom died prior to Week 26); therefore, efficacy results for this cohort will be summarized at the subsequent data cut.

Furthermore, supportive efficacy data are provided from the Phase 2 Study GS-US-200-4334 in treatment-naive PWH. The efficacy data from this study include the secondary efficacy analysis conducted after all participants completed the Week 28 visit or prematurely discontinued the study drug.

4.1. Study Populations for Evaluation of Efficacy

HTE PWH: Study GS-US-200-4625

Overall, for Study GS-US-200-4625, the majority of participants in Cohort 1 were male (72.2%; 26 of 36 participants) and the median age was 54 years (range: 24 to 71 years) (see m2.7.3, Section 3.1.1.2).

In Cohort 1, the baseline disease characteristics were consistent with the profile of the HTE population, with a median number of prior ARV medications of 9 (range: 2 to 24), and 75.0% of participants (27 participants) with CD4 cell count < 200 cells/μL. Baseline differences were observed between the LEN and placebo groups in HIV-1 RNA (log_{10} copies/mL), HIV-1 RNA categories (≤ 100,000 and > 100,000 copies/mL), CD4 cell counts, and CD4 percentage; prespecified subgroup and sensitivity analyses demonstrate that these observed differences did not have an impact on the interpretation of the efficacy data (see m2.7.3, Section 3.2.1.1).

The baseline disease characteristics for Cohort 2 were generally similar to those of Cohort 1.

Treatment-Naive PWH: Study GS-US-200-4334

Overall, for Study GS-US-200-4334, the majority of participants were male (93.4%; 170 of 182 participants) and the median age was 29 years (range: 19 to 72 years) (see m2.7.3, Section 3.1.2.2). Demographic and the baseline disease characteristics were generally similar across the treatment groups.

4.2. Overview of Studies Providing Clinical Efficacy Data

An overview of the primary study supporting the clinical efficacy data (Study GS-US-200-4625) and supportive efficacy data (Study GS-US-200-4334) is provided in Section 1.2.

4.3. Rationale for Efficacy End Points

In accordance with the US FDA guidance on developing ARV drugs for the treatment of HIV-1 infection and the Committee for Medicinal Products for Human Use (CHMP) Guideline on the clinical development of medicinal products for the treatment of HIV infection, a short-term reduction of ≥ 0.5 $\log_{10}$ copies/mL HIV-1 RNA is associated with a reduction in clinical disease progression, based on an analysis by the US FDA of 12 clinical studies that evaluated clinical end points {Mani 2012, U. S. Department of Health and Human Services 2015} (EMEA/CPMP/EWP/633/02 Rev. 3).

In the HTE population with a diverse underlying resistance profile, there is no standardized background regimen that can be used for all individuals. The Functional Monotherapy Period of Study GS-US-200-4625, during which a study drug (LEN) is added to a failing regimen, allows assessments of efficacy of the study drug. Any antiviral activity demonstrated by a reduction in HIV-1 RNA after a short-term treatment (ie, ≤ 2 weeks) can identify an active antiviral drug based on early viral load kinetics, and can be predictive of meaningful clinical benefit toward the durability of HIV-1 RNA suppression. Furthermore, the short duration of the Functional Monotherapy Period allows antiviral efficacy assessment in HTE PWH ethically, without increasing the risk of further drug resistance to LEN or the background drugs. Due to the high unmet medical need and ongoing viremia of HTE participants, the use of placebo over a long period cannot be justified; however, it is acceptable to compare it with a study drug over a short duration of a Functional Monotherapy Period for statistically reliable and scientifically rigorous efficacy data.

Beyond the primary end point of Study GS-US-200-4625, the secondary efficacy end point assesses the virologic suppression at Weeks 26 and 52, which is during the maintenance, open-label period, and without a control group. Longer-term placebo-controlled comparison in this population would not be acceptable to either clinicians or patients as the continued use of the failing regimen or suboptimal background regimen would increase the risk of emerging resistance to LEN and/or the background regimens. In studies of ibalizumab (TMB-301) and fostemsavir (BRIGHTE) in HTE PWH with MDR, no comparator arm was used. Both studies showed the contribution of the study drug (ibalizumab or fostemsavir) by relative high rate of virologic suppression of the study drug plus OBR in a population previously unable to achieve virologic suppression. Given the urgent high unmet medical need for effective treatments for HTE population according to the US FDA guidance “noninferiority trials generally are not feasible in this population because there usually is no appropriate active control with a sufficiently well-described effect that can be used to define a noninferiority margin.” “Longer term placebo-controlled comparisons have fallen out of favor because continued use of the unmodified old (failed) regimen increases the risk of emergence of resistance to the investigational drug or the background drugs.” {U. S. Department of Health and Human Services 2015}.

During the Maintenance Phase, LEN is combined with an individualized and investigator-selected OBR. The importance of this secondary efficacy end point is comparable with the primary as this assesses the long-term virologic suppression in HTE PWH, hence determining the clinical outcome. Although 26 weeks is an earlier time point than time points in

the typical clinical studies in treatment-naive PWH or stably virologically suppressed PWH to assess the durability of a study drug, the US and European Union (EU) guidances consider it an acceptable end point, as the risk of disease progression and death can be lowered when significant short-term reductions in HIV-1 RNA (ie, ≥ 0.5 $\log_{10}$ copies/mL over up to 2 weeks) are maintained over 16 to 24 weeks of treatment {Department for Health and Human Services (DHHS) 2015, Marschner 1998, Murray 1999}. These are important considerations, given the urgent and high unmet medical need for this population.

Lastly, the efficacy of LEN can be indirectly supported by Week 28 efficacy data in Study GS-US-200-4334 in treatment-naive PWH. One of the limitations of Study GS-US-200-4625 is the lack of a comparator beyond the Functional Monotherapy Period. Study GS-US-200-4334 is a single-variable study comparing LEN (SC or oral) versus bictegravir (BIC), each in combination with Descovy® (DVY), in treatment-naive PWH, for 28 weeks. Although this is a Phase 2 study and not powered to demonstrate noninferiority, nonetheless it can clearly demonstrate the contribution of LEN towards efficacy in a comparative fashion, thereby complementing efficacy data from Study GS-US-200-4625.

4.4. Efficacy in PWH: Study GS-US-200-4625

The primary efficacy end point of Study GS-US-200-4625 was 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 14-day Functional Monotherapy Period. The null hypothesis was that there was no difference in the proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period (between the LEN and the placebo groups in Cohort 1). The alternative hypothesis was that there was a difference (LEN − placebo) in the proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period between the 2 treatment groups in Cohort 1. The primary analysis of the efficacy end point was based on the Full Analysis Set (FAS) for the Functional Monotherapy Period analysis (a detailed description of the analysis population is provided in m2.7.3, Section 3.1.1.3).

A total of 36 participants in Cohort 1 provided at least 90% power to detect a 60% difference in the proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at Day 15 of the Functional Monotherapy Period between treatment groups (LEN in Cohort 1A and placebo in Cohort 1B). In this sample size and power computation, it was assumed that 70% and 10% of participants would achieve a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline in HIV-1 in the LEN group (Cohort 1A) and the placebo group (Cohort 1B), respectively (based on data from ibalizumab Phase 3 TMB-301 study {Emu 2018}), and the Fisher exact test is conducted at 2-sided significant level of 0.05.

In this study, LEN met the primary end point of superiority to placebo. A significantly greater percentage of participants receiving LEN had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline than those who received placebo (87.5% vs 16.7%; $P < 0.0001$) (Table 2).

To address the imbalance in baseline HIV-1 RNA between the LEN and placebo groups, a post hoc analysis of the primary efficacy end point with adjustment for baseline HIV-1 RNA using

rank analysis of covariance was conducted. Results from this post hoc analysis confirmed that the difference between the groups remained statistically significant ($P = 0.0003$) (m2.7.3, Section 3.2.1.1). To address the imbalance in baseline CD4 cell counts between the LEN and placebo groups, post hoc analyses of the primary efficacy end point were conducted in participants with comparable or clinically relevant CD4 cell counts. In a subset of participants in the LEN group with the lowest baseline CD4 counts (ie, lower than the overall median) (12 participants; median: 98.5 cells/µL) versus the placebo group (12 participants; median: 84.5 cells/µL), the difference between the 2 groups remained statistically significant (proportional difference: 66.7%; 95% CI: 25.2% to 90.5%; $P = 0.0008$) (GS-US-200-4625 Interim Week 26 CSR, Table req13038.3.1). Results were similar in the subgroup of participants with CD4 count < 200 cells/µL in both treatment groups (LEN, n = 16; placebo, n = 11) (proportional difference: 78.4%; 95% CI: 39.0% to 95.0%; $P < 0.0001$) (GS-US-200-4625 Interim Week 26 CSR, Table req13038.4).

Table 2. GS-US-200-4625: Number and Proportion of Participants Achieving a Reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL From Baseline − Functional Monotherapy Period Analysis (Full Analysis Set)

	Cohort 1		LEN vs Placebo	
	LEN (N = 24)	Placebo (N = 12)	*P* Value	Proportional Difference (95% CI)
Number and proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline	21 (87.5%)	2 (16.7%)	< 0.0001	70.8% (34.9% to 90.0%)

LEN = lenacapavir
The 95% CI of the difference in percentages of response between treatment groups and the corresponding *P* value were calculated based on an unconditional exact method using 2 invert 1-sided tests (Chan and Zhang method).
Source: m2.7.3, Table 12

The mean (SD) change from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period was greater for participants who received LEN than those who received placebo, as follows: LEN −1.93 (0.893) $\log_{10}$ copies/mL; placebo −0.29 (0.614) $\log_{10}$ copies/mL (adjusted difference in least-squares mean [LSM] by baseline $\log_{10}$ HIV-1 RNA: −2.17; 95% CI: −2.74 to −1.59; $P < 0.0001$) (see m2.7.3, Section 3.2.1.3.2).

The results based on the Per Protocol (PP) Analysis Set were consistent with those for the FAS and confirmed the primary efficacy end point (see m2.7.3, Section 3.2.1.1).

For participants receiving LEN in Cohort 1, a high rate of virologic suppression was sustained through Week 26: 80.6% (29 of 36 participants) had HIV-1 RNA < 50 copies/mL using the US FDA–defined snapshot algorithm. The 7 participants (19.4%) with HIV-1 RNA ≥ 50 copies/mL at Week 26 still had substantial antiviral responses sustained over 26 weeks. Specifically, 3 of these participants had an HIV-1 RNA < 200 copies/mL at Week 26, while the other 4 participants had at least 0.8 $\log_{10}$ copies/mL reduction from baseline HIV-1 RNA at

Week 26; 1 of those 4 participants had HIV-1 RNA < 50 copies/mL before and after the Week 26 time point.

A similarly high rate of virologic suppression was sustained at Week 26 in participants with low baseline CD4 counts < 200 cells/μL; 77.8% (21 of 27 participants). A small number of participants had baseline HIV-1 RNA > 100,000 copies/mL; the rate of virologic suppression among this subgroup was 57.1% (4 of 7 participants) at Week 26 (m2.7.3, Table 16).

Eight of 72 participants (11.1%) had emergent LEN-associated mutations. The virologic profiles for these 8 participants suggest that LEN may have been the sole ARV in these participants at the time of virologic failure. No resistance to agents from the OBR was observed.

Other key efficacy end points also support the use of LEN in HTE PWH, as shown in participants receiving at least 1 dose of LEN in Cohorts 1 and 2, as follows (see m2.7.3, Section 3.2.1.3):

- The mean (SD) change from baseline in HIV-1 RNA at Week 26 was −2.45 (1.162) $\log_{10}$ copies/mL.
- The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 26 was 78.6% (33 of 42 participants) based on the missing = failure (M = F) analysis. Similar results were observed for the missing = excluded (M = E) analysis.
- There were clinically meaningful increases in the mean (SD) CD4 cell count from baseline to Week 26 (90 [102.1] cells/μL).
- Lenacapavir in combination with an OBR led to high rates of virologic suppression at Week 26. These results were consistent even in participants who had suboptimal OBR (eg, low overall susceptibility score [OSS], 0 or 1 fully active agent, INSTI resistance, no dolutegravir [DTG] or darunavir [DRV]), demonstrating a clinically meaningful contribution of LEN toward virologic suppression.

4.5. Efficacy in ART-Naive PWH: Study GS-US-200-4334

The primary efficacy end point of Study GS-US-200-4334 is the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the US FDA–defined snapshot algorithm, and the time point has not yet been reached; thus, the results will not be presented herein.

One of the secondary efficacy end points is the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 as determined by the US FDA–defined snapshot algorithm. Only efficacy end points at Weeks 28 will be summarized herein as the majority of participants have not reached the other time points of interest (ie, Weeks 38, 54, and 80).

In this study, high rates of virologic suppression (HIV-1 RNA < 50 copies/mL using the US FDA–defined snapshot algorithm) were achieved at Week 28 in participants receiving SC or oral LEN (LEN total). The percentage of virologic suppression was similar across treatment group, which includes Biktarvy® (BVY) group, as follows (Table 3):

- LEN total: 93.6%, 147 of 157 participants
- BVY: 100.0%, 25 of 25 participants

Table 3. GS-US-200-4334: Virologic Outcome at Week 28 Using the US FDA–Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (Full Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
HIV-1 RNA < 50 copies/mL	49 (94.2%)	49 (92.5%)	49 (94.2%)	25 (100.0%)	98 (93.3%)	147 (93.6%)
HIV-1 RNA ≥ 50 copies/mL	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)
HIV-1 RNA ≥ 50 copies/mL in Week 28 window	0	0	0	0	0	0
Discontinued study drug due to lack of efficacy	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Discontinued study drug due to other reasons* and last available HIV-1 RNA ≥ 50 copies/mL	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
No virologic data in Week 28 window	3 (5.8%)	2 (3.8%)	3 (5.8%)	0	5 (4.8%)	8 (5.1%)
Discontinued study drug due to adverse event/death	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Discontinued study drug due to other reasons* and last available HIV-1 RNA < 50 copies/mL	2 (3.8%)	1 (1.9%)	3 (5.8%)	0	3 (2.9%)	6 (3.8%)
Missing data during window but on study drug	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
LEN vs BVY						
P value	0.2398	0.1639	0.2307	—	0.1794	0.1916
Difference in percentage (95% CI)	−5.5% (−15.9% to 4.8%)	−7.4% (−18.3% to 3.4%)	−5.7% (−16.3% to 4.9%)	—	−6.9% (−16.1% to 2.4%)	−6.5% (−15.1% to 2.2%)

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); FDA = Food and Drug Administration; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; US = United States

* Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

The Week 28 window was between Days 176 and 231 (inclusive).

The difference in percentage of participants with HIV-1 RNA < 50 copies/mL between each of the LEN-containing treatment groups and the BVY group, and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

P value was from the Cochran-Mantel-Haenszel tests stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

Source: m2.7.3, Table 15

Two participants (3.8%) in the SC LEN + (DVY → BIC) group had HIV-1 RNA ≥ 50 copies/mL and prematurely discontinued study drugs before the Week 28 window, as follows: 1 participant prematurely discontinued due to lack of efficacy as defined in the protocol (HIV-1 RNA ≥ 50 copies/mL at Weeks 16 and 22 to initiate the maintenance regimen at Week 28), and the other participant prematurely discontinued due to withdrawal of consent on Day 2 with last available on treatment HIV-1 RNA ≥ 50 copies/mL at predose.

Other key efficacy end points were as follows (m2.7.3, Sections 3.2.2.1 and 3.2.2.2):

- HIV-1 RNA decreased for the LEN total group following the initiation of LEN. The mean (SD) changes from baseline in HIV-1 RNA at Week 28 were as follows: LEN total group: −2.99 (0.666) $\log_{10}$ copies/mL; BVY group: −3.07 (0.774) $\log_{10}$ copies/mL

- Using the imputation methods, the majority of participants in the LEN total group achieved virologic suppression (HIV-1 RNA < 50 copies/mL) by Week 4, with a high rate of virologic suppression at Week 28, as follows (GS-US-200-4334 Interim Week 28 CSR, Tables 15.8.8 and 15.8.9):

  — M = F:

    ■ Week 4: LEN total group: 83.4% (131 of 157 participants); BVY group: 84.0% (21 of 25 participants)

    ■ Week 28: LEN total group: 95.5% (150 participants); BVY group: 100.0% (25 participants)

  — M = E:

    ■ Week 4: LEN total group: 85.1% (131 of 154 participants); BVY group: 84.0% (21 of 25 participants)

    ■ Week 28: LEN total group: 100.0% (all 150 participants); BVY group: 100.0% (all 25 participants)

4.6. Efficacy Discussion and Conclusions:

In HTE PWH participants:

- Lenacapavir met the primary end point of superiority to placebo. A significantly greater proportion of participants who received LEN (87.5%) had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline compared with those who received placebo (16.7%) ($P < 0.0001$).

- Lenacapavir led to a rapid and clinically relevant decline in viral load when added to a failing regimen in HTE PWH.

- There were clinically meaningful increases in CD4 cell count from baseline to Week 26.

- Lenacapavir in combination with an OBR led to high rates of virologic suppression at Week 26. These results were consistent even in participants who had suboptimal OBR (eg, low OSS, no or 1 fully active agent, INSTI resistance, no DTG or DRV), demonstrating a clinically meaningful contribution of LEN toward virologic suppression.

In treatment-naive participants:

- A high rate of virologic suppression was achieved at Week 28 in participants receiving LEN (SC or oral formulation): 93.6% (147 of 157 participants) had HIV-1 RNA < 50 copies/mL as determined by the US FDA–defined snapshot algorithm.

5. OVERVIEW OF SAFETY

5.1. Summary of Clinical Study Safety Experience

The proposed indication for LEN is primarily based on data from a Phase 2/3 study in HTE PWH with MDR (Study GS-US-200-4625). This clinical overview provides available safety data through [redacted] 20[redacted] (the date on which the last participant from Cohort 1 completed the Week 26 SC visit) for Study GS-US-200-4625. Supportive safety data for LEN are provided from a Phase 2 study in treatment-naive PWH (Study GS-US-200-4334) and from a pooled analysis of 2 Phase 1 studies (GS-US-200-4538 and GS-US-200-5709) of LEN in healthy participants (Table 1).

Safety was evaluated through the incidence of treatment-emergent adverse events (AEs) and treatment-emergent clinical laboratory abnormalities using descriptive statistics. Adverse events were coded using the MedDRA, Version 23.1. For the individual Studies GS-US-200-4625 and GS-US-200-4334, additional analysis of AEs was performed for injection site reactions (ISR) related to study drug, which was defined as an AE related to study drug by the investigator reported as any event within the MedDRA high-level term of "injection site reactions."

Graded laboratory abnormalities were defined using the grading scheme in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017). Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time after baseline, was summarized by treatment group. Laboratory data that are categorical were summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

5.1.1. Extent of Exposure

5.1.1.1. HTE PWH: Study GS-US-200-4625

Extent of exposure for Study GS-US-200-4625 is presented in m2.7.4, Section 1.3.1.

5.1.1.2. Treatment-Naive PWH: Study GS-US-200-4334

Extent of exposure for Study GS-US-200-4334 is presented in m2.7.4, Section 1.3.2.

5.1.1.3. Healthy Participants: Pooled Studies GS-US-200-4538 and GS-US-200-5709

Extent of exposure for pooled Studies GS-US-200-4538 and GS-US-200-5709 is presented in m2.7.4, Section 1.3.3.

5.1.2. Participant Demographics

5.1.2.1. HTE PWH**:** Study GS-US-200-4625

Demographic and baseline characteristics for Study GS-US-200-4625 are presented in m2.7.3, Section 3.1.1.2.

5.1.2.2. Treatment-Naive PWH: Study GS-US-200-4334

Demographic and baseline characteristics for Study GS-US-200-434 are presented in m2.7.3, Section 3.1.2.2.

5.1.2.3. Healthy Participants: Pooled Studies GS-US-200-4538 and GS-US-200-5709

Demographic and baseline characteristics in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 were generally similar between the LEN and placebo groups. The majority of participants in the Safety Analysis Set were male (65.3%; 49 of 75 participants), White (73.3%, 55 participants) and Hispanic or Latino (98.7%, 74 participants. Median age was 33 years (range: 20 to 45 years) and median (first quartile [Q1], third quartile [Q3]) body mass index was 26.8 (24.5, 28.8) kg/m^2.

5.1.3. Adverse Events

5.1.3.1. HTE PWH: Study GS-US-200-4625

During the Functional Monotherapy Period for Cohort 1, the percentages of participants who experienced AEs were: LEN 37.5% (9 of 24 participants); placebo 25.0% (3 of 12 participants) (m2.7.4, Section 2.1.1). Nausea was the only AE reported in > 1 participant (12.5%, 3 participants in the LEN group). All AEs were Grade 1 or 2. The AE considered related to study drug that was reported in > 1 participant was nausea (8.3%, 2 participants in the LEN group).

For the All LEN Analysis (participants who received at least 1 dose of LEN [oral or SC]), the percentage of participants who received LEN in Cohorts 1 and 2 and experienced AEs was 91.7% (66 of 72 participants) (Table 4). The 3 most commonly reported AEs were all ISRs, as follows (m2.7.4, Table 11):

- Injection site swelling (29.2%, 21 of 72 participants)
- Injection site erythema (26.4%, 19 participants)
- Injection site pain (25.0%, 18 participants)

The majority of AEs were Grade 1 or 2 in severity. Grade 3 or higher AEs were reported for 13 participants (18.1%). Grade 3 or higher AEs that were reported for ≥ 2 participants were injection site erythema (5.6%, 4 participants), injection site edema, and injection site swelling (2.8%, 2 participants each). Three participants experienced Grade 3 ISRs that were attributed to enfuvirtide.

Four participants experienced Grade 3 or higher AEs that were considered related to study drug: rash and abdominal abscess, injection site swelling and injection site erythema, injection site pain, and immune reconstitution inflammatory syndrome (1 participant each).

For the All LEN Analysis, 62.5% (45 of 72 participants) experienced study drug–related AEs. The most commonly reported study drug–related AEs (reported in ≥ 5% of participants) were injection site swelling (26.4%, 19 participants), injection site erythema (23.6%, 17 participants), and injection site pain (19.4%, 14 participants). Excluding ISRs, nausea was the most common study drug–related AE (4.2%, 3 participants).

For the All LEN Analysis, 40 participants (55.6%) experienced a study drug-related ISR. All were Grade 1 or 2, with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR that resolved after a few days. The median (Q1, Q3) total duration of any study drug–related ISR was 8 (3, 57) days (m2.7.4, Section 2.1.7.1).

Table 4. GS-US-200-4625: Treatment-Emergent Adverse Events: Overall Summary (All LEN Analysis) (Safety Analysis Set)

Number (%) of Participants With Any	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)		
TEAE	22 (91.7%)	11 (91.7%)	33 (91.7%)	33 (91.7%)	66 (91.7%)
TEAE With Grade 3 or Higher	3 (12.5%)	2 (16.7%)	5 (13.9%)	8 (22.2%)	13 (18.1%)
TEAE With Grade 2 or Higher	12 (50.0%)	5 (41.7%)	17 (47.2%)	22 (61.1%)	39 (54.2%)
TEAE Related to Study Drug	17 (70.8%)	6 (50.0%)	23 (63.9%)	22 (61.1%)	45 (62.5%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0	0	4 (11.1%)	4 (5.6%)
TEAE Related to Study Drug With Grade 2 or Higher	6 (25.0%)	2 (16.7%)	8 (22.2%)	11 (30.6%)	19 (26.4%)
TE Serious AE	1 (4.2%)	1 (8.3%)	2 (5.6%)	2 (5.6%)	4 (5.6%)
TE Serious AE Related to Study Drug	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study	0	0	0	1 (2.8%)	1 (1.4%)
All Deaths	0	0	0	1 (2.8%)	1 (1.4%)

AE = adverse event; LEN = lenacapavir; TE = treatment emergent; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAE was defined as an AE that began on or after the first dose date of LEN.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Death includes any death that occurred on and after the first dose date of LEN.
Source: m2.7.4, Table 7

5.1.3.2. Treatment-Naive PWH: Study GS-US-200-4334

Similar percentages of participants in the LEN-containing (total of 157 participants) and BVY (total of 25 participants) treatment groups had any AE by Week 28 (LEN total group 86.6%, 136 participants; BVY group 84.0%, 21 participants) (Table 5). The most commonly reported AEs by treatment groups were as follows (m2.7.4, Table 12):

- LEN total (157 participants), excluding ISRs: headache (11.5%, 18 participants), nausea (10.8%, 17 participants), and lymphadenopathy (7.6%, 12 participants)
- SC LEN total (105 participants), only ISRs: injection site swelling (22.9%, 24 participants), injection site erythema and injection site pain (each 21.0%, 22 participants)
- Oral LEN + DVY (52 participants): headache (13.5%, 7 participants), nausea, lymphadenopathy, diarrhea, back pain, and urinary tract infection (each 7.7%, 4 participants)
- BVY (25 participants): syphilis, insomnia, and weight increased (each 12.0%, 3 participants).

The majority of the AEs reported in the 4 treatment groups were Grade 1 or 2 in severity. The percentage of participants with Grade 3 or higher AEs was 7.0% (11 of 157 participants) in the LEN-containing treatment groups and 4.0% (1 of 25 participants) in the BVY treatment group. No Grade 3 or higher AEs were reported for more than 1 participant in any treatment group.

The percentages of participants with study drug–related AEs were as follows:

- LEN total (157 participants): 34.4% (54 participants)
- SC LEN total (105 participants): 44.8% (47 participants)
- Oral LEN + DVY (52 participants): 13.5% (7 participants)
- BVY (25 participants): 16.0% (4 participants)

The higher frequency of study drug–related AEs in the SC LEN total group was mainly because of ISRs, as reflected in the most common AEs considered related to study drugs:

- LEN total group (157 participants), excluding ISRs: nausea (4.5%, 7 participants), diarrhea (2.5%, 4 participants), fatigue, and headache (each 1.9%, 3 participants)
- SC LEN total group (105 participants), only ISRs: injection site swelling (18.1%, 19 participants), injection site erythema (16.2%, 17 participants), injection site pain (15.2%, 16 participants)

- Oral LEN + DVY (52 participants): nausea (3.8%, 2 participants), diarrhea (3.8%, 2 participants), fatigue, headache, dyspepsia, flatulence, vomiting, weight increased, overdose, and hot flush (each 1.9%, 1 participant)

- BVY (25 participants): dyspepsia, salivary hypersecretion, insomnia, and weight increased (4.0%, 1 participant)

Overall, 40 of 103 participants (38.8%) who received SC LEN had a study drug–related ISR; all were Grade 1 or 2, except for 1 participant with a Grade 3 injection site nodule (m2.7.4, Section 2.1.7.2). Two of 105 participants (1.9%) in the SC LEN total group experienced AEs of injection site induration that led to a premature discontinuation of study drug.

Table 5. GS-US-200-4334: Treatment-Emergent Adverse Events: Overall Summary (Safety Analysis Set)

Number (%) of Participants With Any	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
TEAE	50 (96.2%)	44 (83.0%)	42 (80.8%)	21 (84.0%)	94 (89.5%)	136 (86.6%)
TEAE With Grade 3 or Higher	1 (1.9%)	4 (7.5%)	6 (11.5%)	1 (4.0%)	5 (4.8%)	11 (7.0%)
TEAE With Grade 2 or Higher	18 (34.6%)	15 (28.3%)	18 (34.6%)	11 (44.0%)	33 (31.4%)	51 (32.5%)
TEAE Related to Study Drug	27 (51.9%)	20 (37.7%)	7 (13.5%)	4 (16.0%)	47 (44.8%)	54 (34.4%)
TEAE Related to Study Drug With Grade 3 or Higher	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
TEAE Related to Study Drug With Grade 2 or Higher	8 (15.4%)	2 (3.8%)	0	0	10 (9.5%)	10 (6.4%)
TE Serious AE	2 (3.8%)	2 (3.8%)	4 (7.7%)	0	4 (3.8%)	8 (5.1%)
TE Serious AE Related to Study Drug	0	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)
TEAE Leading to Premature Discontinuation of Study	0	0	0	0	0	0
Death	0	0	0	0	0	0

AE = adverse event; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; TE = treatment-emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Source: m2.7.4, Table 8

5.1.3.3. Healthy Participants: Pooled Studies GS-US-200-4538 and GS-US-200-5709

The percentages of participants with any AE in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 were as follows: LEN 92.7%, 51 of 55 participants; placebo 85.0%, 17 of 20 participants (Table 6).

The majority of AEs were Grade 1 in severity. Grade 3 or higher AEs were reported as follows: LEN 1.8%, 1 participant (tibia fracture); placebo 5.0%, 1 participant (sepsis). The AEs considered related to study drug were reported as follows: LEN 83.6%, 46 of 55 participants; placebo 70.0%, 14 of 20 participants. There were no Grade 3 or higher AEs considered related to study drugs reported. The 3 most commonly reported AEs considered related to study drug in each treatment group were:

- LEN: injection site induration (70.9%, 39 participants), injection site pain (56.4%, 31 participants) and injection site erythema (45.5%, 25 participants)
- Placebo: injection site bruising (40.0%, 8 participants), injection site induration (30.0%, 6 participants), and injection site pain (20.0%, 4 participants)

Table 6. GS-US-200-4538 and GS-US-200-5709: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	LEN (N = 55)	Placebo (N = 20)
TEAE	51 (92.7%)	17 (85.0%)
TEAE With Grade 3 or Higher	1 (1.8%)	1 (5.0%)
TEAE With Grade 2 or Higher	7 (12.7%)	2 (10.0%)
TEAE Related to Study Drug	46 (83.6%)	14 (70.0%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0
TEAE Related to Study Drug With Grade 2 or Higher	3 (5.5%)	0
TE Serious AE	1 (1.8%)	1 (5.0%)
TE Serious AE Related to Study Drug	0	0
TEAE Leading to Discontinuation of Study Drug	1 (1.8%)	0
TEAE Leading to Discontinuation of Study	1 (1.8%)	0
Death	0	0

AE = adverse event; TE = treatment-emergent; TEAE = treatment-emergent adverse event.
AEs were coded according to MedDRA Version 23.1.
TEAEs began on or after the study drug start date, or led to premature study drug discontinuation.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Death includes any death that occurred during the study.
Source: m2.7.4, Table 9

5.1.4. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

5.1.4.1. Deaths

In Study GS-US-200-4625, no deaths were reported during the Functional Monotherapy Period. One participant in Cohort 2 died on Study Day 90; the cause of death was cancer.

No deaths were reported in Study GS-US-200-4334 or in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709.

5.1.4.2. Serious Adverse Events

In Study GS-US-200-4625, no serious AEs (SAEs) were reported during the Functional Monotherapy Period. For the All LEN Analysis (through the entire follow-up period), SAEs were reported for 5.6% (4 of 72 participants); no SAEs were reported in > 1 participant. One SAE of cancer resulted in death.

In Study GS-US-200-4334, SAEs were reported for 5.1% (8 of 157 participants) in the LEN-containing treatment groups and none of the participants in the BVY treatment group. No SAEs were reported in > 1 participant in any treatment group. For the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709, SAEs were reported for 1 participant (1.8%) in the LEN group (tibia fracture) and 1 participant (5.0%) in the placebo group (sepsis).

None of the SAEs were considered related to study drug or led to discontinuation of study drug.

5.1.4.3. Adverse Events Leading to Discontinuation of Study Drug

No participants in Study GS-US-200-4625 prematurely discontinued study drugs due to AEs.

For Study GS-US-200-4334, the only AE that led to a premature discontinuation of study drug was injection site induration, which occurred in 2 of 105 participants (1.9%) in the SC LEN total group. Both occurrences were nonserious and Grade 1 in severity. For the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709, 1 participant in the LEN group prematurely discontinued study drug and the study due to an AE (SARS-CoV-2 test positive).

5.1.5. Clinical Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for hematology, clinical chemistry (including metabolic parameters) in Studies GS-US-200-4625, GS-US-200-4334, and the pooled Studies GS-US-200-4538 and GS-US-200-5709.

5.1.5.1. Graded Laboratory Abnormalities

5.1.5.1.1. HTE PWH: Study GS-US-200-4625

The majority of participants in the Functional Monotherapy Period had at least 1 graded laboratory abnormality (LEN 75.0% [18 of 24 participants]; placebo 75.0% [9 of 12 participants]). The majority of abnormalities were Grade 1 or 2. Grade 3 laboratory abnormalities were reported for 3 participants (12.5%) in the LEN group (increased creatinine, hyperglycemia [nonfasting], and increased lipase) and no participants in the placebo group. No participants experienced Grade 4 laboratory abnormalities.

For the All LEN Analysis, the majority of the participants had at least 1 graded laboratory abnormality (91.7%, 66 of 72 participants). The majority of abnormalities were Grade 1 or 2. Grade 3 laboratory abnormalities were reported for 15 participants (20.8%) and Grade 4 laboratory abnormalities were reported for 4 participants (5.6%).

For both the Functional Monotherapy Period and All LEN Analysis, none of these laboratory abnormalities were considered clinically relevant, all were transient, improved on subsequent visits despite continued exposure to the study drug, or participants had previous underlying conditions such as diabetes. No participants had Grade 3 or higher increased creatine kinase (CK) or CK-associated AEs such as rhabdomyolysis during the study.

5.1.5.1.2. Treatment-Naive PWH: Study GS-US-200-4334

Graded laboratory abnormalities in Study GS-US-200-4334 were reported for the majority of the participants in all treatment groups and the majority of the laboratory abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 19 of 157 participants (12.1%) in the LEN total group and 3 participants (12.0%) in the BVY group. Grade 3 laboratory abnormalities reported for > 2 participants in either the LEN total or BVY groups were low CL_{cr} or estimated glomerular filtration rate (eGFR) (LEN total 6 participants, BVY 2 participants), high aspartate aminotransferase (AST) (LEN total 4 participants), glycosuria (LEN total 4 participants), high CK (LEN total 4 participants), high creatinine (LEN total 3 participants, BVY 1 participant), fasting hyperglycemia (LEN total 3 participants).

Grade 4 laboratory abnormalities were reported in the LEN total group only (4.5% [7 of 157 participants]) and included high CK (3 participants), high alanine aminotransferase (ALT) (1 participant), hyperbilirubinemia (1 participant), fasting triglycerides (1 participant), high lipase (1 participant), and nonfasting hyperglycemia (1 participant).

None of these laboratory abnormalities were considered clinically relevant, all were transient or unconfirmed, or participants had a medical history of underlying conditions such as diabetes. Grade 3 or higher abnormalities of high CK were isolated and infrequent, improved on subsequent visits despite continued exposure to the study drug and were attributed to strenuous activity, dehydration, or use of creatine. There were no CK-associated AEs such as rhabdomyolysis during the study.

5.1.5.1.3. Healthy Participants: Pooled Studies GS-US-200-4538 and GS-US-200-5709

Graded laboratory abnormalities in the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 were reported for the majority of participants. Most of them were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 8 of 55 participants (14.5%) in the LEN group and 4 participants (20.0%) in the placebo group. Grade 3 laboratory abnormalities reported for > 1 participant were decreased CL_{cr} (2 of 55 participants, 3.6%), increased low density lipoprotein (fasting) (3 of 55 participants, 5.5%), and increased triglycerides (fasting) (3 of 55 participants, 5.5%) in the LEN group and increased creatinine phosphokinase (CPK) (2 of 20 participants, 10.0%) in the placebo group.

Grade 4 laboratory abnormalities were reported for 2 of 55 participants (3.6%) who received LEN (increased fasting triglycerides) and 1 of 20 participants (5.0%) who received placebo (increased CPK, increased lipase, and increased AST).

None of the graded laboratory abnormalities were considered clinically relevant as they were transient or unconfirmed, or participants had a medical history of underlying conditions.

In Cohort 3 of Study GS-US-200-4329, evaluating the safety, tolerability, PK, metabolism, and excretion of LEN following a single IV dose in healthy participants, 1 participant who received LEN 20 mg had a Grade 4 SAE of rhabdomyolysis, which was considered related to study drug by the investigator. The SAE started 21 days after the C_{max}, when the LEN concentration was approximately 150-fold lower than C_{max} (Day 22: 1.43 ng/mL; Day 1: 210 ng/mL), and the SAE resolved during continued exposure to LEN, which makes the causal relationship unlikely (m2.7.4, Section 3.1).

5.1.5.2. Analysis of Laboratory Parameters for Selected Organs

5.1.5.2.1. Hepatic Safety

Across studies, Grade 3 or higher hepatic laboratory abnormalities were infrequent. There were no clinically relevant changes from baseline in ALT, AST, alkaline phosphatase, or total bilirubin (m2.7.4, Section 3.1.1).

5.1.5.2.2. Renal Safety

Across studies, Grade 3 or higher renal laboratory abnormalities were infrequent. There were no clinically relevant changes from baseline in serum creatinine or eGFR (m2.7.4, Section 3.1.2).

5.1.6. Analysis of Adverse Drug Reactions

The primary safety data supporting the Adverse Reactions section of the LEN prescribing information are provided from the Phase 2/3 Study GS-US-200-4625. Supportive safety data for LEN are provided from the Phase 2 Study GS-US-200-4334, and the integrated summary of safety presenting a pooled analyses of 2 Phase 1 studies (GS-US-200-4538 and GS-US-200-5709) evaluating the safety and PK of LEN in healthy participants.

Based on an assessment of safety data from these studies, nausea and ISRs (including injection site swelling, erythema, nodule, pain, induration, pruritus, discomfort, granuloma, extravasation, hematoma, edema, and ulcer) were identified as adverse drug reactions for LEN.

A higher proportion of participants experienced nausea in the LEN group than the placebo group during the Functional Monotherapy Period in Study GS-US-200-4625 (3 participants [12.5%] versus 0 participants) and in the LEN total group than the BVY group in Study GS-US-200-4334 (17 participants [10.8%] versus 1 participant [4.0%]). Most AEs of nausea were Grade 1 in severity, and resolved while participants remained on treatment; none resulted in premature study drug discontinuation.

Across all 3 datasets, ISRs were the most frequently reported AEs considered related to study drug (Section 5.1.3). The majority of ISRs associated with LEN were Grade 1 or 2 in severity, with very few leading to discontinuation; 2 participants (1.9%) in Study GS-US-200-4334 prematurely discontinued due to Grade 1 AEs of injection site induration.

5.2. Safety in Special Populations

5.2.1. Safety by Demographic Factors

No impact of age, sex, and race was identified on the PK of LEN (m2.7.2, Section 3.1.6.4).

Summaries of AE incidence by subgroup are provided by age group, sex, and race in the individual clinical study reports (CSRs) (GS-US-200-4625 Interim Week 26 CSR, Tables 15.11.2.1.4.1 to 15.11.2.1.4.3 and GS-US-200-4334 Interim Week 28 CSR, Tables 15.11.2.1.4.1 to 15.11.2.1.4.3). No clinically meaningful conclusions can be made due to the low number of participants in each subgroup; however, based on the available data, there is no difference in the safety profile of LEN in subgroups based on age, sex, or race.

5.2.2. Safety in Hepatic Impairment

The effect of hepatic impairment on the PK of LEN was evaluated in a dedicated Phase 1 study (GS-US-200-4331) in participants with moderate hepatic impairment (Child-Pugh-Turcotte Class B) and healthy matched control participants with normal hepatic function (m2.7.2, Section 3.1.6.3.2).

Based on cumulative PK data, no dose adjustment of LEN is recommended in people with mild to moderate hepatic impairment (Child-Pugh Class A or B). The PK of LEN has not been evaluated in participants with severe hepatic impairment (Child-Pugh Class C).

5.2.3. Safety in Renal Impairment

The effect of renal impairment on the PK of LEN was evaluated in a dedicated Phase 1 study (GS-US-200-4330) in participants with severe renal impairment ($15 \leq CL_{cr} \leq 29$ mL/min at screening that was unchanged over 3 months) and healthy matched control participants with normal renal function (m2.7.2, Section 3.1.6.3.1).

Based on cumulative safety data in the LEN SC and oral clinical program, including clinical safety and PK data at supratherapeutic exposure, no dose adjustment of LEN is required in people with renal impairment ($CL_{cr} \geq 15$ mL/min). In agreement with the dedicated renal impairment study, findings in the population PK modeling did not identify eGFR as a statistically significant covariate on LEN exposure. Lenacapavir has not been studied in people with end-stage renal disease not on dialysis. As LEN is greater than 98.5% protein bound, dialysis is not expected to alter exposures of LEN.

5.2.4. Safety in Pediatrics and Adolescents

Use of LEN in pediatric participants has not been evaluated in clinical studies at this time. Furthermore, while the protocol allowed it, no adolescents have been enrolled in the LEN clinical development program. In the absence of observed LEN PK data, model-based simulations were performed in pediatric participants 12 to < 18 years of age and weighing ≥ 35 kg following the Phase 2/3 dosing regimen. LEN-simulated exposures were largely contained within the range observed in the adult Phase 2/3 population. The median simulated exposures were found to be within the 25th and 75th percentiles of adult's exposure across all weight groups. Based on these simulations, LEN may be administered to adolescent HTE PWH 12 to < 18 years of age and weighing ≥ 35 kg without any dose modification (m2.7.2, Section 3.1.6.4.1.2).

5.2.5. Safety in Pregnancy and Lactation

No clinical studies of LEN have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of LEN with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. No pregnancies were reported in the LEN clinical studies.

No formal DDI studies between LEN and hormonal contraceptives have been conducted. Based on in vitro and in vivo DDI liability assessments, clinically significant DDIs between LEN and hormonal contraceptives are not anticipated.

LEN was detected in the plasma of nursing rat pups. It is not known if LEN is secreted in human milk.

5.3. Safety Discussion and Conclusions

In summary, the safety results from the Phase 2/3 study in HTE PWH with MDR (Study GS-US-200-4625), the Phase 2 study in treatment-naive PWH (Study GS-US-200-4334), and from the pooled analyses of 2 Phase 1 studies (GS-US-200-4538 and GS-US-200-5709) of LEN in healthy participants demonstrated the following:

- Treatment with LEN for up to 28 weeks was generally safe and well tolerated. There were no study drug-related SAEs and only 2 treatment-naive participants experienced study drug-related AEs leading to premature discontinuation of study drug (AEs of injection site induration, both Grade 1).
- The most common study drug–related AEs were ISRs; the majority were Grade 1 or 2 in severity.

- There was a low incidence of Grade 3 or higher laboratory abnormalities (approximately 20% of all participants who received LEN). Most were transient, improved on subsequent visits despite continued exposure to the study drug, or participants had alterative etiologies.

- LEN has a favorable hepatic and renal profile, based on the low frequency of Grade 3 or higher laboratory abnormalities, and no clinically relevant changes from baseline in hepatic and renal parameters. No safety issues have been identified for LEN in participants with mild to moderate hepatic or severe renal impairment.

- Based on the available data, there is no difference in the safety profile of LEN due to age, sex, or race, although the number of participants in each subgroup is too low to draw meaningful conclusions.

In conclusion, LEN was generally safe and well tolerated in HTE PWH and treatment-naive PWH.

6. BENEFITS AND RISKS CONCLUSIONS

Once every 6 months SC LEN together with OBR forms a suitable treatment for HTE PWH, and the following considerations support a favorable benefit-risk profile for LEN treatment in this population with limited treatment options and high unmet need.

6.1. Therapeutic Context

There is a significant unmet need for developing safe and effective therapies that are not impacted by resistance to existing ARVs for PWH with MDR who are failing their current ARV regimen due to resistance, intolerance, or safety considerations. For these individuals who are not effectively treated with currently available medications, treatments with novel mechanisms of action are needed to control viral replication, preserve immune function, and prevent clinical progression.

6.1.1. Disease or Condition

HIV-1 infection is a life–threatening and serious disease of major public health significance, with approximately 38 million people infected worldwide of which approximately 26 million are on ARV treatment. However, in 2019, 690,000 people died from AIDS−related causes worldwide.

Standard-of–care for the treatment of most PWH involves the use of a combination of oral ARV drugs {European AIDS Clinical Society (EACS) 2020, U. S. Department of Health & Human Services (DHHS) 2019}. Combination treatment has led to significant improvements in morbidity and mortality among PWH by suppressing viral replication, preserving and reconstituting immunologic function, preventing HIV transmission, and averting disease progression to AIDS {UNAIDS 2020}.

Some treatment−experienced PWH, however, eventually lose virologic, immunologic, or clinical benefit from their current regimens. Several factors drive multiple treatment failures such as interruption of or intermittent access to ART, adverse drug effects, high pill burden and/or dosing frequency, lack of adherence to treatment, inappropriate ARV combinations (eg, numbers of active agents in a regimen, preexisting resistance mutations), DDIs, or drug-food interaction. Patients with multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV viral suppression {U. S. Department of Health & Human Services (DHHS) 2019}. In certain situations, virological suppression is not considered possible due to the viral resistance profile and the treatment goal is to keep the viral load as low and the CD4 count as high as possible {U. S. Department of Health & Human Services (DHHS) 2019}.

People with HIV with MDR frequently do not have a single fully active ARV agent available, and are even less likely to have 2 or 3 active agents. Those PWH are often treated only with suboptimal partially active agents, and are not able to achieve or maintain virologic suppression, which can lead to ongoing viremia and decreasing CD4 cell count, putting them at risk of AIDS-defining opportunistic infections and death. Specifically, PWH with MDR have a greater risk of death and of developing new comorbidities (AIDS and non-AIDS related), including

malignancies {Cossarini 2013, Deeks 2009, Galli 2020, Pelchen-Matthews 2021, Phillips 2007}. Furthermore, the clinical response to ART for PWH with low CD4 counts, opportunistic infections and comorbidities can be limited, making the need for effective therapies that limit disease progression urgent. In these patients there remains a high unmet medical need for new well-tolerated therapies that are effective despite the presence of resistance to available ARVs and low CD4 counts, that do not exacerbate ARV-related toxicities, and are simple for people already taking complex combination ARV regimens.

6.1.1.1. Current Therapies

Use of current ARV drugs has resulted in a dramatic decline in the number of PWH with MDR who have few treatment options. Despite this progress, there remain people who have experienced treatment-limiting toxicities or have developed resistance to all or most currently available drugs.

The goal of treatment for ART−experienced PWH with MDR who are experiencing virologic failure is to establish virologic suppression. If maximal virologic suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize the development of further resistance that may compromise future regimens {U. S. Department of Health & Human Services (DHHS) 2019}.

The choice of ARV agents in the management of HTE PWH with MDR is not standardized but general principles apply. The new regimen should generally contain at least 2, preferably 3, fully active ARV agents, based on resistance mutations present in current and earlier genotypic analyses {U. S. Department of Health & Human Services (DHHS) 2019, UNAIDS 2020}. Many HTE PWH with MDR have regimens comprised of more than 3 ARV agents, each of which may have only partial activity.

When options are limited, using an experimental/newly approved agent is a frequent option as a new mechanism of action usually implies no cross resistance with existing available agents {European AIDS Clinical Society (EACS) 2020, Panel on Antiretroviral Guidelines for Adults and Adolescents 2019}.

Currently 2 novel treatments are available for PWH with MDR:

- Ibalizumab, a monoclonal humanized antibody that targets CD4 cell receptors to prevent HIV entry, for IV infusion every 2 weeks.
  - In a Phase 3 study of HTE PWH failing treatment with at least 1 fully active ARV agent available for use in an OBR, 83% (33 of 40 participants) had a decline in HIV-1 RNA ≥ 0.5 $\log_{10}$ copies/mL after 7 days of functional monotherapy
  - 43% of participants had HIV-1 RNA < 50 copies/mL at Week 25 of treatment with ibalizumab plus OBR {Emu 2018}

- Fostemsavir, an orally administered twice daily attachment inhibitor that selectively inhibits the interaction between HIV and cellular CD4 receptors, thereby preventing viral entry into the host cells.

  — In a Phase 3 study of HTE PWH failing treatment with at least 1 fully active ARV agent available for use in an OBR, 65% (131 of 203 participants) had a decline in HIV-1 RNA ≥ 0.5 $\log_{10}$ copies/mL after 7 days of functional monotherapy {RUKOBIA 2020}

  — 53% of participants had HIV-1 RNA < 40 copies/mL at Week 24 of treatment with fostemsavir plus OBR {Kozal 2020}

Other older products that are approved in the EU and US for use in treatment-experienced adults are often used in the treatment of HTE patients and include the following:

- Maraviroc, a chemokine receptor 5 (CCR5) antagonist, which selectively binds to the human chemokine receptor CCR5, preventing CCR5−tropic HIV from entering cells. However, many treatment-experienced PWH do not have CCR5−tropic HIV, but instead CXCR4-tropic HIV or mixed-tropic HIV, which thereby precludes its use.

- Enfuvirtide, is a fusion inhibitor of the structural rearrangement of the HIV-1 glycoprotein 41 (gp41) binding to this protein and blocking fusion between the viral and target cell membranes preventing viral RNA from entering the cell. It is administered by SC injection twice daily and is commonly associated with clinically significant ISRs.

- Protease inhibitors such as DRV twice daily, given together with a pharmacoenhancer such as ritonavir, the INSTI DTG twice daily, and the NNRTI etravirine (ETV) twice daily are also often used as part of a regimen for HTE PWH.

Treatment adherence is key for these patients as ART regimens in HTE PWH are usually complex with multiple pills taken several times per day; in addition, these patients are often taking other concomitant medications to prevent or treat opportunistic infections or comorbid diseases. Despite multiple agents for the HTE population, individuals still fail therapy, including with resistance to these agents. Agents with novel mechanisms of action can bypass the challenges posed by resistance and easier delivery mechanisms can facilitate effective use ensuring therapeutic drug levels over long-term therapy.

6.2. Benefits

Lenacapavir led to a rapid and clinically relevant decline in viral load when added to a failing regimen in HTE PWH.

Following initiation of LEN in Study GS-US-200-4625, a rapid decline in HIV-1 RNA was observed; 87.5% (21 of 24) of participants receiving LEN had a ≥ 0.5 $\log_{10}$ copies/mL reduction of HIV-1 RNA as compared to 16.7% (2 of 12) participants receiving placebo at the end of the 14-day Functional Monotherapy Period (proportional difference: 70.8%; 95% CI: 34.9% to 90.0%; $P < 0.0001$) (Section 4.4). High efficacy was demonstrated across participants with a high baseline HIV-1 viral load and in those with a low baseline CD4 cell count. This study was

designed in accordance with the guidance of FDA for study designs to show efficacy in PWH who have drug resistance to multiple drugs and multiple−drug classes and are unable to construct a viable suppressive regimen {U. S. Department of Health and Human Services 2015}. In this patient population, LEN has demonstrated clinically significant short-term antiviral activity by reducing HIV-1 RNA ≥ 0.5 $\log_{10}$ copies/mL.

In addition to meeting the primary end point of the study, the mean (SD) change in HIV-1 RNA in participants receiving LEN during the Functional Monotherapy Period was −1.93 (0.893) $\log_{10}$ copies/mL at Day 15, compared with −0.29 (0.614) $\log_{10}$ copies/mL for those receiving placebo (difference in LSM: −2.17; 95% CI: −2.74, −1.59; $P < 0.0001$) (see Section 4.4).

Such significant reductions in HIV-1 RNA over a 2-week period as demonstrated with LEN functional monotherapy (−1.93 $\log_{10}$ copies/mL) have been associated with a reduced risk of disease progression and death when maintained over at least 16 to 24 weeks of treatment, as they were through Week 26 in Study GS-US-200-4625 (−2.45 $\log_{10}$ copies/mL) {Department for Health and Human Services (DHHS) 2015, Marschner 1998, Murray 1999}. These data demonstrate the potent antiviral activity of LEN in HTE PWH with MDR and low baseline CD4 cell counts.

LEN in combination with an OBR led to sustained viral load reductions and high rates of virologic suppression at Week 26 in HTE PWH.

In Study GS-US-200-4625, after the initial rapid short−term decline in HIV-1 RNA, viral load reductions increased on treatment with LEN plus OBR and were sustained through Week 26. In the All LEN Analysis, the mean (SD) baseline HIV-1 RNA values were 4.11 (1.031) $\log_{10}$ copies/mL and the mean (SD) change from baseline in HIV-1 RNA at Week 26 was −2.45 (1.162) $\log_{10}$ copies/mL (m2.7.3, Section 3.2.1.3).

High rates of virologic suppression were achieved at Week 26 in HTE participants when LEN was combined with an OBR. In Cohort 1, 80.6% of participants (29 of 36) had HIV-1 RNA < 50 copies/mL at Week 26 using FDA-Snapshot algorithm. When using a threshold of HIV-1 RNA of < 200 copies/mL, 88.9% of participants (32 of 36) in Cohort 1 had HIV-1 RNA < 200 copies/mL at Week 26 (m2.7.3, Section 3.2.1.2). Even the participants who had HIV-1 RNA ≥ 200 copies/mL in the Week 26 Snapshot analysis demonstrated and maintained clinically significant antiviral responses after starting the study regimen of LEN plus OBR (see Section 4.4).

For further context to the efficacy data from Study GS-US-200-4625, Table 7 provides the efficacy data for LEN and 2 other products approved for the treatment of adults PWH with MDR.

Table 7. Virologic Suppression in Functional Monotherapy and Maintenance Periods Following LEN, Ibalizumab, or Fostemsavir Treatment

	LEN	Ibalizumab	Fostemsavir
Duration of the Functional Monotherapy Period (days)[a]	**14**	**7**	**7**
Participants with HIV-1 RNA ≥ 0.5 $\log_{10}$ copies/mL reduction	88% (21/24)	83% (33/40)[b]	65% (131/203)[c]
Mean change in HIV-1 RNA ($\log_{10}$ copies/mL)	−1.9	−1.1	−0.8
Maintenance Period	**No minimum number of fully active OBR agents**	**≥ 1 fully active OBR agent**	
Participants with HIV-1 RNA < 50 copies/mL	81% (Week 26)	43% (Week 25)	53% (Week 24)[d]

LEN = lenacapavir; OBR = optimized background regimen
a. Time points: Day 14 for LEN and ibalizumab (treatment from Day 7 to Day 14 for Ibalizumab), Day 8 for fostemsavir
b. {Emu 2018}
c. {RUKOBIA 2020}
d. Cutoff for fostemsavir was < 40 copies/mL

Moreover in Study GS-US-200-4625, high rates of virologic suppression at Week 26 were consistently achieved even in participants with suboptimal OBR. In the total population analysis, high rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were observed at Week 26 in subgroups with OSS < 2, those with either 0 or only 1 fully active agent in the OBR, those with neither DTG nor DRV in the OBR and participants with resistance to INSTIs, thus demonstrating a clinically significant contribution of LEN toward virologic suppression across a diverse and difficult-to–treat population (m2.7.3, Table 16).

Data are complete for the participants in Cohort 1 of Study GS-US-200-4625 through 6 months after receiving SC LEN and continued follow-up of participants in the study will allow the longer-term efficacy of LEN with an OBR to be evaluated.

Clinically meaningful increases in CD4 cell counts were observed over 26 weeks following LEN administration together with OBR.

In PWH, CD4 cell count is the most important laboratory indicator of immune function. It is the strongest predictor of subsequent disease progression and survival {Egger 2002, Mellors 1997}. Most life-threatening opportunistic infections or malignancies occur in PWH with CD4 counts < 200 cells/µL, which is indicative of advanced HIV infection and is an AIDS defining criterion {Selik 2014}. The PWH with CD4 cell counts < 200 cells/µL have over 2.5 times higher risk for death within 3 years than PWH with CD4 cell counts > 200 cells/µL {Engsig 2014}, and most PWH who die of AIDS-related complications have CD4 cell counts < 200 cells/µL. In the absence of an effective ART, the median survival of patients with advanced HIV infection and a CD4 cell count < 50 cells/µL is 12 to 18 months {Easterbrook 1993, Phillips 1992, Yarchoan 1991}. In addition, the immunologic recovery via increased CD4 cell count is generally less robust for an individual who starts ART with a low CD4 cell count, making treatment of PWH with advanced disease urgent.

In Study GS-US-200-4625, HTE participants in Cohorts 1 and 2 were severely immunosuppressed, as demonstrated by low baseline median (Q1, Q3) CD4 cell counts 150 (76, 286) cells/µL. A total of 63.9% of participants had CD4 cell counts < 200 cells/µL, and 22.2% had CD4 cell counts < 50 cells/µL. At Week 26, increase in the mean (SD) CD4 cells from baseline in the 40 participants receiving at least 1 dose of LEN was 90 (102.1) cells/µL. Moreover, among 36 participants in Cohort 1, where the follow-up is complete through Week 26, the categorical distribution of CD4 cell counts markedly improved: the percentage of participants with CD4 cell counts < 350 cells/µL decreased from 91.7% (33 of 36 participants) at baseline to 73.5% (25 of 34 participants) at Week 26; CD4 cell counts < 200 cells/µL decreased from 75.0% (27 of 36 participants) to 50.0% (17 of 34 participants); CD4 cell counts < 50 cells/µL decreased from 22.2% (8 of 36 participants) to none (Table req13067.1.1). These improvements through Week 26 in HTE PWH demonstrate the immunologic benefit of treatment with LEN plus OBR.

For PWH with low CD4 cell counts at baseline, the increase in CD4 cells can substantially reduce the risk of mortality, morbidity from HIV/AIDS-related diseases including opportunistic infections and non-AIDS conditions including cardiovascular disease, osteoporosis, liver disease, and infection-related cancers {U. S. Department of Health & Human Services (DHHS) 2019}. The benefits of incremental increases in CD4 cell counts are measurable at any baseline CD4 level, but are most significant for patients with low CD4 cell counts < 200 cells/µL commonly observed in HTE PWH {Young 2012}. Even in virologically suppressed PWH, low CD4 cell counts remain an important risk factor for long-term mortality {Loutfy 2010}.

Combined with the antiviral response to ART, as measured by HIV-1 RNA, these improvements in CD4 counts may also enable patients to discontinue medications for primary and secondary prophylaxis against opportunistic infections, reducing the risks associated with polypharmacy including harmful DDIs and unwanted drug-related adverse effects.

LEN has a novel mechanism of action without preexisting resistance or cross resistance to other drug classes.

Lenacapavir is a first-in–class inhibitor of HIV capsid function. Lenacapavir retains full antiviral activity in the presence of mutations associated with resistance to other ARV classes. In clinical studies of both HTE and treatment-naive PWH, no LEN-associated substitutions were detected at baseline in HIV capsid that would confer LEN resistance in any participants (Studies GS-US-200-4625 and GS-US-200-4334). These data indicate that LEN will retain full antiviral activity across the diverse populations of HTE PWH, regardless of their prior treatment exposure or drug resistance (eg, PIs). In addition, PWH who are naive to capsid inhibitor can start LEN in combination with OBR without the need for additional genotypic or phenotypic testing for sensitivity to LEN.

Virologic breakthrough with emergent resistance to LEN occurred infrequently in HTE PWH.

In Study GS-US-200-4625, 8 of 72 participants (4 in each Cohorts 1 and 2) had emergent LEN resistance of whom 3 participants resuppressed at later visits (2 who continued treatment unchanged and 1 adjusted their OBR); 5 participants who were never virologically suppressed in the current data cut nevertheless had HIV-1 RNA reduction of ≥ 1.7 $\log_{10}$ copies/mL. Of those 5 participants, 2 did not have any fully active agent in the OBR, 2 had at least 2 fully active agents in the OBR (1 with reported poor adherence), and 1 died due to cancer on Day 90. No participant developed emergent resistance to the agents in the OBR. Other than the 1 participant who died, all 7 participants continue to remain in the study receiving LEN.

HIV-1 variants with LEN resistance have a significant reduction in replication capacity suggesting that these viruses are less fit in establishing or maintaining infection. Given some participants achieved virologic suppression while continuing LEN after emergent LEN resistance with minor or no changes to the OBR, the clinical relevance of LEN resistance and a causative relationship between LEN resistance and virologic failure has not been established (PC-200-2043).

Oral dosing of LEN rapidly achieves therapeutic concentrations, while SC LEN maintains predictable therapeutic target concentrations over 6 months.

The near maximal antiviral effect of LEN was observed at a concentration representing an IQ4 for wild−type virus. Oral dosing of LEN (600 mg on Days 1 and 2) rapidly reaches therapeutic plasma concentrations above the target IQ4 by approximately 1 hour postdose on Day 1 and SC dosing maintains concentrations that exceed the IQ4 for 6 months without the need for redosing. At the end of 26 weeks after SC dosing, LEN was predicted to maintain a mean concentration (90% CI) of 29.2 (24.6, 32.5) ng/mL corresponding to IQ (90% CI) of 7.5 (6.3, 8.4) in PWH, based on simulated data (m2.7.2, Section 3.2.1.1). Twenty-eight weeks after LEN SC dosing, the mean LEN concentration (90% CI) is 24.5 ng/mL (20.4, 27.3) corresponding to a mean IQ (90% CI) of 6.3 (5.2, 7.1) (m2.7.2, Section 3.2.1.2). Therefore, participants dosed with LEN will have concentrations above the therapeutic target threshold for HIV-1 treatment for at least 2 weeks after their next scheduled dose (ie, 26 weeks after the last LEN SC dosing), thus providing a safe and flexible window for receiving their subsequent dose. Steady and constant therapeutic concentrations over a long duration may be beneficial in maintaining durable virologic suppression, as it does not have the uncertainty and variability that often occur with missed daily doses or incomplete adherence to daily medications.

Subcutaneous LEN dose at 6-monthly interval is synchronous with clinical care.

Every-6-month SC LEN dosing does not significantly increase the treatment burden on HTE PWH when added to an OBR, and can easily be integrated into routine clinical care. Most PWH receive complex treatment regimens, consisting of agents that require twice daily oral dosing with food (eg, boosted DRV) or without regard to food (eg, DTG, fostemsavir, and ETV), require SC twice daily (eg, enfuvirtide), or IV infusion every 2 weeks (eg, ibalizumab), making them challenging to adhere to consistently as a long-term therapy.

The dosing for LEN shifts and reduces the burden of maintaining therapeutic drug concentrations away from the requirement for daily pill taking behavior and towards less frequent clinical care visits every 6 months for SC LEN administration. Treatment guidelines recommend clinical and laboratory monitoring visits at a minimum of every 6 months for PWH and many HTE PWH may have more frequent monitoring. Dosing of LEN is done by SC injection that can be integrated into ongoing clinical care for these PWH where existing clinical structures can facilitate both dosing and adherence.

LEN can be administered to PWH with estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 15 mL/min without dose adjustment.

Many PWH with MDR have a long history of ARV treatment, are older, and thus are at greater risk of having comorbidities including chronic kidney disease. In Study GS-US-200-4625, participants with $eGFR_{CG}$ as low as 50 mL/min were allowed to enroll, the median age was 52 years (range: 23 to 78 years) and there were no clinically relevant changes in $eGFR_{CG}$ in participants treated with LEN.

Furthermore, LEN is not renally eliminated and no clinically meaningful changes in LEN PK were observed in participants with $eGFR_{CG}$ between 15 and 29 mL/min (inclusive) in a dedicated renal impairment study. The population PK modeling did not identify $eGFR_{CG}$ as a statistically significant covariate on LEN exposure. Therefore, LEN can be administered without dose adjustment in PWH with $eGFR_{CG} \geq 15$ mL/min.

LEN can be administered without dose adjustment in PWH with mild or moderate hepatic impairment.

Moderate hepatic impairment did not result in clinically relevant changes in LEN exposure. Therefore, LEN may be administered without dose adjustment in PWH with mild to moderate hepatic impairment.

LEN can benefit HTE adolescents, as the efficacy and safety profile are expected to be similar to adults.

There are limited ARV regimen options available for HTE adolescents PWH with MDR, who still require long-term sustained virologic suppression for a healthy adulthood. A clinical study in HTE adolescent PWH is not feasible due to the rarity of such individuals so that extrapolation of the results from adult participants in Study GS-US-200-4625 to adolescents is warranted. Extrapolation of efficacy for LEN from adults to adolescents is in accordance with the ICH E11 (R1) Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population and the FDA Draft Guidance How to Comply with the Pediatric Research Equity Act (2005), based on the similarity of the HIV disease process in adolescents and adults. Although LEN PK has not been evaluated in pediatric participants, simulated LEN exposures in adolescents 12 to < 18 years of age and weighing ≥ 35 kg were within the 25th to 75th percentile of observed adult exposures in the Phase 2/3 program (see Section 3.3.2); of note, the similarity of ARV PK in adolescents and adults is supported by the observation that no single ARV drug is dosed differently in children weighing > 35 kg than in adults {Burger 2016}. In addition, nonclinical data suggest the safety profile of LEN will not differ in adolescents relative to adults. These

considerations support an HTE indication for LEN in adolescent PWH with MDR and would expeditiously address their high unmet medical need for new therapies without overlapping resistance with approved agents.

LEN is safe and well tolerated.

Lenacapavir was generally safe and well tolerated. In the studies in HTE and treatment-naive PWH, the most common study drug-related AEs were ISRs, the majority of which were Grade 1 or 2. No participants in Study GS-US-200-4625 discontinued LEN due to a treatment-related AE or intolerance.

6.3. Risks

Gilead acknowledges that the small clinical safety database limits our ability to detect less common safety signals and increases reliance on postmarketing pharmacovigilance. However, this is consistent with the low prevalence of the target population being PWH with resistance to multiple drugs and classes who are not able to construct a fully suppressive regimen. Given the high unmet medical need for effective treatments for this population and in accordance with the guidance on developing an investigational agent, the safety database for LEN is acceptable in size and in the duration of follow-up {European Medicines Agency (EMEA) 2016, U. S. Department of Health and Human Services 2015}, considering the demonstrated clinical benefit provided by LEN.

Lenacapavir was generally safe and well tolerated across all populations in the LEN development program (HTE PWH with MDR, treatment-naive PWH, and healthy participants). The AEs that occurred in HTE PWH with MDR were generally consistent with those expected in people with advanced HIV/AIDS or with SC administration of a drug product. Excluding ISRs, the most common AEs were nausea and headache, all were Grade 1 or 2. Adverse reactions identified for LEN are ISRs and nausea. Injection site reactions were expected from the LEN depot formation, and include injection site swelling, injection site erythema, and injection site pain as well as longer lasting injection site induration and injection site nodule (m2.7.4, Section 2.1.7). In HTE PWH, 55.6% of participants (40 of 72) experienced a study drug-related ISR. All were Grade 1 or 2 with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR that resolved after a few days (m2.7.4, Section 2.1.7.1). In ARV treatment-naive PWH, 38.8% of participants (40 of 103) had a study drug-related ISR; all were Grade 1 or 2, except for 1 participant with a Grade 3 injection site nodule (m2.7.4, Section 2.1.7.2); 2 participants discontinued LEN due to injection site induration (m2.7.4, Section 2.1.6.2). Subcutaneous LEN injection has not been associated with hypersensitivity reactions. Inherent in any safety database, is a limited ability to detect rare events. The clinical studies in HTE PWH and in treatment-naive PWH are ongoing with accumulating safety data that will contribute to our understanding of LEN safety, and Gilead is committed to appropriate postmarketing pharmacovigilance for LEN. Furthermore, LEN will continue to be evaluated in a broader population (eg, virologically suppressed PWH and individuals at risk for HIV), thus providing additional safety information. Given the high risk of disease progression and death in the HTE population, HTE PWH need access to new treatment options while balancing the potential clinical benefit and limited information on safety.

The long-acting nature of LEN (SC every 6 months) and its need to be combined with other oral once- or twice-daily ARVs presents a potential risk for unintended LEN monotherapy if other ARVs are poorly adhered to, interrupted, or discontinued prematurely. People with HIV receiving unintended LEN monotherapy may be at increased risk for emergent resistance to LEN, particularly in the setting of an ongoing viremia. In Study GS-US-200-4625, emergent LEN resistance was observed in 11.1% of participants (8 of 72; 4 participants from the randomized and 4 from the nonrandomized cohort). To minimize the potential risk of emergent LEN resistance, it is essential that HTE PWH receiving LEN maintain optimal adherence to their LEN and OBR to achieve and maintain virologic suppression. Of note, HIV-1 isolates resistant to LEN still retain susceptibility to all existing ARV classes due to the novel mechanism of action. Viral resistance potentially occurring due to unintended monotherapy will be monitored through routine pharmacovigilance activities.

Lenacapavir is recommended to be administered every 6 months by a health care professional. For many PWH, the likelihood of maintaining therapeutic concentrations with SC LEN every 6 months is higher than that with oral daily tablets due to the challenges in adhering to daily dosing consistently over the long term, although there is a risk of PWH missing an injection visit. The recommended dosing window of 4 weeks (ie, 26 weeks ± 2 weeks relative to when LEN was last administered) allows flexibility for PWH so that they can align their next SC injection with their regular 6-monthly visit to a health care provider. In addition, if it has been more than 28 weeks since the last SC LEN injection, and if clinically appropriate to continue LEN treatment, the patient should restart the initiation dosage regimen (ie, Day 1: LEN 600 mg oral and LEN 927 mg SC; Day 2 LEN 600 mg oral). However, PWH with frequent history of unplanned missed clinic visits may not be appropriate candidates for long-term LEN treatment. As such, it is important for clinicians to appropriately select HTE PWH who agree to the required 6-month injection dosing schedule and counsel them about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance.

The drug interaction profile of LEN has been evaluated extensively both preclinically and clinically. As LEN concentrations can be detected at a level relevant for drug interaction up to 9 months after the SC injection at the recommended dose, there is a potential for LEN to interact with other drugs long after discontinuing LEN and go unrecognized by clinicians. Lenacapavir is a moderate CYP3A inhibitor, and therefore can increase the concentrations of a sensitive CYP3A substrates. Otherwise, LEN has a low potential to affect other coadministered drugs. Specifically, the residual concentrations of LEN are not expected to affect the exposures of other ARV drugs that are initiated after discontinuation of LEN. Lenacapavir is a substrate of CYP3A, UGT1A1, and P-gp. Drugs that are strong inducers of CYP3A, UGT1A1, and P-gp like RIF, may significantly decrease plasma concentrations of LEN, which may result in loss of therapeutic effect of LEN and development of resistance. Concomitant administration with strong inducers such as RIF is contraindicated.

Due to the limited data in pregnant women, LEN should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Precautionary language has also been included in the proposed prescribing information for class effects of ARVs including immune reconstitution syndrome.

6.4. Benefit-Risk Assessment

Lenacapavir is proposed in combination with other ARVs for the treatment of PWH with MDR HIV-1 infection failing their current ARV regimen. There is a high unmet need for new treatments that can contribute to durable viral suppression in this patient group despite resistance to multiple existing drug classes.

Lenacapavir has demonstrated potent antiviral efficacy in HTE PWH with resistance to multiple other ARV classes, contributing to durable viral suppression and immunologic recovery. Lenacapavir has a favorable safety profile in HTE PWH, treatment-naive PWH, and healthy participants. There is no evidence of renal or hepatic toxicities with LEN, it does not require dose adjustment in people with severe renal impairment or mild to moderate hepatic impairment, and has a limited potential for DDIs. As noted in Section 6.3 and as expected in a patient population with low prevalence, the safety database of LEN is relatively small, but nonetheless sufficient to assess its benefit-risk in PWH with MDR, considering the high unmet medical need.

Lenacapavir is initiated with a 2-day oral loading dose and initial SC injection followed by maintenance therapy with SC injections every 6 months, leading to consistent predictable therapeutic systemic LEN concentrations without the need for adherence to a daily dosing regimen. The SC dosing can be administered by appropriate healthcare providers without additional drug administration training, and the dosing interval fits seamlessly into the schedule for recommended routine clinical care for all PWH. The efficacy, safety, tolerability, and dosing of LEN offer substantial benefit to HTE PWH failing on currently available ARVs for whom there is a high unmet need for new classes of potent ARVs.

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8. APPENDICES

8.1. Categorical Distribution of CD4 Cell Count by Visit

Table req13067.1.1 presents the categorical distribution of CD4 cell count by visit for Study GS-US-200-4625.

Justification for Absent Clinical Data in Module 5

Section	Comment
5.3.1.1 Bioavailability (BA) Study Reports	No absolute bioavailability (BA) studies have been conducted with lenacapavir (LEN) tablets or injection. Absolute BA was estimated based on the observed exposure of LEN following administration to healthy participants for both oral (Studies GS-US-200-4329, m2.7.2, Section 2.2.1 and GS-US-200-4071, m2.7.1, Section 2.2.1) and subcutaneous administration (Studies GS-US-200-4329, m2.7.2, Section 2.2.1, and GS-US-200-4538, m2.7.1, Section 2.1.2). The effect of food on oral LEN was evaluated with a high- or low-fat meal relative to fasted conditions using the 300-mg tablet formulation (intended commercial formulation, Study GS-US-200-4071, Section 2.2.1). For the SC LEN formulation, the effect of food was not evaluated.
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports	No comparative BA or BE studies have been conducted.
5.3.1.3 In vitro-In vivo Correlation Study Reports	No in vitro-in vivo correlation studies have been conducted. For LEN tablets, in vitro dissolution profiles are discussed in m2.7.1 Section 1.2. Reports of in vitro dissolution tests can be found in m3.2.P.5.4.
5.3.2.1 Plasma Protein Binding Study Reports	Nonclinical studies using human biomaterials are discussed in detail, and in the context of PK data in other species, in the Nonclinical Pharmacokinetics Written Summary (m2.6.4).
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies	
5.3.2.3 Reports of Studies Using Other Human Biomaterials	
5.3.5.2 Study Reports of Uncontrolled Clinical Studies	No uncontrolled clinical studies have been conducted.
5.3.6 Reports of Post-Marketing Experience	Not applicable

Additional Documentation Requested at Lenacapavir MAA Pre-Submission Meeting

Requested Document(s)	Description	Document Location
Treatment Randomisation Process SOPs for studies GS-US-200-4625 and GS-US-200-4334.	A description of the randomization process used in the pivotal study GS-US-200-4625 and the supportive study GS-US-200-4334. Gilead SOPs followed for treatment assignment for randomization studies (SOP-[redacted]), unblinding in clinical studies (SOP-[redacted]) and receipt, assignment and approval of randomized IMP numbers (SOP-[redacted])	Module 5.3.5.1, Treatment Randomisation SOPs