EU Risk Management Plan for Lenacapavir

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RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
2.0	27 October 2021	Refer to ELECTRONIC SIGNATURES

Rationale for submitting an updated RMP: To update the due date for milestone of Category 3 additional pharmacovigilance activity GS-US-200-4334 study to 30 September 2024.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant Changes to RMP
Part II Safety Specification	Part II: Module SI—Epidemiology of the Indication(s) and Target Populations(s)	None
	Part II: Module SII—Nonclinical Part of the Safety Specification	None
	Part II: Module SIII—Clinical Study Exposure	None
	Part II: Module SIV—Populations Not Studied in Clinical Studies	None
	Part II: Module SV—Postauthorization Experience	None
	Part II: Module SVI—Additional EU Requirements for the Safety Specification	None
	Part II: Module SVII—Identified and Potential Risks	None
	Part II: Module SVIII—Summary of the Safety Concerns	None
Part III Pharmacovigilance Plan		To update the due date for milestone of Category 3 additional pharmacovigilance activity GS-US-200-4334 study to 30 September 2024.
Part IV Plan for Postauthorization Efficacy Studies		None

Part	Module/Annex	Significant Changes to RMP
Part V Risk Minimization Measures		None
Part VI Summary of the Risk Management Plan		None
Part VII Annexes		Annex 2: Update the due date of Category 3 GS-US-200-4334 CSR Submission Annex 3: Update to include the latest protocol for GS-US-200-4625 Annex 8: Initial summary of changes

Other RMP versions under evaluation:

Not applicable.

Details of the currently approved RMP:

Not applicable.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical (classification system)
AUC	area under the plasma concentration versus time curve
BSEP	bile salt export pump
BRCP	breast cancer resistance protein
CA	capsid inhibitor
CD4	cluster determinant 4
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed concentration of drug
CNS	central nervous system
CV	cardiovascular
CYP	cytochrome P450 enzyme
DDI	drug drug interaction
DLP	data-lock point
DNA	deoxyribonucleic acid
EACS	European AIDS Clinical Society
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GD	gestation day
GSI	Gilead Sciences International Ltd.
GRT	genotypic resistance testing
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IV	intravenous
HTE	heavily treatment experienced
IC_{50}	concentration required to produce 50% inhibition
IDU	injection drug users

INN	International Non-proprietary Name
INSTI	integrase strand-transfer inhibitor
ISS	Integrated summary of safety
m	module
LEN	Lenacapavir
LLOQ	lower limit of quantification
MAA	Marketing Authorization Application
MATE	multidrug and toxin extrusion
MDR	multidrug resistance
MSM	men who have sex with men
NOAEL	no observed adverse effect level
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
OATP	organic anion transporting polypeptides
OBR	optimised background regimen
OCT	organic cation transporter
OSS	Overall susceptibility score
PEG	polyethylene glycol
P-gp	P-glycoprotein
PI	protease inhibitor
PL	package leaflet
PK	pharmacokinetics
PSUR	periodic safety update reports
PWH	People with HIV
QD	once daily
QPPV	Qualified Person for Pharmacovigilance
RMP	risk management plan
RNA	ribonucleic acid
SC	subcutaneous
SmPC	Summary of Product Characteristics
TE	treatment experienced
ULN	upper limit of normal
UNAIDs	Joint United Nations Programme on HIV and AIDS

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Lenacapavir (LEN)
Pharmaco-therapeutic group(s) (ATC Code):	Other antivirals (J05AX31)
Marketing Authorization Applicant:	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	2
Invented name(s) in the European Economic Area (EEA)	Invented name not yet determined.
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Capsid inhibitor
	Summary of mode of action: Lenacapavir is a multistage, selective inhibitor of human immunodeficiency virus type 1 (HIV-1) capsid function that directly binds to the interface between capsid protein (CA) subunits. Lenacapavir inhibits HIV-1 replication by interfering with multiple, essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral deoxyribonucleic acid (DNA) (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of CA subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).
	Important information about its composition: None.
Hyperlink to the Product Information	Lenacapavir Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Lenacapavir, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.
Dosage in the EEA	Current: Initiation On treatment Day 1 and Day 2, the recommended dose of lenacapavir is 600 mg per day taken orally. On treatment Day 8, the recommended dose is 300 mg taken orally. Then, on treatment Day 15, the recommended dose is 927 mg administered by subcutaneous injection. Maintenance The recommended dose is 927 mg of lenacapavir administered by subcutaneous injection once every 6 months (26 weeks) from the date of the last injection (+/- 2 weeks).

Pharmaceutical form(s) and strengths	Current: 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 of LEN free acid in the form of LEN sodium salt. In addition to the active ingredient, the tablets contain the following inactive ingredients: microcrystalline cellulose, mannitol, poloxamer 407, copovidone, croscarmellose sodium, magnesium stearate, polyethylene glycol (PEG), polyvinyl alcohol, talc, titanium dioxide, iron oxide red, iron oxide black, and iron oxide yellow. Lenacapavir 309 mg/mL solution for injection is a clear, yellow to brown solution for subcutaneous (SC) injection and contains the following inactive ingredients: polyethylene glycol (PEG) 300 and water for injection.
Is/Will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. HIV Infection

SI.1.1. Epidemiology of the Disease

Human immunodeficiency virus is a retrovirus that attacks helper T cells, macrophages, and dendritic cells of the immune system, and weakens the body's ability to fight infections and disease. A person with HIV infection is considered to have developed acquired immune deficiency syndrome (AIDS) when the immune system becomes depleted in that it can no longer fight off a range of opportunistic diseases with which it would normally cope. HIV infection is predominantly transmitted through unprotected sexual intercourse and contact with infected blood and certain bodily products (e.g., needle exchanges, maternal blood during childbirth, and breast milk). Along with the development of prevention strategies to decrease transmission rates, the advent of highly active antiretroviral therapy (HAART) in 1996 and subsequent medications have dramatically changed the natural history of HIV/AIDS by improving clinical outcomes, leading to reductions in morbidity and mortality worldwide. However, HIV/AIDS remains a major public health problem worldwide.

SI.1.2. Incidence

Worldwide, the number of new HIV infections continues to decrease over time. In 2019, 1.7 million (95% CI: 1.2 million-2.2 million), resulting in a 23% decline since 2010 (Table SI-1) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Among adults (15 years and older), there was a 17% decline between 2010 and 2019, with the total number of new adult infections in 2019 estimated at 1.5 million (95% CI: 1.1-2.0 million) {UNAIDS AidsInfo 2020b}. Among children (<15 years old), the number of new infections in 2019 (n=150,000 [95% CI: 94,000-240,000]) declined by 52% during the same time (2010 to 2019) {UNAIDS AidsInfo 2020c}. However, incidence rates vary by country and region due to differences in structural and societal determinants across the globe. Notable declines in the number of new HIV infections overall have been observed in Eastern and Southern Africa (38%), the Caribbean (29%), Western and Central Africa (25%), Central Europe and North America (15%), and Asia and the Pacific (12%). In contrast, new HIV infections have been on the rise in Eastern Europe and Central Asia, with an increase of 72% between 2010 and 2019, largely due to transmission among injection drug users (IDU) and their sexual partners, as well as political and technical barriers to HIV treatment programs. The Middle East and North Africa and Latin America regions have also seen an increase in the number of new infections since 2010 (by 25% and 21%, respectively), where stigma against those living with HIV and lack of resources for HIV prevention and treatment programs are major barriers to preventing infection and antiretroviral therapy (ART) access. Disparate groups within these and other regions also experience disproportionately higher rates of HIV incidence, such as adolescent girls and young women in Eastern and Southern Africa, children in Western and Central Africa, and men who have sex with men (MSM) in certain countries within the Asian and the Pacific region {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

SI.1.3. Prevalence

The distribution of HIV-infected individuals varies enormously across geographical regions. Approximately 36.2 million adults and 1.8 million children were living with HIV globally at the end of 2019 (total: 38 million; 95% confidence interval [CI]: 31.6-44.5 million [Table SI-1]) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. An estimated 0.6% (95% CI: 0.5-0.8%) of adults (15 years and above) worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions {UNAIDS 2019, UNAIDS AidsInfo 2020d}.

The Eastern and Southern Africa region is most severely affected, with an estimated 20.7 million (95% CI: 18.4-23.0 million) people living with HIV infection in 2019 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Although this region comprises 6.2% of the global population, it accounts for over 50% of people living with HIV worldwide. Western and Central Africa is the second most affected region with 4.9 million (95% CI: 3.9-6.2 million) people living with HIV. In both these African regions, which are referred to collectively as Sub-Saharan Africa, prevalence is high among key populations including MSM, sex workers, injection drug users (IDUs), and sexual partners of these groups. After Sub-Saharan Africa, the regions most heavily affected are the Caribbean, Eastern Europe, Central Asia and Latin America where 0.5-1.1% of adults were living with HIV in 2019 {UNAIDS 2019, UNAIDS AidsInfo 2020d}. Eastern Europe and Central Asia is the only region where HIV prevalence remains on the rise, reaching an estimated 1.7 million in 2019 (95% CI: 1.4-1.9 million), resulting largely from a surge of infections among IDU and their sexual partners {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}In contrast, estimated regional prevalence is lower in Western and Central Europe and North America (0.3% [95% CI: 0.2-0.3]) in adults) {UNAIDS AidsInfo 2020d}. In this region, although more than 81% of people living with HIV are accessing ART, unprotected sex between men continues to dominate patterns of HIV transmission. In the Western and Central Europe, stigma and discrimination within the health-care system persist as significant barriers to accessing HIV treatment among MSM, in addition to sex workers and IDUs {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

Table SI-1. Regional Prevalent and Incident Cases of HIV Infection in 2019

	Incident Cases (n; 95% CI)		Prevalent Cases (n; 95% CI)	
	Overall	Adults[a]	Overall	Adults[a]
Asia and Pacific	300,000 (210,000-390,000)	280,000 (200,000-370,000)	5.8 million (4.3-7.2 million)	5.7 million (4.2-7.1 million)
Caribbean	13,000 (8,700-19,000)	12,000 (8,000-17,000)	330,000 (270,000-400,000)	320,000 (260,000-390,000)
Eastern and Southern Africa	730,000 (580,000-940,000)	660,000 (520,000-850,000)	20.7 million (18.4-23.0 million)	19.6 million (17.5-21.8 million)
Eastern Europe and Central Asia	170,000 (140,000-190,000)	160,000 (140,000-190,000)	1.7 million (1.4-1.9 million)	1.6 million (1.4-1.8 million)
Latin America	120,000 (73,000-180,000)	120,000 (71,000-170,000)	2.1 million (1.4-2.8 million)	2.1 million (1.4-2.8 million)
Middle East and North Africa	20,000 (11,000-38,000)	18,000 (9,500-36,000)	240,000 (170,000-400,000)	230,000 (160,000-380,000)

	Incident Cases (n; 95% CI)		Prevalent Cases (n; 95% CI)	
	Overall	**Adults[a]**	**Overall**	**Adults[a]**
Western and Central Africa	240,000 (150,000-390,000)	190,000 (120,000-310,000)	4.9 million (3.9-6.2 million)	4.5 million (3.6-5.7 million)
Western and Central Europe and North America	65,000 (49,000-87,000)	65,000 (48,000-87,000)	2.2 million (1.7-2.6 million)	2.2 million (1.7-2.6 million)
Total [b]	**1.7 million (1.2-2.2 million)**	**1.5 million (1.1-2.0 million)**	**38.0 million (31.6-44.5 million)**	**36.2 million (30.2-42.5 million)**

a Aged 15 years and older.
b Numbers in the columns may not add up to match the totals exactly due to the effect of rounding.
Source: {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020, UNAIDS AidsInfo 2020d, UNAIDS AidsInfo 2020e}

SI.1.4. Epidemiology of HIV Infection in Heavily-Treatment-Experienced (HTE) People with HIV (PWH) With Multidrug Resistance (MDR)

The definition of people with HIV (PWH) who are heavily-treatment-experienced (HTE) involves the assessment of multidrug resistance (MDR) based on genotypic resistance testing (GRT), an individual's remaining treatment options based on safety/tolerability concerns, and antiretroviral (ARV) treatment history. However, a uniform definition of HTE across studies is lacking, and prevalence measures can vary widely depending upon whether the population studied includes only PWH who had GRT or a wider PWH population {Gill 2017}. As a result, robust data on the size of a well-defined HTE population are not readily available.

Nonetheless, findings from analyses of narrowly and broadly defined HTE populations provide insight into the prevalence of the HTE population with MDR in Europe. In an Italian cohort of treatment-experienced PWH with GRT (15628 isolates from 6802 patients), the prevalence of four-class MDR (i.e., nucleoside reverse transcriptase inhibitors [NRTIs], nonnucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], and integrase strand-transfer inhibitors [INSTIs]) was 2% in 2018, which significantly increased from 0.7% in 2008 {Lombardi 2021}. In the same analysis, prevalence of triple-class MDR remained constant at 9% from 2010-2018, after significantly decreasing from 17% to 13% in 1998-2001 and 2008-2010, respectively. A review of clinical trials and observational studies involving PWH with triple-class resistance found prevalence measures for 2000-2012 ranging from 2% to 16%, with more strict definitions of triple-class resistance (i.e., requiring treatment failure of each ARV subclass) resulting in lower measured prevalence {Cossarini 2013}. In a EuroSIDA analysis, which utilized a broader HTE definition including patients with or without GRT and accounting for MDR with at least 2 ARV options remaining, HTE prevalence from 2010-2016 was 10.4% (95% confidence interval [CI] 9.9-10.9%), with a statistically significant yearly increase of 0.5% (95% CI 0.34-0.66%) during that time {Pelchen-Matthews 2021}. Among those who were not HTE at study start, the incidence rate was 1.76 (95% CI 1.66-1.97) per 100 person-years. The true size of the HTE population is greater than these estimates capture as resistance is only one driver limiting treatment options along with medication intolerance, previous side effects, adherence challenges, and difficulty with frequent dosing. The actual burden of PWH with MDR who require novel therapies to establish and maintain viral suppression and immunological response is greater than what is reflected in some prevalence estimates {Gill 2017}.

There is also evidence of subpopulations with increased prevalence of MDR and the existence of drug-resistant strain transmission. Among PWH who were initially treated with non-highly active ART regimens, perinatally infected children and adolescents, the prevalence of MDR is elevated likely due to prolonged exposure to ART and poor adherence {Koay 2021}. In resource-limited settings, PWH also experience greater burden of MDR, where three-quarters of patients may have at least some level of MDR {Pennings 2013, Stadeli 2013}. This difference may be due to lack of monitoring in resource-limited countries, in addition to suboptimal GRT availability and lack of widely accessible HIV services, consistent ARV treatment, and retention in care {Choi 2014, de Mulder 2014, Galli 2020, Judd 2017, Koay 2021, Napravnik 2007}, {Puertas 2020}.

Several cases of pan-resistant new HIV-1 infections have been recently reported in Spain and France {Puertas 2020, Raymond 2020}, and transmission of MDR HIV-1 strains have been reported previously {Blick 2007, Markowitz 2005}, including in patients taking pre-exposure prophylaxis {Colby 2018, Knox 2017, Markowitz 2017}.

SI.1.5. Treatment Options for HIV-1 Infection in HTE PWH With MDR

The goal of treatment for ART-experienced patients 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 two, and preferably three, fully active molecules, based on resistance mutations present in current and earlier genotypic analyses {U. S. Department of Health & Human Services (DHHS) 2019}.

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}.

Currently two novel treatments are available for PWH with MDR in the European Union (EU):

- Ibalizumab (Trogarzo®), a monoclonal humanized antibody which targets cluster of differentiation 4 (CD4) cell receptors to prevent HIV entry, for intravenous infusion every two weeks. This medicine has been authorized for use in the EU since September 2019.

- Fostemsavir (Rukobia®), an orally administered twice a day attachment inhibitor that selectively inhibits the interaction between HIV and cellular CD4 receptors, thereby preventing viral entry into the host cells. This medicine has been authorized for use in the EU since February 2021.

Other older products which are approved in the EU for use in treatment-experienced (TE) adults are often used in the treatment of HTE patients and include the following;

- Maraviroc (Celsentri®), a CCR5 antagonist, which selectively binds to the human chemokine receptor CCR5, preventing CCR5-tropic HIV from entering cells. This medicine has been authorized for use in the EU since September 2007.

- Enfuvirtide (Fuzeon®), is a fusion inhibitor of the structural rearrangement of the HIV-1 gp41 binding to this protein and blocking fusion between the viral and target cell membranes preventing viral ribonucleic acid (RNA) from entering the cell. This medicine has been authorized has been authorized in the EU since May 2003.

- Protease inhibitors such as Darunavir (Prezista®) twice daily, given together with a pharmacoenhancer such as ritonavir (Norvir®) the INSTI dolutegravir (Tivicay®) twice daily, and the NNRTI etravirine (Intelence®) 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 a 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.

SI.1.6. Natural History of the Indicated Condition

Untreated HIV compromises the host's immune system, which makes it susceptible to opportunistic infections and malignancies, and is associated with comorbidities that affect all organ systems. When untreated, HIV advances through three stages of infection: acute infection, clinical latency, and AIDS. The development of specific comorbidities and adverse events among those with HIV is dependent on a number of factors including stage of infection, the presence of coinfections, and treatment status. It is therefore difficult to provide frequency estimates of adverse events among the undiagnosed and untreated HIV population, which are also likely to differ substantially by geography, reflecting local conditions {Bradley 2014, Hamers 2008}. Although no effective cure currently exists, ART administered at an early enough stage can dramatically improve an HIV patient's prognosis, decreasing morbidity, mortality, and the risk of spreading the infection to others {Schwarcz 2013}. However, as the number of HIV patients with lifelong access to treatment is increasing, HIV-associated complications and chronic diseases related to inflammation, immunodeficiency, and ageing are also emerging, as well as health-related quality of life and depression {Deeks 2013, Langebeek 2017}.

SI.1.6.1. Mortality and Morbidity

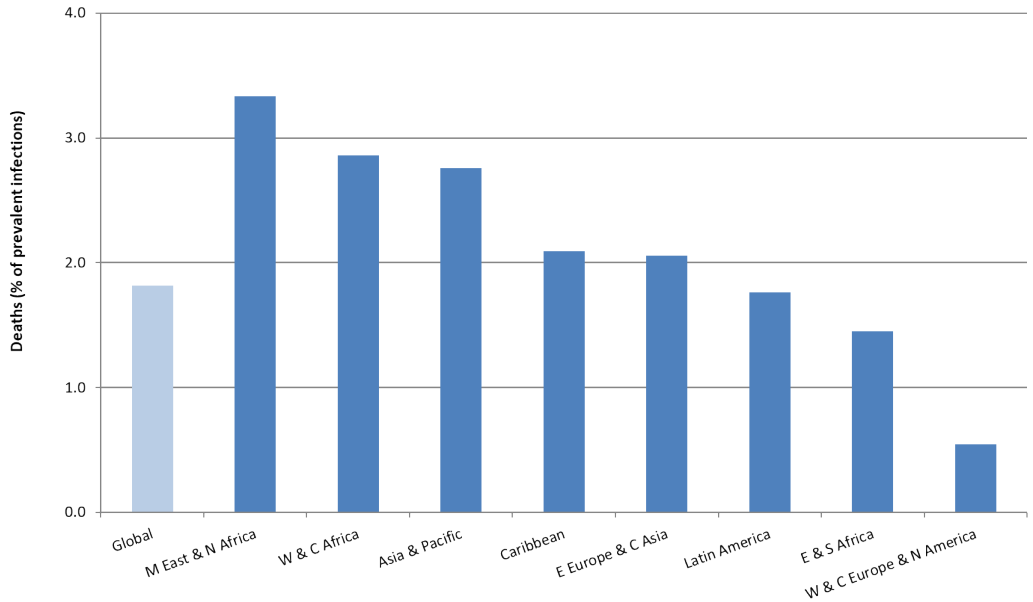
Access to effective treatment varies considerably, accounting for different rates of mortality by region. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled up ART and the steady decline in HIV incidence since the peak in 1997. Since its peak in 2004, AIDS-related deaths have reduced by more than 55% {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. In 2019, this decline continued, with evidence that

the drop in the number of people dying from AIDS-related causes is accelerating in several countries. In 2019, 690,000 (95% CI: 500,000-970,00) people died from AIDS-related causes worldwide, representing a 39% decline compared to 2010 {UNAIDS AidsInfo 2020a}. AIDS-related mortality among men tends to be higher than women worldwide, which is likely reflective of women being more likely to test for HIV, receive treatment, and adhere to treatment compared to men {UNAIDS 2018}.The leading cause of death among those living with HIV continues to be tuberculosis, which accounts for around one in three AIDS-related deaths {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

The number of people dying from AIDS-related causes in Eastern and Southern Africa declined by 49% from 2010 to 2019, although the region still accounted for 31% of all the people dying from AIDS in 2019 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Declines in AIDS-related deaths between 2010 and 2019 also occurred in the Caribbean (37%), Western and Central Europe and North America (37%), Western and Central Africa (37%), Asia and Pacific (28%), Latin America (8%), and Middle East and North Africa (2%). Eastern Europe and Central Asia, however, experienced a 24% increase in mortality from AIDS during the same time. Figure SI.1 provides regional variations in HIV related mortality (deaths as a percentage of prevalent HIV infections in 2019) {UNAIDS AidsInfo 2020a}.

Following the introduction of HAART, mortality rates declined due to decreases in both non-AIDS and AIDS-related deaths, although the proportion of deaths associated with non-AIDS-related diseases has increased in patients on ART {Ingle 2014, Palella 2013, Weber 2013}. Common causes of non-AIDS-related deaths are non-AIDS-related malignancies, liver failure, non-AIDS-related infections, substance use-related, suicide, and myocardial infarction {Weber 2013}.

Figure SI.1. Regional Variation in HIV-Related Mortality



Source: {UNAIDS AidsInfo 2020a, UNAIDS AidsInfo 2020f}

SI.1.6.2. Mortality and Morbidity in HTE PWH With MDR

Higher rates of adverse clinical events and/or mortality (AIDS and non-AIDS-related) among patients with MDR HIV-1 infection have been observed in various HTE cohorts {Cossarini 2013, Deeks 2009, Galli 2020, Pelchen-Matthews 2021, Phillips 2007}. In a EuroSIDA analysis, HTE patients had significantly higher incidence of AIDS-related clinical events or deaths compared to controls {Pelchen-Matthews 2021}. Although the differences were no longer statistically significant after adjusting for potential confounders, the excess risk observed in the unadjusted analyses was mainly attributed to differences in baseline CD4 counts, whereby the HTE patients had markedly lower counts compared to non-HTE patients despite having similar viral suppression rates.

In an analysis from the Italian PRESTIGIO Registry, among 148 PWH followed for a median (interquartile range) of 47 (32–84) months after 4-drug resistance (4DR) evidence, 38 PWH had 62 new events or died from any cause (incidence rate, 9.12/100 person-years of follow-up; 95% CI = 6.85–11.39): 12 deaths (6 AIDS-related and 6 non-AIDS-related), 18 AIDS-defining events (ADEs,) and 32 non-ADEs; 20 of the incident clinical events were malignancies. The 4-year cumulative incidence of death was 6% (95% CI, 3%–13%), and that of ≥ 1 event or death was 22% (95% CI, 16%–31%).{Galli 2020}.

These findings emphasize the importance of effective treatment options among HTE patients that achieve and sustain virologic suppression and lead to immunologic recovery, thereby lowering the risk of AIDS-related events and death.

SI.1.7. Concomitant Medication(s) in the Target Population

In HIV-1 infected patients, particularly those with low CD4 counts, concomitant medications which could be used to treat common comorbidities and coinfections of HIV infection include antibiotics, antifungals, antivirals, and chemotherapeutic agents.

SI.1.7.1. Important Comorbidities

Prior to the success of ART for the treatment of HIV/AIDS, the most common co-morbidities were those traditionally defined as AIDS-related illnesses and correlated with CD4 cell count, such as Guillain-Barre Syndrome, Kaposi's sarcoma, and Non-Hodgkin's lymphoma {Hanson 1995}. As HIV patients on ART are living longer with viral suppression, the more prevalent co-morbidities are chronic health conditions in both resource-limited settings and wealthy regions {Balderson 2013, Deeks 2013, Hirschhorn 2012, Hsue 2016, Langebeek 2017}. Below is a list of important conditions that have evidence of higher risk among HIV patients and/or those accessing ART:

- Arthritis
- Bone disease (i.e., osteopenia, osteoporosis, and fracture)
- Cardiovascular disease (i.e., hypertension and hyperlipidemia)

- Chronic pain
- Endocrine disease including diabetes
- Frailty
- Hepatitis
- Mental illness (i.e., depression and suicidal ideation)
- Neurocognitive disorders
- Other sexually transmitted diseases
- Pulmonary disease (i.e., Chronic obstructive pulmonary disease)
- Renal disease
- Some non-HIV-related malignancies (i.e., liver, cervical, anal, and Hodgkin's lymphoma)
- Tuberculosis

PART II: MODULE SII- NONCLINICAL PART OF THE SAFETY SPECIFICATION

Table SII.1. Table of Key Safety Findings from Nonclinical Studies

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Toxicity	
Single and repeat dose toxicity: No systemic toxicity was observed in rats after SC or oral administration of LEN, or in dogs after oral administration of LEN. Reversible changes in liver function were observed in Beagle dogs after very large single intravenous (IV) doses and SC repeat doses, consistent with the inhibition of the Bile Salt Export Pump (BSEP) transporter: • In dogs, after a single IV dose of 10 or 30 mg/kg, LEN-related serum chemistry changes were observed 24 hours after dosing and included mildly to markedly increased serum alanine and aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) activity, and total bilirubin with correlative microscopic findings of hepatocyte degeneration and hepatocyte necrosis (TX-200-2030). At the 14-day terminal sacrifice, clinical pathology changes had partially or fully reversed and there were no LEN-related microscopic findings. The no observed adverse effect level (NOAEL) was determined to be 3 mg/kg in this study. Based on the time course, the liver changes appear to be C_{max} related. The C_{max} achieved at the 3 mg/kg NOAEL (5.1 µg/mL) is 38-fold higher than the clinical C_{max} observed after the 6-month clinical oral loading and SC dosing regimen. • Two repeat toxicity studies in dogs were conducted via monthly SC injection of LEN for up to 9 months (10 doses). In the first study (TX-200-2017), LEN was well tolerated when administered as 10 monthly SC injections of 20 mg/kg/dose with or without NaOH or 40 mg/kg/dose without NaOH, and no systemic toxicity was observed at LEN exposures up to 8-fold higher than clinical exposure based on the $AUC_{Day1\text{-}week26}$. The NOAEL was determined to be 40 mg/kg in this study. • In the second study (TX-200-2047), animals were administered LEN at dosages of 0 (vehicle control), 130, or 411 mg/kg/dose. In the 411 mg/kg/dose group, clinical observations, clinical pathology and anatomic pathology data indicated hepatobiliary changes indicative of cholestasis and hepatobiliary injury. Less severe changes in clinical pathology test results, and fewer and less severe liver and gall bladder microscopic findings were observed in the 130 mg/kg/dose group, but included periductular fibrosis in one dog, considered adverse. Mean LEN exposures in the 411 mg/kg/dose group were ≥ 51-fold higher than the clinical exposure based on the $AUC_{Day1\text{-}week26}$.	The transient acute toxicity and the clinical, clinical pathology and histopathology observations in study TX-200-2047 are consistent with disruption in secretion of bilirubin into bile. Inhibition of the BSEP transporter induces hepatotoxicity by causing intracellular concentrations of bile acids to rise above a toxic threshold. Lenacapavir is a much more potent inhibitor of dog BSEP (dBSEP) transporter (IC_{50} = 0.124 µg/mL) than the human BSEP (hBSEP) transporter (IC_{50} = 1.15 µg/mL); the average dog plasma LEN concentration (C_{ave}) after 9 months of 130 mg/kg/dose or 3 months of 411 mg/kg is at least 39-fold higher than the dBSEP transporter IC_{50}, while the average clinical plasma LEN concentration is 27-fold lower than the hBSEP transporter IC_{50}. Given the significant exposure margins observed in the single dose IV and repeat dose SC studies, and the higher sensitivity of the dBSEP to LEN compared to the hBSEP, these findings do not suggest a significant risk of organ toxicity at or near the expected clinical exposure.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Genotoxicity: A standard battery of in vitro and in vivo studies was performed to assess the genotoxic potential of LEN. Lenacapavir was not genotoxic in the bacterial reverse mutation test (TX 200 2007), the in vitro chromosomal aberrations assay using cultured human peripheral blood lymphocytes (TX 200 2008) and the in vivo micronucleus assay in rats conducted as part of the repeat dose toxicity study (TX 200 2005).	There were no specific concerns raised by nonclinical genotoxicity studies.
Carcinogenicity: A 6-month transgenic mouse carcinogenicity study was conducted to evaluate the carcinogenic potential of LEN when administered once every 13 weeks at SC injection to 001178-T (hemizygous) RasH2 mice for at least 26 weeks (TX-200-2068). Subcutaneous injection of LEN at levels of 0 (control), 30, 100, and 300 mg/kg/dose resulted in no carcinogenic effect by Day 183, and no effect of LEN on survival or the incidence of neoplasms was observed.	There were no specific concerns raised by the nonclinical carcinogenicity study.
Reproductive/developmental toxicity: No changes in reproductive organ weights and no macroscopic or microscopic findings were noted in rat and rabbit repeat-dose studies. In a SC rat fertility study (TX-200-2043), no adverse effects occurred in male or female fertility at 100 mg/kg, the highest dose administered. No LEN-related effects on mean body weights, body weight gains, and food consumption were noted, and no effects on male and female reproductive performance (mating, fertility, and pregnancy), male spermatogenesis (sperm numbers, sperm production rate, and motility), and male or female organ weights were noted. No LEN related macroscopic findings were noted. Intrauterine survival of the embryos was unaffected by LEN administration at all doses. Oral administration of LEN to pregnant rats during gestation day (GD) 6 through 17 at dose levels of 3, 10, and 30 mg/kg/day resulted in no LEN-related effects on maternal animals or embryo/fetal development (TX-200-2031, TX-200-2036). Intravenous administration of LEN to pregnant rabbits during GD 7 through 19 at dose levels of 5, 10 and 20 mg/kg/day also resulted in no LEN- related effects on maternal animals or embryo/fetal development (TX-200-2032, TX-200-2037). In a rat SC peri- and postnatal toxicity study (TX-200-2049), pregnant rats were administered a single dose of either 30 or 300 mg/kg LEN on GD 6. Parameters evaluated included pregnancy, parturition, and lactation of the maternal (F_0) animals and on the growth, viability, and development of the F_1 neonates. Reproductive performance of the F_1 generation was also assessed. No LEN-related systemic effects were noted at any dose level tested in the F_0 or F_1 generation.	There were no specific concerns raised by nonclinical reproductive/developmental toxicity studies.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Safety Pharmacology	
In safety pharmacology studies, LEN did not show significant effects on the cardiovascular (CV) (dogs), respiratory (rats), or central nervous system (CNS) (rats) at NOAEL exposures that were 20-, 1.4- and 1.4-fold higher, respectively, than the free LEN C_{max} after the 6-month clinical oral loading and subcutaneous dosing regimen.	There were no specific concerns raised by nonclinical safety pharmacology studies.
Local tolerance	
In single and repeat-dose nonclinical local tolerance studies, the macroscopic observation of thickening and the microscopic observations of mixed cell or granulomatous inflammation, necrosis, and mononuclear cell infiltrates were observed at the subcutaneous injection site of animals administered various SC formulations of LEN. These observations were expected reactions of SC depots.	There were no specific concerns raised by nonclinical local tolerance studies. Injection site reactions have been observed in the Phase 2 and Phase 2/3 clinical studies, and are listed adverse drug reactions (ADRs) for LEN in the SmPC.
Other toxicity studies	
Antigenicity: In in vitro studies, LEN was positive with low reactivity in the Direct Peptide Reactivity Assay (TX-200-2071), negative in the ARE-Nrf2 Luciferase assay (TX-200-2072) and positive in the Human Cell Line Activation Test (TX-200-2073). In vivo, LEN was not a sensitizer in the mouse local lymph node assay (TX-200-2053). Immunotoxicity: Data from repeat-dose toxicity studies with LEN (hematology, lymphoid organ weights, microscopy of lymphoid tissues, bone marrow cellularity) did not suggest immunotoxic potential. Dependence: No specific studies on dependency of LEN were conducted. There was no evidence of development of dependence in nonclinical studies with LEN. Tissue distribution studies using radiolabeled LEN in both rat and dog indicated that very low concentrations of radioactivity at Cmax were observed in the central nervous system. Impurities: Two repeat-dose toxicity studies were conducted in rats to determine if there were unexpected adverse effects from LEN-related process impurities. Male and female rats were administered a single SC dose of 100 mg/kg LEN solutions using a pure (at least 98.7%) LEN batch or batches with added impurities and observed for 4 weeks (TX 200 2042) or 13 weeks (TX-200-2050). Lenacapavir plasma exposure was confirmed for the duration of observation. No adverse LEN-related effects were observed and there were no differences in findings in animals treated with lots containing LEN related impurities to those observed in previous studies, or to a comparator lot.	There were no specific concerns raised by other nonclinical toxicology studies.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Pharmacokinetic Drug-Drug Interactions	
Nonclinical assessment of LEN as a victim of drug-drug interactions (DDIs) showed inhibitors or inducers of cytochrome P450 3A (CYP3A) and UDP Glucuronosyltransferase Family 1 Member A1 (UGT1A1) may affect the pharmacokinetics (PK) of LEN. Assessment of LEN as a perpetrator of drug interactions indicates low potential for reversible inhibition of CYP enzymes or UGT1A1 at the clinical systemic concentrations observed following oral or SC administration. Inhibition of intestinal efflux transporters (P-glycoprotein [P-gp] and breast cancer resistance protein [BCRP]) following oral dosing of LEN cannot be ruled out from in vitro data as the maximum concentration that could be tested in vitro was 1 µM wherein no inhibition of either transporter was observed. While LEN was a potent inhibitor of hepatic uptake transporters organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 in vitro, there was no effect of orally administered LEN on the PK of pitavastatin in humans. From potencies determined in vitro, LEN exhibits no potential for inhibition of renal transporters (organic anion transporter 1 (OAT1), OAT3, organic cation transporter 1 (OCT2), multidrug and toxin extrusion protein 2K (MATE2K) and weak inhibition of MATE1.	In a Phase 1 clinical DDI study (GS-US-200-4333), CYP3A/P-gp inhibitor, cobicistat, increased exposure of orally administered LEN, but the CYP3A selective inhibitor, voriconazole, had less effect. Coadministration of LEN and medicinal products that potently induce CYP3A, P-gp, and UGT1A1 (i.e., all 3 pathways), such as rifampin, may significantly decrease plasma concentrations of LEN, resulting in loos of therapeutic effect and development of resistance, therefore coadministration of rifampin is contraindicated in the SmPC. Moderate inducers of CYP3A and P-gp, such as efavirenz (EFV), may also decrease plasma concentrations of LEN, therefore coadministration is not recommended. Lenacapavir exposures may significantly increase upon coadministration with strong inhibitors of CYP3A, P-gp, and UGT1A1 together (i.e., all 3 pathways) such as atazanavir/cobicistat, therefore coadministration with these products is not recommended. There was no clinically meaningful effect of orally administered LEN on tenofovir alafenamide (a P-gp substrate) or rosuvastatin (a BCRP substrate). Additional potential DDIs are described in Section 4.5 of the SmPC.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

The tables in this section present exposure data to LEN in participants with HIV-1 infection from the following studies:

- Heavily treatment-experienced participants with multidrug resistant (MDR) HIV-1 infection - Phase 2/3 study GS-US-200-4625
- Treatment-naïve participants with HIV-1 infection – Phase 2 study GS-US-200-4334

In addition, 55 healthy participants who received LEN in 2 Phase 1 studies (GS-US-200-4538 and GS-US-200-5709) were included in an integrated summary of safety (ISS); exposure data is presented separately below.

Table SIII.1. Duration of Exposure in Participants With HIV-1 Infection (GS-US-200-4625 and GS-US-200-4334)

Duration of Exposure	PWH with MDR HIV-1 (GS-US-200-4625)		Treatment-naïve PWH (GS-US-200-4334)	
	Participants	Person-days	Participants	Person-days
>= 1 Day	72	16,345	157	46,702
>= 30 Days	72	16,345	157	46,702
>= 90 Days	62	15,538	154	46,500
>= 180 Days	43	12,957	151	46,031
>= 365 Days	13	5312	62	24,507
>= 730 Days	0	0	0	0

Table SIII.2. Duration of Exposure in Healthy Participants (GS-US-200-4538 and GS-US-200-5709)

Duration of Exposure	Participants	Person-days
>= 1 Day	55	2354
>= 30 Days	14	1890
>= 90 Days	14	1890
>= 180 Days	0	0

Table SIII.3. Exposure by Age Group and Gender in Participants With HIV-1 Infection (GS-US-200-4625 and GS-US-200-4334)

	PWH With MDR HIV-1 (GS-US-200-4625)				Treatment-Naïve PWH (GS-US-200-4334)			
	Participants		Person-days		Participants		Person-days	
Age Group	Male	Female	Male	Female	Male	Female	Male	Female
< 18 years	0	0	0	0	0	0	0	0
18 – 40 years	11	5	1705	1048	123	6	36,031	2138
41 - 64 years	37	13	9582	2982	21	6	6800	1542
65 - 75 years	5	0	871	0	1	0	191	0
> 75 years	1	0	157	0	0	0	0	0

Table SIII.4. Exposure by Age Group and Gender in Healthy Participants (GS-US-200-4538 and GS-US-200-5709)

	Patients		Person-days	
Age Group	Male	Female	Male	Female
< 18 years	0	0	0	0
18 - 40 years	27	18	1307	851
41 - 64 years	8	2	194	2
65 - 75 years	0	0	0	0
> 75 years	0	0	0	0

Table SIII.5. Exposure by Ethnic Origin in Participants With HIV-1 Infection (GS-US-200-4625 and GS-US-200-4334)

	PWH With MDR HIV-1 (GS-US-200-4625)		Treatment-Naïve PWH (GS-US-200-4334)	
Ethnic Origin	Patients	Person-days	Patients	Person-days
White	29	6938	70	22,969
Black or African American	27	6977	79	21,498
Asian	15	2237	2	617
American Indian or Alaska Native	0	0	1	207
Native Hawaiian or Other Pacific Islander	0	0	2	796
Other	0	0	3	615
Not permitted	1	193	0	0
Multiple	0	0	0	0
Missing	0	0	0	0

Table SIII.6. Exposure by Ethnic Origin in Healthy Participants (GS-US-200-4538 and GS-US-200-5709)

Ethnic Origin	Patients	Person-days
White	40	1405
Black or African American	15	949
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not permitted	0	0
Multiple	0	0
Missing	0	0

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Pregnant females and females who are breastfeeding	Prior to the initiation of studies GS-US-200-4625 and GS-US-200-4334, limited data were available on the use of LEN in these patient populations. It is not known if LEN is secreted in human milk.	Yes
Patients with moderate to severe renal impairment	Prior to the initiation of studies GS-US-200-4625 and GS-US-200-4334, limited data were available on the use of LEN in this patient population.	No Rationale: No safety concerns for LEN are anticipated in patients with severe renal impairment. LEN is not renally eliminated, and no clinically relevant changes in LEN PK were observed in participants with severe renal impairment ($eGFR_{CG}$ between 15 and 29 mL/min [inclusive]) in a dedicated renal impairment study (GS-US-200-4330). As LEN is highly protein bound, it is unlikely to be removed by dialysis.
Patients with ALT > 5 x ULN, and direct bilirubin > 1.5 x ULN	Prior to the initiation of studies GS-US-200-4625 and GS-US-200-4334, limited data were available on the use of LEN in this patient population.	No Rationale: The effect of hepatic impairment was evaluated in a dedicated Phase 1 study in participants with mild to moderate hepatic function matched to healthy controls (GS-US-200-4331). No clinically relevant changes in LEN PK were observed in this study, and based on cumulative PK data from the LEN development program, no dose adjustment of LEN is recommended in people with mild to moderate hepatic impairment (Child-Pugh Class A or B). LEN has not been studied in participants with severe hepatic impairment (Child-Pugh Class C) and is therefore not recommended in these patients. However, no safety concerns for LEN are anticipated in patients with severe hepatic impairment, and no additional studies are planned in this patient population.

Criterion	Reason for Exclusion	Considered to be Missing Information
Patients with untreated or newly treated Hepatitis B Virus (HBV) who were not receiving treatment with anti-HBV therapy	Prior to the initiation of studies GS-US-200-4625 and GS-US-200-4334, limited data were available on the use of LEN in this patient population.	No Rationale: The safety profile of LEN in this patient population is not expected to differ from the safety profile of LEN in the indicated population.
Patients with Hepatitis C Virus (HCV) antibody positive, and HCV RNA > lower limit of quantification (LLOQ)	Prior to the initiation of studies GS-US-200-4625 and GS-US-200-4334, limited data were available on the use of LEN in this patient population.	No Rationale: The safety profile of LEN in this patient population is not expected to differ from the safety profile of LEN in the indicated population.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV.2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	229 HIV-1 infected participants have been exposed to LEN in studies GS-US-200-4334 and GS-US-200-4625.	The detection of rare reactions in the datasets available to date is limited.
Due to prolonged exposure	75 HIV-1 infected participants have been exposed to LEN for ≥ 1 year in studies GS-US-200-4334 and GS-US-200-4625.	The detection of ADRs potentially associated with long exposure in the datasets to date is limited.
Due to cumulative effects	75 HIV-1 infected participants have been exposed to LEN for more than 1 year in studies GS-US-200-4334 and GS-US-200-4625.	The detection of cumulative effects in the datasets available to date is limited.
Which have a long latency	75 HIV-1 infected participants have been exposed to LEN for more than 1 year in studies GS-US-200-4334 and GS-US-200-4625.	The detection of ADRs with a long latency in the datasets available to date is limited.

SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs

Table SIV.3. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure	Considered to be Missing Information
Pregnant women	No pregnancies were reported in the LEN clinical development program.	Yes
Breastfeeding women	Not included in the clinical development program.	Yes
Patients with severe renal impairment	Not known. Participants were required to have an estimated glomerular filtration rate (eGFR) of > 50 mL/min to be included in studies GS-US-200-4625 and GS-US-200-4334.	No Rationale: No safety concerns for LEN are anticipated in patients with severe renal impairment. Lenacapavir is not renally eliminated, and no clinically meaningful changes in LEN PK were observed in participants with severe renal impairment ($eGFR_{CG}$ between 15 and 29 mL/min [inclusive]) in a dedicated renal impairment study (GS-US-200-4330). As LEN is highly protein bound, it is unlikely to be removed by dialysis.
Patients with hepatic impairment	Not known. Patients were required to have ALT ≤ 5 x upper limit of normal (ULN) and total bilirubin ≤ 1.5 x ULN to be included in studies GS-US-200-4625 and GS-US-200-4334.	No Rationale: The effect of hepatic impairment was evaluated in a dedicated Phase 1 study in participants with mild to moderate hepatic function matched to healthy controls (GS-US-200-4331). Clinically relevant changes in the PK of LEN were not observed in this study, and based on cumulative PK data from the LEN development program, no dose adjustment of LEN is recommended in people with mild to moderate hepatic impairment (Child-Pugh Class A or B). LEN has not been studied in participants with severe hepatic impairment (Child-Pugh Class C) and is therefore not recommended in these patients. However, no safety concerns for LEN are anticipated in patients with severe hepatic impairment, and no additional studies are planned in this patient population.
Paediatric patients	Not included in studies GS-US-200-4334 and GS-US-200-4625.	No Rationale: Adolescents and children < 18 years old are not included in the indication.
Elderly patients	Seven patients ≥ 65 years old were included in studies GS-US-200-4334 and GS-US-200-4625.	No. Rationale:The safety profile in elderly patients is expected to be similar to the safety profile in adult patients. Population PK analyses did not identify any clinically relevant differences due to age on the PK of LEN, and no dose adjustment is required for elderly patients.

PART II: MODULE SV - POSTAUTHORIZATION EXPERIENCE

SV.1. Postauthorization Exposure

Lenacapavir is not yet approved, there is currently no information on post-authorization exposure of LEN.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for LEN to be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

SVII.1.1. Risk(s) Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Based on the current data from the LEN clinical development program, there are no risks not considered important for LEN. The adverse reactions included in Section 4.8 of the SmPC for LEN are not associated with undesirable clinical outcomes and are therefore not considered to be risks for LEN.

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

Table SVII.1. Important Identified Risks

Important Identified Risks	Risk-Benefit Impact
None	Not applicable

SVII.1.2.2. Important Potential Risks

Table SVII.2. Important Potential Risks

Important Potential Risks	Risk-Benefit Impact
None	Not applicable

SVII.1.2.3. Missing Information

Table SVII.3. Missing Information

Missing Information	Risk-Benefit Impact
Long-term safety information	Limited safety data are available for LEN beyond 54 weeks of treatment.
Safety in pregnancy and lactation	No adequate and well-controlled studies of LEN have been conducted in pregnant women. It is not known whether LEN is excreted in human milk.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

There are no important identified risks for LEN.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for LEN.

SVII.3.2. Presentation of the Missing Information

Table SVII.4. Missing Information

Missing Information:	Evidence source
Long-term Safety Information	Population in need of further characterization: Limited data are available on the long-term safety of LEN in adults. LEN was well tolerated through 52 weeks in HTE participants with MDR HIV-1 infection (study GS-US-200-4625), and through 54 weeks in 157 treatment-naïve, HIV-1 infected participants (study GS-US-200-4334).
Safety in Pregnancy and Lactation	Population in need of further characterization: No studies of LEN have been conducted in pregnant women. In non-clinical studies, LEN was detected in the plasma of nursing rat pups. It is not known if LEN is secreted in human milk.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Long-term safety information
	Safety in pregnancy and lactation

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection.

There are no specific adverse reaction follow-up questionnaires for any of the safety concerns.

III.2. Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.3. Additional Pharmacovigilance activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

GS-US-200-4625: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection with Multidrug Resistance	
Rationale and Study Objectives	Safety concern addressed: Long-term safety information (missing information). Objectives: To evaluate the safety of LEN in combination with an OBR through 52 weeks of treatment.
Study Design	A phase 2/3, global, randomized, placebo-controlled multicenter study of LEN together with an OBR in PWH with MDR who are failing their current regimen.
Study Populations	HTE adults with MDR HIV-1 who are failing their current regimen.
Milestones	Submission of Final Study Report.
GS-US-200-4334: A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 with Other Antiretroviral Agents in People Living with HIV	
Rationale and Study Objectives	Safety concern addressed: Long-term safety information (missing information). Objectives: To evaluate the safety and tolerability of LEN-containing regimens through 80 weeks of treatment.
Study Design	A Phase 2, randomized, open-label, active controlled study evaluating the safety and efficacy of LEN in combination with other antiretroviral agents.
Study Populations	Treatment-naïve PWH.
Milestones	Submission of Final Study Report.
Antiretroviral Pregnancy Registry (APR)	
Rationale and Study Objectives	Safety concern addressed: Safety in pregnancy and lactation (missing information). Objectives: To collect information on the risk of birth defects with antiretroviral drugs, including LEN, to which pregnant women are exposed.
Study Design	Prospective, observational, exposure registration, and follow-up study.
Study Populations	Pregnant women exposed to antiretroviral drugs.
Milestones	Submission of interim reports in the LEN periodic safety update report (PSUR) (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs).

III.4. Summary Table of Additional Pharmacovigilance Activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
GS-US-200-4625 Ongoing	To evaluate the safety of LEN in combination with an OBR through 52 weeks of treatment in adults with MDR HIV-1 who are failing their current regimen.	Long-term safety information (missing information)	Submission of Final Clinical Study Report	30 September 2024
GS-US-200-4334 Ongoing	To evaluate the safety and tolerability of LEN-containing regimens through 80 weeks of treatment in treatment-naïve participants with HIV-1.	Long-term safety information (missing information)	Submission of Final Clinical Study Report	30 September 2024
Antiretroviral Pregnancy Registry (APR) Ongoing	To collect information on the risk of birth defects with antiretroviral drugs, including LEN, to which pregnant women are exposed.	Safety in pregnancy and lactation (missing information)	Submission of interim reports	In the LEN PSUR (DLP and periodicity described in the list of EU Reference Dates and frequency of submission of PSURs)

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies for LEN.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. Routine Risk Minimization Measures

The routine risk minimization measure for LEN in the EU comprise the SmPC, the package leaflet (PL), and the legal status of the product. Lenacapavir is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection (SmPC section 4.2). The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in the table below. The legal status can be considered a general measure applicable to all individual safety concerns.

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Long-term safety information (missing information)	Routine risk communication: None Other routine risk minimization measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection
Safety in Pregnancy and Lactation (missing information)	Routine risk communication: SmPC section 4.6 PL section 2 Other routine risk minimization measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection

V.2. Additional Risk Minimization Measures

Routine risk minimization measures as described in Part V, Section V.1, are sufficient to manage the safety concerns of LEN.

V.3. Summary Risk Minimization Measures

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risks		
None	N/A	N/A
Important potential risk		
None	N/A	N/A

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Long-term safety information	Routine risk communication: None Other routine risk minimization measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: GS-US-200-4625 – safety of LEN in HTE PWH with multidrug resistance GS-US-200-4334 – safety of LEN in treatment-naïve PWH
Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2 Other routine risk minimization measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities Antiretroviral Pregnancy Registry (APR)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR LENACAPAVIR

This is a summary of the risk management plan (RMP) for lenacapavir (LEN). The RMP details important risks of LEN, how these risks can be minimized, and how more information will be obtained about LEN's risks and uncertainties (missing information).

The LEN summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LEN should be used.

This summary of the RMP for LEN should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the LEN RMP.

VI.1 The Medicine and What Is It Used For

Lenacapavir, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen. It contains LEN as the active substance, and it is given as both an oral tablet and a subcutaneous (SC) injection.

Further information about the evaluation of LEN's benefits can be found in the LEN EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/sunlenca

VI.2 Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of LEN, together with measures to minimize such risks and the proposed studies for learning more about LEN's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of LEN is not yet available, it is listed under 'missing information' below.

VI.2.A List of Important Risks and Missing Information

Important risks are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of a medicinal product. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Long-term safety
	Safety in pregnancy and lactation

VI.2.B Summary of Important Risks

Lenacapavir has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a doctor experienced in the management of HIV-1 infection (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risks	**None**
Important Potential Risk	**None**
Missing information	**Long-term safety**
Risk Minimization Measure(s)	Other routine risk minimization measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection

Additional Pharmacovigilance activities	Additional pharmacovigilance activities: **Study GS-US-200-4625** - Safety of LEN in Heavily-Treatment-Experienced (HTE) participants with multi drug resistant HIV-1 infection • **Study GS-US-200-4334** - Safety of LEN in treatment-naive participants with HIV1 infection See Section VI.2.C of this summary for an overview of the post-authorization development plan.
Missing information	**Safety in pregnancy and lactation**
Risk Minimization Measure(s)	Routine risk communication: SmPC section 4.6 PL section 2 Other routine risk minimization measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: **Antiretroviral Pregnancy Registry (APR)** See Section II.C of this summary for an overview of the post-authorization development plan.

VI.2.C Postauthorization Development Plan

VI.2.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of LEN.

VI.2.C.2 Other Studies in Postauthorization Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
Study GS-US-200-4625 - Safety of LEN in HTE participants with multi drug resistant HIV-1 infection	To evaluate the safety of LEN in combination with an optimized background regimen (OBR) through 52 weeks of treatment in adults with MDR HIV-1 who are failing their current regimen.
Study GS-US-200-4334 - Safety of LEN in treatment-naive participants with HIV-1 infection	To evaluate the safety of LEN-containing regimens through 80 weeks of treatment in treatment-naïve participants with HIV-1.
Antiretroviral Pregnancy Registry (APR)	To collect information on the risk of birth defects with antiretroviral drugs, including LEN, to which pregnant women are exposed.

PART VII: ANNEXES

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Not applicable

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

None

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material (Refer to References)

Annex 8. Summary of Changes to the Risk Management Plan over Time

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